SYNTHESIS OF SOME ANALOGUES OF N-SUBSTITUTED PHTHALIMIDE AND BENZO-TETRACYANOQUINODIMETHANE

by

Gerard M. McDermott, B.Sc. (HONS), M.R.S.C.

A Thesis presented to Dublin City University for the degree of Doctor of Philosophy

Supervisor: Prof. A.C. Pratt
School of Chemical Sciences
Dublin City University

September 2007

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Ph.D is entirely my own work 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.

Signed: Conrad W Rowlett (Candidate)
ID No.: 9897615
Date: 25 Sept. 2007.

Acknowledgements

I would like to thank most sincerely Prof. Albert Pratt for giving me the opportunity to carry out this research. I am also extremely grateful for his advice and guidance during the course of the work.

I would also like to thank Dr. Michael Oelgemöller for his words of advice and for providing some literature that was difficult to find.

Thank you to all the Technical staff of the School of Chemical Sciences: Mick, Damian, Veronica, Ann, Maurice, Vinny, John, Ambrose, Mary and the many other trainees – you are the heart beat of the department, over-utilised and, sometimes, under valued.

To the members of X2-49 that came and went in my time – Ben, Colm, Ollie and Ray from the APRG, Mairéad, Cathal, Rob, Neil, Yang, Ji Feng, Nameer, Sarah, Frankie, Noel, Dave, Paula, Brian M., Alan, Fadi, Sonia, Emma, Saibh, Ewa, Brian D., and to the many others that darkened the doors of the lab that are not named here.

To all the other postgrads, the inorganic folk from X2-46, the analytical and physical people that lived downstairs, and to those that were assigned to demonstrate with me, thanks for not causing any stress.

To my friends, Neil aka "Shaggy", Jenni, Mairéad, Helen, Johan, Carol, Davnat and Richard. Also to the old gang from the class of '98 – Caroline, Eimer, Jenni (again), Niall, and Siobhán.

To Sandra, for nagging me constantly, for making my life less of a misery and for putting up with me.

Finally, to my family. A big thanks to Mam & Dad for absolutely everything, to Aidan even though he is a royal pain in the ass and to Ciara, for being nice.

Abbreviations

ADDP – 1,1'-(azodicarbonyl)dipiperdine

BET – Back electron transfer

CE – Counter electrode

CV – Cyclic voltammetry

DEAD – Diethylazodicarboxylate

DHTD – 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione

DIAD – Diisopropylazodicarboxylate

DMB – 2,3-dimethyl-2-butene

DMF – Dimethylformamide

HMBC – Heteronuclear multiple bond correlation

HMQC – Heteronuclear multiple quantum correlation

IR – Infra red

ISC – Intersystem crossing

LSV – Linear sweep voltammetry

NMP – *N*-methylphthalimide

NMR – Nuclear magnetic resonance

PET – Photoinduced electron transfer

RE – Reference electrode

SCE – saturated calomel electrode

SET – Single electron transfer

TBP – Tributylphosphine

TCNQ – Tetracyanoquinodimethane

THF – Tetrahydrofuran

TLC – Thin layer chromatography

TMAD – N,N,N',N'-tetramethylazodicarboxamide

TMS – Trimethyl silyl

TPP – triphenylphosphine

WE – Working electrode

Abstract

This thesis will begin with a brief introduction of the photochemistry of the carbonyl group, followed by a detailed literature survey concerning the *intra* and *inter*-molecular photochemical reactions of the phthalimide system.

It will also be shown that *N*-(2-hydroxyphenyl)phthalimide and *N*-(2-aminophenyl)phthalimide do not behave in the same photochemical manner as the analogous *N*-(2-methylphenyl)phthalimide and *N*-(2-ethylphenyl)phthalimide, which both undergo δ-hydrogen abstraction forming a tetracyclic system, as well as a photoreduced product. However, *N*-(2-hydroxyphenyl)phthalimide does undergo an interesting *intra*-molecular thermal process to yield 2-phenylbenzoxazole, while *N*-(2-aminophenyl)phthalimide also undergoes an *intra*-molecular thermal cyclisation to a tetra cyclic system, benzo[4,5]imidazo[2,1-a]isoindol-11-one, which is believed is initiated by an *inter*-molecular reaction. It will also show that esters of *N*-(2-hydroxyphenyl)phthalimide and amides of *N*-(2-aminophenyl)phthalimide are photochemically inert.

This thesis will describe the application of the Mitsunobu reaction for the synthesis and identification of *N*-alkyl derivatives of 3-dicyanomethylene-2,3-dihydroisoindol-1-one. These derivatives are structural analogues of *N*-substituted phthalimides and also of benzo-tetracycnoquinodimethane. Electrochemical studies with some selected members of this series will show that, like the phthalimides and benzo-tetracyanoquinodimethane, these compounds are good electron acceptors. The photochemistry of this family of compounds has also been investigated.

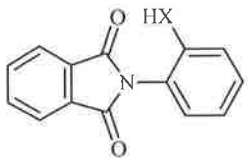
It will also show that the Mitsunobu reaction with isopropyl alcohol give products from both *N*-alkylation and *O*-alkylation. Molecular modelling calculations are in line with this observeration.

Chapter 1: Photochemistry of the Carbonyl Group

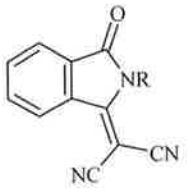
1.1 Introduction

It has long been accepted that chemical change can be effected using ultraviolet (200–400nm) and visible light (400–750nm). An ever-increasing number of investigations since the 1960s has shown that many novel and synthetically useful reactions including dimerisation, cycloaddition, rearrangement, oxidation, reduction, substitution and elimination may be resultant upon the absorption of light by organic molecules. This development in synthetic organic photochemistry has been aided by the understanding that many photochemical reactions occur quite cleanly to give good yields of the desired products. In addition, the photochemical experiments can often be carried out much more simply than many standard thermal chemical reactions.[1]

The work contained in this thesis was initially aimed at the synthesis and investigation of *N*-substituted phthalimides of the type (A), and later at the synthesis and investigation of dicyanomethylene compounds of the type (B). This family of compounds is structurally analogous to *N*-substituted phthalimides (A), differing only in the replacement of a carbonyl group with a dicyanomethylene group.



A



B

Figure 1

This introduction will contain a brief discussion of the photochemistry of the carbonyl chromophore, including some general photophysical aspects and the most important photochemical reactions. Much of the photoreactions of the phthalimide system are analogous with the photoreactions of simple carbonyl systems. This will be followed by a comprehensive literature review of phthalimide photochemistry from the early 1970s, through the 1980s and on to the present day. Kanaoka[2] in 1978, Mazzocchi[3] in 1982, Yoon and Mariano[4] in 2001 and more recently McDermott, Yoo and Oelgemöller,[5] have published reviews of the photochemistry of the phthalimide system. Several other groups are also conducting research into the

photoreactions of phthalimides, including those of Griesbeck[6] and Suau.[7] As much of the work published since complements earlier publications, this review will include publications discussed by both Kanaoka and Mazzocchi.

1.2 Photochemistry of the carbonyl group[8]

The total energy of a molecule is the sum of its electronic, vibrational, rotational and translational energies. While the translational energy increases continuously with the temperature of the system, the other three energy states are quantised and the excitation to higher energy levels requires the absorption of discrete amounts of energy (quanta), which can be supplied by electromagnetic radiation. The amount of energy associated with such radiation depends on its wavelength, the longer the wavelength the smaller the energy. Excitation of a molecule to a higher rotational and vibrational energy level can occur on absorption of radiation in the far infrared and is associated with relatively small increases in the energy of the molecule (~ 0.5 – 42kJmol^{-1}). Absorption of ultraviolet and visible radiation by a molecule is associated with an increase in energy in the range 600–160kJmol^{-1} and results in the excitation of its valence electrons to higher energy levels. The energy associated with a photon of radiation in the ultraviolet region is of the same order as the bond energies of many of the bonds present in organic molecules (C-H, 410kJmol^{-1}). It is thus not surprising that absorption of light in this region can result in chemical reactions and that the reactions of molecules in such electronically excited states are often quite novel.[1]

Excitation of a carbonyl group to a higher energy level, involves the promotion of an electron from a bonding (σ or π) or a non-bonding (n) orbital to an antibonding (σ^* or π^*) orbital. There are four types of transitions possible and the energy associated with each decreases in the order $\sigma\rightarrow\sigma^* > n\rightarrow\sigma^* > \pi\rightarrow\pi^* \approx n\rightarrow\pi^*$.[1]

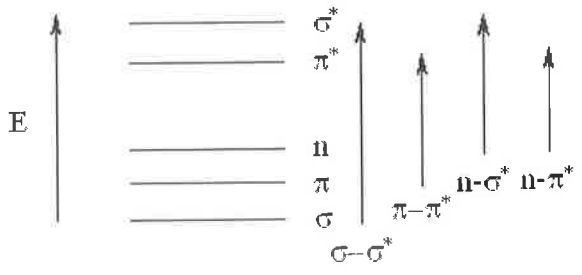


Figure 2: Four transition types of C=O and their associated energies.[1]

The $\sigma \rightarrow \sigma^*$ and $n \rightarrow \sigma^*$ transitions are of little consequence in organic photochemistry as they take place in the far UV (< 200nm), a region which is not readily accessible in practice due to the absorption of radiation by atmospheric oxygen in this region. However, the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions occur in the ultraviolet region and are accountable for the substantial majority of useful photochemical reactions.

In simple ketones, for example, the $n \rightarrow \pi^*$ transition occurs at ~ 270nm with an associated energy of 443.1kJmol^{-1}, while the $\pi \rightarrow \pi^*$ transition of butadiene occurs at 217nm with an associated energy of 551.5kJmol^{-1}. While the overall magnitude of the energy required to effect these electron transitions explains why bonds may be broken during irradiation, a more detailed consideration of these electronically excited states is necessary to understand the various possible ways in which the absorbed energy is dissipated. In particular the importance of the concept of singlet and triplet states must be considered.[1]

Most organic molecules have an even number of electrons and are spin paired. Energy states with antiparallel electrons are called singlet (S) states. They have no net electronic magnetic moment and hence only have one possible energy state in a magnetic field. The ground state of the molecule is referred to as S_0 and the higher excited states as S_1, S_2, S_3, etc. Inversion of the spin of one electron results in the formation of a different electronic state having two unpaired, parallel electrons. This is referred to as a triplet (T) state, which has a net electronic magnetic moment and therefore has three possible energy states in a magnetic field. For each possible singlet state (S_x), there is a correspondingly lower energy triplet state (T_x). Transitions between states of the same multiplicity are allowed, while transitions between states of different multiplicity are formally forbidden.[1]

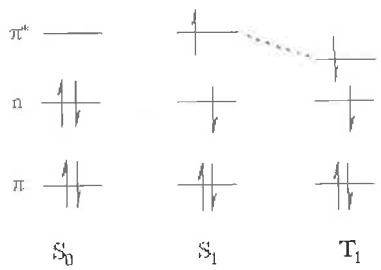


Figure 3: The n, π* excitation of a carbonyl chromophore leading to formation of S_1 and T_1 by intersystem crossing, showing the ground state and lowest singlet and triplet states.

Compounds containing the carbonyl group are among the most widely studied in organic photochemistry. They are capable of forming $\pi \rightarrow \pi^*$ and also $n \rightarrow \pi^*$ excited states, the former common to compounds with C=C such as ethylene while the latter are common to molecules containing heteroatoms such as sulphur, nitrogen and oxygen. Both transitions give rise to population of the singlet excited state (S_1). Inter system crossing (ISC), which leads to the triplet excited state (T_1), is common for all ketones and aldehydes, and is particularly efficient and rapid for aromatic carbonyl compounds. However $n \rightarrow \pi^*$ transitions are of lower energy and hence occur at longer wavelength than do the corresponding $\pi \rightarrow \pi^*$ transitions for the same chromophore.

Aldehydes and ketones are the favoured carbonyl compounds for study as they are photochemically more reactive than carboxylic acids, esters or amides. This is primarily due to the fact that their longest wavelength absorptions are in a readily accessible region of the electromagnetic spectrum. The λ_{max} for transition of a non bonding n electron on oxygen to an antibonding π^* orbital of the carbonyl group ($n \rightarrow \pi^*$) for simple aliphatic aldehydes and ketones are in the region $\geq$ 280-300 nm, while λ_{max} for carboxylic acids and derivatives $\geq$ 200-220 nm. Quantum mechanics tells us that $n \rightarrow \pi^*$ transitions are symmetry forbidden, their intensities are weak with extinction coefficients in the region of 15-60 $dm^3mol^{-1}cm^{-1}$.[9] This excitation results in an extensive change brought about by the redistribution of electrons around the carbonyl group. In the ground state, the carbonyl bond is polarised and is therefore susceptible to nucleophilic attack at carbon, however in the first excited state (S_1) there is an unpaired electron in a p-type orbital on oxygen and another unpaired electron in a π^* antibonding orbital. The result of this is that oxygen becomes electron deficient, while the carbon becomes somewhat electron rich and can therefore exhibit nucleophilic behaviour.[9] The electrons in the $n \rightarrow \pi^*$ triplet state, having parallel spin and being as far removed from each other as possible, impart upon the carbonyl chromophore chemical and physical characteristics of a diradical. Consequently, the $n \rightarrow \pi^*$ triplet carbonyl is similar to alkoxy radicals with respect to hydrogen abstraction reactions, α–cleavage reactions and attack at carbon-carbon multiple bonds.[9]

The energy difference between the singlet and triplet $n\rightarrow\pi^*$ states in aliphatic ketones is small in comparison to alkenes, but in some cases the rate of intersystem crossing ($k_{isc} \cong 10^8 s^{-1}$) is slow enough to allow chemical reactions of the $n\rightarrow\pi^*$ singlet state to occur. However, since the energy of and electronic distribution in the two states are similar the same type of process may occur from singlet or triplet states or a mixture of the two.[9]

In conjugated systems, such as aryl ketones and enones, the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ singlet excited states are lower in energy, therefore their associated absorptions appear at longer wavelengths compared to those in the isolated chromophore. Consequently, for certain unsaturated compounds, the $n\rightarrow\pi^*$ states are not always the lowest in energy due to delocalisation on the individual π and π^* bonds. For compounds such as acyl naphthalenes, the lowest triplet state is definitely $\pi\rightarrow\pi^*$ in nature, for others such as *p*-methoxyphenyl ketones the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ triplet states are very close in energy and because of the differences in the reactions of these two triplet states, there is a profound effect on the observed photochemistry.

1.3 The Jablonski Diagram

The Jablonski diagram is a pictorial representation of the energy transitions that result from the simple absorption by a molecule of ultraviolet radiation.

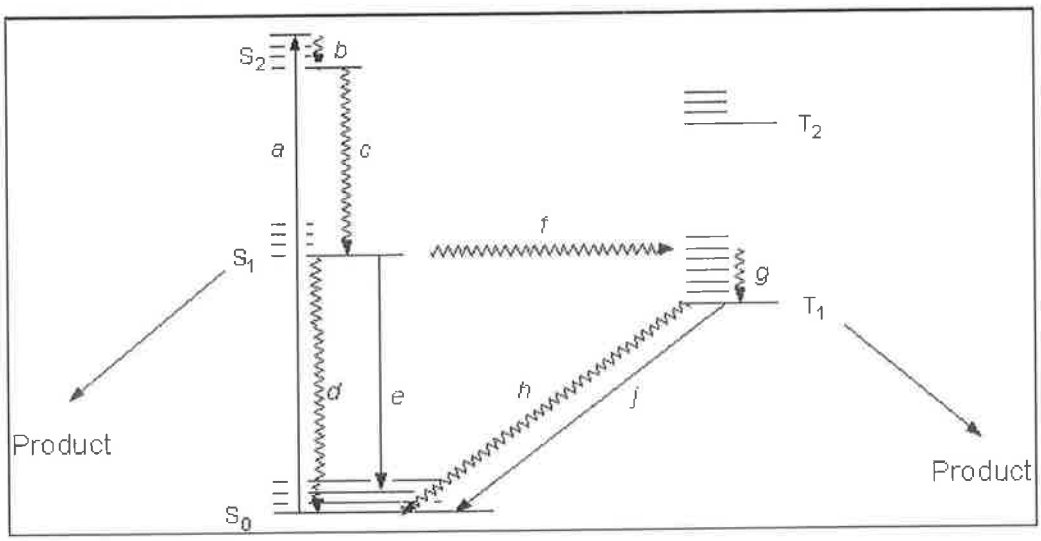


Figure 4: The Jablonski diagram[10]

Radiative transition Non-radiative transition

a Transition to upper vibrational level of S_2.

b Vibrational cascade.

c Internal conversion to upper vibrational level of S_1 followed by rapid vibrational cascade.

d Internal conversion to upper vibrational level of S_0 followed by rapid vibrational cascade.

e Fluorescence from S_1.

f Intersystem crossing to upper vibrational level of T_1.

g Vibrational cascade.

h Intersystem crossing to upper vibrational level of S_0 followed by vibrational cascade.

i Phosphorescence from T_1.

The molecule is excited to one of the excited singlet electronic states S_1 or S_2, and through a series of radiationless transitions, or internal conversions, it converts to the excited singlet state from which any resulting transitions usually occur. The whole excitation process takes less than 10^{-12} s. From the first excited singlet state one of five processes may occur to the molecule:

1. Vibrational relaxation - initially excess vibrational energy, in the form of vibrations and rotations, is rapidly lost, $< 10^{-12}$ s, by radiationless processes, such as collisions with solvent molecules. This means that most excited state molecules never emit any energy because in liquid samples the solvent molecules that are present "quench" the energy before other deactivation processes can occur.
2. Fluorescence – observed when photon emission occurs between states of the same spin state. For example the radiative decay of S_1 to S_0 requires about 10^{-9}s.
3. Intersystem crossing (ISC) – the conversion to the lower energy triplet (T_1) by spin inversion, a radiationless transition between different spin states. Although this is a formally forbidden process, it can occur with very high efficiency when the energy difference between the two states is small.[1] ISC is most notable in carbonyl and aromatic compounds and occurs with 100 % efficiency in the case of benzophenone.
4. Internal conversion – is the thermal dissipation of energy to surrounding molecules, it is a radiationless transition between energy states of the same spin state. For example from S_1 to S_0, with the energy being dissipated to solvent.

5. Chemical change – results in products differing from irradiated material.

If formed from S_1 by ISC, process (3), the triplet excited state (T_1) of the molecule may, in turn, undergo any one of a number of physical or chemical changes:

6. Phosphorescence – emission of light from the excited molecule may occur with return to the ground state, but at longer wavelength than fluorescence. This process is formally forbidden as spin inversion is involved, it does eventually occur with the important consequence that the T_1 state has a much longer lifetime than the S_1 state.[1]
7. The species may decay by internal conversion.
8. Chemical change – results in products differing from irradiated material. The longer lifetime of the T_1 state compared to the S_1 state means that chemical change is a much more important feature, and the T_1 state is of prime importance in synthetic photochemistry.[1]
9. Energy transfer to a neighbouring molecule may occur so that the acceptor molecule is promoted to a triplet state of either equal or lower energy than the donor triplet species, which itself undergoes spin inversion and returns to the ground state S_0. Such a transfer will occur only if the acceptor molecule has an available lower energy excited level.[1]

It is more likely that fluorescence will occur than phosphorescence. The lifetimes of fluorescent states are extremely short, between 10^{-5} and 10^{-8} seconds. The lifetimes of phosphorescent states are longer, ranging from 10^{-4} seconds to minutes and in some cases hours.[11]

There are two types of photochemical processes which lead to these various transitions and, therefore, to a realisation of the synthetic possibilities of processes 8 and 9 above.[1]

a. Direct photolysis – where the incident radiation is directly absorbed by the substrate X, which is then promoted to the excited state X^* which then loses its energy by the process outlined in 8 above.

$$X \xrightarrow{h\upsilon} X^* \longrightarrow \text{products}$$

Figure 5: Direct photolysis.[1]

b. Indirect or sensitised photolysis – where a photo-excited state donor molecule D^* in the triplet state, referred to as a sensitiser and produced by absorption of the incident radiation, transfers its energy to the substrate X which is thereby promoted to an excited state, 9 above. In this process the sensitiser returns to the ground state and may be further excited by incident radiation.

$$D \xrightarrow{h\upsilon} D^*$$

$$D^* + X \longrightarrow D + X^*$$

$$X^* \longrightarrow \text{products}$$

Figure 6: Sensitisation[1]

Many compounds, such as alkenes, do not undergo intersystem crossing from the singlet state to the synthetically more useful triplet state as the energy difference between the two states is large. However, provided that the energy of the triplet state of the sensitiser molecule is about 21 $kJmol^{-1}$ greater than that of the triplet state of the substrate,[9] energy may be transferred to provide excited molecules in the triplet state which may then undergo chemical reaction. The procedure is useful for populating triplet states of a compound whose singlet state is in an inaccessible part of the ultraviolet spectrum, < 200 nm.[1]

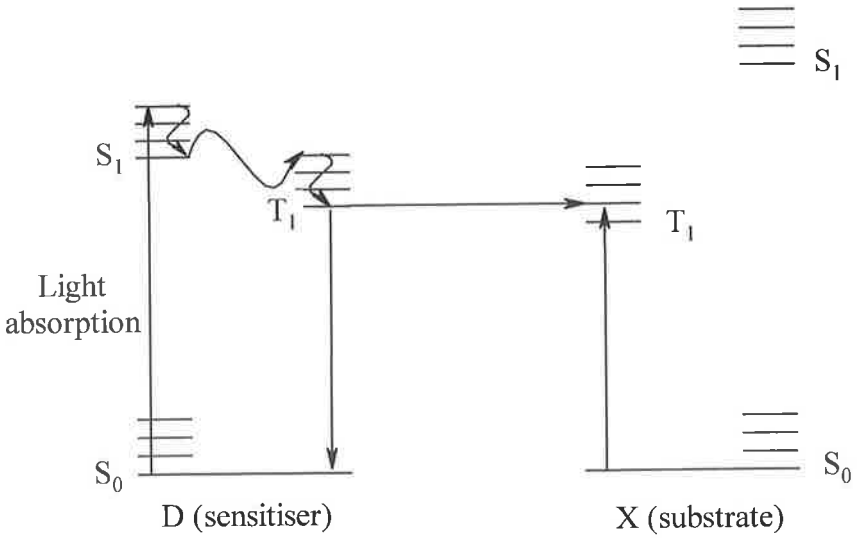


Figure 7: The sensitising process.

