Green Photochemistry

the synthesis of fine chemicals with sunlight

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Ph.D. Thesis

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Project Submission Form

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Abbreviations

AU	absorbance units
AM	Aurélien Marseault (June 2009-September 2009)
AOT	bis(2-ethylhexyl) sulfosuccinate sodium salt
$bmpy^+$	1,1-butylmethylpyridinium
$bmim^+$	1-butyl-3-methylimidazolium
CPC	compound parabolic collector
d	doublet
DCM	dichloromethane
DCTMB	1,4-dicyano-2,3,5,6-tetramethylbenzene
DCU	Dublin City University
dd	doublet of doublets
DLR	German Aerospace Centre, Cologne, Germany
EATOS	environmental assessment tool for organic syntheses
EC	Emma Coyle (October 2006-September 2009)
EH	Elodie Haggiage (June 2008-September 2008)
$emim^+$	1-ethyl-3-methylimidazolium
$empy^+$	1,1-ethylmethylpyrrolidinium
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
hν	light
IL	ionic liquid
IMM	Institut für MikrotechnikMainz
IR	infrared
ISC	intersystem crossing
KC	Kate Corcoran (February 2009-May 2009)

KJ	Kieran Joyce (February 2007-May 2007)
LED	light emitting diode
m	multiplet
MB	methylene blue
MB_{IE}	methylene blue on ion exchange resin
MPI	Max Planck Institute
MS^+	mass spectrometry, positive mode
MS^-	mass spectrometry, negative mode
ND	not determined
NMR	nuclear magnetic resonance
NQ	not quantifiable
NTf_2^-	bis(trifluoromethylsulfonyl)imide
[O]	oxidation/ oxidising agent
OTf^-	trifluoromethanesulfonate (triflate)
PEG	poly(ethylene glycol)
PROPHIS	parabolic trough facility for organic photochemical syntheses
PS	polymeric support
PSA	Platforma Solar de Almeria, Spain
PyTPP	monopyridyltriphenylporphyrin
RB	rose bengal
RB_{MF}	rose bengal on Merrifield resin
Red.	reduction
RT	room temperature
s	singlet
$scCO_2$	supercritical carbon dioxide
SDS	sodium dodecyl sulfate
t	triplet
t-AmOH	*tert*-amyl alcohol

TLC	thin layer chromatography
TPP	tetraphenylporphyrin
UV	ultraviolet
UV-vis	ultraviolet-visible
w/w	percentage by weight
Δ	heat

Acknowledgements

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Abstract

This research examines the dye-sensitised photooxygenation procedure as a case study to demonstrate 'green' photochemistry. There are three main streams to the research, namely the optimisation of juglone (5-hydroxy-1,4-naphthoquinone) synthesis under green conditions, the extension of the optimised procedure to a library of 1-naphthols and the investigation of photooxygenation reactions in alternative media.

The dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene to form juglone ([4+2]-cycloaddition reaction) was used as a model reaction to develop an entirely 'green' photochemical synthesis, taking into account all steps of the process. This approach looks at the reaction conditions, follow-up procedures and recycling and recovery of solvents and catalysts.

Following optimisation, use of non-concentrated solar irradiation was demonstrated in Irish sunlight conditions at Dublin City University. Use of concentrated sunlight was investigated in collaboration with the German Aerospace Centre (DLR), Cologne. In all cases, solar irradiation gave yields greater than those obtained under artificial light conditions (26-70% and 19-47%, respectively).

In the second part of this work, the optimised conditions from above were applied to photooxygenation of other 1-naphthol substrates. A library of 5-amido-1-naphthols were prepared and converted to the corresponding 1,4-naphthoquinones, giving yields of 12-72% for artificial light irradiation (4 hours) and 23-90% for solar synthesis (6 hours).

A final study looked at synthesis of juglone using alternative reaction media such as solvent-free (polymer supported) synthesis, ionic liquids, microemulsions and supercritical fluids. Of these methods microemulsions proved most effective, with isolated yields of up to 88% (4 hours).

Chapter 1 Literature Survey

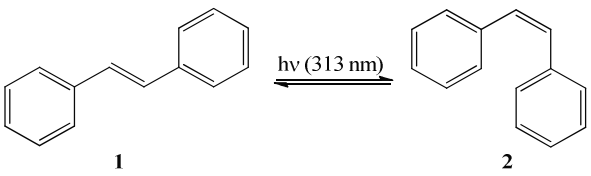
1.1 Photochemistry

IUPAC defines photochemistry as *the branch of chemistry concerned with the chemical effects of light (far UV to IR)*[1]. The basis of photochemistry is that the substrate, or part of the substrate, must absorb a photon of light (Grotthuss-Draper Law) and enter an excited state[2, 3]. In addition, a single photon can activate only one molecule (Stark-Einstein Law) into the excited state[2, 3]. The photon absorbed must have the required energy for the excitation to occur. The region of the electromagnetic spectrum of greatest interest for synthetic photochemistry is 200-700 nm (598-171 kJ mol^{-1})[4], as the energy of this radiation tends to correspond to the excitation energy of many organic compounds, such as alkenes, carbonyls and other chromophores. Once in the excited state, the fate of the substrate is determined by its photophysical properties, reaction partners and conditions. Common photochemical transformations include, among others, isomerisations, carbonyl chemistry (such as α-cleavage, γ-cleavage or reaction with alkenes), photo-redox reactions and photooxygenations.

1.1.1 Common photochemical transformations

1.1.1.1 Isomerisations

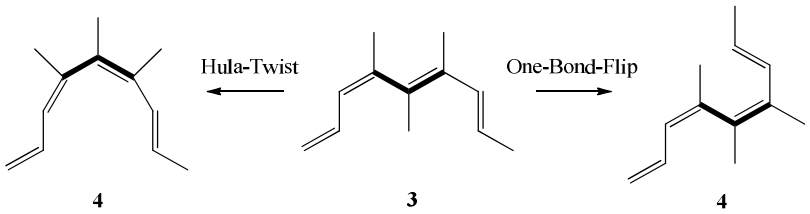
Photo-*cis-trans* isomerisations are of interest as with careful selection of irradiation wavelength it is possible to induce a photostationary state in which the more thermodynamically unstable isomer predominates[5]. The classical mechanism ("one bond flip") for this reaction is via the first excited state of alkenes (ππ*), in which there is negligible π bonding, and so 180° rotation can occur, yielding the opposite isomer. When the wavelength of the light is chosen to selectively irradiate the more stable isomer, it is possible to force formation of the more unstable isomer in a 'photostationary state'. This may be observed for the *trans-cis* isomerisation of stilbene at 313 nm (Scheme 1).



Scheme 1: Photoisomerisation of stilbene.

The *cis*-isomer **2** may convert back to the *trans*-isomer **1** over time via a thermal method when light irradiation is not sustained.

An alternative mechanism for *cis-trans* photoisomerisation is the Hula-Twist process (via a two bond isomerisation) as reported by Liu in 1985 and later supported by Fuss (Scheme 2)[6-10].



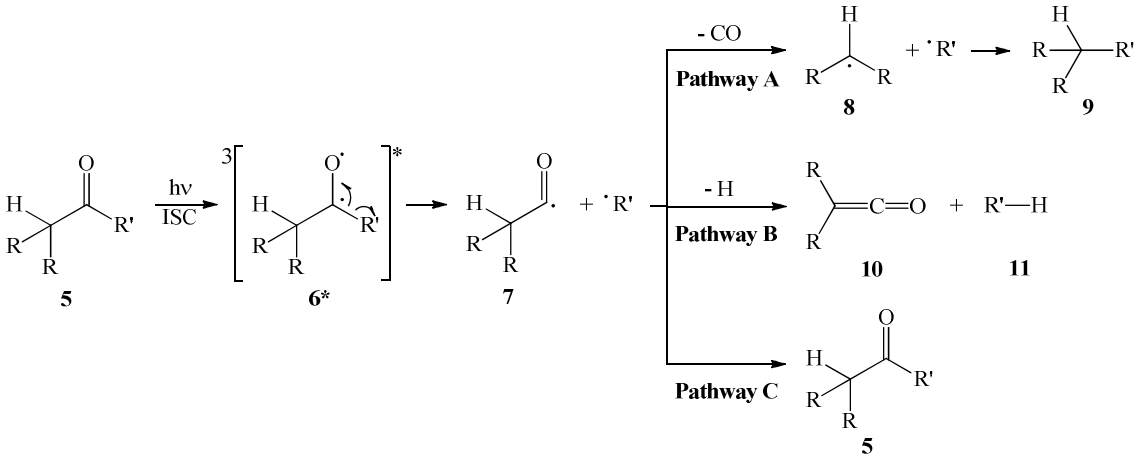
Scheme 2: Hula-twist and one-bond-flip mechanism of photoisomerisation.

The Hula-Twist mechanism is observed in spatially hindered compounds, such as those frozen in solvents or located within macrostructural restraints, which are unable to undergo the standard one-bond flip process.

1.1.1.2 Carbonyl photochemistry

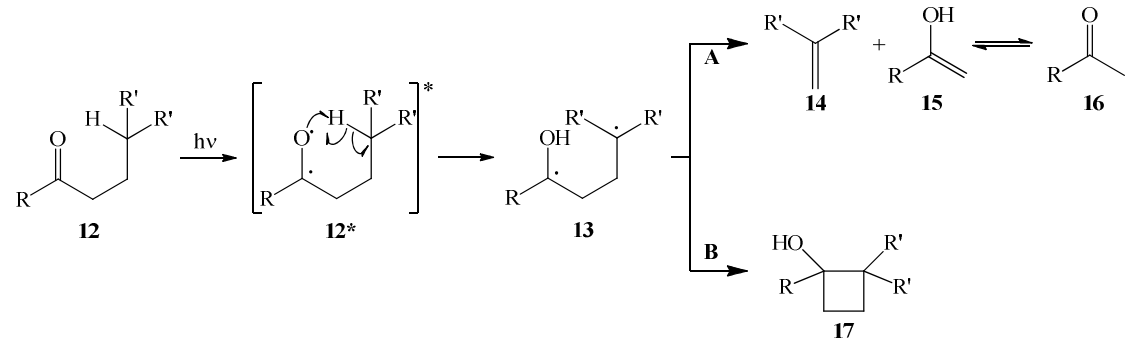
Carbonyl compounds absorb in the UV region (230 - 340 nm), which corresponds to excitation of a non-bonding 2p electron of the oxygen atom to the anti-bonding π orbital of the carbonyl ($n\pi^*$, ε = 15-30 l mol^{-1} cm^{-1}). This weak transition results in a wealth of carbonyl photochemistry, including α-cleavage (Norrish Type I), γ-H abstraction (Norrish type II), cycloadditions with alkenes (Paternò-Büchi reaction) and photoreduction.

α-Cleavage (Norrish Type I) is observed for excited state carbonyl compounds **6***, where an acyl radical **7** and an alkyl radical are formed. These can undergo several follow-up reactions (Scheme 3), namely decarbonylation (Pathway A) to yield alkanes **9**, disproportionation (Pathway B) to ketenes **10** (unstable and usually undergo follow-up reactions) and recombination (C) to re-form starting material **5**.



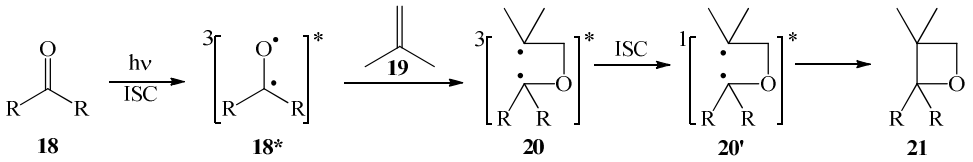
Scheme 3: α-Cleavage of excited state carbonyl 6*.

γ-H abstraction from excited state ketones or aldehydes **12*** leads to formation of 1,4-biradicals **13**. The biradical can undergo several follow up reactions, notably the Norrish Type II cleavage (A) leading to alkenes **14** and enols **15** or Yang cyclisation (B) forming cyclobutanols **17** (Scheme 4)[11].



Scheme 4: γ-H abstraction of excited state carbonyl.

Cycloaddition reactions between the excited state carbonyl and alkenes have been investigated for the past century and are well documented in the literature. Examples of these [2+2]-cycloadditions have been reported for ketones, aldehydes, quinones, carboxylic acids and other carbonyl compounds[12]. The Paternò-Büchi reaction (known since 1909) in which an excited state carbonyl **18*** reacts with an alkene **19** to form an oxetane **21**, is a prime example of photochemical [2+2]-cycloaddition (Scheme 5).

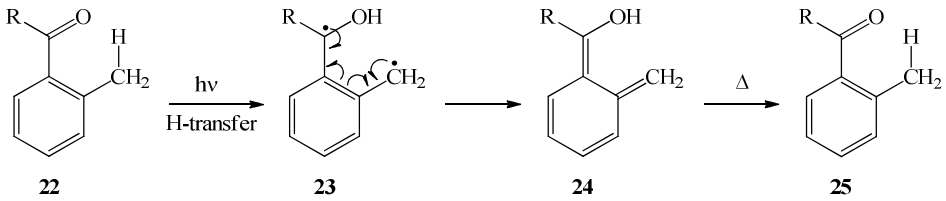


Scheme 5: The Paternò-Büchi reaction of an excited state carbonyl.

1.1.1.3 Rearrangements/pericyclic reactions (photo-redox reactions)

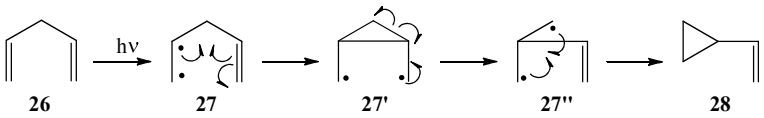
Many photochemically induced rearrangements and transformations are possible, some of which are listed here. Cyclisations such as intramolecular Paternò-Büchi reactions, intramolecular [2+2]- and [4+2]-cycloadditions are observed, as well as phototautomerisation and photocyclisation of arene-ethylene systems (e.g. intramolecular *ortho*-cycloadditions).

Phototautomerisations have been reported, such as photoenolisations (Scheme 6). These are of interest for application in sunscreen lotions, where UV light initiates the phototautomerisation of the active compound, thus preventing light causing damage to skin.



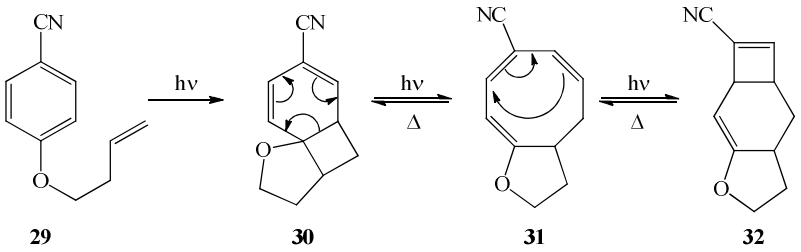
Scheme 6: Phototautomerisation of 2-methylphenone 22**.**

A common photo-rearrangement is the di-π-methane rearrangement in which 1,4-dienes **26** undergo a photochemical transformation to yield vinylcyclopropanes **28** (Scheme 7)[13].



Scheme 7: Di-π-methane rearrangement of 1,4-pentadiene.

Intramolecular *ortho*-cycloadditions refer to the addition of a C-C double bond to the 1,2-positions of an arene **29**. An example is shown in Scheme 8, in which the *ortho*-cyclisation reaction is followed by a cascade of electrocyclic reactions.

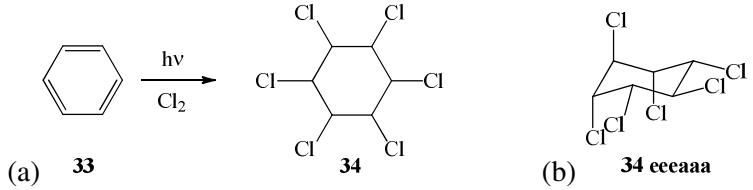


Scheme 8: Intramolecular *ortho*-cycloaddition of 4-(but-3-enyloxy)benzonitrile 29**.**

1.1.1.4 Photo-initiated radical reactions

Most photo-initiated radical reactions involve the initial formation of halogen radicals[14]. The most common example of this is the photo-chlorination of methane, in which UV light is used to homolytically split chlorine (Cl_2) into two chlorine radicals. These highly reactive species then propagate the reaction by attacking the C-H bonds of methane.

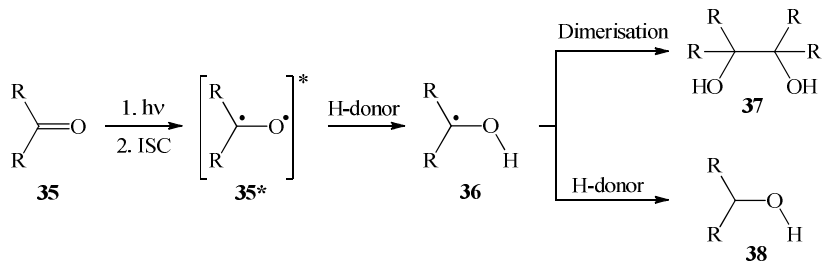
An example of an industrial application of photo-initiated radical reactions is the formation of hexachlorocycylohexane **34**, in which chlorine radicals are added to benzene **33** (Scheme 9). The γ-isomer (eeeaaa) product is used as an insecticide (lindane **34 eeeaaa**).



Scheme 9: (a) Synthesis and (b) structure of lindane 34**.**

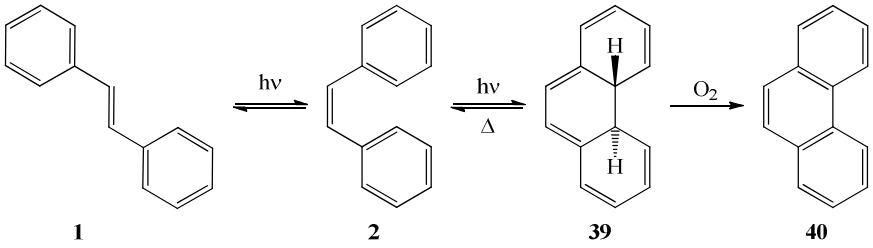
1.1.1.5 Photo redox reactions

Photoreduction is defined as the addition of one or more electrons to a photoexcited species or the photochemical hydrogenation of a substance[1]. In these reactions a photo-excited species **35*** reacts with a suitable H-donor (such as alcohols with α-hydrogens, toluene and even cyclohexane). The radical formed (**36)** may undergo reaction with other hydrogen donors to form alcohols **38** or other reaction partners (Scheme 10).



Scheme 10: Photoreduction of a ketone 35**.**

Photooxidation refers to the loss of one or more electrons from a species as a result of photoexcitation[1]. This can also refer to the reaction of a species with molecular oxygen as a result of light irradiation. An example of photooxidation is the photochemical conversion of *trans*-stilbene **1** to phenanthrene **40**. During this transformation, *trans*-stilbene **1** undergoes a photo-isomerisation to *cis*-stilbene **2**, followed by an electrocyclic ring closure. The final step of the reaction is an irreversible oxidation to form phenanthrene **40** (Scheme 11).

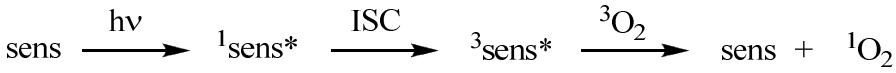


Scheme 11: Oxidation of *trans*-stilbene 1 **to form phenanthrene** 40**.**

1.1.1.6 Photooxygenation

Photooxygenation is defined by IUPAC as the photoinduced incorporation of molecular dioxygen into a molecular entity[1]. In Type I photooxygenations a substrate in the excited state reacts with triplet state oxygen, which is then incorporated into the product. Type II photooxygenations involve the light initiated formation of singlet oxygen and subsequent reactions of this reactive species. There are three main Type II photooxygenation reactions: ene-reactions (Schenck reaction), [2+2]-cycloadditions and [4+2]-cycloadditions of singlet oxygen.

Singlet oxygen was first identified in 1931 when Kautsky postulated that the reactive intermediate in dye sensitised reactions was an activated species of molecular oxygen[15]. He proposed the following mechanism for the generation of singlet oxygen (Scheme 12):



Scheme 12: Dye-sensitised generation of singlet oxygen.

Further advances in the understanding of this chemistry came in 1963 when Khan and co-workers identified this activated molecular oxygen species as singlet oxygen[16]. Investigations in 1964 by Foote[17, 18] and by Corey[19] confirmed both the existence of singlet oxygen and the mechanism by which it is generated, as proposed by Kautsky (Scheme 12).

Singlet oxygen may be generated chemically (such as through the disproportionation of hydrogen peroxide[20, 21]), thermally (for example through the reverse Diels-Alder reaction of endoperoxides[22, 23]) or through light induced dye-sensitisation[24-26]. In light induced dye-sensitisation a photon of the correct wavelength causes excitation of the sensitiser to the singlet state, which then undergoes intersystem crossing to form the longer lived triplet state sensitiser (Scheme 12). Upon interaction with molecular oxygen, energy transfer occurs to yield singlet oxygen (requiring 94 kJ.mol^{-1} of energy). This highly reactive species can then undergo a range of photochemical reactions.

Some of the most commonly used sensitisers are shown in Figure 1, namely rose bengal **41** (RB), methylene blue **42** (MB) and tetraphenylporphyrin **43** (TPP)[27].

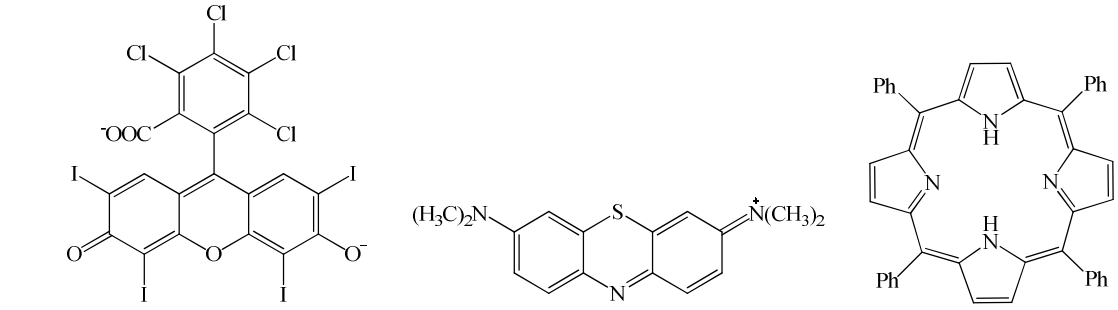


Figure 1: Commonly used sensitisers for generation of singlet oxygen (a) rose bengal 41**, (b) methylene blue** 42 **and (c) tetraphenylporphyrin** 43 **(counter ions not shown).**

Using these sensitisers, relatively high quantum yields may be obtained for singlet oxygen formation ($\Phi(CH_3OH)_{RB} = 0.8$, $\Phi(CH_3OH)_{MB} = 0.51$ and $\Phi(C_6H_6)_{TPP} = 0.66$).

The maximum absorbance of rose bengal **41** is in the region 500 – 600 nm (Figure 2), which corresponds to absorbance of 170 kJ/mol of energy. This enables excitation of the sensitiser to

its singlet state, from which it undergoes intersystem crossing to its triplet state (E_T = 165-174 kJ/mol), which can then selectively transfer energy to molecular oxygen (E_S = 94 kJ/mol).

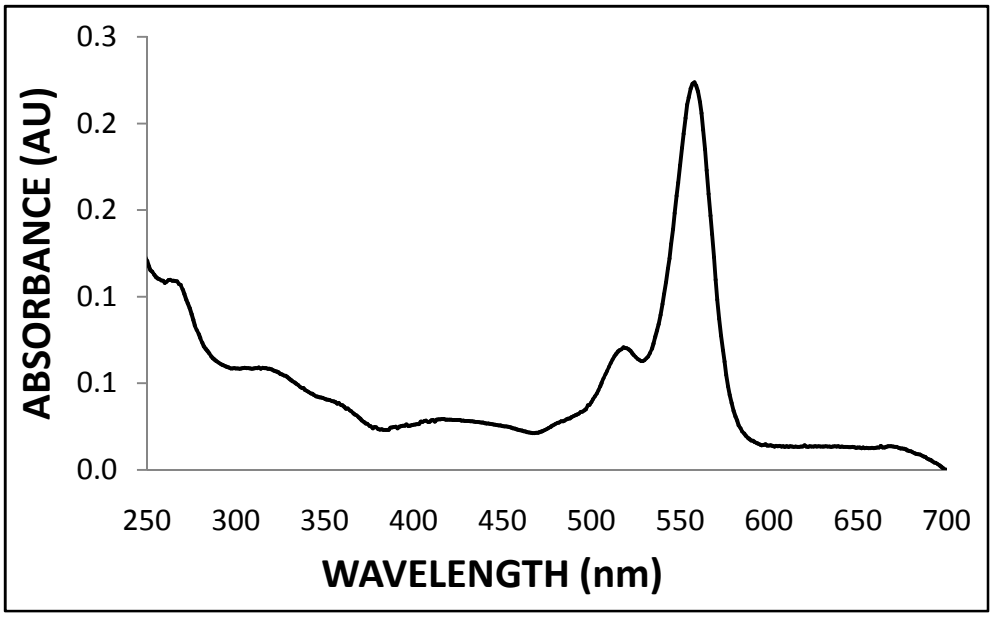


Figure 2: UV spectrum of rose bengal 41 **(in methanol).**

The maximum absorbance of methylene blue **42** is in the region 600 - 700 nm (Figure 3). In a similar process to that of rose bengal **41**, the dye is excited to its singlet state before intersystem crossing to the triplet state (142 kJ/mol). Once in the triplet state, the dye can readily transfer energy to molecular oxygen.

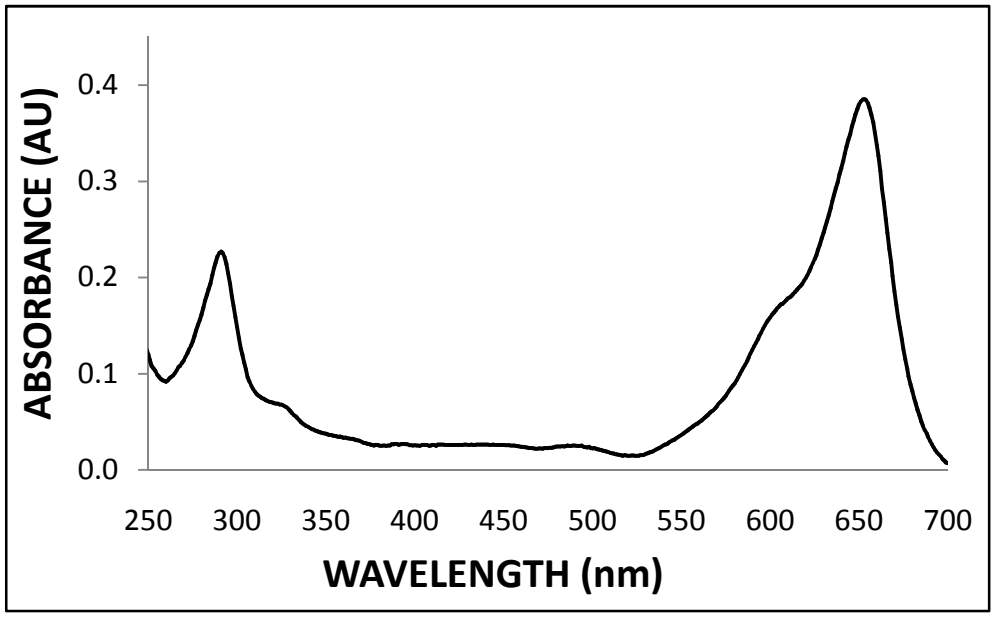


Figure 3: UV spectrum of methylene blue 42 (in methanol).

TPP **43** also absorbs in the visible light region of the electromagnetic spectrum with a maximum absorbance in the region of 400-450 nm (Figure 4), enabling absorption of 142 kJ/mol, which is sufficient to reach the triplet excited state.

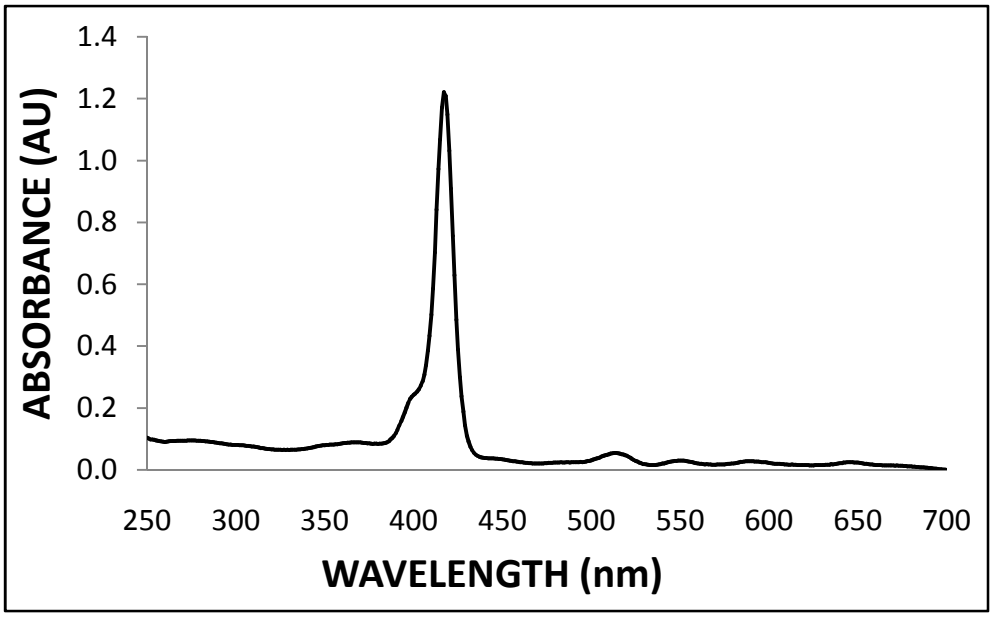


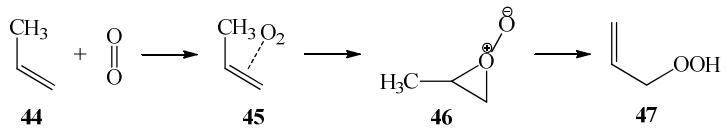
Figure 4: UV spectrum of TPP 43 **(in dichloromethane).**

Porphyrins are commonly reported as excellent sensitising agents[28, 29] and despite lower quantum yields of singlet oxygen than rose bengal **41**, they often give greater yields for

photooxygenations. This is generally attributed to their greater UV stability than other dyes[30]. Tetraphenylporphyrin **43** is used less frequently than rose bengal **41** or methylene blue **42** due to its poor solubility in polar solvents. It is primarily soluble in halogenated solvents, which makes it unfavourable for use in industrial processes[31].

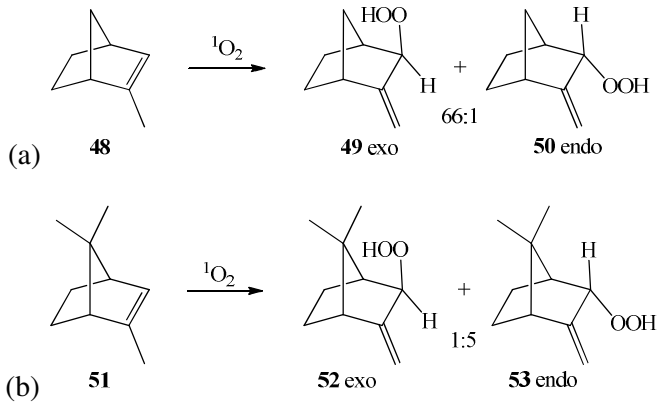
Once generated, singlet oxygen can undergo follow up reactions or quenching. Quenching of singlet oxygen can occur by deactivation by an external environmental influence (through energy transfer or charge transfer) or through non-radiative processes[1]. The main types of photooxygenation are ene-reactions (Schenck reaction), [2+2]-cycloadditions and [4+2]-cycloadditions.

Schenck-ene reactions involve the reaction of singlet oxygen with alkenes with an allylic hydrogen **44**, with conversion to allylic hydroperoxides **47**[27]. These were first reported in 1943 in a patent by Schenck, but the mechanism of this reaction is still not fully known, although it is believed to be a three step process via an exciplex **45** and perepoxide **46** (Scheme 13).



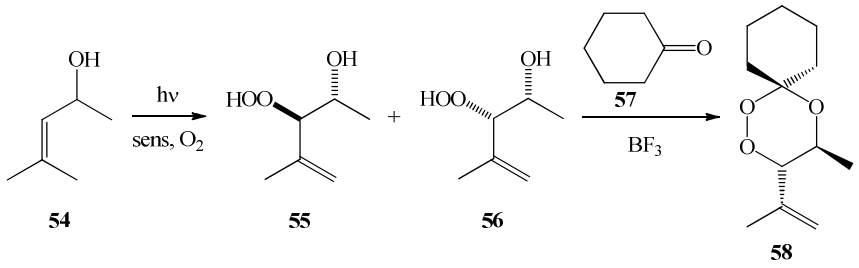
Scheme 13: The Schenck-ene reaction.

Both stereoselective and regioselective trends are observed for the Schenck-ene reaction. Hydrogen abstraction occurs preferentially at the most substituted side of the C-C double bond (side selectivity). Steric effects are evident, as singlet oxygen approaches from the less hindered side of the substrate, as is eloquently demonstrated by Griesbeck for the ene-reaction of norbornene derivatives **48** and **51**(Scheme 14)[27].



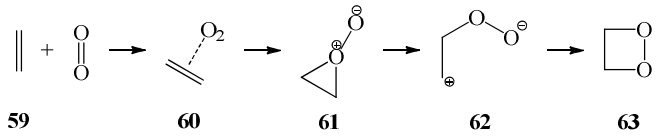
Scheme 14: Photooxygenation of norbornene derivatives 48 **and** 51**.**

Application of the Schenck-ene reaction as a photochemical key step in the synthesis of novel anti-malarial agents has been investigated by Griesbeck, in particular preparation of leads based on the 1,2,4-trioxane core structure in the naturally derived antimalarial agent artemisin (Scheme 15)[32, 33].



Scheme 15: Synthesis of trioxanes.

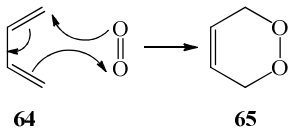
[2+2]-Cycloadditions of singlet oxygen to alkenes **59** (resulting in formation of 1,2-dioxetanes **63**) were identified later than the ene-reaction and [4+2]-cycloadditions, as they are more rare. Fenical first proposed the formation of 1,2-dioxetanes **63** as an alternative reaction pathway to the ene-reaction[34]. [2+2]-Photooxygenations are commonly observed for electron rich alkenes, such as vinyl ethers, enamines and alkenes which do not have allylic hydrogens[35]. Like the ene-reaction, the mechanism is not fully elucidated, but is believed to proceed via an exciplex **60**, a perepoxide **61** and a zwitterionic species **62** (Scheme 16).



Scheme 16: The [2+2]-cycloaddition of singlet oxygen and alkenes.

Dioxetanes tend to be thermally labile and therefore are difficult to isolate safely. They are commonly converted to less hazardous functionalities, by reactions such as conversion to carbonyls, reduction to 1,2-diols or epoxides, or nucleophilic opening with amines.

Of great significance is the [4+2]-cycloaddition of singlet oxygen. This is an example of a photo-Diels-Alder reaction, where singlet oxygen acts as a dienophile (Scheme 17).



Scheme 17: Proposed concerted mechanism of the [4+2]-cycloaddition of singlet oxygen.

Singlet oxygen is a highly reactive species and as a result [4+2]-photooxygenations can occur for a range of substrates with a 1,3-diene substructure. These can range from small molecules such as furan and cyclopentadiene to larger substrates such as α-terpinene. This reaction can even be observed for aromatic compounds, such as naphthalenes and anthracenes.

The product of a [4+2]-cycloaddition of singlet oxygen is an endoperoxide, many of which are unstable and subsequently undergo further reactions. However, stable endoperoxides such as ascaridole **66** and the endoperoxides of 9,10-diphenylanthracene **67** and 9,10-dicyanoanthracene **68** (Figure 5) have been identified.

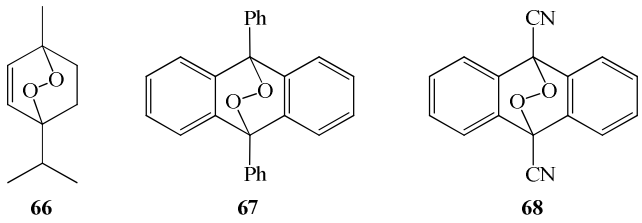
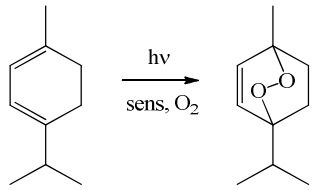


Figure 5: Examples of stable endoperoxides: ascardiole 66**, 9,10-diphenylanthracene** 67 **and 9,10-dicyanophenylanthracene** 68**.**

The reaction of singlet oxygen with α-terpinene **69** to form ascaridole **66** is one of the most noteworthy photo-[4+2]-cycloaddition reactions. This endoperoxide was used to treat ascaris infections in humans in the aftermath of World War II and was prepared in large quantities via the photochemical route using sunlight (Scheme 18)[36].



69 **66**

Scheme 18: Synthesis of ascaridole 66**.**

Common follow-up reactions for the endoperoxides are rearrangements or treatment with a reducing agent such as thiosulfate to yield diols[37].

1.2 Green Chemistry

Green chemistry is a multi-disciplinary concept that has emerged over the past two decades, commencing in academia and research and development, which has subsequently impacted greatly on the chemical industry[31]. The rapid growth in this area emphasises the drive towards more energy efficient and less harmful processes. In particular green chemistry refers to the use of sustainable resources, development of cleaner, non-toxic substances, streamlining of existing industrial processes within a green framework and the introduction of highly selective biotechnological routes into the chemical industry[38].

The growth of interest in green chemistry has been driven in particular by the increasing desire for sustainable developments and reduction of carbon dioxide emissions. This has led to increasing interest in environmentally friendly technologies and the adoption of green chemistry approaches in both academia and industry[38, 39]. Among the many approaches are, for example, solvent-free and microwave initiated synthesis or the use of supercritical carbon dioxide or ionic liquids as solvent. Development of 'green' catalysts, e.g. biocatalysts, and other novel green approaches to various chemical processes have been investigated[40]. Use of light as a 'clean reagent' has been reported and indicates that use of light (in particular solar light) may provide a green access to chemical reactions[41]. These concepts have been examined in academia over the past century; however they have only recently come to the fore in mainstream applications.

Green chemistry was defined by Anastas in 1998 as *the utilisation of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products*[38]. This definition summarises the 12 Principles of Green Chemistry:

1. **Prevention:**

   It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom economy:**

   Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.

3. **Less hazardous chemical synthesis:**

   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

4. **Designing safer chemicals:**

   Chemical products should be designed to effect their desired function while minimising their toxicity.

5. **Safer solvents and auxillaries:**

The use of auxiliary substances (e.g. solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

6. **Design for energy efficiency:**

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of renewable feedstocks:**

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce derivatives:**

Unnecessary derivatisation (use of blocking groups, protection/ de-protection and temporary modification of physical/ chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis:**

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for degradation:**

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for pollution prevention:**

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently safer chemistry for accident preventions:**

Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions and fires.

The field of Green Chemistry has been evolving at a fast pace over the past two decades. This expansion may be attributed to the increased awareness regarding the effects of industry on the environment, increasing costs for waste disposal and increased environmental legislation. As a consequence, a drive towards sustainable chemistry is inevitable.

Following the emergence of green chemistry as a discrete research area, the journal *Green Chemistry* (published by the Royal Society of Chemistry (RSC)) was founded in 1999 by

Professor James Clark, University of York, UK. As interest in green issues has expanded, other publishers have also founded journals focussing on green chemistry, such as *ChemSusChem* by Wiley-VCH and *Green Chemistry Letters and Reviews* by Taylor & Francis. *Pure and Applied Chemistry*, published by IUPAC, has featured Special Topics on 'Green-Chemistry' (2000, volume 72, issue 7) and on 'Green-Sustainable Chemistry' (2007, volume 79, issue 11). *Chemical Reviews*, published by the American Chemical Society (ACS), has also featured a special issue on 'Green Chemistry' (2007, volume 107, issue 6). These have served to highlight research in green chemistry.

In addition to a large research interest, green chemistry has become important within industry. For example, the ACS Green Chemistry Institute joined with a number of industrial partners to found the ACS GCI Pharmaceutical Roundtable in 2005[42]. The aim of this partnership is to promote green chemistry and green engineering in the pharmaceutical industry.

1.2.1 Photochemistry and green chemistry

In general, synthetic photochemistry has had little impact in industry, although some examples of photochemical processes exist[43-45]. This low impact is attributed to the high running costs of the commonly used light sources (energy demands and cooling), such as mercury or halogen lamps. The typical energy demand of a medium pressure mercury lamp (400 W) is 1343 kJ/h. Of the electrical energy supplied, less than half is converted to light energy, resulting in a large quantity of wasted energy. Over time the lamps degenerate and although they draw the same energy the quality of the light produced decreases significantly. The limited lifetime of such lamps is a contributor to the high cost of photochemical processes (installation, maintenance and particularly operational costs). In addition, while UV light may cause desirable photochemical transformations, in many cases filtering of the light source is needed to prevent unwanted side reactions. Therefore, the percentage of the light generated that contributes to the desired chemical reaction may be very low. Such photochemical processes are very inefficient.

The efficiency of a photochemical process may be expressed using the quantum yield (Φ). This is defined by IUPAC as[1]

$$\Phi(\lambda) = \frac{\text{amount of reactant consumed or product formed}}{\text{amount of photons absorbed}}$$

In an ideal system all photons lead to a photochemical transformation and so the quantum yield is one. However, for practical applications a quantum yield of greater than 0.3 is considered

very efficient. Exceptions to this are photo-initiated free radical chain reactions, where quantum yields of far greater than one may be obtained.

Recent interest in light emitting diodes (LEDs) has offered an alternative to these costly and inefficient light sources[46]. These are small, versatile and available in a large number of wavelengths, allowing for selectivity of the light source. In addition, there is minimal heat generation so little or no cooling is needed.

Another factor that limits the perceived greenness of photochemical processes is the typical reaction conditions, in particular the solvents used and the concentration of the solutions. Many photochemical transformations are carried out in benzene or acetonitrile, as these solvents are less reactive towards free radicals. However, these are less favourable solvents due to their toxicity[31]. Photochemical reactions, in particular on the large-scale, tend to use rather dilute reaction mixtures. The amount of photons absorbed by a reaction mixture is directly related to the concentration of the reaction mixture and is expressed by the Beer-Lambert Law

$$A = log\left(\frac{P_{\lambda_0}}{P_\lambda}\right) = \varepsilon cl$$

where A is absorbance, c is concentration, l is path length (through the reaction mixture) and ε is the molar absorption coefficient (wavelength dependent constant). P_λ is the observed spectral radiant power, i.e. the power of the radiation at wavelength λ per unit wavelength interval, while $P_{\lambda 0}$ is the spectral radiant power of the incident light. In scale-up, this is a particular disadvantage as the light must irradiate a far larger quantity of reaction mixture and it is difficult to reproduce the same l value as the smaller scale synthesis. Consequently, the concentration of the reaction mixture is usually quite low, to enable light penetration of the entire reaction mixture.

Despite the disadvantages detailed above, there are several examples in the literature of 'green' photochemical transformations. The potential of photochemistry as a "clean" technology has been discussed by Bochet[47], who outlines the perceived disadvantages of photochemistry and some approaches to avoid these issues. Albini has discussed the relative merits of photochemistry compared to thermal synthesis using EATOS (Environmental Assessment Tool for Organic Syntheses[48]) models[49]. EATOS evaluates the "greenness" of a reaction based on four parameters – the sum of raw materials needed to produce one kg of product, the sum of waste per kg of product, the environmental impact of material imput and of materials produced as a result of the reaction. These values are combined to give an overall 'greenness' value for

each process. However, one failing of this model is that is does not include energy demand of the processes, which can be a considerable factor in the overall 'greenness' of any process[50]. From the EATOS values obtained, Albini concludes that the major drawback of photochemical methods compared to thermal processes is the concentration of photochemical solutions. He proposes that recovery of solvent can lead to significant decreasing of environmental impact.

However, there are many advantages of photochemistry as a green chemistry, for example the use of mild conditions. In addition, many photochemical processes demonstrate good to perfect atom economy, as the transformation is initiated by a photon, rather than an extra reagent[51].

Early work by the groups of Scharf, Demuth and Oelgemöller has demonstrated the application of photochemistry as a green technology. In particular, use of solar light in photooxygenation and photoacylation reactions provides an effective green route to fine chemicals[52-57]. In addition, elimination of halogenated solvents and use of catalytic amounts of sensitiser give a process that adheres to the twelve principles of green chemistry.

The concept of photochemistry as a green technology is over one hundred years old, as envisaged by Ciamician in the 1900s. At the International Congress of Applied Chemistry in New York in 1912, he presented his remarkable vision of The Photochemistry of the Future[58]. In this speech he outlined his belief that photochemistry, which was an entirely solar discipline at that time, could be a key component of industry in the future:

> *"On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains, and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them even more abundant fruit than nature, for nature is not in a hurry and mankind is."*

This eloquently foretells a key role for photochemistry in future industrial processes. Therefore, despite the advent of artificial light sources and other leaps in technology, it is not unexpected that mankind turns to the sun as a free energy and light source for solarchemical transformations and true 'green' photochemistry.

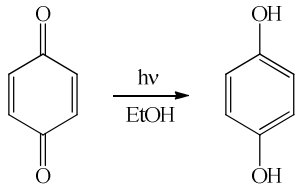
1.3 Solar Chemistry

1.3.1 Origins of photochemistry

Solar chemistry is the earliest form of photochemistry, as photochemical transformations have occurred on earth since before human life came into existence. However, interest in synthetic organic photochemistry did not commence until the eighteenth century, when Joseph Priestly began his investigations into the chemical effects of light, leading to recognition of photosynthesis[59, 60]. Following this work, interest in photochemical transformations slowly increased, until interest peaked in the nineteenth and twentieth centuries. The earliest photochemical processes were all solar in nature, often consisting of jars of solution phase reagents allowed to stand in sunlight for days, weeks and even months! Two of the main 'pioneers' of photochemistry are Giacomo Ciamician and Alexander Schönberg, whose work provides a wealth of information regarding solarchemical transformations.

1.3.1.1 Ciamician

Giacomo Ciamician (1857-1922) entered the field of photochemistry as a student working for Stanislao Cannizzaro at the Institute of General chemistry in Rome. Cannizzaro's early photochemical investigations were into the effect of light on santonin and, with Sestini, he is credited with the discovery of photosantonic acid (and *iso*-photosantonic acid). Ciamician joined this group in 1881 and in 1885 commenced his work on photochemical reactions. This was the beginning of an extensive interest in photochemistry, earning Ciamician the title "father of organic photochemistry". He was aided in his work by Paolo Silber (1851-1932) and together they investigated the effects of solar irradiation on benzoquinone **70** (Scheme 19) and nitrobenzene.



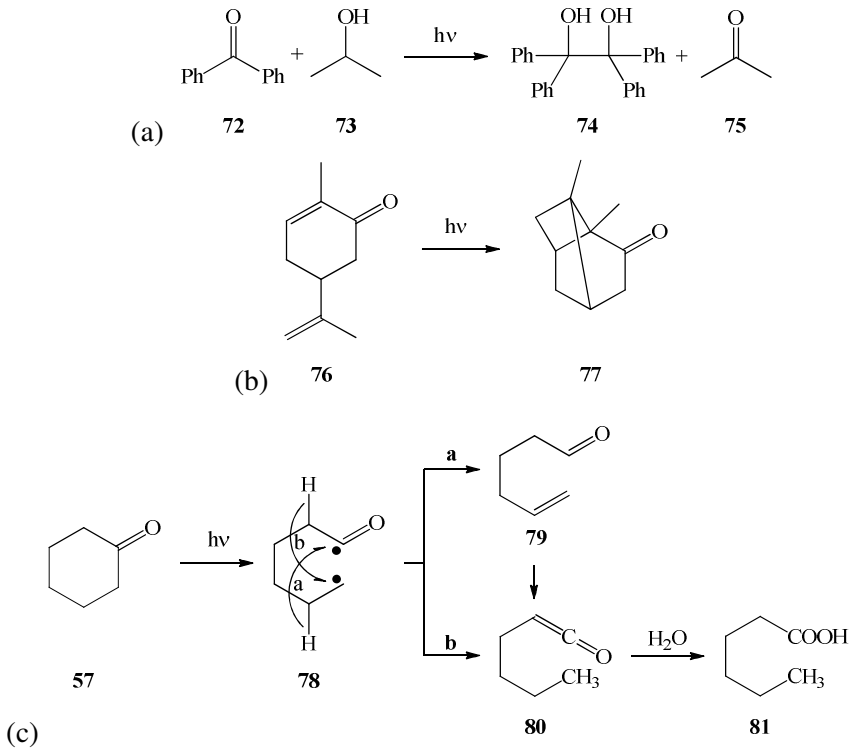
70 **71**

Scheme 19: Conversion of 1,4-benzoquinone 70 **to 1,4-hydroquinone** 71**.**

However, this investigation did not progress for long, as a publication by Klinger in *Sitzungberichte Niederrheinische Gesellschaft für Natur- und Heilkunde* reserved this area of

research for himself[61]. As a result, Ciamician and Silber did not return to photochemistry for over a decade.

In 1900, in the University of Bologna, Ciamician and Silber resumed their photochemical studies. Over the next 15 years they carried out an extensive evaluation of the chemical effects of light and published 85 notes, papers and memoirs on the topic[62]. In the course of this research they identified many types of photochemical reactions, in particular ketone chemistry such as photoreduction, photopinacolisation (Scheme 20a), intramolecular cycloadditions (e.g intramolecular [2+2]-cycloaddition of carvone **76**, and α- and β-cleavage (Scheme 20))[59, 60].



Scheme 20: (a) Pinacol reaction of benzophenone 72**, (b) intramolecular [2+2]-cycloaddition of carvone** 76**, and (c) α-cleavage (now known as Norrish Type I).**

The results of a systematic study of photochemistry were published in a series of 32 papers in *Berichte der deutschen chemischen Gesellschaft*, *Rendi Conti della Regia Accademia dei Lincei* and *Gazzeta Chimica Italiana*. These reactions are summarised in some detail by Roth in the newsletter of the European Photochemistry Association[63]. What is of note is that all of these reactions were identified using the effect of solar irradiation. Following Ciamician's death in 1922, McPherson stated in his obituary that "*anyone visiting the chemical laboratory of the University of Bologna during the early part of the present century [twentieth], could easily surmise the character of the researches being carried out in that laboratory; for the exterior*

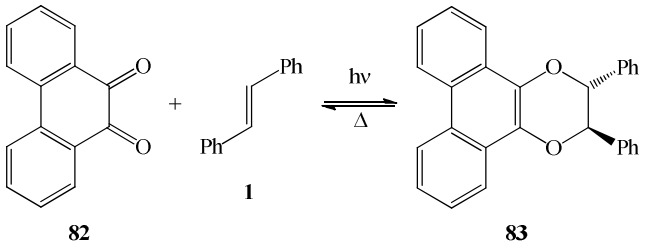
rear of the building was fitted with shelves and on these rested hundreds of bottles and sealed tubes of every description, all exposed to the sun's rays"[64]. Ciamician's legacy is not only in the wealth of photochemical transformations identified, but in his vision for the future. He began an initiative that is becoming stronger as the years pass, a desire to see the 'photochemistry of the future' as he envisaged it, a true green chemistry[65].

1.3.1.2 Schönberg

Alexander Schönberg (1892-1985) was a German chemist who emigrated to Egypt prior to the Second World War. At the University of Cairo, over the course of twenty years, he carried out extensive studies of the chemical effect of sunlight. The results of these studies were published in international journals, such as *Chemische Berichte* in Germany, *Journal of the Chemical Society* (RSC) in England and *Journal of the American Chemical Society* (ACS) in the United States. He is credited with the compilation of the first book on "Preparative Organic Photochemistry", in 1958, which was revised and translated to English in 1968[66, 67].

Schönberg's first photochemical investigations looked at the photodimerisation of thiophosgene, and in 1933 he determined the structure of the photodimeric form[68]. Between 1934 and 1936, he examined rubrene and its peroxide and determined that the peroxide was capable of releasing an active oxygen species. For this reason, Schönberg is considered one of the pioneers of singlet oxygen research[69].

During his work on sunlight induced chemistry, Schönberg published more than 20 articles in a series entitled "Photochemical reactions". The results reported in these papers included the reaction of aldehydes with phenanthraquinoneimine to form 2-hydroxy-2,3-dihydrophenanthroxazole derivatives[70], photopolymerisation of coumarins and related substances (in aqueous solutions), photo-addition and photo-reduction of aromatic ketones[71, 72]. The Schönberg reaction (also known as the Schönberg-Mustafa reaction) is the cycloaddition of alkenes to *o*-quinones **82** (Scheme 21), which proceeds via a concerted mechanism[73].



82 **1** **83**

Scheme 21: The Schönberg reaction.

1.3.2 Development of technology

The earliest photochemical experiments were carried out in uncooled flasks, using natural light. Ciamician and other early photochemists had outdoor shelves where numerous flasks could be irradiated for days, weeks or even months (Figure 6). However, there were hazards associated with these laboratories, in particular early results often stated that reaction mixtures were lost in windstorms or other accidents. In addition, the reaction mixtures were often placed in sealed containers, leading to a risk of explosion during exposure, such as gas evolution or evaporation of volatile solvents. Despite these risks a wealth of solar chemical reactions were investigated under these conditions. With the significant advances in lamp technology in the latter half of the twentieth century, photochemistry moved indoors and became a successful research area[43].

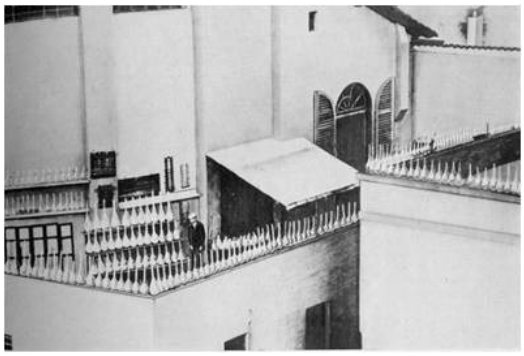
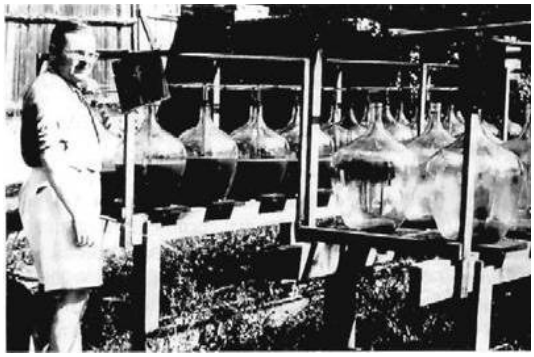
(a)  (b) 

Figure 6: Early solar sites (a) Ciamician's laboratory in Bologna, ca. 1912, and (b) Schenck's production of ascaridole in Heidelberg, ca. 1949.

Use of mercury or xenon lamps enables access to lower wavelength UV light, down to 200 nm, thus achieving a larger range of reactions than attained using sunlight. In addition, greater power (greater numbers of photons) can be achieved, giving shorter reaction times. More recently, interest has turned to the use of light emitting diodes (LEDs) as alternative light sources. These offer a range of wavelengths, with less energy required than other artificial light sources. In addition, little or no heat is generated, giving a reduction in cooling costs.

With the move towards artificial light sources, reactor shape was also re-engineered. A modified Schlenk tube can be used, thus ensuring a shallow depth of reaction mixture and more even light distribution. Light may be applied externally, such as through the use of a Rayonet reactor system, or internally using an immersion lamp. For larger scale photoreactions, further engineering of the reactor design led to the development of large scale immersion reactors as well as falling film reactors and batch reactors[43].

The ‘indoor period’ of photochemistry continued until the end of the last century, until rising oil prices and awareness of global warming led to a revolution in thought and a re-emergence of interest in solar chemistry. To accompany this renewed interest in solar work, new reactors were designed, which could use non-concentrated and concentrated sunlight. Much of the new technology is based on modified reactors for energy production, for example the PROPHIS (parabolic trough-facility for organic photochemical syntheses) reactor at the DLR in Cologne, which is based on reactor design for solar-thermal applications. The compound parabolic collector (CPC) reactor was designed for water treatment processes, but has since been adopted for use in synthetic applications.

The main types of solar chemical reactors at the Platforma Solar de Almeria (PSA) were described in a review by Malato[74], in particular parabolic trough reactors, CPC reactors and non-concentrating reactors.

1.3.2.1 Non-concentrating reactors

At their most basic, a Schlenk flask can be used as non-concentrated reactor (Figure 7a), however more sophisticated designs have been developed, such as a flatbed reactor (Figure 7b). This reactor can use both direct and diffuse sunlight[52], which makes the flatbed reactor suitable for use in countries such as Germany and Ireland, where up to 60% of sunlight is diffuse in nature.

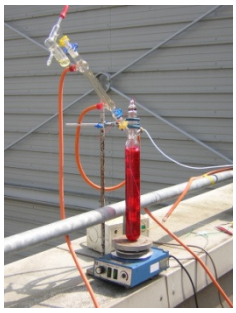
(a)  (b)  (c) 

Figure 7: Non-concentrating reactors, (a) Schlenk flask, (b) flatbed reactor and (c) vertical tube reactor.

Other non-concentrating designs include a free-falling film reactor, pressurised flat plate reactor or a solar pond[74]. A novel reactor recently reported by Liu is the floating reactor (“lab on a surfboard”) which utilises the ocean as a ‘heat sink’ for cooling solar chemical isomerisation reactions[75]. This reactor effectively eliminates both cooling and irradiation costs for the process.

1.3.2.2 Concentrating reactors

Reactors for concentrating sunlight were initially developed for solar energy production, such as the line-focus parabolic trough concentrator. This reactor design was easily modified for photochemical work, where the central tube is replaced with a transparent glass (for example Pyrex) tube through which the reaction mixture is passed.

Many of these parabolic trough reactors are now in use for solar chemical applications, for example at the German Aerospace Centre in Cologne, where laboratory scale experiments or industrial scale production can be carried out[54].

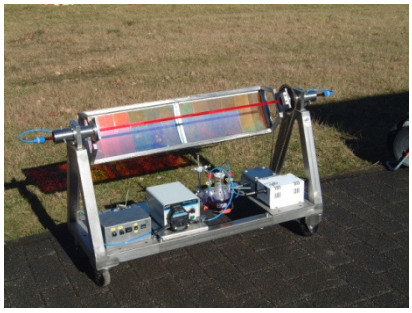
(a)  (b)  (c) 

Figure 8: Moderately concentrating reactors (a) and (b) laboratory scale reactors, (c) PROPHIS loop.

For small scale reactions in moderately concentrated sunlight, two laboratory-scale parabolic trough collectors were designed in the DLR. One reactor was constructed from common laboratory equipment, using a Liebig condenser and an aluminium mirror (Figure 8a) for reactions of up to 500 ml[55]. A more advanced prototype is the laboratory-scale parabolic trough collector with exchangeable mirrors and tubing, thus accommodating a larger volume of reaction mixture (Figure 8b)[54, 56, 57]. Both of these reactors require direct sunlight and theoretically provide the power of 15-18 suns (concentration factor). However, this concentration factor is affected by imperfections in the mirrors and tubing, and may be lower than calculated.

For industrial scale reactions, the PROPHIS loop (Figure 8c, modified from the SOLARIS loop, previously located at the PSA) may be used, through which 35-120 L of reaction mixture may be passed[76]. This is a line-focussing parabolic trough design, with four troughs, equipped with sun tracking systems. The concentrating power is 30-32 suns; however it is reliant on direct sunlight and cannot be operated in diffuse conditions.

1.3.2.3 Compound parabolic trough reactors

Compound parabolic trough reactors are a cross between a parabolic trough collector and a non-concentrating reactor, and are capable of utilising both direct and diffuse sunlight[74]. The reflective surface is in an involute shape around a cylindrical tube with a large diameter (Figure 9). As the diameter of the tube is so similar to that of the reflective surface, the concentration factor is considered to be the equivalent of a single sun.

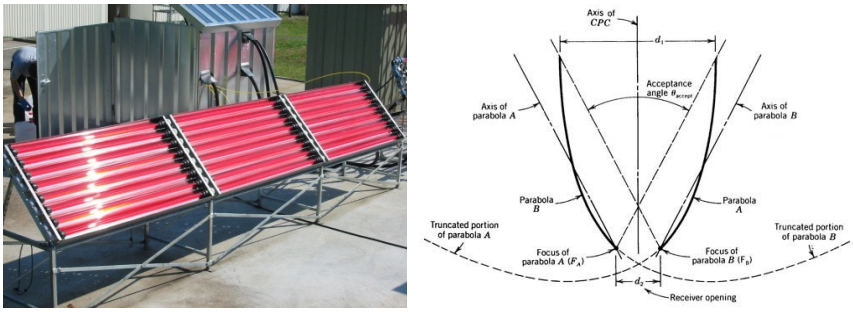


Figure 9: Compound parabolic collector (CPC).

1.3.2.4 Highly concentrating reactors

Use of highly concentrated sunlight for photochemical transformations has been investigated, to achieve this a solar furnace is used. The solar furnace at the German Aerospace centre uses a flat 52 m^2 heliostat and a concentrator composed of 147 spherical mirror facets to focus a highly concentrated beam of sunlight into the laboratory building (Figure 10)[77]. Other solar furnaces are located in Golden, Colorado[78] and Odeillo, France[79]. Concentrations of 5000-20000 suns may be achieved using these furnaces.

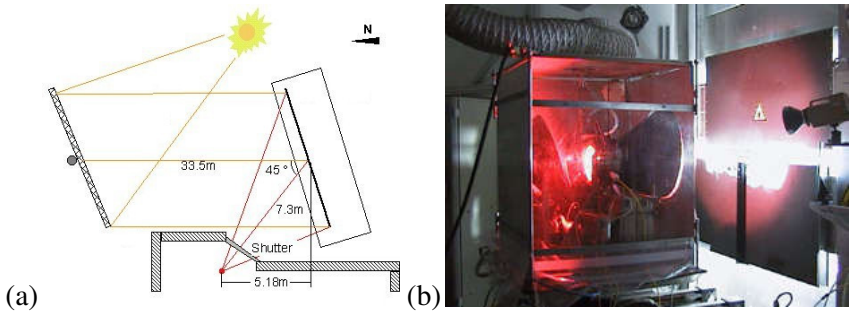


Figure 10: The solar furnace at the DLR, Cologne (a) schematic representation of the solar furnace, and (b) reaction vessel in highly concentrated solar light.

The use of highly concentrated sunlight can give higher yields in a shorter amount of time when compared to moderately concentrated light. However, the high costs for installation of these systems offset the advantages of the high concentration factor.

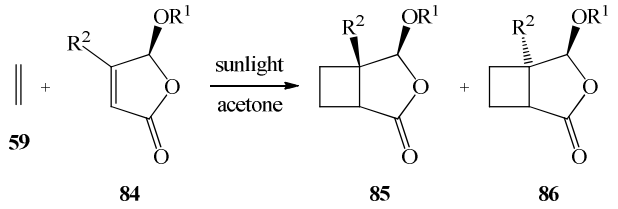
1.3.3 Recent solar chemical reactions using solarchemical reactors

Solar applications have become widespread in recent years, within energy production, hydrogen production and even wastewater treatment. The area of solar chemistry research has also expanded, with investigations into syntheses using both concentrated and non-concentrated sunlight. In particular, the use of new technology has revolutionised solar chemical production, and some studies have suggested that solar plants are viable for industrial scale production.

1.3.3.1 Reactions using moderately concentrated sunlight

Many groups carry out their research using moderately concentrated sunlight, using both small scale and large scale apparatus. Several solar campaigns have been reported, in particular those by Scharf *et al.*, Heller *et al.*, Oelgemöller *et al.* and Funken *et al.*

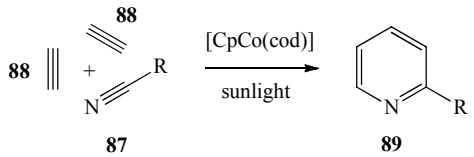
Campaigns by Scharf at the PSA (SOLARIS) and DLR (PROPHIS) looked at the production of fine chemicals using sunlight[80, 81]. Three reaction types were chosen, based on the wavelength of light needed, namely the Paternò-Büchi reaction (about 400 nm), [2+2]-cycloadditions (acetone sensitised, ca. 330 nm) and dye-sensitised photooxygenations (using rose bengal **41**, 550 nm). These reactions were carried out on the mulitgram scale (21-45 mol in 30-35 L). This study demonstrated that the [2+2]-cycloaddition reaction was feasible under solar conditions, despite the fact that only ca. 4.5% of light from the solar spectrum is ultraviolet (Scheme 22).



Scheme 22: [2+2]-Cycloaddition investigated by Scharf.

Heller *et al.* have reported the synthesis of pyridines **89** via [2+2+2]-cycloaddition using a cobalt (I) catalyst and concentrated solar light (Scheme 23)[82-87]. Several studies were conducted at the DLR (using the PROPHIS reactor) and PSA (two small solar campaigns), investigating

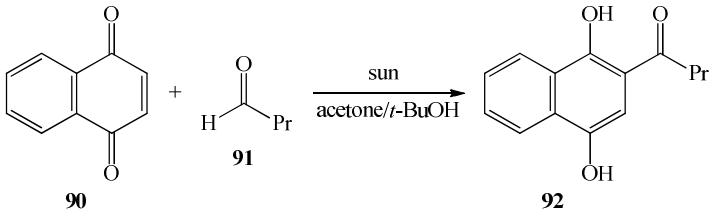
variation of starting material **87** and reaction solvents. Syntheses in aqueous media and emulsions of water-toluene have proven successful.



Scheme 23: Synthesis of pyridines 89 **via [2+2+2]-cycloaddition.**

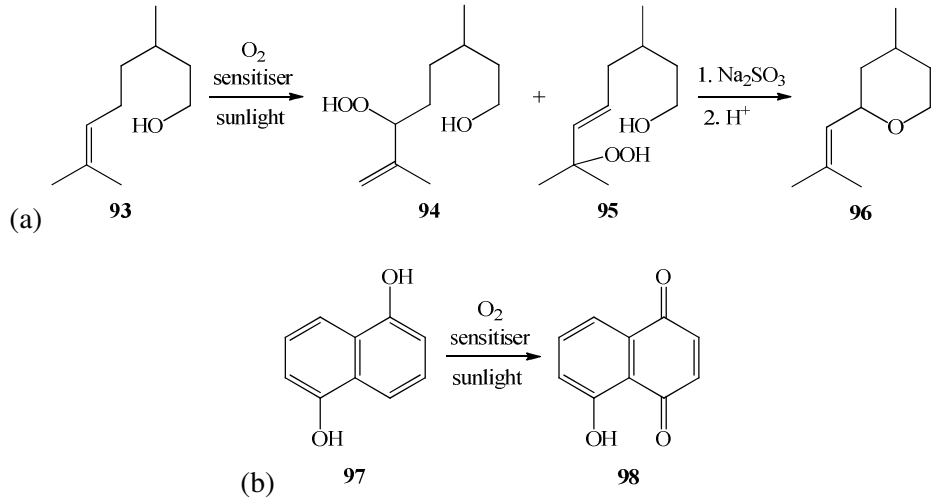
Oelgemöller *et al.* have investigated the synthesis of fine chemicals, via photo-Friedel-Crafts acylations and photooxygenations, using the solar facilities at the DLR[52, 55-57, 88-90].

The photo-Friedel-Crafts acylation of 1,4-naphthoquinone **90** with butyraldehyde **91** (Scheme 24) was performed on a 500 g (3.2 mol) scale in the PROPHIS loop using three troughs (24 m^2)[52]. Although the reaction was run for 3 days, examination of the photon counts for each day shows that almost full conversion was achieved on the first day of irradiation. A final yield of 90% **92** was determined using gas chromatography (GC).



Scheme 24: Photo-Friedel-Crafts acylation of 1,4-naphthoquinone 90**.**

Photooxygenation reactions, namely ene-reaction of citronellol **93** (a photochemical key step in the synthesis of rose oxide **96**, Scheme 25a) and [4+2]-cycloaddition of 1,5-dihydroxynaphthalene **97** (Scheme 25b), were also investigated.



Scheme 25: Photooxygenation reaction of (a) citronellol 93 **and (b) 1,5-dihydroxynaphthalene** 97**.**

Photooxygenation of citronellol **93** was carried out on large scale, using one (32 mol in 40 L) or four (44 mol in 72 L) of the PROPHIS troughs. Photooxygenation of 1,5-dihydroxynaphthalene **97** was carried out using smaller parabolic trough collectors (1-2 g in 200-250 ml of solvent). Yields of up to 79% were obtained.

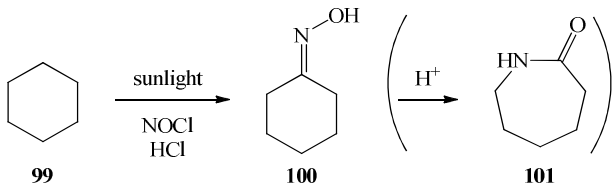
In addition, Jung has summarised the reactions carried out in the PROPHIS loop at the DLR, outlining synthesis of pyridines, photooxygenations, photo-Friedel-Crafts acylations, as well as *trans-cis* isomerisation of stilbene **1**[76].

An interesting study by Dincalp reports the synthesis of rose oxide **96** from citronellol **93** using singlet sensitisers to generate the superoxide anion radical (rather than the commonly encountered singlet oxygen method)[91]. This was achieved on a scale of 0.02 mol of starting material in 100 ml acetonitrile, using a Fix Focus FF 3.5 concentrator, which gives a concentration factor of 90-100 suns.

Other photooxidations (including photooxygenations) using moderately concentrated sunlight have been reported by Avcibasi[92] (α-terpinene **69**, 12 mmol in 50 ml, 40 suns) and Gerdes[30, 93] (photooxidation of thiols, sulfides, phenols and cyclopentadiene, small scale (50 ml), satellite bowl covered in aluminium foil).

Further reactions using solar concentrators were reported by Cermenati[94] (catalytic reaction using TiO_2) using a parabolic mirror reactor, and Icli[95] (dehydrogenation of abietic acid from both pure acid and pine resin) using a satellite dish of 1 m diameter.

Funken *et al.* have evaluated the economic viability of solar synthesis of cyclohexanone oxime **100** as an industrial process, which is used in the synthesis of ε-caprolactam **101** (Scheme 26) [96-98].



Scheme 26: Synthesis of cyclohexanone oxime 100 **and subsequent formation of ε-caprolactam** 101**.**

Modelling of a solar industrial plant indicate that energy savings may be achieved on the light source and cooling, as well as reduced carbon dioxide emissions compared to a plant using artificial light sources.

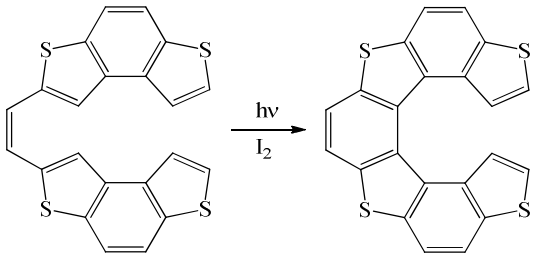
Similarly, Monnerie has reported an economic evaluation of solar synthesis of rose oxide **96** via a photochemical key step, in which the Schenck-ene reaction of citronellol **93** yields hydroperoxide precursors **94** and **95**, comparing the use of parabolic trough reactors to synthesis using artificial light sources[99].

1.3.3.2 Synthesis in non-concentrating reactors

To date CPC reactors have primarily been used for water treatment, using titanium dioxide to facilitate the degradation of pesticides[100] or chlorinated organics[101-103] The degradation of reactive dyes in water using titanium dioxide[104] or the photo-Fenton-reaction[105, 106] has been reported.

Recently the breakdown of bacteria in a CPC reactor, using titanium dioxide[107] or ruthenium based sensitisers[108, 109] has been studied.

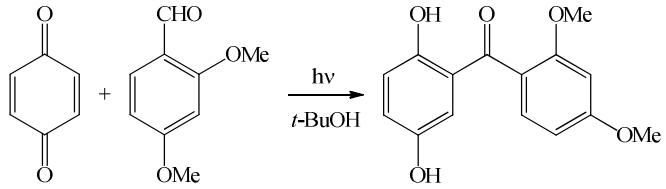
A synthetic study using a CPC reactor was reported by Caronna, in which thiohelicenes **103** with five, seven, nine or eleven rings were synthesised by photo-induced cyclodehydrogenation of the corresponding 1,2-diheteroarylethylenes **102** (Scheme 27)[110]. In a comparison with artificial light sources, the solar study gave the same yield in shorter irradiation times.



102 **103**

Scheme 27: Synthesis of 7-membered thiohelicene 102 **via photo-induced cyclodehydrogenation.**

Another synthetic study was carried out by Oelgemöller *et al.* at the DLR in Cologne, where the photo-Friedel-Crafts reaction of 1,4-benzoquinone **70** and aromatic aldehydes **104** was investigated[52, 89]. The photo-Friedel-Crafts reaction (Scheme 28) was used as a model reaction for comparison of reactors (non-concentrated, concentrated and PROPHIS), which demonstrated that the use of a non-concentrating reactor gave superior results to those achieved in the PROPHIS loop under cloudy and partially cloudy conditions. The CPC reactor was shown to give greater conversion and product yield under diffuse conditions.

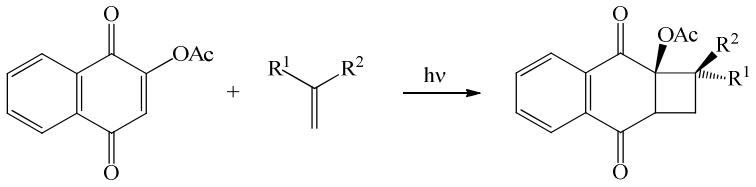


70 **104** **105**

Scheme 28: Photo-Friedel-Crafts acylation of benzoquinone 70**.**

In a similar study, the photooxygenation of (-)-citronellol **93** was used in a reactor comparison study[57]. Once again, the CPC reactor was found to give the greatest performance in diffuse conditions.

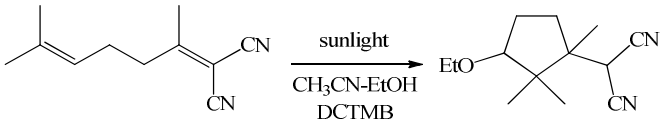
Covell has reported the [2+2]-cycloaddition of arylethenes **107** to 2-substituted-1,4-naphthoquinones **105** (Scheme 29) on a multi-gram scale in a small-scale CPC reactor[111].



106 **107** **108**

Scheme 29: [2+2]-cycloaddition of arylethenes 107 **to 2-substituted-1,4-naphthoquinones** 106**.**

Use of a flatbed reactor was reported by Heinemann for photo-induced cyclisation of 1,1-dicarbonitrile **109** using 1,4-dicyano-2,3,5,6-tetramethylbenzene (DCTMB) as an electron acceptor (Scheme 30)[112]. Comparison with concentrating reactors show that use of a flatbed reactor gives superior results under partially sunny or cloudy conditions.



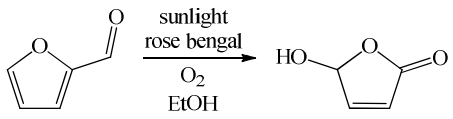
109 **110**

Scheme 30: Photo-induced cyclisation of 1,1-dicarbonitrile 109**.**

1.3.3.3 Reactions using highly concentrated sunlight

Although the solar furnace is primarily used for thermal applications, such as the synthesis of fullerenes (C_{60} and C_{70}) through vaporisation of graphite[78, 79, 113], there have been some reports of photochemical transformations using this technology.

The synthesis of fine chemicals has been the subject of some investigations, such as the solar furnace campaign investigating photooxygenations, [2+2]-cycloadditions and the Paternò-Büchi reaction at the German Aerospace Centre in 1995[80-81]. This demonstrated the feasibility of the use of highly concentrated sunlight for synthesis of fine chemicals, such as 5-hydroxyfuranone **112** (Scheme 31).



111 **112**

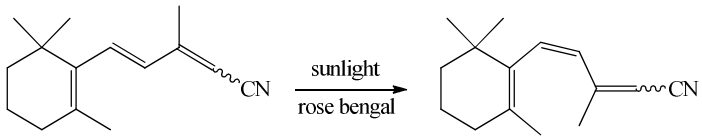
Scheme 31: Photooxygenation of furfural 111**.**

Further success in the synthesis of fine chemicals in highly concentrated sunlight was reported by Funken, who synthesised ε-caprolactam **101**[98] in yields up to 83.5% at the DLR in 2000.

1.3.3.4 Selected examples of recent reactions using non-concentrated sunlight

Over the past number of years, many researchers have continued to follow the examples set by Ciamician and Schönberg by simply leaving flasks in non-concentrated sunlight. This has proved successful for many reaction types, for both solution phase and solid state reactions. Reactions investigated include isomerisations, dimerisations, rearrangements, cyclisations and other catalytic reactions. The use of solar light in synthesis has been subject of a recent review by Protti and Fagnoni, which outlines many reactions carried out in non-concentrated sunlight, some examples of which are described below[114].

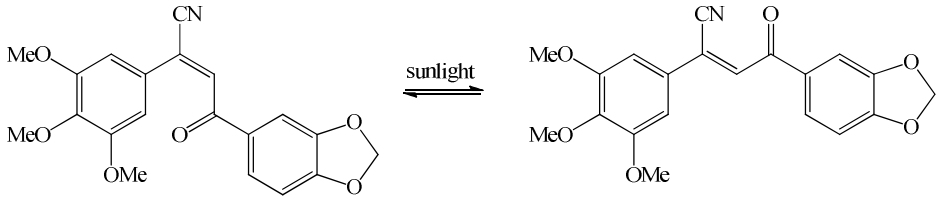
A recent report by Liu looks at the isomerisation of 7-*trans*-isomers of vitamin A **113** to the more hindered *cis*-isomer **114**, using rose bengal **41** as a sensitiser (Scheme 32)[75, 115]. Use of natural water reservoirs, such as the ocean, as heat sinks for photochemical reactions was demonstrated using a photochemical reactor incorporated into the body of a surfboard or body board. Using this reactor, complete conversion was achieved after just 15 minutes in May sunlight in Hawaii.



113 **114**

Scheme 32: Rose bengal sensitised *trans*-*cis*-isomerisation.

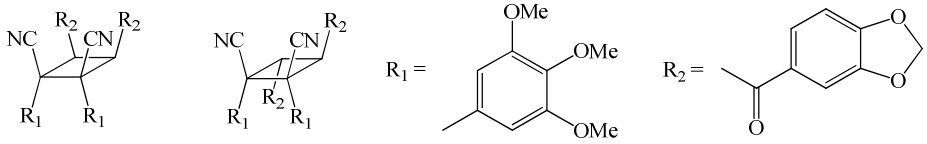
Studies by Ishii looked at the sunlight induced isomerisation of *beta*-substituted chalcones **115** (Scheme 33), followed by dimerisation through a [2+2]-cycloaddition reaction[116, 117]. This reaction proceeded in the solid state and solution phase.



115 **116**

Scheme 33: Isomerisation of a beta-substituted chalcone 115**.**

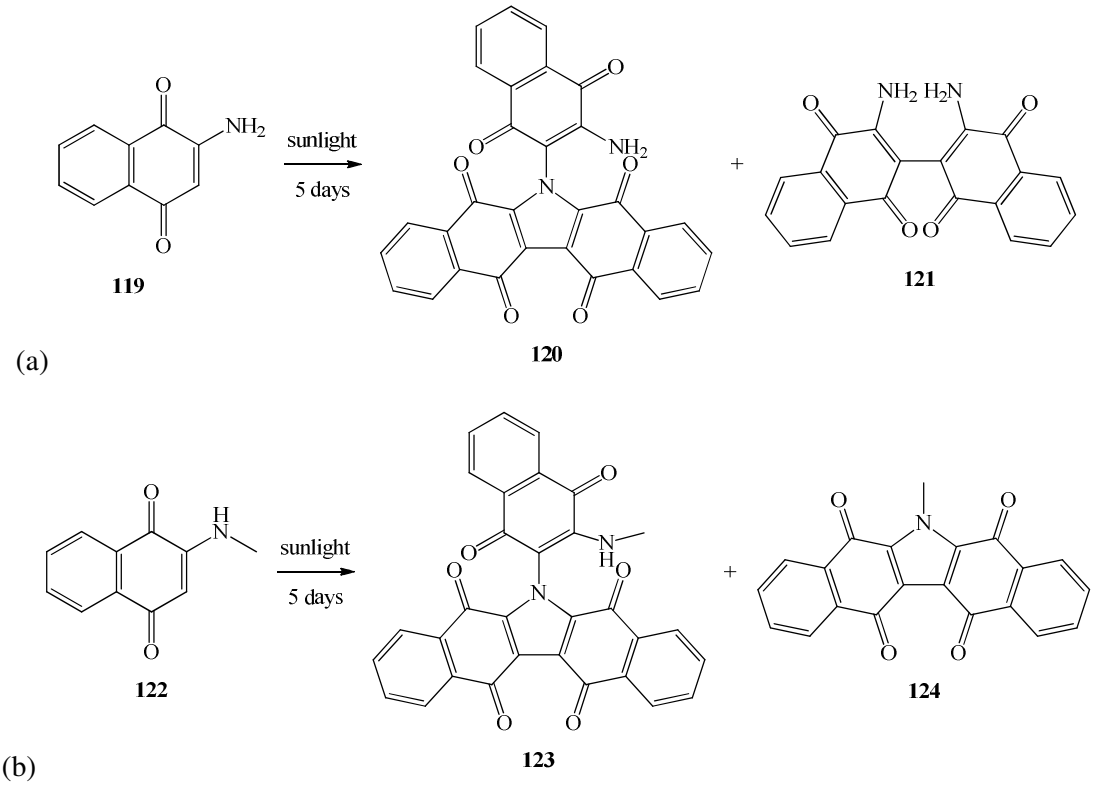
Both *Z,Z* **117** and *E,Z* **118** dimers may be obtained from the *E*-isomer of 2-(3,4,5-trimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4-oxo-2-butenonitrile (*β*-cyanochalcone), via solar light induced isomerisation and subsequent dimerisation when irradiated for 37.5 h (Figure 11).



117 **118**

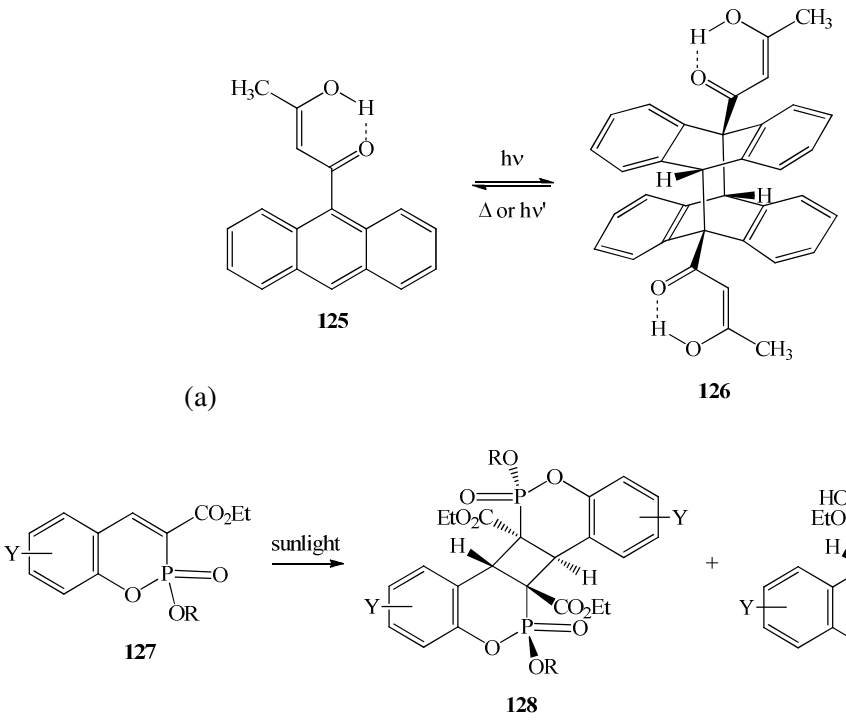
Figure 11: *Z,Z* 117 **and *E,Z*** 118 **dimers of β-cyanochalcone.**

Martins has studied the behaviour of two 2-amino-1,4-naphthoquinones **119** and **122** in acetic anhydride using solar light[118, 119]. The products obtained were not the anticipated cyclobutanes, but instead stable trimeric structures **120** and **123** were identified (Scheme 34).