1.4 Photoreactions of the carbonyl group.

1.4.1 α–Cleavage reactions (Norrish Type I process)

As was mentioned earlier, the reactions of the $n\rightarrow\pi^*$ excited states of carbonyl compounds can be likened to those of alkoxy radicals and in particular may undergo cleavage of the α bond. The α–cleavage of ketones was first described by Ciamician and Silber in 1907. It is generally known as the Norrish Type I process after the originator of the mechanistic studies of this reaction.[9] One of the earliest photochemical systems studied was the photolysis of acetone, which from the n, π^* state yields alkyl and acyl radicals which undergo their typical thermal reactions. This process is known as a Norrish type I reaction. α–cleavage is a fundamental reaction of electronically excited carbonyl compounds. Upon α–cleavage, aliphatic acyclic ketones yield both alkyl and acyl radicals, whereas for aliphatic aldehydes, the C-H bond undergoes preferential homolytic cleavage. Diaryl ketones do not fragment since their excitation energies are too low for there to be sufficient energy, however they may hydrogen abstract, which will be discussed later.

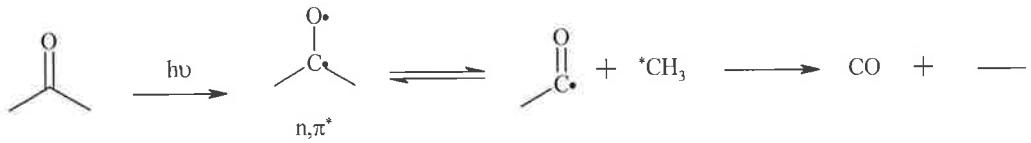


Figure 8: Norrish type I process.

The occurrence of this process can be understood in terms of the weakening of the α bond by overlap with the vacant n orbital. The α–cleavage reaction is induced by excitation within the $n\rightarrow\pi^*$ absorption band of the ketone, and for most aliphatic ketones, the triplet state will be considerably more reactive than the corresponding singlet state in the α–cleavage reaction. All of the reactions of aryl ketones are due to their triplet state as they have a high intersystem crossing efficiency. The presence of β, γ unsaturation in ketones aids α–cleavage due to the allylic stabilisation in the allyl radical.[9]

Like acyclic ketones, $n\rightarrow\pi^*$ excitation of cyclic ketones leads to α–cleavage, with the triplet excited state being significantly more reactive than the singlet excited state. However, the α–cleavage in cyclobutanone arises mainly from the $n\rightarrow\pi^*$ singlet state. When the two α bonds are not identical, it is the weaker bond which

cleaves preferentially forming the more stable radicals. Radical stability exerts a measure of control on the reactivity of cyclic ketones. Cleavage occurs preferentially, if not exclusively, at the α carbon bearing the greater number of alkyl substituents (Figure 9).[9]

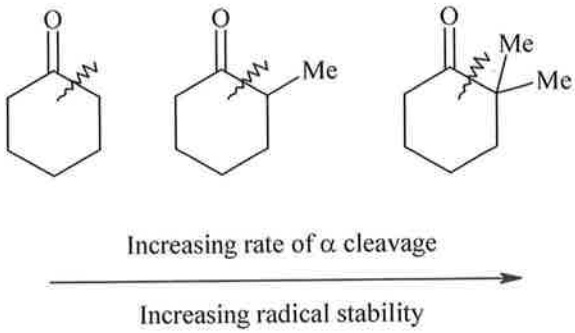


Figure 9: Relationship between increasing rate of α–cleavage and radical stability.

Four reaction pathways are available from an α–cleavage reaction. The resulting acyl-alkyl diradicals can recombine, forming the original compound, they can undergo a second α–cleavage reaction, resulting in the loss of carbon monoxide (decarbonylation), internal disproportionation and rearrangement to an oxacarbene.

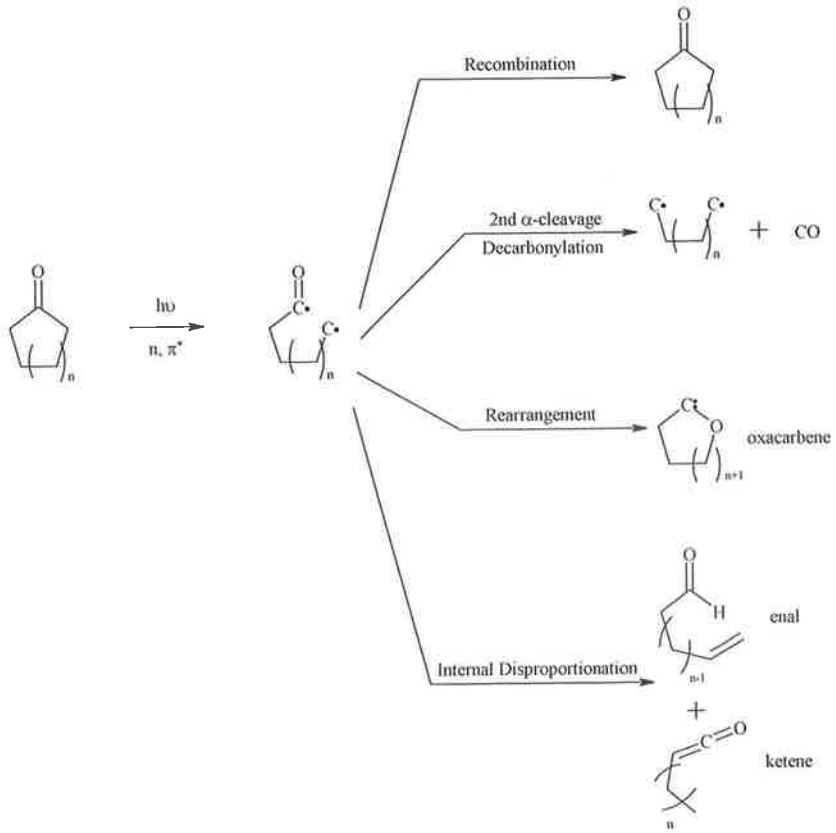


Figure 10: Pathways resulting from α–cleavage

As the energy of the absorbed quantum increases, the selectivity between the two processes (i) and (ii) decreases considerably. Following the initial absorption of light and depending on the energy of the absorbed quantum, various fractions of the acyl radicals may also be vibrationally excited (hot) and may decompose rapidly into an alkyl radical and carbon monoxide (Figure 11).

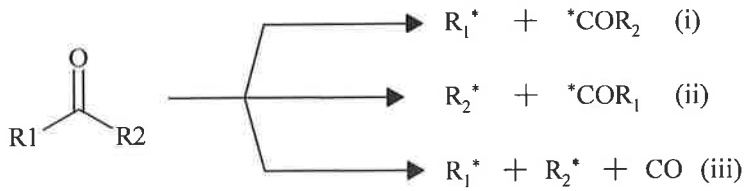


Figure 11: α-cleavage of a ketone

The dissociation of acyl radicals to alkyl radicals and carbon monoxide is very temperature dependent, with acyl radicals being practically completely dissociated at temperatures above 120°C. Other simple acyl radicals are less stable and completely dissociated at accordingly lower temperatures.

The formation of products by the α–cleavage reaction is not a major reaction in solution at room temperature because the initially formed radicals are produced in a cage of solvent molecules and a major secondary process is recombination to reform the ground state starting material. Indeed the reaction is usually only observed when the acyl group has an adjacent stabilising substituent present, for example R_3CCO and $PhCH_2CO$ radicals, to promote a second α–cleavage. Cyclic ketones undergo α–cleavage to give biradical species on photolysis in gas or solution phase. For these cyclic systems the reactivity pattern of ring opening follows that expected for relief of ring strain.

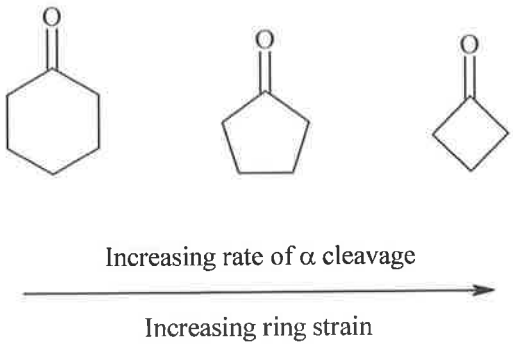


Figure 12: Relationship between increasing rate of α–cleavage and ring strain.

1.4.2 Hydrogen abstraction (Norrish Type II photoreactions)

Hydrogen abstraction is the most important pathway that competes with the α–cleavage reaction. An excited carbonyl compound may bring about an inter-molecular abstraction (by abstracting a hydrogen atom from a second molecule, resulting in a radical pair); or intra-molecular abstraction (when a six membered transition state is available, possibly forming a cyclobutanol system). For the inter-molecular abstraction, the efficiency of the process is strongly dependent on the strength of the C-H bond in the hydrogen donor molecule, while the intra-molecular reaction depends on the molecular conformation. Hydrogen abstraction efficiency is also affected by the energy and the electronic configuration of the excited carbonyl.[9]

1.4.2.1 Inter-molecular Hydrogen Abstraction

In aliphatic ketones, the process can occur from singlet or triplet states, while the process is solely from the triplet state in the case of aromatic ketones. However, the relative reactivity of the singlet excited species in the inter-molecular reaction is not always clear. Inter-molecular hydrogen abstraction occurs efficiently from carbonyls with a lowest $n \rightarrow \pi^*$ triplet excited state. The efficiency of those carbonyls with a lowest $\pi \rightarrow \pi^*$ triplet excited states is very low, or inter-molecular hydrogen abstraction does not occur, due to the relatively high electron density on the oxygen atom in the $\pi \rightarrow \pi^*$ state.[9]

A radical pair results from inter-molecular hydrogen abstraction. This radical pair may achieve stability by several competing pathways: radical combination resulting in addition to the C=O bond, dimerisation of the primary radical to form a pinacol or abstraction of another hydrogen resulting in reduction, forming a secondary alcohol in the process.[9]

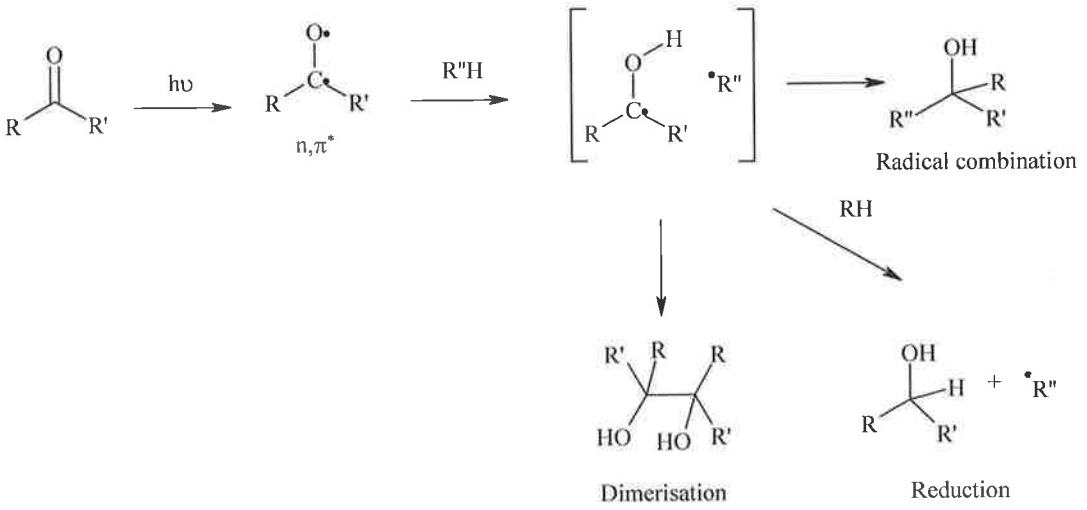


Figure 13: Intermolecular hydrogen abstraction outcomes

The initial step of the mechanism involves either the transfer of an electron or hydrogen to the oxygen atom of the carbonyl excited state from a donor molecule which may be solvent, an added reagent or a ground state molecule of reactant. For electron transfer to take place the donor molecule must have a low ionisation potential, 9 eV or less. For example, electron transfer occurs to excited carbonyl compounds from amines or sulphides, but not from alcohols. These reactions take place by initial electron transfer from the donor to the excited state carbonyl compound, which forms a radical anion/radical cation pair.

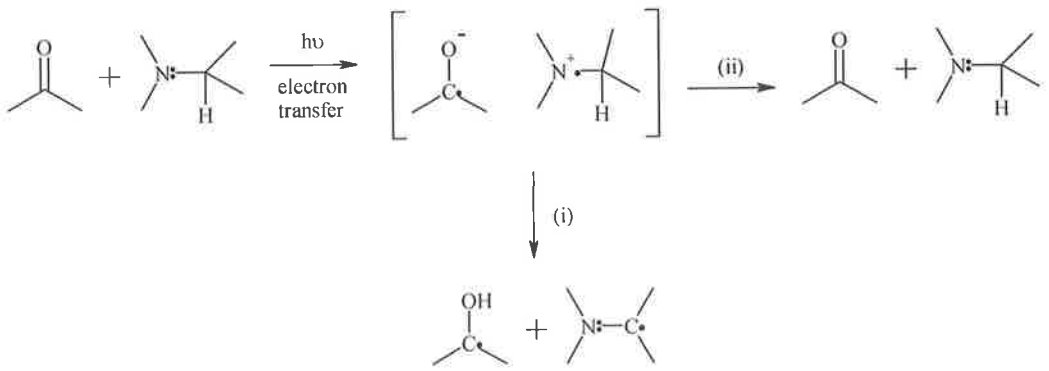


Figure 14: Electron transfer outcomes

This is followed by transfer of a proton and formation of radicals, path (i), or by back electron transfer to form starting materials, path (ii), (Figure 14). An example of this is the photoreduction of fluorenone by triethylamine. Fluorenone is not photoreduced

by aliphatic alcohols or by cyclohexane. This marked difference from benzophenone reflects its low triplet energy, 53 compared to 69 kcal/mol and possibly the lower inherent reactivity of a $\pi \rightarrow \pi^*$, than an $n \rightarrow \pi^*$ triplet.[12] The process follows an electron transfer mechanism with fluorenone pinacol and amine addition product being obtained as products.

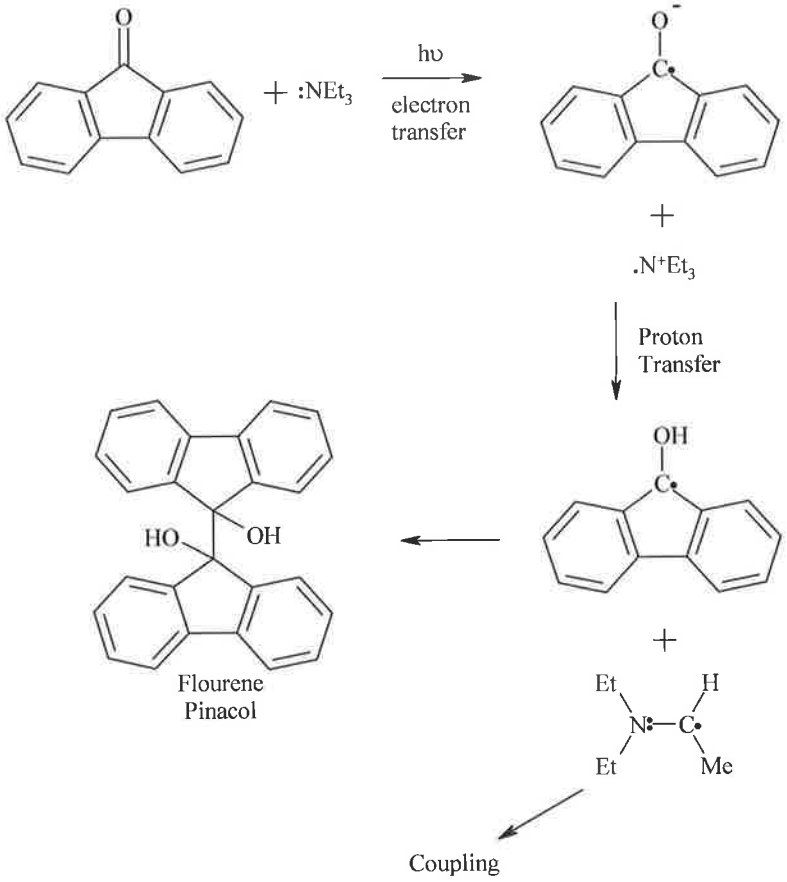


Figure 15: Photoreduction of fluorenone by triethylamine

One of the earliest known hydrogen abstraction photoreactions is the photo-pinacolisation of benzophenone. Alcohols are commonly used as hydrogen donors as are ethers and alkylbenzenes. Alkylbenzenes can also participate in the photoreduction of excited carbonyl species by way of electron transfer mechanism. The initially formed ketyl radical can form products through a number of different routes and the favoured path depends on the structure of the radical species, the concentration of reagents, the hydrogen donor power of the reducing agent and on the temperature. The reaction is so efficient that under certain conditions benzopinacol can be obtained from benzophenone in up to 90% yield.[13]

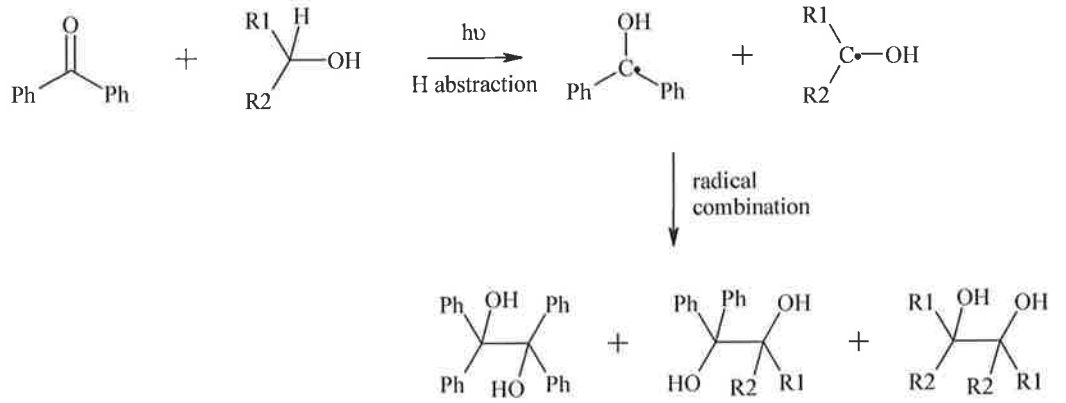


Figure 16: Photoreduction of benzophenone

1.4.2.2 Intra-molecular Hydrogen Abstraction

Molecules containing the carbonyl chromophore in which the molecular structure allows a close approach between the excited state carbonyl group and a hydrogen atom attached to an sp^3 hybridised carbon atom can undergo intramolecular H-abstraction. This process proceeds via a chair like six membered transition and it is a γ hydrogen that is favoured for extraction. The biradical that is formed can then undergo cyclisation to form a cyclobutanol derivative, via Yang cyclisation, or a β–cleavage to an enol and alkene, via Norrish type II cleavage. The conformation of the initially formed biradical dictates which process is favoured. If the orbitals of the radical centres can overlap (path (i)) a cyclobutanol is formed but if the orbitals of the radical centres are parallel to the β-bond (path (ii)) they will participate in the formation of two double bonds.[14] If there are no γ hydrogens available, then intramolecular hydrogen abstraction will occur from other positions.

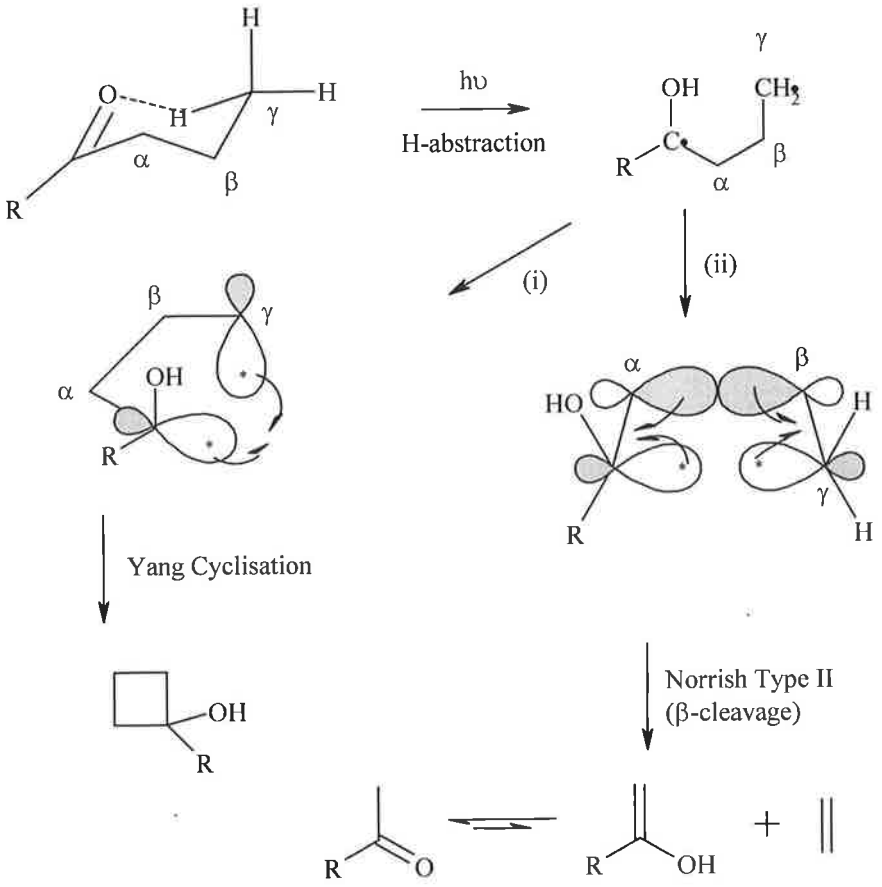


Figure 17: Norrish Type II photoreaction.

1.4.3 Photocycloaddition (Oxetane formation)

On irradiation in the presence of alkenes, dienes or alkynes, carbonyl compounds undergo cycloaddition reactions to give four membered oxygen heterocycles. This $2\pi + 2\pi$ cycloaddition is commonly known as the Paternò-Büchi reaction. The reaction itself is very general and there are many known examples. One example of this is the reaction of benzophenone with *iso*-butene to give (E) and (F) in a ratio of 9:1.[Error! Bookmark not defined.] The reactions are generally thought to proceed from an attack of a $n \rightarrow \pi^*$ singlet or triplet state of the carbonyl compound on the ground state of the alkene to yield the 1,4-diradicals (C) and (D), which subsequently close to yield the observed products.

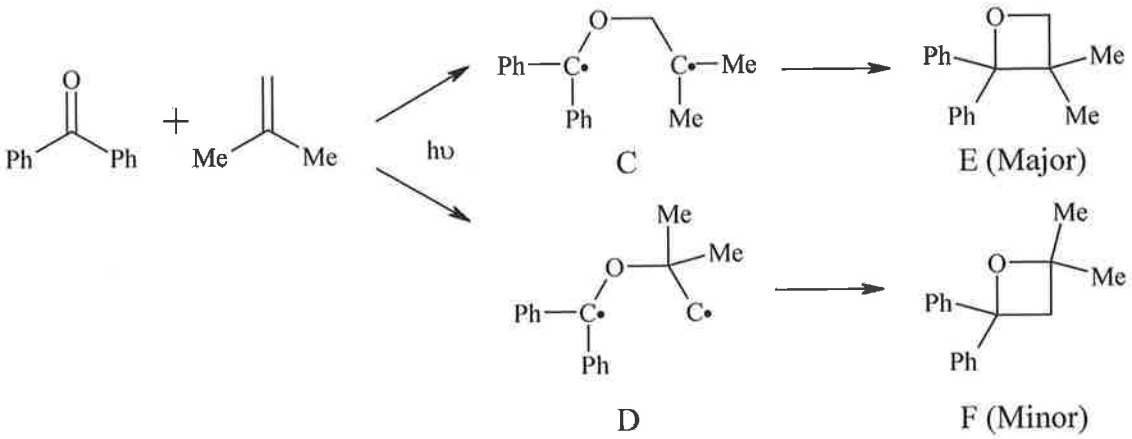


Figure 18: Mechanism of oxetane formation

The more stable 1,4-biradical (C) is formed preferentially. The presence of the two electron donating methyl groups stabilise the radical centre more effectively than two hydrogens in (D), reaulting in the formation of (E) as the major product.

Arnold[15] has shown that the reaction between benzophenone and *cis*-or *trans*-but-2-ene gives a mixture of (G) and (H) in a ratio of 1:1. The biradical intermediate is sufficiently long lived for bond rotation to occur, giving a mixture of products.[16] The reaction of benzophenone with *cis*-but-2-ene is shown (Figure 19).

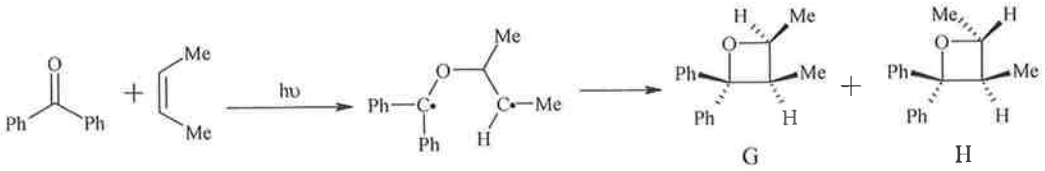
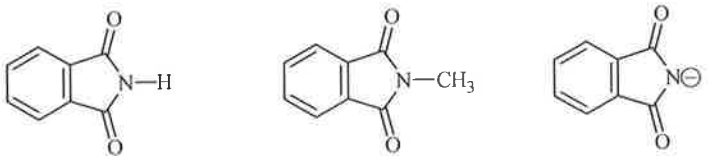


Figure 19: The reaction of benzophenone with *cis*-but-2-ene

Chapter 2: Photochemical reactions of the phthalimide system.

2.1 Introduction

Phthalimide (**1**) consists of a benzene ring fused to a strained five-membered ring containing two carbonyl groups and nitrogen bonded to hydrogen. *N*-Substituted phthalimides will be the most common types discussed, the simplest of these is *N*–methylphthalimide (NMP) (**2**) (Figure 20), although some aromatic substitution is also discussed. The photoreactions of the phthalimide anion (**3**) will also be covered.



1 **2** **3**

Figure 20: Phthalimide (1), N-methylphthalimide (2), Phthalimide anion (3)

In *N*-substituted phthalimides, the carbonyl groups, as part of the strained five-membered ring system, are activated.[17] The phthalimide system shows behaviour resembling that of simple carbonyl systems.[17b] Phthalimide is a symmetrical molecule, however the presence of substituents on the aromatic ring removes this symmetry and can greatly alter any photoreactions that the molecule may undergo.

Since the pioneering work of Kanaoka and coworkers[17] on the photochemistry of the phthalimide system,[2,18] a variety of applications in terms of synthetic organic photochemistry have been developed. Various aspects of the photochemistry of phthalimides have been reviewed over the last 25 years.[3,19] In recent years, there has been a resurgence in interest in the photochemical reactions of phthalimides.[4,7]

N-Substituted phthalimides are known to undergo a number of *inter* and *intra* molecular photochemical reactions (Figure 21).

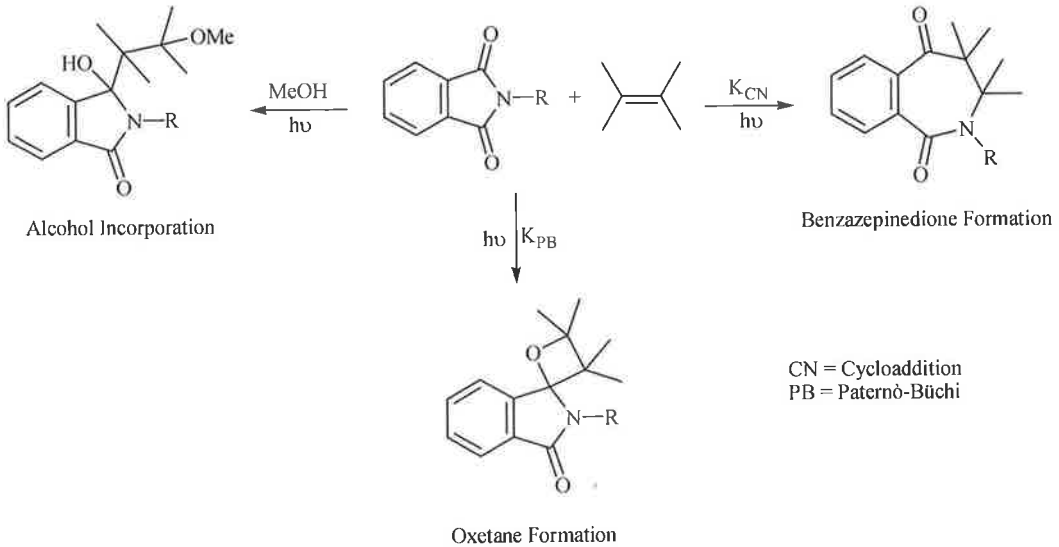
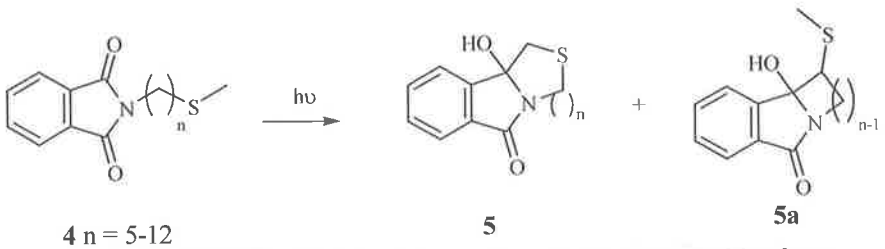


Figure 21: Some inter molecular photochemical reactions of phthalimides.

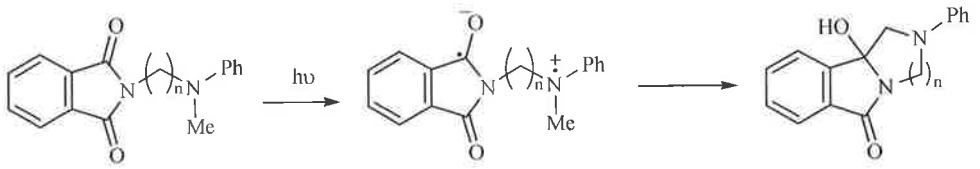
It has been shown that, like their aromatic ketone counterparts, they partake in photo-induced hydrogen abstraction; in addition, irradiation of *N*–alkylphthalimides leads to preferential γ–hydrogen abstraction as part of *N*–heterocyclic ring-forming reactions.[17c]

However, phthalimides that contain a good electron donating heteroatom such as sulphur (**4**)[20] (Figure 22) or nitrogen (**6**) (Figure 23) in their *N*-tethers do not adhere to the preference for γ–hydrogen abstraction in their excited states. Instead, phthalimides of the type (**4**) and (**6**) participate in photo induced *inter* and *intra* molecular single electron transfer (SET) reactions, forming (**5**) and (**8**) respectively. There are many examples of the photoreactions of the sulphur containing phthalimides, and these will be discussed later.



4 n = 5-12 **5** **5a**

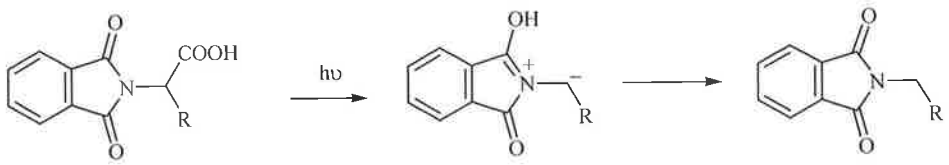
Figure 22: Photochemical transformation of phthalimido-thioethers



6 n = 5-12 **7** **8**

Figure 23: Photochemical transformation of phthalimido-amines

N–Substituted phthalimides have also been shown to undergo single electron transfer[20] and olefin-cycloaddition,[21] while irradiation in the presence of certain alkenes yields oxetanes (Figure 21).[22] It is also been shown that *N*–phthalimido–α–amino acids (**9**) undergo photo-decarboxylation reactions to generate *N*–alkylphthalimides (**11**) (Figure 24).[20b]



9 **10** **11**

Figure 24: Photodecarboxylation of N-phthalimido-α-amino acids.

A Japanese team headed by Kanaoka[17] first reported the photochemistry of the phthalimide system in 1972. Their preliminary results indicated that isoprene significantly quenched a reaction involving a substituted phthalimide. This suggested an excited triplet state intermediate. They presumed that the reaction involved an intramolecular γ–hydrogen abstraction by the excited amide carbonyl, effectively a 1,5–hydrogen transfer (Norrish type II photo-elimination).

Some years later, Mazzocchi[22b] carried out quenching studies on phthalimides. He discovered that normal photochemical quenching was not occurring but that the phthalimides were efficiently reacting with the *cis*-piperylene quencher. This unexpected result prompted further investigation into the reaction of phthalimides using various vinylic systems. It was concluded that in the presence of certain dienes, *N*-methylphthalimide underwent a novel photochemical addition reaction to give benzazepinediones, which corresponds to an addition of the diene across the C(O)-N bond of the imide (Figure 25).

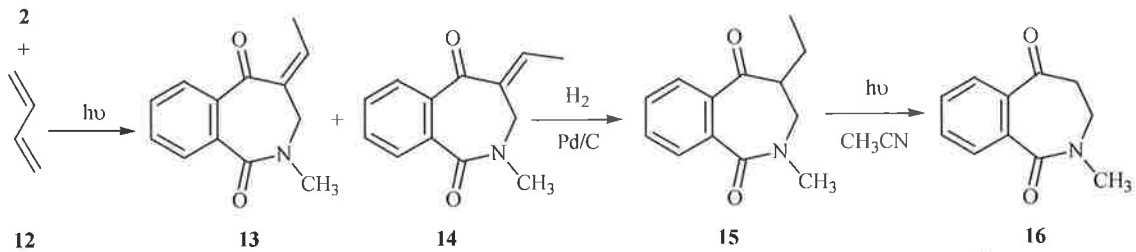


Figure 25: Reaction of NMP and 1,3-butadiene to give a benzazepinedione pair 13 and 14 and follow up reactions.

The reaction has some generality in that it occurs for selected dienes, alkenes, vinyl ethers, vinyl esters and an allene. However, the reaction does not take place with electron-poor alkenes such as acrylonitrile and also fails with very electron-rich alkenes such as 2,3–dimethyl–2–butene. In the latter case, failure to react is attributed to a competing electron-transfer reaction.[22c]

This review will concentrate on developments in phthalimide photochemistry and will pay particular attention to the area of photochemical electron transfer.

2.2 Photophysical and electrochemical properties of phthalimides

The photophysical[23] and electrochemical[24] properties of phthalimides have been intensively studied. In acetonitrile, *N*–alkylphthalimides show relatively unstructured UV absorption spectra with absorption maxima around 235 nm (π,π^*) and 290 nm (n,π^*), respectively.[23a] At room temperature, they exhibit weak fluorescence with low quantum yields ($\Phi_f < 1\times10^{-3}$) in ethanol or acetonitrile.[23b] Under oxygen free conditions, *N*–alkylphthalimides show a broad structureless phosphorescence centred around 450 nm with quantum yields between $\Phi_p = 0.4\text{-}0.7$ and triplet lifetimes between $\tau_p = 0.7\text{-}1.04$ s (at -196°C).[23a-c] The order of the excited states of phthalimides has been controversially discussed.[19b] The level of the (n,π^*) triplet state is either slightly below or above the lowest singlet state, which accounts for the high intersystem crossing rates.

N–Methylphthalimide is reversibly reduced to the corresponding radical anion at ca. -1.35 V in DMF,[24a,b] and at ca. -1.5 V in acetonitrile (*vs.* SCE),[24b] respectively. The presence of a hydrogen donor site in the side chain has a dramatic effect on the redox

properties.[25] In particular, anodically shifted pre-waves emerge in the cyclic voltammograms, which have been assigned to *intra-* and *intermolecular* hydrogen bonds to the phthalimide electrophore.

Due to their favourable photophysical and electrochemical properties, phthalimides are superior substrates for photoinduced electron transfer (PET) reactions.[25a-c] The limiting maximum oxidation potential of the electron donor depends on the excited state of the phthalimide electron acceptor,[23a] and can be estimated by the Rehm-Weller equation.[26] If the first excited singlet state is involved (**1**: $E_{\infty} = 3.8$ eV), the limiting oxidizing power for an isoenergetic electron transfer is *ca.* 2.4 V (*vs.* SCE). For the first excited triplet state (**1**: $E_{\infty} = 3.1$ eV), the limiting oxidizing power decreases to *ca.* 1.7 V (*vs.* SCE). In cases where the spectrocopically non-detectable second triplet state is populated (**1**: $E_{\infty} \approx 3.6$ eV), the oxidizing power increases by about 0.5 V.

The Rehm-Weller equation was proposed for predicting the likelihood of electron transfer for photochemical reactions,[26] and is shown in equation 1.

$$\Delta G_{ET} = 23.06\ (E_D^{OX} - E_A^{RED}) - \Delta E_{\infty} - C$$

Equation 1: The Rehm-Weller Equation.

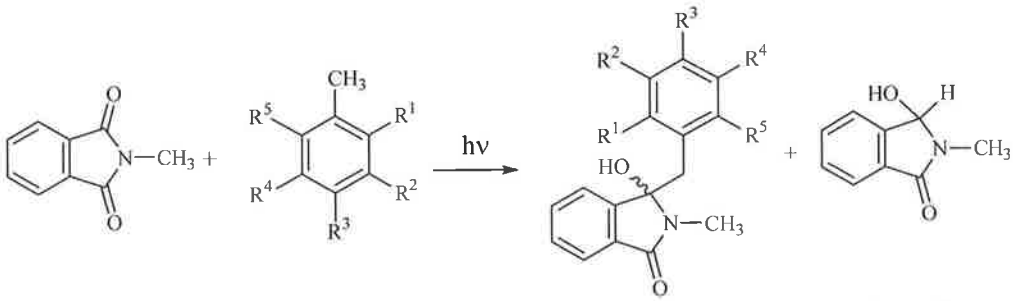
ΔG_{ET} is the free energy for electron transfer, E_D^{OX} and E_A^{RED} are the oxidation and reduction potentials of the donor and acceptor respectively, E_{∞} is the transition energy of the excited state species, and C is the Coulombic interaction term. Using the equation, one can predict whether excited state electron transfer will occur between two molecules. In general, if ΔG_{ET} is positive then electron transfer will not occur, and if ΔG_{ET} is negative electron transfer can occur.

2.3 *Intermolecular* photoaddition reactions to phthalimides

2.3.1 Photoadditions of arenes

It has been reported by Kanaoka *et al.* that a series of toluene derivatives (**17-21**) add to electronically excited phthalimides to give the corresponding addition products (**22-26**) in poor to moderate yields (Figure 26; Table 1).[27] The best result was obtained for *p*-xylene with 35%, and a primary hydrogen abstraction from the

benzylic position was postulated as a crucial key-step. In all cases, the phthalimide was irradiated in the aromatic solvent and the addition products were isolated along with a reduced product and recovered *N*–methylphthalimide. Due to a photoreduction reaction, the hydroxyphthalimide (**27**) was also isolated in low yields.



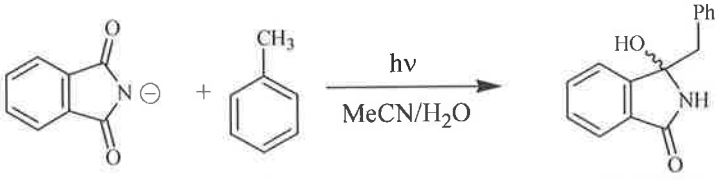
2 **17-21** **22-26** 5-35 % **27** 1-4 %

Figure 26: Photoaddition of toluene derivatives to NMP.

Table 1

Arene	R					Conversion	Yield		
	R^1	R^2	R^3	R^4	R^5	**2** [%]		[%]	**27** [%]
17	H	H	H	H	H	30	**22**	5	2
18	Me	H	H	H	H	79	**23**	23	3
19	H	Me	H	H	H	59	**24**	7	2
20	H	H	Me	H	H	58	**25**	35	4
21	H	Me	H	Me	H	67	**26**	24	1

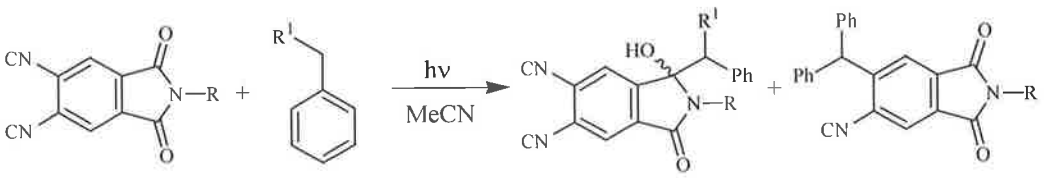
In contrast to (**2**), the phthalimide anion (**3**) readily reacted with toluene (**17**) to the corresponding addition product (**22**) in 84% yield without any further side-products (Figure 27).[28] In the absence of base, no conversion was achieved. Based on these findings, Suau and co-workers suggested an electron transfer mechanism between the anion and the *free* phthalimide prior to hydrogen abstraction from the aromatic side-chain and radical combination.



3 **17** **22** (84%)

Figure 27: Reaction of the phthalimide anion with toluene

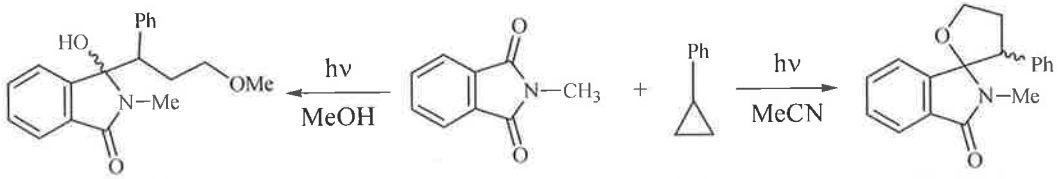
In 1993, Albini *et al.* postulated an alternative electron transfer pathway.[29] The efficiency *via* this electron transfer route could be significantly enhanced for cyano-substituted phthalimides (**28**) as the electron transfer step became more exergonic. Most remarkably, substitution of the cyano-group (→ **31**) was observed as well as addition to the carbonyl-position (→ **30**) when diphenylmethane (**29**) was used as the toluene derivative (Figure 28).[29] The latter process was rationalized on the basis of an *in-cage* versus *out-of-cage* scenario.



28 (R = H, CH_3) **17** (R^1 = H), **29** (R^1 = Ph) **30** (14-50%) **31** (70-79%)

Figure 28: Photoaddition of diphenylmethane to a cyano-substituted phthalimide.

Another solvent-dependent *intermolecular* addition reaction involving phenylcyclopropane (**32**) as the electron donor was reported by Mazzocchi and co-workers.[30] Irradiation of *N*–methylphthalimide (**2**) in acetonitrile in the presence of (**32**) afforded a 1:1 mixture of isomeric *spiro*–tetrahydrofuranyl lactams (**33**) in 22% yield. When the photolysis was performed in methanol, solvent-incorporated addition to give product (**34**) took place (Figure 29). An *intramolecular* version of this PET reaction has also been described.[30c]



34 (23%) **2** **32** **33** (22%)

Figure 29: Addition of phenylcyclopropane to NMP.