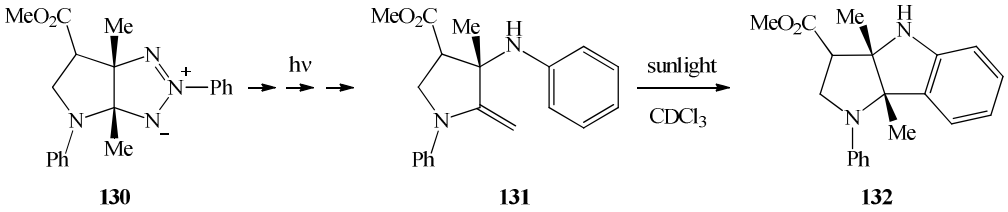
Scheme 34: Reaction of (a) 2-amino-1,4-naphthoquinone 119 **and (b) 2-methylamino-1,4-naphthoquinone** 122 **in acetic anhydride under sunlight irradiation.**

Cicogna observed photodimerisation of 9-anthroylacetone **125** in sunlight on NMR scale (Scheme 35a)[120]. Conversion of 28% **126** was achieved following three hours of irradiation in sunlight. Nikolova reported dimerisation of 3-substituted 2-alkoxy-2-oxo-2*H*-1,2-benzoxaphosphorines **127** via [2+2]-cyclisation[121]. This reaction shows excellent stereoselectivity, giving only the *anti* head-to-tail dimers **128** and **129** (Scheme 35b). Irradiation in methanolic solution for 20 – 90 days gave yields of 26-92% of the dimerised products. Use of glacial acetic acid as solvent led to a conversion of 94% in 4 days, with product selectivity of 3.2:1.



Scheme 35: Photodimerisation of (a) 9-anthroylacetone 125 **and (b) 3-substituted 2-alkoxy-2-oxo-2*H*-1,2-benzoxaphosphorines** 127 **(R=CH_3, C_2H_5; Y=H, 6-Br or 6-Cl).**

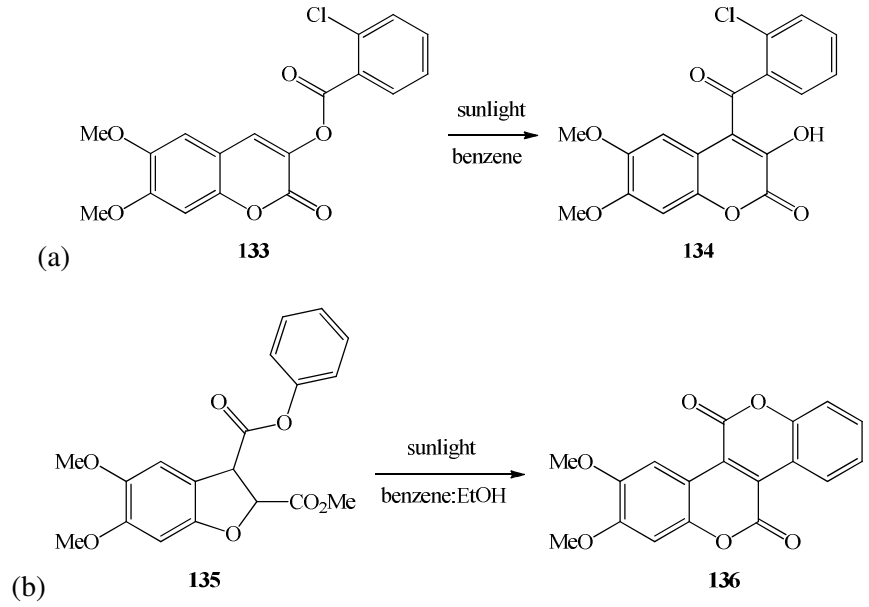
The photorearrangement of cyclic azimines **130** to saturated pyrrolo[3,2-b]indoles was reported by James *et al.* (Scheme 36), which gave yields of up to 78%[122]. Conversion of the intermediate substituted methylidene pyrrolidine **131** to final product **132** was achieved following 8 h solar irradiation.



Scheme 36: The photorearrangement of cyclic azimines 130 **to saturated pyrrolo[3,2-b]indoles.**

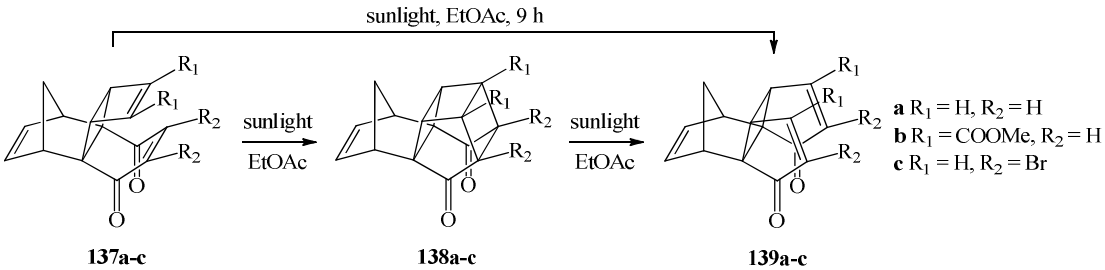
Jackson has studied the solar photo-Fries-rearrangement of the *o*-chlorobenzoate of 3-hydroxy-6,7-dimethoxycoumarin **133** (Scheme 37a), which was shown to give **134** in 27% yield after one day in sunlight[123]. Application of solar light in the photo-Fries-rearrangement of the *o*-fluoroester of 3-hydroxy-6,7-dimethoxycoumarin was also carried out[124]. An unusual reaction of 2-*O*-methyl-3-*O*-phenyl-5,6-dimethoxy-1-benzofuran-2,3-dicarboxylate **135** was observed

under solar reaction conditions (Scheme 37b)[125]. The reaction proceeds slowly and a yield of 24% **136** was obtained following 2 weeks of solar irradiation.



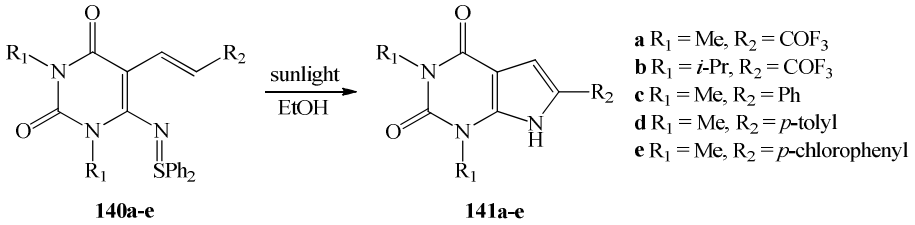
Scheme 37: (a) Photo-Fries-rearrangement of *o*-chlorobenzoate of 3-hydroxy-6,7-dimethoxycoumarin 133**, and (b) solar synthesis of 2,3-dimethoxybenzopyrano[4,3-*c*]benzopyran-5,11-dione** 136**.**

Mehta has investigated the reaction of quinone-cyclobutadienes **137a-c** involving two photochemical steps in one-pot conditions[126]. The intramolecular photo-[2+2]-cycloaddition with subsequent photochemically induced retro-[2+2]-cycloreaction was carried out to generate the final product in yields of 60-91% (Scheme 38). The use of a medium pressure mercury lamp was also employed, and was shown to give extensive degradation compared to sunlight. These systems show potential for use in solar energy storage systems.



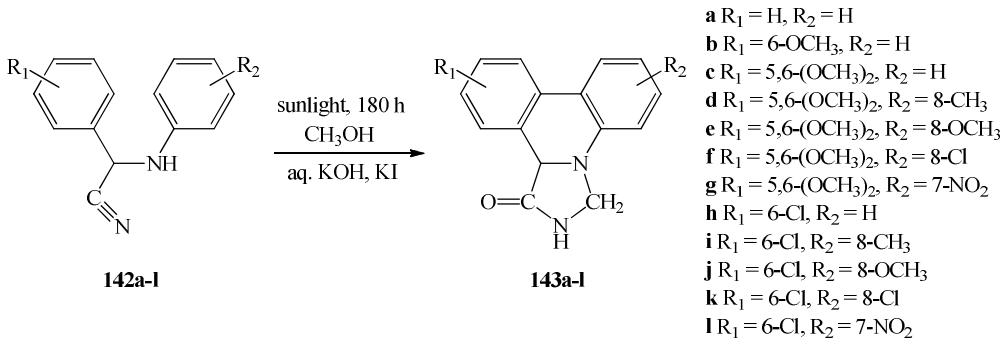
Scheme 38: Two-step, one-pot photochemical reaction of quinone-cyclobutadiene 137a-c**.**

Matsumoto has studied the photocyclisation of *N*-(5-vinyluracil-6-yl)sulfilimines **140a-e** (Scheme 39) and reported yields of 84-91% within 40 mins of solar irradiation (compounds **141c-e**)[127]. A yield of 88% was reported for **141a** and 96% for **141b** in 5 hours and 3.5 hours, respectively.



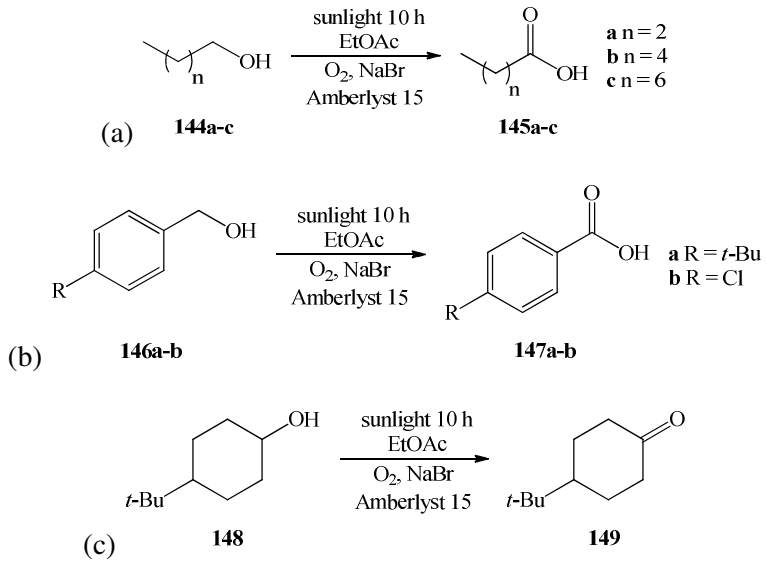
Scheme 39: Photocyclisation of N-(5-vinyluracil-6-yl)sulfilimines 140a-e**.**

Singal has studied the cyclisation of twelve *N*-*α*-cyanoamines **142a-l**, with incorporation of solvent, to yield benzoamidazoloquinolines **143a-l** (Scheme 40)[128]. 180 Hours of solar irradiation produces yields of 50-77%. This reaction proceeds through a free radical mechanism, catalysed by KI.



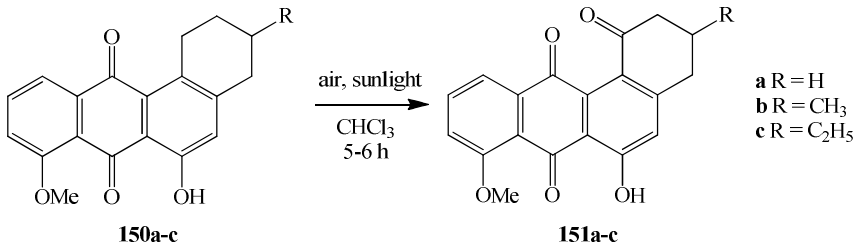
Scheme 40: Photocyclisation of *N*-*α*-cyanoamines 142a-l**.**

Itoh has studied the oxidation of alcohols using sodium bromide and Amberlyst 15 (strongly acidic cation exchange resin) in sunlight[129, 130]. For primary alcohols **144a-c** and **146a-b** the corresponding acids **145a-c** and **147a-b** were obtained in high yields (62-99%), while the yield of ketone **149** for secondary alcohol **148** was poor (21%).



Scheme 41: Oxidation of alcohols 144a-c**,** 146a-b **and** 148 **using sodium bromide and Amberlyst 15 in sunlight.**

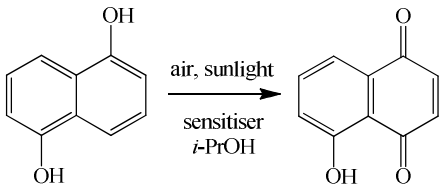
Mal has reported a photooxidation key step in the synthesis of brasiliquinones B **150a** and C **150b** and 3-deoxyrabelomycin **150c**[131]. Irradiation for 5-6 hours gave yields of 93% for **151a**, 70% for **151b** and 76% for **151c** (Scheme 42).



Scheme 42: Photooxidation of substituted 1,2,3,4-tetrahydro-6-hydroxy-8-methoxybenz[*a*]anthracene-7,12-diones 150a-c**.**

Guillet has reported solar reactions in a novel confined media[132-134]. The reaction mixture is adsorbed in beads of cross-linked ethylene-(vinyl acetate) copolymer. The beads can float on water, and are therefore exposed to sunlight by placing in wide dishes of water. Photoisomerisations, photooxygenations and Norrish Type II reactions have been investigated in this way.

Oelgemöller *et al.* have reported juglone **98** preparation by dye-sensitised photooxygenation using non-concentrated sunlight in Dublin (Scheme 43)[55]. This study looks at the use of different sensitisers, namely rose bengal **41** (homogeneous and polymer-bound) and methylene blue **42**, in *i*-propyl alcohol.



97 **98**

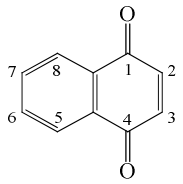
Scheme 43: Photooxygenation of 1,5-dihydroxynaphthalene 97**.**

Yields of 30-39% **98** were obtained using rose bengal **41** in solution with irradiation for around 6 hours. Use of rose bengal on Merrifield resin (RB_{MF}) gave a lower yield, just 19% following 6.5 hours of solar irradiation. The greatest outcome was achieved using methylene blue **42** in *i*-propyl alcohol with irradiation for 5.5 hours.

1.4 1,4-Naphthoquinones as fine chemicals

1.4.1 Structure and properties

1,4-Naphthoquinones are aromatic diketones in which the carbonyls are at the 1 and 4 positions on the naphthalene moiety, as shown Figure 12.



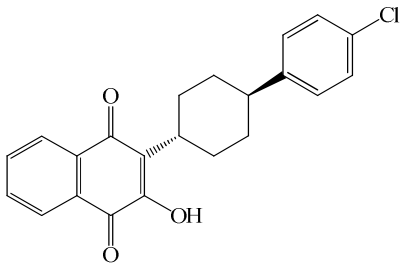
90

Figure 12: Structure of 1,4-naphthoquinone 90**.**

Many 1,4-naphthoquinone derivatives display biological activity, which has been attributed to structural features of the compounds, namely a) they can undergo redox cycling processes in which a reactive oxygen species is generated and b) they may act as electrophiles and undergo Michael-type addition processes. These processes can lead to toxic effects.

1.4.2 Biological effects

The 1,4-naphthoquinone moiety is a key feature in many biologically active compounds. For example, the anti-protozoal drug atovaquone (*trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione **152**) contains a hydroxyl-1,4-naphthoquinone core (Figure 13)[135].

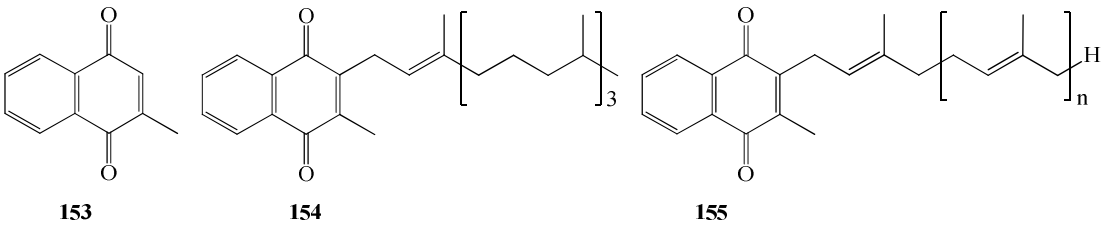


152

Figure 13: Structure of atovaquone 152**.**

As detailed above, 1,4-naphthoquinones tend to exhibit toxicity due to their ability to undergo Michael-type addition. As a result some derivatives have exhibited irreversible inhibition effects in human and animal studies, leading to antibacterial[136, 137], antifungal[136, 138], antimalarial[139] and antiinflammatory activity[140]. In addition, many 1,4-naphthoquinone derivatives have demonstrated moderate to excellent inhibition of tumour growth[141-143].

The 1,4-naphthoquinone structure also forms a key component of some vitamins, such as vitamin K. Menadione (2-methyl-1,4-naphthoquinone **153**) is referred to as K_3, as it is a precursor to other K vitamins, such as phyllaquinone (K_1 **154**) and menaquinones (K_2 **155**) shown in Figure 14.



153 **154** **155**

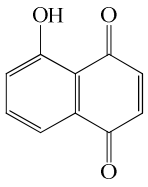
Figure 14: Menadione 153**, vitamin K1** 154 **and vitamin K2** 155**.**

Substitution of the 1,4-naphthoquinone core is essential in the reduction of toxicity and simultaneous increasing of desirable biological activity. As a result, there have been many synthetic studies into the preparation of these compounds. Of particular interest is substitution using hydroxyls or amines, which can enable expansion of substitution.

1.4.3 Juglone

1.4.3.1 Sources, uses and value

Juglone **98** (5-hydroxy-1,4-naphthoquinone, Figure 15) is a natural product which is formed in nature by air oxidation of related hydroquinones found in the black walnut tree[144]. Derivatives of juglone **98** have been isolated from blue spirea and Chinese catalpa[145].



98

Figure 15: Structure of juglone 98**.**

Juglone **98** is of interest due to its alleopathic effects[136, 144, 146] (inhibits growth of plants) as well as its use as a preservative in non-alcoholic drinks[147]. However, the main chemical interest in juglone **98** is its use as a synthon, as it acts as a building block for many valuable compounds[145, 148-152]. Some juglone-derived biologically active compounds include frenolicin B **156**[153], (+)-nocardione A **157**[154, 155], juglomycin A **158**[156], urdamycinone B **159**[157, 158] and the anti-inflammatory (AP-1 inhibitor) K1115-A **160**[159, 160] (Figure 16).

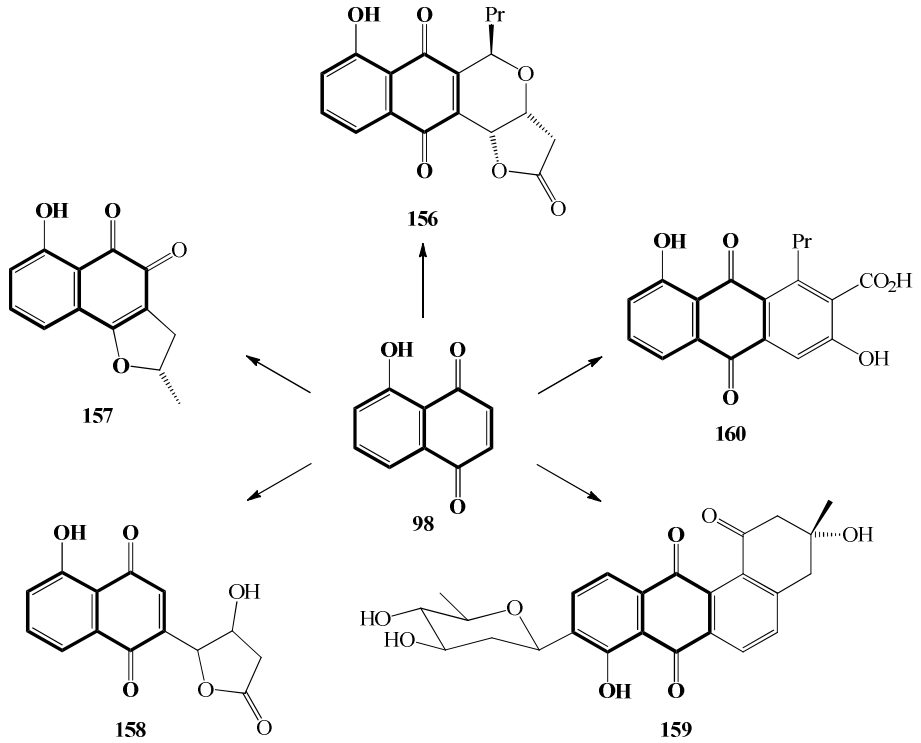


Figure 16: Juglone 98 **as a synthon for biologically active compounds** 156-160**.**

Juglone **98** is considered a fine chemical (is a precursor to many processes and is not prepared in bulk quantities) and as a result is quite expensive. Its price in Sigma-Aldrich is €110 per 5 g, while the cost of the common starting material 1,5-dihydroxynaphthalene **97** is €77.30 per 500 g (based on prices in January 2010). Assuming 100% conversion of 1,5-dihydroxynaphthalene **97**

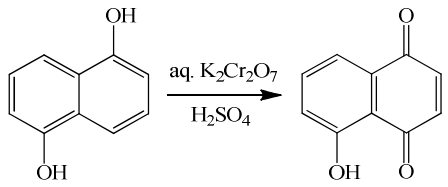
to juglone **98**, this indicates that juglone **98** is 155 times more valuable than its precursor **97**. For this reason a simple and high-yielding conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** is highly desirable.

1.4.3.2 Synthesis of juglone

1.4.3.2.1 Dark synthesis

As demonstrated above, juglone **98** is a valuable product and as a result it is desirable to develop an efficient method for its synthesis. There are many reported procedures, most looking at the oxidation of 1,5-dihydroxynaphthalene **97** using a variety of oxidising agents. 1,5-Dihydroxynaphthalene **97** is a desired starting material as it is cheap and commercially available. Other syntheses involve the use of 1,8-dihydroxynaphthalene **161**[161, 162].

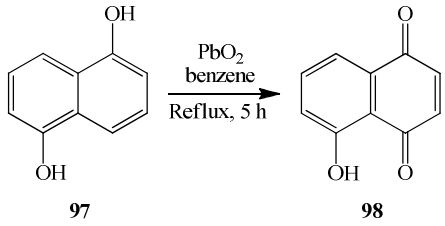
The earliest reported synthesis of juglone **98** was in 1887 by Bernthsen and Semper[163], where 1,5-dihydroxynaphthalene **97** was converted to juglone **98** using chromic acid (aqueous solution of potassium dichromate and sulfuric acid) at room temperature for 24 hours (Scheme 44).



97 **98**

Scheme 44: Synthesis of juglone 98 **using method by Bernthsen and Semper.**

In this study it was reported that juglone **98** was isolated in yields of 26-37%, however later studies by other researchers were unable to reproduce this yield[144, 145, 149, 150, 164-166]. Willstätter investigated three methods of juglone **98** synthesis and could not obtain yields greater than 16% using the Bernthsen method[164, 165]. In addition, the use of lead superoxide (PbO_2) refluxed in benzene for five hours gave juglone **98** in 28% yield (Scheme 45).

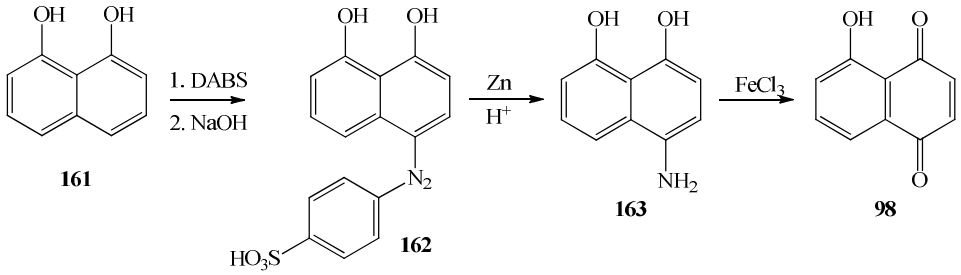


97 **98**

Scheme 45: Synthesis of juglone 98 **using method by Willstätter.**

Other studies of the oxidation of 1,5-dihydroxynaphthalene **97** using chromic acid were carried out by Fieser[165] (15% yield), Jesaitis[144] (50 °C for 30 mins, 10% yield), Jung[149] (3.5% yield), Kapoor[145] (no yield reported) and Laatsch[166] (10-20 °C, 13-17% yield). In contrast to these results, Bingham has reported a yield of 68% using an aqueous suspension of 1,5-dihydroxynaphthalene **97** with sodium dichromate in aqueous sulfuric acid[150].

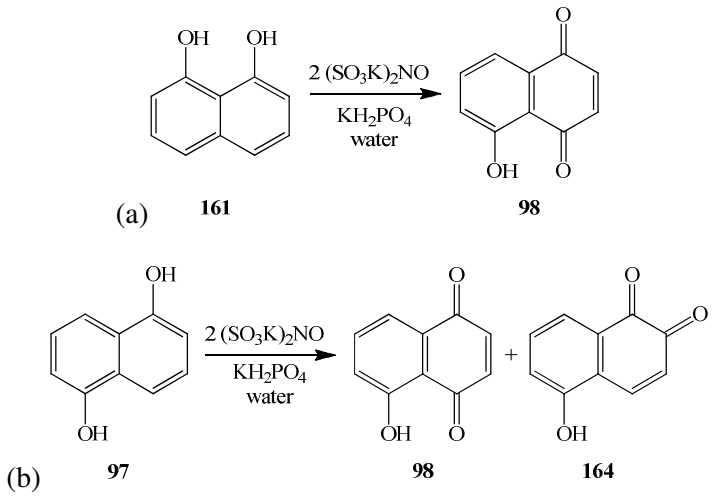
Friedländer investigated the synthesis of juglone **98** from 1,8-dihydroxynaphthalene **161** via a 4-azo derivative **162** formed though a coupling reaction with the diazonium salt of sulfanilic acid (DABS). This was converted to the corresponding 4-amino-1,8-dihydroxynaphthalene **163** through reaction of zinc in hydrochloric acid, followed by treatment with iron chloride (Scheme 46)[161]. However, no yield data was presented for this study. Willstätter repeated this synthesis, reporting crude and purified yields of 50% and 19%, respectively, based on conversion from the azo dye[164].



161 **162** **163** **98**

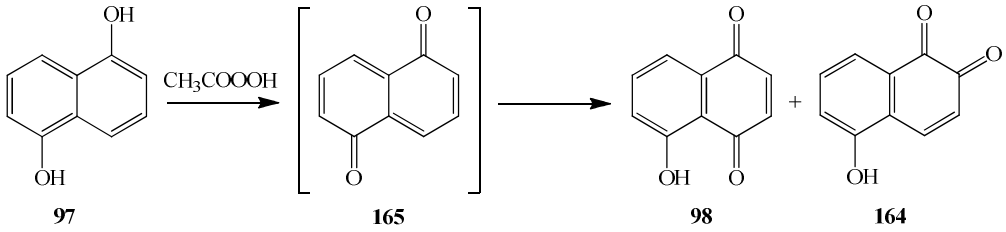
Scheme 46: Synthesis of juglone 98 **as demonstrated by Friedländer and Willstätter.**

A method using Frémy's salt (potassium nitrosodisulfonate, $NO(SO_3K)_2$) in water and KH_2PO_4 was investigated by Teuber, who reports that oxidation of 1,8-dihydroxynaphthalene **161** gives juglone **98** in 81% yield (Scheme 47a)[162]. However, 1,5-dihydroxynaphthalene **97** produced a mixture of juglone **98** and the corresponding 5-hydroxy-1,2-quinone **164** in 49% and 50% yields respectively (Scheme 47b).



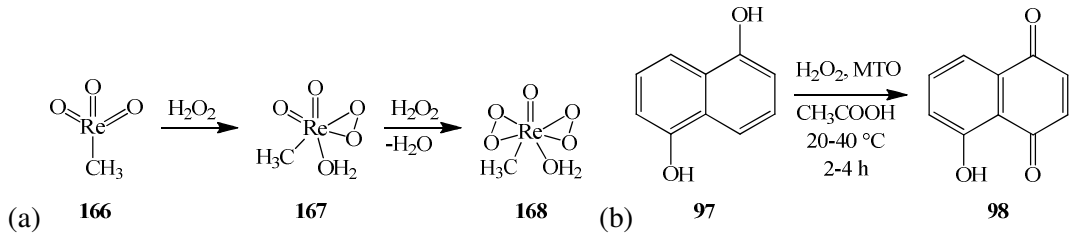
Scheme 47: Use of Frémy's salt in the synthesis of juglone 98**.**

Use of peracetic acid has been studied by Grundmann and found to give yields of 50% juglone **98** and 28% of the 5-hydroxy-1,2-quinone **164** (Scheme 48)[146]. In this study he reports that use of hydrogen peroxide in acetic acid does not lead to juglone **98** formation. However, Eliason has looked at this synthesis as a proposed 'green method', using 30% hydrogen peroxide in acetic acid to generate the peracetic acid *in situ.*, but has not reported any yield data[167, 168].



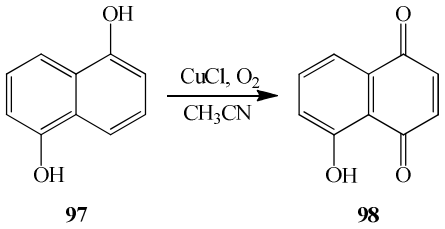
Scheme 48: Synthesis of juglone 98 **using peracetic acid.**

Adam studied oxidations using hydrogen peroxide in acetic acid in association with methyltrioxorhenium(VII) (MTO) **166**[169]. The oxidising agent ($CH_3Re(O_2)_2O\cdot H_2O$) **168** involved in this process is formed *in situ.* by the process shown in Scheme 49a. Oxidation of 1,5-dihydroxynaphthalene **97** was demonstrated, giving juglone **98** in 41% yield (Scheme 49b).



Scheme 49: (a) Preparation of $CH_3Re(O_2)_2O{\cdot}H_2O$ 168**, and (b) use in juglone synthesis.**

Capdevielle reported the oxidation of 1,5-dihydroxynaphthalene **97** using $Cu_4Cl_4O_2$ (generated from CuCl and O_2), which complexes with acetonitrile to form $Cu_4Cl_4O_2(CH_3CN)_3$ (Scheme 50)[170]. This reaction was carried out at ambient temperature and pressure. Juglone **98** was obtained from 1,5-dihydroxynaphthalene **97** in greater than 80% yield using this method.



Scheme 50: Synthesis of juglone 98 **using method by Capdeville.**

Duchstein and Wurm have investigated several methods of juglone **98** synthesis, particularly use of copper chloride[171, 172] or Co(salen) **169** (Figure 17)[173, 174]. Copper(I) chloride, added in multiple portions, gave juglone **98** in yields of 51-60% (Scheme 51a), while use of Co(salen) **169** at room temperature gave yields of 45-90% **98** following reaction for 7 h (Scheme 51b).

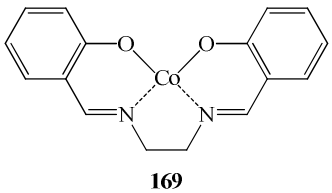
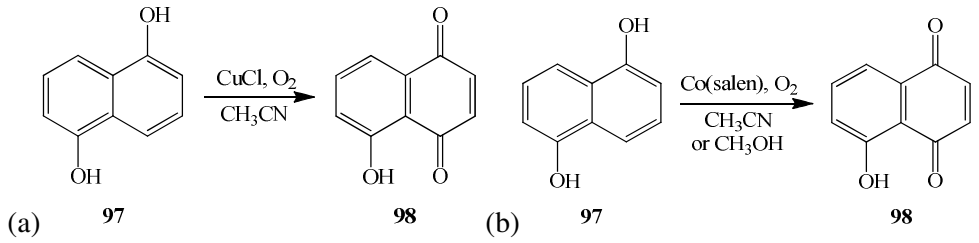


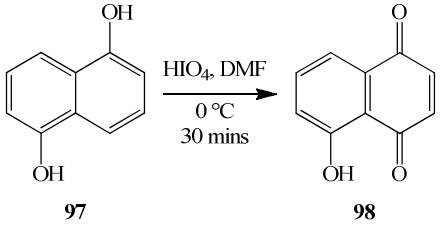
Figure 17: Structure of Co(salen) 169**.**



Scheme 51: Synthesis of juglone 98 **using (a) copper chloride, and (b) Co(salen)** 169**.**

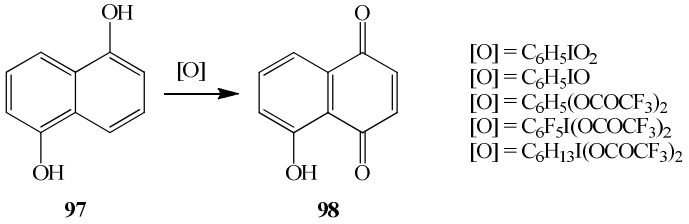
Wakamatsu also studied the use of Co(salen) **169** in acetonitrile, and reports yields of 71% juglone **98** after just 30 minutes[175]. In addition, Adam has used the synthesis of juglone **98** as a model reaction to investigate nickel- and cobalt- salen complexes as oxidising agents[176]. Using three different cobalt complexes, yields of 65-78% were achieved following reaction for 7 h.

Pinto looked at the use periodic acid in dimethylformamide for oxidation of 1,5-dihydroxynaphthalene **97**, to give juglone **98** in 55% yield (Scheme 52)[136].



Scheme 52: Use of periodic acid in synthesis of juglone 98**.**

Barret has reported the use of a range of *bis*-acyloxy-iodo compounds as oxidising agents[148, 177]. Oxidation of 1,5-dihydroxynaphthalene **97** at 0 °C for one hour under a nitrogen atmosphere using five different iodo compounds gave juglone **98** in yields of 30-91% (Scheme 53). Use of bis(trifluoroacetoxy)-iodopentafluorobenzene gave 76% of **98**, while bis(trifluoroacetoxy)-iodoperfluorohexane gave 91% yield.



Scheme 53: Use of hypervalent iodine compounds in synthesis of juglone 98**.**

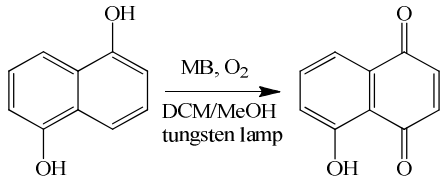
Other oxidising agents that have been applied to juglone **98** synthesis are ammonium peroxydisulfate (6 hours, 10% yield)[178], vanadium trifluoride oxide in trifluoroacetic acid (10 minutes, 35% yield)[179], thallium trinitrate (10 minutes, 64% yield)[151] and manganese dioxide (one hour, 60% yield)[180]. Use of a metallated phthalocyanine supported on montmorillonite in dark conditions produced juglone **98** in yields of 79-87%[181].

Table 1: Summary of the dark syntheses of juglone 98**.**

Oxidising agent	Time (h)	Temp (°C)	Yield (%)
$K_2Cr_2O_7$ / H_2SO_4[144, 149, 150, 163-166]	0.5-24	10-50	3.5-68
PbO_2[164]	5	Reflux (benzene)	27
$Tl(NO_3)_3 \cdot 3H_2O$ (TTN) [151]	0.33	0	64
VOF_3 / TFA[179]	0.16	0	35
$Co(salen)_2$ /O_2[175]	0.5	RT	71
CH_3ReO_3 / H_2O_2[169]	2	20	41
Bis(trifluoroacetoxy)iodobenzol[177]	1	0	58
Bis(trifluoroacetoxy)iodoperfluorohexane[148]	1	0	91
CH_3CO_3H[146]	4	20-24	46-50
Fe-Phthalocyanine / Montmorillonite-K10 / air[181]	6	RT	79-87

1.4.3.2.2 Photochemical synthesis

The first reported photochemical synthesis of juglone **98** was reported by Griffiths in 1976 (Scheme 54), using methylene blue **42** as a sensitiser and irradiation using a tungsten lamp, to obtain juglone **98** in 70% yield[182].



97 **98**

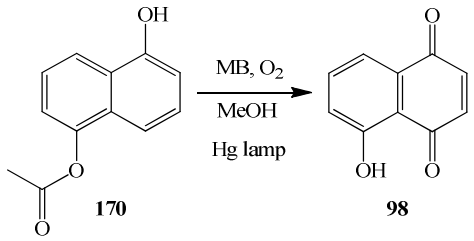
Scheme 54: Photochemical synthesis of juglone 98**.**

An investigation by Duchstein and Wurm looked at the effect of different sensitisers (sensitiser-free, methylene blue **42**, rose bengal **41** and 9,10-dicyanoanthracene), solvents (methanol and acetonitrile) and wavelengths (> 360 nm and < 360 nm) on the yield of this reaction[183, 184]. The optimised conditions were found to be light > 360 nm for a solution of methylene blue **42** in acetonitrile (85%). This was found to give juglone **98** in yields of 70-75% following 8 hours of irradiation[185].

Murtinho has used the synthesis of juglone **98** as a model reaction to study new porphyrin and chlorin sensitisers, giving yields of 84-95% following two hours of irradiation using tungsten lamps[28]. This was compared to methylene blue **42** in the same conditions, which gave a yield of 78% of juglone **98**.

Most recently, studies by Oelgemöller *et al.* have investigated the synthesis of juglone **98** under artificial and solar conditions, reporting yields of up to 88%[54-57]. Use of heterogeneous and homogeneous sensitisers has been reported, as well as a comparison of yield when air is used as an alternative to pure oxygen.

Photooxygenation of 5-acetoxy-1-naphthol **170** using methylene blue **42** in methanol, with irradiation for 4 hours using a high pressure mercury lamp gave juglone **98** as the sole product in 61% yield (Scheme 55)[137].



Scheme 55: Photooxygenation of 5-acetoxy-1-naphthol 170**.**

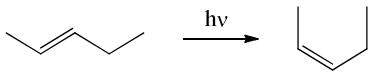
Other studies of jugone **98** in the literature have looked at the kinetics of the reaction of 1,5-dihydroxynaphthalene **97** with singlet oxygen[186-188], in particular noting the ability of this compound to self-sensitise.

1.5 Green Chemistry in alternative media

With the evolution of green chemistry, many green solvents and reaction methods have been applied in photochemistry. Among these is the use of solvent-free conditions, which decreases the release of volatile organic solvents into the atmosphere. Similarly the use of ionic liquids has been propagated as a means of minimising release of volatile agents into the environment. In addition, the use of aqueous media, or microemulsions containing both organic and aqueous components, has been investigated for many chemical transformations, including photochemistry.

1.5.1 Solvent-free synthesis (using polymeric supports)

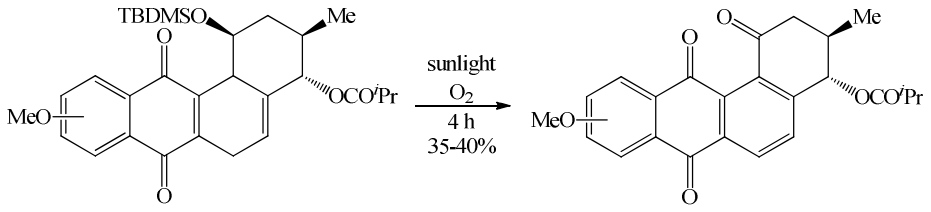
There has been considerable interest in solid state photochemistry, as reviewed by Kaupp[189]. This study looked at the photodimerisation and photoisomerisation of light activated starting materials in the solid state. Other investigations into this type of synthesis were conducted by Liu *et al.*, looking at the isomerisation of spatially hindered substrates, such as frozen (solid state) media[8, 190]. This is through the process referred to as the "Hula-twist" or "W to U" mechanism (Scheme 56).



171 **172**

Scheme 56: Photoisomerisation by the "Hula-twist" method.

Carreño has reported the solid phase, sunlight initiated, 'domino process' in which a tetracyclic starting material **173** underwent three distinct reaction types (aromatisation, deprotection of a silyl ether and oxidation) to form the desired rubiginones **174** (Scheme 57)[191].



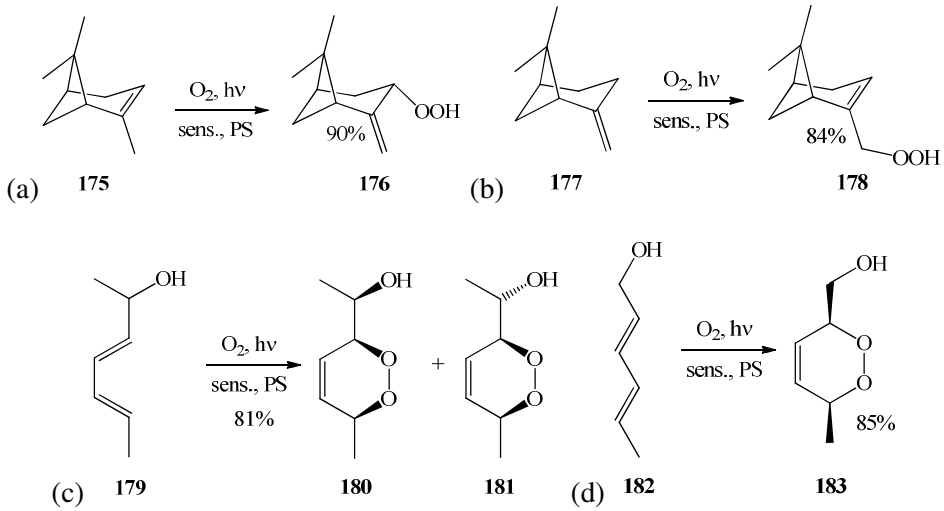
173 **174**

Scheme 57: Solid phase, sunlight induced 'domino process'.

In addition to solid state photochemical synthesis, the use of solid supports in synthesis is of interest. The use of polymeric supports in synthesis is well documented, in particular for combinatorial chemistry[192]. However, these tend to be used in heterogeneous systems, where stepwise addition onto the the polymer supported starting material occurs using solution phase reagents. Following the extension "on the bead" the product is then cleaved from the support. In addition, liquid phase soluble supports have been reported, in which the polymer support is soluble in the reaction mixture, but may be selectively precipitated upon completion of reaction, thus giving ease of recovery.

Although several examples of polymer supported synthesis exist in the literature only a small number deal with photochemical transformations. Bochet has summarised many of these applications, looking at photolabile protecting groups and linkers[193]. In these reactions, the solid-supports are generally used in heterogeneous mixtures, rather than solvent free conditions.

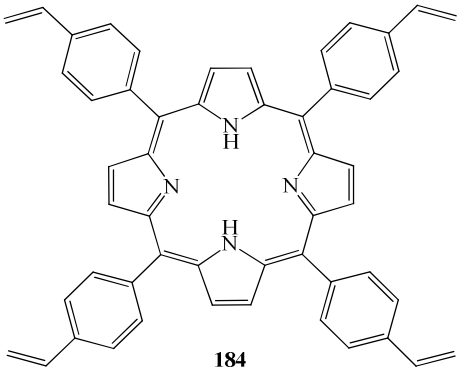
Of particular interest are solvent-free solid supported photoreactions. Griesbeck *et al.* have carried out photooxygenations under these conditions through the use of polymeric supports, with particular emphasis on green synthesis[33, 194]. Griesbeck has outlined the five main difficulties of solution phase oxygenations as (a) solubility of sensitiser, (b) purification and recovery of sensitiser, (c) short singlet oxygen lifetimes in less harmful solvents, (d) photobleaching of sensitiser in chlorinated solvents and (e) supply of pure oxygen on a large scale. Use of solvent-free conditions can overcome these difficulties and so these reactions have been proposed as the 'archetypical green chemistry'. [4+2]-Cycloadditions and ene-reactions have been reported (Scheme 58).



Scheme 58: Examples of photooxygenations on polymeric supports.

Several different polymers have been investigated, namely polystyrene, polylactic acid, cellulose acetate, polyhydroxybutyric acid, polyethylene glycol and poly-*N*-vinylacetamide[194]. Using the photooxygenation of citronellol **93** as a model reaction, the highest yields were obtained when ysing polyhydroxybutyric acid as a solid support. However, polystyrene cross-linked with divinyl benzene offered the greatest ease of handling.

In the previous cases the sensitiser was adsorbed onto the polymeric supports. In addition, polymer matrices with covalently linked sensitisers were investigated. These were prepared by the co-polymerisation of the porphyrin sensitiser (tetrakis-(4-ethenylphenyl)porphyrin) **184** (Figure 18) with styrene and divinylbenzene. An advantage of the covalently bound sensitiser is its high mechanical stability, elimination of leaching of sensitiser and ease of recycling.



184

Figure 18: Tetrakis-(4-ethenylphenyl)porphyrin.

1.5.2 Ionic Liquids (ILs)

Room temperature ionic liquids can be considered green solvents due to their negligible vapour pressure (complete lack of volatility)[195-197] and their suitability for recovery and recycling[198-201]. In addition, their thermal stability and ability to dissolve organic, inorganic and organometallic substrates make them excellent solvents for many chemical reactions[202-204].

In particular, the use of imidazolium based ILs has been reported in many organic chemistry applications. There are many ILs commercially available, such as [bmim]BF_4 **185**, [emim]NTf_2 **186** and [emim]OTf **187** (Figure 19).

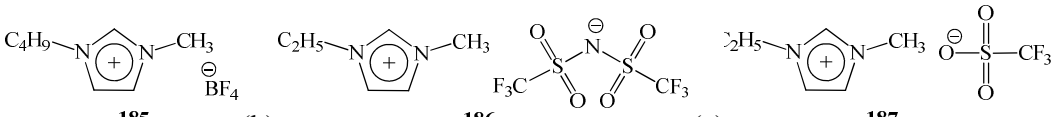
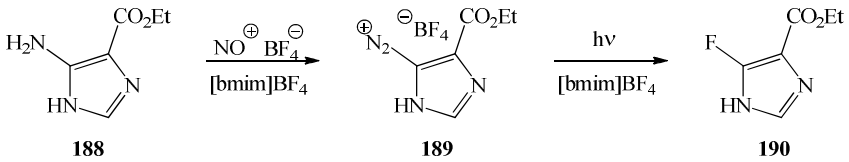


Figure 19: Structure of (a) [bmim]BF_4 185**, (b) [emim]NTf_2** 186 **and (c) [emim]OTf** 187**.**

The application of ILs in oxidation reactions has been investigated, using cerium ammonium nitrate (CAN)[199], hydrogen peroxide[205, 206], hypervalent iodine reagents[207], copper(II)chloride[208, 209] and dioxygen (air)[198, 200, 201] as the oxidant. However, there are varying reports on the solubility of oxygen in the ILs used. Studies by Gomes and Majer have looked at the solubility of eight gases, including oxygen and carbon dioxide, in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) **185**[210, 211]. This work demonstrated that oxygen solubility in this ionic liquid was relatively constant over the temperature range 10-70 °C. Solubility was represented in mole fraction, for which oxygen had a value of 6±1 x 10^{-4}. Solubility of oxygen in another ionic liquid, [bmim]PF_6, was subject of studies by Maurer[212] and Brennecke[195]. Maurer has found that solubility is relatively unaffected by temperature in the range 20-100 °C, while Brennecke reports very low solubility in the IL.

The feasibility of ionic liquids as solvents for photochemical reactions has been assessed, using [bmim]PF_6, looking at polarity, oxygen solubility, molecular diffusion, quenching of triplet excited states, lifetime of radical species and effect on charge-transfer complexes[203]. This study concluded that this IL is suitable for use in electron transfer, hydrogen transfer and energy transfer reactions, but is not considered suitable for singlet oxygen generation. However, singlet oxygen lifetimes have been evaluated in a number of ILs, based on $[bmim]^+$ with different counter ions (BF_4, PF_6, SbF_6, OTf and NTf_2)[213]. Of these, [bmim]OTf exhibits the lowest lifetime (3.5 μs), while [bmim]NTf_2 has the longest lifetime (46 μs).

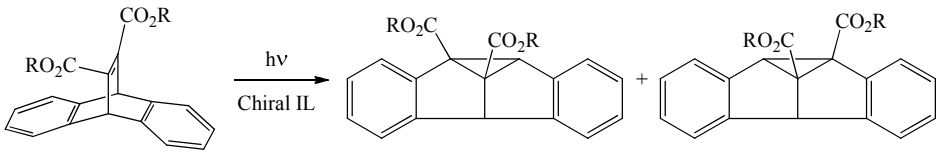
The photochemical Schiemann reaction was carried out in [bmim]BF_4 **185** and the effect of temperature, co-solvent and wavelength were evaluated[214]. The ionic liquid **185** participated in the reaction, providing stabilisation of the diazonium salt intermediate **189** (Scheme 59) and increasing the yield of intermediate **189** at 0 °C. At higher temperatures decomposition of the ionic liquid was observed when a quartz vessel was used.



188 **189** **190**

Scheme 59: Photochemical Schiemann reaction in ionic liquid.

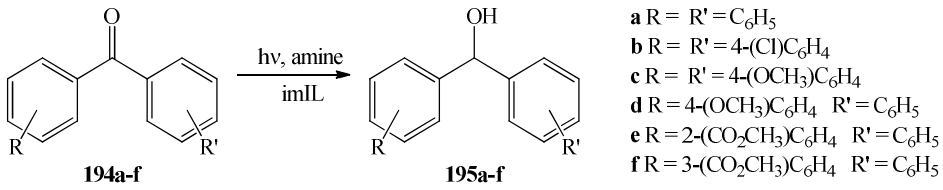
Another interesting application of ionic liquids in organic reactions is the use of chiral ILs to induce enantioselectivity. The photoisomerisation of two different dibenzobicyclo[2.2.2]octatrienes **191**, via a di-π-methane reaarangement, were investigated in six chiral ionic liquids (Scheme 60)[204]. A chiral inductive effect was observed for R=H, which was attributed to the interactions of the deprotonated acid groups with the ionic liquid cation. Enantiomeric excesses of 3-12% were obtained.



191 **192** **193**

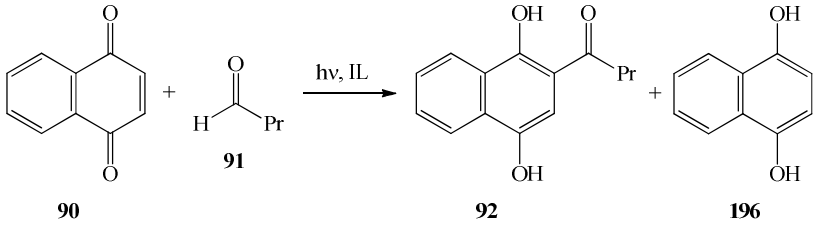
Scheme 60: Photoisomerisation of dibenzobicyclo[2.2.2]octatrienes (R=CH_3 or R=H).

A study of the photoreduction of benzophenones **194a-f** by amines in four ILs was conducted, which demonstrated that the use of imidizolium ILs caused a change in product selectivity[215]. For non-imidizolium based ILs, *sec*-butylammonium trifluoroacetate and *iso*-propylammonium nitrate, the pinacolisation product was observed. However, for **194a-b** and **194e-f** in [bmim]BF_4 and [emim]OTf the only product was the corresponding benzhydrol **195**, indicating participation of the IL in the reaction (Scheme 61).



Scheme 61: Photoreduction of benzophenone 194a-f **to benzhydrol** 195a-f **in imidizolium ionic liquids.**

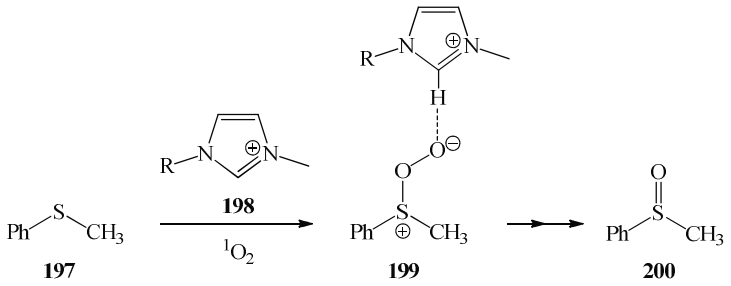
The photo-Friedel-Crafts acylation of 1,4-naphthoquinone **90** with aldehydes has been investigated in a series of [emim] ionic liquids[216]. The photoacylation of 1,4-naphthoquinone **90** with butyraldehyde **91** was used as a model reaction to optimise choice of counter ion (Scheme 62), which showed that OTf and NTf_2 gave the greatest conversion. These ILs were then used as reaction medium for a series of photoacylations using different aldehydes.



Scheme 62: Photo-Friedel Crafts acylation of 1,4-naphthoquinone 90 **with butyraldehyde** 91 **using ionic liquid.**

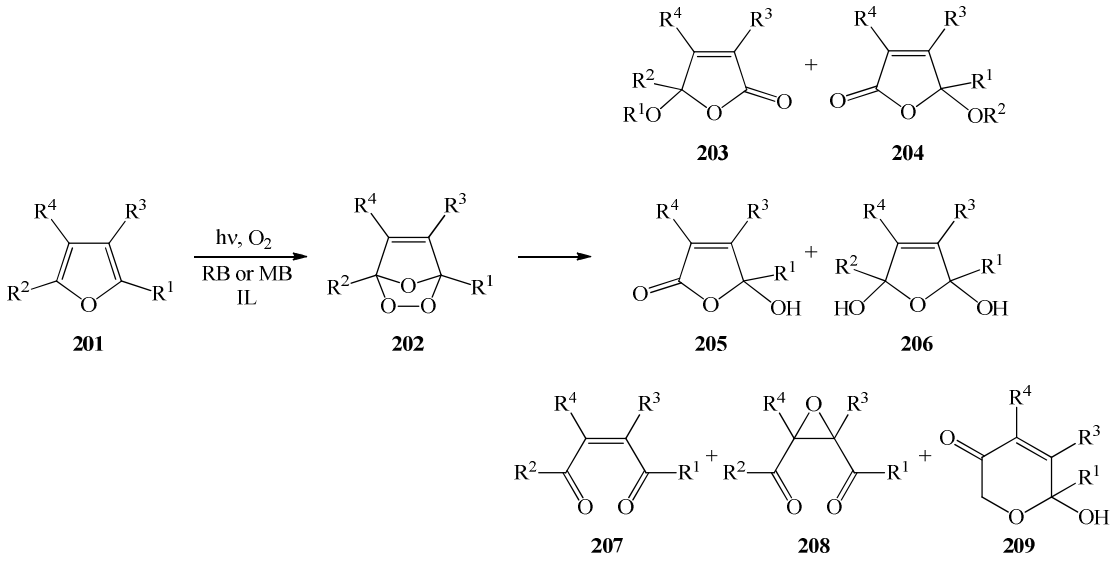
High conversion and selectivity were achieved, and recycling and reuse of solvent was demonstrated. This study shows that ionic liquids provide a green alternative to the use of benzene or acetonitrile in the photo-Friedel Crafts acylation procedure.

Regarding singlet oxygen reaction in ionic liquids, these have been subject to just three studies to date. The first looks at generation of singlet oxygen in [bmim]BF_4 using methylene blue **42** and indigo dyes[217]. These are compared to results in traditional solvents (methanol, DMSO and water). A study by Melai also looks at the use of methylene blue **42** to generate singlet oxygen for reaction with thioanisole **197**[218]. The ionic liquids investigated were [emim]NTf_2 **186**, [bmim]NTf_2, [emim]OTf **187**, [bmpy]NTf_2 and [empy]NTf_2. Reaction in [emim]NTf_2 **186** gave complete conversion to the sulfoxide **200** without overoxidation to sulfone, which is attributed to stabilisation of the persulfoxide intermediate **199** by the IL (Scheme 63).



Scheme 63: Photooxygenation of thioanisole 197 **in IL.**

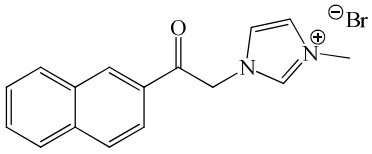
The most recent study of ionic liquids as reaction media for processes using singlet oxygen looks at the photooxygenation of furans **201**[219]. The ionic liquids investigated were [emim]Br and [bmim]BF_4 and results compared to those achieved in water and acetonitrile. Acetonitrile was used as a cosolvent with [emim]Br as this is not a liquid at room temperature (10% v/v, to dissolve the solid salt) and with water (50% v/v, to ensure solubility of substrates). Rose bengal **41** and methylene blue **42** were used as sensitisers, and irradiation provided using a halogen lamp. A range of substituents were investigated, to assess the effect on the fate of the endoperoxide **202** (Scheme 64).



Scheme 64: Photooxygenation of furans 201 **in ionic liquids.**

An interesting study by Jones has looked at the development of photosensitisers that are selectively soluble in ionic liquids[196]. This facilitates the recycling of both sensitiser and solvent, with removal of products by a simple extraction. This was demonstrated using imidazole-tagged

aryl ketones **210** (Figure 20) in [bmim]BF_4 using the photoisomerisation of *trans*-β-ionol as a model reaction.



210

Figure 20: Ionic liquid soluble imidazole tagged acetonaphthone photosensitiser 210**.**

1.5.3 Microemulsions

Under particular conditions surfactants can self-organise to form structured arrays such as bilayers, micelles and microemulsions. Microemulsions are a form of reverse micelle, in which the surfactant surrounds micro-droplets of water in a non-polar organic phase. Microemulsions are thermodynamically stable mixtures of oil (organic solvents), water, surfactants and co-surfactants[220]. The mixtures appear homogeneous but when examined microscopically they consist of nano-sized aqueous droplets in the oil phase.

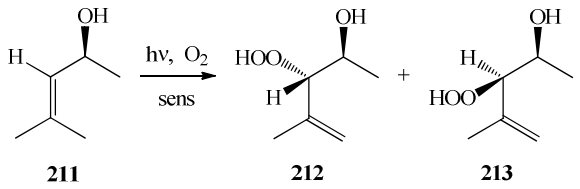
Organic reactions in microemulsions have been the subject of a microreview by Holmberg, who outlines the advantages and disadvantages of this reaction medium[220]. Advantages include increased solubilising ability (to overcome incompatibility problems), increase in reaction rate compared to traditional synthesis and an ability to induce regioselectivity. A down-side to these mixtures is the use of surfactant in large quantities, which may be overcome through recovery and recycling of surfactant during purification.

"Green" microemulsions have been reported, in which the organic component is not a halogenated organic solvent, but instead ethyl acetate is used[221]. These have demonstrated good singlet oxygen lifetimes and suitability for use in oxygenation reactions. However, use in photooxygenation processes has not been reported. In addition, 'solvent-free' microemulsions were prepared, where the reaction substrate acts as the organic phase of the microemulsion. A recent study by Texter has looked at microemulsions where ionic liquids are used, which have much to offer in green solvent applications[222]. The use of IL as oil, aqueous and surfactant was investigated, and it is postulated that a single IL may be fabricated to fulfill all three roles.

Early studies on photochemistry in microemulsions were reported by Jones, who looked at the photodegradation of chlorophyll. The microemulsion used consisted of sodium cetyl sulfate in 1-pentanol, mineral oil and water (or pH 7 phosphate buffer)[223].

Photochemical isomerisation of *trans*-stilbene **1** was carried out in a Triton X-100/*n*-pentanol/water microemulsion[224]. This investigation showed that yields of *cis*-stilbene **2** may be increased in microemulsion when compared to traditional solvent conditions. Photocycloaddition of 9-substituted anthracenes was investigated in water in oil microemulsions of dichloromethane and water, using AOT as surfactant[225]. A change in selectivity was observed, with formation of the head to head dimer favoured in microemulsion, compared to formation of the head to tail dimer in dichloromethane. Polymerisation of methacrylates was achieved in oil in water microemulsions of sodium dodecyl sulfate[226].

The use of microemulsions in oxygenation reactions has been demonstrated previously by Nardello *et al.*, where singlet oxygen is generated from hydrogen peroxide using a sodium molybdate catalyst[221, 227-229]. Photooxygenation reactions (the Schenck-ene reaction) have also been demonstrated using mesitylol **211** and compared to the chemically generated singlet oxygen reactions (Scheme 65)[227]. For the chemical system, in addition to the hydroperoxide products some epoxide formation is observed, however photochemical generation of singlet oxygen leads only to hydroperoxide products.

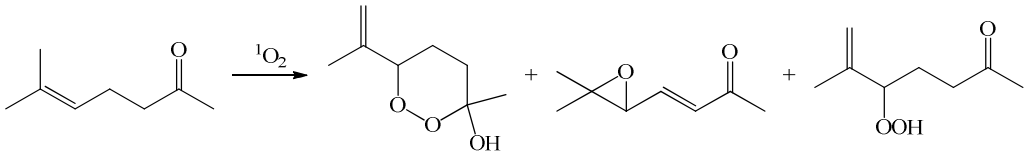


211 **212** **213**

Scheme 65: Photooxygenation of mesitylol 211 **in microemulsion.**

The use of microemulsions of AOT-heptane-water or BHDC (benzylhexadecyldimethyl ammonium chloride)-benzene-water for dye-sensitised photooxidation of 2-nitrophenol and 4-methyl-2-nitrophenol was investigated using rose bengal **41** as sensitiser[230]. This study showed a considerable increase in reaction rate in microemulsion when compared to aqueous solution, which is attributed to longer singlet oxygen lifetime and reduced quenching.

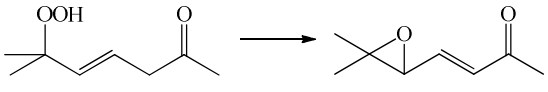
Griesbeck has reported unusual regioselectivity in the singlet oxygen "ene" reaction of **214** in dichloromethane based microemulsions (Scheme 66), when compared to acetonitrile[231].



214 **215** **216** **217**

Scheme 66: Ene reaction of 214 **in dichloromethane-AOT microemulsion.**

The epoxy enone **216** shown in Scheme 66 is not obtained following reaction in acetonitrile. It is believed to be derived from a peroxide precursor **218**, which is obtained under traditional solvent conditions (Scheme 67). This indicates that the use of microemulsions causes a follow-up reaction that is not observed in acetonitrile.

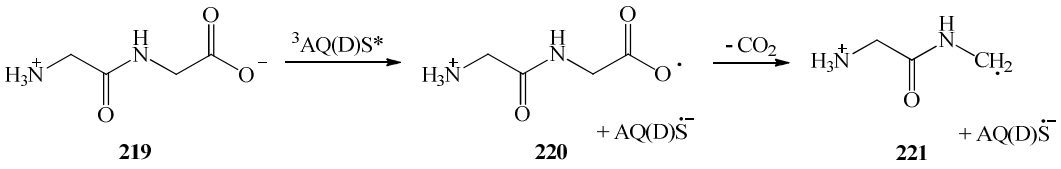


218 **216**

Scheme 67: Conversion of peroxide to epoxy enone.

This conversion is achieved through a Kornblum-Delamere type transformation, in which deprotonation occurs, followed by cleavage of the peroxide bond.

The photooxidation of diglycine **219** in AOT microemulsions using anthroquinone sulfonate salts has been reported (Scheme 68)[232]. This study demonstrates the application of microemulsions as microreactors, in which the radical pair generated may be confined within the microemulsion droplets.



219 **220** **221**

Scheme 68: Photooxidation of diglycine 219**.**

The use of microemulsions for photochemistry and in particular photooxygenation has been demonstrated and these offer a green alternative to traditional solvents.

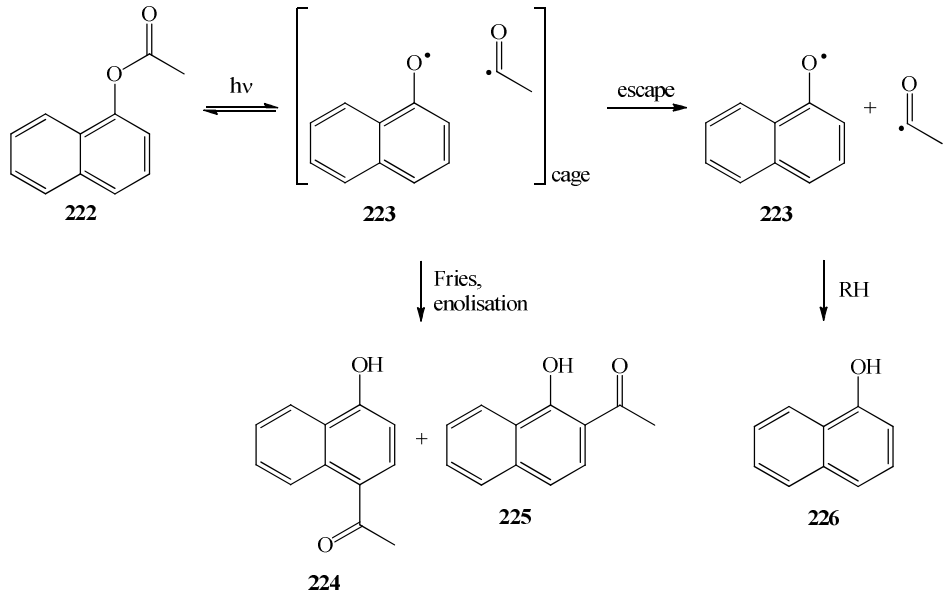
1.5.4 Supercritical carbon dioxide

A supercritical fluid is defined by IUPAC as the defined state of a compound, mixture or element above its critical pressure and critical temperature[233]. Supercritical fluids possess physical properties between those of a liquid and a gas. A particular physical property unique to supercritical fluids is the ability to influence the solubility of substances by varying the pressure. This affects the density of the supercritical fluid, and hence its solubilising ability. In addition, supercritical fluids mix perfectly with gases, giving them a huge advantage over conventional liquid solvents in gas-liquid reactions.

Supercritical carbon dioxide has been proposed as the "ideal green solvent" due to its non-toxicity to the environment[234]. In addition, it is inert to many chemical systems and non-flammable. Although carbon dioxide is a known greenhouse gas, its use as an industrial solvent may be balanced by obtaining the carbon dioxide as a by-product from other industrial processes, e.g. fermentation or combustion. Additionally, the high pressures required for generation of supercritical carbon dioxide pose a risk of explosion and draw a large energy demand. However, despite these drawbacks, use of supercritical carbon dioxide has expanded over the past decades and it is now an accepted medium for synthetic procedures.

Comprehensive reviews by Tanko[235] and Oakes[234] detail known synthetic applications of supercritical fluids (in particular supercritical carbon dioxide), detailing a range of reactions including free-radical reactions, polymerisations, cycloadditions, oxidations, Friedel-Crafts alkylations and a host of catalytic processes. However, at this time there were few reported photochemical transformations in supercritical fluids, namely photo-Fries rearrangement, dimerisation by [2+2]-cycloaddition and light-induced free radical halogenations.

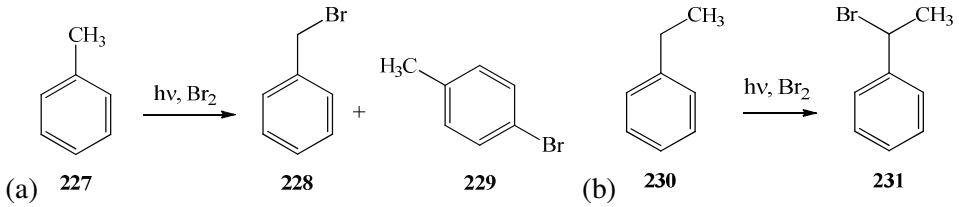
For the photo-Fries rearrangement in supercritical carbon dioxide it was observed that the selectivity of the reaction could be altered by varying density of the supercritical fluid[236]. This was attributed to clustering of the solvent molecules around the solute, causing an increased 'cage-effect' (Scheme 69).



Scheme 69: Photo-Fries rearrangement of 1-acetoxynaphthalene 222**.**

A similar study on the effect of solute-solvent clusters in supercritical carbon dioxide was carried out by Roberts, using the photocleavage of dibenzylketone and subsequent decarbonylation of the phenylacetyl radical[237]. In this case no cage effect was observed. This is attributed to the short lifetime of the solvent-solute clusters relative to the time required for the decarbonylation reaction.

Tanko reported use of supercritical carbon dioxide as an alternative to carbon tetrachloride in the free-radical side-chain bromination of alkylaromatics **227** and **230** (Scheme 70)[238].



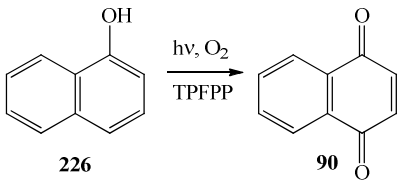
Scheme 70: Side chain bromination of alkyl aromatics 227 **and** 230**.**

There was no significant difference in selectivity, indicating that the change in solvent did not affect the mechanism of the reaction.

More recently, oxidations in supercritical carbon dioxide have been reported. Theyssen *et al.* have studied the oxidation of cycloalkanes or alkylarenes with molecular oxygen and

acetaldehyde (co-reductant)[239]. Interestingly, no catalyst is required as the steel walls of the reactor act as initiators.

Studies by Poliakoff and George have investigated photochemical oxidation in supercritical carbon dioxide. The [4+2]-cycloaddition of singlet oxygen and α-terpinene **69** in $scCO_2$ has been investigated[240]. Singlet oxygen was generated using a fluorinated TPP derivative. Using FTIR analysis, quantitative conversion was achieved after only 160 s of irradiation using a xenon lamp (300W, with UV filter). In addition, the use of a continuous flow reactor has been reported[241]. This consists of a tubular sapphire reactor with an internal diameter of 7.8 mm, wall thickness of 1.2 mm, and irradiated volume of 4.1 mL. This reactor facilitates the scale up of reactions. The preparation of rose oxide **96** by photooxygenation of citronellol **93** and ascaridole **66** from α–terpinene **69** were used as model reactions to demonstrate the reactor efficiency. In a final study the use of co-solvents was reported, which enables solubising of substrates and sensitisers that are not usually soluble in $scCO_2$ alone. In conjunction with surfactants, use of sensitisers rose bengal **41** and methylene blue **42** and substrates such as 1-naphthol **226** have been demonstrated[242]. Use of dimethyl carbonate as a co-solvent facilitated the solubility of 1-naphthol **226** in $scCO_2$ (Scheme 71).



226 **90**

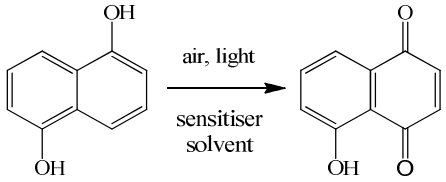
Scheme 71: Synthesis of 1,4-naphthoquinone 90 **in $scCO_2$.**

In addition, the use of fluorinated surfactants, Krytox and Fluorolink, was investigated to enable use of other sensitisers, such as unsubstituted tetraphenylporphyrin **43**, rose bengal **41** and methylene blue **42**. To evaluate this technique, synthesis of ascaridole **66** from α–terpinene **69** was used as a model reaction. This study demonstrated that methylene blue **42** and TPP **43** could be solubilised in this manner, but rose bengal **41** remained only sparingly soluble. However, photobleaching of methylene blue **42** was observed when in $scCO_2$ using Krytox as a surfactant.

These reactions have demonstrated the potential of supercritical carbon dioxide as a green solvent for photochemical transformations.

1.6 Thesis Proposal

Work by short-term students in our group looked at the development of a green synthesis of fine chemicals, using the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** as a model reaction (Scheme 72), with the aim of developing an entirely green process. In particular, the use of alcoholic solvents and solar irradiation were applied.



97 **98**

Scheme 72: Preparation of 5-hydroxy-1,4-naphthoquinone 98 **(juglone).**

Following on from this work a number of issues were raised which we wished to explore, namely:

1. **Can we optimise the reaction to maximise "greenness"?**

In the context of this work, the term "greenness" refers to minimising environmental impact of each stage of the reaction. All aspects of the synthesis will be optimised, in particular the reaction conditions, work up procedures and energy consumption. This research will determine that solarchemical reactions are indeed practicable in Ireland, and that they may be capable of replacing hazardous industrial or laboratory processes.

To achieve these aims, the reaction conditions will be optimised. Hazardous solvents such as dichloromethane, chloroform and *n*-hexane will be replaced by greener substitutes, for example cyclohexane and ethyl acetate. Use of catalysts, and in particular solid-supported catalysis, will be investigated. Recovery and recycling of solvent and catalyst will be probed.

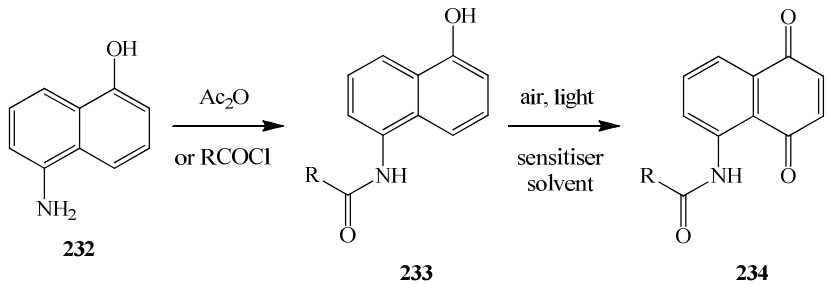
In addition to the above, the purification procedures will be assessed and adapted to ensure minimum environmental impact. The method of purification and reagents used will be examined and optimised.

The energy demand of commonly used lab equipment will be calculated and considered as a key factor in determining the 'greenness' of the process. Investigation of solar irradiation as a substitute for artificial light sources will be a significant focus of this work. Once optimised, the synthesis of juglone **98** will be carried out under solar conditions, with a study of the effect of

various irradiation conditions (e.g. direct sun, cloud and shade). Large scale synthesis will be investigated, particularly using flat-bed reactors, which can use direct and diffuse light.

2. Can we increase the scope of the reaction?

An extension of the above research will look at the synthesis of analogs of juglone **98**, for example using other 1-naphthol substrates such as 5-amido-1-naphthols **233** (Scheme 73) or 5-acetoxy-1,4-naphthol **170**. Use of commercially available 1-naphthols will be investigated. A comparison of yield from artificial light irradiation and solar studies will be carried out, to assess the potential advantages of solar synthesis.



232 **233** **234**

Scheme 73: Preparation of 5-amido-1-naphthols and the corresponding 5-amido-1,4-naphthoquinones.

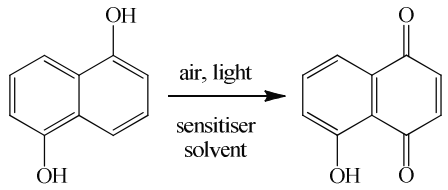
3. Can other reaction media be applied for the dye-sensitised photooxygenation process?

The use of alternative reaction media will also be investigated, in particular the use of microemulsion systems or solvent-free solid-supported synthesis. In addition, use of ionic liquids and supercritical carbon dioxide will be assessed. These reaction media may offer a green alternative to traditional organic solvents.

Chapter 2 Juglone as a model synthesis: validation and optimisation

2.1 Introduction

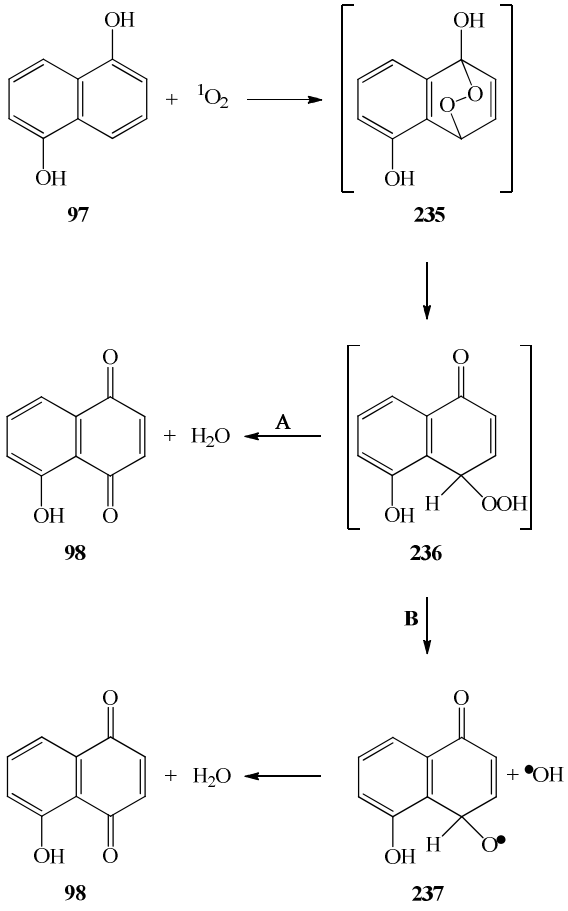
The aim of this work was to use the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** in the synthesis of juglone **98** as a model system (Scheme 74).



97 **98**

Scheme 74: Preparation of 5-hydroxy-1,4-naphthoquinone (juglone) 98**.**

The reaction of singlet oxygen with 1,5-dihydroxynaphthalene **97** is an example of a photo-Diels-Alder reaction ([4+2]-cycloaddition), in which 1,5-dihydroxynaphthalene **97** functions as a diene and singlet oxygen as a dienophile. The photo-Diels-Alder reaction produces an endoperoxide **235**, which subsequently undergoes the loss of water to yield the 1,4-naphthoquinone **98**. The mechanism of this reaction has been proposed by Croux[187] and Murtinho[28] (Scheme 75).



Scheme 75: Mechanism of juglone 98 **synthesis.**

The general mechanism suggests that the conversion of the endoperoxide **235** to the 1,4-naphthoquinone **98** is spontaneous. Croux attributes this to the instability of the endoperoxide **235**, but does not speculate further on the mechanism. However, Murtinho proposes that intramolecular acid catalysis occurs (supported by deuterium isotope studies[188]), causing conversion of the endoperoxide **235** to the hydroperoxide **236**. The hydroperoxide **236** is subsequently converted to the 1,4-naphthoquinone **98** either via heterolytic (**A**) or homolytic pathways (**B**).

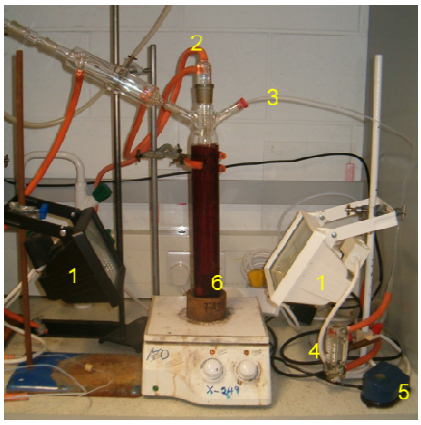
To evaluate dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** to juglone **98** as a green process it was necessary to first validate the essential parameters in this synthesis, namely the use of light, oxygen (obtained from air) and sensitisers. Stability studies were also carried out on the sensitiser rose bengal **41** and on the product juglone **98** to ensure there is no further photochemical process which it may undergo under reaction conditions. The use of ^{1}H NMR spectroscopy for monitoring studies was evaluated.

Following validation of the process, optimisation studies were carried out in artificial light conditions. This led to the establishment of a standardised method for juglone **98** synthesis, which could then be applied to other 1-naphthol substrates.

2.2 Results and Discussion

2.2.1 Experimental set-up

In order to optimise juglone **98** synthesis for greenness, a series of investigations were carried out under artificial light irradiation. Solvent and sensitiser suitability studies were investigated using different light sources. For the irradiation experiments, halogen lamps (IQ Group, 500 W) were used with Pyrex Schlenk flasks. Air bubbling was supplied using standard air pumps (Hagen Elite aquarium pumps). The general set-ups are shown in Figure 21.

(a) 

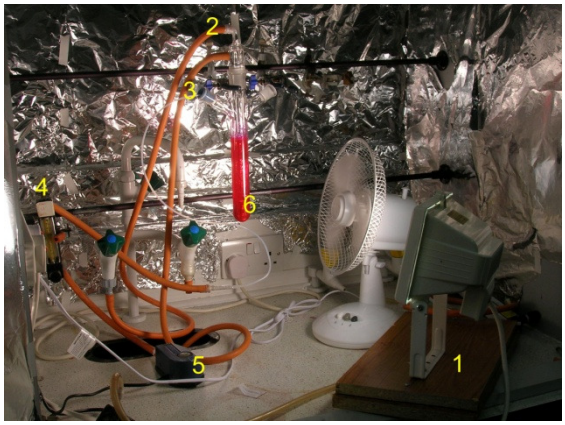
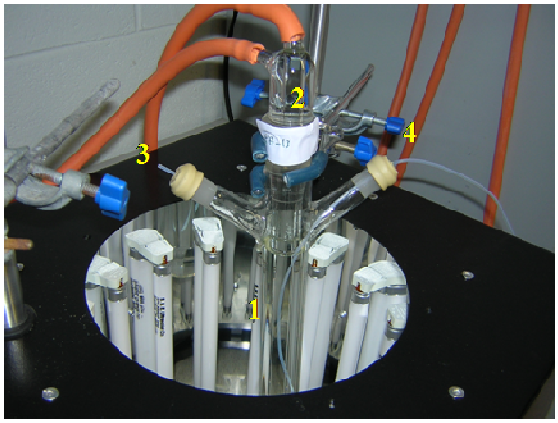
(b) 

Figure 21: (a) Experimental set-up A and (b) Experimental set-up B (1: Halogen lamp, 2: water inlet, 3: air inlet, 4: flow meter, 5: air pump, 6: sparger).

The basic components of both set-ups are the same; the reaction mixture is placed in a Schlenk flask and is cooled with water using a cold-finger. Air is bubbled into the solution from the pump, flow is controlled using the flow meter and small bubbles generated by using a sparger on the air inlet. However set-up A consisted of two halogen lamps, rather than one. Initial experiments were carried out using set-up A but this was modified to set-up B to enable setting up parallel reactions and reduce energy demand of the reactions.

Self-sensitisation of 1,5-dihydroxynaphthalene **97** was investigated using ultraviolet light sources as well as halogen lamps. For this study a Rayonet photochemical chamber reactor (RPR200, Southern New England, fitted with 16 RPR-3000Ǻ lamps (λ = 300±325 nm), Figure 22a) or an immersion well reactor fitted with a medium-pressure mercury lamp (400 W, model 3040 (Photochemical Reactors Limited), Figure 22b) was used.

(a) 

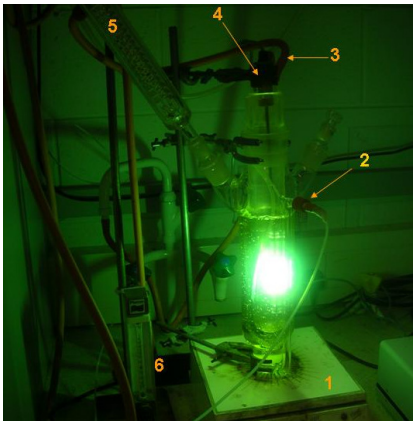
(b) 

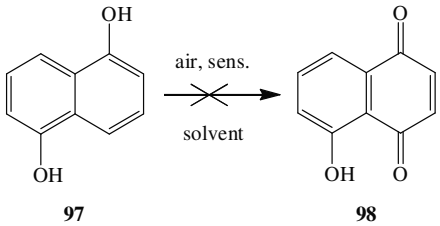
Figure 22: UV reaction set-ups: (a) Rayonet photoreactor and experimental set-up (1: Pyrex reaction tube, 2: cold finger, 3: gas outlet, 4: air inlet) and (b) Mercury lamp (1: Stirring plate, 2: air inlet, 3: Water inlet, 4: UV lamp, 5: Condenser, 6: flow meter).