2.3.2 Photoadditions of alkenes

Photoadditions of alkenes to phthalimides are dominated by five major processes, and although mixtures are commonly obtained, these processes will be highlighted individually:[3, 4]

1. $[\pi^2+\sigma^2]$-Addition to the C(O)-N bond and formation of ring expanded benzazepinediones
2. Electron transfer leading to photoreduction to the corresponding carbinols

3. Electron transfer leading to trapping by alcohols
4. Cycloaddition to the carbonyl bond and formation of oxetanes
5. Cycloaddition to the aromatic ring and formation of [4+2]-photocycloaddition products.

Generally speaking, the outcome of photoreactions of phthalimides with alkenes is dictated by the irradiation conditions and the oxidation potential of the C=C double bond in particular, and numerous studies have been reported independently by the groups of Mazzocchi[30d-e] and Kubo over the last decades.[31] The feasibility of an electron transfer process between the alkene and the phthalimide can be estimated from the Rehm-Weller equation.[26] In cases where an electron transfer was endergonic with ΔG_{ET} >5 kcal/mol, $[\pi^2+\sigma^2]$-addition reactions to benzazepinediones were observed (Figure 30; path **A**). When the electron transfer became more and more exergonic, electron transfer started to dominate (Figure 30; path **B**). In the presence of suitable nucleophiles, *e.g.* alcohols, the intermediary formed radical ionic pair was trapped in an *anti*-Markovnikov fashion. In the absence of suitable trapping agents, back electron transfer, regenerating the starting materials, efficiently competes with proton transfer and radical combination to carbinols. In cases where the ET was only slightly endergonic, both pathways competed and mixtures of $[\pi^2+\sigma^2]$-addition and PET products were obtained.

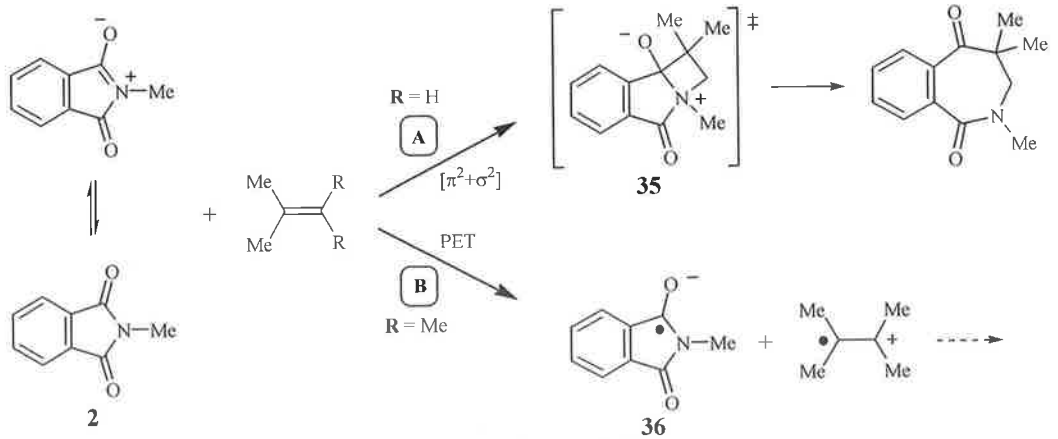


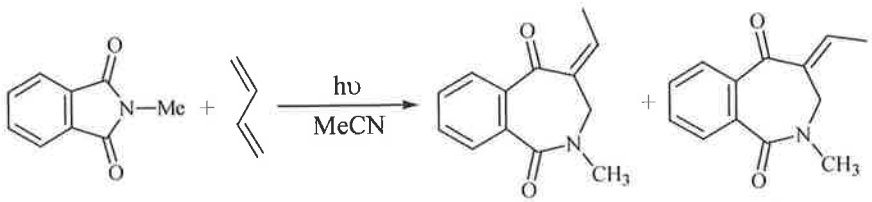
Figure 30: Process of alkene addition to phthalimides.

2.3.2.1 Benzazepinedione formation.

During quenching studies on *N*–alkylphthalimides with *cis*–piperylene, Mazzocchi et al.[22b] noticed that the phthalimide was reacting efficiently with the quencher. In order to avoid complications from competing *intra-* and *intermolecular* processes, the simplified model system NMP (**2**) and butadiene (**12**) was irradiated in

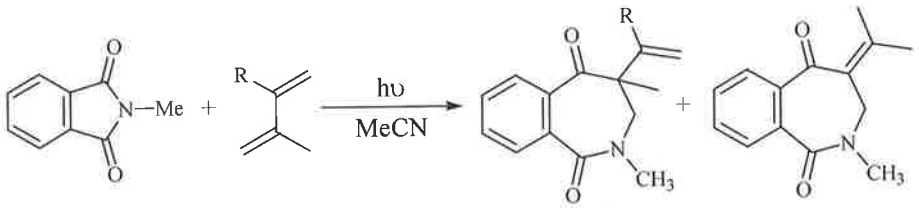
acetonitrile.[22b] The resulting products, which were obtained in a 93% yield based on recovered starting material, were identified as the isomeric benzazepinediones (**13**) and (**14**) *via* a $[\pi^2+\sigma^2]$-photocycloaddition. The **13/14** ratio varied with irradiation conditions and compound **14** readily isomerised to the more stable isomer **13**.

Figure 31



2 **12** **13** **14**

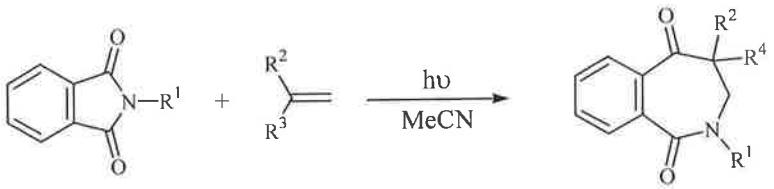
Similarly, the reaction occurred with isoprene (**37**) and 1,3–pentadiene and the corresponding products were isolated in yields of 49% (2 isomers) and 50%. Remarkably, the diene always added in a *regiospecific* manner to (**2**) with its terminal carbon attached to the nitrogen. In contrast, no product formation was observed with cyclopentadiene and 2,5-dimethyl-2,4-hexadiene, or when (**2**) was replaced with *N*–phenylphthalimide or phthalimide, respectively.



2 **37** **38** R = H, **39** R = CH_3 **40**

Figure 32

In 1978, Maruyama and Kubo reported a detailed photoaddition study of various alkenes to either *N*–methylphthalimide (**2**) or phthalimide (**1**).[31b] The corresponding benzazepinediones (**41-47**) were isolated in fair to good yields of 25-67% when *ca.* 3 equivalents of the alkene were used (Figure 33; Table 2). With 2-methyl-1-pentene ($\mathbf{R^2}$ = Me, $\mathbf{R^3}$ = Pr) or 1-pentene ($\mathbf{R^2}$ = H, $\mathbf{R^3}$ = Pr), the primary photoproducts underwent instant Norrish-II cleavages of the propyl substituents.



1, 2 **41-47** (25-67%)

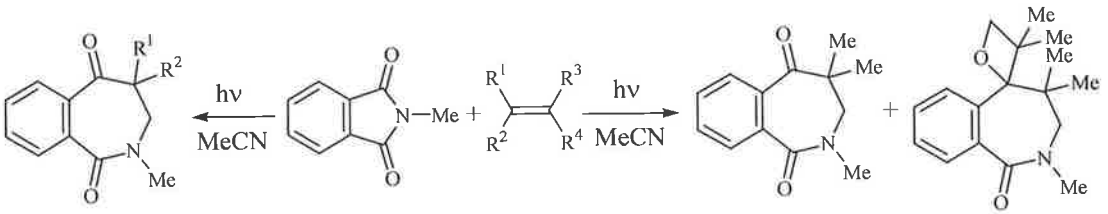
Figure 33

Table 2: Product composition for photoadditions of alkenes to phthalimides (1) and (2).

Phthalimide	Alkene		Benzazepinedione				
R^1	R^2	R^3		R^1	R^2	R^4	yield [%]
Me (**2**)	Me	Me	**41**	Me	Me	Me	67
Me (**2**)	Me	Pr	**42**	Me	Me	H[a]	42
Me (**2**)	H	Pr	**43**	Me	H	H[a]	25
Me (**2**)	H	Ph	**44**	Me	H	Ph	37
Me (**2**)	Me	Ph	**45**	Me	Me	Ph	40
H (**1**)	H	Ph	**46**	H	H	Ph	32
H (**1**)	Me	Ph	**47**	H	Me	Ph	41

[a] Norrish-II cleavages of the propyl substituents

In the same year, Mazzocchi *et al.* published similar results on this application.[22a] In contrast to Maruyama's and Kubo's work, *N*-methylphthalimide (**2**) was irradiated in the presence of fifty equivalents of alkene. As a result, photolysis of (**2**) and 2-methylpropene ($\mathbf{R^1}$, $\mathbf{R^2}$ = Me) in acetonitrile furnished the benzazepinedione (**41**) together with its oxetane derivative (**53**) in yields of 32% and 12% (Figure 34). The oxetane was formed from (**41**) *via* a secondary Paternò-Büchi reaction. 2-Methyl-1-butene ($\mathbf{R^1}$ = Et, $\mathbf{R^2}$ = Me) gave the benzazepinedione (**51**) ($\mathbf{R_2}$ = Me), assumed to be a photoproduct of (**50**), in 43% yield. Likewise, 1-butene ($\mathbf{R^1}$ = Et, $\mathbf{R^2}$ = H) and 1-hexene ($\mathbf{R^1}$ = Bu, $\mathbf{R^2}$ = H) yielded the parent, unsubstituted benzazepinedione (**52**) ($\mathbf{R_2}$ = H) in yields of 60% and 46% respectively, presumable secondary photoproducts of (**48**) and (**49**) respectively (Table 3).



48-52 (43-60%) **2** **41** (32%) **53** (12%)

Figure 34

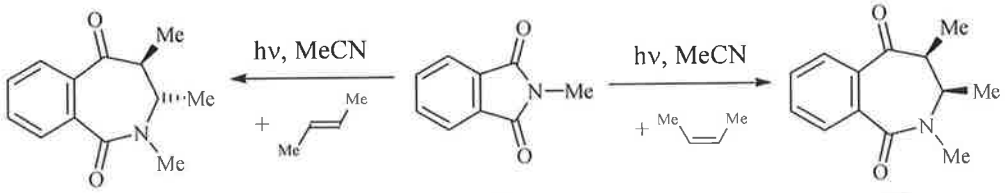
Table 3

Alkene				Composition			
R^1	**R^2**	**R^3**	**R^4**	**(32)**	**R^1**	**R^2**	**Yield**
CH_3	CH_3	H	H	**41**	CH_3	CH_3	32 %
C_2H_5	H	H	H	**48**	C_2H_5	H	—
$(CH_2)_3CH_3$	H	H	H	**49**	$(CH_2)_3CH_3$	H	—
C_2H_5	CH_3	H	H	**50**	C_2H_5	CH_3	—
CH_3	CH_3	CH_3	H	**51**	CH_3	H	43 %
C_2H_5	CH_3	CH_3	H	**52**	H	H	46-60%

In contrast, no products were observed for 2-methyl-2-butene, 2-methyl-2-pentene or 2,3-dimethyl-2-butene. The latter olefin solely gave a small amount (5%) of the photoreduced *N*-methylphthalimidine (**54**). This differing behaviour was striking and was associated with the oxidation potentials of the alkenes. Mazzocchi concluded that a *non*-productive electron transfer quenching was occurring with alkenes having low oxidation potentials (Figure 30; *vide supra*).[22,30d-e,] In an extension of this work, Mazzocchi *et al.* studied a larger variety of different olefins, and the authors noted that benzazepinedione formation generally occurred with 1-substituted, 1,1-disubstituted and 1,2-disubstituted alkenes. While there were few examples of benzazepinedione formation with *tri*-substituted alkenes, no addition products were observed with *tetra*-substituted or cyclic ones.[22c] In the latter cases, *N*–methylphthalimide (**2**) tended to undergo photoreduction with these compounds instead.

In order to prove the mechanism for the photoaddition reaction, *N*–methylphthalimide (**2**) was reacted with *cis*- and *trans*-2-butene. To avoid epimerisation or interference via a slow *cis/trans*-isomerisation of the alkene, the

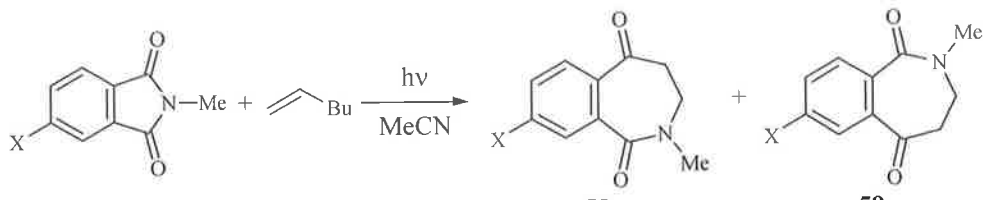
reaction was stopped at low conversion rates. Following this strategy, the corresponding benzazepinediones (**55**) and (**56**) were formed in stereoselectivities >95%.[32] Based on these findings, a concerted $[\pi^2+\sigma^2]$-cycloaddition through a dipolar intermediate or alternatively an addition through a biradical with hindered rotation around the C-C bond has be favoured (Figure 35).



55 **2** **56**

Figure 35: Reaction of NMP with *cis* and *trans* butene.

To further prove the mechanistic scenario, Mazzocchi and co-workers studied the regioselectivity of the cycloaddition for unsymmetrically substituted phthalimides.[32c-d] In line with other known photochemical reactions at that time,[33] the authors predicted that donor substituents would preferentially direct the incoming alkene to the *meta* position, whereas acceptor groups would direct to the *para* position. Consequently, a series of unsymmetrically substituted phthalimides (**57**) was irradiated in the presence of 1-hexene in acetonitrile and the dealkylated products (**58**) and (**59**) arising from a secondary Norrish type-II cleavage were isolated (Figure 36). As correctly predicted, the methoxy-phthalimide derivative (**56**; **X** = MeO) exclusively gave the *meta* product (**58**) in a yield of 32%. Other donor substituents still slightly favoured the formation of the *meta* product (**58**), whereas the strong accepting carboxymethyl-group (**57**; **X** = CO_2Me) preferentially gave the *para* product (**59**) (Table 4). The results were inconsistent with those of a proven radiacl anion trapping mechanism, through which only single regioiosmers were obtained, and thus, a concerted reaction pathway was postulated.



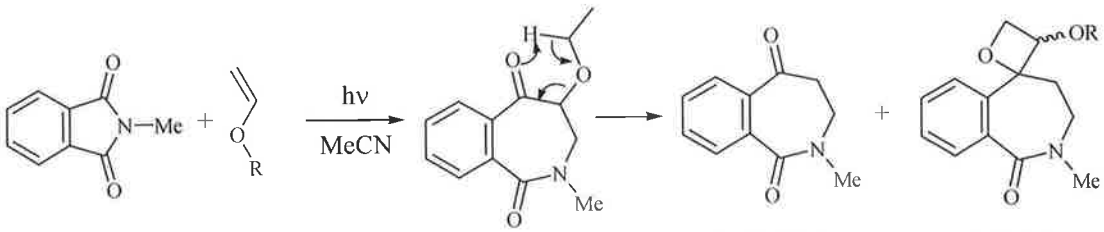
57 **58** **59**

Figure 36: Irradiation of unsymmetrical phthalimides with 1-hexene

Table 4: Photoadditions of 1-hexene to unsymmetrically substituted phthalimides (57).

57	Yield	Composition	
X	**58** + **59** [%]	**58**	**59**
MeO	32	100	—
Me	32	57	43
Cl	45	52	48
CO_2Me	46	27	73

On irradiation of *N*–methylphthalimide (**2**) with a fifty-fold excess of either ethyl vinyl ether (**60**, **R** = Et) or *n*-butyl vinyl ether (**60**, **R** = Bu) in acetonitrile, Mazzocchi and co-workers found that the vinyl ethers reacted in a similar manner as alkenes, ultimately leading to the benzazepinedione (**52**), after type II cleavage of the primary photoproduct, in low yields of 8% and 20% (Figure 37).[32e] Subsequent Paternò-Büchi reaction of (**52**) with (**60**) furnished the corresponding oxetanes (**61**) in 9% and 4% yield. Decomposition products arising from a primary Paternò-Büchi reaction to (**2**) were also obtained in small amounts. In contrast, isopropenyl ethyl ether and 1,1-dimethoxy ethylene showed no reaction.

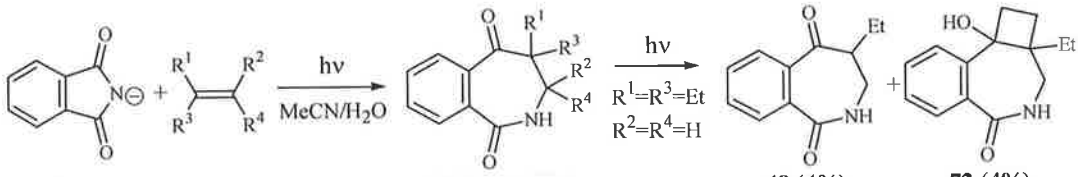


2 **60** **52** (8-20%) **61** (4-9%)

Figure 37

Recently, Suau and co-workers reported that benzazepinediones were formed during the irradiation of the phthalimide anion (**3**) in the presence of alkenes.[34] To circumvent reaction with the solvent, the originally applied alcohols were replaced by a 7:1 mixture of acetonitrile and water. The outcome of the reaction was, however, sensitive to the concentration of the base and best results were obtained at [phthalimide] > [OH^-]. Applying these conditions, photolysis of (**3**) with cyclopentene, cyclohexene, 2,3-dimethyl-2-butene or 2-ethyl-1-butene gave the respective photocycloaddition products (**62-65**) in good to excellent yields of 59-89% based on conversion (Figure 38; Table 5). Most remarkably, these alkenes had previously failed to give benzazepinediones with both free phthalimide and *N*–methylphthalimide.[22b,30d] This differing behaviour was associated with the low

reduction potential of (**3**) and the efficient quenching of its fluorescence by alkenes. In case of 2-ethyl-1-butene (R^1, R^3 = Et, R^2, R^4 = H), the primary photoproduct (**65**) partially underwent Norrish-II cleavage to (**48**) and Yang-cyclisation to (**72**).[34b] The photocycloaddition of phthalimide also worked with alkenylbenzenes and the corresponding products (**66-71**) were found with high regioselectivity and moderate to excellent yields of 41-90% based on conversions (Table 5).[34b]



3 **62-71** (41-89%) **48** (4%) **72** (4%)

Figure 38

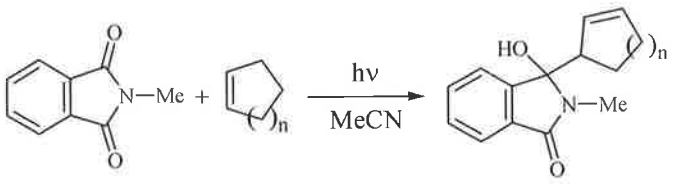
Table 5: Photoadditions of alkenes to the phthalimide anion (3).

Alkene				Conversion	Yield	
R^1	R^2	R^3	R^4	**3** [%]		[%]
$(CH_2)_3$		H	H	80	**62**	86[a]
$(CH_2)_4$		H	H	90	**63**	89[a]
Me	Me	Me	Me	85	**64**	84[a]
Et	H	Et	H	85	**65**	59[b]
Ph	H	H	H	92	**66**	90[a]
Ph	H	H	Me	88	**67**	72[a]
Ph	Me	H	H	93	**68**	68[a]
4-$MeOC_6H_4$	H	H	H	74	**69**	41[c]
3,4-$(OCH_2O)C_6H_3$	H	H	Me	28	**70**	51[c]
Ph	H	Ph	H	20	**71**	78[c]

Phthalimide/NaOH ratios: [a] 1:1.5 – [b] 1:1.2 – [c] 3.4:1.

2.3.2.2 Photoreduction.

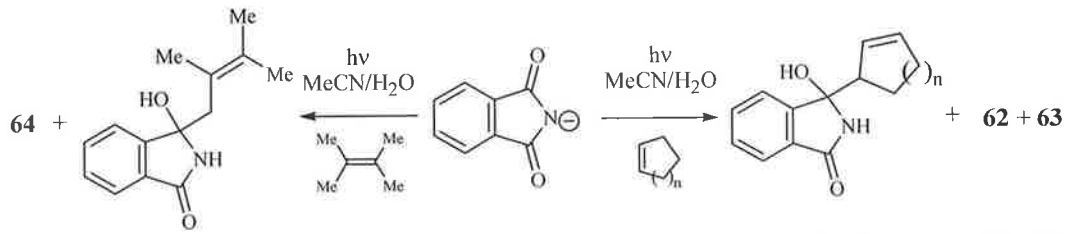
In 1974, Kanaoka and Hatanaka briefly reported the earliest examples of photoadditions of alkenes to phthalimides.[35] Photolysis of *N*-methylphthalimide (**2**) with either cyclopentene or cyclohexene in acetonitrile furnished the corresponding addition products (**73**) in low yields of 3% and 10% (Figure 39), respectively. The authors noted particularly that no oxetane was detected from a competing Paternò-Büchi reaction. The reaction of (**2**) and cyclohexene was subsequently confirmed by Mazzocchi and co-workers in 1978.[22a]



2 **73** (3-10%)

Figure 39

Likewise, cyclohexene underwent a similar reaction with *N*-ethylphthalimide in methanol and gave, besides 27% of the corresponding methanol-trapping product, the photoreduced product (similar to **73**; n = 2) in 25% yield. The reaction was postulated to proceed through the triplet (T_1) state.[23c] Similarly, photoreduction products (**73**) and (**74**) were isolated in minor amounts of 9-12 % during irradiations of the phthalimide anion (**3**) with either cyclopentene, cyclohexene or 2,3-dimethyl-2-butene, when a pH of 10 was kept or the ratio of phthalimide: NaOH was set to 1: 1.2 (Figure 40), respectively.[34b] In contrast, 2-ethyl-1-butene failed to give any carbinols under these conditions. The main products in all cases were benzazepinediones (**64**).