2.2.2 Validation of juglone synthesis

The synthesis of juglone **98** by dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** is believed to require sensitiser, light and an oxygen source to enable formation of singlet oxygen. Validation of juglone **98** synthesis was carried out by assessing the results of several control experiments evaluating the role of these parameters.

2.2.2.1 Dark room reactions

Control dark room reactions were carried out to demonstrate the role of light in the dye-sensitised production of singlet oxygen. To evaluate the dark reaction of 1,5-dihydroxynaphthalene **97** under reaction conditions (sensitiser and air supplied) a dark room (with red light) was used (Scheme 76). The reaction mixtures were prepared under red lighting and then bubbled with air in darkness for 4-12 hours. After this time ^{1}H NMR spectroscopy was used to evaluate the quantity of juglone **98** formed.



97 **98**

Scheme 76: Dark room study of 1,5-dihydroxynaphthalene 97 **(Experiments 1-6).**

As summarised in Table 2, solutions of 1,5-dihydroxynaphthalene **97** bubbled with air in darkness for 4 h or 12 h did not produce juglone **98**. The reaction mixture and residue after evaporation did not show the distinctive yellow colour of juglone **98**. ^{1}H NMR analysis (DMSO-d_6) showed that the characteristic juglone peaks were absent.

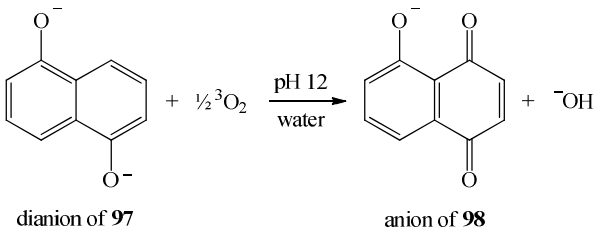
Table 2: Production of juglone 98 **in dark-room conditions (Experiments 1-6).**

Expt no.	Sensitiser	Solvent	Time (h)	Outcome
1	rose bengal **41**	*i*-propyl alcohol	4	No reaction
2	None	*i*-propyl alcohol	4	No reaction
3	rose bengal **41**	*t*-amyl alcohol	4	No reaction
4	None	*t*-amyl alcohol	4	No reaction
5	None	*t*-amyl alcohol	4	No reaction
6	rose bengal **41**	*t*-amyl alcohol	12	No reaction

This study demonstrates that under the standard reaction conditions of alcoholic solvent and a sensitiser, the use of light is essential for the reaction to proceed. 1,5-Dihydroxynaphthalene **97** does not undergo a dark oxidation under these reaction conditions. Therefore any juglone **98** formed following light irradiation is a result of the photons absorbed.

2.2.2.2 pH study of the oxidation of 1,5-dihydroxynaphthalene

Luiz has reported the spontaneous oxidation of 1,5-dihydroxynaphthalene **97** under basic conditions (pH 12)[186]. This process was examined to see if juglone **98** can be produced under dark conditions in alkaline solutions (Scheme 77).

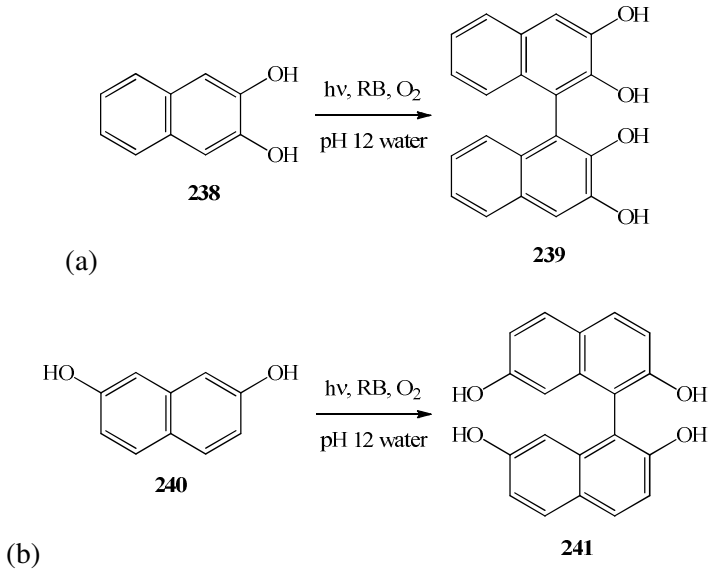


Scheme 77: Proposed spontaneous dark synthesis of juglone 98 **(Experiments 7-10).**

To assess the formation of juglone under these conditions, a solution of 1,5-dihydroxynaphthalene **97** in alkaline water (pH 12.2) was stirred at room temperature in darkness for four hours (Experiment 7). It was then acidified using HCl (the pH of the reaction mixture changed from 12.2 to 10.2 during the reaction process) and extracted using ethyl

acetate. The resultant product was analysed by TLC and ^{1}H NMR spectroscopy and did not contain juglone **98**. A reference study on the recovery of juglone **98** from aqueous alkaline solutions following pH adjustment using hydrochloric acid showed that this method is suitable for juglone **98** recovery (Experiment 8).

Studies of 2,3-dihydroxynaphthalene **238** and 2,7-dihydroxynaphthalene **240** have shown the formation of dimeric products **239** and **241** following oxygenation in aqueous solutions at pH 12 (Scheme 78)[243].



Scheme 78: Oxygenation of dihydroxynaphthalenes in pH 12 water.

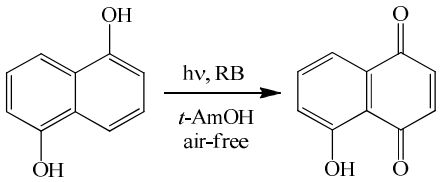
A similar process may be underlying the reaction of 1,5-dihydroxynaphthalene **97** in aqueous alkaline solution. In a test reaction a solution of 1,5-dihydroxynaphthalene **97** and rose bengal **41** was prepared in water adjusted to pH 12 using sodium hydroxide (Experiment 9). This was irradiated for four hours using a halogen lamp, then acidified using HCl and extracted with ethyl acetate. TLC and ^{1}H NMR spectroscopy of the extracted product did not show the presence of juglone **98**.

The above results were compared to synthesis in the presence of a buffer, which was carried out by Kieran Joyce (Experiment 10A). A solution of 1,5-dihydroxynaphthalene **97** in pH 12 buffer was irradiated for 6 hours using one 500W halogen lamp. The reaction was monitored hourly using ^{1}H NMR spectroscopy and after 6 hours of irradiation there was no formation of juglone **98**. As observed in the dark oxidation study, the anionic form of the 1,5-dihydroxynaphthalene **97** develops a deep purple colour at pH 12. However, there was no juglone **98** formed in this

reaction. This may be due to no formation of singlet oxygen or the anionic form is simply not reactive. It could also be due to the very short life time of singlet oxygen in aqueous solutions.

2.2.2.3 Oxygen-free synthesis

To evaluate the need to provide oxygen to the reaction solution a study was carried out using degassed *t*-amyl alcohol (Scheme 79, Table 3).



97 **98**

Scheme 79: Synthesis of juglone 98 **in the absence of oxygen (Experiments 11-13).**

A test reaction was carried out using nitrogen to degas *t*-amyl alcohol (purged for 1 hour using nitrogen gas). The starting material **97** and sensitiser **41** were added to the degassed solvent in the reaction flask, which was then bubbled with nitrogen during irradiation for 6 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 10% occurred in this time.

Use of helium for degassing was also investigated. The reaction solvent was purged for 25 minutes. 1,5-Dihydroxynaphthalene **97** and rose bengal **41** were added and dissolved with sonication. The reaction was then irradiated without gas bubbling for 6 hours using a halogen lamp. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 30% was achieved. This high conversion indicates that to ensure full removal of oxygen, purging with helium for a greater length of time was necessary. In addition, purging throughout the reaction time could help ensure that oxygen does not re-dissolve in the reaction solution.

The optimum conditions for degassing were determined to be use of helium (purging for one hour) to degas *t*-amyl alcohol prior to reaction. Nitrogen bubbling was used throughout the irradiation period. ^{1}H NMR spectroscopy (acetone-d_6) showed that there was no conversion to juglone **98** under these reaction conditions.

Table 3: Synthesis of juglone 98 **in the absence of oxygen, using rose bengal** 41 **in *t*-amyl alcohol.**

Expt. no.	Degassing procedure	Duration (min)	Gas bubbling during reaction	Time (h)	Yield (%)
11	Nitrogen purge	60	Nitrogen	6	10
12	Helium purge	25	-	6	30
13	Helium purge	60	Nitrogen	4	0

2.2.2.4 Self-sensitised synthesis of juglone (sensitiser-free)

Control reactions were carried out to investigate the use of sensitiser-free conditions for the photooxygenation of 1,5-dihydroxynaphthalene **97**. The UV-vis spectrum of 1,5-dihydroxynaphthalene **97** (technical grade) shows that the starting material does not absorb at wavelengths greater than 350 nm (Figure 23).

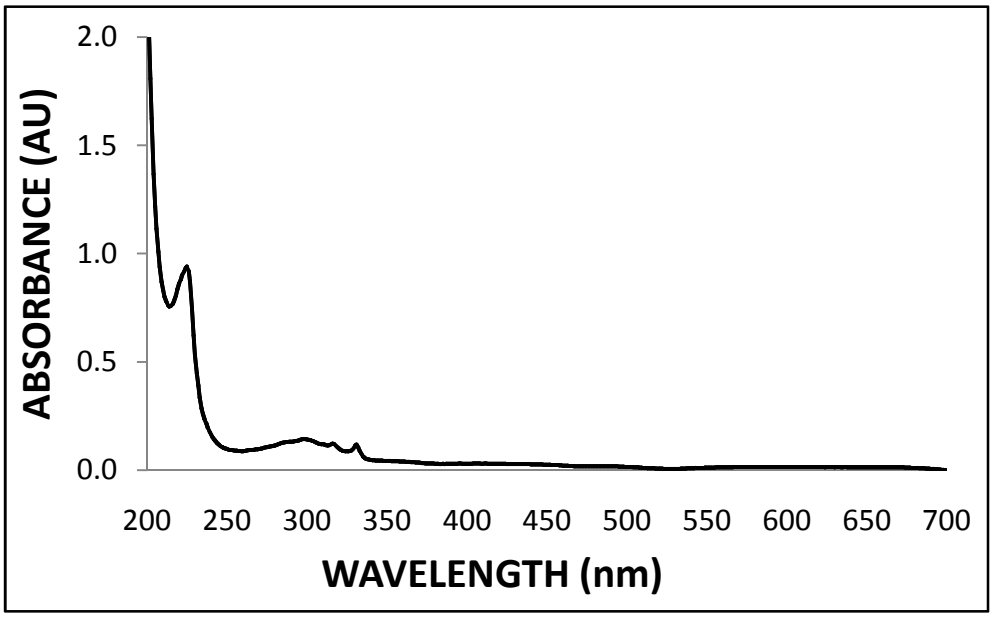
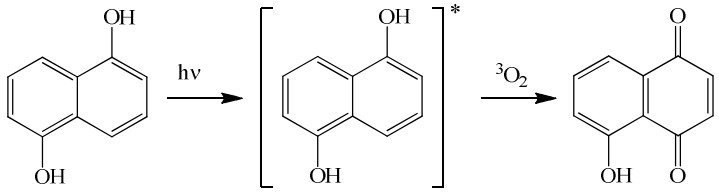


Figure 23: UV spectrum of technical grade 1,5-dihydroxynaphthalene 97 **(in *i*-propyl alcohol).**

The absorbance band with a maximum at 300 nm may enable excitation of the molecule under UV irradiation, leading to self-sensitisation. Following absorption of a photon, the starting material **97*** may interact with ground state oxygen ($^3O_2$) and form juglone **98** via a type I photooxidation process (Scheme 80)[55].



97 **97*** **98**

Scheme 80: Self-sensitised formation of juglone 98**.**

A study using a range of light sources was carried out in conjunction with Kieran Joyce, which showed that some self-sensitisation occurs in the absence of a sensitiser. This self-sensitisation is greater when ultraviolet light is applied, using a mercury lamp or Rayonet reactor (300 nm), when compared to halogen lamps (Table 4).

Table 4: Juglone 98 **synthesis in sensitiser-free conditions.**

Expt. no.	Starting material	Light Source	Solvent	Time (h)	Yield (%)
14A	Sublimed	Halogen lamp	*t*-amyl alcohol	6	14
15A	Technical grade	Halogen lamp	*t*-amyl alcohol	6	8
16	Technical grade	Hg Lamp (400 W)	*t*-amyl alcohol	6	24
17	Technical grade	Rayonet (300 nm)	*t*-amyl alcohol	6	19

As summarised in Table 4, irradiation of 1,5-dihydroxynaphthalene **97** in Pyrex vessels ($\lambda \geq 300$ nm) in the absence of a sensitiser, using different light sources for 6 hours gave juglone **98** in yields of 8-24% after purification. Little self-sensitisation is observed when a halogen lamp is used, as this lamp does not emit light of less than 400 nm (Figure 24).

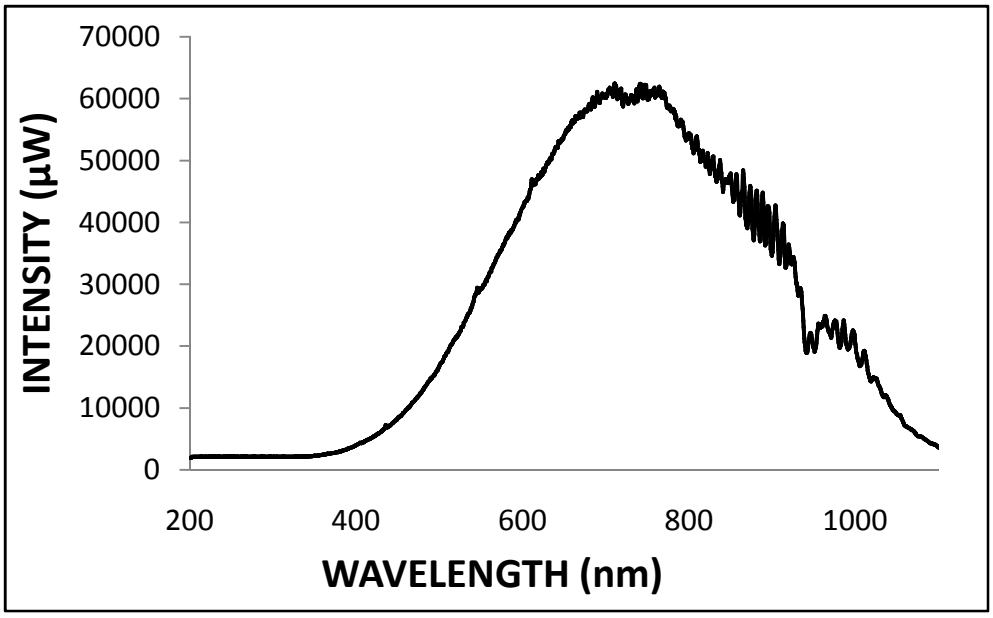


Figure 24: Emission spectrum of a halogen lamp, measured using a Maya 2000 Pro thin layer CCD spectrophotometer.

These results are supported by observations by Duchstein, who noted that yields of juglone **98** of up to 20% (20% in acetonitrile, 4% in methanol) were obtained using light >360 nm (halogen lamp), with yields of 12-15% for light < 360 nm (high pressure mercury lamp)[184]. In addition Luiz has suggested that 1,5-dihydroxynaphthalenes are good self-sensitisers at 337 nm[186] and Murtinho reports yields of up to 28% using Tungsten lamps[28].

Solar irradiation provides light below 400 nm (Figure 25), thus the diol **97** may be excited under solar conditions. This self-sensitisation may lead to enhanced yields of juglone **98** under solar conditions, compared to those in artificial light.

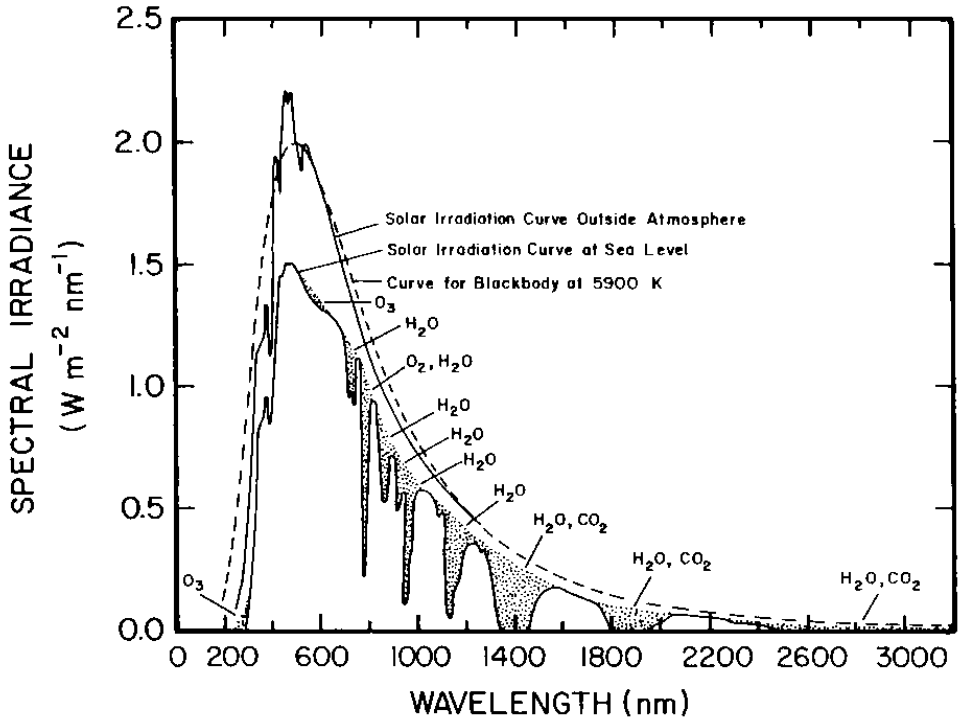


Figure 25: Solar Spectrum[244].

Julone **98** has a weak absorption at 400 nm (Figure 26), which suggests that it may be capable of acting as a sensitiser for formation of singlet oxygen. To assess this, a control reaction was carried out irradiating 1,5-dihydroxynaphthalene **97** in *t*-amyl alcohol using one 500 W halogen map in the presence of juglone **98** (Experiment 18). ^{1}H NMR spectroscopy was used to monitor conversion after 4 hours. This showed that a small degree of conversion was observed. However, this was not significantly greater than that observed for self-sensitised reactions, indicating that juglone **98** does not act as a sensitiser.

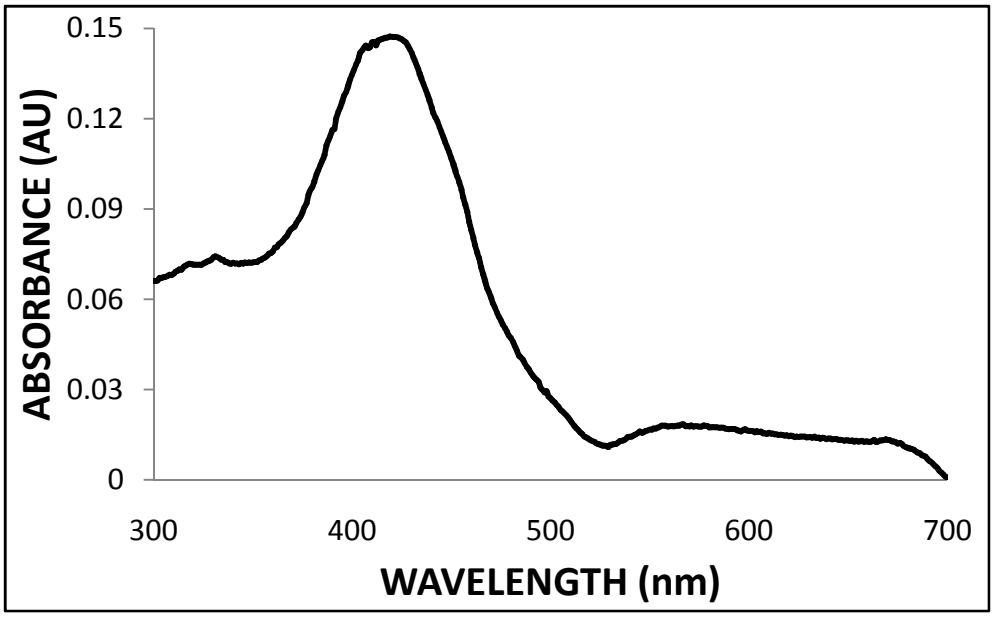
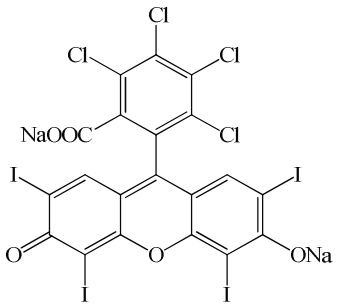


Figure 26: UV-vis spectrum of juglone 98 (in methanol).

2.2.2.5 Sensitiser stability study

Rose bengal **41** is the standard sensitiser used for photooxygenation reactions by our group and is usually used as the sodium salt (Figure 27). As a consequence, this structure can act as a base, and its sensitising activity is affected by pH. To determine the suitability of this sensitiser in standard reaction conditions a pH study was carried out.



41

Figure 27: Structure of rose bengal 41**.**

The stability of rose bengal **41** in aqueous solutions in the pH range 2-13 was measured using UV-vis spectrophotometry (Figure 28), and it was shown that at pH 3 or less the dye is deactivated. This suggests that protonation of rose bengal **41** has occurred. No precipitate is observed, which indicates that the protonated form of rose bengal **41** remains water soluble at

this concentration. The change in absorbance spectrum can be attributed to the colourless nature of the protonated compound, indicating that rose bengal **41** is an acidochromic dye.

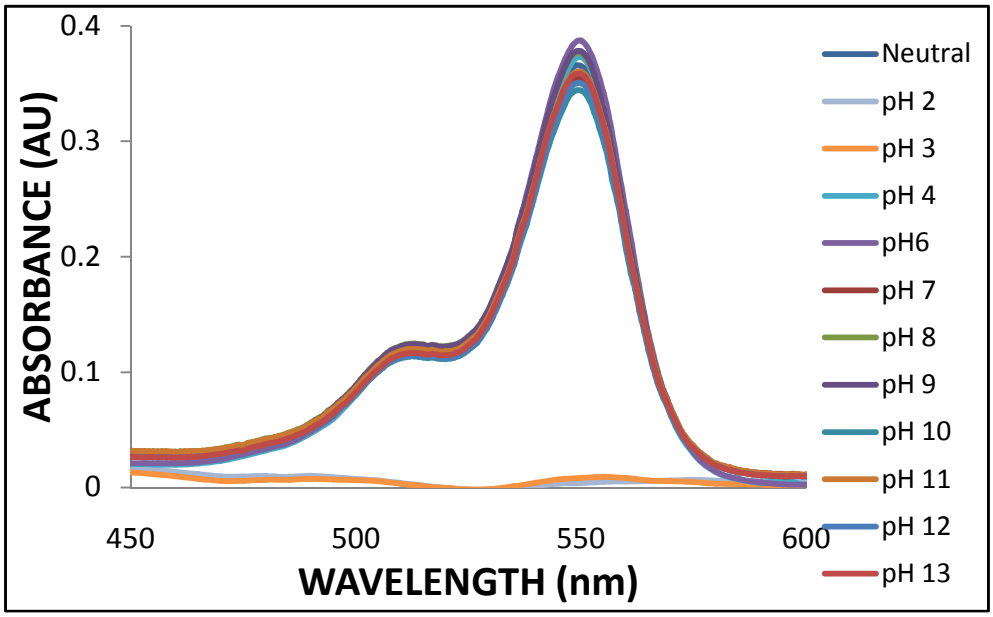


Figure 28: Absorbance of rose bengal 41 at pH range 2-13 in aqueous solutions (Experiment 19).

To assess the stability of rose bengal in organic solvents a series of samples were prepared in the pH range 3-13, in a methanol-water mix (50:50) and measured using UV-Vis spectrophotometry (Figure 29). This showed a shift in λ_{max} compared to water (evident in samples neutral in methanol and neutral in water-methanol mixture). This shift was not observed in pH adjusted samples.

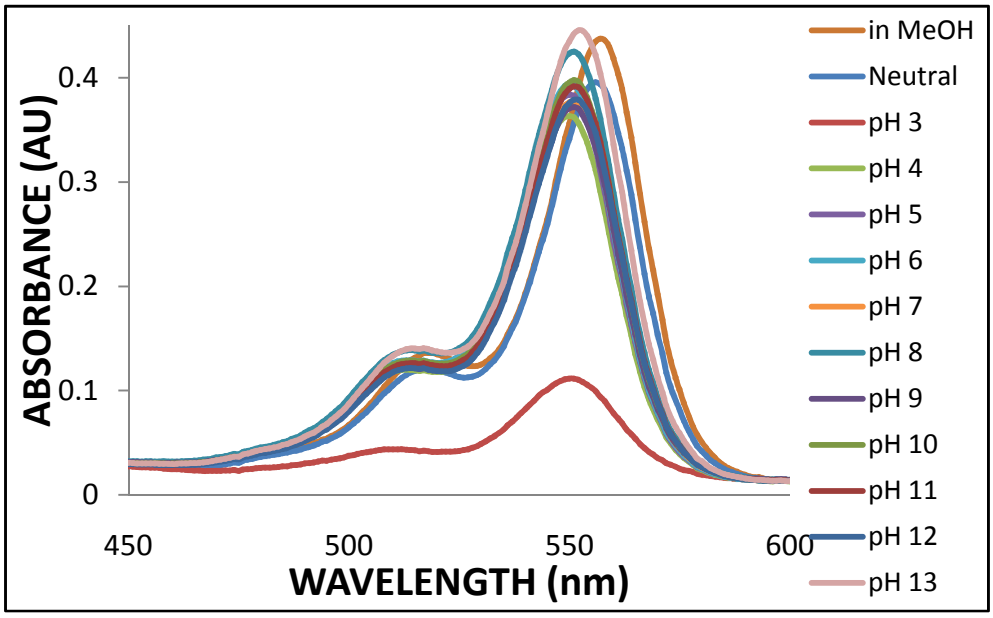


Figure 29: Absorbance of rose bengal 41 **at pH range 3-13 in water-methanol (1:1) solutions (Experiment 20).**

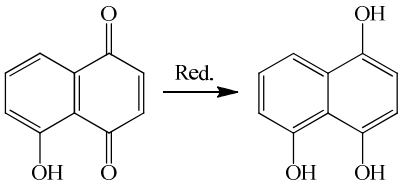
At pH 3 in the methanol-water solution a notable decrease in absorbance was observed, however, this was not as significant as in the aqueous pH 3 sample. This indicates that rose bengal **41** is stable between a pH range of 4 to 13, and therefore should be stable under standard photooxygenation conditions.

2.2.2.6 NMR solvent studies

To monitor the progress of reaction, a method using ^{1}H NMR spectroscopy was developed. Studies were carried out to evaluate the most suitable solvent for use in monitoring studies, with an emphasis on solubility and stability. Deuterated chloroform ($CDCl_3$), deuterated dimethylsulfoxide (DMSO-d_6) and deuterated acetone (acetone-d_6) were investigated for use in monitoring the progress of juglone **98** synthesis.

Deuterated chloroform is often used as a solvent for NMR analysis of juglone **98**[55]. However, chloroform was rejected as a solvent for monitoring studies, due to the lack of solubility of 1,5-dihydroxynaphthalene **97** in this solvent.

Both juglone **98** and 1,5-dihydroxynaphthalene **97** are soluble in DMSO-d_6, and so this was used in early monitoring studies. However degradation of samples was observed over time in DMSO-d_6, with 1,4,5-trihydroxynaphthalene **242** observed to be present as a degradation product. This indicates that reduction of juglone **98** is occurring, most likely through two electron transfer steps (Scheme 81, as proposed by Hernandez-Munoz[245]).



98 **242**

Scheme 81: Reduction of juglone 98 **to 1,4,5-trihydroxynaphthalene** 242**.**

A UV-vis study was carried out to demonstrate degradation in DMSO-d_6. A sample of juglone **98** was dissolved in DMSO-d_6 in a quartz cuvette. The absorbance of the solution was recorded at intervals over an 8 hour period. There was a notable increase in absorbance at 421 nm, and a corresponding decrease in absorbance at 596 nm (Figure 30). This change occurred slowly, however this confirms that DMSO-d_6 is not a suitable solvent for monitoring studies using NMR spectroscopy for juglone **98** synthesis where samples may need to be left overnight.

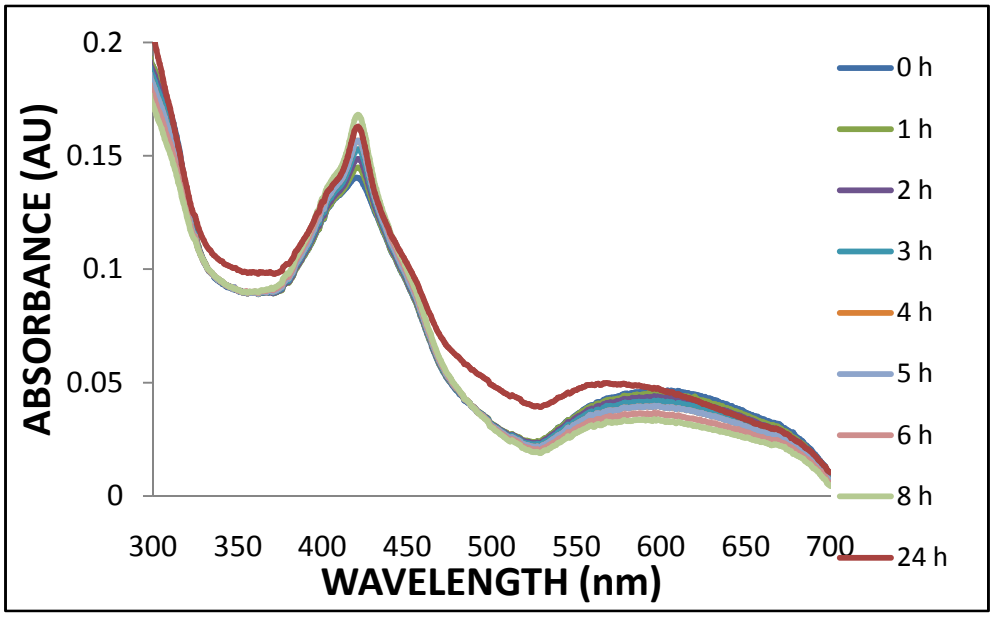


Figure 30: Stability of juglone in DMSO-d_6 (Experiment 21).

To confirm this, a sample of juglone **98** was placed in DMSO-d_6 for 2 days, during which time the solution changed from clear yellow to opaque black (it was then stored at -20°C for 3 weeks). ^{1}H NMR spectroscopy and UV-vis spectrophotometry (300-700 nm) of this sample showed degradation of juglone **98** (Figure 31).

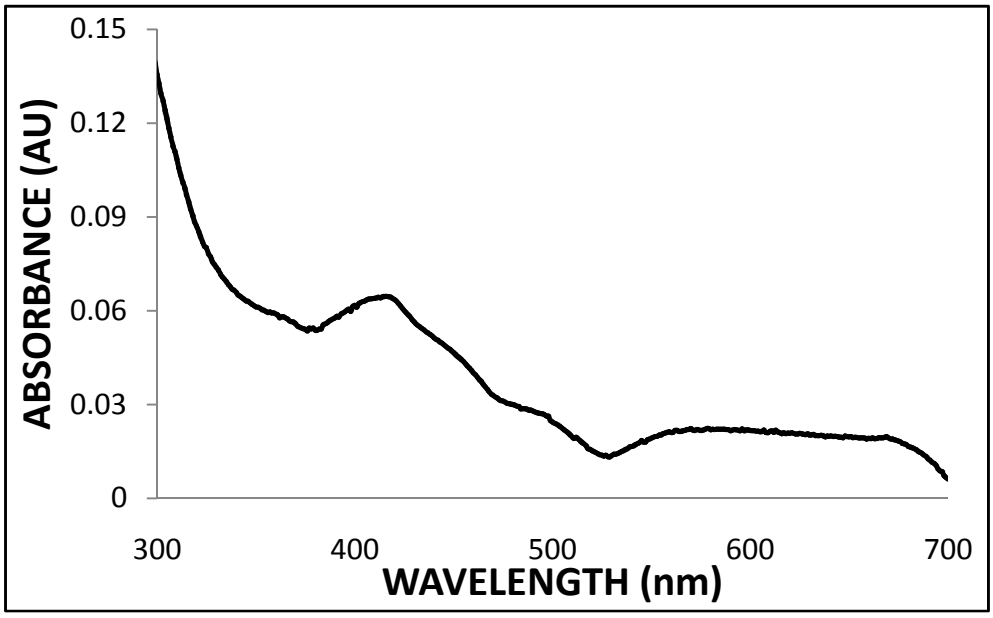


Figure 31: UV-vis spectrum of juglone 98 **in DMSO-d_6 after 2 days (Experiment 22).**

Both juglone **98** and 1,5-dihydroxynaphthalene **97** are soluble in acetone-d_6 and no degradation is observed in samples left for several days in this solvent. Therefore acetone-d_6 is suitable for use in monitoring the conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** by ^{1}H NMR spectroscopy.

In the ^{1}H NMR spectrum of juglone **98** in acetone-d_6, the quinonoid hydrogens are resolved as two doublets at about 7 ppm, the hydroxy proton is present as a singlet at about 12 ppm and the aromatic protons are well resolved, present as two doublets and a triplet at 7.3, 7.5 and 7.7 ppm, respectively (Figure 32).

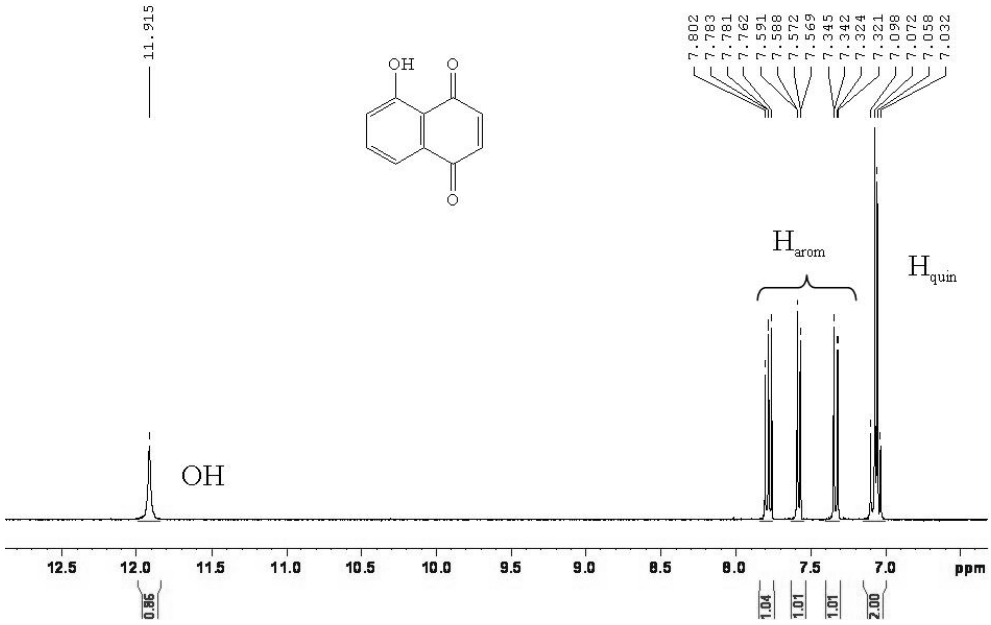


Figure 32: ^{1}H NMR spectrum of juglone 98 **in deuterated acetone (H_{arom}: aromatic H, H_{quin}: quinonoid H).**

The quinonoid H peaks (2 doublets with an integration of 2) for juglone **98** and the most upfield doublet (with additional poorly resolved long range coupling) of 1,5-dihydroxynaphthalene **97** (integration of 2) were chosen as representative peaks for monitoring studies Figure 33.

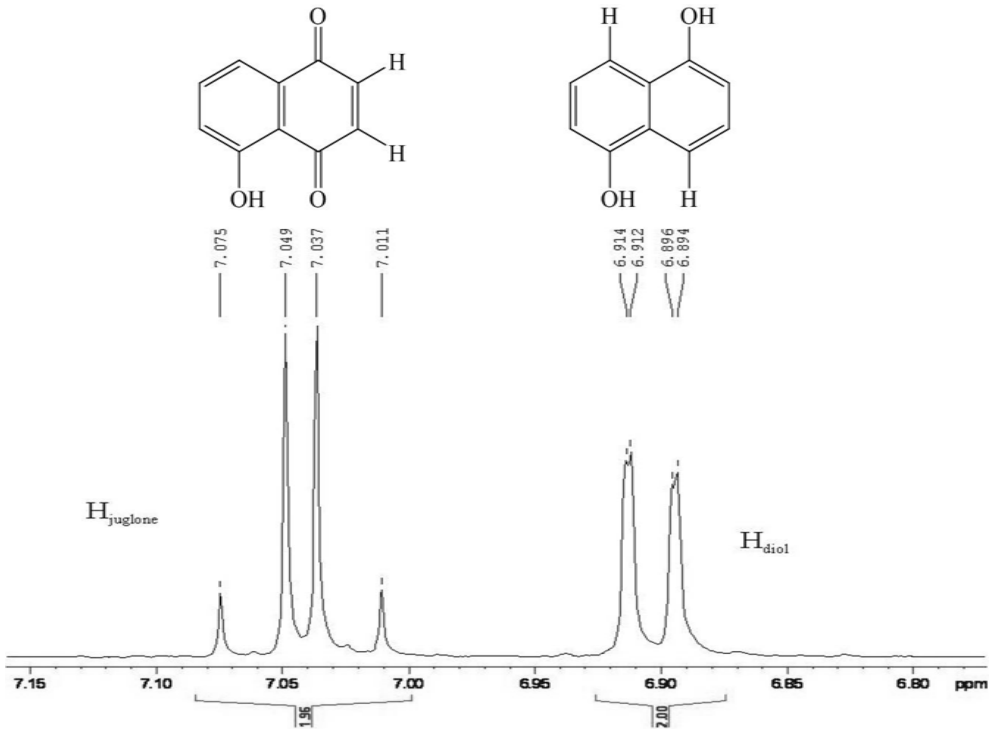


Figure 33: Peaks for juglone 98 **and 1,5-dihydroxynaphthalene** 97 **used in monitoring studies in acetone-d_6.**

2.2.3 Optimisation of juglone synthesis

After completion of the control experiments, and demonstrating the parameters necessary for the dye-sensitised photooxygenation to proceed, optimisation of the synthesis was carried out. To optimise the entire dye-sensitised photooxygenation process it is necessary to optimise all aspects of the reaction, in particular reaction solvent, light sources employed, work-up procedure and energy usage.

2.2.3.1 Optimisation of reaction solvent

Previous studies on the photochemical synthesis of juglone **98** have involved the use of chlorinated solvents. However, it is desirable to replace existing solvents with greener alternatives. The Pfizer Global Research and Development team have developed a solvent selection guide which classifies solvents into three categories – preferred, usable and undesirable (Figure 34)[31]. Using this guide, it is possible to replace undesirable solvents with greener alternatives from the preferred or usuable categories.

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl *t*-butyl ether	Dichloromethane
Ethyl acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MethylTHF	Dimethyl formamide
Methyl ethyl ketone	Tetrahydrofuran	*N*-Methylpyrrolidinone
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl sulfoxide	Dimethyl acetate
	Acetic acid	Dioxane
	Ethylene glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Figure 34: Pfizer's solvent selection guide (Source: *Green Chem*., 2008)[31].

A study of solvent for juglone **98** synthesis was carried out previously, looking at the use of acetone or *i*-propyl alcohol[55], but this was extended in this work to include *t*-amyl alcohol and ethyl acetate. As *t*-amyl alcohol is a longer chain alcohol, with physical properties similar to those of *t*-butyl alcohol, it is expected that the singlet oxygen lifetime is about 31 μs or even longer (Table 5), which is longer than shorter chain alcohols (methanol, ethanol and *i*-propyl alcohol). Therefore greater yields may be achieved for photooxygenation in *t*-amyl alcohol, than in shorter chain alcohols.

Table 5: Singlet oxygen lifetimes in selected solvents[43, 246].

Solvent	$^1O_2$ lifetime (μs)
Acetone	34-65
Ethyl acetate	45-50
Methanol	9.5-10.4
Ethanol	9.7-15.3
i-Propyl alcohol	22
t-Butyl alcohol	31
Dichloromethane	59-100

In addition to the expected longer singlet oxygen lifetime, the 'green' nature of *t*-amyl alcohol was also considered. Using the German Water Hazard Class (WGK) assessment criteria, *t*-amyl alcohol is classified as level 1, indicating that it possesses low aquatic toxicity. In addition, using the Pfizer solvent selection guide (Figure 34), *t*-butyl alcohol (and hence *t*-amyl alcohol) is considered a preferred solvent.

Ethyl acetate was also investigated as a solvent for photooxygenation as it is also a preferred solvent (Figure 34). Ethyl acetate is a main component of microemulsion systems, and it was necessary to carry out a reference reaction to determine the contribution of ethyl acetate to the overall effectiveness of the microemulsion system.

As summarised in Table 6, irradiation of 1,5-dihydroxynaphthalene **97** in different solvents for 4 hours, using one 500 W halogen lamp, gave conversion to juglone of 9.5-39%.

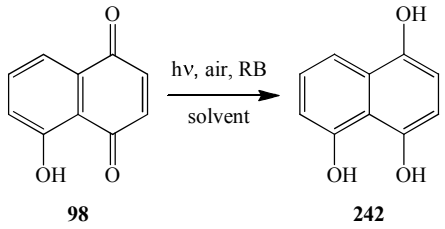
Table 6: Optimisation of solvent for juglone 98 **synthesis (Experiments 23-29).**

Expt. No.	Solvent	Sensitiser	Time (h)	Conversion (%)
23	MeOH	rose bengal	4	22
24	EtOH	rose bengal	4	30
25	*i*-PrOH	rose bengal	4	32
26	*t*-AmOH	rose bengal	4	39
27	Acetone	rose bengal	4	14
28	EtOAc	rose bengal	4	9.5
29	Water	rose bengal	4	11

As shown in the table above, use of different alcoholic solvents gave the best conversion in just 4 hours. This work showed that photooxygenation in *t*-amyl alcohol produces more oxidation product than *i*-propyl alcohol or acetone, in a shorter length of time, making it most suitable for further reactions.

2.2.3.2 Stability of juglone in reaction solvents

The possibile photoreduction of juglone **98** to 1,4,5-trihydroxynaphthalene **242** under reaction conditions has been investigated (Scheme 82). This process could be initiated by the high oxidation potential of *i*-propyl alcohol (due to the lability of the α-hydrogen), while the use of a tertiary alcohol, *t*-amyl alcohol, should avoid this process.



98 **242**

Scheme 82: Proposed photoreduction of juglone 98 **under reaction conditions (Experiments 30-31).**

A study of juglone **98** stability under reaction conditions shows that after 4 hours of irradiation there is no detectable degradation of juglone **98** under oxygenation conditions, using *i*-propyl alcohol or *t*-amyl alcohol. ^{1}H NMR spectroscopy and TLC showed no evidence of degradation products.

A further study to investigate the photoreduction of juglone in reaction solvents involved the irradiation of solutions of juglone **98** in *i*-propyl alcohol or *t*-amyl alcohol for 63 hours (Experiments 32-33). The resulting solutions were analysed by TLC and ^{1}H NMR spectroscopy to look for the formation of any photoreduction products. ^{1}H NMR spectroscopy showed that small amount of degradation product may have formed in both solvents, but these were below the limit of quanitation of ^{1}H NMR spectroscopy. However, the degradation product was present in samples from both *i*-propyl alcohol and *t*-amyl alcohol, indicating that this is not a result of a photoreduction process. This indicates that *t*-amyl alcohol and *i*-propyl alcohol are stable to photooxygenation conditions and therefore *t*-amyl alcohol is suitable for use in dye-sensitised photooxygenation reactions.

2.2.3.3 Optimisation of reaction work-up (purification)

The literature purification procedure for juglone **98** synthesis involves Soxhlet extraction using *n*-hexane or column chromatography using chloroform as mobile phase[56]. Both hexane and chloroform are considered undesirable solvents and as a result a preferred alternative was

sought (Figure 34). Green alternatives for both Soxhlet extraction and column chromatography were investigated.

2.2.3.3.1 Soxhlet extraction

The use of Soxhlet extraction in the reaction work-up for juglone **98** synthesis has been investigated using cyclohexane as an alternative to *n*-hexane. Juglone **98** was adsorbed onto silica and extracted overnight using *n*-hexane and cyclohexane until the solvent from the thimble ran clear.

Table 7: Comparison of *n*-hexane and cyclohexane for Soxhlet extraction of juglone 98 **(Experiments 34-35).**

Expt. No.	Solvent	Amount (ml)	% Recovery
34	*n*-hexane	200	84
35	cyclohexane	200	46

As summarised in Table 7, use of cyclohexane for Soxhlet extraction of juglone **98** was less favourable than *n*-hexane. Extraction of juglone **98** overnight (until eluent in thimble was clear) gave recovery yields of 46% for cyclohexane, compared to 84% for *n*-hexane. This indicates that use of cyclohexane as an alternative to *n*-hexane is not practical in this application.

2.2.3.3.2 Column chromatography

The use of a 1:3 mixture of ethyl acetate and cyclohexane has been proposed as an alternative to chloroform as a mobile phase in the reaction work-up by column chromatography in juglone **98** synthesis.

Table 8: Comparison of chloroform to an ethyl acetate: cyclohexane mixture for column chromatography of juglone 98 **(Experiments 36-37).**

Expt. No.	Mobile Phase	% Recovery	R_f
36	chloroform	96	0.72
37	cyclohexane: ethyl acetate (3:1)	96	0.53

As summarised in Table 8, column chromatography of juglone **98** on a silica column (diameter 2 cm and length 25 cm) gave recovery yields of 96% for both methods.

Following this study, the optimised work-up was determined to be column chromatography using ethyl acetate and cyclohexane, both of which are considered safer and less environmentally harmful than previously reported work ups[31]. In addition, recovery using this

mobile phase was (a) comparable to that when chloroform was used as a mobile phase, and (b) greater than that achieved by Soxhlet extraction.

2.2.4 Energy usage study

Following the investigation of parameters necessary for the dye-sensitised photooxygenation to proceed, it was demonstrated that a supply of light and air was necessary. Following from this work, an assessment of the energy demand of the electrical equipment used in this procedure was carried out. The energy drawn by each appliance was measured in kilojoules per hour (kJ/h) using a plug-in electricity cost and energy meter. The results of this study are shown in Table 9.

Table 9: Energy demand of commonly used lab equipment.

Entry	Appliance	Model	Energy drawn (kJ/h)
1	Halogen lamp	IQ Group, 500 W	1556.4
2	Rayonet	RPR200, 300±25 nm	537.6
3	Medium pressure mercury lamp	Model 3040, 400 W	1342.8
4	Heating mantle heating to 100 °C	Yellowline MST	302.4
5	Heating mantle maintained at 100 °C	Yellowline MST	194.4
6	9” Fan	GET Plc	64.8
7	White pump	Dymax 30, Charles Austen Pumps Ltd.	72.0
8	Single pump A	Stellar S-20, Oscar Enterprises Inc.	5.2
9	Single pump B	Hagen Elite 200	7.2
10	Double pump	Hagen Elite 802	12.6

From this data, it is evident that the light sources employed in the reaction are the greatest contributors to the total energy demand (Entries 1-3). In particular, the halogen lamp (Entry 1) consumes the greatest amount of energy of all the light sources investigated. Therefore the use of solar light as an alternative is proposed, which will facilitate saving up to 1556.4 kJ of energy per hour of irradiation.

The air pumps used to supply air to the reaction vessels are also electrical. However, the amount of energy required by these pumps is low, with an average requirement of 6 kJ/h for a single Schlenk flask reactor (Entries 8-10). The pump for larger reactions (Entry 7) requires a greater amount of energy, 72 kJ/h, but even this is low compared to the energy required by thermal equipment, such as the heating mantle (Entries 4-5).

Use of external cooling has also been investigated, using a fan. This is necessary for use in conjunction with the halogen lamp, which generates a considerable amount of heat. However, use of solar irradiation will also eliminate the need for external cooling.

2.2.5 Optimisation of reactor: use of microreactor technology

Of recent interest is the use of microreactors (also known as microstructured reactors or microchannelled reactors) in organic synthesis. In general, microstructured reactors consist of a solid support ('chip') with channels of only several micrometres in width and depth (10–1000 mm). The serpentine dwell device (Figure 35a) is suitable for use in both homogenous and heterogeneous systems. A falling film reactor has been specifically designed for heterogeneous liquid-gas reactions, which provides maximum interfacial region (Figure 35b).

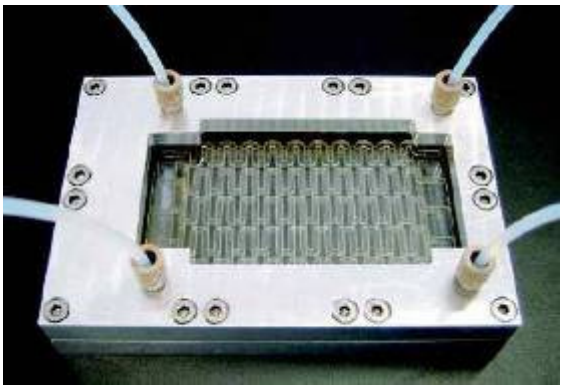
(a)  (b) 

Figure 35: (a) Dwell device (mikroglas) and (b) falling-film microreactor (source of image: IMM).

The application of microreactor technology for photochemical processes has been summarised in a review article, in particular outlining the suitability of these reactors for photochemistry[247]:

1. Uniform irradiation to the entire reaction solution can be achieved, due to the shallow depth of a microreactor (100–1000 mm), even for relatively concentrated solutions,
2. Continuous-flow operation facilitates ease of manipulation of reaction time ('residence time') when compared to batch conditions,
3. High heat transfer coefficients ensure efficient cooling of microstructured reactors,
4. Miniaturised light sources, such as LEDs, may be used, providing an energy-efficient alternative to conventional light sources,
5. Microchip designs allow on-line monitoring of the reaction, *e.g.* by UV-spectroscopic analysis of the effluent.

To evaluate the use of microreactor technology in juglone **98** synthesis a dwell device was utilised (Experiments 38-39). A solution of 1,5-dihydroxynaphthalene **97** and rose bengal **41** was presaturated with oxygen by bubbling with air. This was then introduced into the dwell device at a flow rate of 0.08 ml/min, which corresponds to a residence time of 21 minutes, and

irradiated from above using five LZC-Vis (cool white) lamps.The solution collected from the outlet was evaporated to dryness and analysed by ^{1}H NMR spectroscopy (DMSO-d_6). For these preliminary investigations conversions of up to 11% were observed. This suggests that further optimisation is necessary. It is believed that use of a falling film reactor may provide better results, as this will ensure a continuous supply of oxygen to the system.

2.3 Summary

This study has validated the parameters affecting the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** and shown that light and oxygen are necessary for this reaction to proceed. Some self-sensitisation can be observed, however use of sensitiser gives significantly increased yields.

Optimisation studies have shown that use of alcoholic solvents, in particular *i*-propyl alcohol or *t*-amyl alcohol offer a greener alternative to chlorinated solvents for this reaction. Juglone **98** is stable in these solvents under reaction conditions and over extended periods of time (up to 63 hours). The optimised purification procedure is the use of column chromatography, using a mixture of ethyl acetate and cyclohexane (1:3).

In addition, an assessment of the energy demand of the reaction equipment has shown that use of solar irradiation as an alternative to artificial light sources can offer considerable energy savings.

2.4 Experimental

2.4.1 Spectroscopic methods

2.4.1.1 NMR Spectroscopy

NMR spectra were recorded on (a) a Bruker 400 UltrashieldTM instrument (400 MHz for ^{1}H; 100 MHz for ^{13}C) or (b) a Bruker 600 UltrashieldTM instrument (600 MHz for ^{1}H; 150 MHz for ^{13}C) using the XWin-NMR 2.6 software. Chemical shift values are referred to solvent residual resonances: $CDCl_3$ (7.26/77.36 ppm), DMSO-d_6 (2.54/40.45 ppm) and acetone-d_6 (2.05/30.60 and 206.3 ppm). Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz.

2.4.1.2 IR Spectroscopy

IR spectra were recorded on (a) a Perkin-Elmer system 2000 FT-IR spectrometer as KBr discs or (b) a Perkin-Elmer Spectrum 100 FT-IR spectrometer using ATR (diamond).

2.4.1.3 UV Spectroscopy

UV spectra were recorded on a Varian Cary 50 UV-vis spectrophotometer in spectroscopic grade methanol or *i*-propyl alcohol.

2.4.1.4 Mass Spectrometry

Mass spectra were recorded with direct infusion using a BrukerDaltonics LC ion trap MS with an electrospray ionisation interface at atmospheric pressure (Bruker Daltonics, Coventry). Samples were introduced in mass spec. grade methanol or acetonitrile with formic acid.

2.4.2 Chromatography Methods

2.4.2.1 Column chromatography

Column chromatography was carried out using Merck silica gel 60 (particle size 0.063-0.200 nm for column chromatography) 70-230 mesh.

2.4.2.2 Thin Layer Chromatography (TLC)

Analytical thin-layer chromatography was performed on aluminium sheets coated with 0.20 mm of Fluka silica gel ITCL-cards with fluorescent indicator 254 nm, layer thickness: 0.2 mm. Visualisation was carried out under UV-lamp (245 nm and 366 nm).

2.4.3 Analytical Methods

2.4.3.1 Melting points

Melting points were determined in open capillaries using a Griffin Melting Point Apparatus and are uncorrected.

2.4.4 Photochemical experiments

2.4.4.1 Glassware

Photoreactions were performed in Schlenk tubes made of Pyrex® glass (50 ml, 100 ml and 350 ml). Photoreactions on solid supports were carried out in Petri dishes made of Pyrex® glass. This ensured that the cut-off wavelength for all irradiation experiments was 300 nm.

2.4.4.2 Reactors

For the irradiation experiments in artificial conditions, either one or two halogen lamps (500 W, IQ Group) were used (Figure 21). The reaction mixture, in a Schlenk flask, was constantly bubbled with a slow stream of air (O_2) and the leaving gas stream was allowed to exit through Teflon tube connected to the extraction system. To avoid overheating, a cold finger was used, which was cooled using water ($T < 25\ ^oC$).

For the irradiation experiments using UV light, an immersion well reactor fitted with a medium-pressure mercury lamp (400 W, Model 3040, Photochemical Reactors Limited), with a Pyrex® reaction flask was used (Figure 22b). In addition, a Rayonet photochemical chamber reactor (RPR200, Southern New England), fitted with 16 RPR-3000Å lamps (λ = 300±325 nm)) was used (Figure 22a).

For irradiation of solid supported reactions a Luzchem reactor (LZC-1 top irradiation model) with eight 12 inch 8 W LZC-VIS bulbs, equipped with a carousel, was used (Figure 68b).

2.4.4.3 Solvents and reagents

All solvents and starting materials were obtained from commercial suppliers (Sigma-Aldrich and Fluka) and were used without purification, except where stated.

2.4.5 Dark room reactions of 1,5-dihydroxynaphthalene

General procedure for the dark reaction of 1,5-dihydroxynaphthalene

Solutions of 1,5-dihydroxynaphthalene **97** (0.288 g, 1.80 mmol in 100 ml, 0.018 M) were prepared both with and without sensitiser in a dark room using a red light. These were bubbled with air in darkness for 4-12 hours. After this time a sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy (DMSO-d_6).

Experiment 1 (EC-084): Rose bengal in *i*-propyl alcohol, 4 h

The general procedure was followed, using rose bengal **41** (12 mg, 12 μmol) in *i*-propyl alcohol with irradiation for 4 hours. ^{1}H NMR spectroscopy (DMSO-d_6) showed that there was no evidence of juglone **98** formation.

Experiment 2 (EC-084): Sensitiser-free in *i*-propyl alcohol, 4 h

The general procedure was followed, using *i*-propyl alcohol and with irradiation for 4 hours. ^{1}H NMR spectroscopy (DMSO-d_6) showed that there was no evidence of juglone **98** formation.

Experiment 3 (EC-084): Rose bengal in *t*-amyl alcohol, 4 h

The general procedure was followed, using rose bengal **41** (12 mg, 12 μmol) in *t*-amyl alcohol with irradiation for 4 hours. ^{1}H NMR spectroscopy (DMSO-d_6) showed that there was no evidence of juglone **98** formation.

Experiment 4 (EC-084): Sensitiser-free in *t*-amyl alcohol, 4 h

The general procedure was followed, using *t*-amyl alcohol and with irradiation for 4 hours. ^{1}H NMR spectroscopy (DMSO-d_6) showed that there was no evidence of juglone **98** formation.

Experiment 5 (EC-084): Sensitiser-free in acetone, 4 h

The general procedure was followed, using acetone and with irradiation for 4 hours. ^{1}H NMR spectroscopy (DMSO-d_6) showed that there was no evidence of juglone **98** formation.

Experiment 6 (EC-084): Rose bengal in *t*-amyl alcohol, 12 h

The general procedure was followed, using rose bengal **41** (12 mg, 12 μmol) in *t*-amyl alcohol with irradiation for 12 hours. ^{1}H NMR spectroscopy (DMSO-d_6) showed that there was no evidence of juglone **98** formation.

2.4.6 pH study of the oxidation of 1,5-dihydroxynaphthalene

Experiment 7 (EC-186): Dark reaction of 1,5-dihydroxynaphthalene in pH 12 water

1,5-Dihydroxynaphthalene **97** (0.074 g, 0.46 mmol) was stirred in darkness at room temperature in water (50 ml, from a 500 ml stock adjusted to pH 12.2 using sodium hydroxide) for 4 hours. The resultant solution was extracted using ethyl acetate and the organic layer was dried using sodium sulfate, filtered, evaporated to dryness and analysed by ^{1}H NMR spectroscopy (acetone-d_6), which showed no evidence of juglone **98**.

Experiment 8 (EC-203): Recovery of juglone from pH 12 water

Juglone **98** (0.01 g, 0.06 mmol) was dissolved in an alkaline solution (30 ml, from a 500 ml stock adjusted to pH 12.2 using sodium hydroxide) and stirred vigourously. A colour change from orange to purple was observed. The solution was acidified using concentrated hydrochloric acid, and the solution returned to orange in colour and some precipitation occured. Juglone **98** was recovered by extraction using ethyl acetate and dried using sodium sulfate. The resultant orange solid was analysed by ^{1}H NMR spectroscopy (acetone-d_6), which showed that juglone **98** was recovered using this procedure.

Experiment 9 (EC-187): Photooxygenation of 1,5-dihydroxynaphthalene in pH 12 water

1,5-Dihydroxynaphthalene **97** (0.080g, 0.50 mmol) and rose bengal **41** (12 mg, 12 μmol) in water (50 ml, from a 500 ml stock adjusted to pH 12.2 using sodium hydroxide,) were irradiated, with air bubbling, for 4 hours using one 500 W halogen lamp. The resultant solution was extracted using ethyl acetate and the organic layer was dried using sodium sulfate, filtered,

evaporated to dryness and analysed by ^{1}H NMR spectroscopy (acetone-d_6), which showed no evidence of juglone **98**.

Experiment 10A (KJ-030): Photooxygenation of 1,5-dihydroxynaphthalene in pH 12 water (buffered) *See Appendix A.*

2.4.7 Oxygen-free synthesis

General procedure for oxygen-free synthesis of Juglone

1,5-Dihydroxynaphthalene **97** and rose bengal **41** were dissolved in degassed *t*-amyl alcohol and irradiated using one 500 W halogen lamp for 6 hours. After this time a sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy (acetone-d_6).

Experiment 11 (EC-177): Degassing using nitrogen

The general procedure was followed using 0.160 g (1.00 mmol) of 1,5-dihydroxynaphthalene **97** and rose bengal **41** (33 mg, 33 µmol) in 100 ml of *t*-amyl alcohol degassed by purging nitrogen gas for 1 hour. Nitrogen bubbling was carried out during reaction. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 10% was achieved.

Experiment 12 (EC-179): Degassing using helium

The general procedure was followed using 0.169 g (1.06 mmol) of 1,5-dihydroxynaphthalene **97** and 33 mg (33 µmol) of rose bengal **41** in 100 ml of *t*-amyl alcohol degassed by purging helium gas for 25 minutes. No air or nitrogen bubbling was applied during reaction. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 30% was achieved.

Experiment 13 (EC-204): Degassing using helium and nitrogen

The general procedure was followed using 0.080 g (0.50 mmol) of 1,5-dihydroxynaphthalene **97** and 25 mg (25 µmol) of rose bengal **41** in 50 ml *t*-amyl alcohol degassed by purging helium gas for 1 hour. Nitrogen bubbling was carried out during reaction. ^{1}H NMR spectroscopy (acetone-d_6) showed that no conversion occurred under these conditions.

2.4.8 Self-sensitised synthesis of juglone (sensitiser-free)

General procedure for self-sensitised synthesis of juglone

1,5-Dihydroxynaphthalene **97** was dissolved in *t*-amyl alcohol (10 mM) with sonication. The reaction mixture was irradiated, with air bubbling, for 6 hours. Solvent was removed by rotary evaporation and product purified by column chromatography using ethyl acetate:cyclohexane (1:3).

Experiment 14A (KJ-026): Self sensitisation using a halogen lamp *See Appendix A.*

Experiment 15A (KJ-026): Self sensitisation using a halogen lamp *See Appendix A.*

Experiment 16 (EC-103): Self sensitisation using a medium pressure mercury lamp

The general procedure was followed using technical grade starting material **97** (0.32 g, 0.20 mmol) and irradiation using a medium pressure mercury lamp (400 W) in an immersion well. Juglone **98** was isolated in 24% yield (0.082 g, 0.47 mmol).

Experiment 17 (EC-104): Self sensitisation using a Rayonet reactor (300 nm ±25)

The general procedure was followed using technical grade starting material **97** and irradiation in a Rayonet photoreactor using 300 (± 25) nm lamps. Juglone **98** was isolated in 19% yield.

Experiment 18 (EC-206): Sensitisation by juglone

1,5-Dihydroxynaphthalene **97** (0.080 g, 0.50 mmol) and juglone **98** (0.010 g, 0.057 mmol) were dissolved in *t*-amyl alcohol (50 ml) with sonication. The reaction mixture was irradiated, with air bubbling, using one 500 W halogen lamp for 4 hours. ^{1}H NMR spectroscopy (acetone-d_6) was used to determine ratio of juglone **98** to diol **97** before irradiation and after, and thus to evaluate degree of conversion, which showed that some additional juglone **98** was present, but not significantly greater than that in other self-sensitised reactions.

2.4.9 Sensitiser stability study

Experiment 19 (EC-183, AM-06): pH study in aqueous solutions

A stock solution of rose bengal **41** (0.127 g in 50 ml, 0.25 mM) was diluted to prepare aqueous solutions (50 ml) in the pH range 2-13. Acidic solutions were prepared using HCl adjustment and basic solutions prepared using NaOH adjustment. UV-vis spectrophotometry (450-600 nm) was used to monitor the maximum absorbance of rose bengal **41**.

Experiment 20 (EC-183, AM-06): pH study in water-methanol solutions

A stock solution of rose bengal **41** (0.127 g in 50 ml, 0.25 mM) was diluted to prepare solutions of water and methanol (1:1, 50 ml) in the pH range 2-13. Acidic solutions were prepared using HCl adjustment and basic solutions prepared using NaOH adjustment. UV-vis spectrophotometry (450-600 nm) was used to monitor the maximum absorbance of rose bengal **41**.

2.4.10 NMR spectroscopy solvent studies

^{1}H NMR spectra of juglone **98** were carried out in deuterated chloroform ($CDCl_3$), deuterated dimethylsulfoxide (DMSO-d_6) and deuterated acetone (acetone-d_6). The spectra were interpreted as shown below:

^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) = 6.96 (s, 2H, $\mathbf{H}_{quin.}$); 7.29 (d, 1H, $\mathbf{H}_{arom.}$, J^3 = 7.6 Hz, J^4 = 2.0 Hz); 7.67-7.61 (m, 2H, $\mathbf{H}_{arom.}$); 11.91 (s, 1H, O**H**).

^{1}H NMR (400MHz, DMSO-d_6) δ (ppm) = 7.07 (d, 1H, $\mathbf{H}_{quin}$, J^3 = 10.4 Hz); 7.10 (d, 1H, $\mathbf{H}_{quin}$, J^3 = 10.4 Hz); 7.37 (d, 1H, $\mathbf{H}_{arom}$, J^3 = 8.4 Hz, J^4 = 0.8 Hz); 7.52 (d, 1H, $\mathbf{H}_{arom.}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz); 7.77 (dd, 1H, $\mathbf{H}_{arom.}$, J^3 = 7.6 Hz); 11.78 (s, 1H, O**H**).

^{1}H NMR (400MHz, acetone-d_6) δ (ppm) = 7.04 (d, 1H, $\mathbf{H}_{quin.}$, J^3 = 10.4 Hz); 7.08 (d, 1H, $\mathbf{H}_{quin.}$, J^3 = 10.4 Hz); 7.33 (d, 1H, $\mathbf{H}_{arom.}$, J^3 = 8.4 Hz, J^4 = 1.2 Hz); 7.58 (d, 1H, $H_{arom.}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz); 7.78 (dd, 1H, $\mathbf{H}_{arom.}$, J^3 = 7.6 Hz, 8.4 Hz); 11.92 (s, 1H, O**H**).

Experiment 21 (EC-193): Stability of juglone in DMSO-d_6

A sample of juglone **98** was dissolved in DMSO-d_6 in a quartz cuvette. UV-vis spectrophotometry was used to measure the absorbance of the solution in the range 300-700 nm at intervals over an 8 hour period. There was a notable increase in absorbance at 421 nm, and a corresponding decrease in absorbance at 596 nm.

Experiment 22 (EC-178): Stability of juglone in DMSO-d_6

A sample of juglone **98** was dissolved in DMSO-d_6 and a ^{1}H NMR spectrum obtained within 2 hours. The sample was left overnight and a repeat spectrum obtained after 24 hours. This sample was stored at -20 °C for three weeks before analysis by UV-vis spectrophotometry. ^{1}H NMR spectroscopy (DMSO-d_6) showed degradation of juglone **98** and formation of 1,4,5-trihydroxynaphthalene **242**.

2.4.11 Optimisation of reaction solvent for the preparation of juglone

General procedure for assessment of reaction solvent

1,5-Dihydroxynaphthalene **97** (0.080 g, 0.50 mmol) and rose bengal **41** (12-13 mg, 12-13 μmol) were dissolved in reaction solvent (50 ml) with sonication. The reaction solution was irradiated, with air bubbling, for 4 hours using one 500 W halogen lamp. After this time a sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy (acetone-d_6).

Experiment 23 (EC-196): Methanol

The general procedure was followed using methanol. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion to juglone **98** was 22%.

Experiment 24 (EC-197): Ethanol

The general procedure was followed using ethanol. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion to juglone **98** was 30%.

Experiment 25 (EC-188): *i*-Propyl alcohol

The general procedure was followed using *i*-propyl alcohol. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion to juglone **98** was 32%.

Experiment 26 (EC-188): *t*-Amyl alcohol

The general procedure was followed using *t*-amyl alcohol. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion to juglone **98** was 39%.

Experiment 27 (EC-188): Acetone

The general procedure was followed using acetone. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion to juglone **98** was 14%.

Experiment 28 (EC-196): Ethyl acetate

The general procedure was followed using ethyl acetate. ^{1}H NMR spectroscopy (acetone-d_6) showed conversion to juglone **98** was 9.5%.

Experiment 29 (EC-205): Water

1,5-Dihydroxynaphthalene **97** (0.080 g, 0.50 mmol) was stirred in water (50 ml) in darkness at room temperature for 10 mins. Rose bengal **41** (20 mg, 20 μmol) was added to the reaction mixture, which was irradiated, with air bubbling, for 4 hours using one 500 W halogen lamp. After this time the organic components were extracted using ethyl acetate (50 ml). A sample (2 ml) of the organic layer was evaporated to dryness and analysed by ^{1}H NMR spectroscopy (acetone-d_6), which showed that conversion to juglone **98** was 11%.

2.4.12 Stability of juglone in reaction solvents

General procedure for juglone stability study

Juglone **98** was dissolved in reaction solvent (10 mM) with sonication. The reaction solution was irradiated, with air bubbling, using one 500 W halogen lamp. A sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy (acetone-d_6). TLC (ethyl acetate:cyclohexane 1:3) was used to assess purity.

Experiment 30 (EC-107): Stability in *i*-propyl alcohol with sensitiser

The general procedure was followed using juglone **98** (0.174 g, 1.00 mmol) and rose bengal **41** (50 mg, 49 μmol) in *i*-propyl alcohol (100 ml) and irradiation for 4 hours. ^{1}H NMR

spectroscopy (acetone-d_6) showed no evidence of degradation products. TLC showed only the characteristic juglone **98** spot (Rf = 0.6).

Experiment 31 (EC-106): Stability in *t*-amyl alcohol with sensitiser

The general procedure was followed using juglone **98** (0.174 g, 1.00 mmol) and rose bengal **41** (50 mg, 49 μmol) in *t*-amyl alcohol (100 ml) and irradiation for 4 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed no evidence of degradation products. TLC showed only the characteristic juglone **98** spot (Rf = 0.6).

Experiment 32 (EC-199): Stability in *i*-propyl alcohol without sensitiser

The general procedure was followed using *i*-propyl alcohol and irradiation for 63 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed trace amounts of a degradation product. TLC showed the characteristic juglone **98** spot (Rf = 0.6).

Experiment 33 (EC-199): Stability in *t*-amyl alcohol without sensitiser

The general procedure was followed using *t*-amyl alcohol and irradiation for 63 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed trace amounts of a degradation product. TLC showed only the characteristic juglone **98** spot (Rf = 0.6).

2.4.13 Optimisation of reaction work-up (purification)

General procedure for work-up using Soxhlet extraction

Juglone **98** (0.17 g, 1.0 mmol) was adsorbed onto silica (one heaped spatula) and extracted overnight in a Soxhlet apparatus using 200 ml of solvent. Solvent was removed by rotary evaporation and the recovered yield determined by mass.

Experiment 34 (EC-096): *n*-Hexane

The general procedure was followed using *n*-hexane. Juglone **98** was recovered in 84% yield as a brown orange solid.

Experiment 35 (EC-096): Cyclohexane

The general procedure was followed using cyclohexane. Juglone **98** was recovered in 46% yield as a brown orange solid with some black charring.

General procedure for work-up using column chromatography

A silica column of inner diameter 2 cm and length 25 cm was prepared using the mobile phase under investigation. Juglone **98** (0.10 g, 0.57 mmol) was flushed through the column and the collected fraction reduced to dryness by rotary evaporation. The recovered yield of juglone **98** was determined by mass.

Experiment 36 (EC-097): Chloroform

The general procedure was followed using chloroform. Juglone **98** was recovered in 96% yield as an orange-brown solid.

Experiment 37 (EC-097): Ethyl acetate:cyclohexane

The general procedure was followed using ethyl acetate:cyclohexane (1:3). Juglone **98** was recovered in 96% yield as a bright orange solid.

2.4.14 Optimisation of reactor: use of microreactor technology

General procedure for reactions in dwell device microreactor

1,5-Dihydroxynaphthalene **97** and rose bengal **41** were dissolved in *t*-amyl alcohol with sonication, then saturated with oxygen by bubbling air for 1 hour. The reaction solvent was introduced into the dwell device at a flow rate of 0.08 ml/min and irradiated from above using five LZC-Vis (cool white) lamps. The solution was collected at the outlet and evaporated to dryness before analysis by ^{1}H NMR spectroscopy (DMSO-d_6).

Experiment 38 (EC-083): Without filtration

The general procedure was followed using 1,5-dihydroxynaphthalene **97** (0.057 g, 0.36 mmol) and rose bengal **41** (10 mg, 10 μmol) in *t*-amyl alcohol (20 ml). Reaction solution was not filtered before entering the pump. Some precipitate was observed in the channels as the reaction progressed. ^{1}H NMR spectroscopy (DMSO-d_6) showed a conversion of 11%.

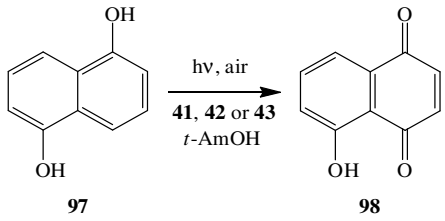
Experiment 39 (EC-087): With filtration

The general procedure was followed using using 1,5-dihydroxynaphthalene **97** (0.029 g, 0.18 mmol) and rose bengal **41** (3 mg, 3 μmol) in *t*-amyl alcohol (10 ml). Reaction solution was filtered by passing through a sparger before entering the pump. ^{1}H NMR spectroscopy (DMSO-d_6) showed a conversion of 7%.

Chapter 3 Sensitiser studies.

3.1 Introduction

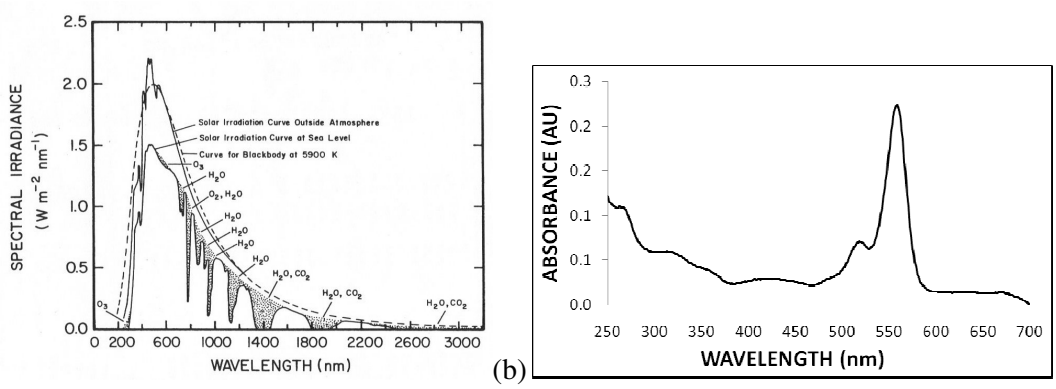
As outlined in Chapter 1, there are many sensitisers available for use in singlet oxygen production. The most commonly encountered of these are rose bengal **41**[54, 55, 80, 248], methylene blue **42**[182, 184] and tetraphenylporphyrin (TPP) **43**[55, 194]. Although TPP **43** is the most effective singlet oxygen generator[249], it is less commonly used than rose bengal **41** due to solubility difficulties. TPP **43** is primarily soluble in halogenated or nonpolar solvents and virtually insoluble in alcohols[55]. It was therefore necessary to carry out a sensitiser study, to assess the most suitable sensitiser for use in the synthesis of juglone **98** through the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** (Scheme 83).



97 **98**

Scheme 83: Synthesis of juglone 98 **using different sensitisers.**

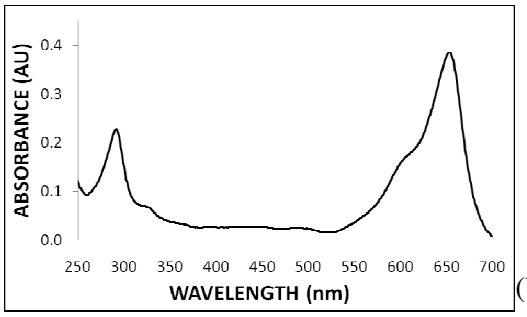
Use of rose bengal **41** as a sensitiser for the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** to form juglone **98** has been reported in several studies[54, 56]. This sensitiser was chosen as it has an excellent overlap with the solar spectrum (Figure 36).



(a) (b)

Figure 36: (a) Solar sectrum and (b) UV-vis spectrum of rose bengal 41 **(in methanol).**

Methylene blue **42**[56, 182, 184] and tetraphenylporphyrin **43**[28] also have absorbance maxima that overlap well with the visible solar spectrum (Figure 37).

(a) 

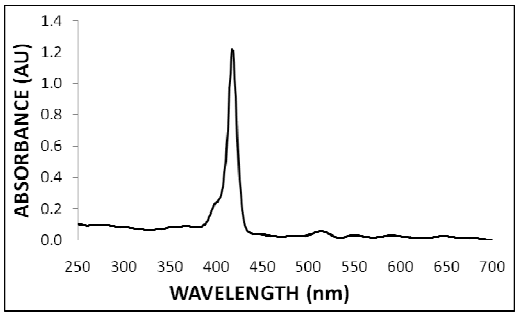
(b) 

Figure 37: UV-vis spectrum of (a) methylene blue 42 **(in methanol) and (b) tetraphenylporphyrin** 43 **(in dichloromethane).**

Solid supported sensitisers have been proposed as alternatives to homogeneous systems[250]. Although use of solid supports (heterogeneous conditions) often results in slower reaction rates, there are many advantages over homogeneous mixtures; (a) less dimerisation of sensitiser, giving less self-quenching (in the case of porphyrins and phthalocyanines), (b) photostability of the sensitiser is increased, (c) greater choice of solvents for reactions, and (d) ease of purification and reuse[194, 250]. Early studies of photooxygenations using solid supported sensitisers have looked at use of rose bengal **41**[248, 251], e.g. rose bengal on Merrifield resin (Sensitox^{TM}), or methylene blue on an ion exchange resin[252]. The use of solid supported rose bengal **41** and methylene blue **42** in the synthesis of juglone **98** have been reported, but were shown to give significantly lower yields than the homogeneous system[55].

3.2 Results and Discussion

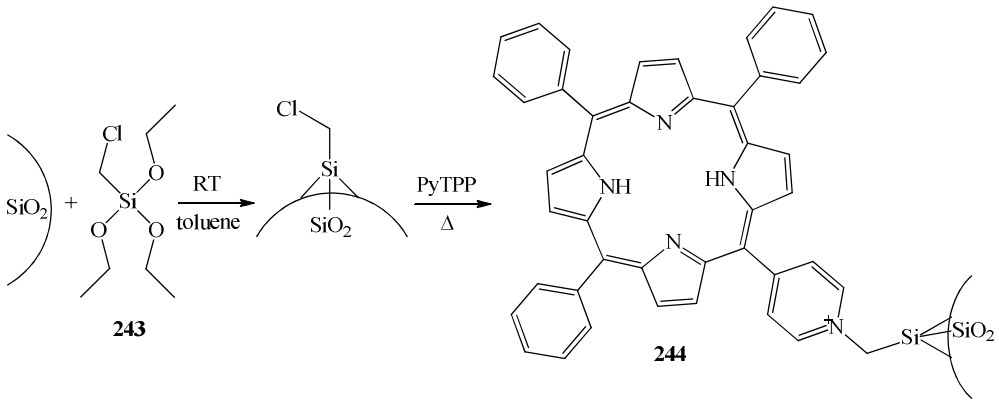
3.2.1 Homogeneous sensitiser studies

Following the optimisation of solvent for dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97**, *t*-amyl alcohol was used for further studies. However, it was then necessary to optimise the sensitiser used for this reaction.

Tetraphenylporphyrin **43** could not be used in *t*-amyl alcohol, as this was completely insoluble. Methylene blue **42** was also insoluble in *t*-amyl alcohol, this may be due to the largely non-polar nature of the solvent and the ionic nature of the sensitiser. Rose bengal **41** was sparingly soluble with sonication, and so was used in studies in *t*-amyl alcohol. Conversion of 39% was achieved following 4 hours of artificial irradiation when rose bengal **41** is used in the synthesis of juglone **98** in *t*-amyl alcohol (Section 2.2.3.1, Table 6, Experiment 26). The optimum concentrations used were 10 mM 1,5-dihydroxynaphthalene **97** with of 0.30-0.50 mM rose bengal **41**.

3.2.2 Synthesis of juglone using solid-supported sensitisers

Since TPP **43** cannot be used in *t*-amyl alcohol we explored the possibility of using an immobilised porphyrin. A silica-supported sensitiser **244** was synthesised by following the procedure reported by Kitamura, in which triphenylpyridylporphyrin (PyTPP) was covalently bonded to silica beads (diameter 35-60 μm), in toluene, using chloromethyltriethoxysilane **243** as a silane coupling reagent (Scheme 84)[253].



Scheme 84: Synthesis of silica-supported PyTPP sensitiser 244 **(Experiment 40).**

Using this method 5 mg of sensitiser was added to one gram of silica. The silica particles after modification were yellow, indicating successful addition of PyTPP to the beads.

This silica-supported PyTPP sensitiser **244** was used under optimised conditions (*t*-amyl alcohol, 4 hours, Experiment 41) to synthesise juglone **98** in 56% yield. Results were compared to those reported by Suchard using rose bengal **41** on a Merrifield support (RB_{MF}, Sensitox®) and methylene blue **42** on an ion exchange resin (MB_{IE}), as shown in Table 10[55].

Table 10: Comparison of solid supported sensitisers for juglone 98 **synthesis (Experiment 41).**

Sensitiser	Solvent	O_2 source	Time (h)	Yield (%)
SiO_2-PyTPP **244**	*t*-amyl alcohol	Air	4	56
RB_{MF}	*i*-propyl alcohol	Pure O_2	5	25[57]
RB_{MF}	*i*-propyl alcohol	Air	10	21[57]
MB_{IE}	*i*-propyl alcohol	Pure O_2	5	34[57]
MB_{IE}	*i*-propyl alcohol	Air	10	45[57]

This showed that the silica-supported sensitiser **244** gave greater yields of juglone **98** in a shorter duration, compared to other solid supported sensitisers. Interestingly, this yield is similar to that achieved using rose bengal **41** in solution. Use of silica-supported porphyrins does offer

a means to use porphyrins in the synthesis of juglone **98** in *t*-amyl alcohol. However, the starting material, triphenylpydriylporphyrin (PyTPP) is quite difficult to obtain, as it is very difficult to isolate this material. As a result, it is not possible to produce this sensitiser on a large scale. However, further studies should look at the reuse and recycling of this substance, as well as the use of other, more accessible analogues of TPP. In particular, use of water or alcohol soluble porphyrins should enhance the efficiency of this reaction.

3.2.3 Mixed sensitiser study

Following a study of individual sensitisers, specifically rose bengal **41**, methylene blue **42** and tetraphenylporphyrin **43**, it was proposed to investigate the use of mixed sensitisers in the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97**.

This should enable utilisation of a greater amount of the visible spectrum and enhance efficiency of the system. To ensure solubility of all sensitisers, acetone was used as solvent, rather than alcohols. Two different methods of determining the optimum ratio of sensitisers were investigated, the first based on relative extinction coefficients and second based on molar amounts.

Commercially available rose bengal **41** and methylene blue **42** were utilised, while tetraphenylporphyrin **43** was synthesised from pyrrole and benzaldehyde (Experiment 42).

3.2.3.1 Using quantities based on extinction coefficients

Individual UV-vis spectra of rose bengal **41**, methylene blue **42** and tetraphenylporphyrin **43** were measured in acetone and used to determine the extinction coefficients using the Beer-Lambert law. The extinction coefficients were determined for each sensitiser (at), and used to determine a ratio at which each sensitiser contributes equal absorbance. Using these values an approximate ratio of sensitisers was determined (Table 11).

Table 11: Determination of extinction coefficient for sensitisers in acetone.

Sensitier	Amount (mol)	Dilution	λ_{max}	Absorbance (for λ_{max})	ε (for λ_{max})	Ratio
Rose bengal **41**	2.456×10^{-4}	1 in 100	550	0.340	135161	1.39
Methylene blue **42**	2.5155×10^{-4}	1 in 100	640	0.234	97204	1.00
Tetraphenylporphyrin **43**	2.4073×10^{-4}	1 in 10	417	0.977	24307	0.25

Each of the sensitisers were used individually in acetone for synthesis of juglone **98** from 1,5-dihydroxynaphthalene **97**, the results of which are shown in Table 12.