(73%) **74** (12%) **3** **73** (9-12%) (80-84%)

Figure 40

Mazzocchi and Klinger studied extensively the photoreaction of *N*-methylphthalimde (**2**) with 2,3-dimethyl-2-butene in acetonitrile.[30e] Prolonged irradiation was necessary to obtain high conversions and a pair of the photoreduction products (**75**) and (**76**) was isolated in equal yields of 13% each (Figure 41). A third product was furthermore obtained in 4% yield, which was identified as an oxetane from a competing Paternò-Büchi reaction. The authors suggested an initial electron transfer as the key step in the mechanistic scenario. As noticeable from the required irradiation time, back electron transfer regenerating the starting materials competed efficiently with follow-up reactions. To account for the equal amounts of carbinols (**75**) and (**76**) formed, two competing proton transfer and radical combination

pathways were postulated. *Intermolecular* proton transfer and radical combination (path **A**) yields the isomeric pair, whereas radical combination and *intramolecular* proton transfer furnishes compound (**75**) exclusively (path **B**). Sensitisation and quenching studies with indanone and fluorene suggested that the carbinol products arise from the singlet state of (**2**),[30e] and not from the triplet state as was previously suggested.[23c]

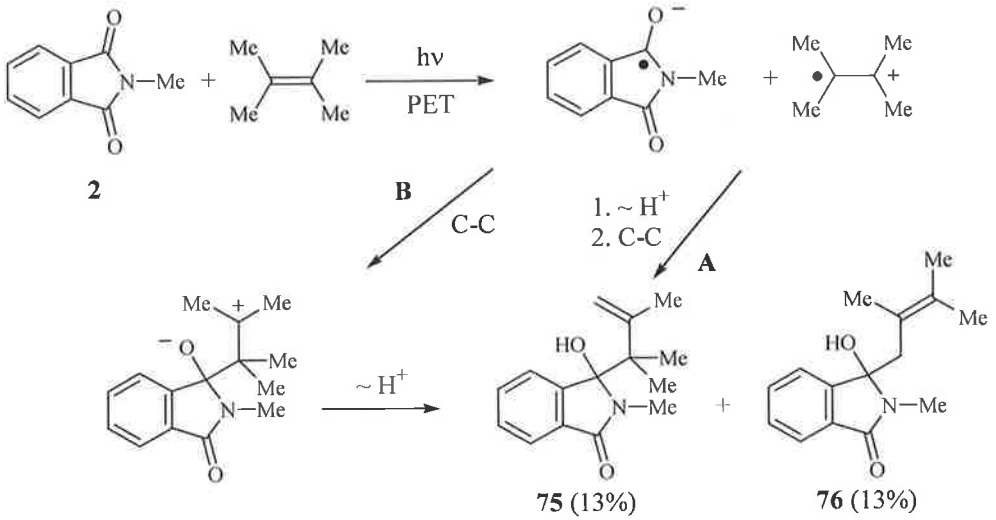


Figure 41

The regiochemistry of the photoreduction was examined by Mazzocchi and co-workers for unsymmetrically substituted *N*-methylphthalimides (**57**).[32d,36a] Upon irradiation in acetonitrile and trapping of the initial radical anion with 2,3-dimethyl-2-butene (Figure 42) it was found that electron-accepting groups (**X** = CO_2Me) direct the incoming substituent in the predicted *para*-manner (→ **77**), while electron-donating groups (**X** = Me, Cl, OMe) gave the corresponding *meta*-products (**78**) (*meta* and *para* with respect to the reduced carbonyl group). Remarkably, only one regioisomer was formed although yields were not given. In comparison to related regioselectivity studies in methanol,[32b] the authors suggested that the directing effect of the aryl substituent is more clearly manifested in the aprotic solvent acetonitrile.

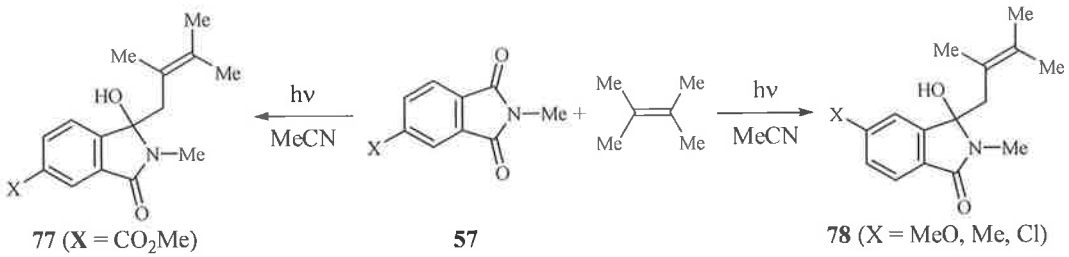


Figure 42

2.3.2.3 Addition of alkenes to TMS substituted phthalimides.

Yoon & Mariano[37] have shown that irradiation of *N*-trimethylsilylmethyl phthalimide (**79**) in acetonitrile containing either acrylonitrile or methyl acrylate results in the formation of (**80**) in excellent yields. While the acrylonitrile and vinyl acetate products provide the *endo* product exclusively, the methyl acrylate product is recovered as inseparable stereosiomers.[37b] However, when (**79**) is irradiated in acetonitrile in the absence of alkene, *N*-methylphthalimide is the sole product in good yield (Figure 43). The authors suggest that the results prove that an azomethine ylide is generated and then trapped by the alkene.

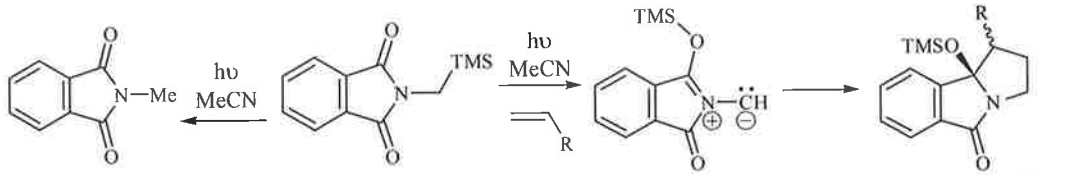


Figure 43

In a similar manner, the irradiation in acetone of (**79**) in the presence of dimethyl fumarate gave (**81**) and (**82**), while dimethyl maleate gave (**83**) in poor to moderate yields.[37b]

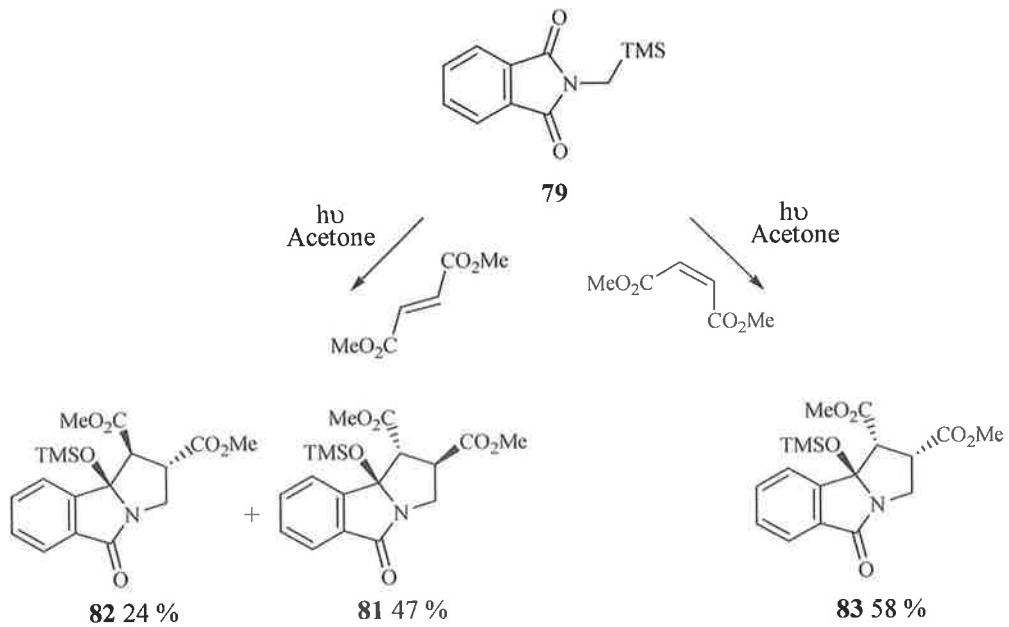
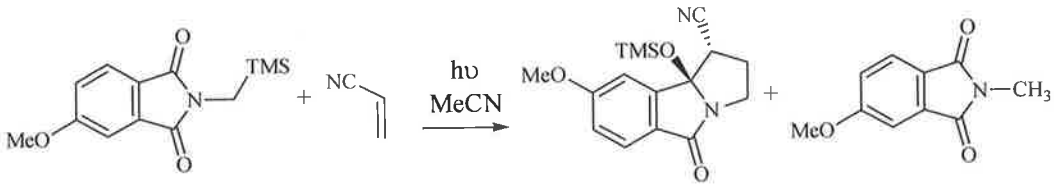


Figure 44

Irradiation of *aryl*-methoxy substituted *N*-trimethylsilylmethylphthalimide (**84**) and acrylonitrile in acetonitrile lead to the formation of (**85**) as a single adduct product in poor yield, along with the *aryl*-methoxy substituted *N*-methylphthalimide (**57**) (Figure 45). The migration of the TMS group occurs exclusively from C to O *meta* to the electron donating methoxy substituent. When an *aryl*-carbomethoxy substituted phthalimide was used, the reaction was more efficient, but a complex mixture of products was obtained.[37b]

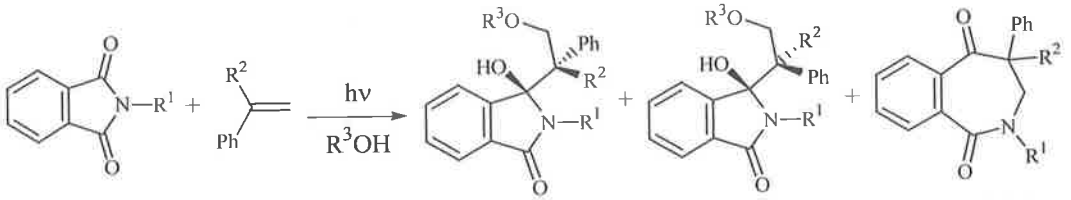


84 **85** 10 % **57** 9 %

Figure 45

2.3.2.4 *Intermolecular* Alcohol incorporation.

Maruyama and Kubo reported that irradiation of *N*-methylphthalimide (**2**), phthalimide (**1**) or *N*-acetoxymethylphthalimide (**86**) in alcoholic solvents with various alkenylbenzenes gave the diastereoisomeric solvent incorporated addition products (**87**) and (**88**) in yields up to 83% based on conversion of 10-15% (Figure 46) and (Table 6).[31a-b] In cases where methanol was replaced by other alcohols, the corresponding benzazepinedione (**44**) was additionally obtained *via* a competing $[\pi^2+\sigma^2]$-addition in yields up to 30%. The authors explained this effect by a decrease in solvent polarity when going from methanol to *tert*-butyl alcohol. Later, Mazzocchi and co-workers demonstrated that the efficiency of the trapping reaction was furthermore depending on the nucleophilicity of the solvent.[36c]



1 R = H
2 R = Me
86 R = OAc

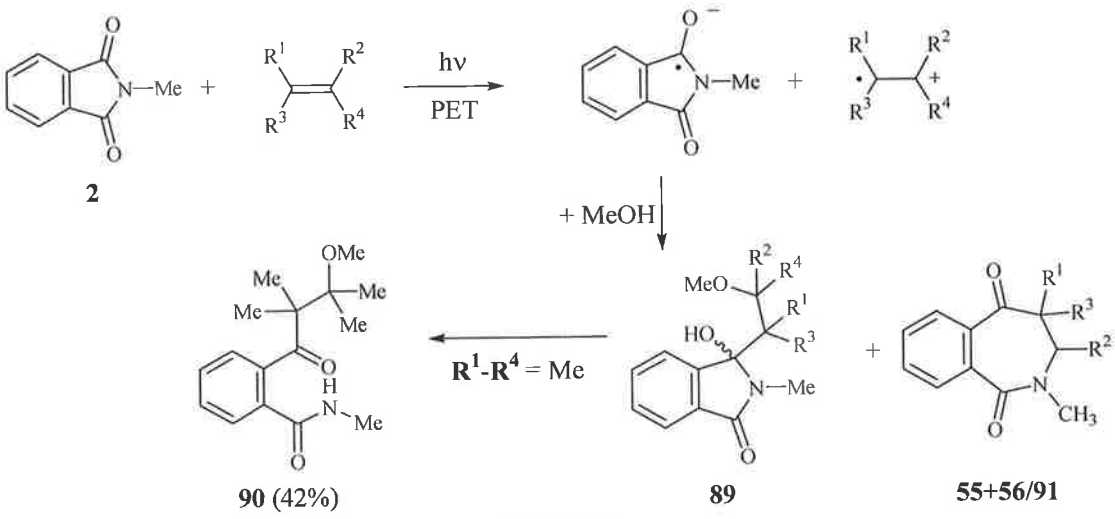
87 (28-40%) **88** (25-34%) **44** (trace-30%)

Figure 46

Table 6: Solvent incorporative photoadditions of alkenylbenzenes to phthalimides (1), (2) and (86).

Phthalimide	Olefin	Alcohol	Yields			
R^1	R^2	R^3	**87** [%]	**88** [%]	**44/45**	**44/45** [%]
Me (**2**)	H	Me	40	34	—	—
Me (**2**)	H	Et	38	31	**44**	trace
Me (**2**)	H	*i*-Pr	32	25	**44**	18
Me (**2**)	H	*t*-Bu	28	26	**44**	30
Me (**2**)	Me	Me	40	30	—	—
Me (**2**)	Me	Et	29	16	**45**	11
Me (**2**)	Ph	Me		83	—	—
H (**1**)	H	Me	39	30	—	—
H (**1**)	H	Et	32	22	**44**	13
H (**1**)	Me	Me	40	35	**45**	trace
H (**1**)	Me	Et	37	34	**45**	8
H (**1**)	Me	*i*-Pr	16	16	**45**	30
CH_2OAc	H	Me	32	32	**44**	30

As stated earlier, photoadditions of aliphatic olefins were sensitive to the number of alkyl substituents and thus the oxidation potential of the C=C double bond.[30d-e,31a] Therefore, the groups of Mazzocchi[36b] and Kubo[31b] independently examined photoreactions of *N*-methylphthalimide (**2**) with a variety of aliphatic alkenes in methanol. In general, the methanol incorporated adducts were obtained by the reaction of olefins possessing at least two alkyl substituents and the corresponding solvent incorporated addition products (**89**) were obtained in yields of 15-52% (Figure 47) and (Table 7). Remarkably, the photoproduct arising from 2,3-dimethyl-2-butene (R^1-R^4 = Me) underwent ring-opening to (**90**). Disubstituted olefins additionally gave [$\pi^2+\sigma^2$]-addition products (**31**) due to their high oxidation potentials.



2 **90** (42%) **89** **55+56/91**

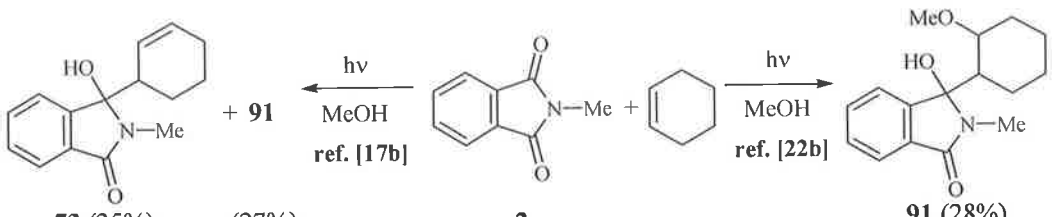
Figure 47

Table 7: Solvent incorporative photoadditions of aliphatic alkenes to *N*-methylphthalimide (2).

Alkene				Yields		
R^1	R^2	R^3	R^4	**89** [%]	**91** [%]	**55** + **56** [%]
Me	H	Me	H	18[a]/15[b]	50[a]/57[b]	—
Me	Me	H	H	15[b]	—	57[b]
Me	Me	Me	H	52[a]/41[b]	—	—
Me	Me	Me	Me	42 (**39**)[b]	—	—

[a] Kubo and Maruyama.[31b] Mazzocchi and coworkers.[36b]

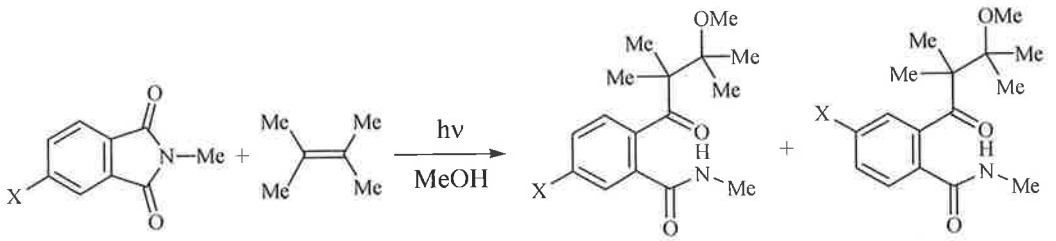
Somewhat contradictory results were reported for the photoaddition in methanol involving cyclohexene (Figure 48). According to Mazzocchi *et al.*, this photoreaction gave exclusively the corresponding trapping product (**91**) in 28% yield,[36b] whereas Kubo and Maruyama isolated the photoreduction product (**73**) in an amount of 25%, along with 27% of (**91**).[31b] Likewise, *N*-ethylphthalimide furnished a mixture of solvent-trapping (similar to (**91**); 27%) and photoreduction product (similar to (**73**); 25%) when irradiated in methanol solution.[23c]



73 (25%) (27%) **2** **91** (28%)

Figure 48

The regioselectivity of the solvent-incorporating photoaddition has been studied by Mazzocchi and Khachik for unsymmetrically substituted phthalimides (**57**) and 2,3-dimethyl-2-butene (DMB) in methanol (Figure 49; Table 8).[32b] In line with their related regioselectivity studies on the photoreduction and the $[\pi^2+\sigma^2]$-addition the authors expected radical ion formation at the imide carbonyl *para* to an acceptor and *meta* to a donor group. Indeed the donor substituted methoxyphthalimide (**57**; **X** = MeO) predominantly gave the *meta* product (**93**), although in a 34:66 mixture with its *para* regioisomer (**92**). Other donor containing phthalimides behaved similarly, while the only product acquired for the strongly accepting carboxymethyl-group (**X** = CO_2Me) was the *para* regioisomer (**92**). Yields were, however, not given by the authors.



57 **92** **93**

Figure 49

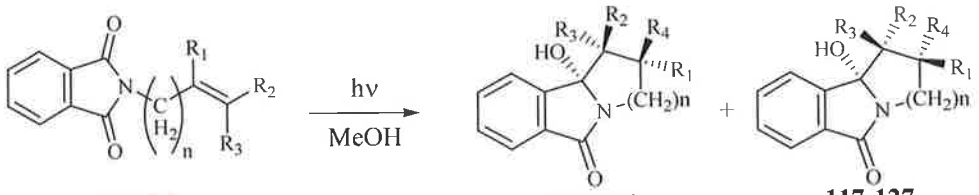
Table 8: Photoadditions of 2,3-dimethyl-2-butene to unsymmetrically substituted phthalimides (57).

57	Composition	
X	**92**	**93**
MeO	34	66
Me	55	45
Cl	56	44
CO_2Me	100	—

2.3.2.5 *Intramolecular* Alcohol Incorporation

Maruyama *et al.*,[21, 38] have reported on the addition of methanol to, and *intramolecular* photocyclisation of *N*-2 and *N*-3-alkenylphthalimides (**94-98**) and (**100-106**). *N*-Allylphthalimide (**94**) gave no photoproduct, *N*-(3-methyl-2-butenyl)-phthalimide (**95**) gave rise to two isomers (**107**) and (**117**). *N*-(2-Butenyl)-phthalimide (**96**) gave a mixture of (**108**) and (**118**), while *N*-(3-phenyl-2-propenyl)phthalimide (**97**) gave (**109**) and (**119**) (Figure 50; Table 9). It is worth

noting that a small change in the phthalimide, influences the reaction.[39a] The authors propose that the mechanism occurs by electron transfer, followed by *anti*-Markovnikov addition of methanol.[39a] Kanaoka *et al.*, have reported on the cyclisation of *N*-cycloalkenylphthalimides, affording *spiro* products.[39b] Macrocycles with up to 16 ring atoms have been synthesised.[38d]



94-106 **107-116** **117-127**

Figure 50

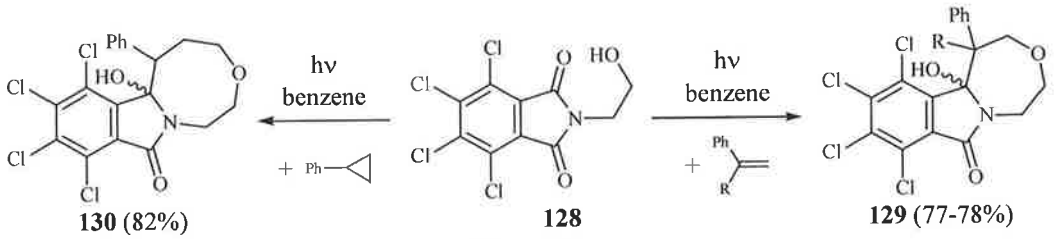
Table 9

Phthalimide					Yields									
	n	R^1	R^2	R^3		n	[%]	R^1	R^2	R^3	R^4		n	[%]
94	1	H	H	H	—	—	—	—	—	—	—	—	—	—
95	1	H	CH_3	CH_3	**107**	1	41	H	CH_3	CH_3	OCH_3	**117**	1	41
96	1	H	CH_3	H	**108**	1	75*	H	CH_3	H	OCH_3	**118**	1	75*
97	1	H	Ph	H	**109**	1	17	H	Ph	H	OCH_3	**119**	1	68
98	1	H	Ph	Ph	**110**	1	54	H	Ph	Ph	OCH_3	**120**	1	27
99	2	H	H	H	**111**	1	9	H	CH_3	H	H		—	—
100	2	CH_3	H	H	**112**	1	52	H	CH_3	CH_2OCH_3	H	**121**	1	31
101	2	H	CH_3	H	**113**	1	18	H	H	$CH(CH_3)OCH_3$	H	**122**	1	14
102	2	H	CH_3	H	—	—	—	H	CH_3	H	OCH_3	**123**	2	39
103	2	CH_3	CH_3	H	**114**	1	17	CH_3	H	$CH(CH_3)OCH_3$	H	**124**	1	27
104	2	H	CH_3	CH_3	**115**	2	42	H	H	$CH(CH_3)_2OCH_3$	OCH_3	**125**	2	41
105	2	CH_3	CH_3	CH_3	**116**	2	11	CH_3	CH_3	CH_3	H	**126**	2	9
106	2	CH_3	CH_3	CH_3	—	—	—	CH_3	CH_3	CH_3	OCH_3	**127**	2	18

* - Indicates combined yields for (**108**) and (**118**).