Table 12: Conversion after 4 h irradiation in acetone using ratios based on extinction coefficient (Experiments 43-45).

Expt. No.	Sensitiser	Amount (mg)	Amount (μmol)	Conversion (%)
43	Rose bengal	9.0	8.8	7
44	Methylene blue	3.9	12.2	11
45	Tetraphenylporphyrin	30.0	48.8	57

A UV-vis spectrum of all three sensitisers in the ratio based on extinction coefficient was obtained (Figure 38), this showed that there was significant absorbance in the region 400-430 nm.

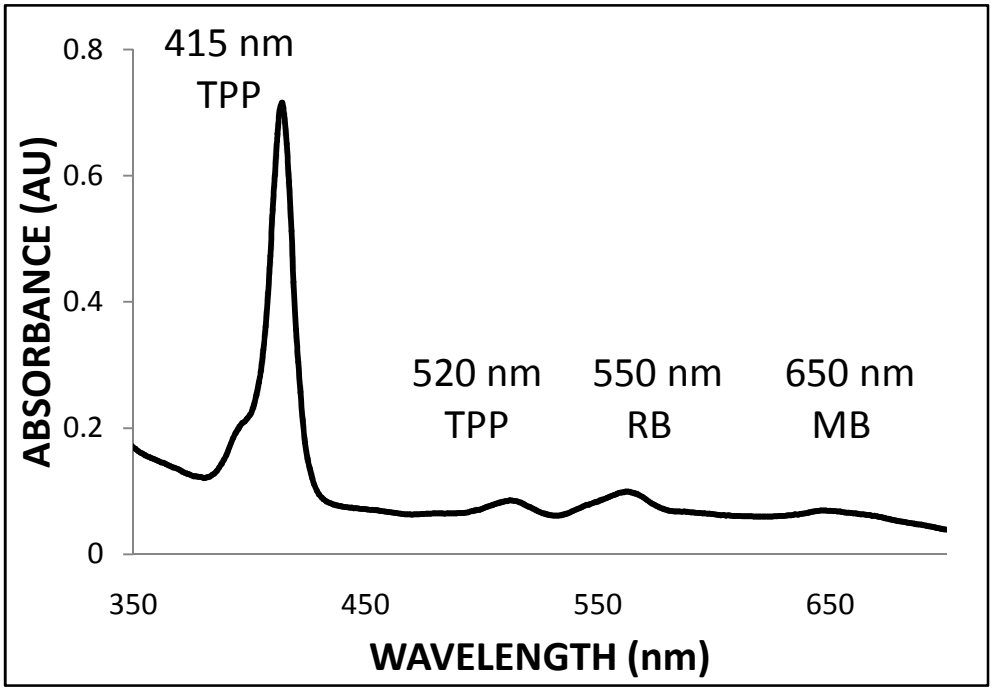


Figure 38: UV-vis spectrum of mixed sensitisers (concentration based on relative extinction coefficient) in acetone.

The synthesis of juglone **98** was then carried out using the sensitisers in this ratio and conversion monitored by ^{1}H NMR spectroscopy (Experiment 46). Some undissolved TPP **43** was evident at the bottom of the flask. After 4 hours of irradiation, no conversion to juglone **98** was observed. Despite the increased amounts of sensitiser compared to single component systems the process was completely impeded. This may be attributed to the aggregation of sensitisers, which is a deactivating process that can occur at higher concentrations. In addition, the increased amount of sensitiser may be causing quenching of the singlet oxygen before it may react with starting material molecules.

3.2.3.2 Using quantities based on molar ratio

To assess the use of sensitisers in a molar ratio each of the sensitisers were used individually for synthesis of juglone **98** from 1,5-dihydroxynaphthalene **97**, then two-component mixtures were investigated. ^{1}H NMR spectroscopy (acetone-d_6) was used to monitor conversion after four hours, the results of which are shown in Table 13.

Table 13: Conversion after 4 h irradiation in acetone using ratio based on molar ratio (Experiments 47-53).

Expt. No.	Sensitiser(s)	Concentration (M)	Conversion (%)
47	None	-	3
48	Rose bengal **41**	2.456×10^{-5}	12
49	Methylene blue **42**	2.456×10^{-5}	11
50	Tetraphenylporphyrin **43**	2.456×10^{-5}	69
51	Rose bengal **41** and Methylene blue **42**	2.456×10^{-5} each	16
52	Rose bengal **41** and tetraphenylporphyrin **43**	2.456×10^{-5} each	34
53	Methylene blue **42** and tetraphenylporphyrin **43**	2.456×10^{-5} each	52

A UV-vis spectrum of all three sensitisers in equimolar ratio was obtained (Figure 39), this showed that there was significant absorbance in the region 400-430 nm, accompanied by absorbance maxima in the region 500-540 and 540-600 nm.

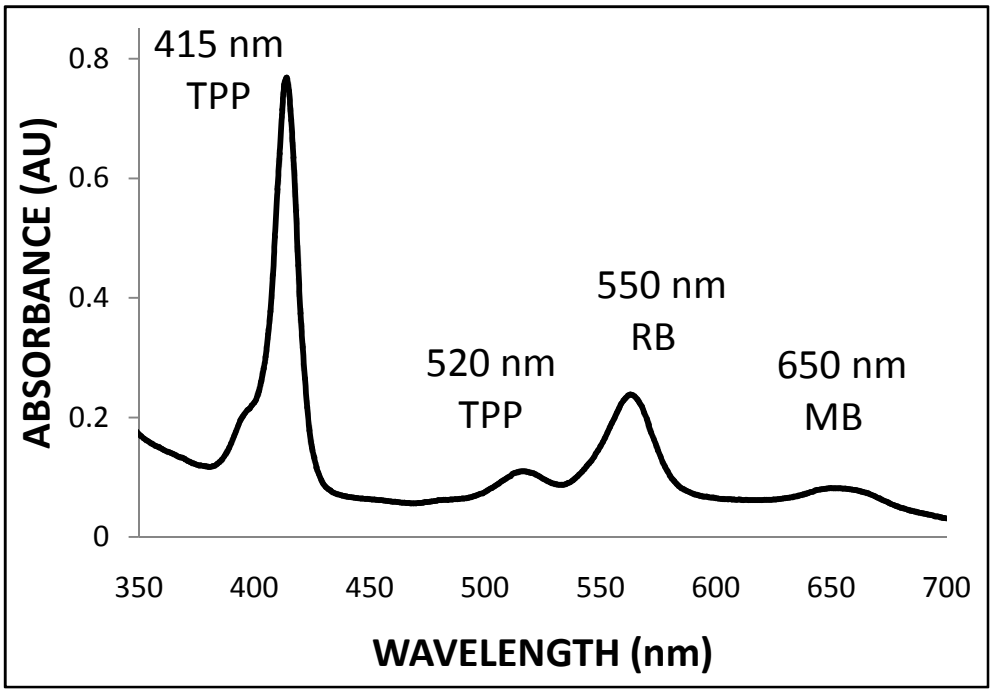


Figure 39: UV-vis spectrum of mixed sensitisers based on molar amounts.

The synthesis of juglone **98** was then carried out using the sensitisers in this ratio and conversion monitored by ^{1}H NMR spectroscopy (acetone-d_6). After 4 hours of irradiation, a conversion of 39% was achieved (Experiment 54). This value is lower than that achieved using TPP **43** alone (69%) or a mixture of TPP **43** and methylene blue **42** (52%). As detailed in Section 3.2.3 above, this may be due to aggregation of the sensitisers at higher concentrations.

3.2.3.3 Assessing concentration effects using mixed sensitisers

To assess the affect of concentration of sensitisers on reaction progress a 1 in 3 dilution of sensitisers was carried out prior to photooxygenation of 1,5-dihydroxynaphthalene **97** (Experiment 55). This ensured that the total sensitiser concentration in the three-component mixture was equal to the total concentration in the one-component solutions assessed in Section 3.2.3.2 above. Following four hours of irradiation a conversion of 26% was achieved. This is lower than that achieved when the concentration of sensitisers was three times greater. This indicates that the decrease in efficiency with mixtures of sensitisers is not due only to concentration effects. This reduction in efficiency may be due to unfavourable interactions between the sensitisers, causing deactivation.

To determine whether or not interaction between sensitisers occurred, mixtures of tetraphenylporhyrin **43** with rose bengal **41** and methylene blue **42** were compared to spectra of the sensitisers alone (Experiment 56). No evidence of interactions was observed (Figure 40), and no shift was observed in the absorbance maxima of tetraphenylporphyrin **43**.

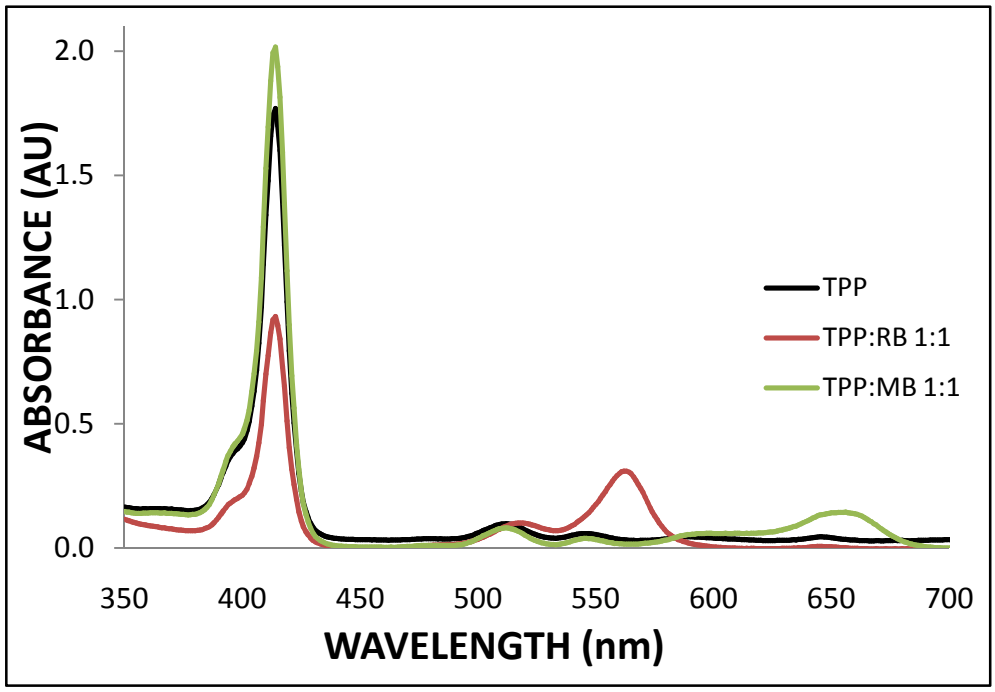


Figure 40: UV-vis spectrum to assess interactions of TPP 43 **with rose bengal** 41 **and methylene blue** 42 **(Experiment 56).**

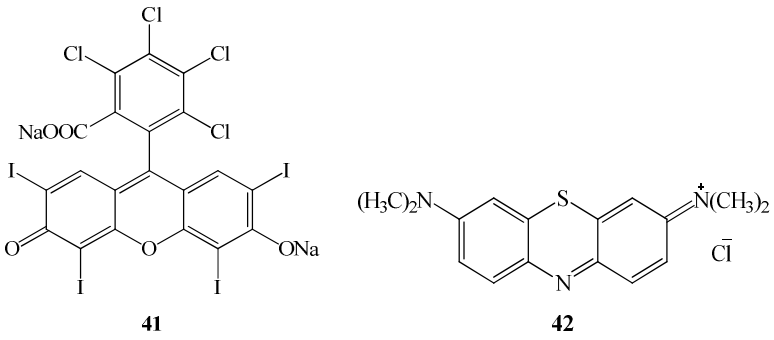
This suggests that the decrease in efficiency observed in this study may be due to interactions of rose bengal **41** and methylene blue **42** with the solvent, acetone.

3.3 Summary

Studies of sensitisers in *t*-amyl alcohol show that for homogeneous systems only rose bengal **41** is soluble and therefore suitable for use in further studies. However, use of a silica-supported porphyrin sensitiser **244** gives similar results, and may offer a heterogeneous alternative. This shows potential as a green method, as the reaction work-up can be simplified greatly. However, this sensitiser cannot be prepared in large quantities, as the starting material triphenylpyridylporphyrin is very difficult to isolate and as a result cannot be obtained easily. For this reason, this sensitiser is not used for further studies in this work.

Acetone was chosen as an alternative to alcohols for a study of mixed sensitisers, as all three sensitisers could be dissolved in this solvent. To overcome solubility difficulties, use of alcohol-soluble porphyrins should be investigated.

As demonstrated in Table 6 in Chapter 2 (Section 2.4.11 above) conversion achieved in acetone is considerably lower than that achieved in alcohols when using rose bengal **41** as the sensitiser. Using TPP **43** alone, conversions are higher than in the paired mixtures, indicating that rose bengal **41** and methylene blue **42** are causing unfavourable interactions resulting in a decreased conversion. Rose bengal **41** and methylene blue **42** are both ionic species which have reactive functional groups that may undergo reaction with other species present in the reaction mixture (Figure 41). This may lead to a quenching effect, with the sensitisers undergoing deactivating interactions with the solvent.



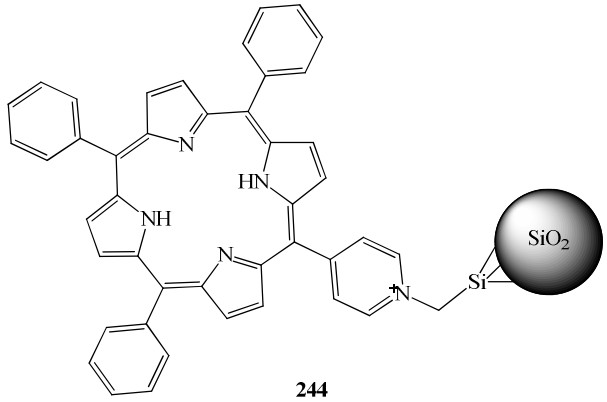
41 **42**

Figure 41: Structure of (a) rose bengal 41 **and (b) methylene blue** 42**.**

3.4 Experimental

3.4.1 Synthesis of juglone using solid-supported sensitisers

Experiment 40 (EC-089): Synthesis of slica-supported TPP derivative, method by Kitamura[253]



244

Silica (1.0 g) and chloromethyltriethoxysilane **243** (0.80 ml, 38 mmol) were stirred in toluene at room temperature for 2 hours. Monopyridyltriphenylporphyrin (5 mg, 8 μmol) was added and the mixture refluxed for 3 hours. The resulting mixture was filtered and washed with toluene, then dried under vacuum to yield yellow silica beads **244** (1.04 g).

The appearance was consistent with the description by Kitamura[253].

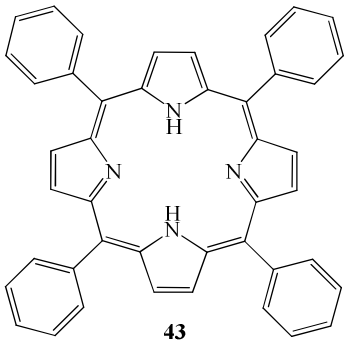
Experiment 41 (EC-090): Synthesis of juglone using a silica-supported sensitiser

1,5-Dihydroxynaphthalene **97** (0.14 g, 0.87 mmol) was dissolved in *t*-amyl alcohol (50 ml) with sonication, before addition of sensitiser (PyTPP-SiO_2 **244**, ca. 1 g). The reaction mixture was irradiated with stirring and air bubbling for 4 hours using one halogen lamp. The sensitiser **244** was recovered by filtration after reaction and the product was purified using column chromatography (ethyl acetate: cyclohexane 1:3) to isolate juglone **98** in 56% yield (0.091 g, 0.52 mmol) as an orange-brown solid.

TLC (ethyl acetate-cyclohexane 1:3) showed a single yellow spot (R_f = 0.56) corresponding to juglone **98**, indicating that pure product was obtained.

3.4.2 Mixed sensitiser study

Experiment 42 (EC-004): Synthesis of tetraphenylporphyrin (TPP), using method by Adler[254]



43

A solution of pyrrole (1.1 ml, 0.016 mol) and benzaldehyde (1.6 ml, 0.016 mol) in propionic acid (52 ml) was refluxed for 2 hours with vigorous stirring. The dark purple-black solution was cooled to room temperature and the product collected by vacuum filtration. The product **43** was purified by multiple washings with methanol to isolate TPP **43** in 18% yield (0.439 g, 0.714 mmol) as a shiny purple solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = -2.77 (s, 2H, N**H**); 7.75 (dd, 12H, $\mathbf{H}_{arom.}$, J^3 = 7.0 Hz); 8.23 (d, 8H, $\mathbf{H}_{arom.}$, J^3 = 7.0 Hz); 8.85 (s, 8H, $\mathbf{H}_{pyrrole}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 144.7; 145.0; 148.3; 148.5; 153.8; 153.8; 159.3; 168.0; 168.1; 178.0; 178.1; 179.3; 188.0; 190.5; 200.9; 202.0.

CAS no. 917-23-7, spectral data consistent with literature.

3.4.2.1 Ratio based on extinction coefficients

General procedure for the study of mixed sensitisers based on extinction coefficient

1,5-Dihydroxynaphthalene **97** (0.080 g, 0.50 mmol) and sensitiser were dissolved in acetone (50 ml) and irradiated, with air bubbling, for 4 hours. A sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy to determine conversion.

Experiment 43 (EC-195): Use of rose bengal

The general procedure was followed using rose bengal **41** (9 mg, 9 μmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 7%.

Experiment 44 (EC-184): Use of methylene blue

The general procedure was followed using methylene blue **42** (3.9 mg, 12 μmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 11%.

Experiment 45 (EC-194): Use of tetraphenylporhyrin

The general procedure was followed using tetraphenylporphyrin **43** (30 mg, 48 μmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 57%.

Experiment 46 (EC-198): Use of rose bengal, methylene blue and tetraphenylporphyrin

The general procedure was followed using rose bengal **41** (9 mg, 9 μmol), methylene blue **42** (3.9 mg, 12 μmol) and tetraphenylporphyrin **43** (30 mg, 48 μmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** did not occur.

3.4.2.2 Ratio based on molar ratio

General procedure for the study of mixed sensitisers based on molar ratios

1,5-Dihydroxynaphthalene **97** (0.080g, 0.50 mmol) and sensitiser (12 μmol each) were dissolved in acetone (50 ml) and irradiated, with air bubbling, for 4 hours. A sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy to determine conversion.

Experiment 47 (EC-182): Self-sensitised formation of juglone in acetone

The general procedure was followed without using any sensitiser. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 3%.

Experiment 48 (EC-183): Use of rose bengal

The general procedure was followed using rose bengal **41** (12.5 mg, 12.5 µmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 12%.

Experiment 49 (EC-184): Use of methylene blue

The general procedure was followed using methylene blue **42** (3.9 mg, 12 µmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 11%.

Experiment 50 (EC-185): Use of tetraphenylporphyrin

The general procedure was followed using tetraphenylporphyrin **43** (7.5 mg, 12 µmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 69%.

Experiment 51 (EC-189): Use of rose bengal and methylene blue

The general procedure was followed using rose bengal **41** (12.5 mg, 12.5 µmol) and methylene blue **42** (3.9 mg, 12 µmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 16%.

Experiment 52 (EC-190): Use of rose bengal and tetraphenylporphyrin

The general procedure was followed using rose bengal **41** (12.5 mg, 12.5 µmol) and tetraphenylporphyrin **43**. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 34%.

Experiment 53 (EC-191): Use of methylene blue and tetraphenylporphyrin

The general procedure was followed using methylene blue **41** (3.9 mg, 12 µmol) and tetraphenylporphyrin **43** (7.5 mg, 12 µmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 52%.

Experiment 54 (EC-192): Use of rose bengal, methylene blue and tetraphenylporphyrin

The general procedure was followed using rose bengal **41** (12.5 mg, 12.5 μmol), methylene blue **42** (3.9 mg, 12 μmol) and tetraphenylporphyrin **43** (7.5 mg, 12 μmol). ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 39%.

3.4.2.3 Concentration effect using mixed sensitisers

Experiment 55 (EC-200): Use of rose bengal, methylene blue and tetraphenylporphyrin

1,5-Dihydroxynaphthalene **97** (0.080 g, 0.50 mmol) and sensitisers (4 μmol each) were dissolved in acetone (50 ml) and irradiated, with air bubbling, for 4 hours. A sample (2 ml) was evaporated to dryness and analysed by ^{1}H NMR spectroscopy, which showed that conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** was 26%.

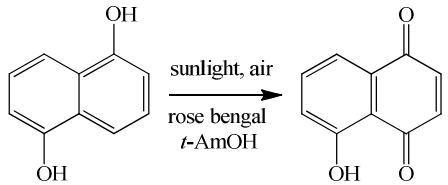
Experiment 56 (EC-202): Interactions of rose bengal and methylene blue with tetraphenylporhyrin

Stock solutions of 0.1 mM rose bengal **41**, methylene blue **42** and tetraphenylporphyrin **43** were prepared in acetone. Individual spectra in the region 350-750 were obtained for each sensitiser. Solutions consisting of TPP **43** and RB **41** (1:1) and TPP **43** and MB **42** (1:1) were prepared and the resultant spectra measured.

Chapter 4 Juglone as a model synthesis: solar studies.

4.1 Introduction

The solar synthesis of juglone **98** was investigated using the validated and optimised conditions for solvent and sensitiser from Chapter 2 and Chapter 3 (Scheme 85). A study of the energy usage of artificial light sources showed that this was a key contributor to the high energy demand of the synthesis. To overcome this disadvantage, a study of the use of solar conditions, in particular Irish sunlight, in the synthesis of juglone **98** was carried out.



97 **98**

Scheme 85: Solar synthesis of juglone 98 **using optimised solvent and sensitiser.**

Dublin City University is located at latitude 53° 23' 08" N, longitude 6° 15' 19" W and elevation 167 m above sea level (Figure 42). MET Eireann data reports that the Dublin Airport weather monitoring site receives on average 1437.8 hours per year of sunlight (averaged for 1978-2008). However, up to 60% of Irish sunlight is diffuse in nature. Small scale experiments in *i*-propyl alcohol and acetone have demonstrated that solar photooxygenations in Irish sunlight conditions are practicable for synthesis of juglone **98**[55].

Figure 42: Location of Dublin City University (Ref: Google Earth).

The use of a reactor which can utilise diffuse sunlight is essential in Ireland, as a large proportion of our sunlight is diffuse in nature. Use of a standard Schlenk flask or a flatbed reactor enables utilisation of both direct and diffuse components of solar irradiance.

Use of a concentrating reactor was investigated at the German Aerospace Centre, Cologne, Germany, located at latitude 50° 51' N, 7° 07' E and 70 m above sea level. This site is situated at a latitude close to that of Dublin City University (Figure 43), and gets a similar number of sunlight hours per year (Deutscher Wetterdienst record 1400-1550 sunlight hours per year, averaged between 1961-1990). The results of a study in August 2007 were compared to results from August 2005 and August 2003.

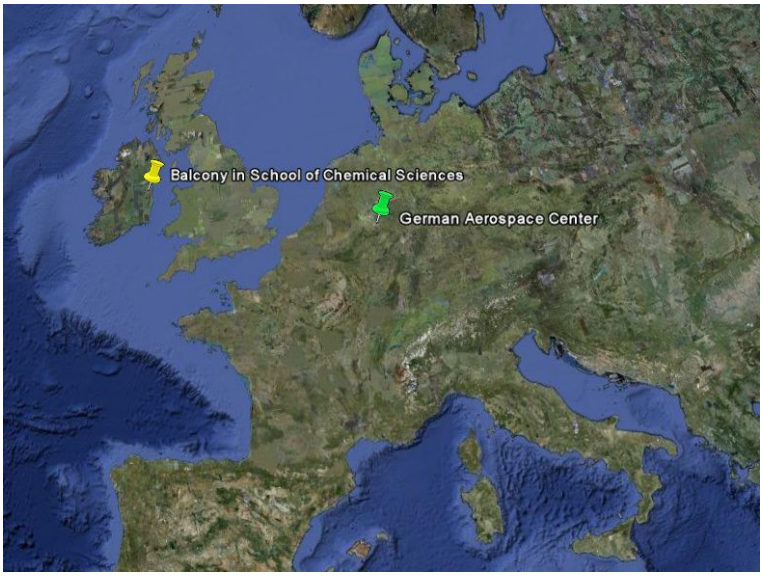
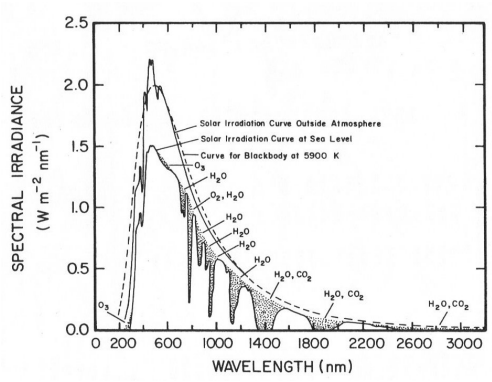


Figure 43: Location of Dublin City University and German Aerospace Centre (Ref: Google Earth).

Juglone **98** synthesis under solar conditions tends to give higher yields compared to those from artificial light sources. This has been attributed to the self-sensitisation of the diol **97** under UV conditions (< 350 nm), as well as the better overlap of solar emission (Figure 25) and dye absorbance spectra. However, the absorbance of rose bengal **41** in the solar spectrum is far greater than that of 1,5-dihydroxynaphthalene **97**, and so the photooxygenation process rather than the self-sensitised process dominates. The solar spectrum overlaps with the absorbance of rose bengal **41** (300-700 nm, Figure 44b) to a higher degree than the halogen lamp (400-700 nm, Figure 44a). Therefore, sunlight can irradiate in the region 300-400 nm and cause self-sensitisation of the starting material **97**, which does not occur for the artificial irradiation using halogen lamps. In addition, the intensity of sunlight is several orders of magnitude greater than that of artificial light sources.

(a) 

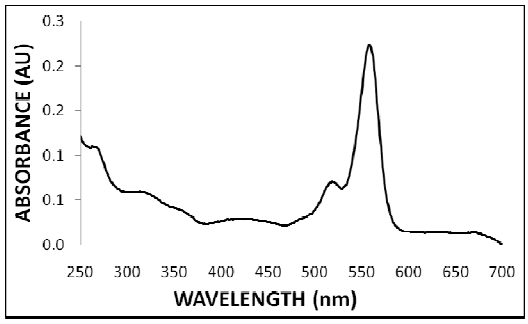
(b) 

Figure 44: (a) Solar spectrum and (b) UV-vis spectrum of rose bengal 41 **(in methanol).**

Juglone **98** has a weak absorbance at 400 nm and therefore may be excited by solar irradiation (Figure 45).

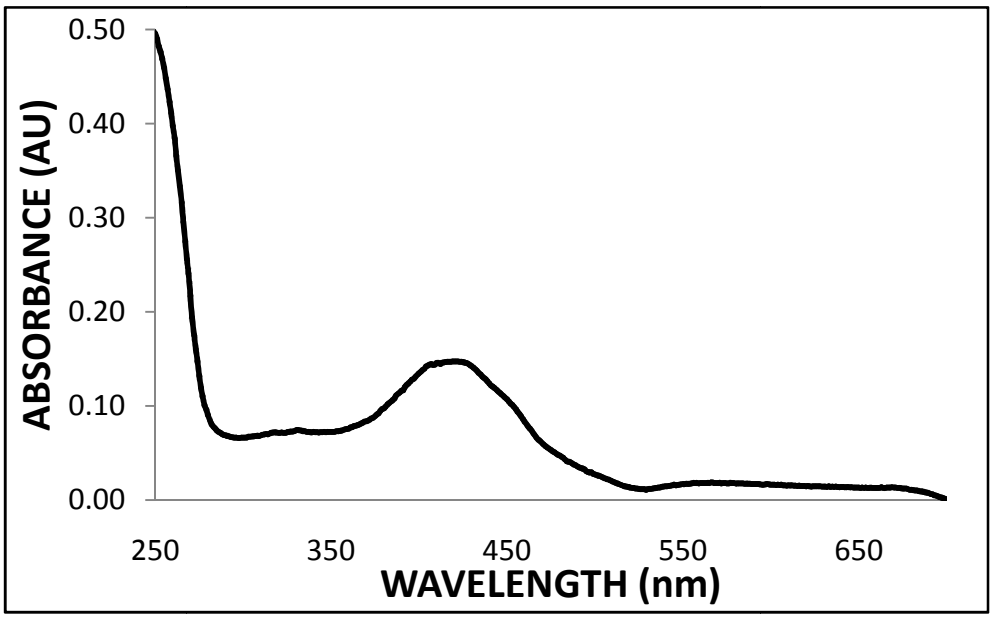
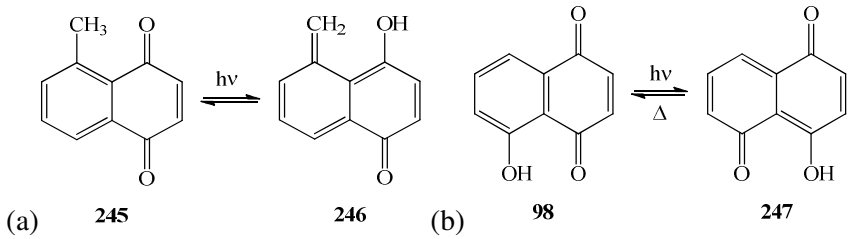


Figure 45: UV-vis spectrum of juglone 98 (in methanol).

However, the excited state juglone does not appear to compete with the photooxygenation process, instead it undergoes a deactivating, i.e. non-productive, keto-enol tautomerisation. This keto-enol tautomerisation has been reported for the related compound, 5-methyl-1,4-naphthoquinone **245** (Scheme 86) and has been confirmed by flash photolysis studies[255, 256].



Scheme 86: Keto-enol tautomerisation of (a) 5-methyl-1,4-naphthoquinone 245 **and (b) juglone** 98**.**

In addition, decomposition of juglone **98** has been observed under prolonged UV irradiation[55, 184]. This degradation has not been observed for halogen lamps, due to the fact that they do not emit light in the UV region.

4.2 Results and Discussion

4.2.1 Definition of weather conditions

Although on-site weather monitoring facilities were not available, records of sunlight conditions were taken every 15-60 minutes during solar reactions. These records were compared to data from MET Eireann regarding total irradiance and diffuse irradiance at the Dublin Airport weather station (3.45 km from DCU, Figure 46) for each date.

Figure 46: Location of Dublin Airport weather station and Dublin City University (Ref: Google Earth).

This data was used to define the terms used to describe weather conditions as direct sun, partial cloud, partial sun and overcast, based on the percentage of diffuse radiation, as shown in Table 14.

Table 14: Classification of sunlight terms using data from MET Eireann for Dublin Airport weather station.

Sunlight Term	Description	Global Radiation (J/cm²)/h		% Diffuse Radiation
		Average	Range	
Direct sun	No cloud cover	238	141-323	< 39%
Partial Cloud	Mainly sunny, occasional cloud cover	190	117-291	40-54%
Partial Sun	Mainly cloudy, occasional sun	183	142-211	55-69%
Overcast	Complete cloud cover	130	51-203	>70%

4.2.2 Non-concentrated solar experiments at DCU – Schlenk flask

4.2.2.1 Experimental set-up

The experimental set-up for small scale solar reactions is similar to that of the indoor reactions. Air is supplied using a pump; regulated using a flow meter and small bubbles generated using a sparger (Figure 47). However, no light source is needed and cooling is not employed, as in non-concentrated sunlight conditions the reaction mixture remains sufficiently cool.

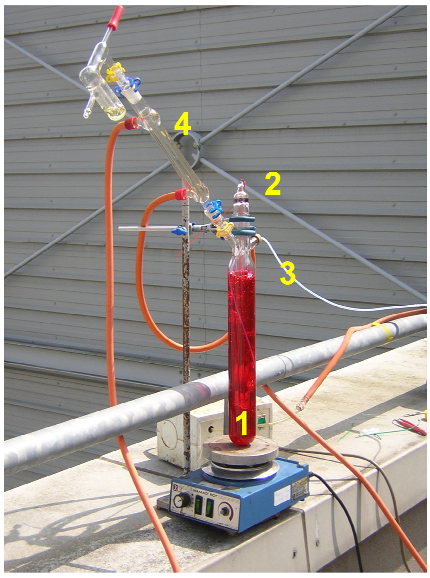


Figure 47: Experimental Set-up for solar experiments (1: sparger, 2: cooling water inlet, 3: air inlet, 4: condenser).

4.2.2.2 Small Scale synthesis (synthesis in Schlenk flask)

In conjunction with a 4th year undergraduate student, Kieran Joyce, a series of reactions were carried out under differing conditions of sunlight. The yields achieved in solar conditions were consistently higher than those obtained using artificial light. This was in keeping with previous observations using the conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** as a model reaction[57]. In direct sunlight, yields of 68-70% juglone **98** were achieved, while even in shade a yield of 26% was obtained. Under conditions of partial sun or partial cloud, juglone **98** was isolated in yields of 33-55%. This is in line with expectations, where greater numbers of photons in the direct sunlight give greater excitation of sensitiser and hence generation of more singlet oxygen. As summarised in Table 15, irradiation of 1,5-dihydroxynaphthalene **97** in different solvents for 3-6 h in sunlight gave juglone **98** in yields of 26-69%.

Table 15: Small scale solar synthesis of juglone 98 **(Experiments 57-62).**

Expt. No.	Weather Conditions	Solvent	Sensitiser	Time (h)	Yield (%)
57A	Partial sun	*t*-amyl alcohol	rose bengal	3	33
58A	Partial sun	*t*-amyl alcohol	rose bengal	3	34
59A	Direct sun	*t*-amyl alcohol	rose bengal	3	69
60A	Shade	*t*-amyl alcohol	rose bengal	5	26
61	Direct sun	*t*-amyl alcohol	rose bengal	4	66
62	Partial cloud	*t*-amyl alcohol	rose bengal	6	53

Of particular interest is Experiment 60A, which was conducted in "shade". In this experiment the reaction flask was placed in the shadow of the building and was not exposed to any direct sunlight. Even under these conditions a yield of 26% **98** was obtained after 5 hours.

Experiment 61 was monitored by ^{1}H NMR spectroscopy (using acetone-d_6) every 15 minutes and a profile of % conversion against reaction time was plotted (Figure 48).

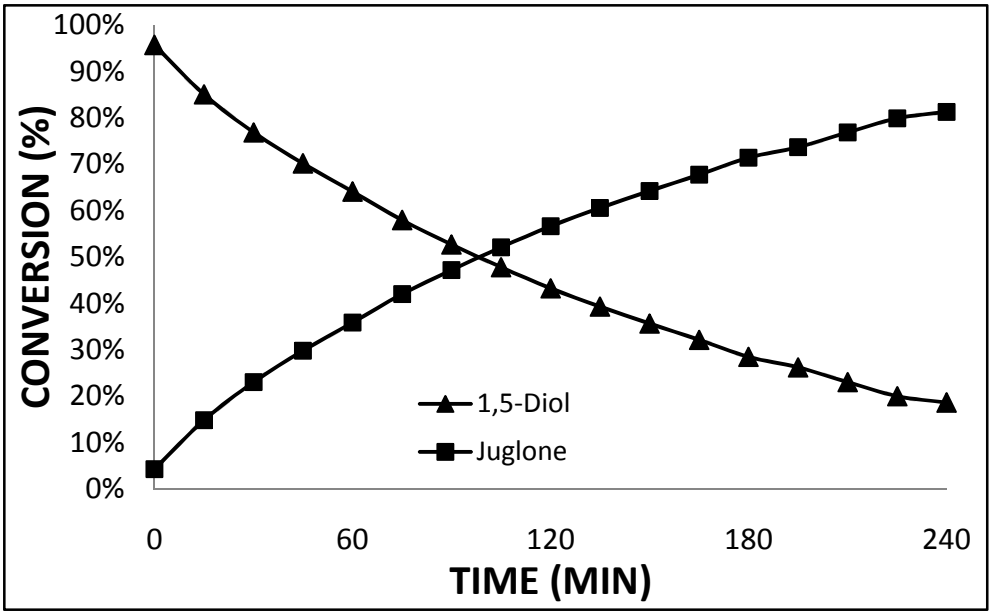


Figure 48: Profile of conversion of 1,5-dihydroxynaphthalene 97 **to juglone** 98 **in *t*-amyl alcohol in non-concentrated sunlight (Experiment 61).**

4.2.3 Non-concentrated solar experiments at DCU – scale up

In order to scale up the dye-sensitised photooxygenation system a new reactor was required. Necessary features are a large area to volume ratio, ensuring adequate irradiation of the entire reaction solution, the ability to bubble air and compatibility with reaction solvents. Use of flatbed reactors was therefore proposed, as this enables use of larger quantities of solvent, as the illuminated area to volume ratio is better than that attained in a Schlenk flask. In addition, the

depth of the solution remains shallow, enabling the sunlight to penetrate through the entire reaction mixture. Three types of flatbed reactor were investigated for juglone **98** synthesis: a plexiglass flatbed (developed by Demuth at MPI in Germany[257]), a home-made glass reactor and a custom-built glass reactor (developed by Viking Glass, Ireland).

4.2.3.1 Plexiglass flatbed reactor

The plexiglass reactor was designed by MPI, Mulheim (Demuth), with dimensions 97 x 37 x 1 cm and had a capacity of 4 L (Figure 49a). The joints were sealed using superglue. However, despite indications in the manual stating stability towards alcohols, this reactor was not stable to *t*-amyl alcohol. Within one minute of adding the reaction mixture, the superglue used dissolved and caused the bottom joint of the reactor to fall off. This may be attributed to the ability of *t*-amyl alcohol to dissolve the superglue on the joints of the reactor and the tension exerted by the weight of the reaction mixture.

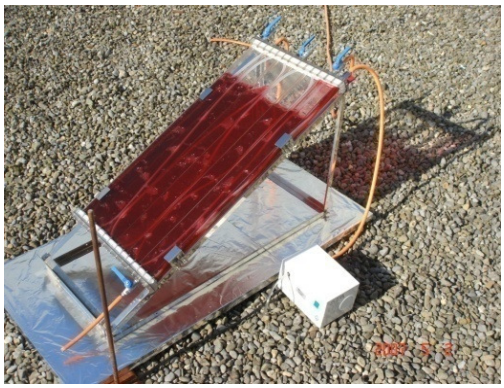
(a)  (b) 

Figure 49: Plexiglass reactor (a) original condition and (b) with methanolic reaction solution.

The reactor was recovered and reassembled using chemically resistant silicon glue. The new dimensions were 80 x 37 x 1 cm and the new capacity was 2.8 L (Figure 49b). Stability of the plexiglass in various alcohols was investigated, with methanol and ethanol identified as most suitable for use. This reactor was used for solar irradiation of a methanolic solution of 1,5-dihydroxynaphthalene **97** and rose bengal **41**. However, on day two of the reaction (after 10 hrs of irradiation and standing in darkness overnight) cracks were observed in the plexiglass, just above the solvent level (Figure 50). In addition, significant colouring of the plexiglass was observed, becoming a deep brown-orange colour.

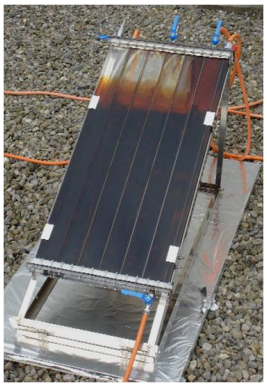
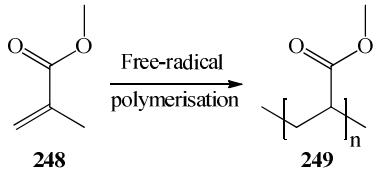
(a)  (b) 

Figure 50: Plexiglass reactor (a) after 8 hours of irradiation and (b) emptied after use.

It is believed that this is due to the interaction of juglone **98** (or an excited state juglone) with the plexiglass. In-lab observations have shown that juglone **98** forms polymeric films on plastics, leading to discoloration of plastic vials in which it is stored. Plexiglass (poly(methyl methacrylate) **249**) is formed from methyl methacrylate **248**, which contains an ester functionality (Scheme 87).



248 **249**

Scheme 87: Synthesis of poly(methyl methacrylate) 249 **(plexiglass) by free-radical initiated polymerisation.**

These flatbed reactors have been used previously in photooxygenation reactions, such as the Schenck-ene reaction of citronellol **93**, and so it is not believed that these problems were caused by singlet oxygen or the sensitiser, rose bengal **41**. This indicates a product incompatibility between juglone **98** and the reactor polymer **249** or plasticiser components.

4.2.3.2 Home-made glass flatbed reactor

To overcome the solvent incompatibility and instability experienced with plexiglass, it was decided to investigate a more chemically inert substance for the reactor, so glass reactors were chosen as an alternative. A double-glaze (soda glass) window was adapted for this purpose, with the dimensions 29 x 39 x 2 cm (Figure 51). The capacity of this reactor was 1.3 L. Stability checks using the sealant from around the glass indicated that, although some plasticisers were removed, it should be suitable for use with *t*-amyl alcohol.

Figure 51: Home-made glass flatbed reactor.

Early results in sunlight gave low yields (Experiment 63, 16% yield of juglone **98** after 6 h, partial cloud), but this can be attributed to losses sustained in the transfer of reaction mixture from reactor to collection flask. However, the stability of this reactor to all chemicals involved in the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** to form juglone **98** show that glass is a suitable reactor substrate. Optimisation of reactor design, specifically to incorporate better air supply and facilitate transfer of solutions into and out of the reactor should lead to enhanced yields in future studies.

4.2.3.3 Custom-built glass flatbed reactor

Having demonstrated the suitability of a glass reactor for the photooxygenation of 1,5-dihydroxynaphthalene **97** in *t*-amyl alcohol, a large scale reactor was designed. This was custom-built by Viking Glass, based on the design of the plexiglass reactor, with dimensions 97 x 35 x 3.5 cm and capacity 8 L. As shown in Figure 52a this reactor is fitted with inlet and outlet valves for introduction and removal of reaction mixture, as well as an in-built air inlet device (Figure 52b), which facilitates even distribution of air across the with of the reactor. In order to accommodate the air inlet system, the depth of this reactor is significantly greater than the plexiglass reactor (3.5 cm, compared to 1-2 cm in earlier reactors). As a result, the volume of the reactor and the depth of the solution for irradiation is significantly increased.

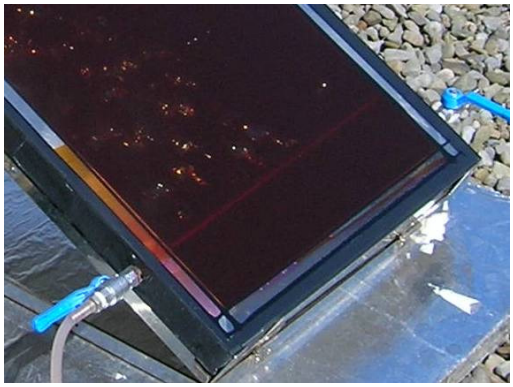
(a)  (b) 

Figure 52: (a) Custom-built glass flatbed reactor (Viking Glass): 1: pump, 2: air inlet device 3: inlet valves 4: outlet valve, and (b) air inlet device.

A key feature of this reactor is the air inlet device, which is located 10 cm from the bottom of the reactor and consists of a steel tube with several small outlet holes. This provides good distribution of air bubbles throughout the width of the reactor. A disadvantage is the 'void volume' beneath the device, which is shown clearly in Figure 52b, but analysis of mixing shows that the disturbances in the reactor due to movement of air enable mixing in this region also.

As summarised in Table 16, irradiation of 1,5-dihydroxynaphthalene **97** using sunlight for 6 hours in the custom-built glass flatbed reactor gave a conversion (based on ^{1}H NMR spectroscopy in acetone-d_6) of 84% in *t*-amyl alcohol. This was compared to a comparison experiment conducted by Kieran Joyce, which showed that a conversion of 72% was obtained using *i*-propyl alcohol as solvent under similar conditions.

Table 16: Large scale synthesis of juglone 98 **in a custom-built glass flatbed reactor using non-concentrated sunlight (Experiments 64-65).**

Expt. No.	Solvent	Sensitiser	Sunlight conditions	Time	Conversion
64A	*i*-propyl alcohol	rose bengal **41**	Partial cloud	6	72%
65	*t*-amyl alcohol	rose bengal **41**	Partial cloud	6	84%

A ^{1}H NMR spectroscopy (acetone-d_6) monitoring study was carried out for Experiment 65 and a profile of % conversion with respect to time was prepared (Figure 53).

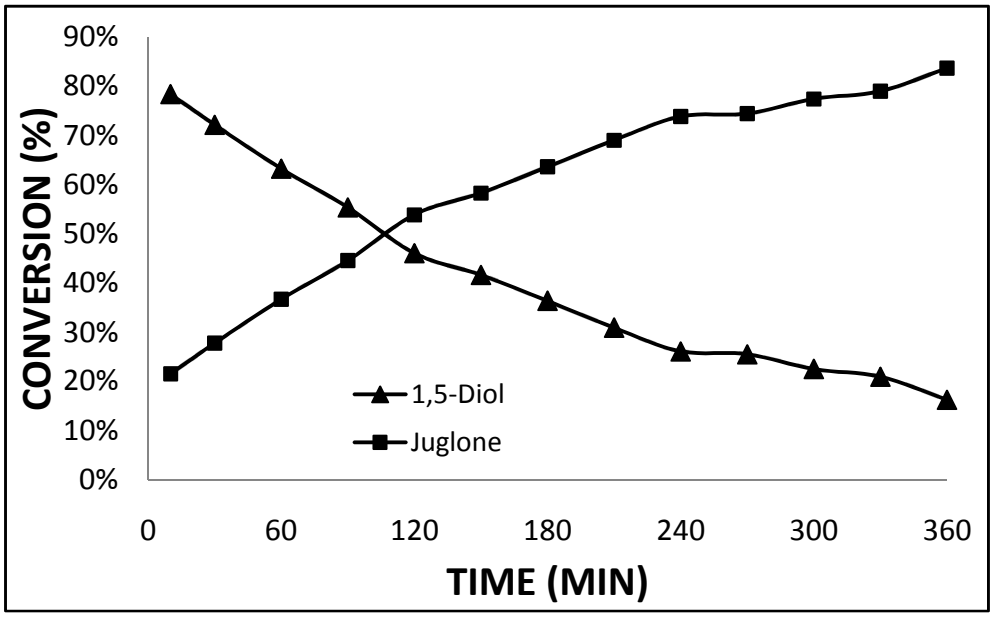


Figure 53: Profile of conversion of 1,5-dihydroxynaphthalene 97 **to juglone** 98 **in *t*-amyl alcohol using a custom-built glass flatbed reactor (Experiment 65).**

These observations are of significance in choosing reactor type for large scale reactions. Although reactions using direct sun give the greatest yield, in Ireland 60% of sunlight is diffuse in nature. Therefore, a reactor that can utilise both direct and diffuse light is more suitable than those that use only direct sun. These results indicate that non-concentrating reactors such as a flatbed reactor or CPC, which utilise both direct and diffuse light, are suitable for use in Irish solar conditions. Concentrating reactors will be less successful, as they are too dependent on direct sunlight and cannot utilise diffuse sunlight, therefore excluding up to 60% of Irish sunlight.

As a result, the use of flatbed reactors was investigated for larger scale reactions. This type of reactor offers considerable advantages compared to the Schlenk flask. The larger surface area (and in some cases shallower depth) of the flatbed reactor enables it to encounter more photons. In addition, the reactor is placed in a stand at an angle of 30°, placing it at a more suitable angle to the sun than the Schlenk flask.

4.2.4 Concentrated solar experiments in the DLR

There have been some studies of the solar synthesis of juglone **98** carried out at the German Aerospace Centre. The use of a laboratory scale parabolic trough reactor has enabled the utilisation of moderately concentrated sunlight in the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97**. Previous studies have looked at the use of *i*-propyl alcohol as

reaction solvent, as well as the use of holographic mirrors as an alternative to traditional aluminium mirrors[55-57]. In the current study, the use of *t*-amyl alcohol as an alternative reaction solvent is assessed and compared to results of earlier studies. Solar synthesis of juglone **98** in *t*-amyl alcohol using moderately concentrated sunlight was carried out at the German Aerospace Center (DLR) in August 2007.

4.2.4.1 Experimental set-up

A parabolic trough collector designed for laboratory-scale applications and equipped with a highly reflecting aluminium mirror was used for this study (Figure 54). This experimental set-up used has been reported previously in the literature[55, 57].

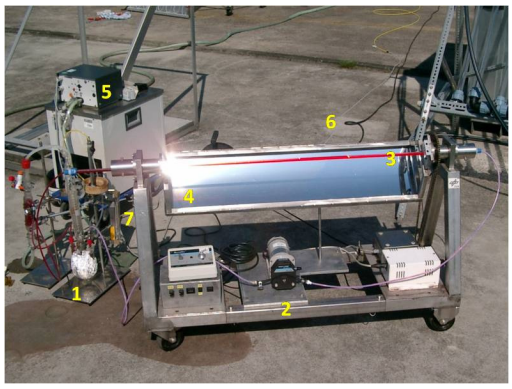


Figure 54: Laboratory scale parabolic trough reactor (1: Collection flask, 2: Pump, 3: Pyrex tube, 4: aluminium mirror, 5: chiller, 6: oxygen supply tube, 7: flow meter).

This reactor can automatically track the elevation of the sun, and can only utilise direct sunlight. The reaction mixture is continuously pumped through a Pyrex tube with diameter of 1.2 cm, which is placed in the focal line of the concentrator. The reaction mixture is cooled externally and oxygen gas fed via a T-connector (not visible in figure). The oxygen bubbles formed are quite large, and form discrete regions within the reactor.

On-site solar monitoring facilities were available and the number of photons was measured over the reaction duration. In addition, it is possible to identify the number of photons in the range 500 - 600 nm, which corresponds to the absorbance band of rose bengal **41**.

4.2.4.2 Results of solar experiments at the DLR

Use of moderately concentrated sunlight in juglone **98** synthesis has been investigated previously using a laboratory scale parabolic trough reactor and *i*-propyl alcohol[54, 56, 57]. An extension of this work looked at the use of *t*-amyl alcohol in the same reactor, using an aluminium mirror.

During August 2007, a solar study was carried out to investigate the synthesis of juglone **98** in *t*-amyl alcohol using moderately concentrated sunlight. During this investigation, experiments were carried out for three hours in direct sunlight and under partially cloudy conditions. Figure 55 shows the sunlight conditions for each day of the study.

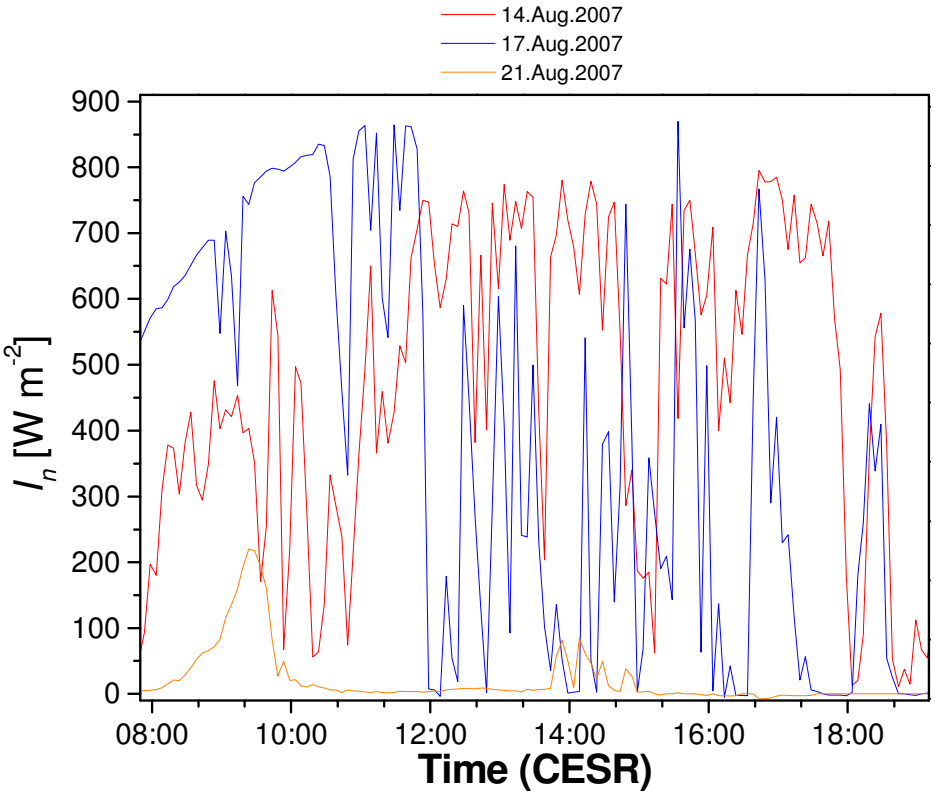


Figure 55: Sunlight data measured on-site at DLR for the August 2007 study.

The photon count and yield for experiments under these solar conditions are summarised in Table 17. The reactions were monitored by ^{1}H NMR spectroscopy (DMSO-D_6), which showed that under direct sunlight conditions (Aug 14, 2007), full conversion was achieved in less than one hour. This time corresponds to 0.43 mol photons, while over the three hour period 1.26 mol of photons were recorded. On a partially cloudy day (Aug 21, 2007), full conversion was achieved in less than 3 hours, with irradiation by just 0.37 mol of photons in three hours.

Table 17: Juglone 98 **synthesis in moderately concentration sunlight (Experiments 66-67).**

Expt. No.	Date	Solvent	Sensitiser	Mirror	Time (h)	Yield (%)	Photons (mol)
-	Aug-03	*i*-propyl alcohol	rose bengal	Holographic	3	79[54]	2.3
-	Aug-05	*i*-propyl alcohol	rose bengal	Aluminium	4	75[56]	2.0
66	14 Aug-07 (14.00 - 17.00)	*t*-amyl alcohol	rose bengal	Aluminium	3	68	1.26
67	21 Aug-07 (10.30 - 13.30)	*t*-amyl alcohol	rose bengal	Aluminium	3	74	0.37

For the 2007 solar study, ^{1}H NMR spectroscopy (DMSO-d_6) monitoring was carried out and a profile of % conversion with respect to time was prepared using the data for Experiment 67 (Figure 56).

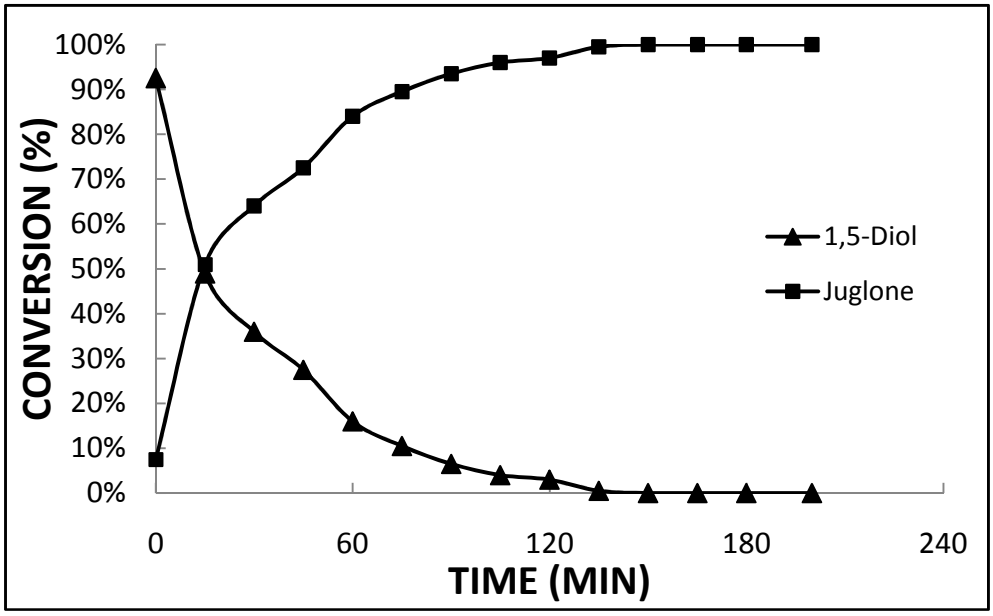


Figure 56: Profile of conversion of 1,5-dihydroxynaphthalene 97 **to juglone** 98 **in *t*-amyl alcohol in a laboratory scale parabolic trough reactor under diffuse sunlight conditions (Experiment 67).**

Interestingly, the yield for the direct sunlight reaction was lower than that in cloudy conditions (68% and 74%, respectively). This may be due to degradation of juglone **98** under concentrated solar conditions. Degradation of juglone **98** is not observed under non-concentrated sunlight conditions, or using halogen lamps, but has been noted for prolonged UV irradiation. In the case of concentrated sunlight, the intensity of the UV portion of the light may be sufficient to cause degradation of juglone **98**. In addition, the reaction was completed within one hour, therefore degradation of product could have occurred over the following 2 hours of irradiation. In the case of the more cloudy weather conditions, the reaction completed after two hours, leaving just one hour for degradation to occur.

An additional explanation for the lower than expected yield is decomposition of the sensitiser. Studies by Gerdes *et al*. have shown that rose bengal **41**, as well as other sensitisers, undergoes some degradation under irradiation conditions[30, 93, 258]. While these studies report the photodegradation of both rose bengal **41** and methylene blue **42**, the degradation products have not been identified. These authors have proposed that the photosensitisers may undergo oxidation by a photo-electron transfer mechanism. In addition, the participation of the superoxide anion ($O_2^{\cdot-}$) has been proposed as a potential side reaction.

4.3 Summary

In Chapters 2 and 3, the reaction conditions for the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** were optimised. As a result, it was determined that the use of *t*-amyl alcohol offered the best green alternative to existing reaction solvents, and rose bengal **41** was the most suitable sensitiser for use. In addition, the high energy demand of artificial light sources was noted, and the use of solar irradiation proposed as an alternative. This has been proven to be successful, in particular under conditions of direct sunlight and partial cloud.

The photooxygenation of 1,5-dihydroxynaphthalene **97** has been reported previously, first by Griffiths[182] in 1976 and a more extensive study by Duchstein and Wurm in the 1980s[184]. However, this project has reassessed this synthesis with a focus on environmental impact and has shown that comparable results may be obtained in solar conditions and 'greener' solvents (Table 18).

Table 18: Comparison of optimised green procedure for juglone 98 **synthesis with literature procedures.**

	'Green' Method	**Griffiths (1976)[182]**	**Duchstein (1984)[184]**
Solvent	*t*-Amyl alcohol	Dichloromethane-methanol (9:1)	Acetonitrile
Sensitiser	Rose bengal	Methylene blue	Methylene blue
Light source	Solar	Tungsten	Halogen (Halostar)
Purification	Column chromatography using ethyl acetate-cyclohexane (1:3)	Extraction using boiling light petroleum ether	Column chromatography using chloroform
O_2 supply	Air	Oxygen	Oxygen
Yield	70%	70%	85%

As shown above, the optimisation of this reaction using green parameters was successful, and a high yielding, relatively low environmental impact procedure has been established. In particular, the use of sunlight has been effectively demonstrated. This "green" light source offers a considerable energy saving, as the use of artificial light sources can increase energy demand of the process by up to 1556 kJ per hour.

Of particular note is the utilisation of Irish sunlight, as a common misconception is that Ireland receives insufficient sunlight for solar processes to be applied in this country. This study has demonstrated that Irish sunlight can be used in dye-sensitised processes, and particularly good yields may be achieved under direct sunlight or partial cloud sunlight conditions. Even under poorer sunlight conditions, i.e. partial sun or overcast conditions, the dye-sensitised photooxygenation reaction can proceed.

4.4 Experimental

4.4.1 Small-scale synthesis (synthesis in Schlenk flask)

General procedure for the small-scale solar synthesis of juglone

1,5-Dihydroxynaphthalene **97** and rose bengal **41** were dissolved in *t*-amyl alcohol with sonication. The reaction solution was irradiated, with air bubbling, in sunlight using the set-up from Figure 47. The product was isolated using Soxhlet extraction or column chromatography.

Experiment 57A (KJ-06): 3 h, partial sun *See Appendix A*

Experiment 58A (KJ-10): 3 h, partial sun *See Appendix A*

Experiment 59A (KJ-12): 3 h, direct sun *See Appendix A*

Experiment 60A (KJ-18): 5 h, shade *See Appendix A*

Experiment 61 (EC-092): 4 h, direct sun

The general procedure was followed using 0.48 g (3.0 mmol) of 1,5-dihydroxynaphthalene **97** and 100 mg (98 μmol) of rose bengal **41** in 300 ml of *t*-amyl alcohol and irradiation for 4 hours. Samples were taken at 15 minute intervals and the reaction was monitored using ^{1}H NMR spectroscopy (acetone-d_6). Product was purified by column chromatography using a mixture of ethyl acetate and cyclohexane (1:3) as mobile phase to give 66% yield of juglone **98** as a bright orange solid.

Experiment 62 (EC-162): 6 h, partial cloud

The general procedure was followed using 0.16 g (1.0 mmol) of 1,5-dihydroxynaphthalene **97** and 45 mg (44 μmol) of rose bengal **41** in 100 ml of *t*-amyl alcohol and irradiation for 6 hours. Product was purified by column chromatography using a mixture of ethyl acetate and cyclohexane (1:3) as mobile phase to give 53% yield of juglone **98** as a bright orange solid.

4.4.2 Use of a home-made glass reactor

Experiment 63 (EC-042): Juglone synthesis, 6 h in home-made glass flatbed reactor

1,5-Dihydroxynaphthalene **97** (1.6 g, 10 mmol) and rose bengal **41** (100 mg, 98 μmol) were dissolved in *t*-amyl alcohol (1.3 L) with sonication. The reaction mixture was irradiated, with air

bubbling, in sunlight for 6 hours in a home-made glass photoreactor (Figure 51). Product was purified by column chromatography using chloroform to give 16% yield of juglone **98** as a bright orange solid.

4.4.3 Use of a custom-built glass flatbed reactor

General procedure for large-scale synthesis of juglone a custom-built glass flatbed reactor

1,5-Dihydroxynaphthalene **97** (12.8 g, 0.080 mol) and rose bengal **41** (2.0 g, 2.0 mmol) were dissolved in reaction solvent (8.0 L) with sonication. The reaction mixture was irradiated, with air bubbling, in sunlight for 6 hours in a custom-built glass flatbed reactor (Figure 52a). Conversion was monitored by ^{1}H NMR spectroscopy (acetone-d_6) and product **98** was not isolated.

Experiment 64 (KJ-027): Use of *i*-propyl alcohol *See Appendix A*

Experiment 65 (EC-110/KJ-035): Use of *t*-amyl alcohol

The general procedure was followed using *t*-amyl alcohol. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 84% was achieved. Samples (2 ml) were taken at 30 minute intervals and ^{1}H NMR spectroscopy (acetone-d_6) was used to monitor conversion with respect to time.

4.4.4 Solar experiments at the DLR using moderately concentrated sunlight

General procedure for the synthesis of juglone in a parabolic trough reactor

1,5-Dihydroxynaphthalene **97** (0.48 g, 3.0 mmol) and rose bengal **41** (0.10 g, 98 μmol) were dissolved in *t*-amyl alcohol (300 ml) with sonication. The reaction mixture was irradiated, with air bubbling, for 3 hours in a laboratory scale parabolic trough reactor (Figure 54). Samples (1.5 ml) were collected throughout the reaction time and monitored using ^{1}H NMR spectroscopy (DMSO-d_6). The product **98** was purified by column chromatography using chloroform as the mobile phase.

Experiment 66 (EC-057): Direct sunlight conditions

The general procedure was followed and samples were collected at 1 hour and every 15 minutes thereafter for ^{1}H NMR spectroscopy (DMSO-d_6) monitoring. However, the spectra indicated that the reaction had reached 100% conversion in less than one hour. Purified product **98** was obtained in 68% yield as a bright orange solid.

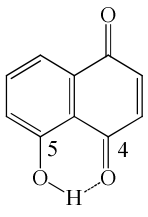
Experiment 67 (EC-057): Diffuse sunlight conditions

The general procedure was followed and samples were collected every 15 minutes for ^{1}H NMR spectroscopy (DMSO-d_6) monitoring. The spectra indicated that the reaction had reached 100% conversion after 2.5 hours. Purified product **98** was obtained in 74% yield as a bright orange solid.

Chapter 5 Extension of optimised synthesis to other 1-naphthols.

5.1 Introduction

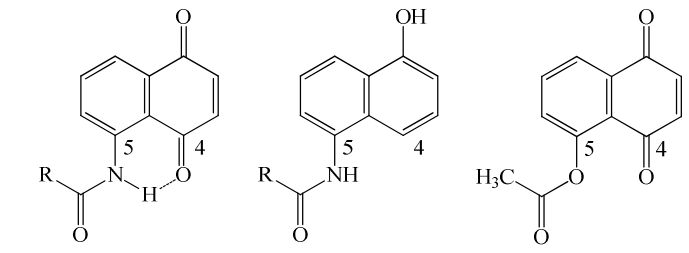
Following optimisation of the synthesis of juglone **98** under artificial and sunlight conditions, this procedure was applied to other 1-naphthol substrates. Photooxygenation of 1,5-dihydroxynaphthalene **97** yields juglone **98** as the only product, which can be isolated easily in high purity. This can be attributed to the relative stability of juglone **98**, facilitated by hydrogen bonding between the hydroxyl at position 5 and the oxygen at position 4 (Figure 57).



98

Figure 57: Structure of juglone, with hydrogen bonding shown.

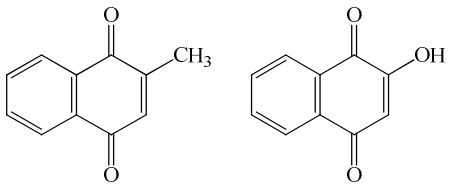
The photooxygenation of substrates with substitution at the 5 position is of interest, as the effect of this hydrogen bonding on the photooxygenation reaction can be assessed. Substitution of the hydroxyl with an amide offers potential to expand the scope of this reaction, as these compounds will retain the ability to hydrogen bond, as well as introduce additional functional groups (Figure 58a). These compounds are of interest as potential biological leads, as the 5-amido-1-naphthol **233** (Figure 58b) or 5-amido-1,4-naphthoquinone **234** moiety is a key feature in some known bioactive compounds. In addition, acetylation of the 5-hydroxyl position is of interest, as this removes the ability to hydrogen bond (Figure 58c). This may have an adverse effect on yield and isolation of the resultant 5-acetoxy-1,4-naphthoquinone **250**.



(a) **234** (b) **233** (c) **250**

Figure 58: Structures of (a) 5-amido-1,4-naphthoquinone, (b) 5-amido-1-naphthol 233**, and (c) 5-acetoxy-1,4-naphthoquinone** 250**.**

As shown in Chapter 1, the 1,4-naphthoquinone **90** core is present in many biologically active compounds, for example menadione **153** (2-methyl-1,4-naphthoquinone, Figure 59a) and lawsone **251** (2-hydroxy-1,4-naphthoquinone, Figure 59b). Photooxygenation of commercially available substrates may offer a green and efficient access to these compounds.



(a) **153** (b) **251**

Figure 59: Structure of (a) menadione, and (b) lawsone.

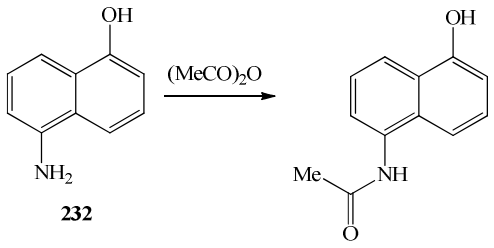
Application of the optimised procedure for juglone **98** synthesis, as determined in Chapters 2-4, for the synthesis of these compounds will demonstrate the scope of this method. In particular, the effect of hydrogen bonding on the ease of preparation and isolation of the target compounds will be assessed. In addition, use of sunlight irradiation will be compared to artificial light sources, thus offering a significant energy saving for this synthesis.

5.2 Results and Discussion

5.2.1 Preparation of 1-naphthol starting materials

5.2.1.1 Preparation of 5-acetamido-1-naphthol

5-Acetamido-1-naphthol **233a** was synthesised by a supervised undergraduate student, Elodie Haggiage, using a method by Jindal[259]. Reaction of 5-amino-1-naphthol **232** and acetic anhydride gave the desired 5-acetamido-1-naphthol **233a** in 61% yield (Scheme 88).

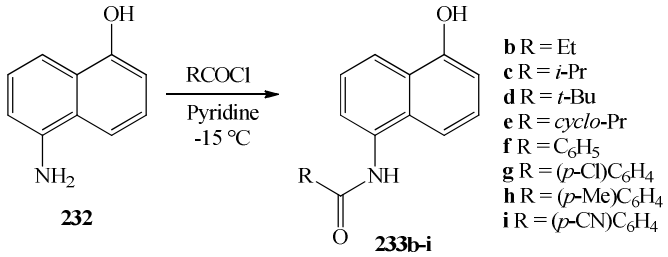


Scheme 88: Preparation of 5-acetamido-1-naphthol 233a **(Experiment 68A).**

The purified product **233a** was a beige solid. In the ^{1}H NMR spectrum (DMSO-d_6), the peaks representing the NH group and the OH groups were seen as singlets at 8.95 ppm and 9.32 ppm, respectively.

5.2.1.2 Preparation of a series of 5-amido-1-naphthols

A series of 5-amido-1-naphthols **233b-i** were synthesised from 5-amino-1-naphthol **232** and the corresponding acid chloride according to the method by Neidlein (Scheme 89) in yields of 15-69% as shown in Table 19[260]. This work was carried out together with a supervised undergraduate student, Elodie Haggiage.



Scheme 89: Preparation of 5-amido-1-naphthol series 233 b-i **(Experiments 69-76).**

Table 19: Preparation of 5-amido-1-naphthols 233b-i **(Experiments 69-76).**

Expt. No.	Compound	R	Product	Yield
69A	**b**	Et	5-propanamido-1-naphthol	36%
70	**c**	*i*-Pr	5-(*iso*-butyramido)-1-naphthol	27%
71A	**d**	*t*-Bu	5-(trimethyl)acetamido-1-naphthol	69%
72A	**e**	*cyclo*-Pr	5-(*cyclo*-propanecarban)amido-1-naphthol	29%
73	**f**	Ph	5-benzamido-1-naphthol	15%
74A	**g**	(*p*-Cl)C_6H_4	5-(4-chlorobenzamido)-1-naphthol	36%
75A	**h**	(*p*-Me)C_6H_4	5-(4-toluamido)-1-naphthol	36%
76A	**i**	(*p*-CN)C_6H_4	5-(4-cyanobenzamido)-1-naphthol	40%

5.2.1.2.1 5-Alkylamido-1-naphthols

The effect of the different alkyl groups on the outcome of the reaction of acid chlorides with 5-amino-1-naphthol **232** was assessed. The *t*-butyl substituted 5-amido-1-naphthol **233d** was obtained in a much higher yield that that of ethyl- **233b**, *i*-propyl- **233c** or *cyclo*-propyl- **233e** substituted 5-amido-1-naphthols (Figure 60).

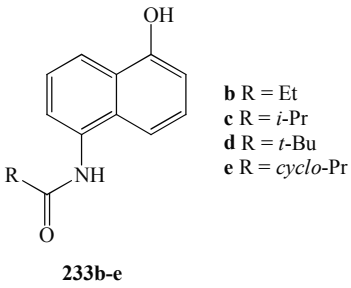


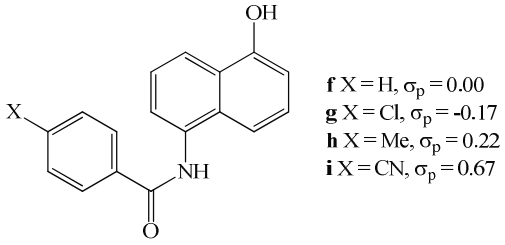
Figure 60: 5-Alkylamido-1-naphthols 233b-e**.**

The yield using (trimethyl)acetyl chloride (R = *t*-Bu) is significantly greater than that obtained for other alkyl acid chlorides, indicating that the presence of the *t*-Bu group has a significant effect on the outcome of the reaction. This may be due to steric effects, as Taft has stated that bulkier groups can lead to slower reaction rates. The major side reaction observed during the

acylation reaction is the formation of a *bis*-acylated compound. The slower reaction rate of (trimethyl)acetyl chloride, compared to other acid chlorides, may result in less by-product formation.

5.2.1.2.2 5-Benzamido-1-naphthol series

The effect of substitution on the phenyl group of the benzoyl acid chlorides on formation of the corresponding 5-amido-1-naphthols **233f-i** was investigated, looking for a correlation between the Hammett *para*-substituent constants (σ_p, Figure 61) and the outcome of the synthesis of amides from 5-amino-1-naphthol and a series of acid chlorides.



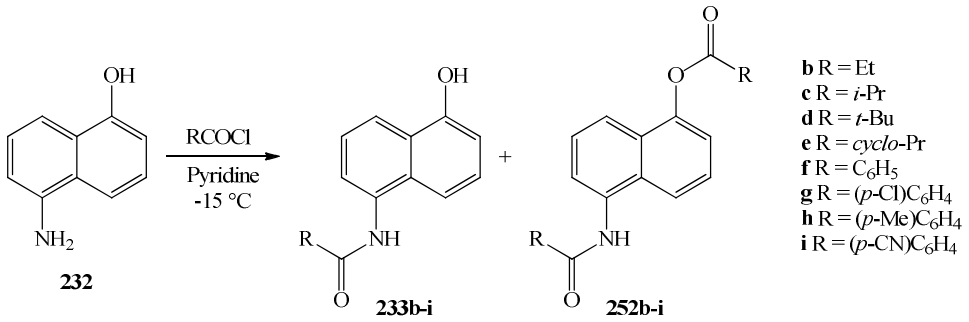
233f-i

Figure 61: 5-Benzamido-1-naphthols 233f-i**.**

All substituted phenyl groups **233g-i** gave an increase in yield from 15% for 5-benzamido-1-naphthol **233f** to ca. 40% for 1-naphthols with *para*-substituted phenyl groups **233g-i**. However, the outcome of the reaction was found be be unrelated to the electron donating and electron withdrawing effect of the substituents, as yields of 36-40% were achieved for all substitutions.

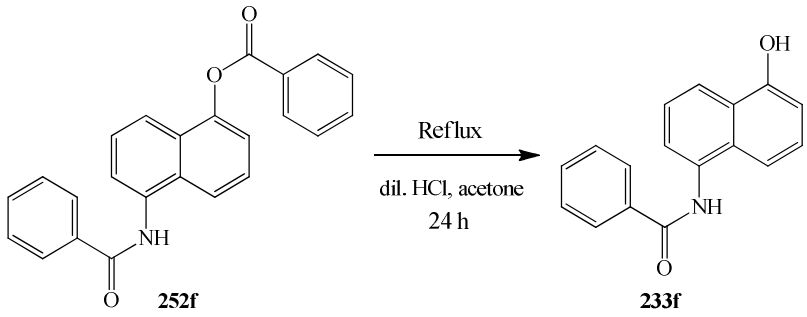
5.2.1.2.3 Hydrolysis of *bis*-acylated side product

During the preparation of 5-amido-1-naphthols **233b-i** using acid chlorides, a common side-reaction is the formation of the corresponding *bis*-acylated 1-ester-5-amidonaphthalene **252b-i** (Scheme 90).



Scheme 90: Synthesis of 5-amido-1-naphthols 233b-i **and the *bis*-acylated side product** 252b-i**.**

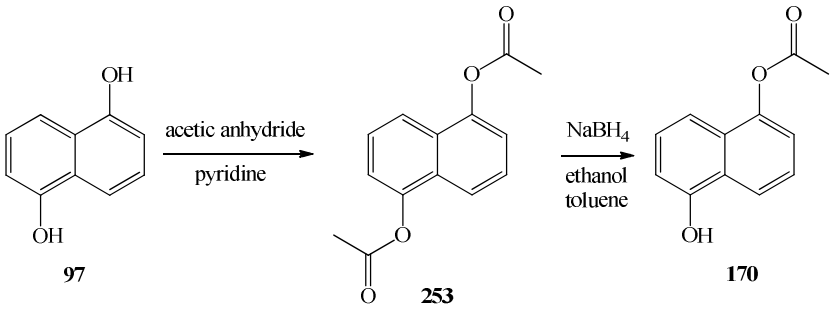
This over-acylation results in lower yields of the desired 5-amido-1-naphthol **233b-i**. To overcome this, the acid-catalysed hydrolysis of the *bis*-acylated compound **252** to regenerate the desired mono acylated 5-amido-1-naphthol **233** was investigated. For this study, the hydrolysis of the *bis*-acylated product **252f** from benzoyl chloride and 5-amino-1-naphthol **233f** was achieved by refluxing in a dilute acid-acetone mixture for 24 hours (Scheme 91). ^{1}H NMR spectroscopy (DMSO-d_6) showed that a conversion of 90% was achieved.



Scheme 91: Acid-catalysed hydrolysis of 1-ester-5-amido-compounds 252 **(Experiment 77).**

5.2.1.3 Preparation of 5-acetoxy-1-naphthol

Preparation of 5-acetoxy-1-naphthol **170** was carried out to investigate the effect of substitution of an alcohol with an acetyl group on the photooxygenation reaction. 5-Acetoxy-1-naphthol **170** was synthesised using the method by Lemaire, by first converting 1,5-dihydroxynaphthalene **97** to the *bis*-acetylated product **253** using acetic anhydride (Experiment 78), which was then treated with sodium borohydride to form the *mono*-acetylated product **170** (Experiment 79, Scheme 92)[261].

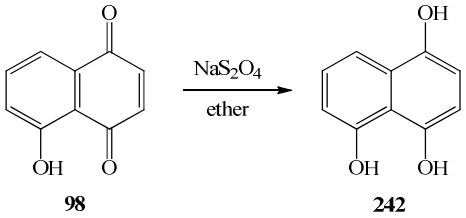


Scheme 92: Synthesis of 5-acetoxy-1-naphthol 170 **from 1,5-dihydroxynaphthalene** 97 **(Experiments 78-79).**

Diacetoxynaphthalene **253** was obtained in 88% yield and 5-acetoxy-1-naphthol **170** was obtained in 44% yield (based on the amount of 1,5-dihydroxynaphthalene **97** used). In the ^{1}H NMR spectrum (DMSO-d_6), the peak representing the methyl groups of the *bis*-acylated product was seen at 2.47 ppm and in the ^{1}H NMR spectrum ($CDCl_3$) for 5-acetoxy-1-naphthol **170** the OH peak was seen as a singlet at 5.41 ppm.

5.2.1.4 Preparation of 1,4,5-trihydoxynaphthalene

Photooxygenation of 1,4,5-trihydroxynaphthalene **242** is of interest as a potential route to naphthazarin **254** (5,8-dihydroxy-1,4-naphthoquinone). 1,4,5-Trihydroxynaphthalene **242** was synthesised from juglone **98** in 67% yield, using a method by Wurm[262]. The reduction of juglone **98** was carried out using sodium dithionite (Scheme 93).

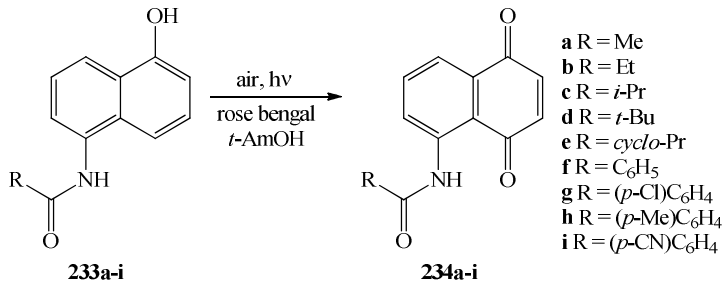


Scheme 93: Preparation of 1,4,5-trihydroxynaphthalene 242 **(Experiment 80).**

The product **242** was a pale brown solid, which turned green over time. Traces of juglone **98** were present, which may be attributed to the known air oxidation of the triol **242**. In the ^{1}H NMR spectrum (DMSO-d_6), the three singlets representing the hydroxy groups were observed at 9.84 ppm, 9.73 ppm and 8.43 ppm.

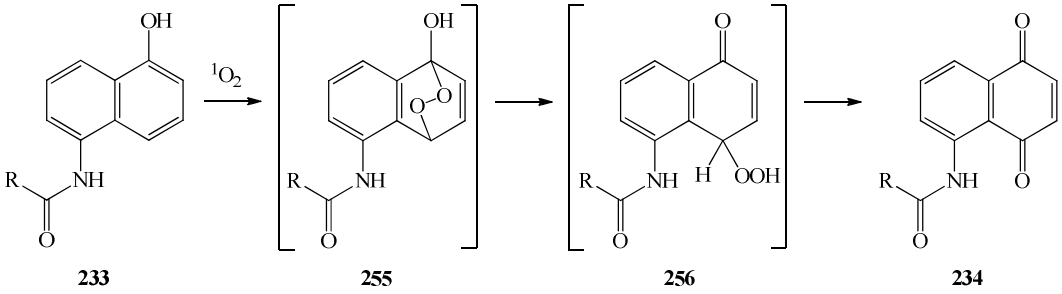
5.2.2 Photooxygenation of 5-amido-1-naphthols

Following preparation of the starting materials **233a-i** they were then subjected to photooxygenation reactions under artificial light and solar illumination. The optimised reaction conditions for juglone **98** synthesis in artificial and solar conditions were applied, using rose bengal **41** in *t*-amyl alcohol (Scheme 94). These reactions were carried out in association with a supervised undergraduate student, Elodie Haggiage.



Scheme 94: Photooxygenation of 5-amido-1-naphthols 233a-i **(Experiments 81-107).**

This reaction proceeds through a similar mechanism to that of juglone **98**, as shown in Scheme 95. During this transformation, an unstable endoperoxide **255** is formed, which then undergoes proton transfer, followed by elimination of water to form the corresponding naphthoquinone **234a-i**. The hydrogen of the amide can undergo hydrogen bonding with the quinone oxygen, thus stabilising the product, in a similar fashion to the hydrogen bonding in juglone **98**. As a result, these compounds are quite stable and further reaction was not observed under photooxygenation conditions.



Scheme 95: Mechanism of the photooxygenation of 5-amido-1-naphthols 233**.**

The photooxygenation of each of the prepared 5-amido-1-naphthols **233a-i** was investigated under indoor irradiation conditions using one 500 W halogen lamp, with irradiation times of 4

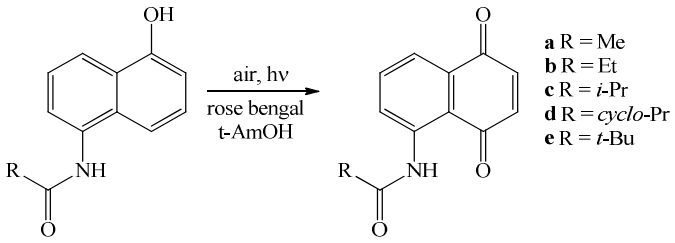
and 24 hours. The results of these experiments were compared to 6 hours of outdoor illumination in different solar conditions. The solar conditions are classified as described in Chapter 4, Section 4.2.1 (Table 14). The results of these studies are summarised in Table 20.