Recently, Xue *et al.* described an interesting modification using tetrachlorophthalimides with remote hydroxyalkyl substituents.[40] During photolysis in benzene, in the presence of alkenes, the alkene radical cation intermediate was trapped by the terminal hydroxy function, followed by an *intramolecular* radical-radical combination to give medium to macrocyclic compounds. For example, irradiation of *N*-(2-hydroxyethyl)-4,5,6,7-tetrachlorophthalimide (**128**) with

1,1-diphenylethylene (**R** = Ph) or α-methylstyrene (**R** = Me) gave the seven-membered ring products (**129**) in yields of 77% and 78% (Figure 51), respectively. Likewise, phenylcyclopropane gave the eight-membered ring system (**140**) in 82% yield. In contrast, the corresponding *N*-(2-hydroxyalkyl) phthalimides were almost photostable when reacted with alkenes under identical conditions.

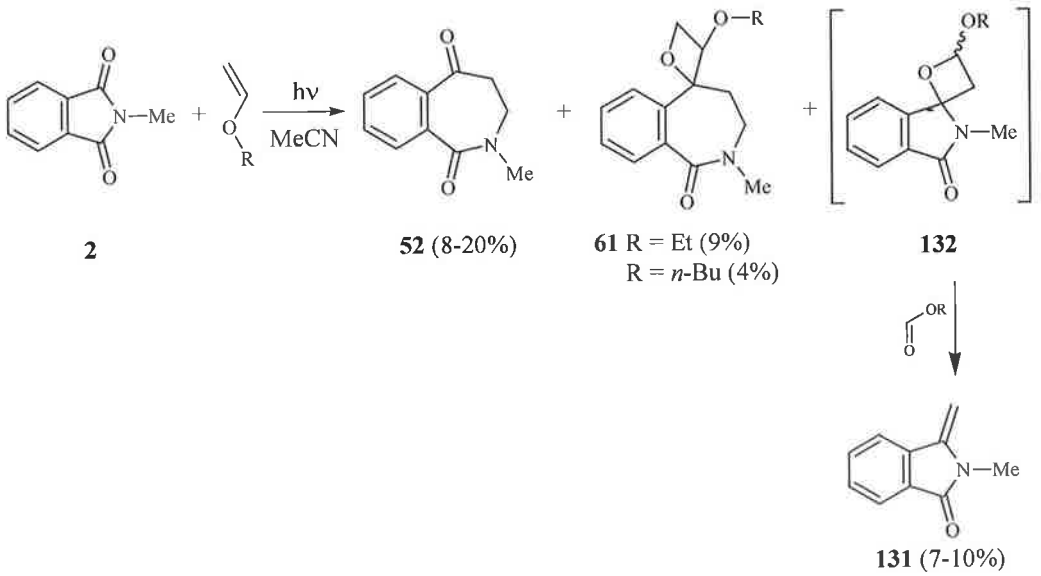


130 (82%) **128** **129** (77-78%)

Figure 51

2.3.2.5 Paternò-Büchi reactions

Paternò-Büchi reactions of phthalimides are rather rare and occur as minor side-reactions with alkenes. In 1978, Mazzocchi and co-workers reported on the reaction of ethyl and *n*-butyl vinyl ethers with *N*-methylphthalimide (**2**).[32e] Beside the benzazepinediones (**52**) and its subsequent Paternò-Büchi product (**61**), the authors isolated small amounts of 3-methylene-isoindolone (**131**) (Figure 52), a decomposition product of the primary formed oxetanes (**132**).



2 **52** (8-20%) **61** R = Et (9%) R = *n*-Bu (4%) **132**

131 (7-10%)

Figure 52

A few years later, Mazzocchi *et al.* finally succeeded in the isolation of an *intermolecularly* formed oxetane.[30e,41] Irradiation of an acetonitrile solution of *N*-methylphthalimide (**2**) and 2,3-dimethyl-2-butene resulted in the formation of the

isomeric photoreduction products (**75**) and (**76**), together with the Paternò-Büchi product (**133** in a 4% yield (Figure 53). The yield of (**133**) increased with increasing olefin concentration. In chloroform, the oxetane (**133**) readily decayed to acetone and (**134**). Sensitisation and quenching experiments showed that (**133**) originated from the triplet state of (**2**), whereas photoreduction to (**75**) and (**76**) occurred *via* the singlet state.

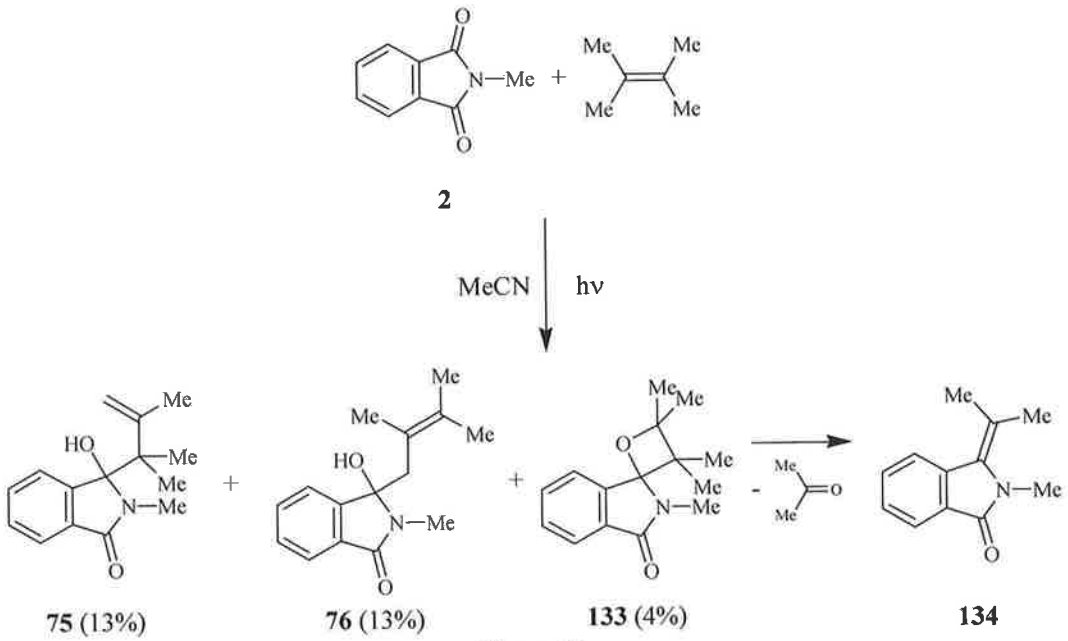


Figure 53

In a similar manner, when (**2**) was irradiated in the presence of α-methylstyrene, the Paternò-Büchi product (**135**) was again isolated in a yield of 4% together with 21% of its isomeric decomposition products (**136**) and (**137**) and the corresponding benzazepinedione (**47**) (60%).[41]

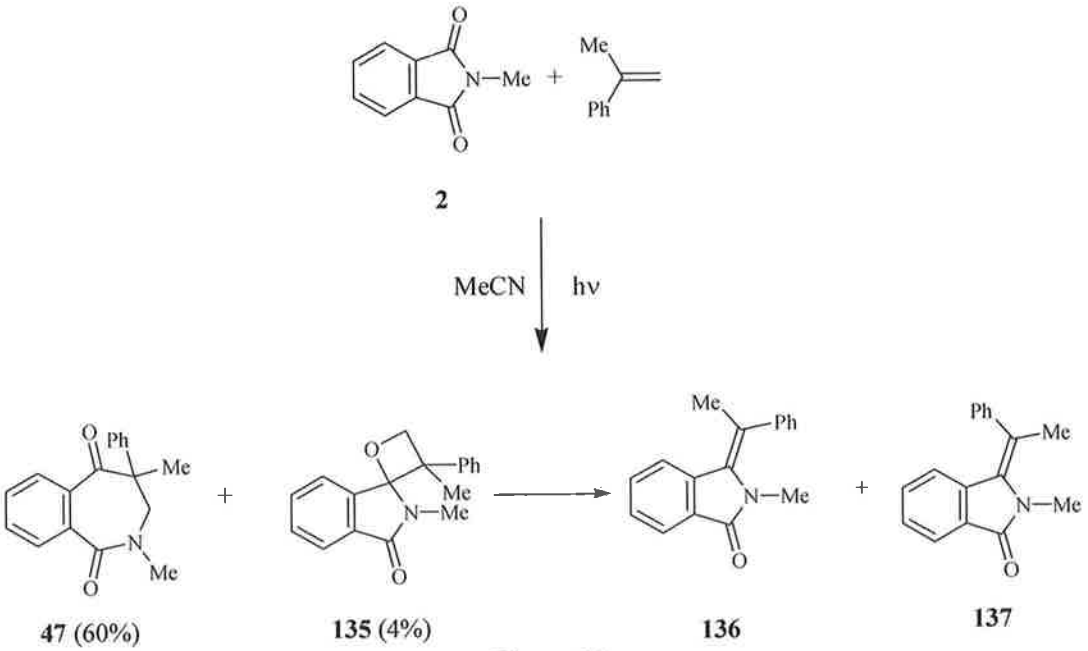


Figure 54

In contrast, photolysis of (**2**) in the presence of 1,1-diphenylethene gave a mixture of the benzazepinedione (**138**) ($\mathbf{R^1}$, $\mathbf{R^2}$ = Ph; 11%) and the decomposition product (**139**) (10%), together with a dimerisation product of the initial alkene.[31a]

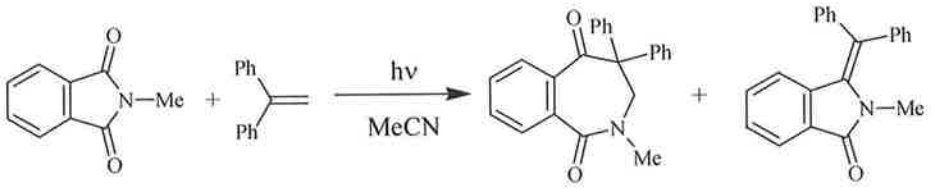
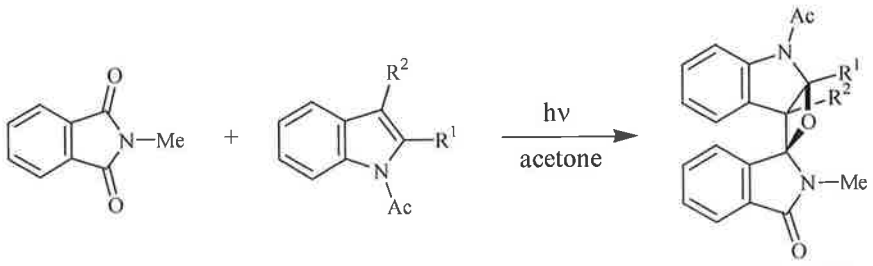


Figure 55

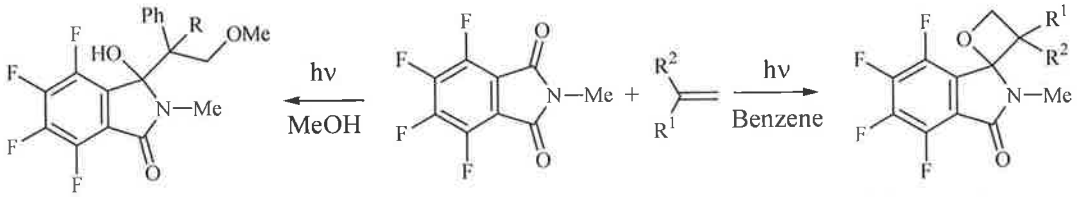
Similar irradiations of (**2**) in acetone, in the presence of 2- and 3-substituted *N*-acylindole derivatives (**140**) furnished the sterically hindered oxetanes (**141**) in moderate yields of 18-62% (Figure 56).[42] In some cases, the isolated products were sensitive towards column chromatography on alumina and underwent ring-opening reactions.



2 **140** **141** (18-62%)

Figure 56

As reported by Kubo and Umehara, 4,5,6,7-tetrafluoro-*N*-methylphthalimide (**142**) exclusively gave oxetanes (**143-145**) in combined yields of 66-68% when irradiated in benzene solutions, under N_2, with styrene, α-methylstyrene or 1,1-diphenylethylene (Figure 57), respectively.[43] When (**142**) was irradiated in benzene with 1,1-diphenylethylene under O_2, benzophenone was obtained as well as the oxetane (**145**). In contrast, photolysis in methanol gave exclusively the expected alcohol incorporation products (**146**) and (**147**) in combined yields of 84-90%.



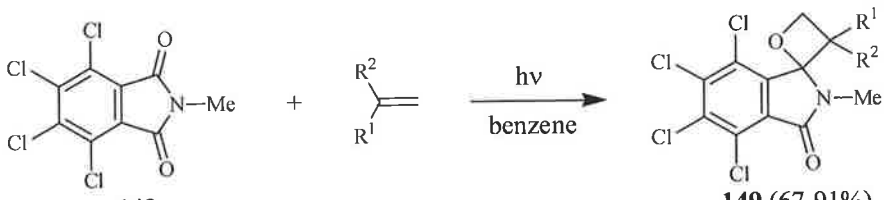
146-147 (84-90%) **142** **143-145** (66-76%)

Figure 57

Table 10

Alkene		Oxetane				Trapped product		
R^1	R^2		R^1	R^2	[%]		R	[%]
Ph	H	**143**	Ph	H	76	**146**	H	84
Ph	Me	**144**	Ph	Me	66	**147**	Me	90
Ph	Ph	**145**	Ph	Ph	68			

Likewise, irradiations of 4,5,6,7-tetrachloro-*N*-methylphthalimide (**148**) in the presence of various styrene derivatives gave the diastereoisomeric spirooxetanes (**149**) as main products in yields of 67-91% based on conversion (Figure 58).[44] With *p*-methylstyrene and α-methylstyrene, the corresponding benzazepinediones, similar to (**47**), were obtained as side-products in 31% and 12% yield, respectively, whereas indene additionally furnished smaller amounts (17%) of its diastereoisomeric photoreduction product, analogous to (**73**).

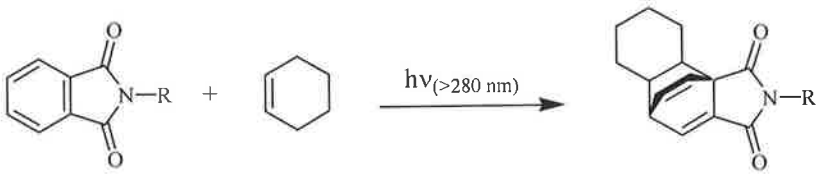


148 **149** (67-91%)

Figure 58

2.3.2.6 *Ortho-* and *para*-cycloadditions

Examples of [4+2]-*para*-photocycloaddition reactions at the benzene moiety of the phthalimide have been reported by Schwack, who examined the irradiation ($\lambda > 280$ nm) of the fungicide *N*-(trichloromethylthio)phthalimide (**150**; R = $SCCl_3$) in cyclohexene.[45] Along with the expected carbinol (similar to (**73**); 80%) and oxetane (analogue to (**133**); 6%), an unexpected third product was isolated in 11% yield, which he identified as the *para*-cycloadduct (**151**) (Figure 59). Similar *para*-cycloadducts were isolated from *N*-methylphthalimide (**2**) and *N*-phenylphthalimide (**152**; R = Ph) in yield of 44% and 90%, respectively, but these products were found to be mixtures of three different isomers.[45]

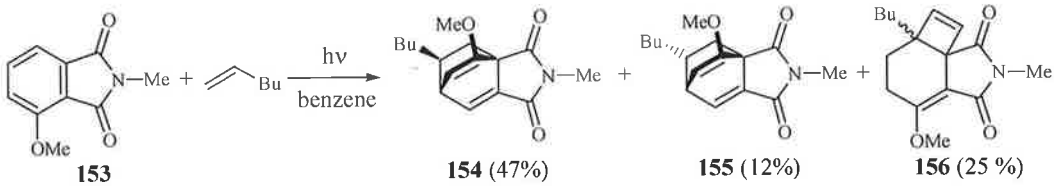


2 R = Me
150 R = $SCCl_3$
152 R = Ph

151 (11-90%)

Figure 59

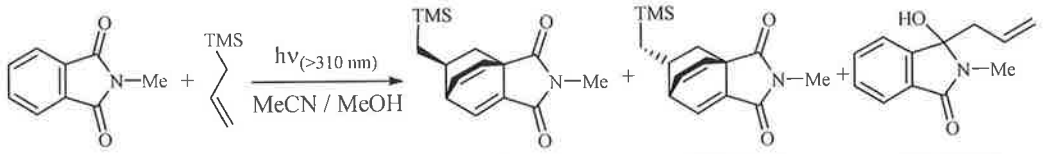
Suau and co-workers reported that the addition of 1-hexene to 3-methoxy-*N*-methylphthalimide (**153**) proceeded in a similar way when irradiated in benzene, giving two *para*-cycloaddition products (**154**) and (**155**), together with an *ortho*-cycloaddition product (**156**).[46] The epimers (**154**) and (**155**) were obtained in a 4:1 ratio (59%), while (**156**) was isolated in a yield of 25% (Figure 60). The same photoproducts were also formed during irradiation in acetonitrile under identical conditions, although at slower rates.[46] The formation of the *para*-cycloaddition adducts (**154**) and (**155**) was rationalized on basis of an initial [2+2]-photoaddition, followed by subsequent electrocyclic ring opening, photoinduced [1,7]-sigmatropic rearrangement and ring closure.



153 **154** (47%) **155** (12%) **156** (25 %)

Figure 60

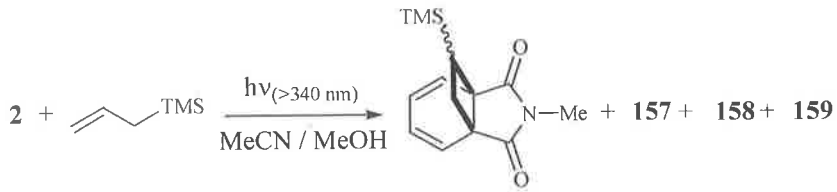
The irradiation ($\lambda > 310$ nm) of *N*-methylphthalimide (**2**) with allyltrimethylsilane in a mixture of acetonitrile and methanol (19:1), has been described by Kubo and co-workers.[47] Two stereoisomeric products (**157**) and (**158**) are formed in 37% and 17% yield, respectively, *via* a [4+2]-*para*-cycloaddition reaction to the benzene moiety of (**2**). Furthermore, the addition product (**159**) was obtained in a yield of 13% (Figure 61). With increasing concentration of the silane, the yield of (**159**) increased steadily whereas the amounts of (**157**) and (**158**) decreased, although their stereoisomer ratios remained almost constant. Sensitisation studies using indanone established that (**157**) and (**158**) are formed through the triplet state.[47]



2 **157** (37%) **158** (17%) **159** (13%)

Figure 61

Irradiation at a longer wavelength ($\lambda > 340$ nm) of a solution of (**2**) and allyltrimethylsilane gave identical products as described above, but also a novel cycloadduct (**160**) arising from [2+2]-addition at the benzene moiety of (**2**) (Figure 62). Yields were not reported since the cycloadduct (**160**) was highly photoreactive and decomposed to (**2**) with increasing irradiation time.[47]

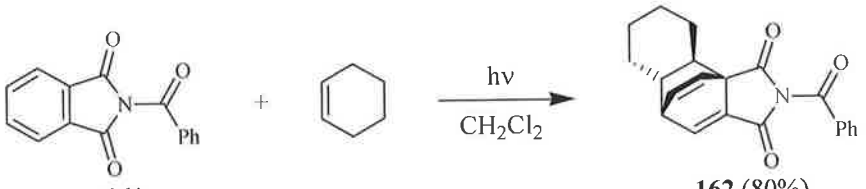


160

Figure 62

More recently, McSweeney *et. al.* reported on the addition of cyclohexene to *N*-benzoylphthalimide (**161**) using dichloromethane as solvent. The *para*-cycloaddition product (**162**) was isolated in 80% yield based on a conversion of just

ca. 5% (Figure 63).[48a] Likewise, *N*-ethyltetrachlorophthalimide gave an analogous [4+2]-*para*-cycloaddition product, although as a diastereoisomeric mixture.[48b] For *N*-acetyltetrachlorophthalimide, however, cleavage of the acetyl group occurred prior to *para*-cycloaddition.[48c]



161 **162** (80%)

Figure 63

2.3.3 Phthalimidations

An interesting reaction of the phthalimide anion (**3**)/alkene system is the photochemical phthalimidation of unactivated double bonds.[7,49] The success of this application strongly depends on the OH^- concentration. At [OH^-] > [phthalimide], [$\pi^2+\sigma^2$]-addition to benzazepinediones is predominantly observed,[34] whereas at [OH^-] < [phthalimide] photoaddition of phthalimide to the double bond of the alkene takes place, resulting in *N*-substituted products. Using the latter conditions, *photophthalimidation* of cyclohexene and a series of styrene derivatives were examined by Suau and coworkers.[49] Irradiation of the olefins in the presence of excess phthalimide (**1**) and a small amount of NaOH gave the expected *photophthalimidation* products (**163-172**) in fair to excellent yields of 30-90%. (Figure 64; Table 11). The use of a high concentration of (**1**) prevented absorption of light by the olefins and thus follow-up reactions of the *phthalimidation* products (**163-172**). In the mechanism proposed by the authors,[49] the phthalimide (**1**) acts as a sensitizer. Electron transfer from the olefin to the phthalimide singlet excited state produces the corresponding radical ion pair. The cation radical is trapped by the phthalimide anion (**3**) to give the most stable radical intermediate. Back electron transfer (BET), followed by protonation, yields the photoaddition products (**163-172**). The mechanism is consistent with the fact that no fluorescence was detected from the phthalimide anion at the phthalimide/hydroxide ion ratio used, confirming that light is indeed absorbed by the phthalimide.