Table 20: Photooxygenation of a series of 5-amido-1-naphthols 233a-i **(using rose bengal** 41 **in *t*-amyl alcohol, Experiments 81-107).**

Expt. No.	Substrate	Product	Artificial light		Sunlight	
			4 h	24 h	6 h	Weather
81-83	5-acetamido-1-naphthol **233a**	**234a**	12%	80%	90%	Direct sun
84-86	5-propanamido-1-naphthol **233b**	**234b**	34%	89%	53%	Overcast
87-89	5-(*iso*-butyramido)-1-naphthol **233c**	**234c**	28%	54%	59%	Direct sun
90-92	5-(*cyclo*-propanecarban)amido-1-naphthol **233d**	**234d**	36%	54%	53%	Overcast
93-95	5-(trimethyl)acetamido-1-naphthol **233e**	**234e**	72%	94%	54%	Partial sun
96-98	5-benzamido-1-naphthol **233f**	**234f**	17%	58%	80%	Partial sun
99-101	5-(4-chlorobenzamido)-1-naphthol **233g**	**234g**	68%	72%	54%	Overcast
102-104	5-(4-toluamido)-1-naphthol **233h**	**234h**	24%	40%	63%	Partial sun
105-107	5-(4-cyanobenzamido)-1-naphthol **233i**	**234i**	35%	96%	23%	Overcast

5.2.2.1 Synthesis of 5-alkylamido-1,4-naphthoquinones

The synthesis of 5-alkylamido-1,4-naphthoquinones **234a-e** was carried out under the optimised conditions for juglone **98** synthesis from Chapters 2-4 (Scheme 96). In particular, yields following artificial light irradiation were compared to those achieved under solar conditions. The effect of different weather conditions on the outcome of the solar reaction was demonstrated using the synthesis of 5-acetamido-1,4-naphthoquinone **234a** as a model reaction.



Scheme 96: Synthesis of 5-alkylamido-1,4-naphthoquinones 234a-e **(Experiments 81-95).**

Synthesis of 5-acetamido-1,4-naphthoquinone **234a** from 5-acetamido-1-naphthol **233a** was shown to give yields of 12 and 80% under indoor irradiation for 4 and 24 h, respectively (Table 20, Experiments 81-83). However, under outdoor illumination under direct sun conditions (less than 30% diffuse sunlight) a yield of 90% was achieved in just 6 hours. The difference in yield achieved under solar and indoor conditions may be attributed to the complete overlap between

the solar spectrum (Figure 62a) and the rose bengal **41** absorbance spectrum (Figure 62b). In addition, the intensity of solar light is greater than that of the halogen lamp, thus more photons are provided to the reaction system.

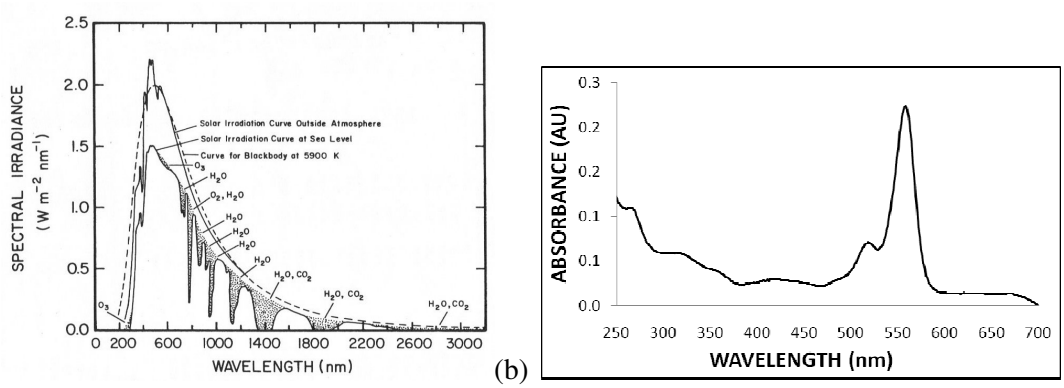


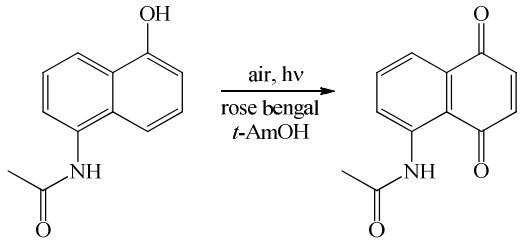
Figure 62: (a) Solar spectrum, and (b) UV-vis spectrum of rose bengal 41 **(in methanol).**

As shown in Table 20, Experiments 84-86, solar synthesis of 5-propanamido-1,4-naphthoquinone **234b** was carried out under overcast solar conditions. As a consequence, the isolated yield after 6 hours (53%) was less than that achieved under artificial light conditions in 24 hours (89%). However, even under poor sunlight conditions the yield was greater than that achieved in 4 hours irradiation in indoor conditions (34%). This demonstrates a robustness of the synthesis to large fluctuations in light intensity. Similarly, for the synthesis of 5-(*cyclo*-propanecarban)amido-1,4-naphthoquinone **234d** (Table 20, Experiments 90-92) under conditions of partial sun the yield obtained after 6 hours of solar illumination (53%) was equal to that achieved in 24 hours of indoor irradiation (54%) and greater than that achieved after 4 hours of artificial irradiation (36%).

In the case of 5-(*iso*-butyramido)-1,4-napthoquinone **234c**, after 6 hours of irradiation under direct sun conditions the yield obtained (59%) was greater than that obtained after both 4 and 24 hours of indoor illumination (28% and 54%, respectively, Table 20, Experiments 87-89).

In disagreement with the above results is the solar synthesis of 5-(trimethyl)acetamido-1,4-naphthoquinone **234e**. Under conditions of partial sun a yield of just 54% was obtained, compared to 72% and 94% under artificial light conditions for 4 and 24 hours, respectively (Table 20, Experiments 93-95).

To further probe the effects of different sunlight conditions on the outcome of the dye-sensitised photooxygenation reaction, the solar synthesis of 5-acetamido-1,4-naphthoquinone **234a** using rose bengal **41** in *t*-amyl alcohol was used as a model reaction (Scheme 97).



233a **234a**

Scheme 97: Preparation of 5-acetamido-1,4-naphthoquinone 234a **(Experiment 108-109).**

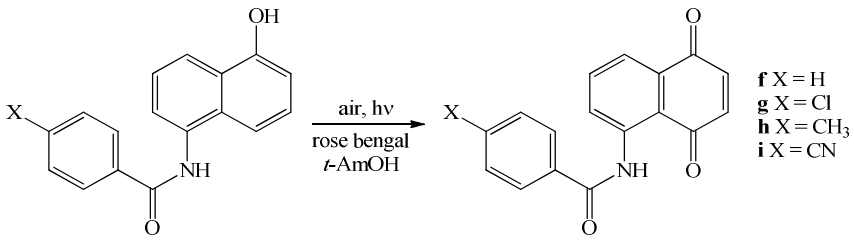
This study showed that yields of 35-90% **234a** were achieved following solar irradiation for 2-6 h (Table 21). The effect of sunlight conditions on yield is clearly evident, as a yield of 45% could be achieved in just 2 hours under conditions of partial cloud (30-55% diffuse sunlight), while a yield of 35% was achieved under 4 hours of illumination under overcast conditions (greater than 70% diffuse sunlight). As expected, the outcome under direct sunlight conditions is greatest (90% yield).

Table 21: Synthesis of 5-acetamido-1,4-naphthoquinone 234a **in sunlight.**

Expt. No.	Solvent	Sensitiser	Time (h)	Yield (%)	Weather conditions
108	*t*-amyl alcohol	rose bengal	2	45	Partial cloud
109	*t*-amyl alcohol	rose bengal	4	35	Overcast
83	*t*-amyl alcohol	rose bengal	6	90	Direct sun

5.2.2.1.1 Synthesis of 5-arylamido-1,4-naphthoquinones

Synthesis of 5-arylamido-1,4-naphthoquinones **234f-i** from the corresponding 5-arylamido-1-naphthols **233f-i** was carried out in indoor conditions (4 h and 24 h) and solar conditions (6 hours) (Scheme 98).



233f-i **234f-i**

Scheme 98: Synthesis of 5-arylamido-1,4-naphthoquinones 234f-i **(Experiments 96-107).**

5-Benzamido-1,4-naphthoquinone **234f** was synthesised from 5-benzamido-1-naphthol **233f** using rose bengal **41** in *t*-amyl alcohol using artificial light (halogen lamp) or sunlight. As summarised in Table 20 (Experiments 96-98), yields of 17% and 58% were achieved on irradiation for 4 h and 24 h in artificial conditions, respectively, while irradiation for 6 h in sunlight gave a yield of 80%. The sunlight conditions were classified as partial sun, indicating that 55-70% of the sunlight was diffuse in nature.

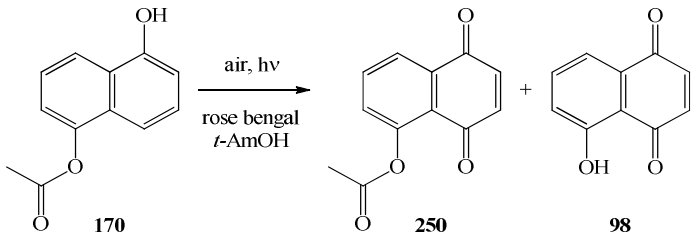
Like 5-acetamido-1,4-naphthoquinone **234a**, the yield for the solar reaction was greater than that obtained following 24 hours of artificial light irradiation. This may again be attributed to the greater overlap of the solar spectrum (300-700 nm) and the dye, and the higher wavelength cut-off point of the artificial lamp (400-700 nm), as well as the greater intensity of the light.

For substitution with chloro **234g** or cyano **234i**, the sunlight conditions employed were overcast, consisting of greater than 70% diffuse sunlight. In both cases, the yields achieved in 6 hours of solar irradiation were less than that achieved in 4 hours (and 24 hours) of indoor irradiation (Table 20, Experiments 99-101 and 105-107). Solar irradiation of 5-(4-chlorobenzamido)-1-naphthol **233g** for 6 hours gave the corresponding 1,4-naphthoquinone **234g** in a yield of 54%, which was compared to yields of 68% and 72% obtained following 4 and 24 hours of artificial irradiation, respectively. Similarly, solar irradiation of 5-(4-cyanobenzamido)-1-naphthol **233i** for 6 hours gave the corresponding 1,4-naphthoquinone **234i** in a yield of 23%, which was compared to yields of 35% and 96% obtained following 4 and 24 hours of artificial irradiation, respectively.

For irradiation of 5-(4-toluamido)-1-naphthol **233h** under sunlight conditions of partial sun (55-70% diffuse irradiation) a yield of 63% **234h** was achieved, which is significantly greater than the yields of 24% and 40% achieved in indoor conditions with irradiation for 4 and 24 h, respectively (Table 20, Experiments 102-104). However, although the yield in sunlight was considerably greater than that achieved in indoor conditions, the overall yield was low when compared to that of the cyano **234i** or chloro **234g** substituted aryl groups.

5.2.2.2 Synthesis of 5-acetoxy-1,4-naphthoquinone

Using the optimised conditions for the synthesis of juglone **98**, synthesis of 5-acetoxy-1,4-naphthoquinone **250** from 5-acetoxy-1-naphthol **170** using rose bengal **41** in *t*-amyl alcohol was investigated (Scheme 99).

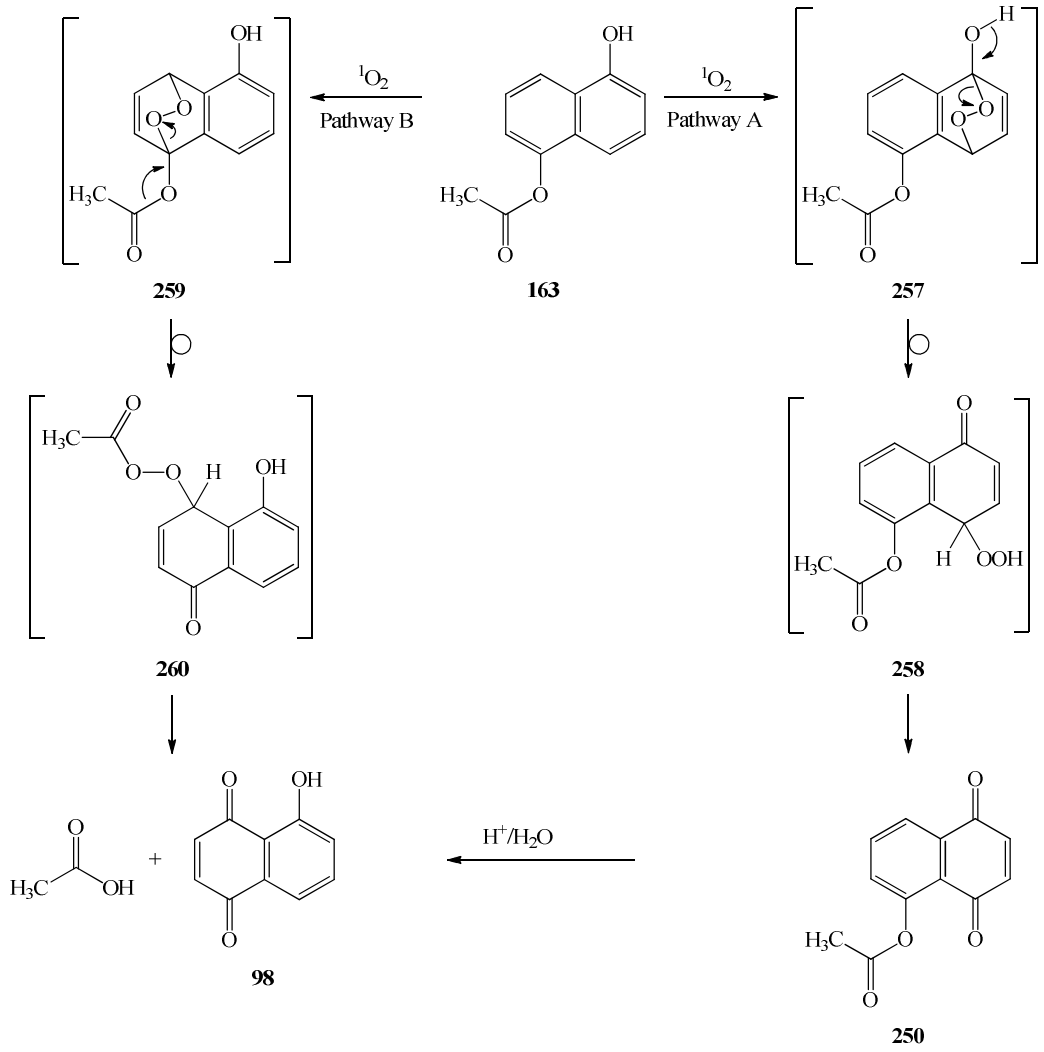


Scheme 99: Synthesis of 5-acetoxy-1,4-naphthoquinone 250**.**

Literature reports of the photooxygenation of 5-acetoxy-1-naphthol **170** have claimed that juglone **98** is produced as the only product, rather than the corresponding 5-acetoxy-1,4-naphthoquinone **250**[137]. The formation of the corresponding 1,4-naphthoquinone **250** is the expected major product, but formation of juglone **98** may perhaps be explained through examination of the mechanism (Scheme 100).

Pathway **A** indicates the expected mechanism for this transformation, assuming it follows that postulated for juglone **98**. Following photooxygenation, hydrolysis of the acetoxy group in **170** would yield juglone **98**.

Pathway **B** addresses the possible formation of a regioisomeric endoperoxide **259**. Although this results in the formation of juglone **98**, this pathway is less likely as a comparable endoperoxide is not evident for the analogous 5-amido-1-naphthols **233**.

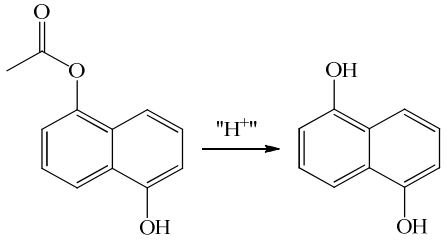


Scheme 100: Mechanism for the photooxygenation of 5-acetoxy-1-naphthol 170**.**

A preliminary investigation of this photoreaction using *t*-amyl alcohol as solvent showed that the desired 1,4-naphthoquinone **250** is produced (Experiment 110). The ^{1}H NMR spectroscopy ($CDCl_3$) spectrum of the crude product showed that a mixture of starting material **170** (79%), juglone **98** (3%) and 5-acetoxy-1,4-naphthoquinone **250** (17%) was present. This indicates that following artificial light irradiation for 5.5 hours, conversion of 26% was achieved, leading to product composition of 85% of the desired 1,4-naphthoquinone **250** and 15% juglone **98**. This suggests that 5-acetoxy-1,4-naphthoquinone **250** is formed initially and undergoes subsequent hydrolysis to yield juglone **98**. This provides support for Pathway A as the likely mechanism for this reaction.

Another explanation for the formation of juglone **98** is the self-catalysed (acid-catalysed) hydrolysis of the ester functional group, prior to photooxygenation (Scheme 101). However, ^{1}H

NMR spectroscopy does not show the presence of 1,5-dihydroxynaphtalene **97**, thus providing support for the hydrolysis of the ester after photooxygenation of the starting material **170**.



163 **97**

Scheme 101: Hydrolysis of 5-acetoxy-1-naphthol 170 **to 1,5-dihydroxynaphthalene** 97**.**

To further probe this mechanism, the degradation of reference 5-acetoxy-1,4-naphthoquinone **250** under conditions of heat and acid was investigated. This was to mimic work-up conditions and thus evaluate at what stage of the procedure the product is converted to juglone **98**.

To assess the effect of heat, a sample of 5-acetoxy-1,4-naphthoquinone **250** was stirred at 60 °C for 3.5 hours (Experiment 111). This temperature was chosen as the maximum achieved during rotary evaporation of solvent. After this time solvent was removed by rotary evaporation and the residue analysed by ^{1}H NMR spectroscopy ($CDCl_3$). No evidence of juglone **98** formation was observed, which indicates that hydrolysis of the desired 5-acetoxy-1,4-naphthoquinone **250** is not caused by heat.

To assess the effect of silica, i.e. acidity, on the conversion of 5-acetoxy-1,4-naphthoquinone **250** to juglone **98**, a reference sample was stirred with silica in cyclohexane and ethyl acetate (3:1 ratio, to mimic mobile phase used in work-up, Experiment 112). After 4 hours, the solution was passed through a sintered glass filter and the silica was flushed with mobile phase to remove any residues. Following evaporation of the solvent, the resulting product was analysed by ^{1}H NMR spectroscopy ($CDCl_3$). Once again, no evidence of juglone **98** formation was observed.

However, to further evaluate the effect of acidity on this conversion, a reference sample of 5-acetoxy-1,4-naphthoquinone **250** was spotted on a silica TLC plate and left overnight. Upon running the sample the next day (cyclohexane: ethyl acetate 3:1), a spot corresponding to juglone **98** was observed. This suggests that the acidity of silica can cause the desired product 5-acetoxy-1,4-naphthoquinone **250** to undergo hydrolysis to form juglone **98**. Therefore it is essential not to allow the compound to sit on silica.

Early studies showed that a conversion of 26% was achieved following 5.5 hours of artificial irradiation (Experiment 110), therefore this reaction was repeated with a greater irradiation time (12 h, Experiment 113). In this time, a conversion of 43% was achieved, giving the products 5-acetoxy-1,4-naphthoquinone **250** and juglone **98** in a ratio of 3:1 in the crude product. Following column chromatography a yield of 27% was achieved (63% based on conversion) for 5-acetoxy-1,4-naphthoquinone **250**. Juglone **98** was obtained as the minor product, with a yield of 8% (18% based on conversion).

5.2.3 Use of commercially available 1-naphthols

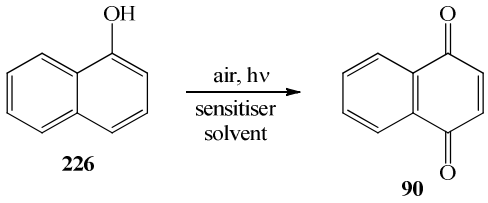
Some commercially available 1-naphthols were used in the dye sensitised photooxygenation process using the optimised conditions for juglone **98** synthesis (rose bengal **41** in *t*-amyl alcohol). Conversions were measured using ^{1}H NMR spectroscopy (acetone-d_6) and are shown in Table 22.

Table 22: Photooxygenation of commercially available 1-naphthols (Experiments 110-115).

Expt. No.	Substrate	Product	Artificial light		Sunlight	
			4 h	24 h	6 h	weather
114-115	1-naphthol **226**	1,4-naphthoquinone **90**	18%	70%	100%	Sunny
116-117	1,6-dihydroxynaphthalene **261**	6-hydroxy-1,4-naphthoquinone **262**	25%	80%	68%*	Sunny
118	2-methyl-1-naphthol **263**	menadione **153**	53%	100%	-	-
119-120	3-hydroxy-1-naphthol **264**	lawsone **251**	66%	100%	-	-
* Isolated yield, conversion not available						

5.2.3.1 Synthesis of 1,4-naphthoquinone

The synthesis of 1,4-naphthoquinone **90** from 1-naphthol **226** by photooxygenation reaction (Scheme 102) was investigated previously by a 4th year student (Bernard Roe). This was shown to be successful using a solid supported sensitiser (RB_{MF}, Sensitox®) in acetone using a medium pressure mercury lamp (53% yield)[55].



Scheme 102: Synthesis of 1,4-naphthoquinone 90 **(Experiments 114-115).**

Synthesis of 1,4-naphthoquinone **90** in *t*-amyl alcohol using rose bengal **41** and artificial light irradiation was investigated using a halogen lamp (Experiment 114). Samples were taken at 2, 4, 6 and 24 hours to identify the conversion. After 24 hours irradiation under artificial light conditions a conversion of 70% was achieved (Figure 63).

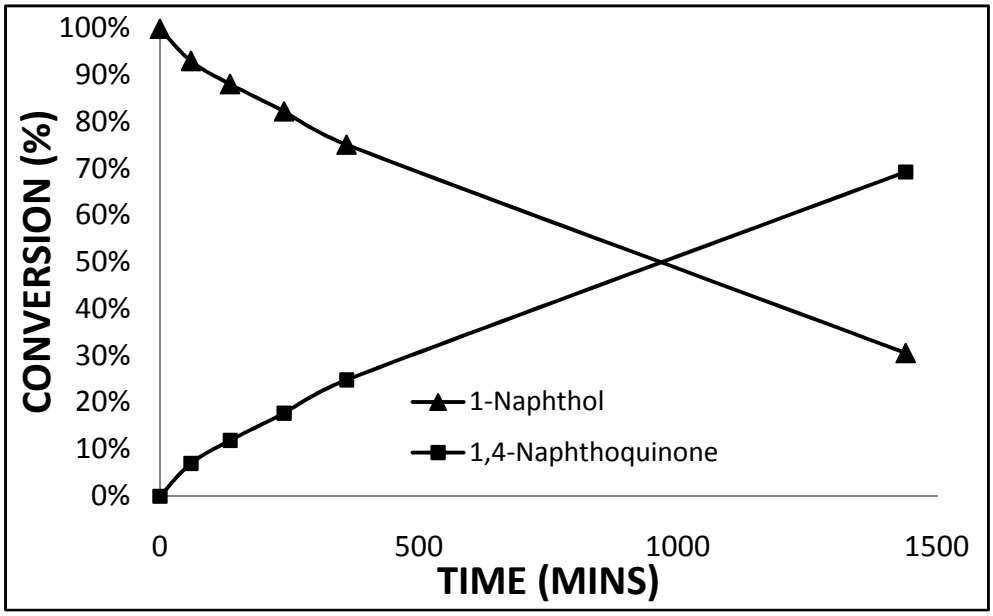
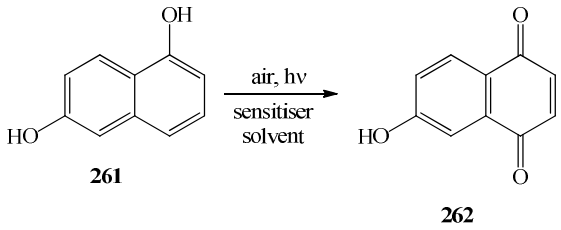


Figure 63: Synthesis of 1,4-naphthoquinone 90 **under optimised conditions (Experiment 114).**

Early studies of the application of the optimised juglone **98** conditions using solar light resulted in a black, charred residue after evaporation of the reaction solvent. To avoid this apparent degradation, during rotary evaporation the temperature was maintained at less than 43 °C. Under sunlight conditions reaction was not successful (Experiment 115). Following 6 hours of irradiation under sunlight conditions, no residual starting material **226** was observed in the ^{1}H HMR (acetone-d_6) spectrum. A complicated mixture was obtained, which gave uninterpretible ^{1}H NMR data upon passing though a silica column.

5.2.3.2 Synthesis of 6-hydroxy-1,4-naphthoquinone

The synthesis of 6-hydroxy-1,4-naphthoquinone **262** from 1,6-dihydroxynaphthalene **261** by photooxygenation reaction (Scheme 103) has been investigated previously by a 4th year student (Niall Healy). This was shown to be successful in *i*-propyl alcohol using methylene blue **42** (49%, 10 hrs in sunlight), as well as using TPP **43** in a mixture of methanol and dichloromethane (1:9).



261 **262**

Scheme 103: Synthesis of 6-hydroxy-1,4-naphthoquinone 262 **(Experiment 116-117).**

This study looked at the synthesis using conditions optimised for juglone **98** synthesis, using rose bengal **41** and *t*-amyl alcohol under artificial light irradiation using one 500 W halogen lamp (Experiment 112). Samples were taken at 2, 4, 6 and 24 hours to evaluate conversion (Figure 64). After 24 hours irradiation a conversion of 80% was achieved.

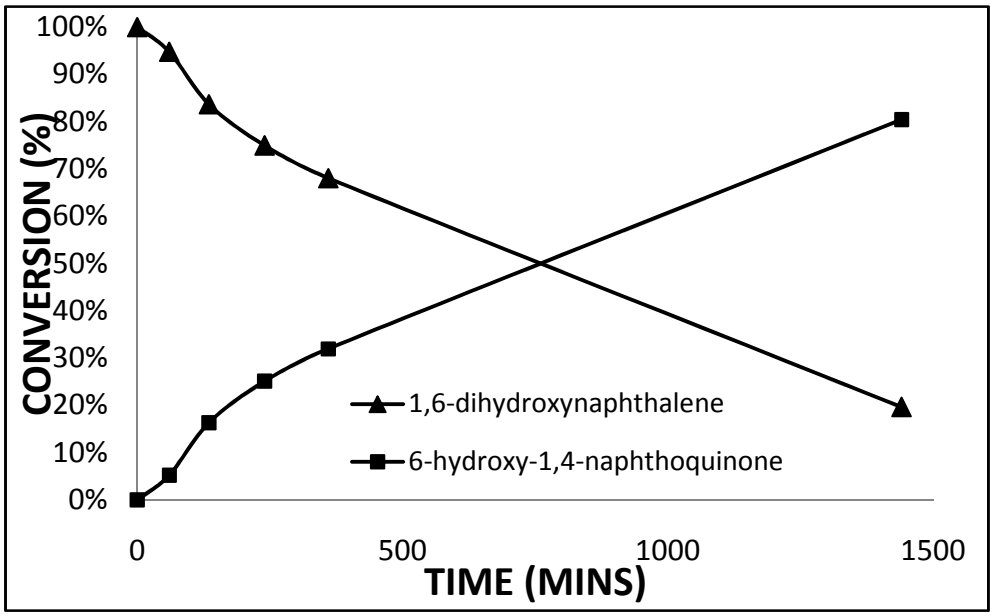


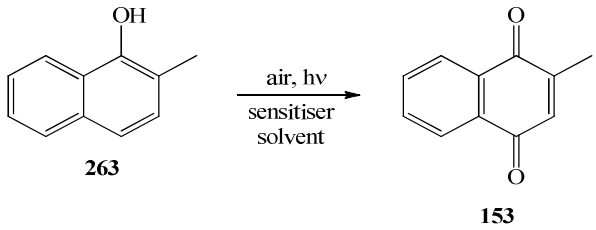
Figure 64: Synthesis of 6-hydroxy-1,4-naphthoquinone 262 **(Experiment 116).**

In previous studies, purification of the 6-hydroxy-1,4-naphthoquinone **262** product was achieved using a gradient elution using ethyl acetate (30-60%) in *n*-hexane. However, in order to conform to the 'green' parameters previously defined the use of *n*-hexane was substituted using cyclohexane. Using cyclohexane:ethyl acetate (3:1) as mobile phase, the use of gradient elution was not necessary and the product **262** was isolated as a bright orange solid.

Using solar irradiation for 6 hours, in direct sunight conditions, an isolated yield of 68% was obtained (Experiment 117). There was no observed side reaction and the sole product obtained was 6-hydroxy-1,4-naphthoquinone **262**.

5.2.3.3 Synthesis of 2-methyl-1,4-naphthoquinone

The synthesis of 2-methyl-1,4-naphthoquinone **153** from 2-methyl-1-naphthol **263** by photooxygenation reaction (Scheme 104) is of interest as the product, menadione **153**, is a precursor to Vitamin K compounds.



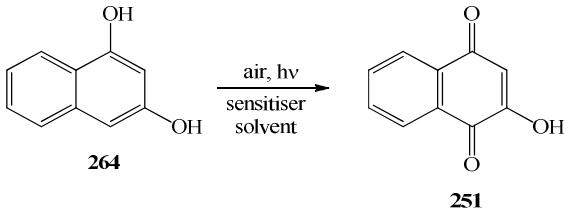
263 **153**

Scheme 104: Synthesis of 2-methyl-1,4-naphthoquinone 153 **(Experiment 118).**

Artificial light irradiation studies were carried out, with samples taken at 1, 2, 4, 6, 8 and 24 hours to monitor conversion. After 4 hours of irradiation a conversion of 53% was observed and conversion of 100% was achieved after 24 hours. A repeat experiment showed that a conversion of close to 100% could be achieved in 12 hours. However, there appears to be more than one product formed during this process, the first is the anticipated 2-methyl-1,4-naphthoquinone **153**, while the other is unidentified. ^{1}H NMR spectroscopy (acetone-d_6) shows the presence of two peaks in a 1:1 ratio, with one doublet at ca. 8.3 ppm and one quartet at 6.9 ppm.

5.2.3.4 Synthesis of 2-hydroxy-1,4-naphthoquinone

The synthesis of 2-hydroxy-1,4-naphthoquinone **251** (lawsone) from 3-hydroxy-1-naphthol **264** by photooxygenation reaction (Scheme 105) was investigated.



264 **251**

Scheme 105: Synthesis of 2-hydroxy-1,4-naphthoquinone 251 **(Experient 119-120).**

Artificial light irradiation studies were carried out, with samples taken at 1, 2, 4, 6, 8 and 24 hours to monitor conversion (Experiment 119). A conversion of 66% was observed after 4 hours irradiation and conversion of 100% was achieved after 24 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that the desired product **251** was obtained (88%), as well as a small amount of an unidentified by-product (12%).

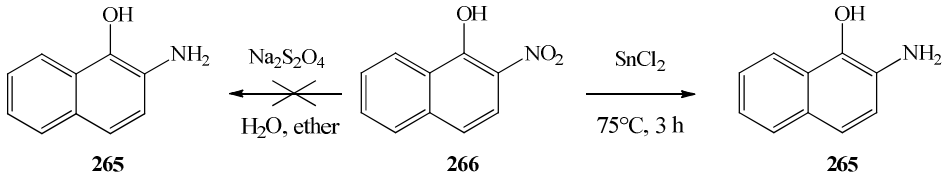
A repeat experiment showed that a conversion of 66% was achieved in 12 hours (Experiment 120). ^{1}H NMR spectroscopy (acetone-d_6) showed no evidence of a by-product. This suggests that the by-product is only produced as a result of prolonged exposure to light.

5.2.4 Synthesis of 2-amido-1-naphthols

Following the synthesis of a series of 5-amido-1-naphthols **233** and their conversion to the corresponding 5-amido-1,4-naphthoquinones **234** by dye-sensitised photooxygenation it was decided to assess the application of 2-amido-1-naphthols in a similar fashion. The 2-amido-1,4-naphthoquinone is a key moiety in some biologically active substances, and are therefore of interest as target compounds[136].

5.2.4.1 Synthesis of 2-amino-1-naphthol

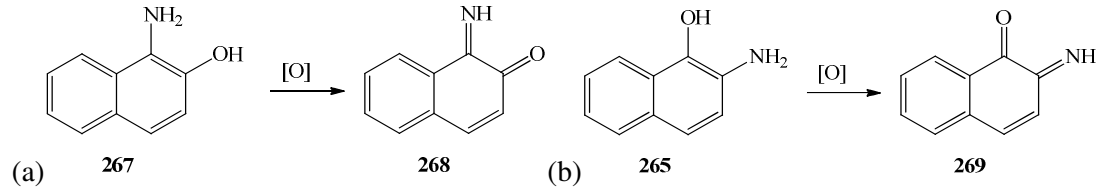
The 2-amino-1-naphthol **265** starting moiety was not commercially available, and was therefore prepared by reduction of 2-nitro-1-naphthol **266**. Use of sodium dithionite as a reducing agent was investigated by a supervised undergraduate student, Kate Corcoran (Experiments 121A-122A), but this proved unsuccessful[263]. Therefore the use of tin (II) chloride was assessed as an alternative (Scheme 106, Experiments 123-125).



Scheme 106: Preparation of 2-amino-1-naphthol 265 **(Experiments 121-125).**

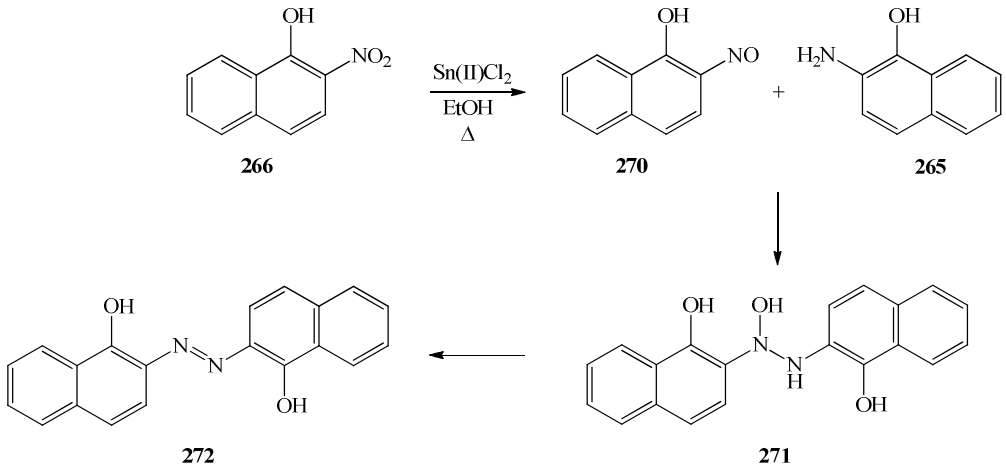
Tin (II) chloride dihydrate and 2-nitro-1-naphthol **266** were refluxed in ethanol (or an ethanol-ethyl acetate mixture) for 3-16 h, following a method by Bellamy (Experiments 118-120)[264]. However, the desired product was not obtained as the sole product. Small scale reaction (0.15 mmol, Experiment 124) yielded a single product, while larger scale (1 mmol, Experiment 125) gave a mixture of two products.

Literature studies have shown that 1-amino-2-naphthol **267** can undergo a two electron transfer process under oxidation conditions, leading to the formation of the corresponding 1,2-naphthoquinone-1-imine **268** (Scheme 107a)[265]. A similar process may be observed for 2-amino-1-naphthol **265**, forming the corresponding 1,2-naphthoquinone-2-imine **269** (Scheme 107b)[266].



Scheme 107: Conversion of (a) 1-amino-2-naphthol 267 **to 1,2-naphthoquinone-1-imine** 268 **and (b) 2-amino-1-naphthol** 265 **to 1,2-naphthoquinone-2-imine** 269**.**

^{1}H NMR spectroscopy of the crude product following reduction of 2-nitro-1-napthol **266** using tin (II) chloride indicates the presence of more than one substance. Mass spectrometry (ESI, MS^+) of the crude product shows evidence that a coupling reaction has occurred, as shown in Scheme 108. The desired product, 2-amino-1-naphthol **265** is expected to have a parent ion m/z value of 159.1. However, the masses observed are much larger, in particular peaks of m/z 304.8, 315.5 and 332.7. The nitrosyl intermediate **270** formed may react with the desired amine **265**, resulting in an N-N coupled compound **271** (expected m/z of 332), which can undergo dehydration to the azo compound **272** (expected m/z of 314).

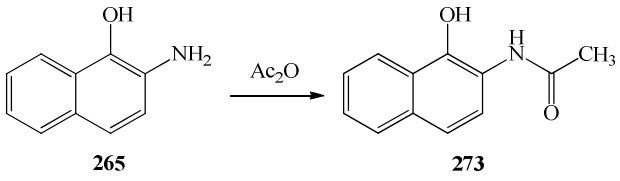


Scheme 108: Synthesis of N-N coupled compounds 271 **and** 272 **from 2-nitro-1-naphthol** 266**.**

IR analysis showed the presence of the characteristic OH stretch at 3266 cm^{-1} which is consistent with expectations for both dimeric structures **271** and **272**, as well as the desired product **265**. The absence of the characteristic C=O stretch at 1600-1800 cm^{-1} indicates that conversion to the 1,2-naphthoquinone-2-imine **269** has not occurred.

5.2.4.2 Synthesis of 2-acetamido-1-naphthol

The crude product from the reduction of 2-nitro-1-naphthol **266** using tin (II) chloride was used in efforts to prepare 2-acetamido-1-naphthol **273**. Crude 2-amino-1-naphthol **265** was converted to the corresponding amide **273** using acetic anhydride (Scheme 109), following the procedure for 5-acetamido-1-naphthol **233a** (Chapter 4, Section 5.2.1.1).



Scheme 109: Preparation of 2-acetamido-1-naphthol 273 **from 2-amino-1-naphthol** 265 **(Experiments 126-127).**

The product **273**, a yellow powder, was obtained in yields of 8-9%. Analysis by ^{1}H NMR spectroscopy and ^{13}C NMR spectroscopy indicated that a single mono-acylated product was formed. However, UV-vis spectrophotometry indicated a significant red shift that was consistent with a conjugated system, rather than the anticipated aromatic system. The absorbance of the acylated product **273** (Figure 65) was compared to that of 5-acetamido-1-

naphthol **233a** (Figure 66), which is considered a closely related compound. Of significance is the absorbance of the acetylation product **273** in the region 340-490 nm, which indicates the presence of an extended conjugated system.

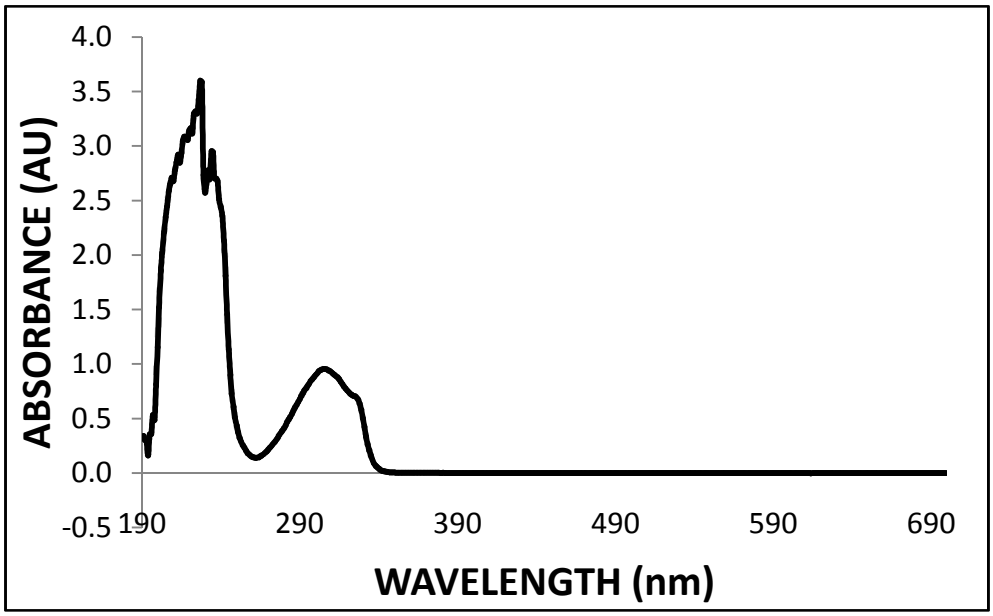


Figure 65: UV-vis spectrum of 5-acetamido-1-naphthol 233a **(in methanol).**

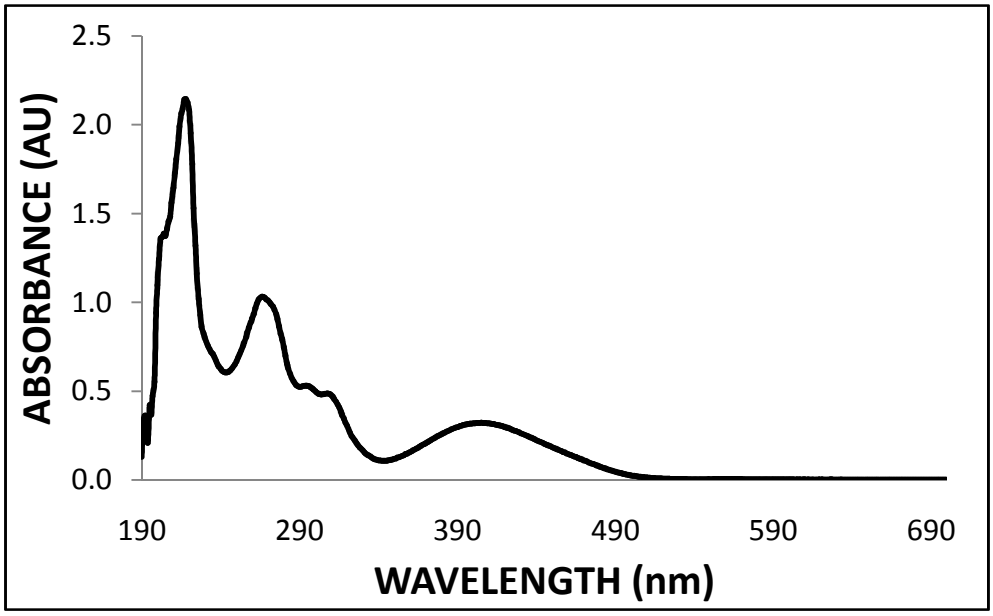
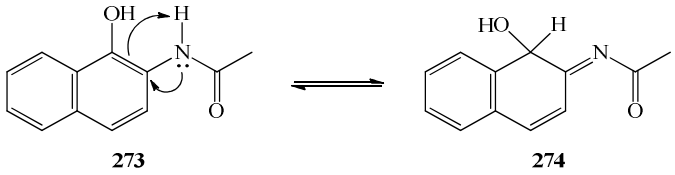


Figure 66: UV-vis spectrum of isolated product 273 **after acetylation of crude 2-amino-1-naphthol 265 (in methanol).**

Two possible products were proposed. The first is a structural isomer **274**, which involves a proton shift from the amide to the aromatic ring, as shown in Scheme 110. The loss of

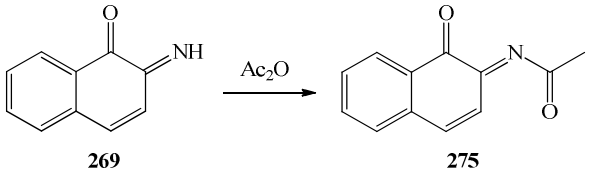
aromaticity caused by this shift is compensated for by the extension of conjugation. This structure has been proposed in the literature by Novak[267].



273 **274**

Scheme 110: Isomerisation of 2-acetamido-1-naphthol 274**.**

Another possible product is the result of the reaction of 1,2-naphthoquinone-2-imine **269** with acetic anhydride, giving acetylation of the imine to form an amide **275**, as shown in Scheme 111.



269 **275**

Scheme 111: Acetylation of 1,2-naphthoquinone-2-imine 269**.**

However, analysis of the starting material has shown that the 1,2-naphthoquinone-2-imine **269** is not formed, thus **275** cannot be obtained by this route.

To confirm the structure of the product, full characterisation was carried out using ^{1}H NMR, ^{13}C NMR and IR spectroscopy (Figure 67). ^{1}H NMR spectroscopy showed the presence of 6 distinct protons, with a singlet at 2.1 ppm confirming acetylation has occurred, and peaks in the region 7.4-8.1 corresponding to all six of the naphthalene protons, showing that substitution has not occurred on the ring. However, there is a broad singlet at 9.6 ppm, which may correspond to an alcohol or amine proton. This suggests that the product is not from the acetylation of 1,2-naphthoquinone-2-imine **269**, as this structure would have neither alcohol or amine protons present.

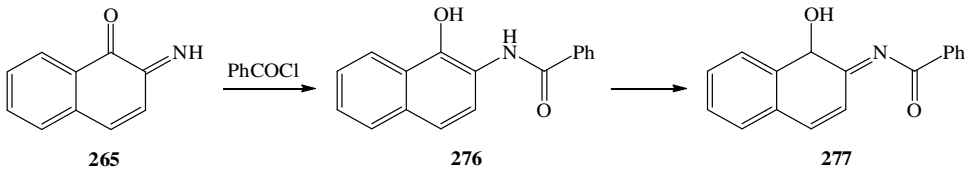
The ^{13}C NMR spectrum provided further confirmation that acetylation was successful, as the characteristic amide carbon was present at 169 ppm. The spectra showed that there were 12 distinct carbon atoms present in the molecule, as expected for the acetylation of either possible substrate.

However, the IR spectrum (solid phase) does not appear to have an OH stretch, which would suggest that the product is not the structural isomer **274** of 2-acetamido-1-naphthol **270**.

Figure 67: IR spectrum of isolated acylated product 273**.**

5.2.4.3 Synthesis of 2-benzamido-1-naphthols

Following the study of 2-acetamido-1-naphthol **273** and the proposed formation of a conjugated derivative **274**, the extension of this synthesis to 2-benzamido-1-naphthol **276** was investigated (Scheme 112). This compound offers potential as a novel dye, as the presence of the phenyl substituent could enable extended conjugation **277**.



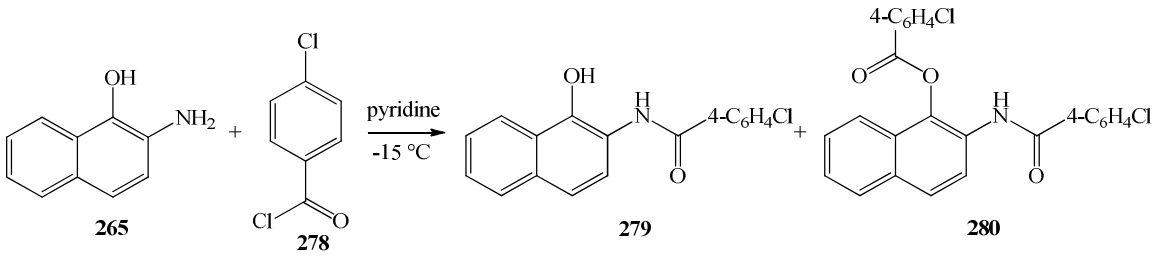
265 **276** **277**

Scheme 112: Synthesis of aryl substituted 2-amido-1-naphthol 276 **and conversion to conjugated isomer** 277 **(Experiment 128).**

The crude product obtained was reddish-brown in colour. Recrystallisation using ethyl acetate and *n*-hexane yielded three precipitates. A major by-product of the reaction was benzoic acid, formed from the acid chloride. Mass spectrometry of the crude starting material showed that

there were many impurities present. As a result, there was a large excess of acid chloride used, leading to formation of benzoic acid side product. Mass spectrometry of the product indicated formation of both the desired *mono*-acylated product **276** (ESI, MS^- expected m/z = 263.1, observed m/z 262.3 M-1) and the *bis*-acylated side product **277** (ESI, MS^+ expected m/z = 367.1, observed m/z 368.4 M+1) occurred.

In addition, the reaction of crude 2-amino-1-naphthol **265** with 4-chlorobenzoyl chloride **278** was investigated in association with a supervised undergraduate student, Kate Corcoran, (Scheme 113). Following recrystallisation, the *bis*-acylated 2-amino-1-naphthol product **280**, similar to that observed in the preparation of 5-amido-1-naphthols **133b-i**, was obtained. This indicates that the crude 2-amino-1-naphthol **265** contained some of the desired 2-amino-1-naphthol **265**, and had not undergone complete conversion to 1,2-naphthoquinone-2-imine **269**. In addition, mixtures of the *mono*-product **279** and *bis*-acylated product **280** were obtained. Mass spectrometry (ESI, MS^+) confirmed the presence of the *bis*-acylated compound **280** (expected m/z = 435.0, observed m/z = 436.1 M+1), while the *mono*-acylated product **279** was observed in negative mode (ESI, MS^- expected m/z = 297.1, observed m/z = 296.3 M-1).

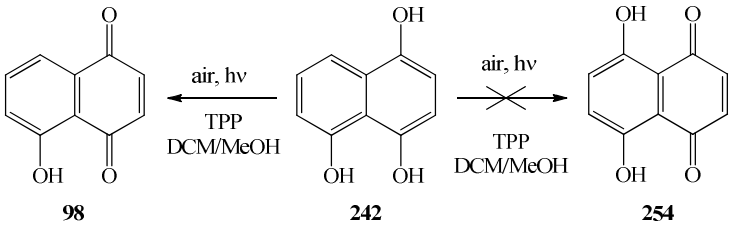


Scheme 113: Reaction of 2-amino-1-naphthol 265 **with 4-chlorobenzoyl chloride** 278 **(Experiment 129A).**

5.2.5 Other photooxygenation experiments

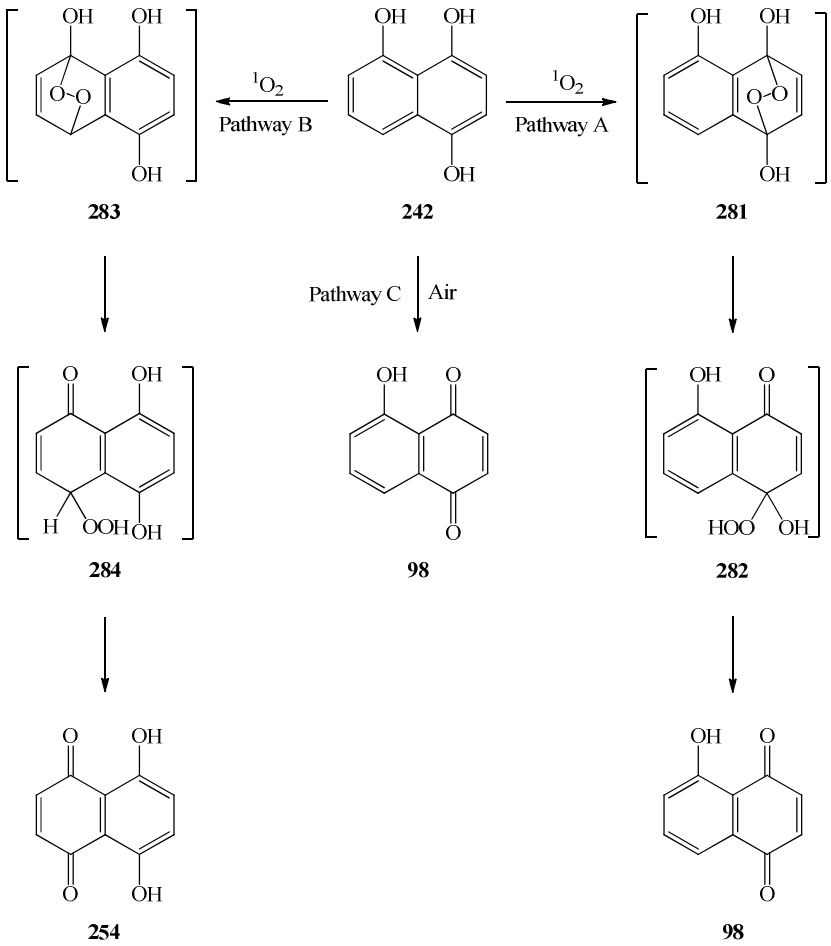
5.2.5.1 Attempted photochemical synthesis of naphthazarin

Synthesis of naphthazarin **254** (5,8-dihydroxy-1,4-naphthoquinone) by photooxygenation of 1,4,5-trihydroxynaphthalene **242** using TPP **43** in dichloromethane:methanol (9:1) was investigated (Scheme 114).



Scheme 114: Attempted synthesis of naphthazarin 254 **(Experiment 130).**

Although the reaction solution turned green in colour, indicating some change had occurred, ^{1}H NMR spectroscopy (DMSO-d_6) after 4 h did not show the presence of naphthazarin **254**. The main product formed was juglone **98**, while trace amounts of 1,4,5-trihydroxynaphthalene **242** were present. The colour change may be attributed to the reaction of TPP with acid in the chlorinated solvent, as this causes a colour change from pink to green (Scheme 115).



Scheme 115: Mechanism for the photooxygenation of 1,4,5-trihydroxynaphthalene 242**.**

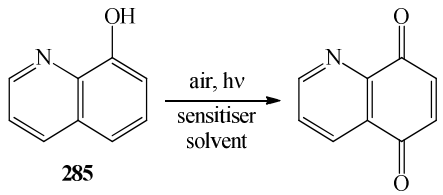
There are two possible endoperoxides that may be formed. However, following the mechanism for juglone synthesis, the endoperoxide **281** formed by pathway **A** cannot open to a non-hydroxyl side. In this case, naphthazarin **254** cannot be formed and the endoperoxide may cleave via retro-Diels-Alder reaction to regenerate the starting material **242**. This is known for other endoperoxides and is used to thermally generate singlet oxygen, for example from the endoperoxides of 9,10-disubstituted-anthracene compounds. Juglone **98** may be formed following formation of the hydroperoxide **282** and subsequent elimination of water.

In pathway **B**, the endoperoxide **283** formed has an available *para*-position, where it can undergo ring opening to form naphthazarin **254**, however ^{1}H NMR analysis shows that this is not the case as no naphthazarin **254** is obtained. The endoperoxide **283** may be formed, but undergoes retro-Diels-Alder conversion back to the triol **242** with release of singlet oxygen.

An alternative explanation for the formation of juglone **98** in this process is the air oxidation of 1,4,5-trihydroxynaphthalene **242**, as shown in pathway **C**. This autooxidation is known for 1,4,5-trihydroxynaphthalene **242**[256].

5.2.5.2 Photooxygenation of 8-hydroxyquinoline

An investigation into the photooxygenation of 8-hydroxyquinoline **285** using a variety of sensitisers and solvents was carried out, with the aim of synthesising quinoline-5,8-dione **286** (Scheme 116).



285 **286**

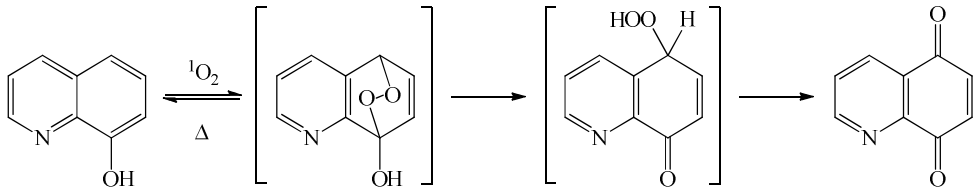
Scheme 116: Photooxygenation of 8-hydroxyquinoline 285 **(Experiments 131-138).**

Following the procedure by Cossy, synthesis of quinoline-5,8-dione **286** from 8-hydroxyquinoline **285** using TPP **43** in dichloromethane produced the desired product **286** (Experiment 131)[268]. The crude ^{1}H NMR spectrum ($CDCl_3$) showed two doublets representing the two quinonoid protons at 7.01 ppm and 7.02 ppm. However, following recrystallisation from ethyl acetate the product **286** was not isolated.

Following the procedure by Amarasekara (methylene blue **42** in dichloromethane:methanol (4:1)) synthesis of quinoline-5,8-dione **286** from 8-hydroxyquinoline **285** was unsuccessful (Experiment 132)[269]. It is noted in the literature that this reaction is very temperature dependent and does not proceed at temperatures greater than 15 °C. In the current reaction set-up, temperature control is achieved only through the use of a cold finger, and the reaction temperature is usually greater than 20 °C, through the heat generated by the lamp. This may explain why the reaction did not proceed.

Investigation of the use of alcohols as solvent (*i*-propyl alcohol or *t*-amyl alcohol, Experiments 133-138) demonstrated that the desired product could not be isolated. For the above reactions, TLC indicated reduction in starting material and formation of a new substance, however the ^1H NMR spectra ($CDCl_3$) were consistent with 8-hydroxyquinoline **285** and the quinonoid proton peaks were absent. This may be a result of the higher temperatures required to remove alcoholic solvents by rotary evaporation. In general, photooxygenation of 8-hydroxyquinoline **285** worked poorly, which may be attributed to the lack of temperature control during the photooxygenation reaction.

Like the photooxygenation of 1,5-dihydroxynaphthalene **97**, this reaction proceeds via an endoperoxide **287** (Scheme 117). This endoperoxide **287** may undergo a thermal retro-Diels-Alder reaction to regenerate singlet oxygen. Therefore, the reaction of singlet oxygen and 8-hydroxyquinoline **285** may proceed initially, but the rate of the retro-Diels-Alder reaction is greater than that of the elimination of water, hence starting material **285** is regenerated unless the reaction is cooled significantly.



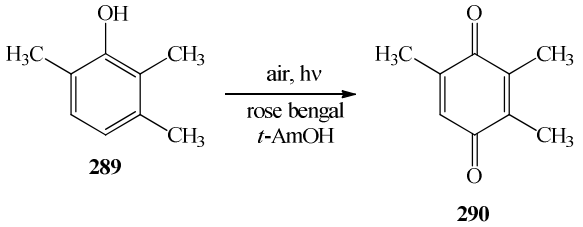
Scheme 117: Mechanism for the photooxygenation of 8-hydroxyquinoline 281**.**

The synthesis of this compound **286** was achieved (although in low yields) using the procedure by Cossy, in which tetraphenylporphyrin **43** is used as a sensitiser, while experiments using rose bengal **41** and methylene blue **42** were unsuccessful. The success of this reaction may be attributed to the lifetime of singlet oxygen in chlorinated solvents being far greater than that in *t*-amyl alcohol (Table 5). The reaction using methylene blue **42** in a dichloromethane-methanol mixture did not generate the desired product **286**, despite having the same singlet oxygen

lifetime. This may be attributed to the lower quantum yield of singlet oxygen from methylene blue **42** compared to tetraphenylporhyrin **43**.

5.2.5.3 Photooxygenation of 2,3,6-trimethylphenol

Following the optimised procedure for juglone **98** synthesis, 2,3,6-trimethyl-1,4-benzoquinone **290** was synthesised from 2,3,6-trimethylphenol **289** using rose bengal **41** in *t*-amyl alcohol (Scheme 118).

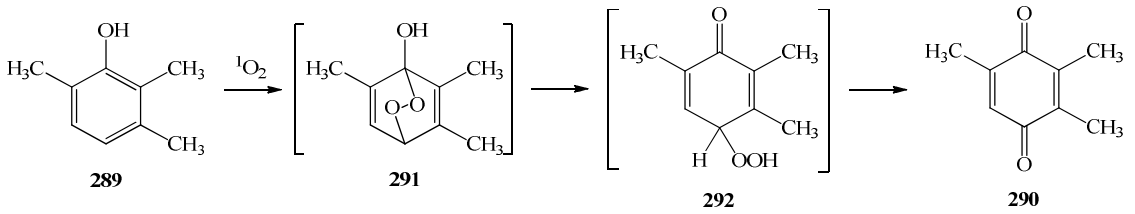


Scheme 118: Synthesis of 2,3,6-trimethyl-1,4-benzoquinone 290 **(Experiment 139).**

Photooxygenation of 2,3,6-trimethylphenol **289** to 2,3,6-trimethyl-1,4-benzoquinone **290** was investigated under the optimised conditions for juglone **98** synthesis. This was chosen as a model reaction as the photooxygenation of 2,3,6-trimethylphenol **289** has been reported previously[28].

Following artificial light irradiation for 4 hours, ^{1}H NMR spectroscopy (DMSO-d_6) showed a characteristic aromatic proton peak, which presented as a singlet at 6.55 ppm, indicating that some conversion to product **290** was achieved. In addition, one of the methyl singlets was identified at 2.12 ppm. However doublets representing the two aromatic H peaks of starting material **289** were evident at around 6.5 ppm and the three methyl groups masked those of the product. The ratio of starting material **289** to product **290** was determined from the integrations as 75:25, indicating that conversion of 25% was achieved in 4 hours irradiation.

The mechanism of this reaction is a photo-Diels-Alder reaction of singlet oxygen and the phenolic starting material **289**. This then undergoes spontaneous elimination of water to yield the corresponding 1,4-benzoquinone **290** (Scheme 119).

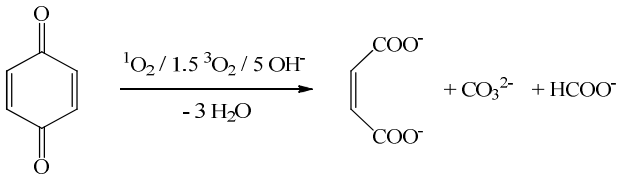


289 **291** **292** **290**

Scheme 119: Mechanism for the photooxygenation of 2,3,6-trimethylphenol 289**.**

Following irradiation for 4 hours and 6 hours conversion was incomplete. This was consistent with observations by Murtinho, who demonstrated that conversions of 6-93% **290** were obtained following 24 hours of irradiation using a variety of sensitisers[28].

Gerdes has investigated the mechanism for singlet oxygen oxidation of non-substituted phenol[30, 258]. In this procedure, 1,4-benzoquinone **70** is formed, but is unstable under reaction conditions and undergoes further reaction to succinic acid **293** (Scheme 120). This indicates that the presence of methyl substituents stabilises the 2,3,6-trimethyl-1,4-benzoquinone **290**.



70 **293**

Scheme 120: Degradation of 1,4-benzoquinone 70 **upon photooxygenation.**

5.3 Summary

Following optimisation of the synthesis of juglone **98** under artificial and sunlight conditions, this procedure was applied to other 1-naphthol substrates.

The synthesis of a library of 5-amido-1-naphthols **233** was carried out, which were converted to the corresponding 5-amido-1,4-naphthoquinones **234** by photooxygenation in artificial and solar conditions. These 5-amido-1,4-naphthoquinones **234** were of interest due to their ability to hydrogen bond at the 5-position, similar to juglone **97**. The 5-amido-1-naphthols **233** were synthesised from 5-amino-1-naphthol **232** in yields of 15-69%. Conversion to the corresponding 5-amido-1,4-naphthoquinones **234** was carried out using optimised conditions for juglone **98** synthesis in artificial light conditions (4 hours and 24 hours) and in sunlight (6 hours). Using solar light yields of up to 90% were achieved.

Synthesis of 5-acetoxy-1-naphthol **170** was also carried out, followed by conversion to 5-acetoxy-1,4-naphthoquinone **250**. Literature reports that the product of this photooxygenation is juglone **98**, however this study shows juglone **98** formation as a by-product, with the desired naphthoquinone **250** as the major product.

5.4 Experimental

5.4.1 Preparation of 5-substituted-1-naphthols

General procedure for preparation of 5-amido-1-naphthols 234b-i

Acid chloride was added dropwise to a solution of 5-amino-1-naphthol **232** in pyridine (-10 °C, under N_2), and the resultant mixture stirred for 3 hours at room temperature. The reaction mixture was poured over ice water. The resultant precipitate was vacuum-filtered and washed with ice cold water (or if no product precipitated an extraction with dichloromethane or ethyl acetate was carried out). The product was purified by recrystallisation, using either method A or method B. The purified product was characterised by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and UV spectrophotometry.

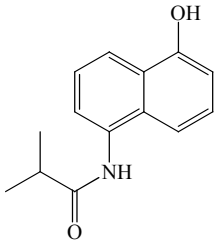
Recrystallisation method A: The crude product is dissolved in hot ethanol and addition of hot water (1:1) causes precipitation of the *bis*-acylated side product. This is removed by vacuum filtration. Upon cooling the filtrate, the desired amide precipitates out and is collected by vacuum filtration. The purified product is washed with a mixture of ice cold ethanol and water (1:1).

Recrystallisation method B: The crude product is dissolved in hot ethyl acetate and filtered to remove insoluble impurities. The filtrate is concentrated by rotary evaporation, and cyclohexane added dropwise until the product crystallises. The purified product is collected by vacuum filtration and washed with ice cold cyclohexane.

Experiment 68A (EH-04): 5-Acetamido-1-naphthol *See Appendix A*

Experiment 69A (EH-14): 5-Propanamido-1-naphthol *See Appendix A*

Experiment 70 (EC-164): 5-(*iso*-Butyramido)-1-naphthol



233c

The general procedure was followed using *iso*-butyryl chloride (1.3 ml, 12 mmol) and 5-amino-1-naphthol **232** (2.39 g, 15.0 mmol) in 20 ml of pyridine. Only a small amount of precipitate was formed after the reaction mixture was poured onto ice water and so the solution was extracted with ethyl acetate. The precipitate was filtered off and washed twice with cold water. The product was recrystallised using method B. 5-(*iso*-Butyramido)-1-naphthol **233c** was obtained in 27% yield (0.752 g, 3.28 mmol) as a dark purple solid.

^{1}H NMR (600 MHz, acetone-d$_6$) δ (ppm) = 1.26 (d, 6H, 2C**H**$_3$, J^3 = 6.7 Hz); 2.88 (m, 1H, C**H**$(CH_3)_2$, J^3 = 5.9 Hz); 6.92 (d, 1H, **H**$_{arom.}$, J^3 = 7.3 Hz); 7.30 (t, 1H, **H**$_{arom.}$, J^3 = 7.9 Hz); 7.42 (t, 1H, **H**$_{arom.}$, J^3 = 8.0 Hz); 7.58 (d, 1H, **H**$_{arom.}$, J^3 = 8.5 Hz); 7.88 (d, 1H, **H**$_{arom.}$, J^3 = 7.3 Hz); 8.09 (d, 1H, **H**$_{arom.}$, J^3 = 8.3 Hz); 8.96 (s, 1H, O**H**); 9.07 (s, 1H, N**H**).

^{13}C NMR (150 MHz, acetone-d$_6$) δ (ppm) = 20.1 (2**C**H_3); 36.4 (**C**$H(CH_3)_2$); 109.0, 114.0, 120.0, 122.4, 125.0, 126.6, 126.9, 130.2 (8 **C**$_{arom.}$); 134.5 (**C**-OH); 154.4 (**C**-NH); 176.5 (**C**=O).

IR (ATR) υ (cm^{-1}) = 3231 (O-H), 2976 (N-H), 1528 (C=O), 1273 (C-N) and 1221 (Ar-OH).

UV (methanol) λ (nm) = 223, 305.

Melting point: 219 °C.

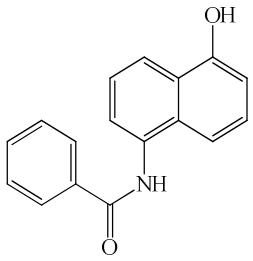
Mass Spectrometry (ESI, MS$^-$) m/z = 228.5 (M-1, expected m/z 229.1).

CAS no. not assigned, new compound.

Experiment 71A (EH-22): 5-(Trimethyl)acetamido-1-naphthol *See Appendix A*

Experiment 72A (EH-30): 5-(*cyclo*-Propanecarban)amido-1-naphthol *See Appendix A*

Experiment 73 (EC-047/EH-05): 5-Benzamido-1-naphthol



233f

The general procedure was followed using benzoyl chloride (7.0 ml, 0.060 mol) and 5-amino-1-naphthol **232** (7.0 g, 0.044 mol) in pyridine (75 ml). Product was purified using recrystallisation method A. 5-Benzamido-1-naphthol **233f** was obtained in 15% yield (1.72 g, 6.53 mmol) as a pale pink solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.89 (d, J^3 = 7.2 Hz, 1H, H_{arom}); 7.30 (dd, J^3 = 7.6 Hz, 8.4 Hz, 1H, H_{arom}); 7.41 (d, J^3 = 8.4 Hz, 1H, H_{arom}); 7.47 (dd, J^3 = 7.2 Hz, 8.4 Hz, 1H, H_{arom}); 7.65-7.28 (m., 7H, $H_{arom.}$); 8.12-8.06 (m, 3H, $H_{arom.}$); 10.22 (s, 1H, N**H**); 10.34 (s, 1H, O**H**).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 108.2; 113.8; 120.5; 124.0; 124.4; 125.4; 126.5; 127.8; 128.5; 130.8; 133.5; 134.5; 153.4; 168.1.

IR (KBr) υ (cm^{-1}) = 3256, 1734, 1634, 1598, 1577, 1517, 1487, 1408, 1377, 1353, 1307, 1276, 1246, 1207, 1175, 1145, 1121, 1069, 1025, 951, 920, 875, 781, 708, 647, 571, 419.

UV (methanol) λ (nm) = 203, 221, 272.

Melting point: 160 °C (lit. 284 °C).

CAS no. 75528-55-1, IR consistent with literature data[260].

Experiment 74A (EH-13): 5-(4-Chlorobenzamido)-1-naphthol *See Appendix A*

Experiment 75A (EH-19): 5-(4-Toluamido)-1-naphthol *See Appendix A*

Experiment 76A (EH-27): 5-(4-Cyanobenzamido)-1-naphthol *See Appendix A*

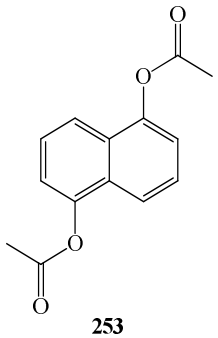
5.4.1.1 Hydrolysis of *bis*-acylated side product

Experiment 77 (EC-047/KC-05): Hydrolysis of 1-benzoxy-5-benzamidonaphthalene

The *bis*-acylated product **252f** (0.02 g, 0.05 mmol) was dissolved in acetone (20 ml) in a round bottom flask. Water (20 ml) was added and then conc HCl (6 ml). The mixture was refluxed for 24 hours and stirred at room temperature for 2 days. Water (25 ml) was added to dilute the acid and the acetone was removed by evaporation. The product was extracted using DCM (30ml) and dried using magnesium sulfate. ^{1}H NMR spectroscopy (DMSO-d_6) of the extract was used to determine the conversion from *bis*-acylated compound **252f** to 5-amido-1-naphthol **233f**, which was shown to be 90%.

5.4.1.2 Preparation of 5-acetoxy-1-naphthol

Experiment 78 (EC-051): Synthesis of 1,5-diacetoxynaphthalene



253

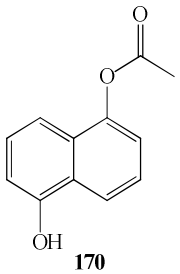
1,5-Dihydroxynaphthalene **97** (4.04 g, 25.2 mmol) and acetic anhydride (20.0 ml, 0.212 mol) were refluxed in pyridine (22 ml), under an atmosphere of N_2, for 7 hours. After this time, water was added to degrade excess acetic anhydride and the reaction mixture was poured over water (200 ml) and stirred for 20 mins. Vacuum filtration yielded an orange solid, which was purified by passing through a silica plug using dichloromethane and acetone (99:1) as eluent to yield 1,5-diacetoxynaphthalene **253** in 88% yield (5.34 g, 21.9 mmol) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.47 (s, 6H, C**H**$_3$); 7.38 (d, J^3 = 7.6 Hz, 2H, H_{arom}); 7.59 (dd, J^3 = 7.6 Hz, 8.4 Hz, 2H, H_{arom}); 7.84 (d, J^3 = 8.4 Hz, 2H, H_{arom}).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 2.47 (s, 6H, C**H**$_3$); 7.29 (d, J^3 = 7.6 Hz, 2H, H_{arom}); 7.51 (t, J^3 = 7.6 Hz, 8.4 Hz, 2H, H_{arom}); 7.78 (d, J^3 = 8.4 Hz, 2H, H_{arom}).

CAS no. 605-89-0.

Experiment 79 (EC-094): Synthesis of 5-acetoxy-1-naphthol



170

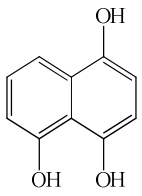
1,5-Diacetoxynaphthalene **253** (2.0 g, 8.1 mmol) and sodium borohydride (0.16 g, 4.2 mmol) in a mixture of ethanol and toluene (1:3) were stirred under an atmosphere of N_2 for 5.5 h. Diethyl ether (80 ml) was added and five extractions with water were carried out (5 x 50 ml). The organic layer was dried over sodium sulfate, filtered and evaporated to yield a yellow powder. This was purified by column chromatography using a mixture of cyclohexane, dichloromethane and acetone (15:4:3) as eluent to yield 0.73 g (3.6 mmol, 44%) of a white solid **170**.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 2.47 (s, 3H, C**H**$_3$); 5.65 (s, 1H, O**H**); 6.77 (d, J^3 = 7.6 Hz, J^4 = 0.8 Hz, 1H, H_{arom}); 7.26 (d, J^3 = 7.2 Hz, J^4 = 1.2 Hz, 1H, H_{arom}); 7.31 (dd, J^3 = 7.6 Hz, 1H, H_{arom}); 7.40 (d, J^3 = 8.4 Hz, 1H, H_{arom});, 7.45 (dd, J^3 = 7.6 Hz,1H, H_{arom}); 8.06 (d; J^3 = 8.4 Hz, 1H, H_{arom}).

CAS no. 94807-85-9, spectral data consistent with literature[261].

5.4.1.3 Preparation of 1,4,5-trihydoxynaphthalene

Experiment 80 (EC-036): Synthesis of 1,4,5-trihydroxynaphthalene



242

Juglone **98** (1.0 g, 5.7 mmol) and sodium dithionite (50 ml of saturated aqueous solution) were stirred vigorously in ether (50 ml) for 6 h. The solution turned from deep orange in colour to pale yellow. The ether layer was dried over magnesium sulfate and evaporation of the solvent yielded a pale green-brown solid. The product was purified by washing repeatedly with

chloroform to remove juglone **98** impurities. Following purification, 1,4,5-trihydroxynaphthalene **242** was obtained in 67% yield (0.68 g, 3.8 mmol) as a green-grey solid.

^{1}H NMR (400MHz, acetone-d$_6$) δ (ppm) = 6.62 (d, J^3 = 8.0 Hz, 1H, H_{arom}); 6.72 (d, J^3 = 8.4 Hz, 1H, H_{arom}); 6.78 (d, J^3 = 7.6 Hz, J^4 = 1.2 Hz, 1H, H_{arom}); 7.26 (dd, J^3 = 7.6 Hz, 8.4 Hz, 1H, H_{arom}); 7.66 (d, J^3 = 8.4 Hz, J^4 = 0.8 Hz, 1H, H_{arom}); 8.43 (s, 1H, O**H**); 9.73 (s, 1H, O**H**); 9.84 (s, 1H, O**H**).

CAS no. 481-40-3.

5.4.2 Photooxygenation of 5-amido-1-naphthols

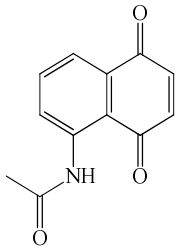
General procedure for artificial irradiation of 5-amido-1-naphthol series

The 5-amido-1-naphthol and rose bengal **41** were dissolved in *t*-amyl alcohol with sonication. The reaction solution was irradiated, with air bubbling, using one 500 W halogen lamp. The product was purified by column chromatography using a mixture of ethyl acetate and cyclohexane (1:3) as mobile phase.

General procedure for solar irradiation of 5-amido-1-naphthol series

The 5-amido-1-naphthol and rose bengal **41** were dissolved in *t*-amyl alcohol with sonication. The reaction solution was irradiated, with air bubbling, in sunlight for 6 hours. The product was purified by column chromatography using a mixture of ethyl acetate and cyclohexane (1:3) as mobile phase.

5.4.2.1 5-Acetamido-1,4-naphthoquinone



234a

Experiment 81 (EC-049/EH-06): Artificial irradiation for 4 hours

The general procedure was followed using 5-acetamido-1-naphthol **233a** (0.10 g, 0.50 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 4 hours. 5-Acetamido-1,4-naphthoquinone **234a** was obtained in 12% yield (0.013 g, 0.060 mmol) as a yellow solid.

Experiment 82 (EC-049/EH-07): Artificial irradiation for 24 hours

The general procedure was followed using 5-acetamido-1-naphthol **233a** (0.10 g, 0.50 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 24 hours. 5-Acetamido-1,4-naphthoquinone **234a** was obtained in 80% yield (0.086 g, 0.40 mmol) as a yellow solid.

Experiment 83 (EC-055/EH-08): Solar irradiation for 6 hours

The general procedure was followed using 5-acetamido-1-naphthol **233a** (0.10 g, 0.50 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 6 hours in direct sunlight conditions. 5-Acetamido-1,4-naphthoquinone **234a** was obtained in 90% yield (0.101 g, 0.47 mmol) as a yellow-orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 2.30 (s, 3H, C**H**$_3$); 6.91 (d, J^3 = 10.4 Hz, 1H, **H**$_{quin}$); 6.95 (d, J^3 = 10.4 Hz, 1H, **H**$_{quin}$); 7.73 (dd, J^3 = 7.6 Hz, 8.8 Hz, 1H, **H**$_{arom}$); 7.83 (d, J^3 = 7.6 Hz, J^4 = 1.2 Hz, 1H, **H**$_{arom}$); 9.08 (d, J^3 = 8.8 Hz, J^4 = 1.2 Hz, 1H, **H**$_{arom}$); 11.87 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 25.5; 121.8; 126.0; 136.3; 138.7; 140.9; 116.9; 133.4; 142.3; 170.2; 185.2; 190.0.

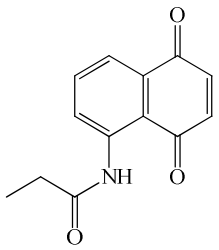
IR (KBr) υ (cm^{-1}) = 2925, 1647, 1263, 1159, 834, 766, 526, 448.

UV (methanol) λ (nm) = 211, 255, 413.

Melting point: 165 °C (lit. 173-174 °C).

CAS no. 5824-46-4, spectral data consistent with literature[270].

5.4.2.2 5-Propanamido-1,4-naphthoquinone



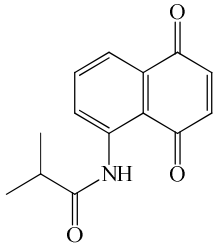
234b

Experiment 84A (EH-23): Artificial irradiation for 4 hours *See Appendix A*

Experiment 85A (EH-24): Artificial irradiation for 24 hours *See Appendix A*

Experiment 86A (EH-20): Solar irradiation for 6 hours *See Appendix A*

5.4.2.3 5-(*iso*-Butyramido)-1,4-naphthoquinone



234c

Experiment 87 (EC-173): Artificial irradiation for 4 hours

The general procedure was followed using 5-(*iso*-butyramido)-1-naphthol **233c** (0.23 g, 1.0 mmol) and rose bengal **41** (0.034 g, 34 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours. 5-(*iso*-Butyramido)-1,4-naphthoquinone **234c** was obtained in 28% yield (0.068 g, 0.28 mmol) as an orange solid.

Experiment 88 (EC-174): Artificial irradiation for 24 hours

The general procedure was followed using 5-(*iso*-butyramido)-1-naphthol **233c** (0.23 g, 1.0 mmol) and rose bengal **41** (0.034 g, 34 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. 5-(*iso*-Butyramido)-1,4-naphthoquinone **234c** was obtained in 54% yield (0.13 g, 0.54 mmol) as an orange solid.

Experiment 89 (EC-167): Solar irradiation for 6 hours

The general procedure was followed using 5-(*iso*-butyramido)-1-naphthol **233c** (2.23 g, 1.00 mmol) and rose bengal **41** (0.037 g, 36 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in direct sunlight conditions. 5-(*iso*-Butyramido)-1,4-naphthoquinone **234c** was obtained in 59% yield (0.144 g, 0.592 mmol) as an orange solid.

^{1}H NMR (600 MHz, acetone-d_6) δ (ppm) = 1.28 (d, 6H, 2C**H**$_3$, J^3 = 6.9 Hz); 2.70 (m, 1H, C**H**$(CH_3)_2$, J^3 = 7.0 Hz); 7.01 (d, 1H, C**H**$_{quin.}$, J^3 = 10.3 Hz); 7.03 (d, 1H, C**H**$_{quin.}$, J^3 = 10.3 Hz); 7.75 (dd, 1H, C**H**$_{arom.}$, J^3 = 7.6 Hz, J^4 = 1.1 Hz); 7.81 (t, 1H, C**H**$_{arom.}$, J^3 = 7.8 Hz); 9.08 (dd, 1H, C**H**$_{arom.}$, J^3 = 8.6 Hz, J^4 = 1.1 Hz); 11.90 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 19.7 (2**C**H_3); 38.2 (**C**H); 117.2, 133.5 (2C, **C**$_{q.\ arom.}$); 121.9, 126.2 (2C, **C**$H_{quin.}$); 136.3, 138.8, 141.0 (3C, **C**$H_{arom.}$); 142.5 (**C**-NH); 177.0 (C=O amide); 185.2, 190.1 (2C, C=O quinone).

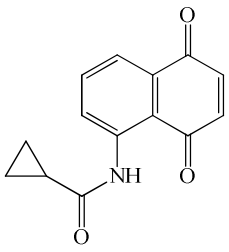
IR (KBr) υ (cm^{-1}) = 2987 (N-H), 1642 (C=O), 1578 (C=O).

UV (methanol) λ (nm) = 211, 256, 417.

Melting point: 149 °C.

CAS no. not assigned, new compound.

5.4.2.4 5-(*cyclo*-Propanecarban)amido-1,4-naphthoquinone



234d

Experiment 90A (EH-34): Artificial irradiation for 4 hours *See Appendix A*

Experiment 91A (EH-35): Artificial irradiation for 24 hours *See Appendix A*

Experiment 92 (EC-111): Solar irradiation for 6 hours

The general procedure was followed using 5-(*cyclo*-propanecarban)amido-1-naphthol **233d** (0.113 g, 0.497 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 6 hours in partial sun sunlight conditions. 5-(*cyclo*-Propanecarban)amido-1,4-naphthoquinone **234d** was obtained in 53% yield (0.065 g, 0.27 mmol) as an orange solid.

^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) = 0.97 (m, 4H, 2 C**H**$_2$); 1.83 (m, 1H, C**H**); 7.06 (2d, 2H, C**H**$_{quin}$, J^3 = 10.0 Hz); 7.75 (dd, 1H, **H**$_{arom}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz,); 7.81 (t, 1H, **H**$_{arom}$, J^3 = 8.0 Hz); 9.05 (dd, 1H, **H**$_{arom}$, J^3 = 8.4 Hz, J^4 = 1.2 Hz); 12.10 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 8.7 (2 **C**H$_2$); 17.1 (**C**H); 121.8, 126.2, 136.3, 138.8, 141.0 (5 **C**H$_{arom.}$); 116.8, 133.4 (2 **C**$_{q.\ arom}$); 142.3 (**C**$_{q.}$ NH); 173.8, 185.2 (**C**$_{q\ quin.}$); 190.1 (**C**=O amide).

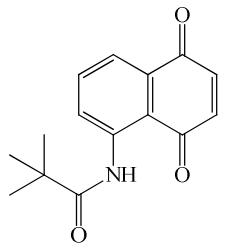
IR (KBr) υ (cm^{-1}) = 2926, 1694, 1670, 1643, 1578, 1495, 1412, 1340, 1294, 1259, 1191, 1157, 1088, 970, 878, 856, 835, 776, 835, 775, 731, 697, 636, 549, 449.

UV (methanol) λ (nm) = 212, 258, 417.

Melting point: 155 °C.

CAS no. 1186211-66-4, new compound.

5.4.2.5 5-(Trimethyl)acetamido-1,4-naphthoquinone



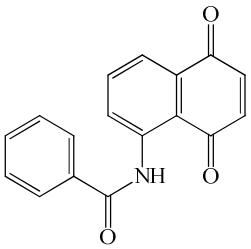
234e

Experiment 93A (EH-28): Artificial irradiation for 4 hours *See Appendix A*

Experiment 94A (EH-29): Artificial irradiation for 24 hours *See Appendix A*

Experiment 95A (EH-33): Solar irradiation for 6 hours *See Appendix A*

5.4.2.6 5-Benzamido-1,4-naphthoquinone



234f

Experiment 96 (EC-071/EH-09): Artificial irradiation for 4 hours

The general procedure was followed using 5-benzamido-1-naphthol **233f** (0.263 g, 1.00 mmol) and rose bengal **41** (0.050 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours. 5-Benzamido-1,4-naphthoquinone **234f** was obtained in 17% yield (0.047 g, 0.17 mmol) as an orange solid.

Experiment 97 (EC-071/EH-10): Artificial irradiation for 24 hours

The general procedure was followed using 5-benzamido-1-naphthol **233f** (0.263 g, 1.00 mmol) and rose bengal **41** (0.05 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. 5-Benzamido-1,4-naphthoquinone **234f** was obtained in 58% yield (0.161 g, 0.581 mmol) as an orange solid.

Experiment 98A (EH-15): Solar irradiation for 6 hours *See Appendix A*

^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) = 7.05 (dd, J^3 = 10.0 Hz, 2H, $\mathbf{H}_{quin}$); 7.64 (m, 3H, $\mathbf{H}_{arom.}$); 7.79 (d, J^3 = 7.6 Hz, J^4 = 1.2 Hz, 1H, $\mathbf{H}_{arom}$); 7.88 (dd, J^3 = 8.0 Hz, 1H, $\mathbf{H}_{arom}$); 8.08 (dt, J^3 = 5.6 Hz, J^4 = 1.2 Hz, 2H, $\mathbf{H}_{arom}$); 9.24 (d, J^3 = 8.4 Hz, J^4 = 1.2 Hz, 1H, $\mathbf{H}_{arom}$); 12.81 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 60.4; 117.6; 122.3; 126.2, 126.3, 129.9, 133.4, 133.5, 136.5, 138.9, 141.0; 135.4; 142.4; 148.7; 190.6.

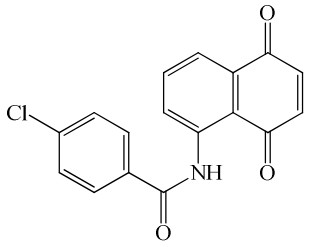
IR (KBr) υ (cm^{-1}) = 2900, 1575, 1263.

UV (methanol) λ (nm) = 201, 263, 421.

Melting point: 153 °C.

CAS no. 5813-59-2, no literature data available.

5.4.2.7 5-(4-Chlorobenzamido)-1,4-naphthoquinone



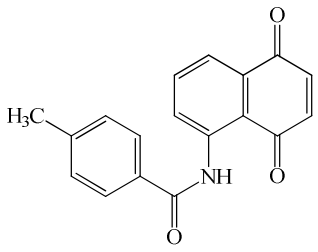
234g

Experiment 99A (EH-17): Artificial irradiation for 4 hours *See Appendix A*

Experiment 100A (EH-18): Artificial irradiation for 24 hours *See Appendix A*

Experiment 101A (EH-16): Solar irradiation for 6 hours *See Appendix A*

5.4.2.8 5-(4-Toluamido)-1,4-naphthoquinone



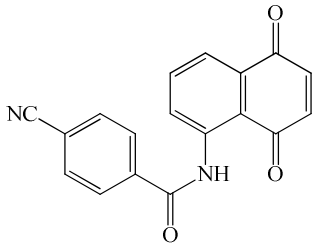
234h

Experiment 102A (EH-25): Artificial irradiation for 4 hours *See Appendix A*

Experiment 103A (EH-26): Artificial irradiation for 24 hours *See Appendix A*

Experiment 104A (EH-21): Solar irradiation for 6 hours *See Appendix A*

5.4.2.9 5-(4-Cyanobenzamido)-1,4-naphthoquinone



234i

Experiment 105A (EH-34): Artificial irradiation for 4 hours *See Appendix A*

Experiment 106A (EH-35): Artificial irradiation for 24 hours *See Appendix A*

Experiment 107 (EC-112): Solar irradiation for 6 hours

The general procedure was followed using 5-(4-cyanobenzamido)-1-naphthol **233i** (0.171 g, 0.593 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 6 hours in overcast sunlight conditions. 5-(4-Cyanobenzamido)-1,4-naphthoquinone **234i** was obtained in 23% yield (0.038 g, 0.13 mmol) as a yellow solid.

^{1}H NMR (400 MHz, acetone-d$_6$) δ (ppm) = 7.10 (2d, 2H, C**H**$_{quin.}$, J^3 = 10.0 Hz); 7.85 (dd, 1H, **H**$_{arom.}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz); 7.95 (t, 1H, **H**$_{arom.}$, J^3 = 8.0 Hz); 8.09 (dt, 2H, **H**$_{arom.}$, J^3 = 8.8 Hz,

J^4 = 1.6 Hz,); 8.27 (dt, 2H, $\mathbf{H}_{arom.}$, J^3 = 9.2 Hz, J^4 = 2.4 Hz); 9.22 (dd, 2H, $\mathbf{H}_{arom.}$, J^3 = 8.8 Hz, J^4 = 1.2 Hz); 12.93 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 116.6, 129.1, 133.9, 136.7, 139.1, 140.9 (7C, $\mathbf{C}H_{arom}$); 122.7, 126.3 (2C, $\mathbf{C}H_{quin.}$); 142.5 ($\mathbf{C}_{q.}$-NH); 182.1, 190.9 (**C**=O quinone); 165.6 (**C**=O amide).

IR (KBr) υ (cm^{-1}) = 2926, 2230, 1737, 1672, 1641, 1603, 1534, 1415, 1344, 1267, 1159, 1087, 861, 833, 786, 755, 677, 544, 448.

UV (methanol) λ (nm) = 203, 241, 282, 411.

Melting point: 217 °C.

CAS no. 1186211-70-0, new compound.

5.4.2.10 Solar study of 5-acetamido-1-naphthol

Experiment 108 (EC-055): Partial cloud conditions

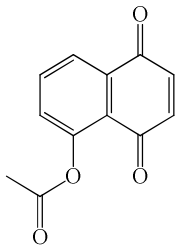
The general procedure was followed using 5-acetamido-1-naphthol **233a** (0.36 g, 1.8 mmol) and rose bengal **41** (0.020 g, 20 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 2 hours in partial cloud sunlight conditions. 5-Acetamido-1,4-naphthoquinone **234 a** was obtained in 45% yield (0.174 g, 0.809 mmol) as an orange solid.

Experiment 109 (EC-060): Overcast conditions

The general procedure was followed using 5-acetamido-1-naphthol **233a** (0.36 g, 1.8 mmol) and rose bengal **41** (0.050 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours in overcast sunlight conditions. 5-Acetamido-1,4-naphthoquinone **234a** was obtained in 35% yield (0.137 g, 0.637 mmol) as an orange solid.

5.4.2.11 Synthesis of 5-acetoxy-1,4-naphthoquinone

Experiment 110 (EC-095): Synthesis of 5-acetoxy-1,4-naphthoquinone (5.5 h)



250

5-Acetoxy-1-naphthol **170** (183 mg, 0.905 mmol) and rose bengal **41** (20 mg, 20 μmol) were dissolved in *t*-amyl alcohol (100 ml) and irradiated for 5.5 hours using one 500 W halogen lamp. Solvent was removed by rotary evaporation and ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed a mixture of starting material **170** (79%), juglone **98** (3%) and 5-acetoxy-1,4-naphthoquinone **250** (17%).

^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) = 2.46 (s, 3H, C**H**$_3$); 6.84 (d, 1H, **H**$_{quin.}$, J^3 = 10.4 Hz); 6.92 (d, 1H, **H**$_{quin.}$, J^3 = 10.5 Hz); 7.76 (t, 1H, **H**$_{arom.}$, J^3 = 8.0 Hz); 8.04 (d (partially masked by starting material peak), 1H, **H**$_{arom.}$, J^4 = 1.2 Hz). One aromatic proton has not been identified, but it is believed to be masked by starting material peaks.

^{1}H NMR (400 MHz acetone-d_6) δ (ppm) = 2.37 (s, 3H, C**H**$_3$); 6.93 (d, 1H, **H**$_{quin.}$, J^3 = 10.3 Hz); 7.03 (d, 1H, **H**$_{quin.}$, J^3 = 10.3 Hz); 7.55 (d, 1H, **H**$_{arom.}$, J^3 = 8.0 Hz, J^4 = 1.2 Hz); 7.91 (dd, 1H, **H**$_{arom.}$, J^3 = 8.0 Hz, 7.6 Hz); 8.01 (d, 1H, H$_{arom.}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz).

CAS no. 5196-28-1.

Experiment 111 (EC-139): Effect of heat on synthesis of 5-acetoxy-1,4-naphthoquinone

5-Acetoxy-1,4-naphthoquinone **250** (0.108 g, 0.500 mmol) was stirred in *t*-amyl alcohol (50 ml) at 60 °C for 3.5 h. Solvent was removed by rotary evaporation (temperature < 60 °C). ^{1}H NMR spectroscopy ($CDCl_3$) showed that no formation of juglone **98** occurred.

Experiment 112 (EC-139): Effect of acidic conditions on synthesis of 5-acetoxy-1,4-naphthoquinone

5-Acetoxy-1,4-naphthoquinone **250** (0.108 g, 0.500 mmol) was added to silica (10.0 g) and stirred in a mixture of ethyl acetate and cyclohexane (1:3, 50 ml) at room temperature for 4 h.

The reaction mixture was passed through a scintered glass filter and the collected silica was washed with mobile phase to remove all substrates. Solvent was removed by rotary evaporation (temperature < 40 °C). ^{1}H NMR spectroscopy ($CDCl_3$) showed that no formation of juglone **98** occurred.

Experiment 113 (EC-147): Synthesis of 5-acetoxy-1,4-naphthoquinone (12 h)

5-Acetoxy-1-naphthol **170** (0.203 g, 1.00 mmol) and rose bengal **41** (50 mg, 49 μmol) were dissolved in *t*-amyl alcohol (100 ml) and irradiated for 12 h using one 500 W halogen lamp. Solvent was removed by rotary evaporation and ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed a conversion of 43%. The ratio of 5-acetoxy-1,4-naphthoquinone **250** to juglone **98** was 3:1.

The product was purified by column chromatography using a mixture of ethyl acetate, acetone and cyclohexane (1:1:5). 5-Acetoxy-1,4-naphthoquinone **250** was obtained in 27% yield (0.058 g, 0.27 mmol, 63% yield based on conversion) as a yellow-orange solid. Juglone **98** was obtained as a minor product in 8% yield (0.014 g, 0.08 mmol, 18% based on conversion) as an orange solid.

5.4.3 Use of commercially available 1-naphthols

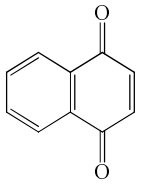
General procedure for artificial irradiation of 1-naphthol derivatives

1-Naphthol derivative and rose bengal **41** were dissolved in *t*-amyl alcohol with sonication. The reaction solution was irradiated, with air bubbling, using one 500 W halogen lamp. Samples (1.5 ml) were taken at 0, 1, 2, 4, 6 and 24 hours and ^{1}H NMR was used to determine conversion.

General procedure for solar irradiation of 1-naphthol derivatives

1-Naphthol derivative and rose bengal **41** were dissolved in *t*-amyl alcohol with sonication. The reaction solution was irradiated, with air bubbling, in sunlight for 6 hours. ^{1}H NMR of the crude product was used to determine conversion.

5.4.3.1 Synthesis of 1,4-naphthoquinone (CAS no. 130-15-4)



70

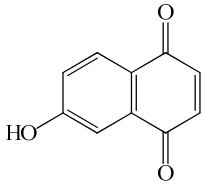
Experiment 114 (EC-148): Artificial irradiation for 24 hours

The general procedure was followed using 1-naphthol **226** (0.144 g, 1.00 mmol) and rose bengal **41** (0.050 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 18% was achieved in 4 hours and 70% in 24 hours.

Experiment 115 (EC-163): Solar irradiation for 6 hours

The general procedure was followed using 1-naphthol **226** (0.144 g, 1.00 mmol) and rose bengal **41** (0.050 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in direct sunlight conditions. ^{1}H NMR spectroscopy (acetone-d_6) showed that no starting material **226** remained after this time.

5.4.3.2 Synthesis of 6-hydroxy-1,4-naphthoquinone



262

Experiment 116 (EC-149): Artificial irradiation for 24 hours

The general procedure was followed using 1,6-dihydroxynaphthalene **261** (0.160 g, 1.00 mmol) and rose bengal **41** (0.050 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 25% was achieved in 4 hours and 80% in 24 hours.

Experiment 117 (EC-166): Solar irradiation for 6 hours

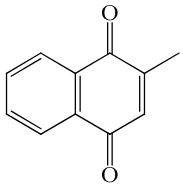
The general procedure was followed using 1,6-dihydroxynaphthalene **261** (0.160 g, 1.00 mmol) and rose bengal **41** (0.033 g, 33 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in partial cloud sunlight conditions. 6-Hydroxy-1,4-naphthoquinone **262** was isolated in 68% yield (0.119 g, 0.683 mmol) as a bright orange solid.

^{1}H NMR (600 MHz, acetone-d_6) δ (ppm) = 6.96 (2d, 2H, C**H**$_{quin.}$, J^3 = 10.2 Hz); 7.16 (dd, 1H, **H**$_{arom.}$, J^3 = 8.5 Hz, J^4 = 2.5 Hz); 7.26 (d, 1H, **H**$_{arom.}$, J^4 = 2.5 Hz); 7.84 (d, 1H, **H**$_{arom.}$, J^3 = 8.5 Hz); 10.96 (s, 1H, O**H**).

^{13}C NMR (150 MHz, acetone-d_6) δ (ppm) = 111.6, 120.8 (2C, **C**H$_{quin.}$); 123.7, 133.7 (2C, **C**$_{q.arom.}$); 128.8, 138.16, 139.0 (3C, **C**H$_{arom}$); 162.7 (1C, **C**-OH); 183.6, 185.0 (2C, **C**=O).

CAS no. 4923-53-9, ^{1}H NMR spectrum consistent with literature data[271].

5.4.3.3 Synthesis of 2-methyl-1,4-naphthoquinone (CAS no. 58-27-5)

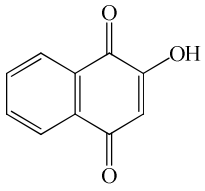


153

Experiment 118 (EC-153): Artificial irradiation for 24 hours

The general procedure was followed using 2-methyl-1-naphthol **263** (0.159 g, 1.00 mmol) and rose bengal **41** (0.050 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 53% was achieved in 4 hours and 100% in 24 hours.

5.4.3.4 Synthesis of 2-hydroxy-1,4-naphthoquinone



251

Experiment 119 (EC-152): Artificial irradiation for 24 hours

The general procedure was followed using 1,3-dihydroxynaphthalene **264** (0.160 g, 1.00 mmol) and rose bengal **41** (0.050 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 66% was achieved in 4 hours and 100% in 24 hours.

Experiment 120 (EC-157): Artificial irradiation for 12 hours

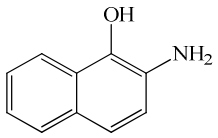
The general procedure was followed using 1,3-dihydroxynaphthalene **264** (0.160 g, 1.00 mmol) and rose bengal **41** (0.050 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 14 hours. ^{1}H NMR spectroscopy (acetone-d_6) showed that a conversion of 66% was achieved in 12 hours.

^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) = 6.24 (s, 1H, $\mathbf{H}_{quin}$); 7.82 (t, 1H, $\mathbf{H}_{arom}$, J^3 = 7.5 Hz, J^4 = 1.5 Hz); 7.88 (t, 1H, $\mathbf{H}_{arom}$, J^3 = 7.3 Hz, J^4 = 1.5 Hz); 8.04 (d, 1H, $\mathbf{H}_{arom}$, J^3 = 7.5 Hz, J^4 = 1.5 Hz, J^5 = 0.5 Hz); 8.09 (d, 1H, $\mathbf{H}_{arom}$, J^3 = 7.7 Hz, J^4 = 1.5 Hz, J^5 = 0.5 Hz).

CAS no. 83-72-7, ^{1}H NMR spectrum consistent with literature data[181].

5.4.4 Synthesis of a 2-amido-1-naphthol series

5.4.4.1 Synthesis of 2-amino-1-naphthol



265

Experiment 121A (KC-01): reduction using sodium dithionite *See Appendix A*

Experiment 122A (KC-03): reduction using sodium dithionite under nitrogen *See Appendix A*

General procedure for reduction using tin(II)chloride dihydrate

2-Nitro-1-naphthol **266** and tin (II) chloride dihydrate were refluxed in ethanol or ethyl acetate solutions before stirring at room temperature. The resultant reaction mixture was precipitated in ice water and neutralised using saturated sodium bicarbonate solution. Product was extracted using ethyl acetate and dried using magnesium sulfate or sodium sulfate. Following removal of the drying agent, the solvent was evaporated to yield crude product. ^{1}H NMR spectroscopy (DMSO-d_6) was used to assess outcome of the reaction.

Experiment 123A (KC-11): Reduction of 2-nitro-1-naphthol using tin(II)chloride dehydrate *See Appendix A*

Experiment 124 (EC-171): Reduction of 2-nitro-1-naphthol using tin(II)chloride dihydrate

2-Nitro-1-naphthol **266** (0.030 g, 0.015 mmol), tin (II) chloride (0.173 g, 0.767 mmol) and ethanol (1.5 ml) were refluxed overnight and cooled to room temperature prior to pH adjustment with saturated sodium bicarbonate (2 ml). The product was extracted using ethyl acetate and precipitates removed by centrifugation. The crude product was obtained as dark purple-black crystals.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 6.15 (s); 6.56 (s); 7. 05 (d, J^3 = 8.8 Hz); 7.44 (m, J^3 = 6.56 Hz, 6.72 Hz, J^4 = 1.12 Hz); 7.71 (m); 7.82 (m); 8.12 (d, J^3 = 7.2 Hz); 8.16 (d, J^3 = 8.08 Hz, J^4 = 1.0 Hz).

CAS no. 606-41-7, no ^{1}H NMR spectra reported in literature.

Experiment 125 (EC-172): Reduction of 2-nitro-1-naphthol using tin(II)chloride

2-Nitro-1-naphthol **266** (0.19 g, 1.0 mmol), tin (II) chloride (1.13 g, 5.01 mmol) and ethanol (4 ml) were refluxed overnight and cooled to room temperature prior to pH adjustment with saturated sodium bicarbonate (8 ml). The product was extracted using ethyl acetate and precipitates removed by centrifugation. The crude product was obtained as dark purple-black crystals. Recrystallisation using cyclohexane and ethyl acetate produced a purple-grey solid.

^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) = 6.91 (d, J^3 = 8.4 Hz); 6.70 (d, J^3 = 8.4 Hz); 7.09 (d, J^3 = 8.4 Hz); 7.14 (t, J^3 = 6.8, 7.2 Hz); 7.20 (t, J^3 = 7.6 Hz); 7.29-7.44 (m); 7.65 (d, J^3 = 8.0 Hz); 7.73-7.78 (m); 8.02 (d, J^3 = 8.4 Hz); 8.16 (d, J^3 = 8.0 Hz).

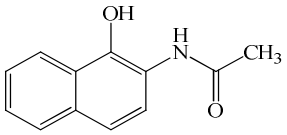
IR (KBr) υ (cm^{-1}) = 3266 (OH), 1597.

Mass Spectrometry (ESI, MS^+, acetonitrile) m/z = 304.8, 332.7 (dimeric structure **271**, expected m/z 332.1 M+1).

Mass Spectrometry (ESI, MS^+, methanol) m/z = 315.5 (dimeric structure **272**, expected m/z 314.1, M+1).

CAS no. 606-41-7, not consistent with literature IR data[266].

5.4.4.2 Synthesis of 2-acetamido-1-naphthol



273

Experiment 126A (KC-09): Synthesis of 2-acetamido-1-naphthol *See Appendix A*

Experiment 127 (EC-159): Synthesis of 2-acetamido-1-naphthol

Crude 2-amino-1-naphthol **265** (1.50 g, 9.43 mmol) and acetic anhydride (4.0 ml) were stirred for three hours at room temperature. Excess acetic anhydride was removed by a steady stream of nitrogen. The reaction mixture was poured over ice water and the resulting precipitate was collected by vacuum filtration and washed with acetone to yield a pink-grey solid that was insoluble in acetone, water, DMSO, chloroform, methanol and benzene. The combined filtrates were reduced by rotary evaporation to form a yellow-brown residue, which ^{1}H NMR spectroscopy (DMSO-d_6) showed to contain a mixture of the tautomer **274** and 2-acetamido-1-naphthol **273** (9:1). The product was purified by recrystallisation to yield bright yellow crystals in a yield of 9%.

^{1}H NMR (400 MHz acetone-d_6) δ (ppm) = 2.1 (s, 3H, C**H**$_3$); 7.44- 7.52 (m, 2H, **H**$_{arom.}$); 7.75-7.80 (t, 2H, J^3 = 7.2 Hz, 9.2 Hz); 7.89- 7.91 (d, 1H, J^3 = 8.8 Hz); 8.29-8.31 (d, 1H, J^3 = 8.8 Hz), 8.88 (s, 1H, N**H**).

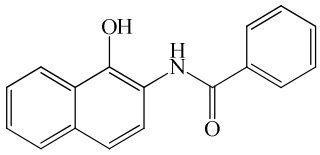
^{13}C NMR (100MHz, acetone-d_6) δ (ppm) = 20.8; 24.1; 121.9; 123.0; 126.0; 126.4; 127.4; 128.1; 128.6; 129.5; 132.0; 169.4.

IR (KBr) υ (cm^{-1}) = 2958, 2924, 2854, 1624, 1603, 1583, 1542, 1497, 1452, 1428, 1395, 1385, 1276, 1237, 1181, 1140, 1092, 1025, 918, 878, 808, 797, 768, 736, 703, 651, 624, 572.

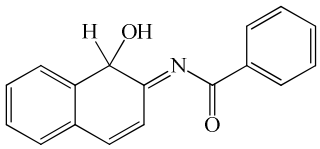
UV (methanol) λ (nm) = 265, 295, 307, 403.

CAS no. 70365-38-7, no spectral data reported[272].

5.4.4.3 Synthesis of 2-benzamido-1-naphthol



276



277

Experiment 128 (EC-160):

Crude 2-amino-1-naphthol **265** (1.50 g, 9.43 mmol) was stirred in pyridine at -15 °C under a nitrogen atmosphere. Benzoyl chloride (1.5 ml, 0.013 mol) was added dropwise (an orange precipitate was observed initially). The reaction mixture was stirred overnight at room temperature and poured over ice water. The resulting sticky solid was collected by vacuum filtration. The remaining residue was collected using acetone. ^{1}H NMR spectroscopy (DMSO-d_6) of the product collected on the filter paper and of the residue from acetone washings showed that the samples contained a mixture of products. The major product present was benzoic acid.

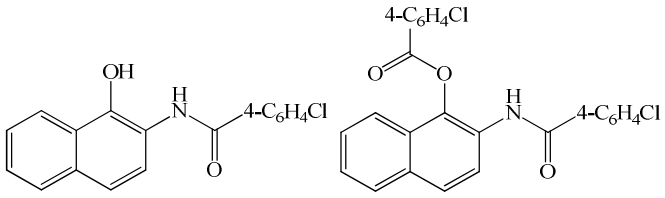
^{1}H NMR (400 MHz DMSO-d_6) δ (ppm) = 7.51 (t, 2H, C**H**$_{arom.}$, J^3 = 7.6 Hz); 7.63 (tt, 1H, C**H**$_{arom.}$, J^3 = 6.8 Hz, J^4 = 1.2 Hz); 7.96 (dd, 2H, C**H**$_{arom.}$, J^3 = 8.4 Hz, J^4 = 1.2 Hz); 12.99 (s, 1H).

Mass spectrometry (ESI, MS$^+$) m/z = Expected 367.1, observed 368.4 (M+1, *bis*-acylated compound **277**).

Mass spectrometry (ESI, MS$^-$) m/z = Expected 263.1, observed 262.3 (M-1, *mono*-acylated compound **276**).

CAS no. 72771-50-7, no ^{1}H NMR data reported.

5.4.4.4 Synthesis of 2-(4-chlorobenzamido)-1-naphthol

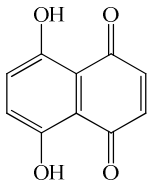


279 **280**

Experiment 129A (KC-12): synthesis of 2-(4-chlorobenzamido)-1-naphthol *See Appendix A*

5.4.5 Other photooxygenation reactions

5.4.5.1 Attempted photochemical synthesis of naphthazarin



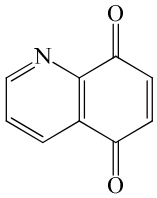
254

Experiment 130 (EC-052):

1,4,5-Trihydroxynaphthalene **242** (0.313 g, 1.80 mmol) and TPP **43** (30 mg, 48 μmol) were dissolved in a mixture of dichloromethane and methanol (9:1). The reaction mixture was irradiated, with air bubbling, using two halogen lamps for 4 hours. Solvent was removed by evaporation and the crude product (black solid) analysed by ^{1}H NMR spectroscopy (DMSO-d_6).

The ^{1}H NMR spectroscopy (DMSO-d_6) characteristic peaks of naphthazarin **254** at 12.23 ppm (s, 2H, O**H**) and 7.29 ppm (s, 4H, $\mathbf{H}_{arom}$) were absent. The ^{1}H NMR spectroscopy (DMSO-d_6) characteristic peaks of juglone **98** were present, as well as small amounts of starting material **242**.

5.4.5.2 Photooxygenation of 8-hydroxyquinoline



286

General Procedure for the photooxygenation of 8-hydroxyquinoline

8-Hydroxyquinoline **285** and sensitiser were dissolved in reaction solvent and irradiated, with air bubbling, using two 500 W halogen lamps. TLC monitoring (ethyl acetate:*n*-hexane 1:2) indicated disappearance of the starting material during irradiation. The solvent was removed by rotary evaporation and the crude product analysed by ^{1}H NMR spectroscopy ($CDCl_3$) to assess conversion.

Experiment 131 (EC-037): Following the method by Cossy[268]

Following the general procedure, 8-hydroxyquinoline **285** (1.45 g, 9.99 mmol) and tetraphenylporphyrin **43** (22 mg, 35 μmol) were dissolved in dichloromethane (100 ml) and irradiated for 23 hours. The crude product was a red-black solid. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that the desired 1,4-naphthoquinone **286** was formed. The product was not isolated.

^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) = 7.08 (d, 1H, $\mathbf{H}_{quin.}$, J^3 = 10.4 Hz); 7.17 (d, 1H, $\mathbf{H}_{quin.}$, J^3 = 10.4 Hz); 7.72 (dd, 1H, $\mathbf{H}_{arom.}$, J^3 = 8.0 Hz); 8.44 (d, 1H, $\mathbf{H}_{arom.}$, J^3 = 8.0 Hz, J^4 = 2.0 Hz); 9.07 (d, 1H, $\mathbf{H}_{arom.}$, J^3 = 4.4 Hz, J^4 = 1.6 Hz).

CAS no. 10470-83-4, ^{1}H NMR spectrum consistent with literature data[273].

Experiment 132 (EC-038): Following the method by Amarasekara[269]

Following the general procedure, 8-hydroxyquinoline **285** (0.147 g, 1.00 mmol) and methylene blue **42** (trace) were dissolved in dichloromethane (80 ml) and methanol (20 ml) and irradiated for 4 hours. The reaction mixture was then treated with activated charcoal and evaporated to dryness (at 30°C). The crude product was a paint-like, red-back solid. This was dissolved in

ethyl acetate and filtered to remove charcoal. The solvent was removed to yield an orange oil, which formed some crystals when allowed to stand for several days.

^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that the desired 1,4-naphthoquinone **286** was not formed and that starting material **285** was recovered.

Experiment 133 (EC-029): *i*-Propyl alcohol and rose bengal: 7 h

Following the general procedure, 8-hydroxyquinoline **285** (0.910 g, 6.27 mmol) and rose bengal **41** (30 mg, 30 μmol) were dissolved in *i*-propyl alcohol (350 ml) and irradiated for 7 hours. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that no conversion occurred.

Experiment 134 (EC-030): *i*-Propyl alcohol and rose bengal: 48 h

Following the general procedure, 8-hydroxyquinoline **285** (0.910 g, 6.27 mmol) and rose bengal **41** (30 mg, 30 μmol) were dissolved in *i*-propyl alcohol (350 ml) and irradiated for 48 hours. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that no conversion occurred.

Experiment 135 (EC-031): *i*-Propyl alcohol and methylene blue: 12.5 h

Following the general procedure, 8-hydroxyquinoline **285** (0.911 g, 6.27 mmol) and methylene blue **42** (12 mg, 75 μmol) were dissolved in *i*-propyl alcohol (350 ml) and irradiated for 12.5 hours. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that no conversion occurred.

Experiment 136 (EC-032): *t*-Amyl alcohol and methylene blue: 7 h

Following the general procedure, 8-hydroxyquinoline **285** (0.390 g, 2.69 mmol) and methylene blue **42** (12 mg, 75 μmol) were dissolved in *t*-amyl alcohol (150 ml) and irradiated for 7 hours. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that no conversion occurred.

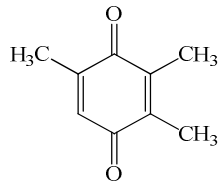
Experiment 137 (EC-039): Dichloromethane and rose bengal: 140 h

Following the general procedure, 8-hydroxyquinoline **285** (0.50 g, 3.4 mmol) and rose bengal **41** (25 mg, 25 μmol) were dissolved in dichloromethane (100 ml) and irradiated for 140 hours. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that no conversion occurred.

Experiment 138 (EC-040): *t*-Amyl alcohol and rose bengal: 140 h

Following the general procedure, 8-hydroxyquinoline **285** (0.50 g, 3.4 mmol) and rose bengal **41** (25 mg, 25 μmol) were dissolved in *t*-amyl alcohol (100 ml) and irradiated for 140 hours. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that some conversion occurred, however product was not isolated.

5.4.5.3 Photooxygenation of 2,3,6-trimethylphenol



290

Experiment 139 (EC-067):

2,3,6-Trimethylphenol **289** (0.25 g, 1.8 mmol) and rose bengal **41** (50 mg, 98 μmol) were dissolved in *t*-amyl alcohol (100 ml). The reaction mixture was irradiated, with air bubbling, for 4 hours using two halogen lamps. Solvent was removed by rotary evaporation to yield a deep red, sticky oil. Yellow crystals formed at the mouth of the flask during evaporation and white crystals formed on the surface of the oil when allowed to stand. Using ^{1}H NMR spectroscopy (DMSO-d_6), the yellow crystals were identified as starting material **289**, while the white crystals contained a mixture of the desired product, 2,3,6-trimethyl-1,4-benzoquinone **290**, and starting material **289** (1:3). The product was not isolated.

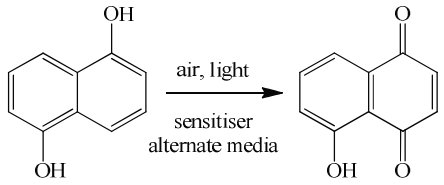
^{1}H NMR (400 MHz DMSO-d_6) δ (ppm) = 2.12 (s, 3H, C**H**$_3$), 6.55 (s, 1H, **H**$_{arom}$). The other methyl group peaks are not identified as they are masked by starting material peaks in the region 2.06-2.13 ppm, however integration values indicate that they are present.

CAS no. 935-92-2, ^{1}H NMR spectra consistent with literature[274].

Chapter 6 Photooxygenations in alternative media.

6.1 Introduction

The synthesis of 1,4-naphthoquinones by dye-sensitised photooxygenation in organic solvents has been demonstrated effectively under green conditions in Chapters 2-5. However, with increasing interest in green methods, alternative media such as ionic liquids, microemulsions, supercritical fluids and even completely solvent-free conditions have been proposed as alternatives to traditional volatile organic solvents. The use of these green media has been demonstrated for some dye-sensitised photooxygenation reactions, but their application to the synthesis of juglone **98** will be assessed as a green procedure (Scheme 121).



97 **98**

Scheme 121: Synthesis of juglone 98 **using alternative media.**

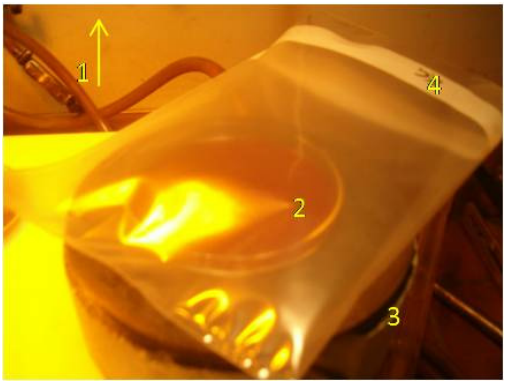
Griesbeck has promoted the use of polymer supported, solvent-free conditions for photooxygenation reactions[194]. These have been suggested as a green alternative to solution phase chemistry. Aubry and Nardello have reported the use of microemulsions for oxygenation processes, using chemically or photochemically produced singlet oxygen[221, 227]. Investigations by the Worrall group in the University of Loughborough have looked at the photochemical generation of singlet oxygen formation in supercritical fluids (carbon dioxide and xenon)[275, 276], as well as evaluating the kinetic behaviour of activated oxygen species in the supercritical phase[277, 278]. Poliakoff and George have recently reported the use of supercritical carbon dioxide for photooxygenation processes, using a novel flow-through reactor[240, 241].

6.2 Results and Discussion

6.2.1 Solvent-free synthesis using polymeric supports (PS)

6.2.1.1 Experimental set-up

Early solvent-free experiments were carried out in the University of Cologne, with irradiation using a Halogen lamp (500 W) and optional cooling (Figure 68a). In Dublin City University, experiments were carried out in a Luzchem (LZC-1) top irradiation reactor (using eight 12 inch 8 W LZC-VIS bulbs) as shown in Figure 68b.

(a) 

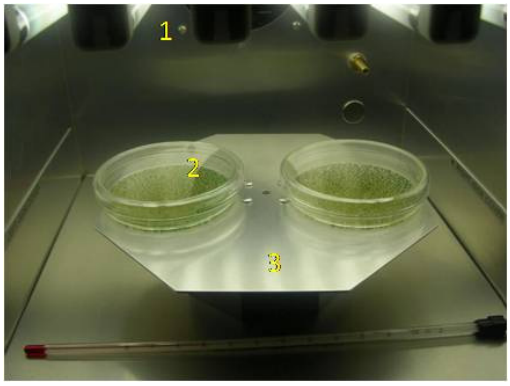
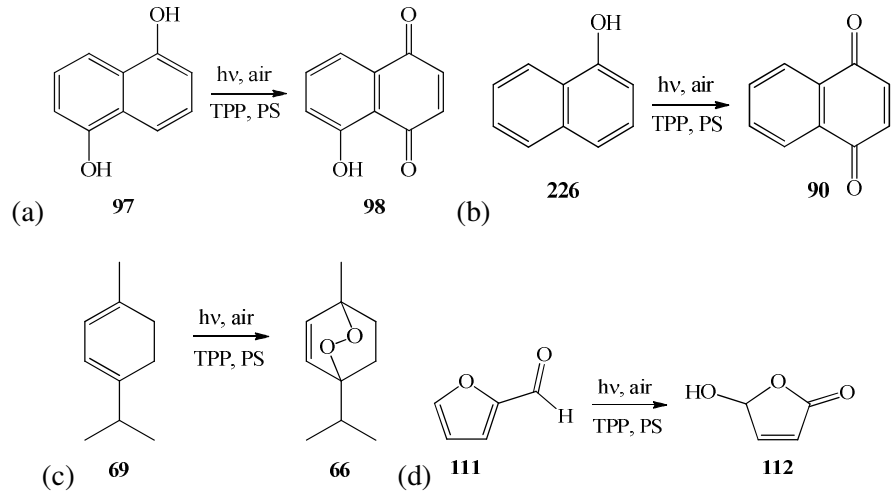
(b) 

Figure 68: Photooxygenation on solid supports (a) in University of Cologne (1: Halogen lamp 2: petri dish with polyer supported reactants 3: cooling plate 4: plastic bag (transparent to light) containing oxygen) and (b) in Dublin City University (1: Luzchem LZC-Vis lamps 2: petri dish with polymer supported reactants 3: rotating carousel).

6.2.1.2 Solvent-free photooxygenation experiments

Using procedures by Griesbeck *et al.*, solvent-free photooxygenations on different polymeric supports were investigated[194]. Use of both solid substrates (1,5-dihydroxynaphthalene **97** and 1-naphthol **226** (Scheme 122a-b)) and liquid substrates (α-terpinene **69** and furfural **111** (Scheme 122c-d)) was demonstrated.



Scheme 122: Synthesis of (a) juglone 98 **(Experiments 140-142), (b) 1,4-naphthoquinone** 90 **(Experiments 143-144), (c) ascaridole** 66 **(Experiments 145-146) and (d) 5-hydroxyfuranone** 112 **(Experiment 147).**

Solvent-free synthesis using polymer supports was carried out using three polymeric supports - cross-linked polystyrene (1% divinylbenzene copolymer beads, 100-200 mesh) **294**, cellulose acetate **295** or polyethylene glycol **296**.

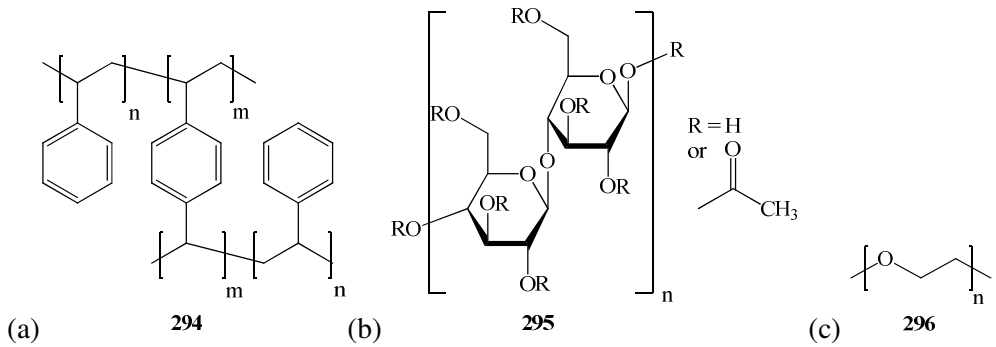


Figure 69: (a) polystyrene cross-linked with divinyl benzene 294**, (b) cellulose acetate** 295 **and (c) poly(ethylene glycol)** 296**.**

To prepare polymeric supports using polystyrene **294**, the polymer **294** was first swollen by placing in dichloromethane in petri dishes, the sensitiser (TPP **43**) was adsorbed onto the polymer **294** in solution phase, and finally the starting material was introduced in an ethyl acetate-methanol solution. The solvent was evaporated by placing the dishes in the fume hood (under a loose cover to provide darkness), ensuring complete evaporation of solvent prior to irradiation. Once dry, the petri dishes were sealed into transparent bags containing oxygen and placed on a heat controlled mantle. Irradiation experiments were conducted at 10 °C and ambient temperatures (up to 40 °C, caused by heat of halogen lamp). Polymeric supports using

linear polymers, such as cellulose acetate **295** and polyethylene glycol **296**, were investigated. However, these tend to lead to uneven films and are not as suitable for use as cross-linked polystyrene **294**.

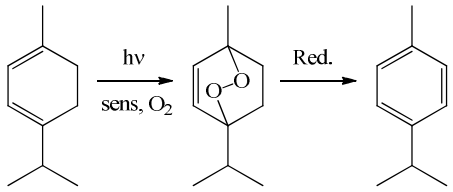
This procedure was carried out for four substrates: solid starting materials 1-naphthol **226** and 1,5-dihydroxynaphthalene **97** and liquid substrates, α-terpinene **69** and furfural **111**. As shown in Table 23, this procedure is only appropriate for use with liquid reagents, although trace amounts of product may be obtained for solid substrates.

Table 23: Solvent-free photooxygenations on polymer supports (Experiments 140-147).

Expt. No.	Starting material	Polymer	Scale (mmol)	Temp	Initial appearance	Final appearance	Product formed
140	**97**	**295**	2	Uncooled	Pink-brown thin film, appears wet	Pink-brown, slightly darker	Trace
141	**97**	**296**	2	Uncooled	Wet, pink-orange, not well distributed	Brown in colour, appears wet	Trace
142	**97**	**294**	2	Uncooled	Brown crystals formed on surface	Darkened, blackish-red	No
143	**226**	**294**	2	Uncooled	Pink-brown, no obvious crystals	Blackened, needles on surface	Trace
144	**226**	**294**	2	10 °C	Pink-brown, no obvious crystals	Blackened, needles on surface	Trace
145	**66**	**294**	2	Uncooled	Pink	No change	Yes
146	**66**	**294**	2	10 °C	Pink	Slight change, pink-orange	Yes
147A	**111**	**294**	2	Uncooled	Pink	Green	Yes

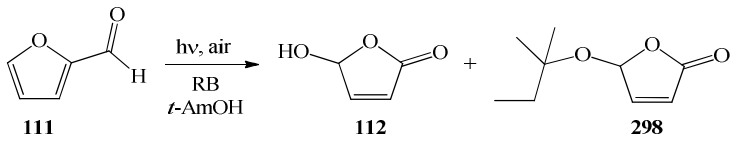
Griesbeck has extensively studied these systems, exclusively focussing on liquid substrates such as citronellol **93** and β-pinene **178**. In these examples, and those of α-terpinene **69** and furfural **111** (Table 23, Experiments 145-147), the polymer and substrate form a paste-like thin film. The liquid substrate thus acts as a "pseudo solvent" and mixes well with the polymer-incorporated sensitiser **43**. As a result the generation of singlet oxygen can occur in solution and travel within its lifetime to encounter substrate.

For the synthesis of ascaridole **66**, a common side product formed is *p*-cymene **297**, in particular at higher temperatures (Scheme 123). However, for the synthesis of ascaridole **66** on polymeric support **294** no conversion to *p*-cymene **297** was observed after photooxygenation with external cooling. In comparison, solution phase synthesis was carried out in *i*-propyl alcohol using rose bengal **41** and was found to give ascaridole **66** and *p*-cymene **297** in a ratio of 24:1 (Experiment 149).



Scheme 123: Formation of *p*-cymene 297 **from ascaridole** 66**.**

During synthesis of 5-hydroxyfuranone **112**, a distinctive green colour was observed, indicating protonation of the sensitiser **43**. The product **112** can be considered a pseudo-acid[80], causing protonation of the sensitiser **43**. For this reaction, use of methylene blue **42** is recommended by Scharf as this sensitiser does not react with the 5-hydroxyfuranone product. ^{1}H NMR spectroscopy ($CDCl_3$) analysis of the crude product showed no evidence of starting material **111**. This synthesis was compared to the solution phase synthesis using the optimised conditions for juglone **98** synthesis (rose bengal **41**, *t*-amyl alcohol) with irradiation using one halogen lamp for 3-4 days (Experiment 150, Scheme 124). During this time, degradation of sensitiser **41** was observed and additional portions were added daily. The formation of a butenolide side product **298**, a result of a pseudo-esterification reaction between 5-hydroxyfuranone **112** and *t*-amyl alcohol, was observed. This side product **298** was avoided by application of solvent-free conditions, during which no reaction partner was available.



Scheme 124: Photooxygenation of furfural 111 **in *t*-amyl alcohol (Experiment 150).**

In the case of solid supported substrates, such as 1,5-dihydroxynaphthalene **97** and 1-naphthol **226**, these are entirely solid-state reactions and do not exhibit good mixing (Figure 70). The starting materials can visibly be seen aggregating in discrete regions, while the sensitiser **43** is well distributed.

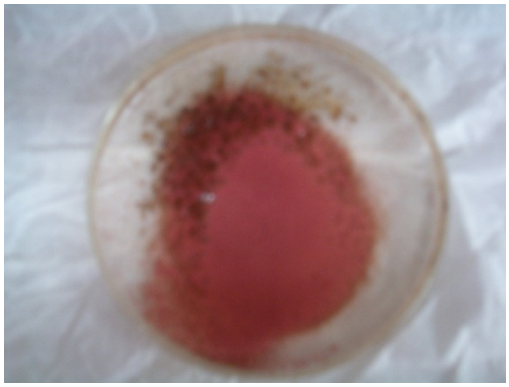


Figure 70: 1,5-Dihydroxynaphthalene 97 **and TPP** 43 **on polystyrene polymeric support.**

Following irradiation trace amounts of product were obtained, but this may be attributed to product formation during solution phase preparation of the 'pancakes' (Table 23, Experiments 140-144). The synthesis of juglone **98** in ethyl acetate has been demonstrated (Chapter 2, Section 2.2.3.1). To confirm that the trace amounts of product are formed during preparation, rather than irradiation of the solid supported system, the preparation of cellulose acetate **295** pancakes was repeated, followed by immediate work-up (no irradiation time) and traces of product were observed in this case (Experiment 148).

To demonstrate that the synthesis of juglone **98** cannot proceed in the solid state, samples of 1,5-dihydroxynaphthalene **97** and sensitiser TPP **43** were ground together using a mortar and pestle and exposed to light (artificial and solar irradiation, Experiments 151 and 152). No juglone **98** was formed during this experiment, indicating that the reaction cannot proceed in solid state. This indicates that the polymeric supported synthesis of juglone **98** is not practicable in the absence of solvent. This may be attributed to the lifetime of singlet oxygen and its ability to travel in a solid-gas heterogeneous system. In homogeneous conditions, the singlet oxygen lifetime is sufficient to enable migration within the reaction mixture to encounter starting material **97**, leading to a reaction. In the solid phase, this process does not occur as there is little possibility for the reactive oxygen species to encounter the starting material **97**.

6.2.1.3 Summary of solvent-free synthesis using polymeric supports

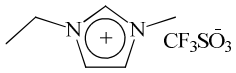
As a green approach, solvent-free synthesis is highly desirable as this will eliminate the use of volatile organic solvents. In addition, an important green aspect of this work is the recovery and recycling of the polymer supported sensitiser (TPP **43** on polystyrene **294**). When the polymeric film is washed with methanol there is minimal removal of tetraphenylporphyrin **43**, and this support may be recovered and reused[279].

However, although the irradiation experiments in this study were carried out on solid state, the use of volatile organic solvents was not avoided. The preparation of the polymeric supports required the use of dichloromethane, ethyl acetate and methanol, all of which were evaporated into the atmosphere. Further solvent was required for the purification procedure.

A further limitation of this approach is its incompatibility with solid substrates, which limits the scope of reactions. In addition, scale-up of the reaction is an issue, as further scale-up would require a very large area for the thin films.

6.2.2 Ionic Liquids (ILs)

The use of ionic liquids was investigated using commercially available 1-ethyl-3-methylimidazolium triflate **187** ([emim]OTf, Figure 71).



187

Figure 71: 1-Ethyl-3-methylimidazolium trifluoromethanesulfonate 187**.**

Ionic liquids have been proposed as green alternative media, due to their negligible volatility and ability to solubilise a range of compounds of varying polarities. In addition, they are easily recovered and can be recycled. Engineering of ionic liquids by varying side chains on the cation or the choice of anion can enhance their suitability for use in different chemical reaction processes.

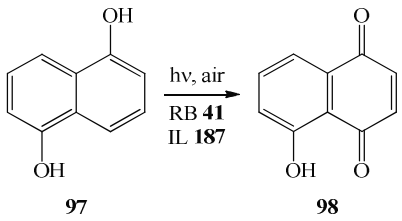
6.2.2.1 Experimental set-up

The reactions were carried out in small scale, using 5 ml of ionic liquid **187**. Air was introduced by bubbling using a fish tank pump. Irradiation was carried out using one 500 W halogen lamp.

6.2.2.2 Photooxygenation experiments

The use of ionic liquids in oxygenation experiments has been demonstrated previously using methylene blue **42**[217, 218]. In this study, rose bengal **41** was used as, like methylene blue **42**, it is a polar salt and should have excellent solubility in ionic liquids.

To investigate the use of commercially available [emim]OTf **187** as reaction medium for dye-sensitised photooxygenation, the synthesis of juglone **98** from 1,5-dihydroxynaphthalene **97** was used as a model reaction (Scheme 125). The reaction was carried out in triplicate, using 5 ml of ionic liquid **187** containing diol **97** (8 mg) and sensitiser **41** (2 mg).



97 **98**

Scheme 125: Synthesis of juglone 98 **in ionic liquid** 187**.**

To assess the affect of oxygen solubility on the outcome of this reaction, each of the reaction samples was treated differently, as shown in Table 24.

Table 24: Supply of oxygen during photooxygenation experiments in [emim]OTf 187 **(Experiment 153).**

Sample	Presaturated	Air bubbling
A	Yes	No
B	Yes	Yes
C	No	Yes

Following irradiation for 4 hours using one 500 W halogen lamp, the reaction mixtures were extracted using diethyl ether, as this solvent is completely immiscible with the IL **187** used. However, this solvent is not suitable for use within a green framework, and may be replaced with toluene. It was not possible to recover rose bengal **41** from the ionic liquid, as it remained soluble in the IL layer during extraction. To assess the outcome of the reaction, UV-vis spectrophotometry was used to monitor the characteristic juglone **98** peak (415 nm) and evaluate relative yield, rather than conversion or isolated yield.

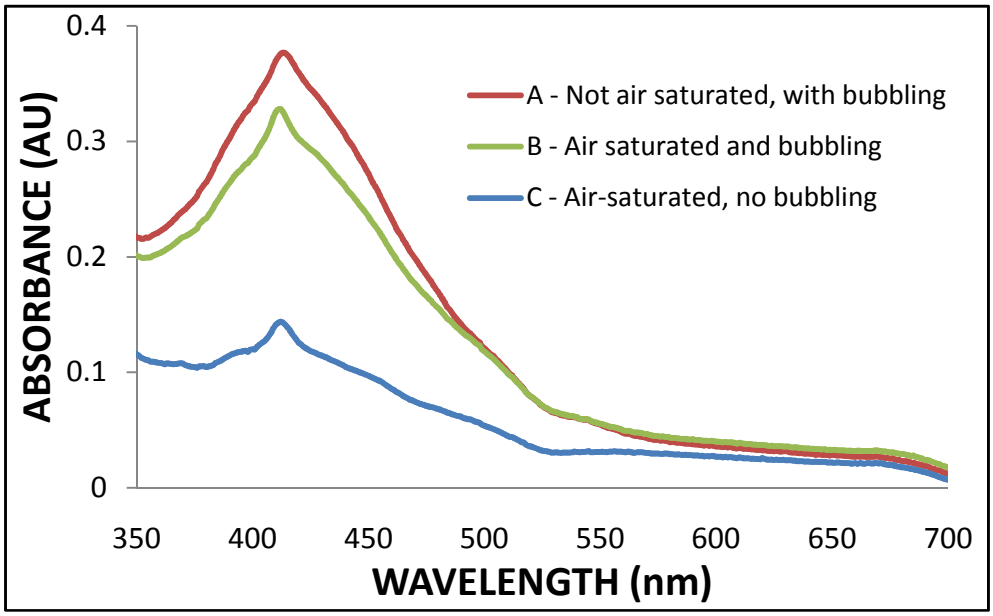


Figure 72: UV-vis Spectra of samples from ionic liquid reactions (Experiment 153).

As can be seen in Figure 72, bubbling with air led to greater formation of juglone **98** than pre-saturation alone. Some juglone **98** formation is observed, which indicates that some oxygen remains soluble in the ionic liquid **187** once air bubbling is completed.

For the samples during which air bubbling was applied, a greater amount of juglone **98** was observed for the sample which had not been pre-saturated. The difference between these samples is quite small, indicating that a majority of the conversion in this experiment can be attributed to the constant air supply, rather than the pre-saturation. These results are consistent with studies regarding poor oxygen solubility in ionic liquids[195, 210-212].

6.2.2.3 Summary of synthesis in ionic liquids

Use of ILs in photooxygenation reaction has been demonstrated using a commercially available ionic liquid, [emim]OTf **187**. However, a major drawback to the use of this IL **187** is the poor oxygen solubility in this solvent. This problem may be overcome by selectively designing an ionic liquid with a greater capacity to dissolve oxygen. Use of highly perfluorinated cation and anion may help to achieve this aim. In addition, incorporation of sensitiser into the ionic liquid structure may enable ease of recovery and reuse of the solvent and sensitiser system.

6.2.3 Microemulsions (MEs)

Nardello has reported the use of microemulsions in which the organic layer is ethyl acetate[221]. These are considered environmentally friendly, as ethyl acetate is a substitute for dichloromethane. These microemulsions have proven effective in "dark oxygenation" reactions, in which singlet oxygen is generated by hydrogen peroxide and a molybdolate catalyst (as discussed in Chapter 1, Section 1.5.1). Using these emulsions as a framework the photochemical generation of singlet oxygen in similar systems has been investigated.

Following the method by Nardello *et al.* 'green' microemulsions of water and ethyl acetate were prepared using sodium dodecyl sulfate (SDS) as surfactant[221]. An investigation of co-surfactant looked at the use of *t*-amyl alcohol or ethanol as alternatives to *n*-butanol.

Microemulsions possess the ability to dissolve substrates of various polarities, as hydrophilic substrates are contained in the micro-droplets of water, while non-polar materials are contained in the organic phase[221]. For this reason they are ideal for use in juglone **98** synthesis, where the sensitisers (rose bengal **41** or methylene blue **42**) may be incorporated in the aqueous phase, while the less polar 1,5-dihydroxynaphthalene **97** is dissolved in the organic phase. The droplets containing sensitiser are sufficiently small that the singlet oxygen generated may travel during its lifetime into the organic phase and react with the substrate (Figure 73).

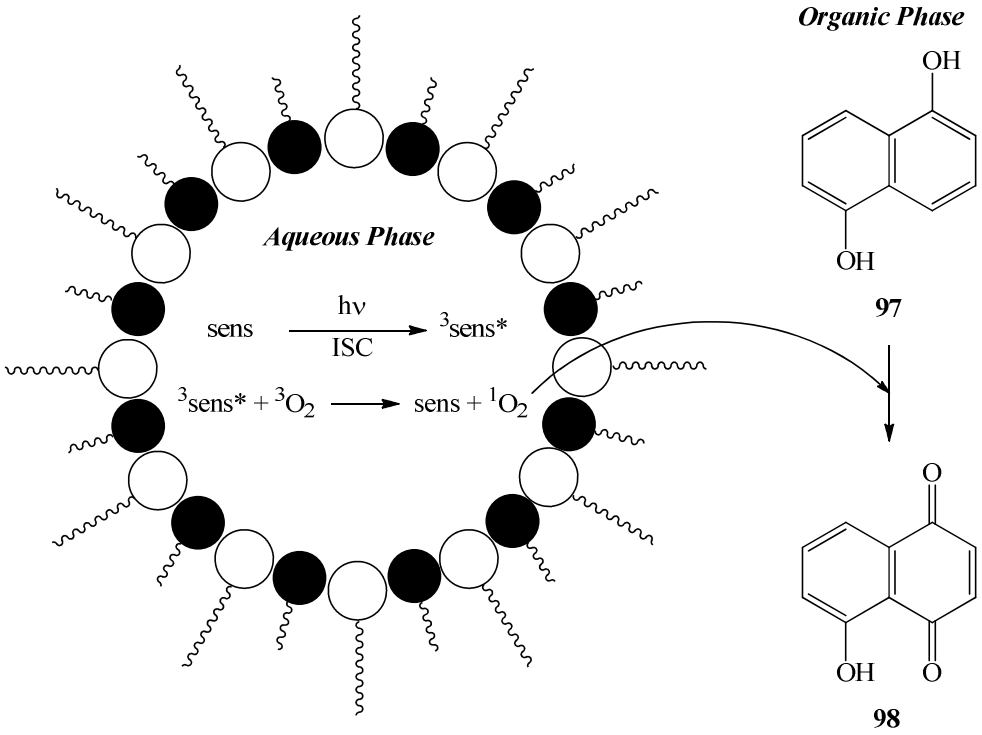


Figure 73: Schematic representation of microemulsions containing rose bengal 41 **or methylene blue** 42**, used in the synthesis of juglone** 98**.**

In the case where tetraphenylporphyrin **43** is used as a sensitiser, it is incorporated into the organic phase. The presence of the surfactant enables TPP **43** to be wholly dissolved in these systems, unlike traditional solvents.

As the stability of microemulsions can be affected by the substrates used, optimisation of the ratio of the components for use with 1,5-dihydroxynaphthalene **97** and rose bengal **41** was required. The optimised microemulsion ratio was then used in the synthesis of juglone.

6.2.3.1 Experimental set-up

Screening studies were carried out on small scale (20 g of microemulsion containing 0.1 g of 1,5-dihydroxynaphthalene **97**), using a halogen lamp (500 W), using a fan for cooling and no cooling water (Figure 74). Larger scale experiments were carried out as in Figure 21b.

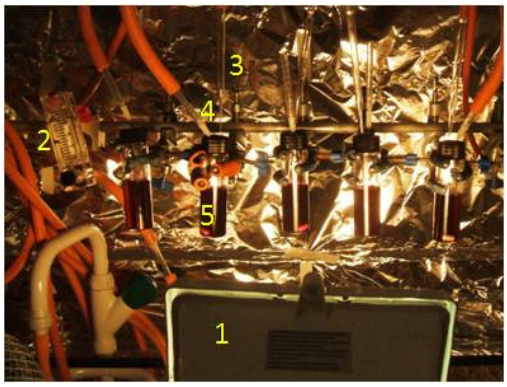


Figure 74: Experimental set-up for microemulsion screening (1: Halogen lamp, 2: flow meter, 3: air inlet, 4: air outlet, 5: reaction flask).

6.2.3.2 Optimisation of ratio

The stability of microemulsions can be affected by the nature of the substrates involved[221]. Therefore optimum ratio of organic solvent, water, surfactant and co-surfactant was needed. Choice of co-surfactant and the optimised ratio of all components of the mixture are shown in Table 25. Stability was assessed by allowing the mixtures to stand at room temperature overnight, followed by visual inspection to assess bilayer formation and/or precipitation. Use of alcohols, in particular *n*-butyl alcohol, as co-surfactant has been reported by Aubry *et al.*[221, 229] and as a consequence use of *t*-amyl alcohol or ethanol was investigated in this study. Both alcohols were shown to be suitable for use as co-surfactant, however ethanol offers the greatest advantages as less surfactant is required when this is used. In addition, use of ethanol offers a greater ease of work-up, as this solvent requires less energy to remove than the higher boiling point alcohols. The optimum microemulsions chosen for further investigations are Entry 6 (*t*-AmOH based) or Entry 10 (ethanolic), as these give stable microemulsions with the minimum quantity of surfactant.

Table 25: Optimisation of ratio for microemulsion preparation (% by weight, Experiment 154).

Entry	Co-surfactant	% co-surfactant	% SDS	% EtOAc	% H_2O	Appearance
1	*n*-BuOH	7.5	7.5	70.0	15.0	clear, homogeneous
2	*n*-BuOH	9.8	7.3	68.3	14.6	clear, homogeneous
3	*n*-BuOH	11.9	7.1	66.7	14.3	cloudy, no bilayer
4	*t*-AmOH	7.5	7.5	70.0	15.0	clear, homogeneous
5	*t*-AmOH	9.8	7.3	68.3	14.6	clear, homogeneous
6	*t*-AmOH	11.9	7.1	66.7	14.3	clear, homogeneous
7	EtOH	7.5	7.5	70.0	15.0	cloudy, no bilayer
8	EtOH	5.1	7.7	71.8	15.4	cloudy, no bilayer
9	EtOH	7.7	5.1	71.8	15.4	cloudy, no bilayer
10	EtOH	7.9	3.1	73.3	15.7	clear, homogeneous

Following preparation of stable microemulsions, the effect of addition of sensitisers (rose bengal **41**, methylene blue **42** or TPP **43**) and substrate (1,5-dihydroxynaphthalene **97**) was assessed (Experiments 155). All microemulsions were stable upon addition of substrate (0.16 g, 1.0 mmol) and sensitiser (25 μmol) to 20 ml of ME. The stability was not affected by the nature of the sensitiser, despite the ionic character of rose bengal **41** and methylene blue **42**. This stability is probably due to the small amounts of sensitiser required in each emulsion. The microemulsions were then irradiated for 4 h and the presence of juglone **98** was determined by TLC (mobile phase ethyl acetate: cyclohexane (1:3)). In all cases juglone **98** was obtained as the sole product (conversion was not complete), indicating that these systems are suitable for use in the photooxygenation process. The optimum microemulsions were determined as Entries 2, 6 and 10 (Table 25), as these are the stable microemulsions which contain the least proportion of surfactant.

6.2.3.3 Optimisation of work-up

Optimisation of work up was carried out for both *t*-amyl alcohol based microemulsions and ethanolic microemulsions. The aim of this study was to ensure the most effective purification using non-hazardous reagents.

6.2.3.3.1 Using *t*-AmOH based microemulsions

To optimise the work-up of *t*-amyl alcohol microemulsions, identical mixtures of 1,5-dihydroxynaphthalene **97** and rose bengal **41** were irradiated for 12 h in *t*-amyl alcohol based microemulsions. These were then worked-up in different ways (Table 26) before column chromatography (mobile phase ethyl acetate:cyclohexane (1:3)) to give yields of julone **98** of up to 57%. Liquid-liquid extraction between water and ethyl acetate provided the best method of purification. Purity was confirmed by TLC (ethyl acetate: cyclohexane (1:3)).

Table 26: Optimisation of work up for *t*-amyl alcohol based microemulsion reactions (Experiments 156-159).

Expt. No.	Work up	Yield (%)
156	Extraction using ethyl acetate	57
157	Evaporation, washed with cyclohexane, then filtered	20
158	Evaporation, Soxhlet extraction using cyclohexane	Trace
159	Evaporation, direct column chromatography	Trace

Of the procedures investigated, addition of water to the reaction mixture to 'break' the emulsion and subsequent extraction using ethyl acetate proved the most effective. Both of the solvents used are components of the microemulsions and are suitable for use in a green system, according to the Pfizer solvent guide[31].

Soxhlet extraction of the evaporated reaction mixture using cyclohexane produced only a small amount of residue. Following column chromatography no product was isolated. This is consistent with earlier studies from this work, which showed that use of cyclohexane rather than *n*-hexane was less effective for juglone **98** recovery (Chapter 2, Section 2.2.3.3). However, use of *n*-hexane was not feasible within the green chemistry framework of this study. Washing with cold cyclohexane, followed by filtration gave some separation of juglone **98** (20%). Even direct column chromatography of the evaporated residue did not offer an easy access to juglone **98**, as no product was isolated in this way. This may be due to the presence of the surfactant, which consists of a long carbon chain (dodecyl) as well as a polar functionality, which may have interacted with the product and silica and prevented recovery of the product.

6.2.3.3.2 Using ethanolic microemulsions

Work-up for ethanolic microemulsions was assessed by dissolving juglone **98** (1 mmol) in Entry 10-type microemulsions (Table 25), and then recovering the juglone **98** by different methods, as shown in Table 27. Use of cyclohexane washing was investigated, as this was reported previously by Nardello. Use of toluene was assessed as the partition of SDS into toluene is zero, thus ensuring separation of surfactant from product. In addition, use of multiple extractions with ethyl acetate was investigated, as this was demonstrated to be effective for *t*-amyl alcohol based microemulsions.

Table 27: Optimisation of work up for ethanolic microemulsion reactions (Experiments 160-162).

Expt. No.	Work up	Recovery (%)	% SDS in purified product
160	Break emulsion with brine, extraction using ethyl acetate	93	8%
161	Break emulsion with brine, dry organic residue, wash with cyclohexane	93	2%
162	Break emulsions with brine, dry organic residue, wash with toluene	92	3%

For each of the above methods, the weight of product recovered was 92-93%, however varying amounts of sodium dodecyl sulfate remained. The use of cyclohexane washing had the least amount of residual sodium dodecyl sulfate. This could be removed by further washings or use of column chromatography.

6.2.3.4 Optimisation of sensitiser

The photooxygenation of 1,5-dihydroxynaphthalene **97** using different sensitisers was investigated in *t*-amyl alcohol based microemulsions (Table 28, Experiments 163-165) and ethanolic microemulsions (Table 28, Experiments 166-169).

Table 28: Sensitiser study in *t*-amyl alcohol based and ethanolic microemulsions (Experiments 163-169).

Expt. No.	Sensitiser	Co-surfactant	Conversion (%)	Isolated Yield (%)
163	Rose bengal	*t*-AmOH	-	52
164	Methylene blue	*t*-AmOH	-	39
165	Tetraphenylporphyrin	*t*-AmOH	-	85
166	Rose bengal	EtOH	44	47 (100*)
167	Methylene blue	EtOH	33	35 (100*)
168	Tetraphenylporphyrin	EtOH	70	58 (83*)
169	None	EtOH	8	7 (87*)

** Yield based on conversion*

Isolated yields of juglone **98** of 35-58% were achieved for ethanolic microemulsions (Table 28, Experiments 166-168), using multiple ethyl acetate extractions and column chromatography for work up. Purity was confirmed using TLC (ethyl acetate: cyclohexane (1:3)) and ^{1}H NMR. In addition, the use of *t*-amyl alcohol based microemulsions was assessed, giving isolated yields of 39-85% (Table 28, Experiments 163-165).

Due to its poor solubility in polar solvents, photooxygenations using TPP **43** are traditionally performed in halogenated solvents such as dichloromethane. For the synthesis of juglone **98**, alcohols are generally required as co-solvent to ensure solubility of starting material. Under these conditions, a comparison photooxygenation reaction using TPP **43** gave juglone **98** in 79% isolated yield (Experiment 170). Due to their excellent solubilising properties; microemulsions enable the use of TPP **43** in a benign, non-chlorinated environment. Consequently, TPP **43** gave the highest conversion of each of the sensitisers assessed and isolated yields of 58%-85% (Table 28, Experiments 165 and 168).

6.2.3.5 Summary of synthesis in microemulsions

Use of microemulsions of water in ethyl acetate, using sodium dodecyl sulfate as surfactant and alcoholic co-surfactants in the dye-sensitised photooxygenation of 1,5-dihydroxynaphthalene **97** has been demonstrated. This complex mixture can be considered a green solvent, as each of the liquid components are considered preferred solvents, according to the Pfizer solvent selection guide.

In particular, optimisation studies were carried out, which showed that ethanol may be used as an alternative to *n*-butanol or *t*-amyl alcohol as co-surfactant. This offers an energy saving for reaction work-up and purification, as ethanol is removed by rotary evaporation at lower temperatures than the longer chain alcohols. In addition, the quantity of surfactant required is reduced compared to the other systems, thus facilitating easier purification.

A further green aspect that has been assessed is the recovery of surfactant. Work-up procedures using toluene or cyclohexane facilitate the removal and recovery of sodium dodecyl sulfate from the reaction mixture.

A key advantage of these systems is the utilisation of tetraphenylporphyrin **43**, without the need to use chlorinated solvents. Traditionally TPP **43** is not used in water or alcoholic solvents, as it is insoluble in these solvents.

6.2.4 Supercritical Carbon Dioxide ($scCO_2$)

Supercritical fluids, such as $scCO_2$ and scH_2O, have been proposed as green solvents, as they are not toxic to the environment or to humans[234]. In addition, $scCO_2$ is chemically inert (in most applications) and non-flammable. This offers an ease of reaction work up, as changes in pressure can enable removal of the solvent as a gas and leaves the dry product.

Use of supercritical fluids as solvents in photoxygenation processes has been reported by Poliakoff and George, who have reported the synthesis of 1,4-naphthoquinone and ascaridole. In these experiments, a flow through device was used, enabling continuous flow.

The synthesis of juglone **98** in supercritical carbon dioxide was investigated at the University of Loughborough in October 2008, using a batch cell. Comparison experiments were conducted, using methanol or *i*-propyl alcohol as examples of conventional organic solvents used in this synthesis. In addition, the energy demand of the supercritical carbon dioxide setup was assessed.

6.2.4.1 Experimental set-up

All experiments were carried out in the supercritical carbon dioxide set-up, as shown in the schematic representation (Figure 75).

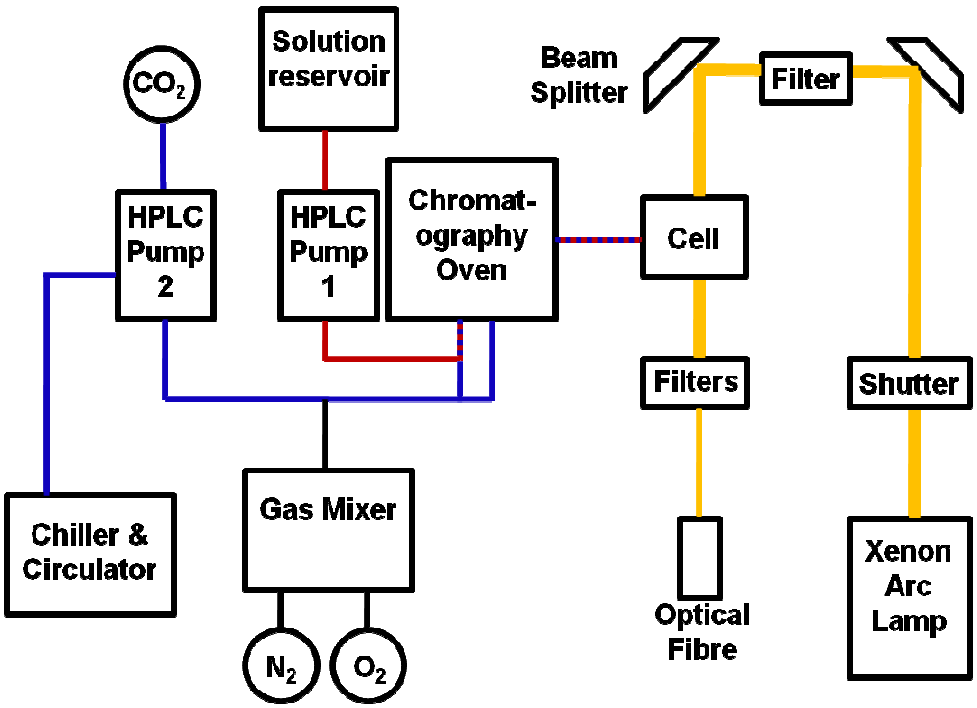


Figure 75: Schematic representation of reaction set-up for $scCO_2$ experiments.

A xenon arc lamp (Light Support, 150 W) was used for irradiation. To prevent irradiation of juglone **98** (around 400-450 nm) a coloured light filter was used (orange, > 490 nm). For monitoring purposes, an optical fibre (Ocean Optics USB 2000, with Ocean Optics Spectrasuite software) was used to measure absorbance. Neutral light filters were used to decrease the light intensity at the scope. This was optimised for the region of interest, i.e. 400-450 nm.

The reaction mixture was introduced into the cell using HPLC Pump 1 (Jasco PU-980 Intelligent HPLC pump). For supercritical carbon dioxide generation, the solvent was removed under a gentle flow of oxygen before liquid carbon dioxide was introduced using HPLC Pump 2 (Jasco PU-980 Intelligent HPLC pump). The carbon dioxide was cooled to -10 °C using the chiller and circulator system. Once in the cell, supercritical carbon dioxide was generated by heating to 50°C and increasing pressure to 100 kg/cm^2.

6.2.4.2 Calibration curves

In order to quantitatively monitor the conversion of 1,5-dihydroxynaphthalene **97** to juglone **98** in the supercritical carbon dioxide apparatus, calibration curves were prepared. Juglone **98** standards of the concentration range 0.0-0.5 mM were prepared (0.0, 0.1, 0.2, 0.3, 0.4 and 0.5 mM). The absorbance of the standards was recorded in triplicate in both conventional solvent (methanol) and in supercritical carbon dioxide. A plot of concentration against absorbance at 415 nm was prepared for both systems.

6.2.4.2.1 Calibration curve for supercritical carbon dioxide

The calibration curve for reactions in supercritical carbon dioxide (Figure 76) was constructed. All data points were included.

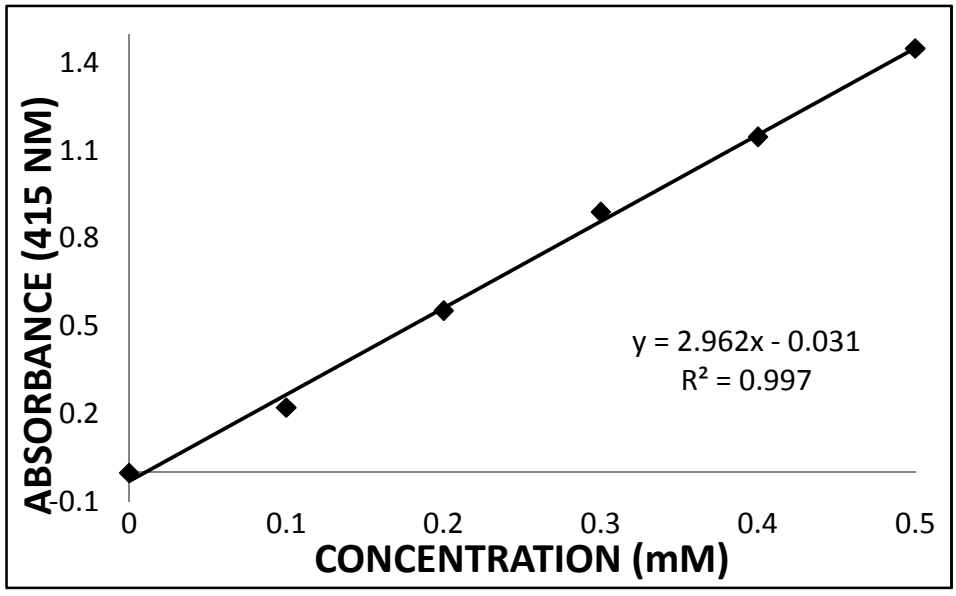


Figure 76: Calibration curve for reactions in supercritical carbon dioxide, measured at 415 nm (Experiment 171).

The equation of the line was used for calculation of concentration (and hence conversion) for reactions carried out in supercritical carbon dioxide.

6.2.4.2.2 Calibration curve for conventional solvent (methanol)

It has been observed that when reaction solutions of the same concentration in conventional solvents and in supercritical carbon dioxide are compared, higher absorbance values are noted for the supercritical carbon dioxide readings. This has been attributed to the formation of 'clusters' of additional density. This pressure in the system causes short lived formations with a greater density of solutes and may cause a localised increase in absorbance of sample. Therefore, it was necessary to prepare a calibration curve for conventional solvents in which this phenomenon does not occur.

Absorbance measurements were taken in triplicate for standards of known concentrations of juglone **98** (0.0, 0.1, 0.2, 0.3, 0.4 and 0.5 mM), and plotted as shown in Figure 77. Of significance is the inconsistency of the 0.1 mM sample, which impacts significantly on the fit of the graph (R^2 value of 0.957).

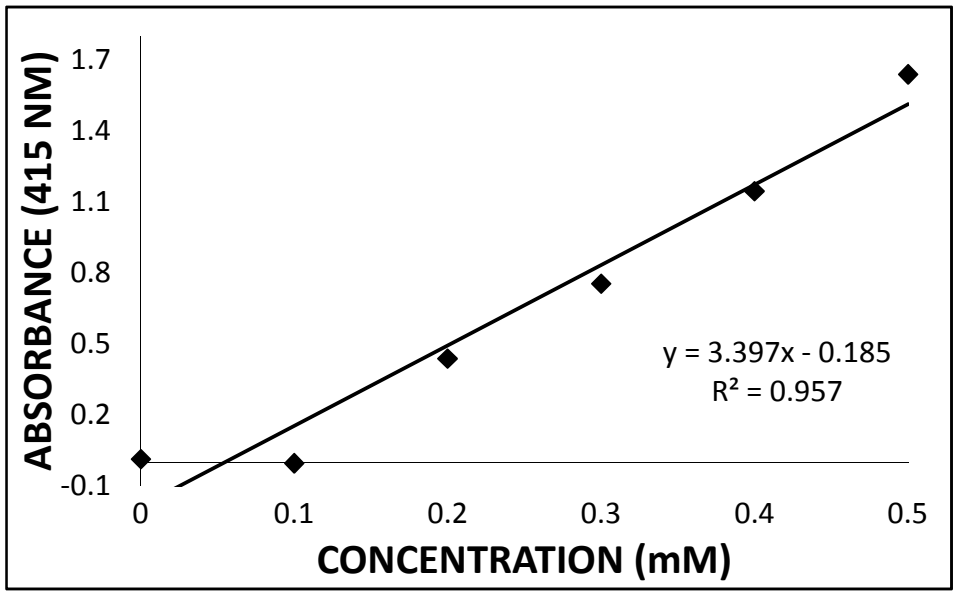


Figure 77: Calibration curve showing standards from 0.0-0.5 mM juglone 98 **measured at 415 nm in reaction set-up (Experiment 172).**

To confirm that these standards were prepared in the correct concentrations absorbance measurements were performed using a UV-vis spectrophotometer (Figure 78). These showed that the 0.1 mM standard was prepared to the correct specification.

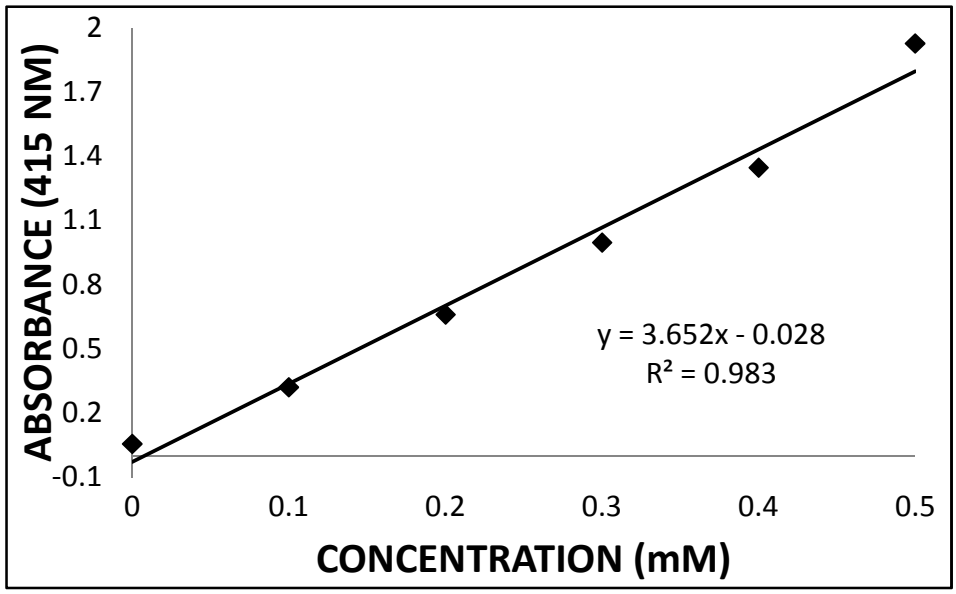


Figure 78: Calibration curve for reactions in conventional solvents measured at 415 nm using UV-vis spectrophotometer.

As the 0.0 and 0.1 mM standards could not be measured accurately, this suggests a technical limitation of the system. The fibre optic scope used in the experimental set-up is unable to measure the absorbance of solutions of less than 0.2 mM concentrations in solution phase. However, concentrations of 0.2-0.5 mM may be measured accurately using this technique. A calibration curve was therefore prepared with the omission of the 0.0 and 0.1 mM standards (Figure 79). With the omission of the 0.0 and 0.1 mM standards a line was obtained with a good fit (R^2 value of 0.9903), this was used to determine conversions in reactions conducted in traditional solvent.

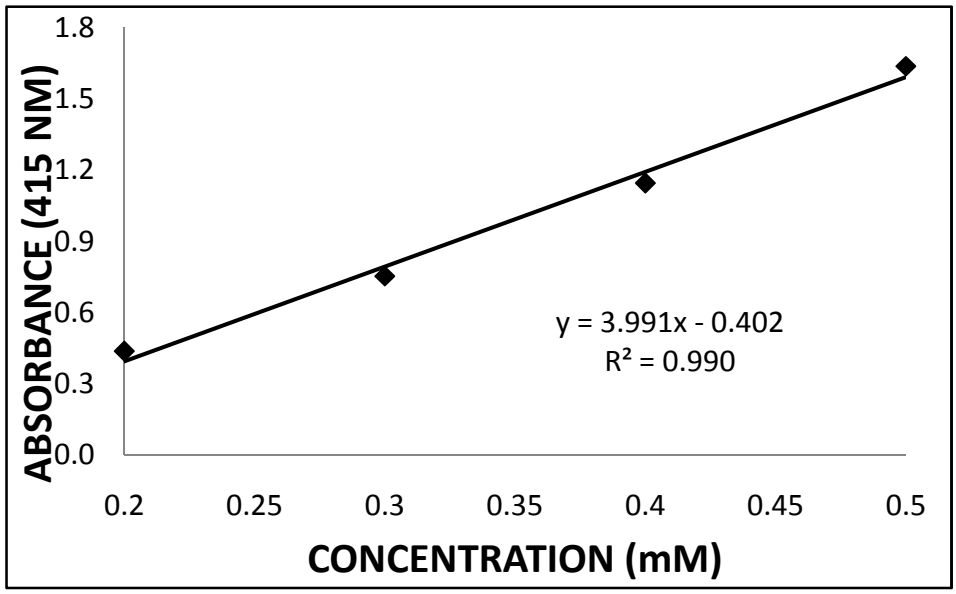


Figure 79: Calibration curve showing standards from 0.2-0.5 mM juglone 98 measured at 415 nm in reaction set-up.

6.2.4.3 Sensitiser study

This study looked at the use of three common singlet oxygen sensitisers, namely rose bengal **41**, methylene blue **42** and tetraphenylporphyrin **43**.

6.2.4.3.1 Methylene blue in supercritical carbon dioxide

Methylene blue **42** was introduced into the apparatus using either methanol or *i*-propyl alcohol. The choice of solvent was shown to affect the rate of the reaction. This indicates that not all of the solvent was removed before introduction of carbon dioxide. The presence of residual solvent may cause quenching of the singlet oxygen generated and therefore slow the reaction compared to solvent-free supercritical carbon dioxide.

However, the presence of residual solvent may give a co-solvent affect leading to better solubility of the sensitiser. Bourne has proposed that the use of surfactants may lead to increased solubility of methlylene blue **42** in supercritical carbon dioxide[240, 242]. This indicates that solubility of traditional sensitisers may be poor.

In this study, the use of methanol for introduction of sample into the cell was shown to give greater conversion in a shorter time than when *i*-propyl alcohol is used. This is in disagreement with results in traditional solvents, where the use of methylene blue **42** in *i*-propyl alcohol has given better results than methanol[55]. This suggests that the concentration of co-solvent is a factor, and the more solvent present a greater quenching effect may be observed.

When methylene blue **42** was introduced in methanol, a conversion of 76% was observed after one hour of irradiation (Figure 80), while introduction in *i*-propyl alcohol gave a conversion of 30% after 2.5 hours of irradiation (Figure 81).