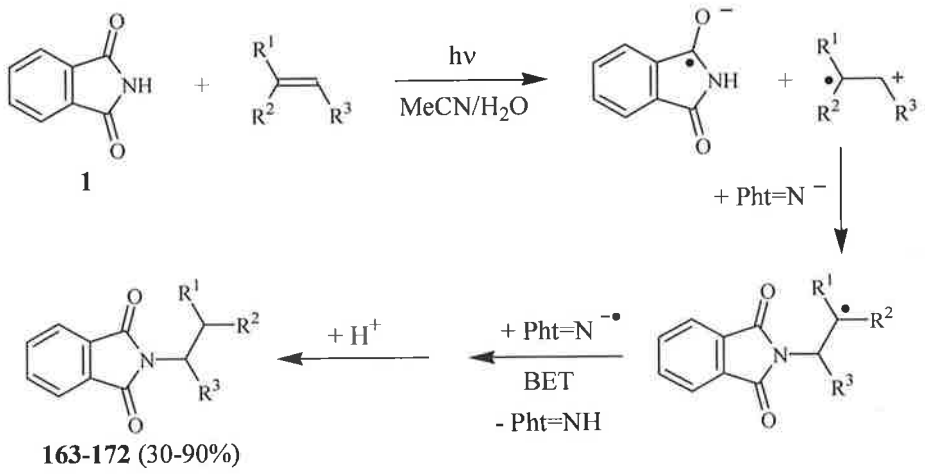


Figure 64

Table 11: Photophthalimidation reactions involving phthalimide (1).

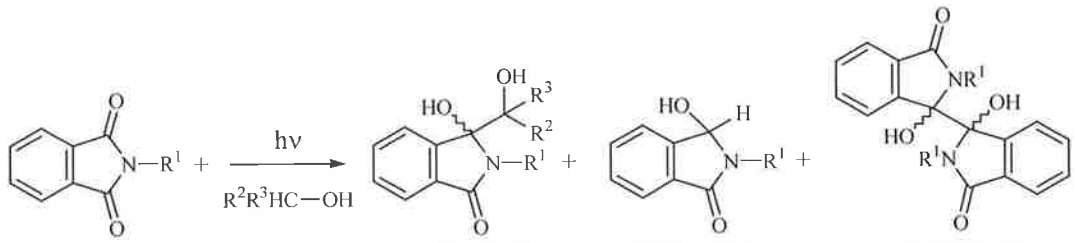
Alkene			Conversion	Product	Yield
R^1	R^2	R^3	**olefin** [%]		[%]
H	$(CH_2)_4$		44	**163**	70
Ph	H	H	75	**164**	53
Ph	Me	H	80	**165**	90
Ph	H	Me	60	**166**	44
Ph	H	Ph	76	**167**	71
Bn	H	H	50	**168**	30
4-$MeOC_6H_4$	H	H	90	**169**	70
4-$MeOC_6H_4$	H	Me	76	**170**	60
3,4-	H	Me	71	**171**	51
	Indene		75	**172**	90

2.3.4 Photoadditions of oxygen containing compounds.

2.3.4.1 Photoadditions of Alcohols

When alcohols are used as solvents in the irradiation of phthalimide (**1**), *N*-methylphthalimide (**2**) or *N*-ethylphthalimide (**173**), addition products (**174**) were obtained in low to moderate yields of 20-45% (Figure 65).[17a,50] Comparable amounts of hydroxyphthalimide (**27**) were isolated from competing photoreduction reactions. Additionally, (**1**) gave larger quantities of its corresponding dimerisation product (**175**). In contrast, *N*-methylenebisphthalimides solely gave dimerisation or

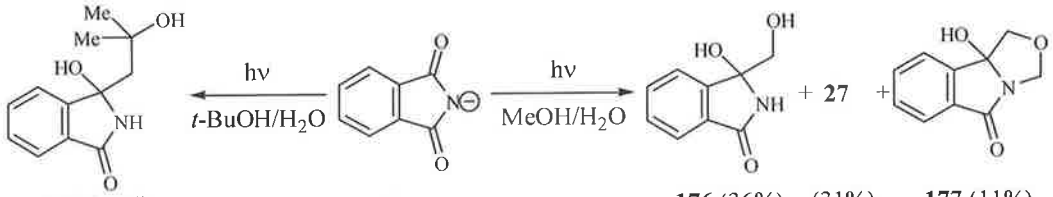
photoreduction products when irradiated in *iso*-propyl alcohol.[51] For all cases examined, the authors suggested that a free radical mechanism involving hydrogen transfer from the α-position of the alcohol was in operation.



1/2/173 **174** (20-45%) **27** (1-40%) **175** (10-40%)

Figure 65

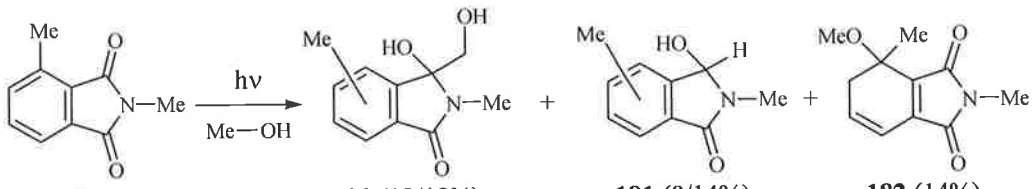
In contrast to the free phthalimide, its anion (**3**) underwent efficient photoreactions with alcohols (Figure 66).[28,34a] In aqueous methanol, the corresponding addition product (**176**) was isolated in 36% yield besides 31% of the primary reduction product (**27**) (R^1 = H). Additionally, the cyclic compound (**177**) was obtained in 11% yield and a follow-up reaction of (**176**) was postulated to explain its formation. The phthalimide anion was also reactive to *tert*-butyl alcohol and irradiation furnished the addition product (**178**) in a good yield of 77%. Significantly, this compound was formed *via* a β-hydrogen abstraction from the alcohol. In contrast, *N*-methylphthalimide (**2**) remained photostable when irradiated in *tert*-butyl alcohol.[28]



178 (77%) **3** **176** (36%) (31%) **177** (11%)

Figure 66

Irradiation of *N*,3-dimethylphthalimide (**179**) in methanol gave, besides two sets of isomeric photoreduction (**180**) and addition products (**181**), the dearomatised compound (**182**) (Figure 67), which was apparently formed by a PET addition of the alcohol to the benzene moiety of the chromophore.[52] In ethanol and propan-2-ol, solely dearomatised products were obtained in yields of 27% and 31%, respectively. Likewise, *N*-methylphthalimide (**2**) and *N*,4-dimethylphthalimide underwent *photodearomatisation* when irradiated in *iso*-propyl alcohol.[52]

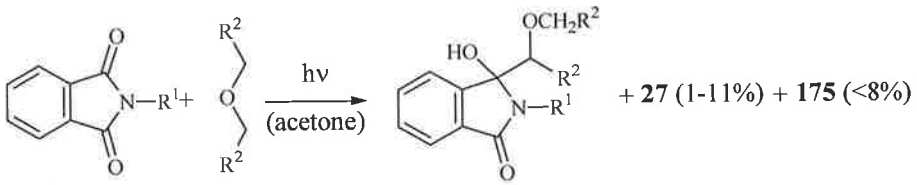


179 **180** (12/18%) **181** (8/14%) **182** (14%)

Figure 67

2.3.4.2 Photoadditions of Ethers

Kanaoka[35] found that diethyl ether, THF and 1,4-dioxane added to *N*-methylphthalimde (**2**), while Roth[50,53] and Tanabe[54] independently reported on the photoadditions of ethers to phthalimide (**1**) and other *N*-substituted phthalimides. Acyclic (*e.g.* diethyl ether) as well as cyclic (*e.g.* THF, 1,4-dioxane) ethers gave the corresponding α-addition products (**183**) in moderate yields of 15-39% (Figure 68). In some cases, minor amounts of the corresponding reduction (**27**) and dimerisation (**175**) products were isolated, and these side reactions were especially pronounced for phthalimide. When acetone was used as diluent, its trapping product (**232**) was additionally isolated as a minor product in 5% for the phthalimide/dioxane pair.[53]

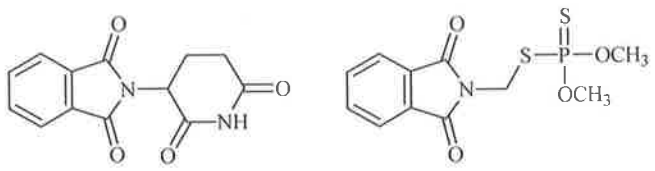


1 R = H
2 R = Me

183 (15-39%)

Figure 68

Thalidomide solely underwent photoreduction in the presence of THF,[53] whereas the pesticide *Imidan* exclusively showed fragmentation of the side-chain when irradiated in diethylether.[54]

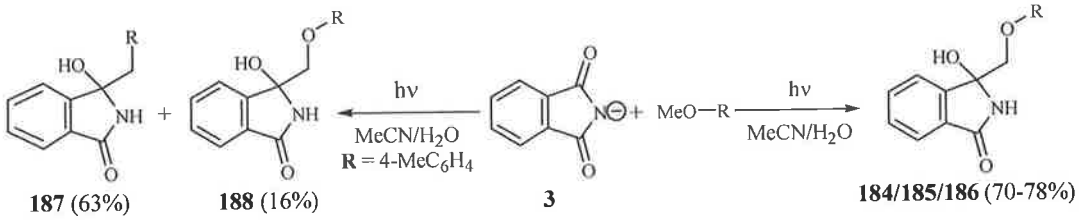


Thalidomide Imidan

Figure 69

The efficiency of the photoaddition was dramatically improved for the phthalimide anion (**3**) and high yields of (**184**, R = $CH_2OC_6H_5$) of 70-78% were achieved (Figure

70). Furthermore, the photoreaction proceeded in a highly selective manner without any side-products arising from photoreduction processes. Similarly, reaction of (**3**) with both *t*-butylmethyl ether and benzyl methyl ether, gave (**185**, R = $CH_2OC(CH_3)_3$) and (**186**, R = $CH(OCH_3)C_6H_5$), respectively in good yields.[28] However, when other potent hydrogen donor sites were present as in 4-methoxytoluene, product mixtures, (**187**, R = *p*-C_6H_5OMe) and (**188**, R = *p*-C_6H_4-Me), arising from competing hydrogen abstraction from both methyl groups were obtained (Figure 70).

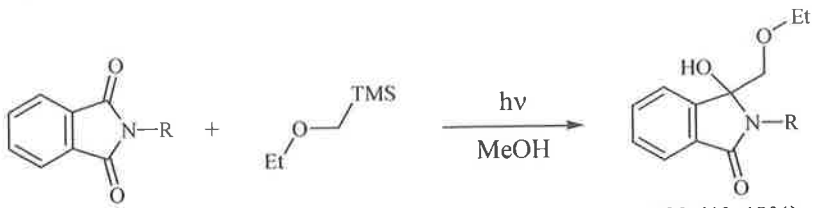


187 (63%) **188** (16%) **3** **184/185/186** (70-78%)

Figure 70

2.3.4.3 Photoadditions of Trialkylsilylmethyl ethers

Intermolecular PET reactions of trimethylsilylmethyl ethyl ethers to phthalimide (**1**) and NMP (**2**) were developed by Yoon and Mariano.[4,55] The α-TMS group has a profound effect on the oxidation potential of the ether oxygen, which is lowered by about 0.5 V.[56] Consequently, electron transfer from the heteroatom to the electronically excited phthalimide becomes energetically feasible. The presence of the silyl group additionally enhances the efficiency and selectivity of the subsequent photoaddition. As an example, phthalimide (**1**) and *N*-methylphthalimide (**2**) yielded the corresponding addition products (**189**) in acceptable yields when irradiated in the presence of trimethylsilylmethyl ethyl ether in methanol (Figure 71).[4] The photoreaction was, however, less efficient in acetonitrile where - in an extreme case - phthalimide (**1**) showed no reaction at all.



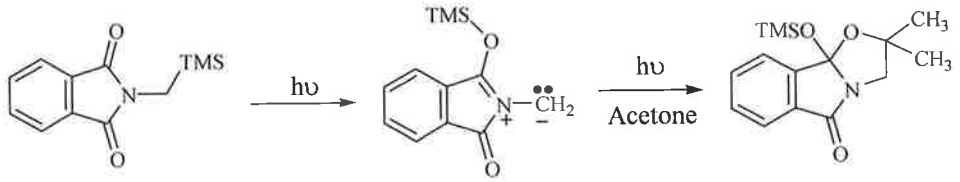
1 R = H
2 R = Me

189 (40-48%)

Figure 71

2.3.4.4 Photoadditions of Ketones

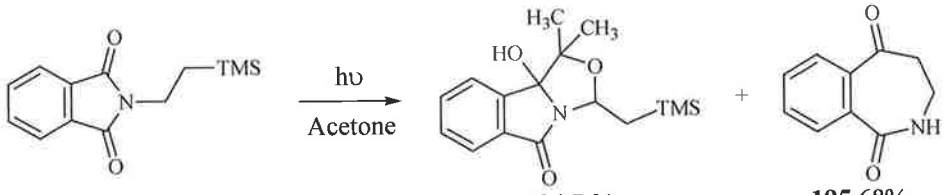
Yoon & Mariano[37a,57] have reported that the irradiation of *N*-trimethylsilylmethyl phthalimide (**190**) in acetone, proceeds via the ylide (**191**), to give (**192**), in reasonable yields.



190 **191** **192** 67 %

Figure 72:Photoaddition of acetone to *N*-trimethylsilylmethyl phthalimide

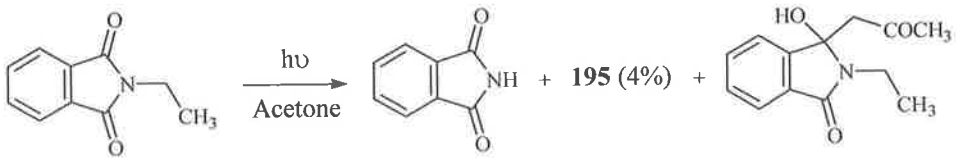
Acetone also undergoes photoaddition to trimethylsilylethyl phthalimide (**193**), to give (**194**), the TMS analogue of (**255**), in poor yield. A benzazepinedione product (**195**) is also produced.[57] It is worth noting that extensive irradiation of (**2**) in acetone fails to form any of the adducts associated with (**190**), suggesting the involvement of an azomethine ylide, which can be trapped.[37b]



193 **194** 7 % **195** 68%

Figure 73

Yoon and Mariano[55d] have also reported that irradiation of *N*-ethylphthalimide (**173**) in acetone affords the photoreduced acetone adduct (**196**), phthalimide (**1**) and the benzazepinedione (**195**).



173 **1** (2%) **196** 29%

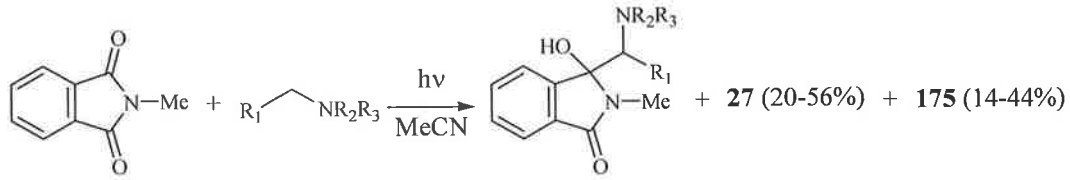
Figure 74

2.3.5 Photoadditions of nitrogen containing compounds.

2.3.5.1 Photoadditions of Amines

The addition of triethylamine, *N*,*N*-dimethylcyclohexyl amine and *N*,*N*-dimethylaniline, which are efficient photoreducing agents for aromatic

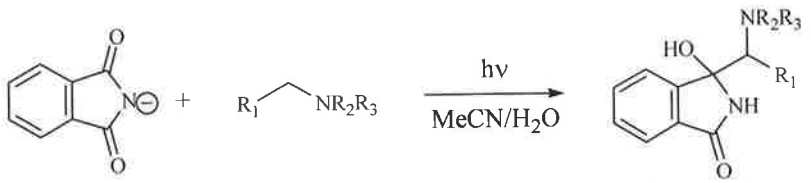
ketones,[58] to *N*-methylphthalimde (**2**) has been briefly reported by Kanaoka *et al.*,[27] affording the amino carbinols (**197**) in low to moderate yields (Figure 75). The photoadditions were, however, sensitive to the reaction conditions and in general proceeded rather sluggishly, and larger amounts of photoreduction (**27**) or dimerisation products (**175**) were observed.



2 **197** (4-37%)

Figure 75

In line with other hydrogen donors, the phthalimide anion (**3**) reacted readily and selectively with either triethylamine or *N*,*N*-dimethylaniline, and the corresponding addition products (**197**) became available in good yields of 74% and 76% (Figure 76).[28]

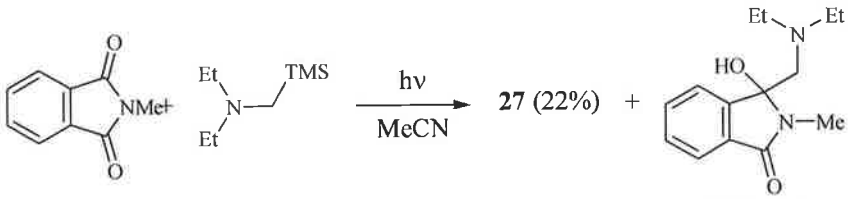


3 **197** (74-76%)

Figure 76

2.3.5.2 Photoadditions of α-Trialkylsilylmethyl-substituted amines

Yoon and Mariano examined PET reactions of *N*-trimethylsilylmethyl-*N*,*N*-diethylamine with phthalimides.[55d] The outcome of the photoaddition showed, however, a remarkable solvent dependency. In acetonitrile or dichloromethane, *N*-methylphthalimide (**2**) gave mixtures of the corresponding addition product (**198**) and the reduced hydroxyphthalimidine (**27**) (Figure 77), whereas irradiations in methanol or *n*-hexane solely furnished (**27**). In sharp contrast, phthalimide (**1**) underwent reductive dimerisation to (**175**) in both methanol and acetonitrile.[55d]



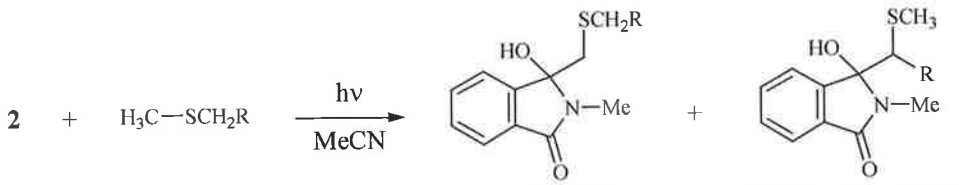
2 **198** (41%)

Figure 77

2.3.6 Photoadditions of sulphur containing compounds.

2.3.6.1 Photoadditions of Thioethers

The photoaddition of some sulfides to *N*-methylphthalimide (**2**) has been described by Kanaoka and co-workers.[59] In methanol, acetone or acetonitrile, a 1:2 ratio of (**2**) to dimethyl sulfide gave (**199**, R = H) in 16, 69 and 80% (Figure 78), respectively. The yield in acetone was increased to 79% if a 1:10 ratio of (**2**) *vs.* sulfide was used, while yields in acetonitrile were improved to 87% when a more powerful lamp was used. A 1:2 ratio of *N*-methylphthalimide and ethyl methyl sulfide in acetonitrile gave (**199**, R = CH_3) in 52% yield, along with *threo*- and *erythro*-(**200**) in 19% and 15% yields (Figure 78), respectively. The quantum yields of the product formation in acetonitrile were determined as $\Phi = 0.06$ (Me_2S) and 0.05 (MeSEt), respectively.