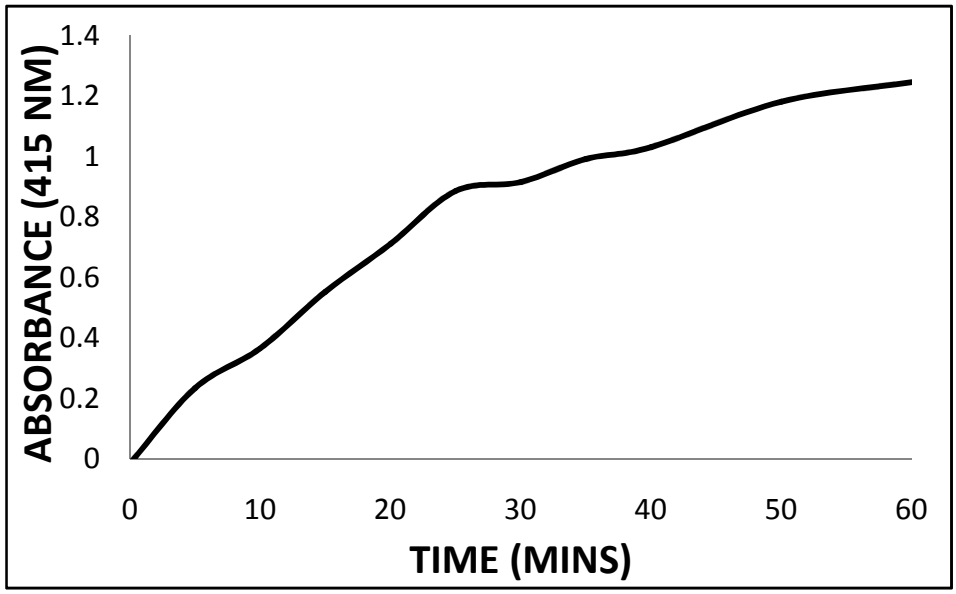


Figure 80: Synthesis of juglone 98 **using methylene blue** 42 **in supercritical carbon dioxide, measured at 415 nm (introduced in methanol, Experiment 173).**

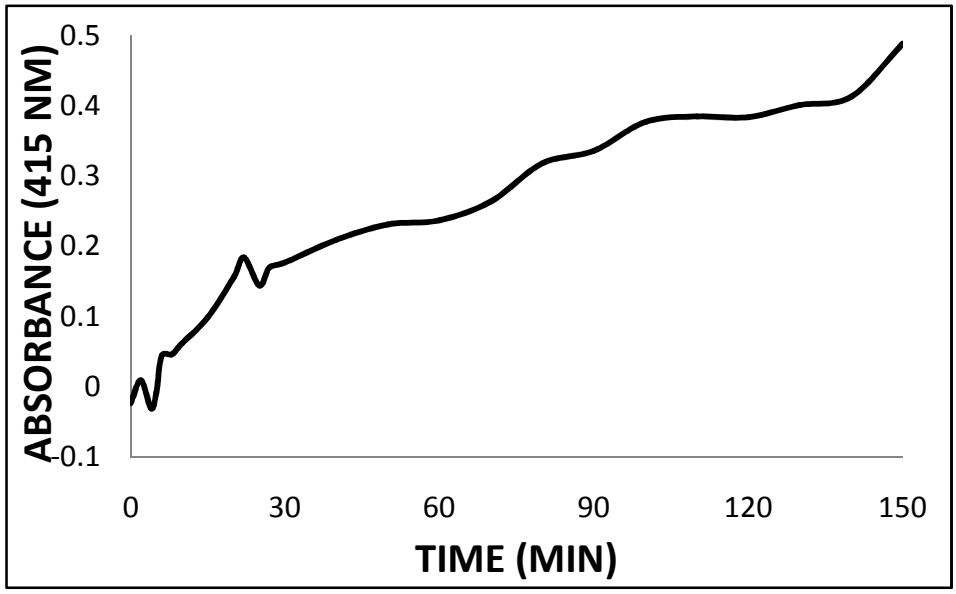


Figure 81: Synthesis of juglone 98 **using methylene blue** 42 **in supercritical carbon dioxide, measured at 415 nm (introduced in *i*-propyl alcohol, Experiment 174).**

6.2.4.3.2 Rose bengal in supercritical carbon dioxide

The use of rose bengal **41** as a sensitiser was investigated, with introduction using methanol and *i*-propyl alcohol. When *i*-propyl alcohol was used for introduction, a conversion of 59% was obtained in just 40 minutes (Figure 82), compared to a conversion of 55% in 60 minutes when methanol was used (Figure 83).

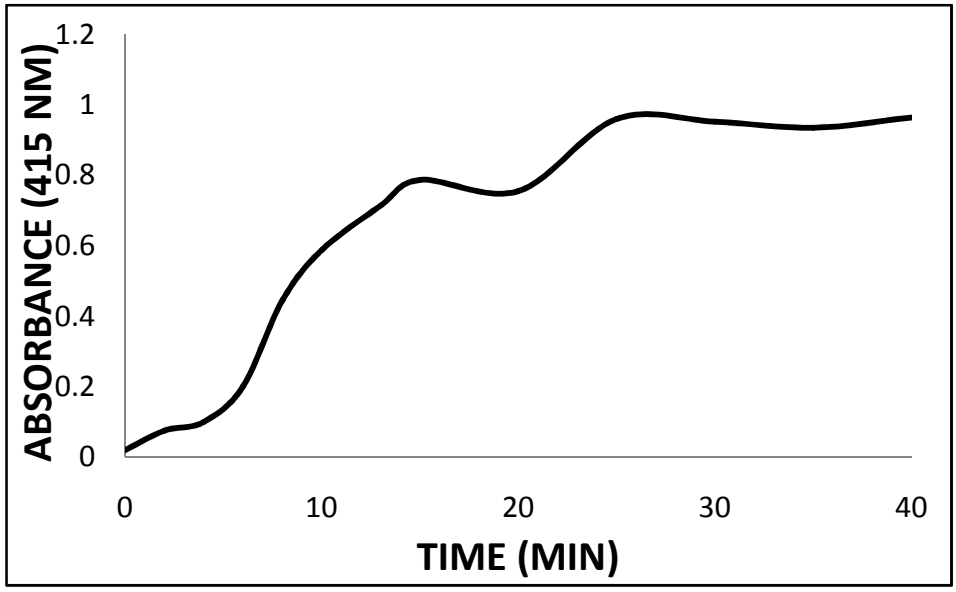


Figure 82: Synthesis of juglone 98 **using rose bengal** 41 **in supercritical carbon dioxide, measured at 415 nm (introduced in *i*-propyl alcohol, Experiment 175).**

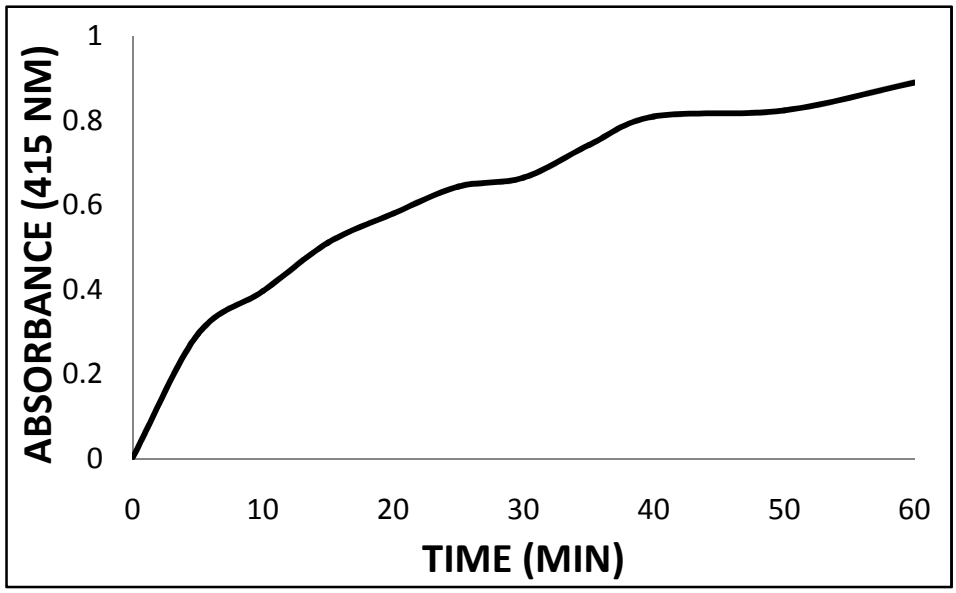


Figure 83: Synthesis of juglone 98 **using rose bengal** 41 **in supercritical carbon dioxide, measured at 415 nm (introduced in methanol, Experiment 176).**

6.2.4.3.3 Tetraphenylporphyrin in supercritical carbon dioxide (introduced in ethyl acetate)

It has been reported that TPP **43** is not soluble in supercritical carbon dioxide, however this was investigated for use when ethyl acetate was used for introduction (and may show some co-solvent effect). As shown in Figure 84, the synthesis of juglone **98** using TPP **43** in supercritical carbon dioxide was not achieved.

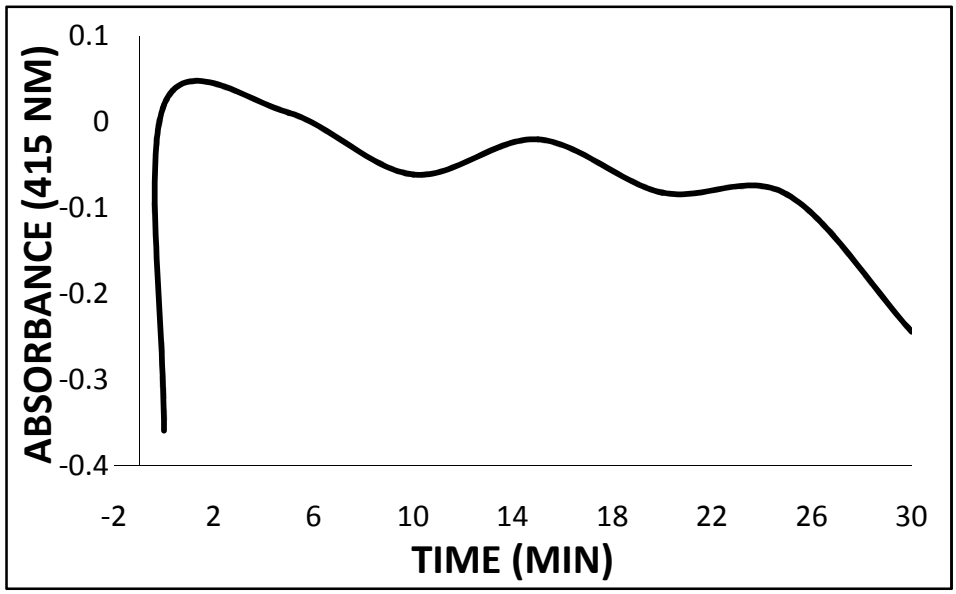


Figure 84: Synthesis of juglone 98 **using TPP** 43 **in supercritical carbon dioxide, measured at 415 nm (introduced in ethyl acetate, Experiment 177).**

6.2.4.3.4 Non-sensitised formation of juglone in supercritical carbon dioxide (introduced in methanol)

The self-sensitised reaction of 1,5-dihydroxynaphthalene **97** to form juglone **98** has been observed, particularly under UV light irradiation. Yields of juglone **98** of 8%-23% have been observed for different light sources, such as solar, halogen lamp, medium-pressure mercury lamp and rayonet (with lamps at 300 nm).

The effect of using a xenon lamp was investigated in both supercritical carbon dioxide and conventional solvent (methanol). When supercritical carbon dioxide was used, a conversion of almost 38% was achieved in just 60 minutes (Experiment 178, Figure 85). For the use of conventional solvents, there was no evidence of juglone **98** formation (Experiment 179).

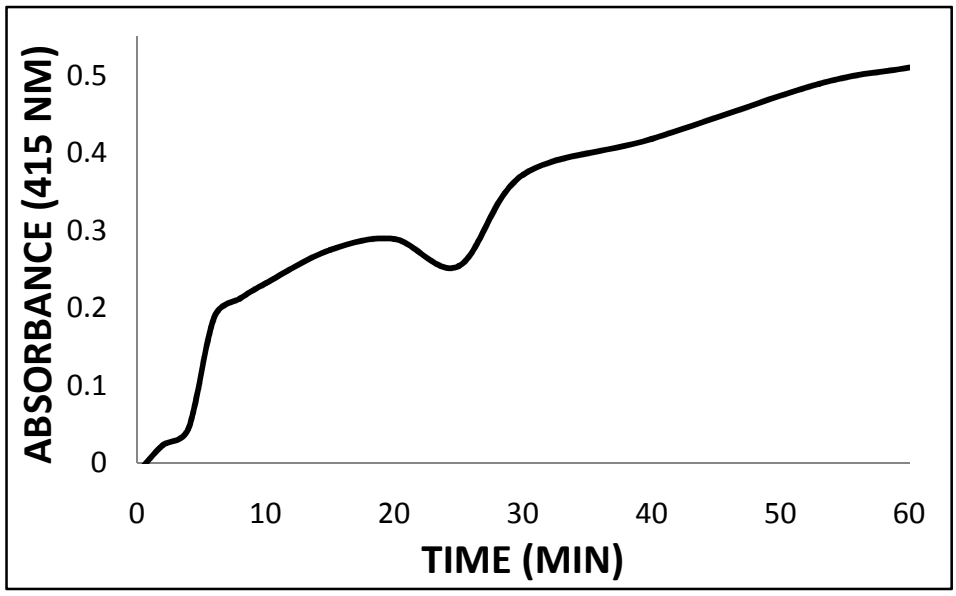


Figure 85: Self-sensitised photooxygenation of 1,5-dihydroxynaphthalene 97 **in supercritical carbon dioxide, measured at 415 nm (introduced in methanol, Experiment 178).**

6.2.4.4 Solvent study

In addition to the supercritical carbon dioxide reactions in section 6.2.4.3, the formation of juglone **98** using conventional solvents was investigated in the reaction set-up. This can be used for comparison of the reaction rate and evaluation of the effectiveness of supercritical carbon dioxide as a suitable reaction solvent. The solvents investigated were methanol and *i*-propyl alcohol. Both of these solvents have been used previously for synthesis of juglone **98** on a laboratory scale (0.01 M solutions), and were shown to give similar results[55]. *i*-Propyl alcohol is the solvent of choiceas it is considered less harmful and more 'green' than methanol[56]. Use of methylene blue **42** and rose bengal **41** as sensitisers was investigated. Previous studies have shown that methylene blue **42** in methanol or in *i*-propyl alcohol gives greater yields than use of rose bengal **41**[55].

6.2.4.4.1 Methylene blue in methanol

Use of a methanolic reaction solution (0.5 mM 1,5-dihydroxynaphthalene **97** and 2.5 μM methylene blue **42**) was investigated in the supercritical carbon dioxide set-up. This was shown to give a conversion of 34% in one hour (Figure 86).

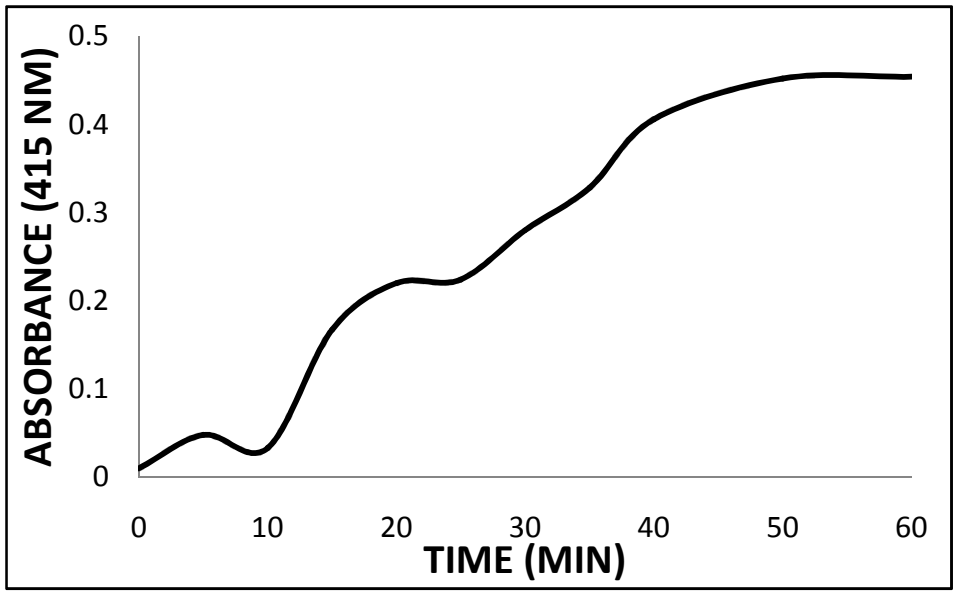


Figure 86: Synthesis of juglone 98 **using methylene blue** 42 **in methanol, measured at 415 nm (Experiment 180).**

6.2.4.4.2 Methylene blue in *i*-propyl alcohol

When *i*-propyl alcohol was used as the solvent the reaction did not appear to proceed. This was not in line with expectations, as usually methylene blue **42** in *i*-propyl alcohol gives results similar, if not slightly higher yields, when compared to methanol[55]. After 30 minutes of reaction time, the study was stopped as the fluctuations in conversion were significant and the reaction did not appear to be proceeding (Figure 87).

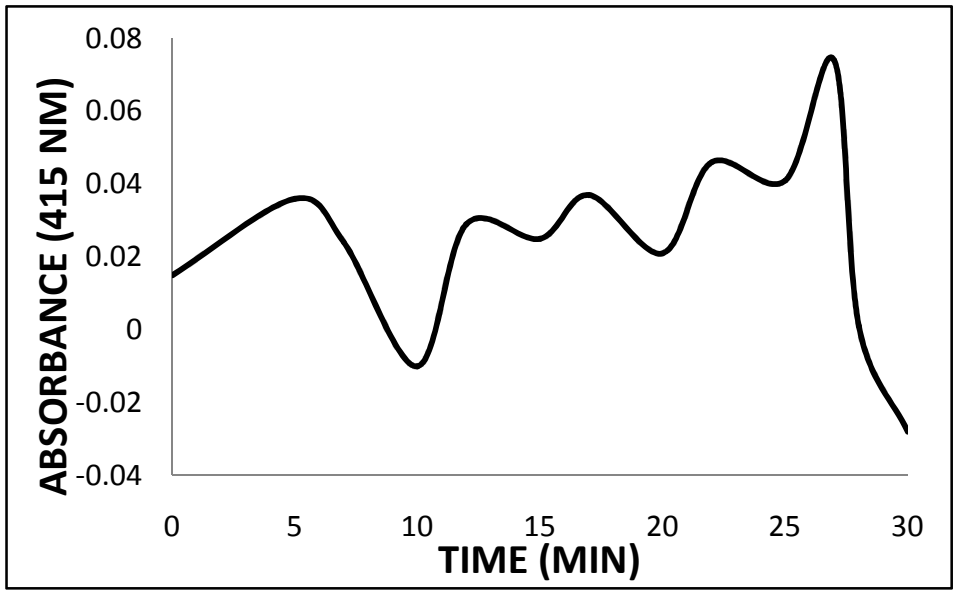


Figure 87: Synthesis of juglone 98 **using methylene blue in** 42 ***i*-propyl alcohol, measured at 415 nm (Experiment 181).**

6.2.4.4.3 Rose bengal in methanol

For the use of rose bengal **41** in methanol a conversion of 42% was achieved in one hour (Figure 88).

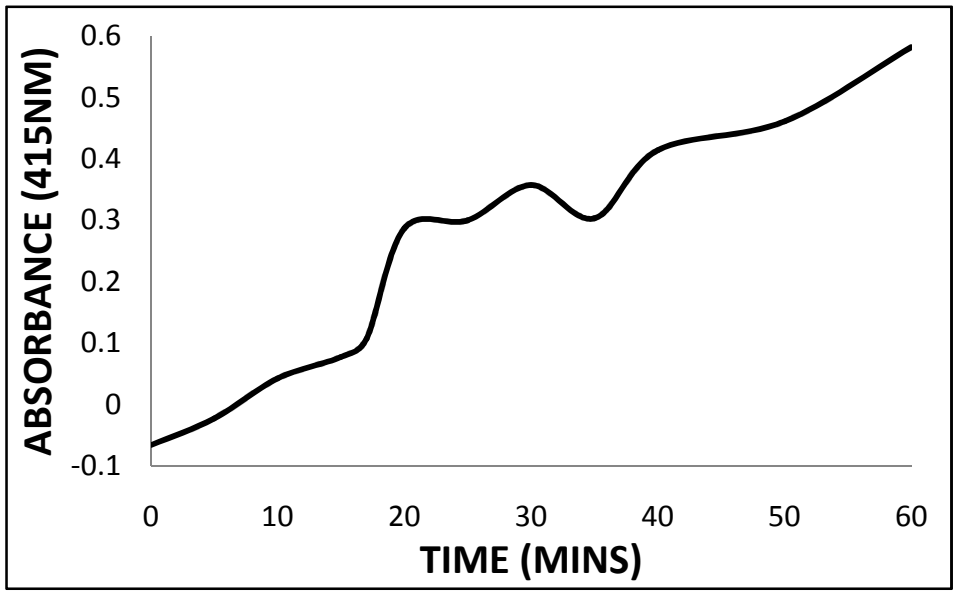


Figure 88: Synthesis of juglone 98 **using rose bengal** 41 **in methanol, measured at 415 nm (Experiment 182).**

6.2.4.4.4 Rose bengal in *i*-propyl alcohol

Use of *i*-propyl alcohol as solvent for synthesis of juglone **98** using rose bengal **41** was shown to be as effective as methanol, giving a conversion of 42% in 60 minutes (Figure 89).

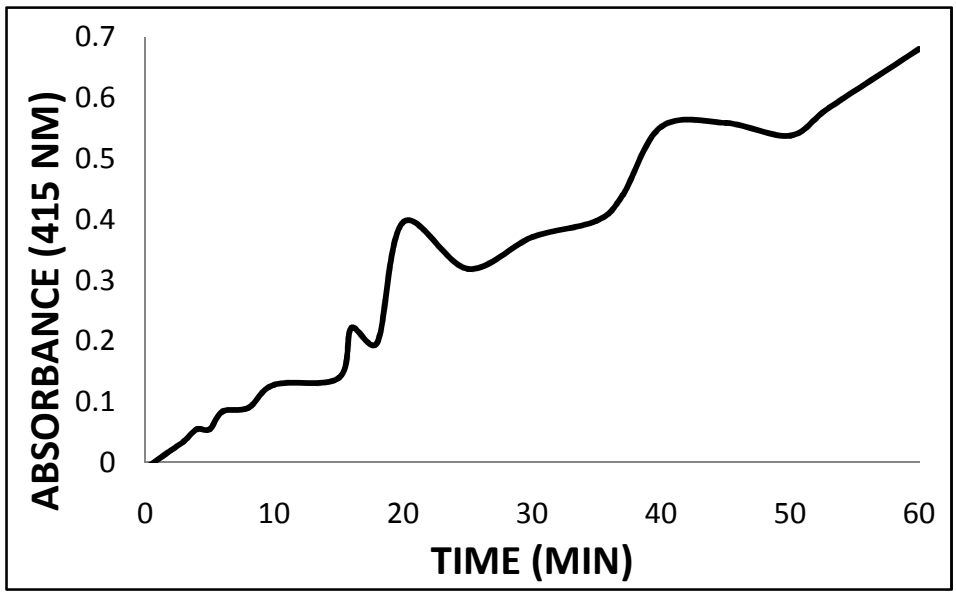


Figure 89: Synthesis of juglone 98 **using rose bengal** 41 **in *i*-propyl alcohol, measured at 415 nm (Experiment 183).**

6.2.4.4.5 Tetraphenylporphyrin (TPP) in ethyl acetate

The synthesis of juglone **98** using TPP **43** was investigated using ethyl acetate as solvent. Solubility of TPP **43** is often a disadvantage, however this is not the case where ethyl acetate is used. The maximum absorbance of TPP **43** is around 415 nm, which is the same region as the characteristic juglone **98** absorbance. Therefore, a filter was not used during this experiment. In addition, the conversion was not calculated, as there is some photo-degradation of TPP **43** which will affect the monitoring of the peak at 415 nm. However, it is evident from the increases in absorbance that juglone **98** is synthesised during this experiment (Figure 90).

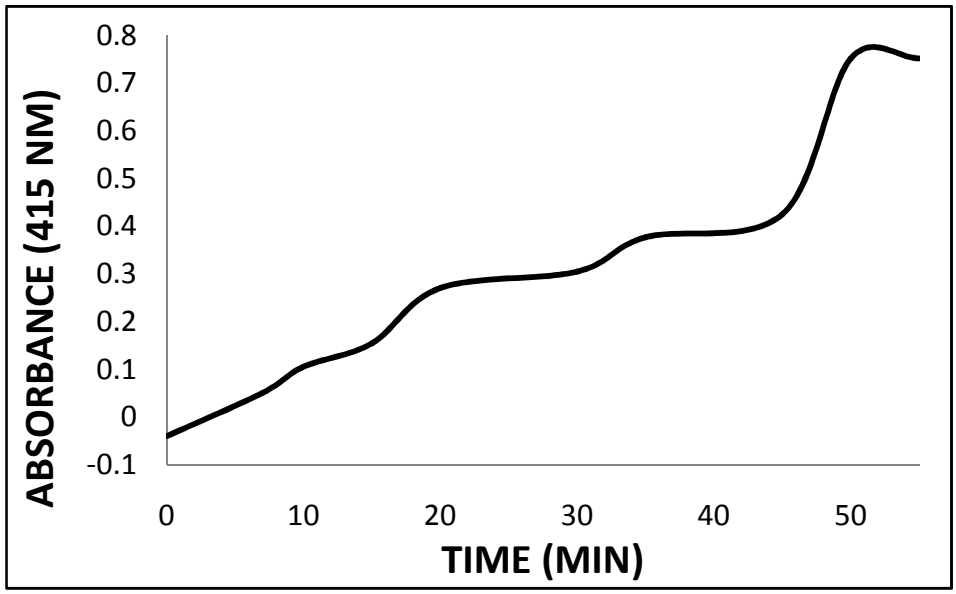


Figure 90: Synthesis of juglone 98 **using TPP** 43 **in ethyl acetate, measured at 415 nm (Experiment 184).**

6.2.4.5 Energy usage study

A plug-in electricity cost and usage meter was used to measure the energy required for each component of the supercritical carbon dioxide apparatus (Table 29). There are many components required for the generation of supercritical fluids, in particular to provide temperature and pressure control, as well as pumping of the fluids throughout the system.

Table 29: Energy required for supercritical carbon dioxide apparatus

Equipment	kJ/h	Notes
Immersion cooler	784.8	Maintaining at -10 °C
Temperature controller	338.4	Maintaining at -10 °C
Circulator	20.8	Maintaining at -10 °C
Oven and controller	352.8	Heating
	266.4	Maintaining
Cell heating unit	80.0	Heating from 24-49 °C
	104.2	Maintaining at 50 °C
CO_2 pump	30.0	Increasing P from 60-100 kg/cm^2
	54.0	Maintaining P at 100 kg/cm^2
Solvent pump	78.3	
Xenon lamp	1569.6	Warm up time (30 mins)
	1738.8	Operation during experiments
Computer and scope	89.2	Continuous absorbance monitoring

Temperature control is required to cool the carbon dioxide upon entry into the system, thus maintaining its liquid form. Once in the cell, heating is applied. This need for both heating and cooling of the system results in very high energy demand for temperature control. In particular, the cooling system draws over 1000 kJ per hour to maintain temperature at -10 °C. In addition, the oven and controller required over 600 kJ per hour of operation.

By far the greatest energy requirement for this system was the use of a xenon lamp, which required 30 minutes to warm up prior to use (thus requiring 869 kJ) and was then run continuously throughout the experiments (using 1739 kJ per hour of operation). This is an energy requirement that could be significantly reduced by employing a lower energy light source, such as a lower wattage halogen lamp or even LEDs, which have been employed successfully in other scCO_2 systems.

6.2.5 Summary of synthesis in supercritical carbon dioxide

The results of this study may be summarised as shown in Table 30. This shows that photooxygenation of 1,5-dihydroxynaphthalene **97** to juglone **98** can be achieved in up to 76% conversion using methylene blue **42** in supercritical carbon dioxide.

Table 30: Summary of results for juglone 98 **synthesis in $scCO_2$ and conventional solvents (Experiments 171-182)**.

Expt. No.	Solvent (reaction)	Solvent (introduction)	Sensitiser	Time (min)	Conversion (%)
173	$scCO_2$	Methanol	MB	60	76
174	$scCO_2$	*i*-Propyl alcohol	MB	150	30
175	$scCO_2$	*i*-Propyl alcohol	RB	40	59
176	$scCO_2$	Methanol	RB	60	55
177	$scCO_2$	Ethyl acetate	TPP	55	-
178	$scCO_2$	Methanol	None	60	38
179	Methanol	Methanol	None	30	-
180	Methanol	Methanol	MB	60	34
181	*i*-Propyl alcohol	*i*-Propyl alcohol	MB	30	-
182	Methanol	Methanol	RB	60	42
183	*i*-Propyl alcohol	*i*-Propyl alcohol	RB	60	42
184	Ethyl acetate	Ethyl acetate	TPP	60	-

However, since this study was conducted there have been reports in the literature showing that methylene blue **41** and rose bengal **42** have limited solubility in supercritical carbon dioxide[240]. This indicates that the results achieved in this study may involve the use of methylene blue **42** and rose bengal **43** as heterogeneous sensitisers. The influence of residual solvent may also be a contributing factor. For these experiments, the reaction mixture is introduced in an alcoholic solvent, which is then removed using a steady stream of oxygen. However, this may not ensure full removal of the alcoholic solvents as they have relatively high boiling points and may be difficult to remove. The presence of a co-solvent effect may explain the variation in results for use of methylene blue **42** in scCO2, as when it is introduced in *i*-propyl alcohol a considerably longer reaction time is observed.

A particular disadvantage of the reaction set-up employed in this study is the small volume of the reaction cell. The system is not suitable for preparative studies, as only trace amounts of each reagent are present. The use of a larger cell, ideally utilising a flow through system, is necessary to make this procedure suitable for large scale applications. In addition, the limitation of the monitoring method should be addressed, in particular facilitating monitoring of the starting material peaks (300-350 nm) and of solution of higher concentrations. During this study it was necessary to perform significant dilutions, as well as use light filters, to ensure that the

light was of a sufficiently low intensity for use with the optical scope. Therefore very dilute reaction mixtures were irradiated, which limits the reaction to non-preparative studies.

A key factor influencing the greenness of this reaction is the significant energy demand. The light source utilised, a xenon lamp, is particularly energy-intensive. However, it is possible to replace this light source with LEDs, which could offer a significant energy saving. Unfortunately, the system still requires a large amount of energy for heating and cooling applications, and this is a fundamental disadvantage of the reaction set-up. Given the large energy demand and the low concentrations utilised, this process cannot be considered green.

6.3 Summary

The synthesis of juglone **98** has been used as a model reaction to assess the application of alternative reaction media in the dye-sensitised photooxygenation process. The methods assessed were use of solvent-free conditions using polymeric supports, or use of alternative solvents, i.e. ionic liquids, microemulsions or supercritical fluids. These approaches have been proposed in the literature as green methods for synthesis.

This study has demonstrated the application of solvent-free conditions in dye-sensitised photooxygenation reactions. However, this procedure is limited to liquid substrates. In addition, significant amounts of volatile organic solvents are required for preparation of the solid supported reaction mixture. Therefore, this method does not offer a green alternative to the use of traditional reaction solvents.

Of solution phase green media, the most promising or truly green procedure was use of microemulsions. These involve the use of solvents that are classified as preferred or acceptable under the Pfizer solvent selection guide. Optimistion studies have minimised the quantity of surfactant required to stabilise ethanolic microemulsions. In addition, the use of cyclohexane or toluene washings can facilitate recovery of surfactant for reuse. A key advantage of microemulsions is the ability to use TPP **43** as sensitiser in this solvent, thus offering a green approach to the utilisation of this sensitier.

The application of ionic liquids has also been demonstrated with limited success, but oxygen solubility is poor in the commercially available [emim]OTf **187**. However an ionic liquid with selectively tuned properties is needed to ensure maximum oxygen solubility.

Use of supercritical carbon dioxide as reaction medium for dye-sensitised photooxygenation has also been demonstrated. However, there were significant technical limitations, such as small cell volume, lamp intensity and fluctuation and low threshold of the monitoring method. Although synthesis in supercritical carbon dioxide is feasible, this is a very energy intensive process and the high energy demand outweighs the greenness of the reaction solvent.

6.4 Experimental

6.4.1 Solvent-free photooxygenation on polymer supports

Experiment 140 (EC-022): Attempted synthesis of juglone 98 **using cellulose acetate** 295 **support**

1,5-Dihydroxynaphthalene **97** (0.32 g, 2.0 mmol) was dissolved in methanol (5 ml) and added to TPP **43** (5 mg, 8 μmol) in ethyl acetate (15 ml) in a conical flask. This mixture was stirred vigorously and cellulose acetate **295** (0.50 g) was added in small portions. The mixture was left to stir for 15 minutes following complete addition of the polymer to ensure homogeneity of the mixture, which was then poured onto a Petri dish. The dish was left to stand in darkness to allow the solvent to evaporate. The dry 'pancake' was irradiated from above using a halogen lamp, without cooling, for 24 hours. Following irradiation, the 'pancake' was washed for 1 hour with methanol before filtering to yield a brown solution.

TLC (chloroform) showed a yellow spot (R_f = 0.70) which indicated the presence of juglone **98**, as well as a brown spot on baseline representing starting material **97**.

Experiment 141 (EC-023): Attempted synthesis of juglone using polyethylene glycol (PEG) support

Polyethylene glycol **296** (PEG, 0.50 g) was stirred in dichloromethane and poured onto a petri dish, from which the solvent was allowed to evaporate. 1,5-Dihydroxynaphthalene **97** (0.32 g, 2.0 mmol) was dissolved in acetone (5 ml) and added to a solution of TPP **43** (5 mg, 8 μmol) in ethyl acetate (15 ml). The mixture was poured over the PEG **296** and the dish was swirled to ensure even distribution over the surface. Ethyl acetate was removed by evaporation in darkness. The dried 'pancake' (poorly distributed and appeared slightly wet) was irradiated from above using a halogen lamp, without cooling, for 24 hours.

TLC (chloroform) of the crude reaction mixture showed that juglone **98** was not formed.

General procedure for preparation and use of polystyrene supports

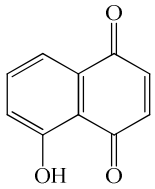
Polystyrene **294** (0.50 g) was placed in a petri dish, swollen using dichloromethane (20 ml) and solvent allowed to evaporate to dryness. Starting material and sensitiser (TPP **43**, 5 mg, 8 μmol) were dissolved in ethyl acetate (20 ml, with small amounts of methanol (7.5 ml) if required to ensure solubility) and introduced onto the polymer. The dish was swirled to ensure even mixing

and placed in darkness to allow solvent to evaporate. The reaction 'pancake' was then ready for irradiation.

All photoreactions were carried out for 24 hours, using the set up shown in Figure 68a (page 204), except for the synthesis of 5-hydroxyfuranone **112**, which was irradiated using the set up shown in Figure 68b (page 204).

Following reaction, the polymer supported reaction mixture was rinsed using methanol (20 ml) to remove starting material **97** and product **98**, while TPP **43** remained on the polymer **290**. Solvent was evaporated to yield the crude product, which was analysed by ^{1}H NMR spectroscopy.

Experiment 142 (EC-014): Synthesis of juglone without external cooling

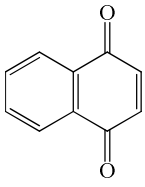


98

Following the general procedure, 1,5-dihydroxynaphthalene **97** (0.32g, 2.0 mmol) was introduced onto polystyrene **292**. This was irradiated without external cooling. The crude product was green-brown in appearance.

TLC (chloroform) showed that juglone **98** was not formed. ^{1}H NMR spectroscopy (DMSO-d_6) was characteristic of 1,5-dihydroxynaphthalene **97**.

Experiment 143 (EC-020): Synthesis of 1,4-naphthoquinone without external cooling



91

Following the general procedure, 1-naphthol **226** (0.29 g, 2.0 mmol) was introduced onto polystyrene **290**. This was irradiated without external cooling. Following irradiation the

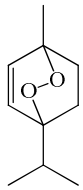
'pancake' had become black in colour and some crystals had formed on the surface. The crude product was a paint-like black-red solid.

TLC (chloroform) showed that 1,4-naphthoquinone **90** was not formed.

Experiment 144 (EC-020): Synthesis of 1,4-naphthoquinone with external cooling

The reaction was carried out as in Experiment 138, with temperature control to maintain the reaction at 10 °C during irradiation.

Experiment 145 (EC-016): Synthesis of ascaridole without external cooling



66

Following the general procedure, α-terpinene **69** (0.38 ml, 2.0 mmol) was introduced onto polystyrene **290** and irradiated without external cooling. Following irradiation the colour of the 'pancake' had changed from pink to orange, indicating some leaching of the sensitiser **43**. The crude product was a honey-coloured, waxy solid.

^{1}H NMR spectroscopy (CD_3OD) showed the presence of ascaridole **66**, with characteristic doublets at 6.4 ppm (with large roof effect) which represent the two vinylic protons, as well as a singlet at 1.3 ppm representing the lone methyl group (integration of 3).

The crude ^{1}H NMR spectroscopy (CD_3OD) showed the presence of other substances, in particular *p*-cymene **293** was identified by the characteristic doublet (dd) at 7.08 ppm representing the four aromatic protons and the singlet at 2.29 ppm, which is characteristic of the long methyl group. However, the product was not purified and yields were not calculated.

^{1}H NMR (300 MHz, CD_3OD) δ (ppm) = 0.97 (d, J^3 = 7.2 Hz, 6H, C**H**$_3$); 1.35 (s, 3H, C**H**$_3$); 1.49 (d, J^3 = 9.3 Hz, 2H, C**H**$_2$); 1.90 (sept., J^3 = 7.2 Hz, 1H, C**H**); 2.00 (m, 2H, C**H**$_2$); 6.38 (d, J^3 = 8.4 Hz, 1H, C=C-**H**); 6.47 (d, J^3 = 8.4 Hz, 1H, C=C-**H**).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 0.97 (d, J^3 = 7.2 Hz, 6H, C**H**$_3$); 1.35 (s, 3H, C**H**$_3$); 1.49 (d, J^3 = 9.3Hz, 2H, C**H**$_2$); 1.92 (sept., J^3 = 6.9 Hz, 1H, C**H**); 2.00 (m, 2H, C**H**$_2$); 6.38 (d, J^3 = 8.4 Hz, 1H, C=C-**H**); 6.47 (d, J^3 = 8.4 Hz, 1H, C=C-**H**).

CAS no. 512-85-6, ^{1}H NMR spectrum consistent with literature[29].

Experiment 146 (EC-017): Synthesis of ascaridole with external cooling

The reaction was carried out as in Experiment 145, with temperature control to maintain the reaction at 10 °C during irradiation. No change was observed in the 'pancake' following irradiation (i.e. no appreciable leaching of sensitiser **43**). The crude product was a white-brown, waxy solid.

^{1}H NMR spectroscopy (CD_3OD) showed characteristic peaks for ascaridole **66**, namely two doublets at about 6.4 ppm (large roof effect) representing the two vinylic protons, as well as the singlet representing the lone methyl group at 1.25 ppm.

The crude ^{1}H NMR spectroscopy (CD_3OD) showed little impurities, indicating excellent conversion and little degradation products.

Experiment 147A (KJ-04): Synthesis of 5-hydroxyfuranone *See Appendix A*

Experiment 148 (EC-034): Synthesis of juglone using cellulose acetate support, reference reaction

The polymer **290** supported reaction mixture was prepared as detailed in Experiment 140. The dry 'pancake' was not irradiated, but was washed for 1 hour with methanol before filtering to yield a brown solution.

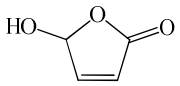
TLC (chloroform) showed a yellow spot (R_f = 0.70) which indicated the presence of juglone **98**, as well as a brown spot on baseline representing starting material **97**.

Experiment 149 (EC-026): Solution phase synthesis of ascaridole

α-Terpinene **69** (1.2 ml, 6.3 mmol) and rose bengal **41** (30 mg, 30 μmol) were dissolved in *i*-propyl alcohol (350 ml) and irradiated, with air bubbling, using two 500 W halogen lamps for 5 hours. Solvent was removed by rotary evaporation (30 °C) and the resultant residue dissolved in diethyl ether and passed through a silica plug to remove sensitiser **41**. ^{1}H NMR spectroscopy

($CDCl_3$) showed that a mixture of ascaridole **66** and *p*-cymene **293** was obtained, in a ratio of 24:1.

Experiment 150 (EC-044/KJ-16): Solution phase synthesis of 5-hydroxyfuranone



111

Furfural **111** (10.0 ml, 120 mmol) and rose bengal **41** (100 mg, 98 µmol) were dissolved in a mixture of *t*-amyl alcohol (105 ml) and water (5 ml) and irradiated, with air bubbling, using two 500 W halogen lamps for 4 days. Rose bengal **41** was added to the solution each day (3 x 100 mg (3 x 98 µmol)). Solvent was removed by rotary evaporation (40 °C) to yield a deep orange-brown oil. ^{1}H NMR spectroscopy ($CDCl_3$) of the crude product showed that a mixture of 5-hydroxyfuranone **112** and the by product **294** was obtained. 5-Hydroxyfuranone **112** was purified by cooling in freezer for one week, followed by recrystallisation in chloroform (-78 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.75 (s, 1H, O**H**); 6.22 (s; 1H; C**H**OH), 6.25 (d; J^3 = 5.6 Hz; J^4 = 1.2 Hz; 1H; C=C-**H**) 7.29 (d; J^3 = 5.6 Hz; J^4 = 1.2 Hz; 1H; C=C-**H**).

CAS no. 14032-66-7, ^{1}H NMR spectrum consistent with literature[280].

General procedure for the irradiation of 1,5-dihydroxynaphthalene with sensitiser in solid phase

1,5-Dihydroxynaphthalene **97** (0.32 g, 2.0 mmol) and tetraphenylporphyrin **43** (5 mg, 8 µmol) were ground together using a mortar and pestle and spread in a thin layer in a petri dish, before exposure to light. After this time, TLC analysis (chloroform) was used to determine the presence of juglone **98** in the reaction mixture.

Experiment 151 (EC-034/KJ-21): Artificial light irradiation

The solid phase mixture was irradiated for 24 hours in a LuzChem photoreactor, with the temperature was maintained at ca. 40 °C using a fan. TLC (chloroform) indicated that no juglone **98** was formed after this time.

Experiment 152 (EC-034/KJ-22): Solar light irradiation

The solid phase mixture was irradiated in sunlight for 3 days (24 hours). TLC (chloroform) indicated that no juglone **98** was formed after this time.

6.4.2 Photoreactions in ionic liquids

Experiment 153 (EC-201): Synthesis of juglone in [emim]OTf

1,5-Dihydroxynaphthalene **87** (8 mg, 0.05 mmol) and rose bengal **41** (2 mg, 2 μmol) were dissolved in [emim]OTf **187** (5 ml) with vigorous shaking. The reaction solutions were irradiated for 4 hours using one 500 W halogen lamp. After this time, the samples were extracted three times using diethyl ether (3 x 3 ml portions). The presence of juglone **98** was determined by UV-vis spectrophotometry.

6.4.3 Photoreactions in microemulsions

General procedure for the preparation of microemulsions

Sodium dodecyl sulfate (SDS), ethyl acetate and co-surfactant (ethanol, *n*-butanol or *t*-amyl alcohol) were stirred vigorously at room temperature to form a slurry. Water was added dropwise to this mixture, which was stirred at room temperature for a further 15 minutes to ensure homogeneity. The ratios investigated are shown in Table 31 below, of which Entries 1-2, 4-6 and 10 were stable over 24 hours.

Table 31: Optimisation of ratio for microemulsion preparation (% by weight).

Entry	Co-surfactant	% Co-surfactant	% SDS	% EtOAc	% H_2O
1	*n*-BuOH	7.5	7.5	70.0	15.0
2	*n*-BuOH	9.8	7.3	68.3	14.6
3	*n*-BuOH	11.9	7.1	66.7	14.3
4	*t*-AmOH	7.5	7.5	70.0	15.0
5	*t*-AmOH	9.8	7.3	68.3	14.6
6	*t*-AmOH	11.9	7.1	66.7	14.3
7	EtOH	7.5	7.5	70.0	15.0
8	EtOH	5.1	7.7	71.8	15.4
9	EtOH	7.7	5.1	71.8	15.4
10	EtOH	7.9	3.1	73.3	15.7

Experiment 154 (EC-077, EC-136): Optimisation of ratio of components of microemulsion

Microemulsions were prepared using the general procedure, using the ratios of components shown shown in Table 31 above. Once prepared, these were allowed to stand for 24 hours and their appearance was noted after this time. Formation of a bilayer was used to determine the stability of the microemulsions in this time.

Of the microemulsions screened, Entries 1-2, 4-6 and 10 were stable over 24 hours.

Experiment 155 (EC-079, EC-140): Screening of microemulsions for juglone synthesis

The stable microemulsions prepared in Experiment 154 (Table 31, Entries 1-2, 4-6 and 10) were investigated for use in juglone **98** synthesis. 1,5-Dihydroxynaphthalene **97** (0.01g, 0.06 mmol) and rose bengal **41** (5 mg, 5 μmol) were added to each microemulsion. The reaction mixtures were irradiated, with air bubbling, for 4 hours using one halogen lamp.

Following irradiation, presence of juglone **98** was confirmed by TLC (ethyl acetate: cyclohexane 1:3, R_f = 0.51-0.56) in all cases.

General procedure for optimisation of purification of juglone following synthesis in *t*-amyl alcohol based microemulsions

A microemulsion (200 g) containing *t*-amyl alcohol (15 g, 7.5% w/w), SDS (15 g, 7.5% w/w), ethyl acetate (140 g, 70% w/w) and water (30 g, 15% w/w) was prepared following the general procedure (Table 31, Entry 4). Four duplicate systems (50 g of microemulsion each) were prepared in parallel using 1,5-dihydroxynaphthalene **97** (0.25 g, 1.6 mmol) and rose bengal **41** (12.5 mg, 12.5 μmol). The reaction mixtures were irradiated, with air bubbling, for 12 hours using one halogen lamp. Four different methods of purification were investigated, as shown below, prior to column chromatography using a mixture of ethyl acetate and cyclohexane (1:3).

Experiment 156 (EC-080): Ethyl acetate extraction

Water (15 ml) was added to break the microemulsion and the organic layer collected. The aqueous layer was extracted three times using ethyl acetate, and the organic layers dried over sodium sulfate. The crude residue was purified by column chromatography to yield juglone **98** in 57% yield (0.16 g, 0.92 mmol) as an orange-brown solid.

Experiment 157 (EC-080): Cyclohexane washing

The liquid components of the microemulsion (ethyl acetate, *t*-amyl alcohol and water) were removed by rotary evaporation. The crude residue was washed three times with cyclohexane (3 x 20 ml) and the product was collected by gravity filtration. The filtrate was dried over sodium sulfate and the resulting crude product was purified by column chromatography to yield juglone **98** in 20% yield (56 mg, 0.32 mmol) as a yellow-brown solid.

Experiment 158 (EC-080): Soxhlet extraction

The liquid components of the microemulsion (ethyl acetate, *t*-amyl alcohol and water) were removed by rotary evaporation. The crude residue was extracted using cyclohexane in a Soxhlet apparatus overnight. Evaporation of the cyclohexane eluant yielded a small amount of a yellow oil, which was insufficient for column chromatography.

Experiment 159 (EC-102): Direct column chromatography

The liquid components of the microemulsion (ethyl acetate, *t*-amyl alcohol and water) were removed by rotary evaporation. This crude product was purified by column chromatography to yield trace amount of yellow oil which contained juglone **98** and surfactant.

General procedure for optimisation of purification of juglone following synthesis in ethanolic microemulsions

Ethanolic microemulsions (Table 31, Entry 10) containing ethanol (3.75 g, 7.9% w/w), SDS (1.5 g, 3.1% w/w), ethyl acetate (34.0 g, 73.3% w/w) and water (7.5 g, 15.7% w/w) were prepared by the general procedure. Juglone **98** was added and the solution was stirred for 15 minutes prior to addition of brine (15 ml) to break the microemulsion. The organic layer was collected and worked up using three different methods of purification, as shown below.

Experiment 160 (EC-146): Ethyl acetate extraction

Juglone **98** (0.087 g, 0.50 mmol) was dissolved in ethanolic microemulsion (50 ml). Following separation using the general procedure, the aqueous layer was extracted three times using ethyl acetate, and the organic layers dried over sodium sulfate. Following filtration and evaporation, juglone **98** was collected in 93% yield (0.081 g, 0.47 mmol) as an orange-brown solid. ^{1}H NMR spectroscopy (acetone-d_6) showed that sodium dodecyl sulfate was present (8%).

Experiment 161 (EC-168): Cyclohexane washing

Juglone **98** (0.087 g, 0.50 mmol) was dissolved in ethanolic microemulsion (25 ml). Following separation using the general procedure, the organic layer was evaporated and the residue washed with cyclohexane in a scintered glass funnel. Following evaporation of the filtrate, juglone **98** was collected in 93% yield (0.081 g, 0.47 mmol) as a deep orange solid. ^{1}H NMR spectroscopy (acetone-d_6) showed that sodium dodecyl sulfate was present (2%).

Experiment 162 (EC-168): Toluene washing

Juglone **98** (0.087 g, 0.50 mmol) was dissolved in ethanolic microemulsion (25 ml). Following separation using the general procedure, the organic layer was evaporated and the residue washed with toluene in a scintered glass funnel. Following evaporation of the filtrate, juglone **98** was collected in 92% yield (0.080 g, 0.46 mmol) as a deep orange solid. ^{1}H NMR spectroscopy (acetone-d_6) showed that sodium dodecyl sulfate was present (3%).

General procedure for sensitiser study in *t*-amyl alcohol based microemulsions

1,5-Dihydroxynaphthalene **97** (0.16 g, 1.0 mmol) and sensitiser (**41**, **42** or **43**) were dissolved in *t*-amyl alcohol based microemulsions (50 g) and irradiated, with air bubbling, for 4 hours using one halogen lamp. The reaction mixtures were purified using ethyl acetate extractions (Experiment 156). TLC (ethyl acetate: cyclohexane (1:3)) was used to determine purity of the products.

Experiment 163 (EC-101): Use of rose bengal

Using rose bengal **41** (20 mg, 20 μmol) as sensitiser, juglone **98** was obtained in 52% yield (0.091 g, 0.52 mmol) as an orange solid. TLC showed the presence of juglone **98** with no side products or starting materials.

Experiment 164 (EC-101): Use of methylene blue

Using methylene blue **42** (7.0 mg, 20 μmol) as sensitiser, juglone **98** was obtained in 39% (0.068 g, 0.39 mmol) as an orange solid. TLC showed the presence of juglone **98** with no side products or starting materials.

Experiment 165 (EC-101): Use of tetraphenylporphyrin

Using tetraphenylporphyrin **43** (12 mg, 20 μmol) as sensitiser, juglone **98** was obtained in 85% yield (0.148 g, 0.850 mmol) as an orange-brown solid. TLC showed the presence of juglone **98** with no side products or starting materials.

General procedure for sensitiser study in ethanolic microemulsions

1,5-Dihydroxynaphthalene **97** (0.081 g, 0.51 mmol) and sensitiser (**41**, **42** or **43**) were dissolved ethanolic microemulsions (50 g) and irradiated, with air bubbling, for 4 hours using one halogen lamp. The reaction mixtures were purified using ethyl acetate extractions (Experiment 160), followed by column chromatography using ethyl acetate and cyclohexane (1:3). ^{1}H NMR spectroscopy (acetone-d_6) was used to determine conversion and TLC (ethyl acetate: cyclohexane (1:3)) was used to determine purity of the products.

Experiment 166 (EC-141): Use of rose bengal

Using rose bengal **41** (25 mg, 25 μmol), a conversion of 44% was achieved and juglone **98** was isolated in 47% yield (0.041 g, 0.24 mmol) as a bright orange solid. TLC showed the presence of juglone **98** with no side products or starting materials.

Experiment 167 (EC-143): Use of methylene blue

Using methylene blue **42** (8.0 mg, 25 μmol), a conversion of 33% was achieved and juglone **98** was isolated in 35% yield (0.032 g, 0.18 mmol) as a bright orange solid. TLC showed the presence of juglone **98** with no side products or starting materials.

Experiment 168 (EC-142): Use of tetraphenylporphyrin

Using tetraphenylporphyrin **43** (15 mg, 25 μmol), a conversion of 70% was achieved and juglone **98** was isolated in 58% yield (0.051 g, 0.29 mmol) as a bright orange solid. TLC showed the presence of juglone **98** with no side products or starting materials.

Experiment 169 (EC-144): Self-sensitised formation of juglone

Under sensitiser free conditions, a conversion of 8% was achieved and juglone **98** was isolated in 7% yield (0.012 g, 0.069 mmol) as a bright orange solid. TLC showed the presence of juglone **98** with no side products or starting materials.

Experiment 170 (EC-004): Synthesis of Juglone using a modified literature procedure

1,5-Dihydroxynaphthalene **97** (1.00 g, 6.24 mmol) and TPP **43** (10 mg, 16 μmol) were dissolved in a mixture of dichloromethane and methanol (9:1). The reaction mixture was irradiated, with air bubbling, for 11.25 hours using two halogen lamps. The solvent level was maintained by periodical addition of solvent to offset any evaporation. The product was concentrated onto silica and purified by Soxhlet extraction using *n*-hexane. Following evaporation of the solvent, juglone **98** was isolated in 79% yield (0.87 g, 5.0 mmol) as a bright orange solid.

6.4.4 Supercritical carbon dioxide

6.4.4.1 General procedures

General procedure for reaction set-up

For the irradiation experiments in both conventional solvents and supercritical carbon dioxide, the set-up shown in Figure 75 (page 219) was used. A xenon lamp (150 W, Light Support) was used for irradiation.

The reaction mixture, in solvent, was introduced into the cell using a standard HPLC pump (Pump 1 in scheme, Jasco PU-980 Intelligent HPLC pump). To ensure the cell was flushed completely, the outlet was closed briefly to allow solvent to accumulate in the cell before re-opening the outlet. This was repeated to ensure complete elimination of wash solvent. The system was then allowed to equilibrate for 3-5 mins.

The outlet was closed and pressure allowed to build in the cell until an error message was presented on the pump output screen. This was cleared (CLR) and then the system was put in constant pressure mode (CP) by pressing CF/CP button. This was set to 50 bar.

For conventional solvent reactions, the irradiation experiments were carried out at this point.

For supercritical carbon dioxide experiments, the cell was heated to 50 °C (± 2 °C) and a gentle stream of oxygen was used to remove the solvent from the cell. The cell was then sealed and liquid carbon dioxide introduced. HPLC pump 2 was used to increase the pressure in the cell to

100 kg/cm^2 and this pressure was maintained (CP mode) for the duration of the experiments. Irradiation using the xenon lamp was carried out at this point.

General procedure for monitoring reactions: UV-vis Spectroscopy

UV-vis monitoring was carried out using an Ocean Optics USB 2000 optical fibre and Spectrasuite software. The absorbance was measured over the range 350 nm- 1000 nm, but the main area of interest was 400 nm – 450 nm (415 nm). Neutral density filters were used to decrease the intensity of the light reaching the optical fibre (after irradiation of the cell). Before commencing any monitoring study, light and dark reference spectra were obtained.

General procedure for irradiation experiments

For each experiment a standard solution containing 1,5-dihydroxynaphthalene **97** (10 mM) and sensitiser (0.5 mM) was prepared as shown below:

Rose bengal **41** (51 mg, 50 μmol) and 1,5-dihydroxynaphthalene **97** (0.162 g, 1.01 mmol),

Methylene blue **42** (20 mg, 63 μmol) and 1,5-dihydroxynaphthalene **97** (0.161 g, 1.01 mmol),

TPP **43** (24 mg, 39 μmol) and 1,5-dihydroxynaphthalene **97** (0.160 g, 0.999 mmol).

These standards were then diluted (1 in 20 dilution) to a concentration of 0.5 mM 1,5-dihydroxynaphthalene **97** and 0.025 mM sensitiser. For experiments using TPP **43** a further 1 in 10 dilution was necessary (50 μM 1,5-dihydroxynaphthalene **97** and 2.5 μM sensitiser **43**). This was due to the absorbance of the sensitiser in the region monitored using the optical fibre.

6.4.4.2 Construction of calibration curves

Experiment 171 (EC-130): Calibration curve for $scCO_2$ experiments

Standards of 0.0, 0.1, 0.2, 0.3 0.4 and 0.5 mM solutions of juglone **98** were prepared by dilution of a stock solution. These standards were introduced into the apparatus and dissolved in supercritical carbon dioxide, as described in the general procedure. The absorbance spectrum of each sample was measured in triplicate (Table 32) and used to construct a calibration curve.

Table 32: Absorbance of juglone 98 **standards in supercritical carbon dioxide at 415 nm.**

Conc. (mM)	Absorbance (at 415 nm)			
	a	b	c	Average
0.0	-0.018	-0.012	0.023	-0.002
0.1	0.353	0.354	0.404	0.370
0.2	0.529	0.576	0.596	0.567
0.3	0.962	0.940	0.980	0.961
0.4	1.335	1.272	1.303	1.303
0.5	1.738	1.715	1.605	1.686

Experiment 172 (EC-131): Calibration curve for conventional solvent experiments (methanol)

Standards of 0.0, 0.1, 0.2, 0.3 0.4 and 0.5 mM solutions of juglone **98** were prepared by dilution of a stock solution. These standards were introduced into the apparatus as described in the general procedure and the absorbance spectrum of each measured in triplicate (Table 33).

Table 33: Absorbance of juglone 98 **standards in methanol at 415 nm.**

Conc. mM	Absorbance (at 415 nm)						
	a	b	c	a (ii)	b (ii)	c (ii)	Average
0.0	0.004	-	0.020	0.026	0.031	0.031	0.022
0.1	-0.010	-0.005	0.000	-	-0.011	-0.004	-0.006
0.2	0.438	0.465	0.412	-	-	-	0.438
0.3	0.766	0.742	0.756	-	-	-	0.755
0.4	1.152	1.139	1.146	-	-	-	1.146
0.5	1.630	1.668	1.617	-	-	-	1.638

Reference measurements were carried out on using a standard UV-vis spectrophotometer (Table 34), which showed that the samples were prepared in the correct ratio.

Table 34: Absorbance of juglone 98 **standards in methanol at 415 nm, measured in UV-vis spectrophotometer.**

Conc. (mM)	Absorbance
0.0	0.0549
0.1	0.3198
0.2	0.6604
0.3	0.9970
0.4	1.3468
0.5	1.9280

6.4.5 Irradiation experiments

Experiment 173 (EC-115): Methylene blue in $scCO_2$, introduced in methanol

Sample introduced into the apparatus and supercritical carbon dioxide generated as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 35).

Table 35: Synthesis of juglone 98 **using methylene blue** 42 **in supercritical carbon dioxide (introduced in methanol).**

Time (min)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	-0.016	0.000	0
5	0.234	0.075	15
10	0.365	0.115	23
15	0.553	0.171	34
20	0.711	0.219	44
25	0.886	0.272	54
30	0.916	0.281	56
35	0.992	0.304	61
40	1.031	0.315	63
50	1.181	0.360	72
60	1.246	0.380	76

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 174 (EC-127): Methylene blue in $scCO_2$, introduced in *i*-propyl alcohol

Sample introduced into the apparatus and supercritical carbon dioxide generated as described in the general procedure. The sample was irradiated for 150 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 36).

Table 36: Synthesis of juglone 98 **using methylene blue** 42 **in supercritical carbon dioxide (introduced in *i*-propyl alcohol).**

Time (min)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	-0.024	-0.002	0
2	0.009	0.008	2
4	-0.031	-0.004	-1
5	-0.009	0.002	0
6	0.044	0.018	4
8	0.046	0.019	4
10	0.062	0.023	5
15	0.099	0.035	7
20	0.156	0.052	10
22	0.184	0.060	12
25	0.144	0.048	10
27	0.170	0.056	11
30	0.177	0.058	12
40	0.209	0.068	14
50	0.231	0.075	15
60	0.237	0.076	15
70	0.264	0.085	17
80	0.318	0.101	20
90	0.336	0.106	21
100	0.377	0.118	24
110	0.385	0.121	24
120	0.384	0.121	24
130	0.401	0.126	25
140	0.413	0.129	26
150	0.489	0.152	30

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 175 (EC-129): Rose bengal in $scCO_2$, introduced in *i*-propyl alcohol

Sample introduced into the apparatus and supercritical carbon dioxide generated as described in the general procedure. The sample was irradiated for 40 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 37).

Table 37: Synthesis of juglone 98 **using rose bengal** 41 **in supercritical carbon dioxide (introduced in *i*-propyl alcohol).**

Time (min)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	0.020	0.011	2
2	0.076	0.028	6
4	0.100	0.035	7
6	0.201	0.066	13
8	0.445	0.139	28
10	0.588	0.182	36
13	0.714	0.220	44
15	0.787	0.242	48
20	0.755	0.232	46
25	0.960	0.294	59
30	0.952	0.291	58
35	0.935	0.286	57
40	0.964	0.295	59

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 176 (EC-118): Rose bengal in $scCO_2$, introduced in methanol

Sample introduced into the apparatus and supercritical carbon dioxide generated as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 38).

Table 38: Synthesis of juglone 98 **using rose bengal** 41 **in supercritical carbon dioxide (introduced in methanol).**

Time (mins)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	0.004	0.006	1
5	0.295	0.094	19
10	0.398	0.124	25
15	0.512	0.159	32
20	0.581	0.180	36
25	0.645	0.199	40
30	0.666	0.205	41
35	0.743	0.229	46
40	0.811	0.249	50
50	0.825	0.253	51
60	0.891	0.273	55

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 177 (EC-123/EC-124): Tetraphenylporphyrin in $scCO_2$, introduced in ethyl acetate

Sample introduced into the apparatus and supercritical carbon dioxide generated as described in the general procedure. The sample was irradiated for 30 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 39).

Table 39: Synthesis of juglone 98 **using TPP** 43 **in supercritical carbon dioxide (introduced in ethyl acetate)**

Time (min)	Absorbance (415 nm)
0	-0.359
0	0.020
5	0.011
10	-0.061
15	-0.02
20	-0.082
25	-0.084
30	-0.244

Experiment 178 (EC-133): Self-sensitised synthesis of juglone in $scCO_2$, introduced in methanol

Sample introduced into the apparatus and supercritical carbon dioxide generated as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 40).

Table 40: Self-sensitised photooxygenation of 1,5-dihydroxynaphthalene 97 **in supercritical carbon dioxide.**

Time (min)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	-0.014	0.02	4.9%
2	0.023	0.04	7.2%
4	0.044	0.04	8.6%
6	0.188	0.09	17.6%
8	0.212	0.10	19.1%
10	0.232	0.10	20.4%
15	0.275	0.12	23.1%
20	0.289	0.12	23.9%
25	0.254	0.11	21.7%
30	0.372	0.15	29.2%
40	0.418	0.16	32.0%
53	0.489	0.18	36.5%
60	0.510	0.19	37.8%

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 179 (EC-132): Self-sensitised synthesis of juglone in methanol

Sample introduced into the apparatus as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 41).

Table 41: Self-sensitised photooxygenation of 1,5-dihydroxynaphthalene 97 **in methanol.**

Time (min)	Absorbance (415 nm)
0	0.001
12	-0.141
12.5	-0.128
15	-0.050
20	-0.051
30	-0.058
40	-0.049
50	-0.032
60	-0.052

Experiment 180 (EC-114): Methylene blue in methanol

Sample introduced into the apparatus as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 42).

Table 42: Synthesis of juglone 98 **using methylene blue** 42 **in methanol.**

Time (mins)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	0.010	0.03	6%
5	0.048	0.04	9%
10	0.033	0.04	8%
15	0.167	0.08	16%
20	0.220	0.10	20%
25	0.224	0.10	20%
30	0.280	0.12	23%
35	0.328	0.13	26%
40	0.406	0.16	31%
50	0.452	0.17	34%
60	0.454	0.17	34%

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 181 (EC-126): Methylene blue in *i*-propyl alcohol

Sample introduced into the apparatus as described in the general procedure. The sample was irradiated for 30 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 43).

Table 43: Synthesis of juglone 98 **using methylene blue** 42 **in *i*-propyl alcohol.**

Time (min)	Absorbance (415 nm)
0	0.015
5	0.036
7	0.024
10	-0.01
12	0.029
15	0.025
17	0.037
20	0.021
22	0.046
25	0.041
27	0.074
28	0.001
30	-0.028

Experiment 182 (EC-116): Rose bengal in methanol

Sample introduced into the apparatus as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 44).

Table 44: Synthesis of juglone 98 **using rose bengal** 42 **in methanol.**

Time (min)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	-0.066	0.01	1.7%
5	-0.023	0.02	4.4%
10	0.042	0.04	8.4%
15	0.077	0.05	10.6%
17	0.107	0.06	12.5%
20	0.287	0.12	23.8%
25	0.300	0.12	24.6%
30	0.357	0.14	28.2%
35	0.303	0.12	24.8%
40	0.414	0.16	31.8%
50	0.461	0.17	34.7%
60	0.582	0.21	42.3%

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 183 (EC-128): Rose bengal in *i*-propyl alcohol

Sample introduced into the apparatus as described in the general procedure. The sample was irradiated for 60 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 45).

Table 45: Synthesis of juglone 98 **using rose bengal** 41 **in *i*-propyl alcohol.**

Time (min)	Absorbance (415 nm)	Concentration (mM)	Conversion* (%)
0	-0.010	0.00	0.4%
2	0.020	0.01	2.2%
3	0.035	0.02	3.1%
4	0.055	0.02	4.3%
5	0.055	0.02	4.3%
6	0.084	0.03	6.1%
8	0.090	0.03	6.4%
10	0.128	0.04	8.7%
15	0.139	0.05	9.4%
16	0.222	0.07	14.4%
18	0.198	0.06	12.9%
20	0.396	0.12	24.8%
25	0.319	0.10	20.2%
30	0.371	0.12	23.3%
35	0.398	0.12	25.0%
37	0.440	0.14	27.5%
40	0.553	0.17	34.3%
45	0.559	0.17	34.6%
50	0.538	0.17	33.4%
53	0.584	0.18	36.2%
60	0.681	0.21	42.0%

* In this context, conversion refers to juglone **98** concentration (determined from calibrations curves) as a percentage of total concentration of starting material **97** used (0.5 mM).

Experiment 184 (EC-122): Tetraphenylporphyrin in ethyl acetate

Sample introduced into the apparatus as described in the general procedure. The sample was irradiated for 55 minutes and absorbance at 415 nm measured regularly for the duration of irradiation (Table 46).

Table 46: Synthesis of juglone 98 **using TPP** 43 **in ethyl acetate.**

Time (min)	Absorbance (415 nm)
0	-0.04
7	0.051
10	0.106
15	0.155
20	0.271
30	0.305
35	0.377
45	0.425
50	0.752
55	0.752

Thesis Conclusions

Following over three years of research on the application of green principles to the dye-sensitised photooxygenation process in the context of the initial research proposals, we can conclude the following:

1. **The synthesis of juglone was optimised to maximise "greenness".**

Validation and optimisation experiments were carried out to develop an optimised green procedure.

Validation: Reaction parameters were validated, in particular supply of oxygen, light source and self-sensitisation study, pH effects and stability studies. Control reactions showed that both light and oxygen were essential for the reaction to proceed (no conversion in the absence of these conditions). Self-sensitisation under UV light exposure irradiation was observed (19-24% isolated yield, following 6 hours irradation), but use visible light gave significantly less yields in the absence of sensitiser (8-14%). The sensitiser rose bengal **41** was evaluated in a pH study, and it was shown that while it may act as an acidochromic dye at pH less than 3, it is stable under reaction conditions. A pH study was carried out on the starting material 1,5-dihydroxynaphthalene **97**, which was shown to undergo a spontaneous oxidation reaction under alkaline conditions.

Optimisation using artificial light irradiation: Optimisation of reaction solvent was carried out. A study of common laboratory solvents showed that alcohols offer a green alternative to the chlorinated solvents often used in photooxygenation reaction. *t*-Amyl alcohol was identified as the most suitable solvent, as this gave a greater conversion than other alcohols (and greater than ethyl acetate or acetone).

A detailed study of sensitisers demonstrated the use of both homogeneous and heterogeneous sensitisers. The advantages of heterogeneous catalysis were demonstrated through the use of a silica supported porphyrin **244**. This sensitiser gave comparable yields to those achieved using rose bengal in a homogeneous solution. However, use of this solid supported sensitiser is limited by the difficulty in obtaining starting material, triphenylpyridylporphyrin PyTPP. For future applications, recycling and reuse of sensitiser should be optimised, as well as a detailed study of optimum concentration and mixing of the sensitiser in the reaction solution.

The use of microreactor technology was investigated in an effort to optimise reactor. These reactors offer several advantages for photochemical synthesis. However, use of a dwell device in preliminary investigations resulted in conversions of only 7-11% when the optimised reaction conditions were applied. Future studies should look at the use of a falling film microreactor, which can ensure maximum contact between reaction solution and oxygen. Manipulation of flow rate and residence time could also increase the conversion achieved, as this study was limited by the minimum capacity of the pump used.

Optimisation using solar light: Following indoor optimisation and development of the general method (rose bengal in *t*-amyl alcohol) this reaction was transferred to outdoor conditions. This study first looked at the characterisation of Irish solar light conditions at direct, partial sun, partial cloud and overcast. The choice of reactor for use in sunlight conditions was optimised, in particular with the aim of maximising the utilisation of both direct and diffuse light. Use of a large scale glass flatbed reactor was identified as the most suitable reactor design for use (conversion of 84% achieved following 6 hours of soalr irradiation). Use of moderately concentrated sunlight was investigated at the German Aerospace Centre, which showed that the optimised procedure could be applied and isolated yields of 68-74% were achieved following 3 hours of irradiation.

2. **The scope of the reaction was extended to other substrates, in particular to a series of 5-amido-1-naphthols.**

The optimised green conditions for juglone synthesis **98** (starting material (10 mM), rose bengal (0.3-0.5 mM) in *t*-amyl alcohol, with artificial light using one halogen lamp or solar irradiation) were successfully applied to other 1-naphthol substrates, in particular a series of 5-amido-1-naphthols. These starting materials **233** were prepared in yields of 15-69% from 5-amino-1-naphthol **232**. The corresponding 5-amido-1,4-naphthoquinones **234** were obtained in moderate to good yields (12-72% following 4 hours of artificial light irradiation, 40-96% following 24 hours of artificial light irradiation and 23-90% following 6 hours of solar irradiation).

In addition, the application of the optimised procedure to 1-naphthol substrates that were not capable of hydrogen bonding at the 5 position were investigated, with photooxygenation of 1,6-dihydroxynaphthalene **261** proceeding effectively in 25% and 80% yield under artificial light irradiation for 4 and 24 hours, respectively. Solar irradiation for 6 hours produced 6-hydroxy-1,4-naphthoquinone **262** in 68% yield. However, while irradiation of 1-naphthol **226** produced 1,4-naphthoquinone **90** under artificial light irradiation, use of solar light led to extensive degradation. Examination of 5-acetoxy-1-naphthol **170** demonstrated that this photooxygenation proceeds slowly, with some conversion of 5-acetoxy-1,4-naphthoquinone **250** to juglone **98**.

This study showed that the scope of the green photooxygenation procedure developed could be extended to any 1-naphthols substrates with substituents at the 5-position capable of hydrogen bonding. Limited success can be achieved for other 1-naphthol substrates, but some degradation or by-products may be observed.

3. Can other reaction media be applied for the dye-sensitised photooxygenation process?

Following optimisation of the synthesis of juglone **98** in alcoholic solution, the use of alternative media was investigated. This study looked at the use of solvent-free conditions, ionic liquids, microemulsions and supercritical carbon dioxide.

Use of supercritical carbon dioxide was investigated at the University of Loughborough, with conversions of up to 76% juglone achieved in one hour. However, the reaction set-up was very limited, especially cell size and monitoring method. As a result, this procedure was not suitable for preparative studies. In addition, the high energy demand of the system precludes this procedure from being considered as green.

Solvent-free synthesis on polymeric support was not suitable for photooxygenation of solid substrates, such as 1,5-dihydroxynaphthalene **97**. However, synthesis using liquid substrates, namely α-terpinene **69** and furfural **111**, was successful. In particular, solvent-free conditions provided a means of avoiding side reactions in the synthesis of 5-hydroxyfuranone **112** and offered a relatively quicker route to this product than solution phase synthesis. However, preparation of the solvent-free polymer supported reaction mixture required use of volatile organic solvents that were not considered green, and thus this procedure is not entirely green.

Use of an ionic liquid, [emim]OTf **187**, was investigated with limited success. This may be due to poor oxygen solubility of oxygen in this solvent. However, the reaction did proceed, which indicates that following optimisation of solvent this could be a green alternative to traditional organic solvents.

Use of microemulsions as alternative media in the synthesis of juglone provided the greatest potential as a green process. Optimisation of co-surfactant used (ethanol, *n*-butanol and *t*-amyl alcohol) and microemulsion component ratios was achieved. The optimised microemulsion consists of ethanol as co-surfactant, as this requires a minimum amount of surfactant and offers ease of purification when compared to longer chain alcohols (*n*-butanol and *t*-amyl alcohol). A particular advantage of this procedure is the possibility of using porphyrins, such as TPP **43**, without the need for chlorinated solvents. Using TPP **43** in an ethanolic microemulsion, conversion of 85% was achieved following four hours of artificial light irradiation.

Outlook

Following completion of this study, a number of future research prospects have arisen:

1. **Sensitiser study**

The use of a silica supported porphyrin as a singlet oxygen sensitiser has been demonstrated. This sensitiser offers ease of purification without loss in efficiency when compared to homogeneous reactions using rose bengal. However, this sensitiser is difficult to prepare in large quantities as it is limited by availability of triphenylpyridylporphyrin. Future studies should look at the optimisation of synthesis, as well as recovery, reuse and recycling of the sensitiser after multiple photooxygenation reactions.

In addition, use of mixed sensitisers, to facilitate total overlap with the solar spectrum should be investigated further. To overcome solvent incompatibility the use of alcohol soluble porpyrins should be studied.

2. **Reactor and light source**

The use of microstructured reactors for photooxygenation reactions has been demonstrated in this work. However, optimisation of reactor design is necessary to maximise efficiency of the system. The use of a falling film reactor should be investigated. In addition, the use of a dwell device of longer channel length, with slower reaction rate, could increase residence time and hence increase conversion.

Use of light emitting diodes (LEDs) also offers a green perspective. These offer a lower energy alternative to halogen lamps, as well as reduce cooling requirements for indoor reactions. The tuning of wavelength to suit sensitiser is a possibility. Combining use of LEDs with microreactor technology may lead to development of a low energy process.

3. **Evaluation of greenness**

Evaluation of greenness for each of the optimised procedures should be carried out through EATOS studies. In addition, the energy demand of the equipment needed will be monitored and these values will be taken into account in evaluating the ‘greenness’ of each process.

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Appendix A Contributions from supervised undergraduate students

Experiment 10A (KJ-030): Photooxygenation of 1,5-dihydroxynaphthalene in pH 12 water (buffered)

1,5-Dihydroxynaphthalene **97** (0.16 g, 1.0 mmol) in water (buffered to pH 12, 100 ml) was irradiated, with air bubbling, for 6 hours using one 500 W halogen lamp. Samples were taken at regular intervals and analysed by ^{1}H NMR spectroscopy in DMSO-d_6 and in D_2O. In both solvents, no evidence of starting material **97** or juglone **98** was evident.

Experiment 14A (KJ-026): Self sensitisation using a halogen lamp

The general procedure was followed using starting material **97** that was purified by sublimation to remove coloured impurities. The reaction solution was irradiated using one 500 W halogen lamp. Juglone **98** was isolated in 14% yield.

Experiment 15A (KJ-026): Self sensitisation using a halogen lamp

The general procedure was followed using technical grade starting material **97** and irradiation using one 500 W halogen lamp. Juglone **98** was isolated in 8% yield.

Experiment 57A (KJ-06): 3 h, partial sun

The general procedure was followed using 0.30 g (1.9 mmol of 1,5-dihydroxynaphthalene **97** and 100 mg (98 μmol of rose bengal **41** in 100 ml of *t*-amyl alcohol and irradiation for 3 hours. Product was purified by Soxhlet extraction using *n*-hexane to give 33% yield of juglone **98** as a brown-orange solid.

Experiment 58A (KJ-10): 3 h, partial sun

The general procedure was followed using 0.30 g (1.9 mmol of 1,5-dihydroxynaphthalene **97** and 100 mg (98 μmol of rose bengal **41** in 100 ml of *t*-amyl alcohol and irradiation for 3 hours. Product was purified by column chromatography using chloroform to give 34% yield of juglone **98** as a bright orange solid.

Experiment 59A (KJ-12): 3 h, direct sun

The general procedure was followed using 0.30 g (1.9 mmol) of 1,5-dihydroxynaphthalene **97** and 100 mg (98 μmol of rose bengal **41** in 100 ml of *t*-amyl alcohol and irradiation for 3 hours.

Product was purified by column chromatography using chloroform to give 69% yield of juglone **98** as a bright orange solid.

Experiment 60A (KJ-18): 5 h, shade

The general procedure was followed using 1.00 g (6.2 mmol) of 1,5-dihydroxynaphthalene **97** and 350 mg (343 μmol) of rose bengal **41** in 350 ml of *t*-amyl alcohol and irradiation for 5 hours. Product was purified by column chromatography using chloroform to give 26% yield of juglone **98** as a bright orange solid.

Experiment 64A (KJ-027): Use of *i*-propyl alcohol

The general procedure was followed using *i*-propyl alcohol. ^{1}H NMR spectroscopy (acetone-d_6) showed that conversion to juglone **98** was 72%.

Experiment 68A (EH-04): 5-Acetamido-1-naphthol

5-Amino-1-naphthol **232** (4.01 g, 25.1 mmol) and acetic anhydride (11.5 ml, 0.12 mol) were stirred together at room temperature for 3 hours. The precipitate was filtered off and washed twice with acetic anhydride. The crude product was purified with activated charcoal in ethanol to yield 3.09 g (15.3 mol, 61%) of 5-acetamido-1-naphthol **233a** as a beige solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 1.30 (s, 3H, C**H**$_3$); 6.02 (d, J^3 = 7.6 Hz, 1H, H_{arom}); 6.02 (dd, J^3 = 7.6 Hz, 8.4 Hz, 1H, H_{arom}); 6.47 (dd, J^3 = 7.6 Hz, 8.4 Hz, 1H, H_{arom}); 6.53 (dd, J^3 = 7.3 Hz, 1H, H_{arom}); 6.64 (d, J^3 = 8.4 Hz, 1H, H_{arom}); 6.79 (d, J^3 = 7.6 Hz, 1H, H_{arom}); 7.10 (d, J^3 = 8.4 Hz, 1H, H_{arom}); 8.95 (s, 1H, N**H**); 9.32 (s, 1H, O**H**).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 23.5; 108.2; 113.3; 113.3; 119.2; 121.9; 124.1; 126.2; 125.3; 129.2; 133.4; 153.4; 168.9.

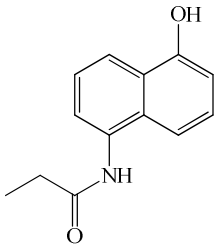
IR (KBr) υ (cm^{-1}) = 3281, 1541, 1273, 1141, 1048, 1023, 984, 965, 923, 900, 870, 776, 722, 659, 618, 578, 544, 531, 479.

UV (methanol) λ (nm) = 225, 305.

Melting point: 172 °C (lit. 176-177 °C[281]).

CAS no. 22302-65-4, spectral data consistent with literature.

Experiment 69A (EH-14): 5-Propanamido-1-naphthol



233b

The general procedure was followed using propanoyl chloride (0.9 ml, 10 mmol) and 5-amino-1-naphthol **232** (1.59 g, 10 mmol) in 20 ml of pyridine. No precipitate was formed after the reaction mixture was poured onto ice water and so the solution was extracted with dichloromethane. The precipitate was filtered off and washed twice with cold water. The product was recrystallised using method B. 5-Propanamido-1-naphthol **233b** was obtained in 36% yield (0.762 g, 3.6 mmol) as a beige-yellow solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm) = 1.13 (t, 3H, C**H**$_3$, J^3 = 4 Hz); 2.43 (quartet, 2H, C**H**$_2$, J^3 = 4.4 Hz); 6.87 (d, 1H, **H**$_{arom.}$, J^3 = 7.2 Hz); 7.32 (t, 1H, **H**$_{arom.}$, J^3 = 7.6 Hz); 7.38 (t, 1H, **H**$_{arom.}$, J^3 = 8 Hz); 7.47 (d, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 7.64 (d, 1H, **H**$_{arom.}$; J^3 = 7.2 Hz); 7.96 (d, 1H, **H**$_{arom.}$ J^3 = 8.4 Hz); 9.7349 (s, 1H, O**H**); 10.164 (s, 1H, N**H**).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm) = 10.0, 26.4, 29.1, 108.1, 113.3, 119.1, 122.0, 124.0, 125.3, 126.2, 129.3, 133.4, 153.4.

IR (KBr) υ (cm^{-1}) = 3241, 2925, 1747, 1638, 1547, 1519, 1450, 1411, 1273, 1226, 1176, 1143, 1082, 950, 902, 866, 820, 780, 583.

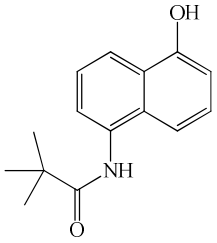
UV (methanol) λ (nm) = 223, 303.

Melting point: 154 °C.

Mass Spectrometry (ESI) m/z = 214.6 (M-1, expected m/z 215.1).

CAS No. 31755-64-3, no spectral data available.

Experiment 71A (EH-22): 5-(Trimethyl)acetamido-1-naphthol



233d

The general procedure was followed using trimethylacetyl chloride (1.2 ml,10 mmol) and 5-amino-1-naphthol **232** (1.59 g, 10 mmol) in 20 ml of pyridine. No precipitated was formed after the reaction mixture was poured onto ice water and so the solution was extracted with dichloromethane. The precipitate was filtered off and washed twice with cold water. The product was recrystallised using method B. 5-(Trimethyl)acetamido-1-naphthol **233d** was obtained in 69% yield (1.678 g, 6.9 mmol) as a purple solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm) = 1.31 (s, 9H, 3C**H**$_3$); 6.86 (dd, 1H, **H**$_{arom.}$, J^3 = 6.4 Hz, J^4 = 2.4 Hz); 7.30 (d, 1H, **H**$_{arom.}$, J^3 = 6.4 Hz); 7.40 (dt, 3H, **H**$_{arom.}$, J^3 = 25.2 Hz, J^4 = 7.6 Hz); 8.02 (d, 1H, **H**$_{arom.}$ J^3 = 8 Hz); 9.37 (s, 1H, O**H**); 10.17 (s, 1H, N**H**).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm) = 26.4 (**C**$_{q.}$); 27.5 (3**C**H$_3$); 108.1,113.7, 120.2, 124.0, 124.5, 126.3 (6C, **C**H$_{arom}$); 125.4, 131.1 (2C, **C**$_{q.\ arom.}$); 133.8 (**C**-OH); 153.4 (**C**-NH); 177.1 (**C**=O).

IR (KBr) υ (cm^{-1}) = 3284, 2970, 1655, 1599, 1579, 1493, 1408, 1377, 1274, 1209, 1169, 1141, 1065, 950, 901, 872, 827, 779, 736, 686, 652, 583, 555, 525, 499.

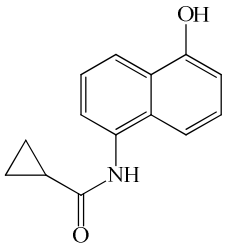
UV (methanol) λ (nm) = 225, 302.

Melting point: 258 °C (lit. 256-258 °C).

Mass Spectrometry (ESI) m/z = 242.2 (M-1, expected m/z 243.1).

CAS no. 173034-97-4, consistent with literature data[282].

Experiment 72A (EH-30): 5-(*cyclo*-Propanecarban)amido-1-naphthol



233e

The general procedure was followed using *cyclo*-propanecarbanoyl chloride (0.9 ml,10 mmol) and 5-amino-1-naphthol **232** (1.59 g, 10 mmol) in 20 ml of pyridine. No precipitate was formed after the reaction mixture was poured onto ice water and so the solution was extracted with dichloromethane. The precipitate was filtered off and washed twice with cold water. The product was recrystallised using method B. 5-(*cyclo*-Propanecarbano)amido-1-naphthol **233e** was obtained in 29% yield (0.651 g, 2.9 mmol) as a pale pink solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm) = 0.82 (2d, 4H, 2C**H**$_2$); 2.06 (s, 1H, C**H**); 6.88 (d, 1H, H$_{arom.}$, J^3=7.6 Hz); 7.32 (d, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 7.54 (t, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 7.67 (d, H, **H**$_{arom.}$, J^3 = 6.8 Hz); 7.96 (d, 1H, **H**$_{arom.}$ J^3 = 8.4 Hz); 10.048 (s, 1H, O**H**); 10.176 (s, 1H, N**H**).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm) = 7.2, 7.4 (2 **C**H$_2$); 14.1 (**C**H); 108.2, 113.2, 119.1, 124.1, 125.3, 126.3 (6C, **C**H$_{arom}$); 121.8, 129.0 (2C, **C**$_{q.\ arom.}$); 133.4 (**C**-OH); 153.4 (C-NH); 172.3 (C=O).

IR (KBr) υ (cm^{-1}) = 3252, 1751, 1614, 1581, 1531, 1450, 1395, 1354, 1274, 1216, 1143, 1100, 971, 935, 883, 823, 777, 582, 419.

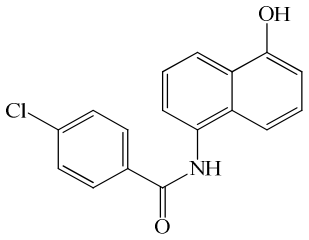
UV (methanol) λ (nm) = 222, 234, 302.

Melting point: 215 °C.

Mass Spectrometry (ESI) m/z = 226.6 (M-1, expected m/z 227.1).

CAS no. 1186211-62-0, new compound.

Experiment 74A (EH-13): 5-(4-Chlorobenzamido)-1-naphthol



233g

The general procedure was followed using 4-chlorobenzoyl chloride (1 ml, 7.8 mmol) and 5-amino-1-naphthol **232** (1.00 g, 6.3 mmol) in pyridine (10 ml). Product was purified using recrystallisation method A. 5-(4-Chlorobenzamido)-1-naphthol **233g** was obtained in 36% yield (1.72 g, 2.8 mmol) as a pale pink-grey solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm) = 6.89 (dd, 1H, $H_{arom.}$, J^3 = 6.4 Hz, J^4 = 0.8 Hz); 7.32 (t, 1H, $H_{arom.}$, J^3 = 7.6 Hz); 7.46 (t, 1H, $H_{arom.}$, J^3 = 8.4 Hz); 7.40 (d, 1H, $H_{arom.}$, J^3 = 8.4 Hz); 7.55 (d, 1H, $H_{arom.}$, J^3 = 6.8 Hz); 7.63 (dd, 2H, $H_{arom.}$; J^3 = 6.8 Hz, J^4 = 2 Hz); 8.09 (d, 3H, $H_{arom.}$ J^3 = 8.4 Hz); 10.249 (s, 1H, O**H**); 10.426 (s, 1H, N**H**).

^{13}C NMR (100 MHz, DMSO-d$_6$) δ (ppm) = 108.2, 113.8, 120.6, 124.0, 124.4, 125.4, 128.6, 129.8 (8C, **C**H_{arom}); 126.5, 130.7, 133.3 (3C, **C**$_{q.\ arom.}$); 136.46 (**C**-NH); 153.44 (**C**-OH); 165.07 (**C**=O).

IR (KBr) υ (cm^{-1}) = 3195, 1643, 1598, 1512, 1486, 1406, 1311, 1260, 1237, 1149, 1117, 1089, 1015, 954, 862, 945, 819, 791, 459, 739, 686, 544, 523, 500.

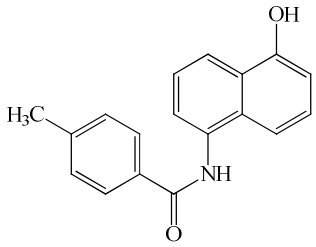
UV (methanol) λ (nm) = 204, 222, 234, 307, 322.

Melting point: 250 °C.

Mass Spectrometry (ESI) m/z = 296.4 (M-1, expected m/z 297.1).

CAS no. 1186211-63-1, new compound.

Experiment 75A (EH-19): 5-(4-Toluamido)-1-naphthol



233h

The general procedure was followed using 4-toluoyl chloride (1.3 ml,10 mmol) and 5-amino-1-naphthol **232** (1.59 g, 10 mmol) in 20 ml of pyridine. The product was recrystallised using method A. 5-(4-toluamido)-1-naphthol **233h** was obtained in 36% yield (0.985 g, 3.6 mmol) as purple needles.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.41 (s, 3H, C**H**$_3$); 6.90 (dd, 1H, **H**$_{arom.}$, J^3 = 6.8 Hz); 7.35 (dt, 4H, **H**$_{arom.}$, J^3 = 8.8 Hz); 7.46 (t, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 7.55 (d, 1H, **H**$_{arom.}$, J^3 = 7.2 Hz); 7.98 (d, 2H, **H**$_{arom.}$, J^3 = 8 Hz); 8.08 (d, 1H, **H**$_{arom.,}$ J^3 = 8.4 Hz); 10.21 (s, 1H, O**H**); 10.26 (s, 1H, N**H**).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 21.1 (**C**H$_3$); 108.2, 113.9, 120.4, 124.0, 124.4, 125.4, 126.4, 130.8, 131.7, 133.6 (10C, **C**H$_{arom}$); 127.8, 129.0 (2C, **C**$_{q.\ arom}$); 141.6 (**C**-NH); 153.4 (**C**-OH); 165.9 (**C**=O).

IR (KBr) υ (cm^{-1}) = 3220, 1619, 1499, 1408, 1377, 1276, 1176, 1117, 947, 877, 863, 820, 776, 751, 686, 584, 505, 468.

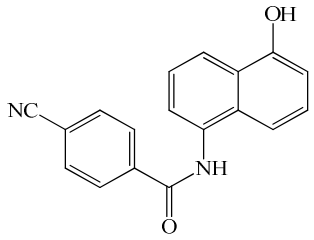
UV (methanol) λ (nm) = 204, 224, 307.

Melting point: 238 °C.

Mass Spectrometry (ESI) m/z = 276.6 (M-1, expected m/z 277.1).

CAS no. 401636-77-9, no spectral data available.

Experiment 76A (EH-27): 5-(4-Cyanobenzamido)-1-naphthol



233i

The general procedure was followed using 4-cyanobenzoyl chloride (1.655 g, 10 mmol) and 5-amino-1-naphthol **232** (1.59 g, 10 mmol) in 20 ml of pyridine. No precipitate was formed after the reaction mixture was poured onto ice water and so the solution was extracted with dichloromethane. The precipitate was filtered off and washed twice with cold water. The product was recrystallised using method B. 5-(4-Cyanobenzamido)-1-naphthol **233i** was obtained in 19% yield (0.541 g, 1.9 mmol) as a grey solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm) = 6.90 (d, 1H, **H**$_{arom.}$, J^3 = 8.2 Hz); 7.34 (t, 1H, **H**$_{arom.}$, J^3 = 7.6 Hz); 7.42 (d, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 7.48 (t, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 7.58 (d, 1H, **H**$_{arom.}$, J^3 = 6.8 Hz); 8.05 (d, 2H, **H**$_{arom.}$, J^3 = 8.0 Hz); 8.10 (d, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz); 8.28 (d, 2H, **H**$_{arom.}$ J^3 = 8.0 Hz); 10.25 (s, 1H, O**H**); 10.59 (s, 1H, N**H**).

^{13}C NMR (150 MHz, acetone-d$_6$) δ (ppm) = 109.2, 114.7, 121.5, 125.0, 127.3, 131.6 (6C, **C**H$_{naph}$); 115.7, 118.9, 124.3, 126.7 (4C, **C**$_{q.\ arom}$); 129.5, 133.3 (2C, **C**H$_{arom}$); 134.0 (**C**-OH); 140.1 (**C**-NH); 154.4 (-**C**N); 165.6 (**C**=O).

IR (KBr) υ (cm^{-1}) = 3398, 3255, 2237, 1648, 1599, 1515, 1444, 1416, 1275, 1116, 1017, 950, 859, 776, 674, 571.

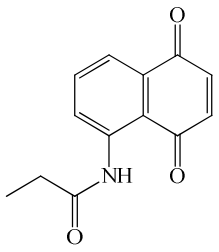
UV (methanol) λ (nm) = 204, 219, 322.

Melting point: 240 °C.

Mass Spectrometry (ESI) m/z = 287.5 (M-1, expected m/z 288.1).

CAS no. 1186211-64-2, new compound.

5-Propanamido-1,4-naphthoquinone



234b

Experiment 84A (EH-23): Artificial irradiation for 4 hours

The general procedure was followed using 5-propanamido-1-naphthol **233b** (0.5 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 4 hours. 5-Propanamido-1,4-naphthoquinone **234b** was obtained in 34% yield (0.078 g, 0.17 mmol) as an orange solid.

Experiment 85A (EH-24): Artificial irradiation for 24 hours

The general procedure was followed using 5-propanamido-1-naphthol **233b** (0.5 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 24 hours. 5-Propanamido-1,4-naphthoquinone **234b** was obtained in 89% yield (0.212 g, 0.45 mmol) as a yellow solid.

Experiment 86A (EH-20): Solar irradiation for 6 hours

The general procedure was followed using 5-propanamido-1-naphthol **233b** (0.5 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 6 hours in overcast sunlight conditions. 5-Propanamido-1,4-naphthoquinone **234b** was obtained in 53% yield (0.121 g, 0.27 mmol) as an orange solid.

^{1}H NMR (400 MHz, acetone-d$_6$) δ (ppm) = 1.23 (t, 3H, C**H**$_3$, J^3 = 7.6 Hz); 2.55 (q, 2H, C**H**$_2$, J^3 = 7.6 Hz); 7.04 (2d, 2H, 2C**H**$_{quin}$, J^3 = 10 Hz, J^4 = 1.4 Hz); 7.77 (dd, 1H, **H**$_{arom}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz); 7.83 (t, 1H, **H**$_{arom}$, J^3 = 8 Hz); 9.10 (dd, 1H, **H**$_{arom}$, J^3 = 8.4 Hz, J^4 = 1.6 Hz); 11.85 (s, 1H, N**H**).

^{13}C NMR (150 MHz, acetone-d$_6$) δ (ppm) = 9.6 (**C**H$_3$), 32.0 (**C**H$_2$), 116.9, 121.8, 126.1, 133.4, 136.3, 138.8, 140.9, 142.4, 173.8, 185.2, 190.0.

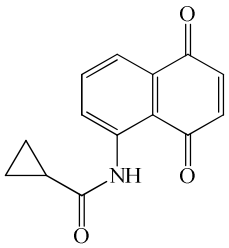
IR (KBr) υ (cm^{-1}) = 2926, 1702, 1670, 1641, 1579, 1522, 1407, 1344, 1302, 1259, 1156, 1103, 861, 833, 752, 447.

UV (methanol) λ (nm) = 212, 255, 415.

Melting point: 128 °C.

CAS no. 1186211-65-3, new compound.

5-(*cyclo*-Propanecarban)amido-1,4-naphthoquinone



234d

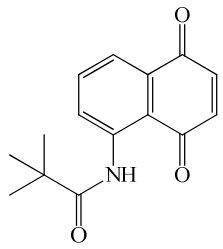
Experiment 90A (EH-34): Artificial irradiation for 4 hours

The general procedure was followed using 5-(*cyclo*-propanecarban)amido-1-naphthol **233d** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours. 5-(*cyclo*-Propanecarban)amido-1,4-naphthoquinone **234d** was obtained in 36% yield (0.084 g, 0.36 mmol) as an orange solid.

Experiment 91A (EH-35): Artificial irradiation for 24 hours

The general procedure was followed using 5-(*cyclo*-propanecarban)amido-1-naphthol **233d** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. 5-(*cyclo*-Propanecarban)amido-1,4-naphthoquinone **234d** was obtained in 54% yield (0.130 g, 0.54 mmol) as an orange solid.

5-(Trimethyl)acetamido-1,4-naphthoquinone



234e

Experiment 93A (EH-28): Artificial irradiation for 4 hours

The general procedure was followed using 5-(trimethyl)acetamido-1-naphthol **233e** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours. 5-(Trimethyl)acetamido-1,4-naphthoquinone **234e** was obtained in 72% yield (0.191 g, 0.06 mmol) as a yellow solid.

Experiment 94A (EH-29): Artificial irradiation for 24 hours

The general procedure was followed using 5-(trimethyl)acetamido-1-naphthol **233e** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. 5-(Trimethyl)acetamido-1,4-naphthoquinone **234e** was obtained in 94% yield (0.248 g, 0.06 mmol) as a yellow solid.

Experiment 95A (EH-33): Solar irradiation for 6 hours

The general procedure was followed using 5-(trimethyl)acetamido-1-naphthol **233e** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in partial sun sunlight conditions. 5-(Trimethyl)acetamido-1,4-naphthoquinone **234e** was obtained in 55% yield (0.139 g, 0.55 mmol) as a yellow solid.

^{1}H NMR (400 MHz, acetone-d$_6$) δ (ppm) = 1.36 (s, 9H, 3C**H**$_3$); 7.04 (2d, 2H, **CH**$_{quin}$, J^3 = 10 Hz); 7.77 (dd, 1H, **H**$_{arom}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz); 7.84 (t, 1H, **H**$_{arom}$, J^3 = 7.6 Hz); 9.13 (dd, 1H, **H**$_{arom}$, J^3 = 8.4 Hz, J^4 = 1.2 Hz); 12.13 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d$_6$) δ (ppm) = 27.1 (3**C**H$_3$); 79.1 (**C**(CH$_3$)$_3$); 116.4, 121.0 (2C, **C**H$_{quin.}$); 125.0, 132.2 (2C, C$_{q.\ arom}$); 135.6, 137.8, 140.2 (3C, **C**H$_{arom.}$); 140.8 (C$_{arom}$-N); 177.7 (**C**=O amide); 184.5, 189.1 (**C**=O quinone).

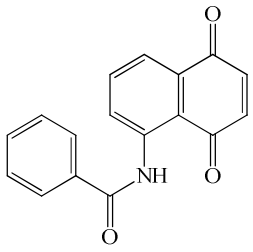
IR (KBr) υ (cm^{-1}) = 3249, 3119, 3051, 2965, 1687, 1646, 1604, 1577, 1491, 1408, 1376, 1366, 1344, 1303, 1253, 1188, 1152, 1200, 1037, 944, 862, 862, 836, 792, 771, 740, 701, 668, 576, 550, 448.

UV (methanol) λ (nm) = 212, 255, 419.

Melting point: 186 °C.

CAS no. 1186211-67-5, new compound.

6.4.5.1 5-Benzamido-1,4-naphthoquinone

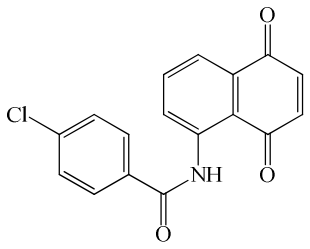


234f

Experiment 98A (EH-15): Solar irradiation for 6 hours

The general procedure was followed using 5-benzamido-1-naphthol **233f** (1.0 mmol) and rose bengal **41** (0.05 g, 49 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in partial sun sunlight conditions. 5-Benzamido-1,4-naphthoquinone **234f** was obtained in 80% yield (0.222 g, 0.80 mmol) as an orange solid.

5-(4-Chlorobenzamido)-1,4-naphthoquinone



234g

Experiment 99A (EH-17): Artificial irradiation for 4 hours

The general procedure was followed using 5-(4-chlorobenzamido)-1-naphthol **233g** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours. 5-(4-Chlorobenzamido)-1,4-naphthoquinone **234g** was obtained in 68% yield (0.203 g, 0.68 mmol) as an orange solid.

Experiment 100A (EH-18): Artificial irradiation for 24 hours

The general procedure was followed using 5-(4-chlorobenzamido)-1-naphthol **233g** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. 5-(4-Chlorobenzamido)-1,4-naphthoquinone **234g** was obtained in 72% yield (0.215 g, 0.72 mmol) as an orange solid.

Experiment 101A (EH-16): Solar irradiation for 6 hours

The general procedure was followed using 5-(4-chlorobenzamido)-1-naphthol **233g** (1.0 mmol) and rose bengal **41** (0.05 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in overcast sunlight conditions. 5-(4-Chlorobenzamido)-1,4-naphthoquinone **234g** was obtained in 54% yield (0.147 g, 0.54 mmol) as an orange solid.

^{1}H NMR (400 MHz, acetone-d$_6$) δ (ppm) = 7.07 (2d, 2H, C**H**$_{quin}$, J^3 = 10 Hz); 7.67 (dt, 2H, **H**$_{arom}$., J^3 = 9.2 Hz, J^4 = 2.4 Hz,); 7.81 (dd, 1H, **H**$_{arom}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz,); 7.90 (t, 1H, **H**$_{arom}$, J^3 = 8 Hz); 8.09 (dt, 2H, **H**$_{arom}$, J^3 = 9.2 Hz, J^4 = 2.4 Hz,); 9.21 (dd, 1H, **H**$_{arom}$, J^3 = 8.4 Hz, J^4 = 1.2 Hz); 12.82 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 122.4, 126.2, 130.0, 130.1, 136.6, 139.0, 140.9 (9C, **C**H_{arom}); 134.1, 133.6 (2C, $\mathbf{C}_{quat.}$); 142.2 ($\mathbf{C}_{q.}$-NH);165.6 (**C**=O amide); 185.1, 190.6 (**C**=O quinone).

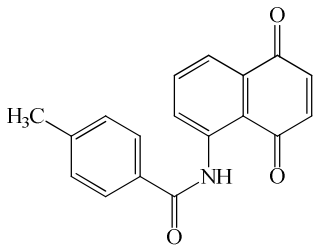
IR (KBr) υ (cm^{-1}) = 2926, 1686, 1638, 1495, 1412, 1347, 1263, 1077, 859, 834, 744, 681, 537, 447.

UV (methanol) λ (nm) = 201, 214, 263, 421.

Melting point: 172 °C.

CAS no. 1186211-68-6, new compound.

5-(4-Toluamido)-1,4-naphthoquinone



234h

Experiment 102A (EH-25): Artificial irradiation for 4 hours

The general procedure was followed using 5-(4-toluamido)-1-naphthol **233h** (1.0 mmol) and rose bengal **41** (0.050 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 4 hours. 5-(4-Toluamido)-1,4-naphthoquinone **234h** was obtained in 24% yield (0.073 g, 0.24 mmol) as an orange solid.

Experiment 103A (EH-26): Artificial irradiation for 24 hours

The general procedure was followed using 5-(4-toluamido)-1-naphthol **233h** (1.0 mmol) and rose bengal **41** (0.050 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 24 hours. 5-(4-Toluamido)-1,4-naphthoquinone **234h** was obtained in 40% yield (0.126 g, 0.40 mmol) as an orange solid.

Experiment 104A (EH-21): Solar irradiation for 6 hours

The general procedure was followed using 5-(4-toluamido)-1-naphthol **233h** (1.0 mmol) and rose bengal **41** (0.050 g, 50 μmol) in *t*-amyl alcohol (100 ml), with irradiation for 6 hours in

partial sun sunlight conditions. 5-(4-Toluamido)-1,4-naphthoquinone **234h** was obtained in 63% yield (0.226 g, 0.63 mmol) as an orange solid.

^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) = 2.45 (s, 3H, C**H**$_3$); 7.09 (2d, 2H, **H**$_{quin.}$, J^3 = 10 Hz); 7.46 (dd, 2H, **H**$_{arom.}$, J^3 = 7.6 Hz, J^4 = 0.8 Hz); 7.83 (dd, 1H, **H**$_{arom.}$, J^3 = 7.6 Hz, J^4 = 1.2 Hz); 7.90 (d, 1H, **H**$_{arom.}$; J^3 = 8.0 Hz); 8.01 (dd, 2H, **H**$_{arom.}$, J^3 = 6.4 Hz, J^4 = 1.6 Hz); 9.28 (dd, 1H, **H**$_{arom.}$, J^3 = 8.4 Hz, J^4 = 1.2 Hz); 12.80 (s, 1H, N**H**).

^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) = 21.5 (**C**H$_3$); 122,1; 126.2, 136.5, 138.9, 141.0 (5C, **C**H$_{arom}$); 117.5, 132.6, 133.5, 142.5, 144.0, 166.5, 190.6 (7C, **C**$_{q.\ arom}$); 128.32; 130.50 (**C**=O quinone).

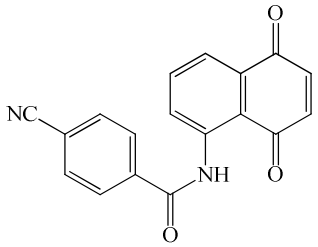
IR (KBr) υ (cm^{-1}) = 2924, 1666, 1537, 1404, 1342, 1268, 1083, 861, 835, 782, 746, 682, 449.

UV (methanol) λ (nm) = 203, 266, 425.

Melting point: 175 °C.

CAS no. 1186211-69-7, new compound.

5-(4-Cyanobenzamido)-1,4-naphthoquinone



234i

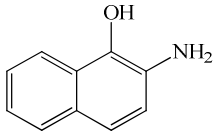
Experiment 105A (EH-34): Artificial irradiation for 4 hours

The general procedure was followed using 5-(4-cyanobenzamido)-1-naphthol **233i** (0.5 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 4 hours. 5-(4-Cyanobenzamido)-1,4-naphthoquinone **234i** was obtained in 35% yield (0.052 g, 0.17 mmol) as a yellow solid.

Experiment 106A (EH-35): Artificial irradiation for 24 hours

The general procedure was followed using 5-(4-cyanobenzamido)-1-naphthol **233i** (0.5 mmol) and rose bengal **41** (0.025 g, 25 μmol) in *t*-amyl alcohol (50 ml), with irradiation for 24 hours. 5-(4-Cyanobenzamido)-1,4-naphthoquinone **234i** was obtained in 96% yield (0.145 g, 0.48 mmol) as a yellow solid.

General procedure for reduction of 2-nitro-1-naphthol using sodium dithionite



265

2-Nitro-1-naphthol **266** in ether was added dropwise to a saturated sodium dithionite solution. The reaction mixture was stirred overnight. After this time, the ether layer was extracted, washed twice with water and dried with magnesium sulfate. This mixture was gravity filtered and the ether removed by rotary evaporation. ^{1}H NMR spectroscopy (DMSO-d_6) was used to assess reaction outcome.

Experiment 121A (KC-01): reduction using sodium dithionite

2-Nitro-1-naphthol **266** (0.199g, mmol) in ether (50 ml) and saturated sodium dithionite solution (50ml) were stirred while open to the atmosphere. The product obtained was dark green-brown in colour. ^{1}H NMR spectroscopy (DMSO-d_6) showed that the reduction was not successful.

Experiment 122A (KC-03): reduction using sodium dithionite under nitrogen

2-Nitro-1-naphthol **266** (0.199g, mmol) in ether (50 ml) and saturated sodium dithionite solution (50ml) were stirred under a nitrogen atmosphere. The product obtained was dark green-brown in colour. ^{1}H NMR spectroscopy (DMSO-d_6) showed that the reduction was not successful.

Experiment 123A (KC-11): Reduction of 2-nitro-1-naphthol using tin(II)chloride

2-Nitro-1-naphthol **266** (6 g, 31.7 mmol), tin (II) chloride (28 g, 0.124 mol), ethanol (4 ml) and ethyl acetate (76 ml) were refluxed for 3 hours and stirred at room temperature overnight. The product was extracted using three ethyl acetate extractions (3 x 50 ml). The crude product was obtained as dark green crystals. ^{1}H NMR spectroscopy (DMSO-d_6) showed that some conversion had occurred, but a large amount of starting material was present. This was removed by washing the crude product with hot *n*-hexane. ^{1}H NMR spectroscopy (DMSO-d_6) of the crude after washing showed that a small amount of starting material remained, but product peaks were identified.

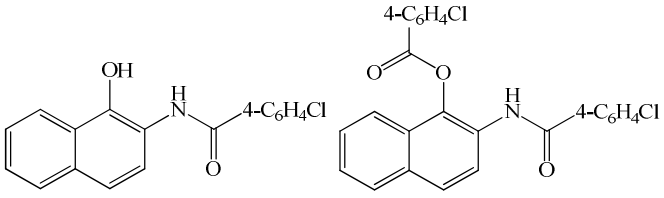
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.20 (d, J^3 = 8.8 Hz); 7.30 (d, J^3 = 8.8 Hz); 7.44 (m); 7.79 (m); 8.12 (m).

Mass Spectrometry (ESI) m/z = 159.5 (product **265**), 188.6 (starting material **266**), 282.7 (dimer), 315.5 (dimer).

Experiment 126A (KC-09): Synthesis of 2-acetamido-1-naphthol

Crude 2-amino-1-naphthol **265** (0.876 g, 5.50 mmol) and acetic anhydride (20 ml) were stirred overnight at room temperature. Excess acetic anhydride was removed by a steady stream of nitrogen. A small amount of water was added to the residue and extracted with dichloromethane. The organic layer was extracted and rotary evaporated off. Bright yellow crystals of **273** were obtained with a yield of 9%.

6.4.5.2 Synthesis of 2-(4-chlorobenzamido)-1-naphthol



279 **280**

Experiment 129A (KC-12):

4-Chlorobenzoyl chloride **278** (0.5 ml) was added drop-wise to crude 2-amino-1-naphthol **265** (0.853 g) in pyridine (10 ml) at -10 °C under nitrogen and stirred overnight at room temperature. The reaction mixture was poured onto ice water (75 ml) and vacuum filtered. The precipitate was washed with the minimum amount of ice-water and allowed to dry. The product

was purified by dissolving in hot ethanol and filtering out the insoluble product (light brown solid). The filtrate was heated and hot water was added to cause precipitation of a second product (pink solid collected by filtration). A dark pink product precipitated in the filtrate upon cooling. ^{1}H NMR spectroscopy (DMSO-d_6) was used to characterise the products. The first precipitate collected consisted only of the *bis*-acylated product **280** (light brown solid). The second and third precipitates collected were both mixtures of *mono*- **279** and *bis*-acylated **280** compounds, in a ratio of 1:1.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.54 (d, J^3 = 8.6 Hz); 7.58 (m); 7.69 (m); 7.78 (m); 7.86 (m); 7.96 (d, J^3 = 8.8 Hz); 8.04 (m); 8.20 (m); 8.27 (d, J^3 = 8.76 Hz); 10.38 (s).

Mass Spectrometry (ESI, MS^+) Expected m/z = 435.0, observed m/z = 436.1 (M+1) *bis*-**280**.

Mass Spectrometry (ESI, MS^-) Expected m/z = 297.1, observed m/z = 296.3 (M-1) *mono*-**279**.

Experiment 147A (KJ-04): Synthesis of 5-hydroxyfuranone

Following the general procedure for solvent-free synthesis on a polystyrene support, furfural **111** (0.8 ml, 10 mmol) was introduced onto polystyrene **294** and irradiated using a LuzChem photoreactor, with the temperature was maintained at ca. 40 °C using a fan. Following irradiation the 'pancake' turned green in colour. The crude product was a small amount of green oil. ^{1}H NMR spectroscopy ($CDCl_3$) was used to characterise the product **112**.

Appendix B Publications

Review article: "Micro-photochemistry: photochemistry in microstructured reactors. The new photochemistry of the future?", E. E. Coyle and M. Oelgemöller, *Photochem. Photobiol. Sci.*, **2008**, 7, 1313-1322.

Short feature: "Photochemistry goes Micro", E. E. Coyle and M. Oelgemöller, *Chem. Technol.*, **2008**, 5, T95.

Communication: "Green Photochemistry: Solarchemical Synthesis of 5-Amido-1,4-naphthoquinones", E. Haggiage, E. E. Coyle, K. Joyce, M. Oelgemöller, *Green Chem.*, **2009**, 11, 318-321.

Book contribution: "Juglone (5-hydroxy-1,4-naphthoquinone)", K. Joyce, E. E. Coyle, J. Mattay and M. Oelgemöller, in *Experiments in Green and Sustainable Chemistry*, W. H. Roesky, D. Kennepohl (Eds.), Wiley-VCh, Weinheim, **2009**, Chapter 30, 199-203.

Green photochemistry: solarchemical synthesis of 5-amido-1,4-naphthoquinones†

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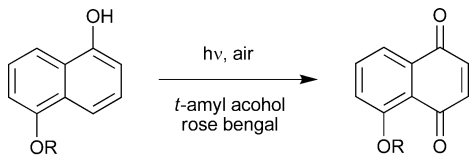
Dye sensitized photooxygenations of 5-amido-1-naphthols were investigated with artificial light and sunlight, and the corresponding 5-amido-1,4-naphthoquinones were isolated in moderate to excellent yields. Under sunny conditions the yields were higher for almost all cases studied. The energy demand of the equipment used was determined, revealing significant energy savings for solar exposures.

Recent concerns regarding global warming and climate change have lead to the establishment of *green chemistry* and its principles in academia and industry.[1] Among the many different *green chemical* approaches, photochemistry can play a central role since light is regarded as a *clean reagent*.[2] So far, however, the high energy demand of most common artificial light-sources has prevented widespread usage of photochemical methods in industry. To overcome this disadvantage, sunlight (direct or concentrated) has recently been applied as sustainable light-source.[3] This concept leads back to the origin of organic photochemistry in the late 19th century.[4] In recent years, we have demonstrated the feasibility of solarchemical syntheses for a number of commodity chemicals.[5] During our ongoing study on photoacylation reactions,[6] we became especially interested in the synthesis of 1,4-naphthoquinones through solar photooxygenations.[7] 1,4-Naphthoquinones are important natural products, serve as valuable building blocks in synthesis and are key-moieties in biologically active compounds.[8] They are most commonly synthesized from the corresponding 1-naphthols by oxidation,[9] but these thermal pathways suffer from severe disadvantages concerning selectivity, sustainability or scale-up.[9a] Dye sensitized photooxygenations represent a useful alternative, and various examples have been reported in the literature.[7,10]

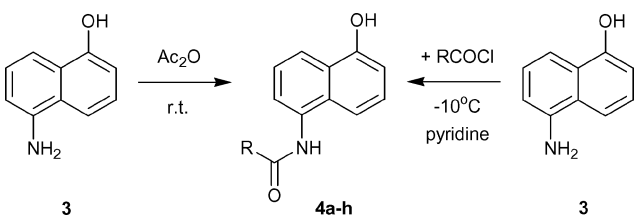
The photooxygenation of 1,5-dihydroxynaphthalene **1** to Juglone (**2**, 5-hydroxy-1,4-naphthoquinone) was selected as a model system to establish the most sustainable reaction conditions (Scheme 1). We were in particular interested in developing an entirely 'green' procedure and, for example, applied the solvent selection criteria developed by Pfizer[11] for the photochemical key-step *and* the subsequent purification.



Scheme 1 Photooxygenation to Juglone **2a** and 5-acetoxy-1,4-naphthoquinone **2b**.

The original irradiation procedures required the usage of the hazardous solvents dichloromethane, acetonitrile or methanol.[10] After extensive optimization we found *tert*-amyl alcohol to be a suitable 'green' substitute instead. Following a standardized procedure, a solution of 1,5-dihydroxynaphthalene **1a** was irradiated in a Schlenk-flask with a 500 W halogen lamp in the presence of rose bengal as a sensitizer while the solution was purged with air. After 2.5 h, Juglone was isolated *via* column chromatography in a yield of 62%. In an attempt to synthesize functionalized derivatives of Juglone, the mono-acetate **1b** was irradiated under the same conditions for 4 to 5.5 h. The outcome of this reaction was somewhat sensitive to workup conditions.‡ When the solvent was evaporated at elevated temperature, Juglone **2a** was isolated in 30% yield as the only product. When the water bath temperature was kept below 40 °C during evaporation, Juglone was only detected in trace amounts by TLC and the 5-acetoxy-1,4-naphthoquinone **2b** was isolated in a yield of 35% instead.

We thus became interested in using 5-amido-1-naphthols as starting materials. Subsequent photooxygenation would yield the corresponding 5-amido-1,4-naphthoquinones, and these compounds are known to show antibiotic properties.[12] The desired starting compounds **4a–h** were readily available through standard acylation from 5-amino-1-naphthol **3** in yields of 15–61% (Scheme 2).[13]



Scheme 2 Synthesis of 5-amido-1-naphthols **4a–h**.

When the amido-derivatives **4a–h** were irradiated for 4 h following the general photooxygenation procedure, the

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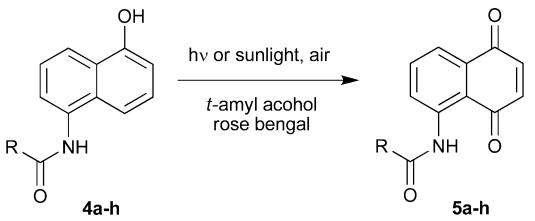
† Dedicated to Prof. Robert S. H. Liu (University of Hawaii) on the occasion of his 70th birthday.

corresponding naphthoquinones **5a–h** were obtained in yields of 12–72% (Scheme 3). When irradiation was extended to 24 h, conversions and consequently yields increased and the desired products were isolated in amounts of 40–96% (Table 1). In July and August 2008, we repeated the photooxygenation reactions under 'outdoor' conditions at Dublin City University (latitude 53°23′ N, 6°15′ W, 50 m above sea level). Solutions of **4a–h** and rose bengal were exposed to direct sunlight for 6 h while the solution was purged with a gentle stream of air. During the course of each illumination the reaction mixture significantly darkened due to the formation of the strongly colored product. All solar experiments went smoothly and gave moderate to excellent yields of **5a–h** without any noticeable side-products or photodecomposition (Table 1). Under sunny or partly sunny conditions, the yields were comparable or higher than those after irradiation with artificial light for 24 h. Even under poor illumination conditions with mainly diffuse radiation the desired products were isolated in moderate to good yields, hence unambiguously proving the feasibility of solar synthesis. Likewise, solar exposure of the diol **1a** under sunny conditions for 4 h furnished Juglone **2a** in 70% yield and excellent quality.



Scheme 3 Photooxygenation of 5-amido-1-naphthols **4a–h**.

In order to compare the energy efficiency of solar exposure *vs.* irradiations with artificial light we measured the energy consumption per hour of operation of all electrical devices applied (Table 2) using a commercially available domestic electricity meter (Nikkai power, N67FU).[14] The 500 W halogen lamp consumed the by far largest amount of electrical power with 0.432 kWh (or 1555.2 kJ). Due to the significant generation of heat by the lamp, the 'indoor' procedure required additional cooling by an electrical fan thus adding 0.018 kW (or 64.8 kJ) for its operation. In contrast, the 'outdoor' procedure solely required the use of an air pump (common for both processes), which consumed just 0.002 kWh (or 7.2 kJ) of energy. Purging additionally avoided the need of a magnetic stirrer. Notably, the mild climate of Dublin (Ireland) in combination with the relatively high boiling point of *tert*-amyl alcohol (102 °C) does not necessarily require the need for cooling water, thus reducing the overall energy demand further.[15] Alternatively, the concept of using natural or artificial water reservoirs as heat sinks has been recently demonstrated by Liu and coworkers.[16] In comparison with the energy demand of a conventional hot plate/magnetic stirrer it is interesting to note that the selected artificial light-source required far more electrical energy per hour of operation.

Conclusions

In conclusion, the photooxygenation of a series of 5-amido-1-naphthols results in the formation of 5-amido-1,4-naphthoquinones in moderate to excellent yields. Solar illuminations under ideal conditions gave significantly higher yields for almost all cases examined. The energy demand of the equipment has been compared for solar exposure *vs.* irradiation for the first time. Significant energy savings could be achieved by completely avoiding artificial light. Hence, this transformation

Table 1 Isolated yields of photooxygenations to **4a–h**

		Artificial light		Sunlight	
5	R	4 h	24 h	6 h	Weather
a	Me	12%	80%	90%	sunny
b	Et	34%	89%	53%	cloudy[a]
c	*cyclo*-Pr	36%	54%	53%	partly sunny
d	*t*-Bu	72%	94%	54%	sunny spells
e	Ph	17%	58%	80%	partly sunny
f	*p*-ClC_6H_4	68%	72%	54%	cloudy[a]
g	*p*-MeC_6H_4	24%	40%	63%	partly sunny
h	*p*-NCC_6H_4	35%	96%	23%	cloudy[a]

[a] Mainly diffuse radiation.

Table 2 Energy consumption of equipment used[a]

	Model	*E*/kWh	*E*/kJ
Halogen lamp	IQ group HB-DFL-500, Armley lamp	0.432	1555.2
Air pump	Hagen Elite 800	0.002	7.2
Electric fan	GET, 9″ desk fan, G9DFAN	0.018	64.8
Oil bath (heating to 100 °C)[b]	IKA, yellowline MST basic	0.084	302.4
Oil bath (maintained at 100 °C)[c]	IKA, yellowline MST basic	0.054	194.4

[a] Energy consumption as measured by a Wattmeter for 1 h of operation. [b] Setting to 100 °C on the TC 1 probe (electronic contactthermometer) and 150 °C on the dial; 50 min heat up time, 10 min maintaining the temperature; 14 cm ∅ crystallization dish; 600 ml silicon oil (Fluka). [c] Same settings and conditions as [b].

can be regarded as another example of 'green photochemistry'[17] and a further contribution to Giacomo Ciamician's vision of '*the photochemistry of the future*' (presented at the International Congress of Applied Chemistry in New York in 1912).[18,19]

Experimental

Compound **4a** was synthesized as described by Jindal and co-workers.[13a] All other 5-amido-1-naphthols **4b–h** were prepared following a modified procedure reported by Neidlein and Moller.[13b] **General procedure:** 7.0 g (44 mmol) of 5-amino-1-naphthol **3** were dissolved in 75 ml of pyridine. 60 mmol of the corresponding acid chloride were added dropwise to the solution at –10 °C. After stirring for 3 h, the reaction mixture was poured onto ice-water. The precipitate was filtered off and washed twice with cold water. The crude product was recrystallized from ethanol–water or ethyl acetate–cyclohexane. Exemplary details for **5-pivaloylamino-1-naphthol (5d)**. Purple solid; m.p.: 258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.31$ (s, 9H), 6.86 (dd, $^3J = 6.4$, $^4J = 2.4$ Hz, 1H), 7.30 (dd, $^3J = 6.4$ Hz, 1H), 7.34-7.43 (m, 3H), 8.02 (d, $^3J = 8.0$ Hz, 1H), 9.37 (br. s, 1H), 10.17 ppm (br. s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 27.5$, 38.9, 108.0, 113.7, 120.2, 124.0, 124.5, 126.3, 125.4, 131.1, 133.8, 153.4, 177.1 ppm; IR (KBr): $\nu = 3284$, 2970, 1655, 1599, 1577, 1493, 1408, 1274, 1209, 1141, 960, 779, 736, 555 cm^{-1}.

General Procedure for photooxygenation

1 mmol of 5-amido-1-naphthol **4** and 50 mg of rose bengal were dissolved in 100 ml of *tert*-amyl alcohol. The clear solution was irradiated (500 W halogen lamp) or exposed to direct sunlight in a Pyrex Schlenk-flask equipped with a cold finger and a reflux condenser for 4, 6 or 24 h at ambient temperature while purging with a gentle stream of air. Evaporated solvent should be refilled whenever necessary. The progress of the reaction was monitored by TLC analysis (SiO_2, cyclohexane:ethyl acetate 3:1). The solvent was removed under vacuum, and the residue was purified by column chromatography (SiO_2, cyclohexane:ethyl acetate 3:1). Experimental details and results are given in Table 1. Exemplary details for **5-pivaloylamino-1,4-naphthoquinone (5d)**. Yellow solid; m.p.: 186 °C; ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 1.36$ (s, 9H), 7.04 (d, $^2J = 14.4$ Hz, 1H), 7.06 (d, $^2J = 14.4$ Hz, 1H), 7.78 (dd, $^3J = 7.6$, $^4J = 1.2$ Hz, 1H), 8.85 (dd, $^3J = 7.6$, 8.4 Hz, 1H), 9.14 (dd, $^3J = 8.4$, $^4J = 1.2$ Hz, 1H), 12.13 ppm (br. s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 27.7$, 40.8, 116.4, 121.9, 126.3, 132.3, 135.9, 138.1, 140.1, 141.9, 179.1, 184.7, 189.3 ppm; IR (KBr): $\nu = 3249$, 2965, 1687, 1646, 1604, 1577, 1491, 1408, 1304, 1254, 1152, 1100, 944, 836, 740, 550, 448 cm^{-1}.

Acknowledgements

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‡ This phenomenon is currently being further investigated. The synthesis of Juglone starting from **1b** has previously been reported.[7b,10g]

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Micro-photochemistry: photochemistry in microstructured reactors. The new photochemistry of the future?†

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The use of a confined space in which to carry out reactions has proven popular in recent years, as demonstrated by the large volume of work published on 'molecular microreactors' such as zeolites, micelles and nanoparticles. This article looks at reactions in microstructured reactors, also known as microchannelled reactors or microreactors. In general, these consist of a 'chip' with narrow channels etched into it. Microstructured reactors have been the subject of several review articles to date, focusing on preparation, types of reactions that may be carried out and on the potential for 'green' applications. However, the use of microstructured reactor technology in photochemistry has, until now, not been subject to review. This perspective aims to outline the work done to date in this area and in particular to demonstrate the advantages and future prospectives of this technology in photochemical processes. Photochemistry in microstructured reactors is an emerging area of interest and to date has demonstrated significant potential as a viable alternative to traditional photochemical synthesis.

Introduction

With the recent interest in miniaturisation, it is no surprise that chemical researchers have shown an interest in microtechnology. This is reflected in the many volumes of work published on micro- and nanotechnologies in chemical synthesis since the beginning of the 21st century. As a consequence, the term '(molecular) microreactor' has become commonplace in chemical communities. This term refers to a confined space in which a chemical reaction can occur and has been used in reference to micelles, zeolites, supramolecular systems and nanoparticles.[1–7] However, it also refers to microstructured reactors, otherwise known as microchannelled reactors. In general, microstructured reactors consist of a solid support with channels of only several micrometres in width and depth (10–1000 μm). The overall size of the 'chip' is usually only several centimetres in length, width and depth. Over the past decade, microstructured reactors have become increasingly more widespread in research, in particular in analytical applications. The 'lab on a chip' concept has lead to a great deal of interest in miniaturisation of technology.[8–12] In particular total miniaturisation is of interest, where the pumping system and detector are part of a micro modular system. Microstructured reactors have also demonstrated significant promise in the area of synthetic organic chemistry, including photochemical transformations, as detailed in many review articles to date.[13–27] However, the application of microstructured reactors in organic photochemistry has not

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† This subtitle refers to Giacomo Ciamician's visionary lecture *The Photochemistry of the Future*, presented before the International Congress of Applied Chemistry in New York in 1912.[48]

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Michael Oelgemöller and Emma Coyle

Michael Oelgemöller, born in 1969, received his PhD, for which he was awarded with the Kurt-Alder award in 2000, from the University of Cologne in 1999. He was a researcher at the Inoue Photochirogenesis project in Osaka (1999–2001) and at Bayer CropScience Japan in Yuki (2001–2004). In August 2004 he joined Dublin City University as Lecturer in Organic Chemistry. His research activities include solar photochemistry, the development of new photochemical synthesis tools and photochemical water treatment.

Emma Coyle was born in 1983 and grew up in Roscommon, Ireland. She was awarded the status of best student of her course for the year 2006, when she received her degree in Chemical and Pharmaceutical Science from Dublin City University. She is currently a PhD student in the School of Chemical Sciences and the National Centre for Sensor Research at Dublin City University. Her work focuses on the study of green chemistry, with a particular interest in solar synthesis of fine chemicals.

been subject to review in its own right. Solely the photochemical activities of Matsushita *et al.* have recently been summarised.[16]

Commercially available microstructured reactors have been commonly adopted for photochemical applications, particularly the serpentine channel and the falling film type reactor. The main feature of the serpentine reactor is its long path length, which may range from several centimetres to a metre or more. The dwell device produced by mikroglas (Fig. 1), for example, has a total path length of 1.15 m (20 turns) on a 118 mm × 73 mm aperture. This reactor consisted of a (bottom) serpentine channel with a second (top), heat-exchanging channel through which water is passed in order to control the reactor temperature. The longer path length can be used to increase residence time, and is therefore suited to reactions in which a longer reaction time is needed. In the serpentine reactor the reagents may be pre-mixed, or mixed on-chip *via* a 'T' (or 'Y') structure, *i.e.* two separate inlets that lead into a single channel.

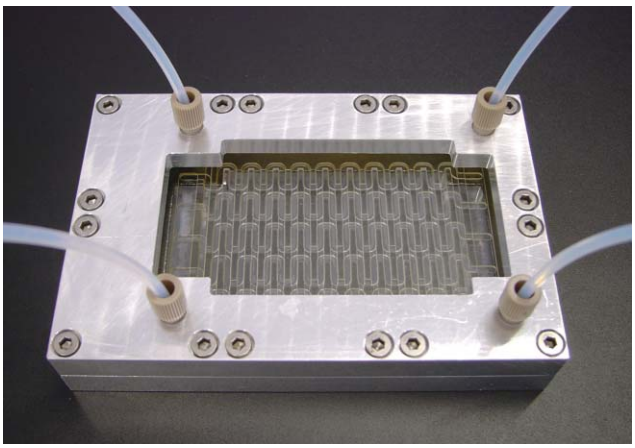


Fig. 1 Dwell device (mikroglas).[28] The parallel heat-exchange channels can be clearly seen.

Another commercially available design is the falling film reactor (Fig. 2), which utilises a multitude of thin falling films that move by gravity force in parallel microstructured channels. These devices are specifically designed for gas-liquid reactions, *e.g.* oxidations and hydrogenations, where the gas flows against a film of liquid. The high specific interface area (up to 20 000 m^2/m^3) enables sufficient saturation of the film with reactant gas. This reactor type is thus more efficient than closed channel devices, which require presaturation of the reaction mixture with reagent gas. Scale-up can be achieved using cylindrical reactor models.

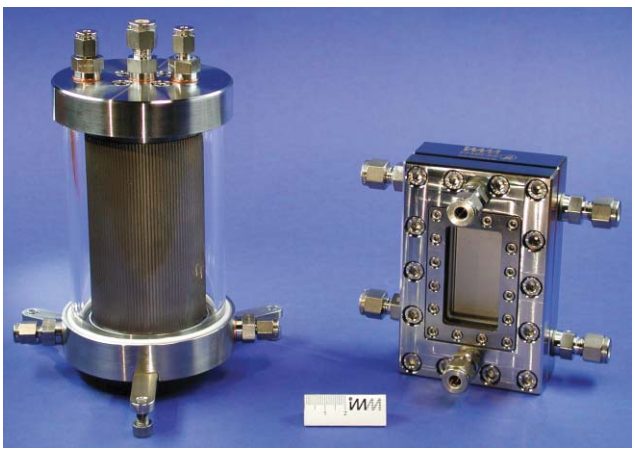


Fig. 2 Cylindrical falling film micro reactor (FFMR-cyl) for 10-fold scale-up and its standard version FFMR (with courtesy of IMM).[29]

Beside commercially available types of micro reactors, many researchers continue to custom build their own reactors. This enables flexibility with respect to solid substrate and glass used, as well as optimisation of path length and depth. An example of a microchip reactor in combination with a UV-LED-array is shown in Fig. 3.

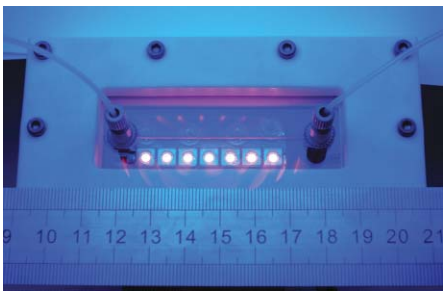


Fig. 3 Quartz microchip design with 365 nm/500 mV UV-LED-array, Matsushita *et al*.[39]

Engineering of microreactors is a significant research area, with many groups working to optimise reactor design using photochemical processes as model reactions. The engineering of a microstructured reactor may be done using a variety of techniques.[30] The solid support used may be glass, silicon, metal, ceramic or polymeric in nature. The choice of solid may depend on the reaction to be carried out, for example some polymers are not stable to all solvents. For photochemical reactions use of glass as the solid substrate is ideal, as this provides a transparent 'window' though which the reaction mixture may be irradiated. The channels are generated using photolithography, hot embossing, microlamination and other microfabrication techniques.

The photochemical reactions carried out to date may be categorised as homogeneous reactions (such as photocyanation,[31] [2 + 2]-cycloadditions,[32,33] the Barton reaction,[34] photochemical pinacolisation[35]), heterogeneous reactions between liquid and gaseous reagents (*e.g.* additions of singlet oxygen[36–38]) or catalytic processes using semiconductors (such as catalytic reactions using titanium dioxide[39–42]).

Photochemistry—past and present

Photochemical reactions have occurred in nature since before life began on Earth, but interest in laboratory applications of photochemistry did not commence in earnest until the eighteenth century. One of the first photochemical reactions noted in a laboratory was Scheele's observation of the blackening of silver halide salts in sunlight (in 1775). A small amount of interest in photochemistry continued through the eighteenth century and nineteenth century.[43]

Understanding of photochemistry improved through the development of the laws of photochemistry—the Grotthaus–Draper law (1842) and the Stark–Einstein law (1913). The scope of organic photochemistry was greatly expanded during the twentieth century,[44] through the works of Giacomo Ciamician in Italy

(1857–1922),[45] Alexander Schönberg in Egypt (1892–1985)[46] and Günther Otto Schenck in Germany (1913–2003)[47] as well as many others. At the International Congress of Applied Chemistry in New York in 1912, Ciamician presented his remarkable vision of "The Photochemistry of the Future".[48] In this speech he outlined his belief that photochemistry, which was an entirely solar discipline at that time, could be a key component of industry in the future: *"On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains, and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them even more abundant fruit than nature, for nature is not in a hurry and mankind is."*

However, early research in organic photochemistry was hindered by the lack of suitable light sources and synthetic photochemical reactions were carried out outdoors in sunlight. As a result, interest in synthetic photochemistry failed to endure and studies in the subject remained rare for many years. With the advent of better technology,[49] organic photochemistry underwent a revival. Developments in reactor design and use of more specific light sources led to an increase in research in the area in the latter part of the 20th century. A recent review by Hoffmann outlines current progress in synthetic organic photochemistry,[50] focussing on research since the beginning of the 21st century. This review demonstrates that organic photochemistry is an evolving and lively topic, with much research into new reactions and technology over the past decade.

However, Ciamician's dream has not been realised to date. Although photochemistry has produced significant research interest in academia,[50] it is rare for photochemical processes to be realised on an industrial scale. There are several contributing factors for this neglect:[49]

• Specialised reaction vessels are required in which a light source may be incorporated. The most commonly used type of photoreactor is an immersion well, in which the light source is placed in the centre of the reaction mixture. However, during scale-up, it is very difficult to reproduce the same ratio of area irradiated to volume of reactant.

• Light sources pose a difficulty on an industrial scale. Lamps used in photochemistry include medium and high pressure mercury lamps, xenon lamps and halogen lamps, all of which are costly to run. These have a limited lifetime and additionally tend to generate a large amount of heat and therefore require additional cooling systems.

• Photochemical reactions are typically carried out under batch reaction conditions. This method tends to be relatively inefficient compared to a continuous-flow process. Photochemical reactions operated in continuous-flow have been investigated and have proven to be far more effective at large-scale photochemical synthesis than the corresponding batch approach.[51] However, batch reactions continue to be the most common approach to photochemistry.

Some examples of large-scale photochemical synthesis in industry do exist.[49,52–55] Despite these examples, however, the acceptance of synthetic photochemistry in industrial research laboratories, *e.g.* for the development of new lead compounds, remains low. A recent account by Bochet[56] addresses the perceived disadvantages of photochemical synthesis and endeavours to show that these difficulties are easily overcome.

To this end, many researchers are seeking to develop new photochemical techniques, leading to an emerging field of new technologies. While this review focuses on microstructured reactors, other concepts and reactor designs have emerged,[21,57] for example *spinning disc reactors*,[58,59] *continuous flow reactors* (for macro-[51] and micro-scale[60,61] synthesis), *excimer radiation systems*,[62–64] *thin film reactors*,[65] *solar parabolic trough reactors* (*e.g.* the PROPHIS-plant[66–69]) or *microbatch reactors.*[70,71] Reactions carried out in various 'microspaces' have also been reported.[1,7] These include micelles,[2] zeolites,[3] supramolecular systems,[4] nanoparticles[6] and porous ceramics.[72,73] However, of all the emerging technologies, microstructured reactors show the most potential for widespread use in preparative organic chemistry including photochemistry.[13–27] The advent of microstructured reactor technology may furthermore provide a means to carry out large scale photochemical reactions. Giacomo Ciamician's vision for the future may yet be realised, but in the form of a microchip, rather than the dramatic scene he envisaged. By scaling down photochemical reactions using microstructured reactors it may be possible to have key photochemical steps carried out in research laboratories. In addition, 'numbering up', *i.e.* using several microreactors in parallel, rather than scaling up may enable the industrial production of large amounts of photochemical products. There are several additional advantages of microstructured reactors, which make them ideal for photochemical processes:[24]

• They provide a means of ensuring uniform irradiation to the entire reaction solution. As the depth of a microreactor is small (100–1000 μm), maximum penetration of light and thus irradiation of the reaction mixture can be achieved readily, even for relatively concentrated solutions.

• Microphotochemistry is commonly performed under continuous-flow rather than batch conditions. Consequently, irradiation time for photochemical processes in a microreactor is easily altered, as this is directly proportional to the flow rate of the system. This feature allows rapid optimisation of microphotochemical reactions.

• Microstructured reactors possess high heat transfer coefficients. As a result, microstructured reactors are cooled very efficiently.

• Miniaturised light sources may be employed, for example light-emitting diodes (LEDs).[60,70,74–77] These provide a clear alternative to conventional light sources, as they are available in a range of wavelengths, small in size and energy efficient. In addition, they produce less or no heat, thus reducing the need for coolant.

• Microchip designs allow on-line monitoring of the reaction, *e.g.* by UV-spectroscopic analysis of the effluent.[35]

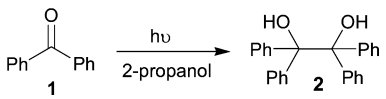
Already many examples exist in the literature documenting the advantages of microstructured reactor technology in photochemical synthesis. The reactions carried out to date may be divided in three categories, based not on reaction type, but rather on conditions required.

Homogeneous reactions

In these reactions the reagents are all in the same phase, *i.e.* all in solution. Therefore there are few additional requirements for the microstructured reactor beyond the ability to pump the reagents

in solution through the reactor. A preprepared mixture may be introduced through a single inlet or mixing of reagents may occur on-chip by applying a T-inlet.

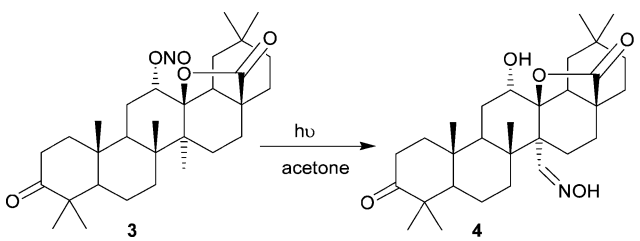
One of the earliest reported photochemical reactions in a microstructured reactor was the photo-pinacolisation of benzophenone **1** in isopropanol (Scheme 1).[35] Microstructured reactors were prepared in-house, one with a Pyrex cover-plate and one consisting of a silicon wafer sandwiched between 2 quartz wafers. This type of microstructured reactor is of significance as lower wavelengths of light may be used for irradiation than allowed by Pyrex.[49] The light source used was a mini UV lamp, which provided light of 365 nm. The typical concentration of the benzophenone solution was 0.5 M. The use of a concentrated solution effectively demonstrated the advantage of a microstructured reactor, as the shallow channel depth ensured complete irradiation of the reaction mixture which would not have been possible under conventional photochemical set ups. The progress of the transformation was monitored *off-chip* using HPLC and *on-line* using UV-spectroscopy.



Scheme 1 Photo-pinacolisation of benzophenone.

The authors reported that this reaction required flow rates of less than 10 μl min^{-1} to ensure adequate residence time on the chip. Although a larger residence time results in greater conversion, rates above 3 μl min^{-1} were used to avoid precipitation of product **2** in the microstructured reactor. Above this threshold, crystallisation of the product was observed in the effluent storage device instead. At a flow rate of 4 μl min^{-1} conversions of up to 60% were achieved.

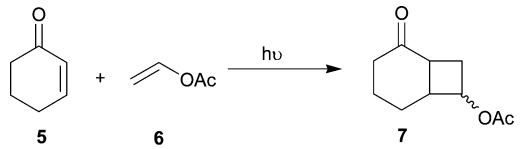
Sugimoto and co-workers have reported the application of microstructured reactors in the preparation of the key steroidal substrate **4** *via* Barton reaction (Scheme 2).[34] The microstructured reactors used (manufactured by Dainippon Screen[78]) were made from stainless steel with channels 1000 μm wide, 107 μm deep and total path length of 2.2 m.



Scheme 2 Barton reaction.

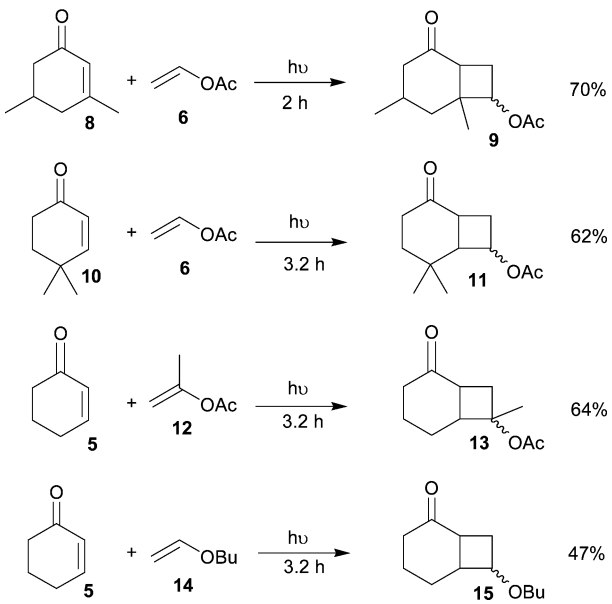
The study compared the effectiveness of three different types of transparent cover—quartz, soda lime glass and Pyrex—and determined that Pyrex was most suited to the light source, a 15 W black light. In addition, the authors mention studies of temperature dependence (extensive degradation of the product at temperatures greater than 50 °C) and distance between microreactor and the light source, which was optimised at 7.5 cm. Following optimisation, a residence time of 12 minutes produced the desired product **4** in 71% yield. Also reported is a gram-scale synthesis of the target compound, using two microstructured reactors (1000 μm wide, 500 μm deep and 1 m total length, manufactured by Dainippon Screen[78]) connected in series and 8 × 20 W black lights. After continuous operation for 20 h the desired product was isolated in 60% yield. This clearly demonstrates the potential for numbering up of microstructured reactors for the large scale production of chemicals.

An investigation into the use of microstructured reactor technology for photochemical [2 + 2]-cycloadditions was carried out by Fukuyama *et al*. (Scheme 3).[33] This study demonstrates the application of a commercially available microreactor (mikroglas dwell device with FOTURAN® glass, Fig. 1) for a range of substrates. A common high pressure mercury lamp (300 W) was used as a light source. The model reaction examined was the reaction of cyclohex-2-enone **5** with vinyl acetate **6** (Scheme 3).



Scheme 3 [2 + 2]-Cycloaddition of cyclohex-2-enone with vinyl acetate.

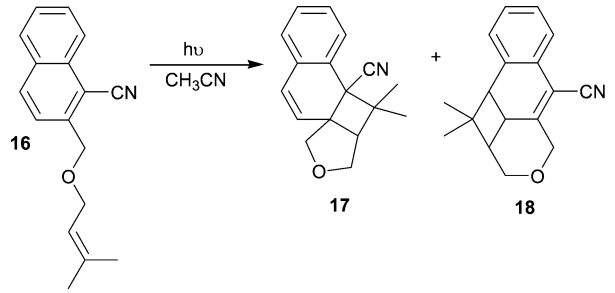
At a flow rate of 0.5 mL h^{-1}, which corresponds to a residence time of 2 h, a yield of **7** of 88% was achieved. This was compared to a batch reactor (10 mL) irradiated using the same light source for 2 h, which yielded only 8% of **7**. This demonstrates that the use of microstructured reactor technology can both shorten irradiation times and increase yield. The reaction was repeated with 2 reactors in series at a flow rate of 1 mL h^{-1}, which resulted in a similar yield of 85%. A study of other cyclohexenones, **8** and **10**, and alkenes, **12** and **14**, was carried out and the corresponding photoaddition products (a mixture of regioisomers) were obtained in yields of 47–70%. These findings effectively showed the ability to transfer this technology to related reactions (Scheme 4).



Scheme 4 Series of photochemical [2 + 2]-cycloadditions.

Microstructured reactors have been shown to increase regioselectivity of some reactions. A communication by Maeda *et al.* reports a comparison of regioselectivity of the intramolecular

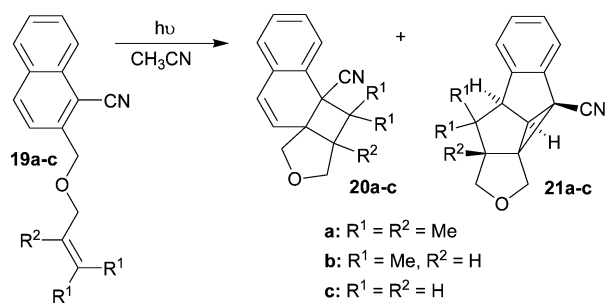
[2 + 2]-photocycloaddition of 1-cyano-2-((3-methyl-2-butenyloxy)methyl)naphthalene **16** in acetonitrile under batch conditions and following the microstructured reactor approach (Scheme 5).[32]



Scheme 5 Intramolecular [2 + 2]-photocycloaddition of 1-cyano-2-((3-methyl-2-butenyloxy)methyl)naphthalene.

The reaction was carried out in custom-built reactors made from poly(dimethylsiloxane) with inserted capillary tubes as the channels (diameter 100 μm, total length 45 mm or 202 mm). Flow rates of 0.03–0.05 mL h^{-1} were used. The reaction was optimised to use a path length of 202 mm and flow rate of 0.05 mL h^{-1}. Under these conditions the regioselectivity of the reaction was improved compared to batch conditions (55 : 7 for microreactor compared to 56 : 17 for batch). This is explained by the rapid flow rate, the cycloadduct **17** initially formed is rapidly expelled from the system, thus reducing photocycloreversion back to the starting material **16**. Longer irradiation times (greater residence times) gives increased yield of **18** as reversion to starting material does not occur for this product. The effect on enantiomeric excess was also examined when the products were eluted using $Eu(hfc)_3$ and was shown to have a small but significant effect (2% ee).

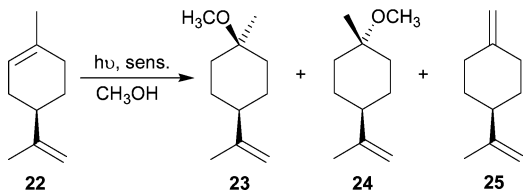
In an extension of this work, Mizuno investigated other intramolecular photocycloaddition of 2-(2-alkenyloxymethyl)-naphthalene-1-carbonitriles **19a–c** (Scheme 6).[79] This study includes a comparison to a batch reaction (Pyrex tube, diameter 8 mm) and investigation of effects of substituents, solvent, residence time and flow rate and the dimensions of the microchannel. The first (Type A) microreactor was commercially available (ICCDI05, Institute of Microchemical Technology[80]), with a width of 100 μm, depth 40 μm and length 120 mm. A second (Type B) microreactor was made in-house, using Pyrex plates, with channel width 2.5 mm, depth 50 μm and length 60 mm. The light source used was a xenon lamp (500 W).



Scheme 6 Intramolecular photocycloaddition of 2-(2-alkenyloxymethyl)-naphthalene-1-carbonitriles.

The findings of this study show, once again, that microreactors enable increased regioselectivity, as the initial photoproducts **20a–c** may be selectively formed and the undesirable photocycloreversion reaction may be avoided. The rapid flow rate ensures that the initial product is removed from the irradiation chamber before the secondary reaction, yielding **21a–c**, may occur. In addition, this study demonstrated the efficiency of reactions in microstructured reactors, with conversions of 69–75% achieved after one minute in the microreactor, compared to 74% after 3 h in a batch reactor. It was also shown that use of a wider channel while maintaining a shallow channel depth could significantly increase output.

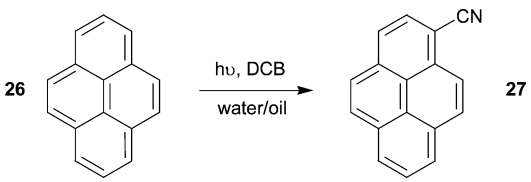
As discussed in the previous example, use of microstructured reactors has been shown to reduce the occurrence of unwanted side reactions. Rapid flow rates decrease the residence time of the substrates and can ensure that the products are rapidly removed from the reactor. Sakeda *et al.* have demonstrated this principle using the asymmetric photosensitised addition of methanol to (*R*)-(+)-(*Z*)-limonene **22** as a model reaction (Scheme 7).[81]



Scheme 7 Asymmetric photosensitised addition of methanol to (*R*)-(+)-(*Z*)-limonene.

Three microstructured reactors of different dimensions were made from quartz. A low-pressure mercury lamp (40 W) was used as light source. A study of the effect of channel size on photon efficiency was carried out. Photon efficiency was shown to increase with decreasing channel size and was significantly greater for microstructured reactors than batch conditions. High spatial illumination homogeneity, excellent light penetration and short exposure times were used as an explanation. In addition, the diastereomeric excess (de) of the photoproduct was found to be slightly larger than that obtained under batch conditions. This was explained by suppression of side reactions in the microstructured reactors.

An unusual example of use of microreactors in photochemical synthesis is the photocyanation of pyrene **26** (Scheme 8) across an oil/water interface as reported by Ueno and co-workers.[31] The chips used were fabricated in-house by imprinting method using commercially available polystyrol substrate, with width of 100 μm, depth 20 μm and length 350 mm. The reactors used had either 2 inlets or 3 inlets at the start of the serpentine reaction channels. This facilitated the introduction of the oil and water phases separately, with equal flow rates, thus ensuring formation of a stable water/oil or water/oil/water interface, respectively. Once stable interfaces were established the reactors were irradiated



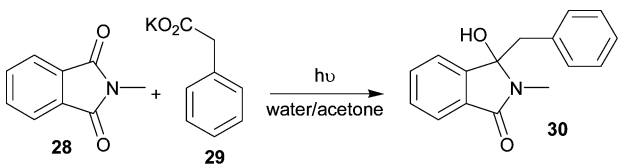
Scheme 8 Photocyanation of pyrene.

using a high-pressure mercury lamp (300 W) with a copper sulfate solution filter (>330 nm).

An aqueous solution of sodium cyanide and a solution of pyrene and 1,4-dicyanobenzene (DCB, electron acceptor) in propylene carbonate were used. During irradiation, photo-induced electron transfer (PET) occurs between pyrene and DCB and the resulting radical undergoes nucleophilic attack by CN^- at the oil/water interface. The product, 1-cyanopyrene **27**, remains in the oil phase.

The results from this investigation show that after a residence time of 210 s the photoproduct was obtained in 28% yield for the oil/water system and in 73% yield for the water/oil/water system. Decreasing flow rate would increase residence time, and hence yield, but at rates below 0.2 µl min^{-1} a stable oil/water interface could not be obtained. It is anticipated that optimisation of channel length can increase this yield, as 100% conversion had not occurred.

Recent investigations in the synthesis of bioactive compounds through photodecarboxylative addition of carboxylates to phthalimides[82] in our laboratory have shown that these are feasible in microreactors.[83] The microreactor used is a dwell device (mikroglas, Fig. 1) with a reaction channel of 500 µm in depth, 2 000 µm in width and length 1.15 m. The reaction of N-methylphthalimide (NMP) **28** with potassium phenylacetate **29** was used as a model reaction (Scheme 9).



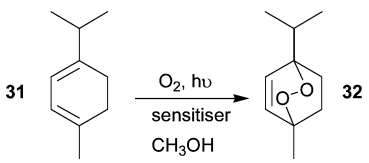
Scheme 9 Reaction of N-methylphthalimide with potassium phenylacetate.

Using UV irradiation (300 nm), the effect of flow rate on yield of the addition product was investigated. At a flow rate of 0.8 mL min^{-1} (residence time 21 mins), conversion of 97% to the benzylated product **30** was achieved.

Heterogeneous reactions

In heterogeneous liquid–gas reactions, it is necessary to provide a supply of gas to the microstructured reactor. The falling-film type reactor is commercially available for this purpose, while other reactors have been adapted for use also.

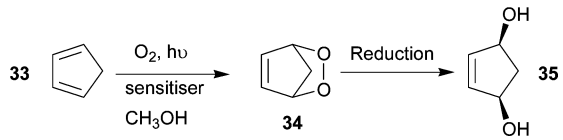
The use of microstructured reactors for reactions requiring singlet oxygen has been the subject of several investigations. For example, the synthesis of ascaridole **32** from α-terpinene **31** *via* dye-sensitised photooxygenation (Scheme 10) has been used as a model reaction for generation and use of singlet oxygen in a microstructured reactor.[38]



Scheme 10 Dye-sensitised photooxygenation of α-terpinene.

The reactor was prepared in-house using a glass substrate and consisted of two inlets, for reaction solution and oxygen, a serpentine irradiation sector (of total length 50 mm) and an outlet channel. The channels had an average depth of 50 µm and an average width of 150 µm. A mixture of methanol and rose bengal (sensitiser) was introduced *via* a divergent inlet channel and mixed with oxygen on-chip. Singlet oxygen was generated within the serpentine channel of the microstructured reactor when irradiated with a tungsten lamp (20 W, 6 V). The volume of aerated solvent in the system at any time was in the region of picolitres. This represents far less of a danger than the larger quantities of aerated solvent required in the laboratory procedure. The yield of ascaridole after workup was greater than 80%, as determined by GC analysis. This work demonstrates clearly that microstructured reactors provide a novel platform for photooxygenation reactions.

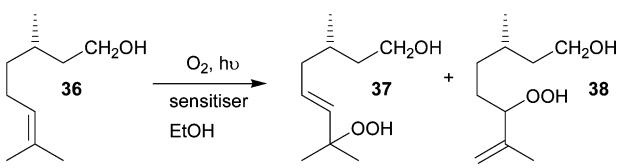
This was further demonstrated by Jähnisch and Dingerdissen, who reported the photooxygenation of cyclopentadiene **33**, followed by reduction to 2-cyclopenten-1,4-diol **35**, (Scheme 11) in a falling film microstructured reactor (FFMR by IMM, Fig. 2).[37,84]



Scheme 11 Dye-sensitised photooxygenation of cyclopentadiene and reductive ring-opening.

This reaction proceeds *via* a potentially explosive endoperoxide **34**, which is a concern for large scale conventional synthesis. However, in the microstructured reactor, the concentration of the intermediate remains low at all times. The reactor was furthermore cooled to 10–15 °C. The endoperoxide is reduced immediately after leaving the reactor by passing the effluent into a solution of thiourea in methanol at 10 °C. This ensures that the quantity of the endoperoxide intermediate present is always kept at a safe level. At an influent flow-rate of 1mL min^{-1} (and an O_2 flow of 15 L h^{-1}), the authors reported a yield of 20% of **35** for the non-optimised procedure.

In a recent study, microstructured reactors have been shown to be applicable in the Schenck-ene reaction of (–)-citronellol **36** (Scheme 12),[36] a key step in the synthesis of rose oxide.[55]



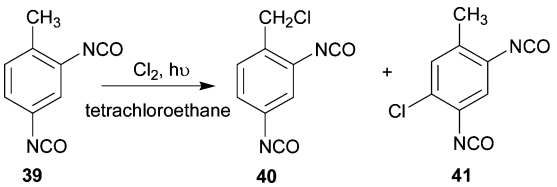
Scheme 12 Dye-sensitised photooxygenation of (–)-citronellol.

This study compared the efficiency of a commercially available microstructured reactor (HT-residence glass, Little Things Factory[85]) to a batch reactor in terms of space-time yield and photonic efficiency. The microreactor consisted of a serpentine channel of width 1 mm. The sensitiser used was a ruthenium polypyridyl complex, $Ru(^t bpy)_3Cl_2$(tris(4,4′-*tert*-butyl-2,2′-dipyridyl) ruthenium(II)-dichloride) and the light source an LED array (4 × 10 LEDs, nearly monochromatic at 468 nm). The reaction mixture was purged with compressed air and was

continuously pumped through the microreactor in a loop for about 60–70 h. The progress of the reaction was monitored by HPLC.

The results of this investigation demonstrated that the microstructured reactor method has a greater photonic efficiency and space-time yield than the batch reactor method. In addition, this study demonstrated the use of miniaturised light sources, *i.e.* LED arrays, for photochemical reactions.

Heterogeneous reactions in microstructured reactors are not limited to reactions of singlet oxygen. The photochlorination of toluene-2,4-diisocyanate (TDI, Scheme 13) **39** has been demonstrated in a falling film reactor (FFMR by IMM, Fig. 2), with 32 parallel channels of width 600 μm, depth 300 μm and length 66 mm and a Quartz cover.[86] The light source was a xenon lamp (1000 W, unfiltered). The reactor was maintained at a temperature of 130 °C to decrease side reaction to form a ring chlorinated product **41**.



Scheme 13 Photochlorination of toluene-2,4-diisocyanate.

The microreactor results were compared to those obtained in a batch reaction and demonstrated that use of the microstructured reactor led to increased product selectivity. This is due to the high surface to volume ratio and hence a lower local concentration of chlorine radicals in the microstructured reactor. In addition, the space-time yields were orders of magnitude higher compared to the conventional reactor.

To investigate the effect of the reactor material on the reaction, two reaction plates were used, one nickel and one iron. This study showed that the selectivity of the desired product **40** was affected significantly by the microreactor material (50% for iron, 67% for nickel), which is attributed to the formation of $FeCl_3$, which acts as a Lewis acid. This led to enhanced production of resin-like condensation products.

An investigation of effect of flow rate and residence time revealed that shorter residence times gave higher selectivity, by avoiding follow up reactions. However, increased residence times give a thinner film and consequently greater conversion rates.

These examples of liquid–gas reactions have clearly shown that microstructured reactors offer a viable route to many fine chemicals, with potential to reduce safety risks in the laboratory. However, optimisation of the technology to maximise effectiveness of mixing is essential.

Catalytic reactions

Microstructured reactors show potential for use in catalytic reactions. One of their key features is a large surface to volume ratio, therefore if a catalyst were immobilised on the walls of the channels it could be possible to maximise interaction of catalyst and reagents. Microstructured catalytic photoreactors show potential for use in the treatment of waste water and exhaust air, as well as some synthetic processes. Several examples have been documented in the literature to date, in particular focussing on the use of titanium dioxide as a catalyst.[87]

The photodegradation of chlorophenol in the presence of a titanium dioxide catalyst was one of the first microstructured reactor based catalytic reactions to be investigated.[75,88] A microstructured reactor was prepared with TiO_2 as a photocatalyst on the walls of the channels (cross-section 300 μm × 200 μm). This was irradiated using an array of eleven UV-A LEDs, with a peak emission of 385 nm.

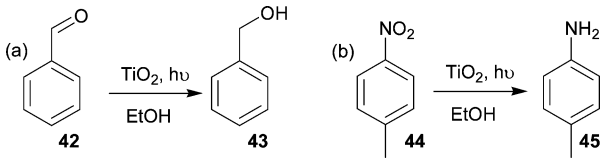
The degradation study was carried out using different initial concentrations of chlorophenol and different flow rates. It was shown that greater degradation was achieved for lower concentrations and lower flow rates. The specific surface area irradiated in the microstructured reactor was 4–400 times greater than that of other reactor types, *e.g.* slurry or immersion type reactors. This study also demonstrated miniaturisation of the light source, thus showing potential of this technology for total-miniaturisation. However, a downside of this reactor type is its minute capacity. To prove beneficial on a larger scale numbering-up is necessary.

Another decomposition study looked at the coating of capillary tubes for use as microchannel reactors.[89] In this case the microchannel is not embedded in a solid substrate, the capillary acts as a single microchannel. The photocatalytic degradation of methylene blue was used as a model reaction to investigate the use of catalytic coatings (TiO_2 coating, with and without silica) in microspace in comparison to a batch reaction. The reactions were irradiated at a wavelength of 254 nm. Results of this study show that without titania the conversion is very slow, and rate increases with the use of TiO_2, with most rapid degradation occurring using SiO_2/TiO_2 coating. The reaction rate was affected by diameter of the capillary, *i.e.* depth of the solution, with completion of the reaction after just 40 s in a channel with 200 μm diameter, compared to 2 min for a diameter of 530 μm. In the case of the batch reaction the reaction reached completion after one hour.

Further photodegradation studies in microstructured reactors were carried out by Kitamura *et al*, in which a silica supported porphyrin derivative was used to catalyse degradation of phenol by singlet oxygen.[90] Polystyrene was used as a substrate and the silica beads covalently modified with metal-free monopyridyltriphenylprophyrin were incorporated. These were not fused to the channel walls, therefore the reactor was constructed with a 'dam' (130 μm height) to prevent elution of the beads during the reaction. Irradiation was performed with a 300 W high-pressure Hg lamp and the emitted light was passed through a $CuSO_4$ filter solution (>330 nm).

The investigation looked at the effect of flow rate and channel depth on decomposition yield. In accordance with expectations, decreased flow rates led to increased decompositions (65% at 3 μL min^{-1} and 93% for 0.5 μL min^{-1}). Decreasing channel depth from 130 μm to 30 μm also led to an increase in yield (35% to 65%, respectively), which is believed to be due to greater interaction between sensitiser and dissolved oxygen. When compared to a batch reaction, with similar concentrations of sensitiser, the microreactor was shown to be more effective, with decomposition yields of 93% after 42 s, compared to 70% after two hours for the batch experiment.

Also of interest is the use of photocatalytic microstructured reactors in synthesis, rather than degradation. A communication on the reduction of benzaldehyde **42** and nitrotoluene **44** (Scheme 14)



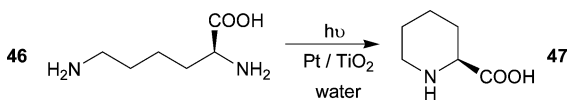
Scheme 14 Photocatalytic reduction of (a) benzaldehyde and (b) nitrotoluene.

using titanium dioxide was reported in 2006.[42] This report also focuses on full miniaturisation, and UV-LEDs with an emission of 365 nm were chosen. Quartz microreactors were fabricated with a catalytic coating on the bottom and sides of the channels (width 500 μm, depth 100 μm and length 40 mm).

Alcoholic solutions of benzaldehyde were used and ethanol was found to be the most efficient solvent, with a yield of **43** of 11% after 60 s. Photoreduction of nitrotoluene was found to be more rapid, with yields of 46% for **45** after 60 s. Although these reactions are not optimised, they show that microstructured reactor technology provides an effective route to reduction of these compounds.

Further photocatalytic degradations have been recently summarised by Matsushita *et al.*[39] In this comparison study, model pollutants such as chlorophenols, bisphenols and dimethylformamide were treated in the presence of titanium dioxide and UV light (LED and tuneable OPO laser). Light source optimisation, using a microreactor with a depth of 100 μm and degradation of DMF as a model reaction (Fig. 3), revealed that LEDs demonstrated a significant photonic efficiency compared to an OPO laser or xenon laser.

Another example of a synthetically useful transformation has been reported by Takei *et al.*[91] The authors examined the photocatalytic synthesis of L-pipecolinic acid **47** from L-lysine **46** (Scheme 15) in a self-fabricated reactor.

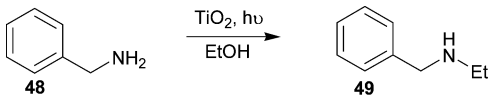


Scheme 15 Photocatalytic synthesis of L-pipecolinic acid.

A Pyrex microstructured reactor with channels 770 μm wide and 3.5 μm deep was fused to a substrate with a 300 nm thick coating of TiO_2. Platinum was used as a reducing agent at 0.2 wt% in the film. The reaction set-up was irradiated using a high-pressure mercury lamp with a UV transmitting filter. The reaction was compared to a batch set-up using a cuvette and TiO_2 particles in suspension. Conversion of L-lysine to L-pipecolinic acid **47** in the microstructured reactor was 87% after a residence time of 0.86 min. This conversion rate was 70 times greater than that of the batch reaction.

Examination of selectivity and enantiomeric excess (ee) showed that these were independent of reaction time. However, looking at productivity in terms of moles produced per minute the batch reactor was superior. This is due to the larger capacity (4 mL) but this disadvantage may be overcome through numbering up of microreactors in the future. A significant advantage of the catalytic microstructured reactor is the elimination of a separation step, as the photocatalyst remains in the microstructured reactor while the product is eluted.

Another study on synthetic reactions in microstructured reactors is the N-alkylation of benzylamine **48** (Scheme 16).[39,40] Quartz microreactors (width 500 μm, 40 mm length, various depths) were used, with the bottom and sides coated with titania (Pt-loaded and Pt-free). UV-LED arrays were employed as light sources (365 nm). The reaction products were analysed by GC or HPLC methods.



Scheme 16 N-ethylation of benzylamine.

It was shown that benzylamine could be converted to the alkylated product **49** in yields of up to 43% in just 90 s. Optimisation of the reaction solvent was carried out, resulting in use of ethanol in further studies. Other amines were investigated as well and aniline and butylamine were N-alkylated in yields of 11% and 36%, respectively. An investigation of the effect of decreasing depth was performed, using reactors with depths of 300 μm, 500 μm and 1000 μm. It was shown that the efficiency of N-alkylation was enhanced by decreasing depth, this is attributed to the increased surface to volume ratio. Interestingly, this reaction was shown to proceed in the presence of titanium dioxide photocatalyst, even without platinum. Yields of 98% were achieved after 90 s. In contrast, this reaction does not occur in batch conditions without the presence of platinum. In addition, no bis-alkylated product was obtained when platinum was present, as is usually the case in batch conditions. The absence of bis-alkylation was achieved by the continuous-flow mode, which prevents the undesired follow-up reaction.

In a recent extension of this work, the authors further investigated the N-alkylation of aniline and piperidine.[41] Again, the transformation proceeded quite rapidly in the microstructured reactors with immobilised TiO_2 (with and without Pt-loading). Prolonged irradiation in the microreactor resulted in efficient bis-alkylation as demonstrated for benylamine.

Finally, the decomposition of Fe(III) oxalate has been studied by Kirner and co-workers to test a novel static micromixer.[92]

Conclusions

The literature to date clearly demonstrates the versatility and potential of microstructured reactors in organic photochemistry, as reactors may be used for a range of reaction types. Advantages discussed include elimination of side reactions, enhanced selectivities, increased photonic efficiency and reduction of hazards. In catalytic applications a large area-volume ratio is possible, resulting in improved catalytic effect.

Some difficulties have been encountered, particularly in the minute volumes handled. To overcome this challenge, the concept of 'numbering up' has been proposed. By operating many reactors in parallel or in series the output volume may be significantly increased.

Although a range of photochemical reactions have been carried out in microreactors to date, a lot of work remains in this area. However, optimisation of reactor dimensions, flow rates and other conditions affecting reactions should lead to further successes in the future. Hence, Giacomo Ciamician's vision of

the *Photochemistry of the Future* may actually be realised in 'miniaturised' formats.[48]

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