199 (52-87%) **200** (R = Me; 34%)

Figure 78

Irradiation of *N*-(5-methylthiopentyl)phthalimide (**201**), which was shown by the authors to undergo an *intramolecular* cyclisation reaction to (**202**) and (**203**) in acetonitrile, in the presence of dimethyl sulfide afforded the addition product (**204**). By varying the concentration of dimethyl sulfide, the competition between the addition and cyclisation reactions was also studied. The addition reaction was found to be competitive with the cyclisation reaction only at dimethyl sulfide concentrations 10-times higher than that of (**201**) (Figure 79).[59]

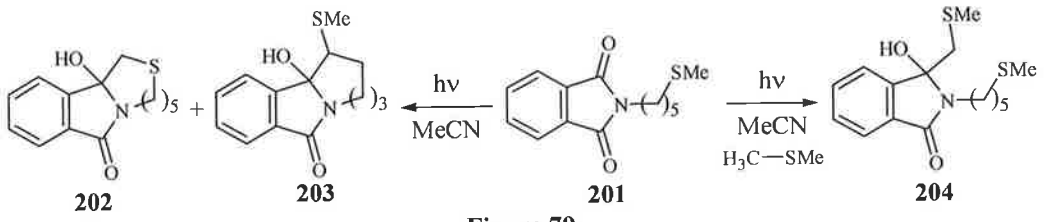


Figure 79

2.3.6.2 Photoadditions of α-Trialkylsilylmethyl-substituted thioethers

Yoon and Mariano described photoadditions of trimethylsilylmethyl *n*-propyl thioether with phthalimide (**1**) and *N*-methylphthalimide (**2**).[55d] The corresponding products (**205**) were isolated in good yields of 78-85% when irradiated in methanol (Figure 80). In acetonitrile, the reaction proceeded with much lower conversions and larger amounts of dehydration products were additionally obtained.

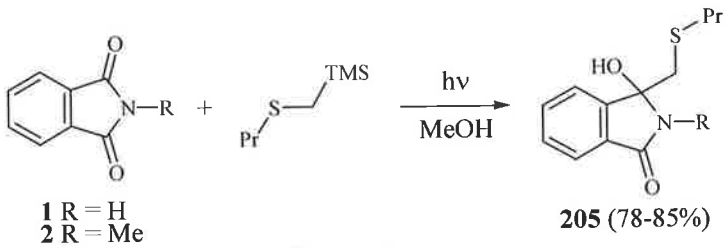
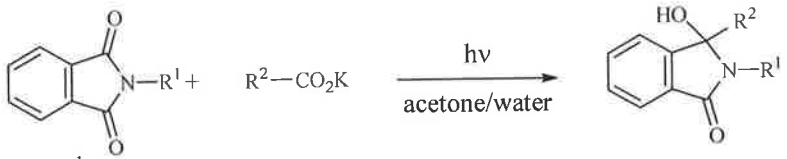


Figure 80

2.3.7 Photoadditions of carboxylates

2.3.7.1 Photoadditions of alkyl carboxylates

Griesbeck and co-workers have recently established the photodecarboxylation of ω-phthalimido carboxylates as a versatile strategy for the construction of medium to macrocyclic ring-systems.[60] Likewise, alkyl carboxylates undergo *intermolecular* addition reactions to give the corresponding alkyl hydroxy-phthalimidines (**206**) in good to excellent yields (Figure 81).[61] The reaction was also applied to large multigram scales using a 308nm XeCl excimer light source.[61b,62] Consequently, this method represents a mild and convenient alternative to thermal procedures, *e.g.* SmI_2-mediated coupling of organic halides (SmI_2/R-X),[63a] addition of organometallic compounds (R-Mg-X or R-Li),[63b-d] or alkylation with organic halides using lithium in liquid ammonia (Li/NH_3/R-X),[63e] respectively.

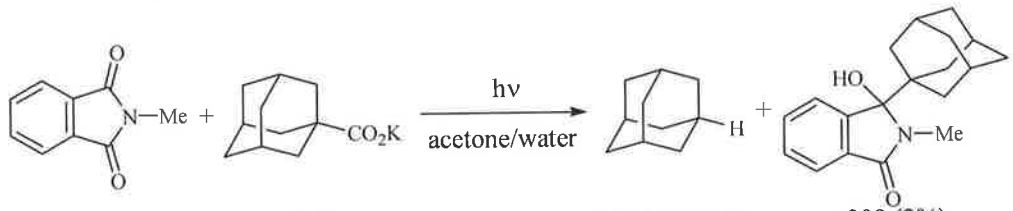


2 R^1 = Me
152 R^1 = Ph

206 (39-89%)

Figure 81

When the potassium salt of 1-adamantanecarboxylic acid (**207**) was used the corresponding alkane, adamantane (**208**) was isolated as the main product in yields of 60-69% (Figure 82). Most of the *N*-methylphthalimide (**2**) remained unchanged and could be reisolated. In one experiment the photoaddition product (**209**) was obtained in 2% yield next to 60% of (**208**).



2 **207** **208** (60-69%) **209** (2%)

Figure 82

Although the oxidation potentials of carboxylates are relatively high compared to other electron donor groups (*e.g.* acetate: $E_{Ox.}$ = 1.54 V in MeCN, 2.65 V in H_2O *vs.* SCE[64]), rapid *intermolecular* photoinduced electron transfer *via* the excited $^3\pi,\pi^*$ state or the higher $^3n,\pi^*$ state has been proposed (Figure 83).[65] Subsequent decarboxylation of the carboxy radical gives the terminal carbon radical. In case of 1-adamantanecarboxylic acid, back electron transfer (BET) generates the corresponding carbanion,[66] which is subsequently protonated by water (path **A**). For all other derivatives, protonation and biradical combination afforded the addition products (path **B**).

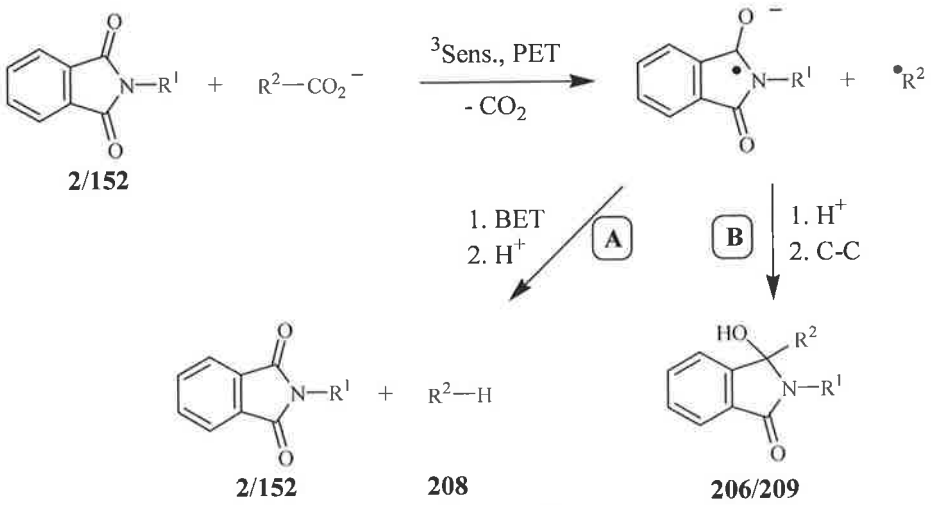
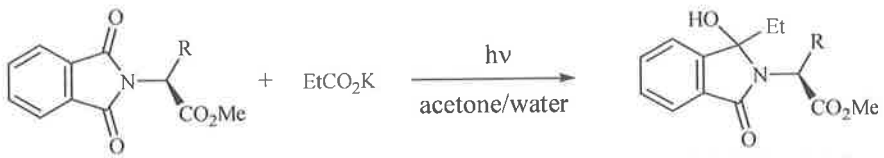


Figure 83

A special case was the irradiation of (**2**) in the presence of sodium formate as the product composition was sensitive to the reaction conditions applied. Hence, the outcome of the irradiation was dominated by stepwise *photoreduction* or *photo-dearomatisation*, and both pathways are known for phthalimides[27,52] and related imide chromophores.[67]

An interesting application for this remarkably efficient photoaddition was the highly *chemoselective* ethylation of *N*-phthaloyl amino acid methyl esters (**210-218**).[61a] In all cases examined (Figure 84), the *intermolecular* decarboxylative addition to give (**219-227**) dominated and products arising from *intramolecular* hydrogen abstractions[68] were not observed. Unlike alternative nucleophilic additions (*e.g.* Grignard reaction[63b,c]), the photoinduced alkylation proceeded selectively at the imide carbonyl group and not the corresponding ester group. The diastereoselectivity for the ethyl transfer reaction was negligible to moderate (Table 12).[69]



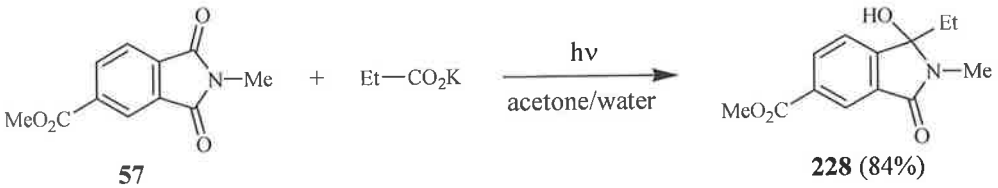
210-218 **219-227** (51-88%)

Figure 84

Table 12: Photodecarboxylative ethylation of *N*-phthaloyl amino acid methyl esters (210-218).

	210-218			219-227	
	R	Amino acid		Yield [%]	*d.e.* [%]
210	H	Gly	**219**	88	—
211	Me	*L*-Ala	**220**	89	4
212	*i*-Pr	*L*-Val	**221**	51	6
213	*i*-Bu	*L*-Leu	**222**	55	14
214	*s*-Bu	*L*-Ile	**223**	63	38
215	Ph	*D*-Phg	**224**	85	30
216	Bn	*L*-Phe	**225**	72	28
217	CH_2CO_2Me	*L*-Asp	**226**	64	14
218	$C_2H_4CO_2Me$	*L*-Glu	**227**	62	28

A highly regioselective alkylation of *N*-methyltrimellitic acid imide (**57**) has been described.[70] Photolysis in the presence of potassium propionate solely gave the *para*-addition product (**228**) in 84% yield (Figure 85). Its preferred formation was explained on the basis of the differences in spin densities in the corresponding imide radical anions. For $(\mathbf{57})^{\bullet-}$, the spin densities were significantly higher for the imido *para*-carbon atom than for the *meta*-carbon atom thus indicating preferential *para* coupling. In contrast, *N*-methylquinolinic acid imide only showed a slight preference for formation of its *ortho* isomer.



57 **228** (84%)

Figure 85

Recently, Griesbeck and co-workers used the photodecarboxylative benzylation of phthalimides (**229**) as a concise route to *Artistolactam* precursors (Figure 86).[71] However, the necessary final electrocyclisation step appears problematic.[72]

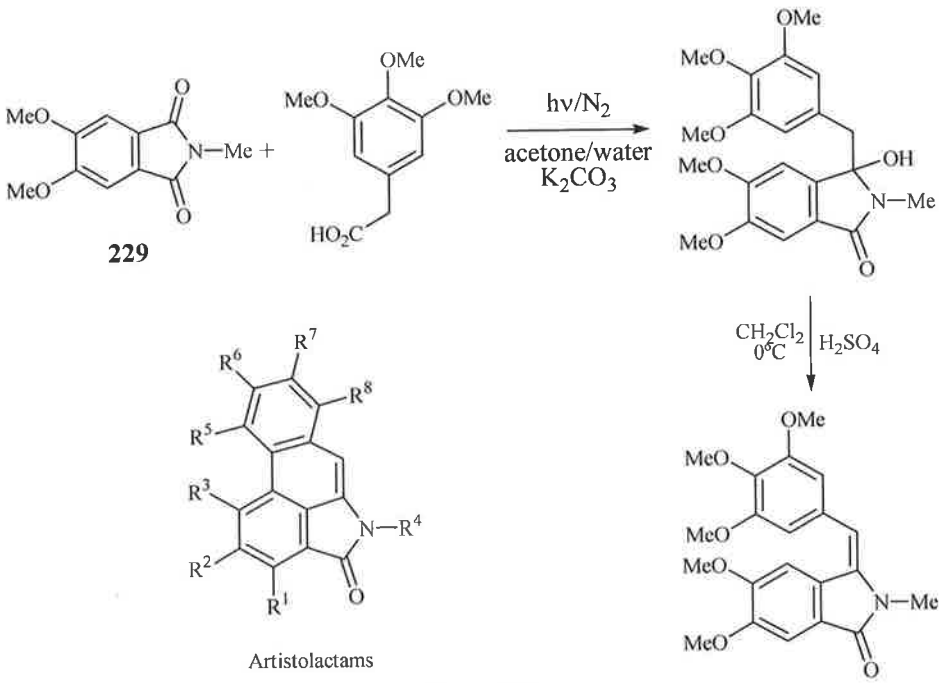
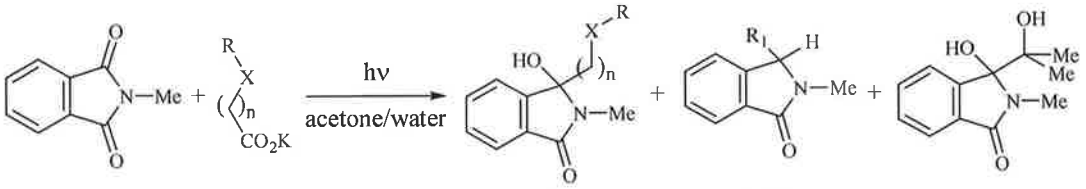


Figure 86

2.3.7.2 Photoadditions of heteroatom substituted carboxylates

The incorporation of additional heteroatoms in the alkylcarboxylate altered the respective electron donor capacity,[73] and either strongly increased or decreased the addition efficiency.[74] α-Thioalkyl and α-oxoalkyl-substituted carboxylates readily gave the corresponding addition products (**230**) in moderate to good yields of 57-90% from *N*-methylphthalimide (**2**). In sharp contrast, the β-thioalkyl-substituted carboxylate remained inert, whereas the corresponding β- to ω-oxoalkyl carboxylate reacted efficiently to give the addition products in 45-76% yield (Figure 87; Table 13).[74] Accounting for the different reactivity of sulfur- *vs.* oxygen-substituted carboxylates, it was concluded that oxidation of the heteroatom plays the dominant role for thioethers. In case of the β-thioalkyl substrate, the sulfur atom acts as a hole trap due to fast non-productive back electron transfer[75] and prevents oxidation of the carboxylate. The photoreactions involving alkylamino-substituted carboxylates gave exclusively photoreduction to (**231**) (**R**^{1} = H) or trapping of the solvent acetone (→ **232**).[74a]



2 **230** (51-90%) **27/231** **232**

Figure 87

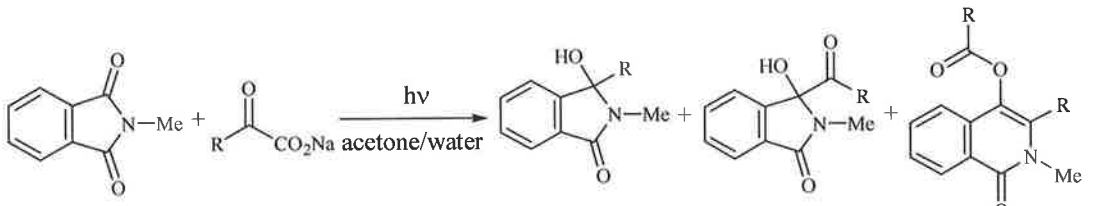
Table 13: Photoadditions of heteroatom substituted carboxylates to *N*-methylphthalimide (2).

Carboxylate			Yields		
X	n	**R**	**230** [%]	**27/231** [%]	**232** [%]
S	1	Me	90	—	—
S	1	Ph	57	—	—
S	2	Me	—	—	—
O	1	Me	57	—	—
O	1	Ph	73	—	—
O	1	2,4-Cl_2Ph	76	—	—
O	2	Me	51	—	—
O	2	Ph	65	—	—
O	3	Ph	55	—	—
O	4	Ph	45	—	—
O	9	Ph	47	—	—
O	10	Ph	49	—	—
O	1	H	57	<5 (**27**: OH)	—
NMe	1	Me	—	21 (**231**: H)	—
NMe	2	Me	—	57 (**231**: H)	36

2.3.7.3 Photoadditions of α-keto carboxylates

The spectrum of products from irradiation of phthalimides in the presence of α-keto carboxylates included alkylation, acylation and ring expansion (Figure 88), respectively.[76] Glyoxylate as well as secondary and tertiary α-keto carboxylates gave the corresponding reduction or alkylation products (**233**) in yields of 52-86%. In contrast, pyruvate and α-keto leucine gave dihydroisoquinolinyl esters (**235**) as ring expansion products in yields of 40-53%. In the latter case the acylated product (**234**) was additionally isolated in 43% yield. Based on the results it was assumed that the course of the reaction is controlled by the stability of the acyl radical intermediates.[77] When less reactive acyl radicals are generated, C-C-bond formation successfully

competes with decarbonylation, whereas in case of more reactive acyl radicals, decarbonylation preceded C-C-bond formation. The unusual ring-expansion products (**235**) most reasonably originate from the monoacylated compounds (**234**) *via* rearrangement to the corresponding isomeric isoquinolines.

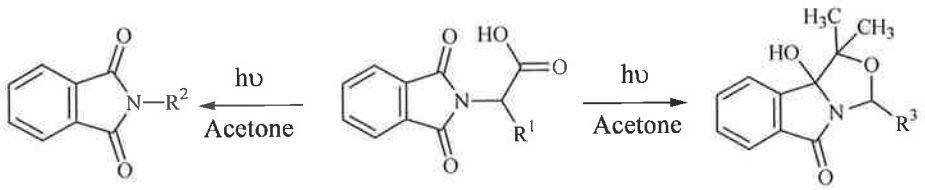


2 **233** (52-84%) **234** (40%) **235** (40-53%)

Figure 88

2.3.7.4 *Intramolecular* Photodecarboxylation/Trapping

When *N*-phthaloyl-α-amino acids (**236-246**), are irradiated in acetone, an *intramolecular* photodecarboxylation reaction occurs, resulting in the corresponding decarboxylated products (**1,** $R^2 = H$; **2,** $R^2 = CH_3$; **152,** $R^2 = C_6H_5$; **247-257**) (Figure 89; Table 14). In the case of *N*-phthaloyl leucine (**248**, $R^1 = CH_2CH(CH_3)_2$), a secondary photochemical reaction also occurs, giving a minor product (**255**, $R^3 = CH_2CH(CH_3)_2$), which was the result of trapping of the phthalimide radical by acetone.[17d] It should be noted that (**255**) is similar in structure to (**193**), with (**193**) effectively being the TMS analogue of (**255**).



1/ 2/ 152 **236-246** **255** 3 %
247-257 (11-89%)

Figure 89: Photodecarboxylation of *N*-phthaloyl-α-amino acids (236-246).

Table 14

	R^1	Yields [%]		R^2	**255** [%]	R^3
236	H	**1**	89	CH_3	—	—
237	CH_3	**2**	38	CH_2CH_3	—	—
238	$CH(CH_3)_2$	**247**	27	$CH_2CH(CH_3)_2$	—	—
239	$CH_2CH(CH_3)_2$	**248**	47	$(CH_2)_2CH(CH_3)_2$	3	$CH_2CH(CH_3)_2$
240	C_6H_5	**249**	32	C_6H_5	—	—
241	$CH_2C_6H_5$	**250**	65	$(CH_2)_2C_6H_5$	—	—
242	CH_2CO_2H	**251**	37	$(CH_2)_2CO_2H$	—	—
243	CH_2CONH_2	**252**	62	$(CH_2)_2CONH_2$	—	—
244	CH_2(C=CH-N=CH-NH)	**253**	30	$(CH_2)_2$(C=CH-N=CH-NH)	—	—
245	*p*-$CH_2C_6H_4OCH_3$	**254**	11	*p*-$(CH_2)_2C_6H_4OCH_3$	—	—
246	CH_2OH	**255**	30	CH=CH2	—	—

Kanaoka *et al.*,[78] have also described the decarboxylation of *S*-substituted *N*-(thioalkyl)phthalimides, which undergo *intramolecular* cyclisation, *via* δ, ε, and ζ hydrogen abstractions.

Yoon and Mariano[37b] have also shown that when the *N*-phthaloyl-α-amino acid derivatives (**256-259**) are irradiated in acetonitrile, in the presence of methyl acrylate or acrylonitrile, the decarboxylated phthalimide can be trapped by the alkene forming (**260-263**) in yields up to 86% (Figure 90; Table 15). The authors proposed that the reaction proceeded *via* an azomethine ylide.

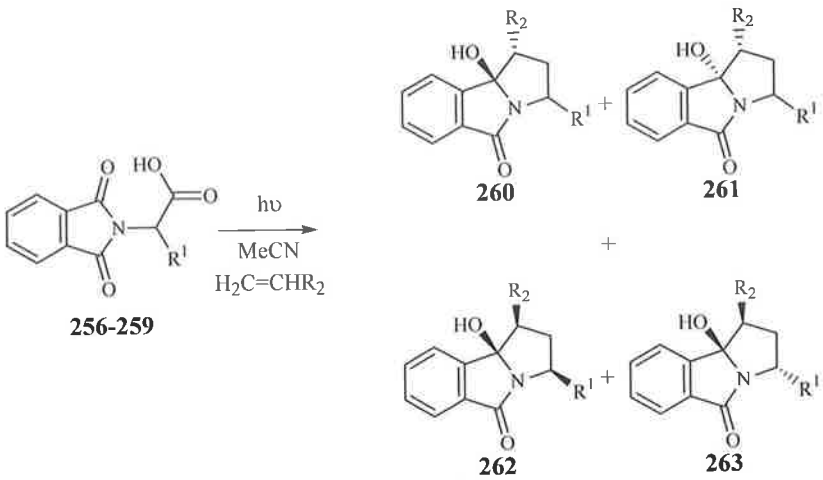


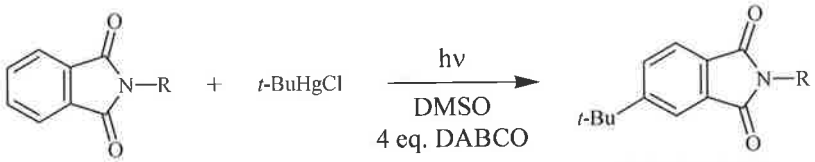
Figure 90

Table 15

			Yields			
	R^1	R^2	**260** [%]	**261** [%]	**262** [%]	**263** [%]
256	H	CO_2CH_3	39		—	—
257	H	CN	89		—	—
258	CH_3	CO_2CH_3	42	—	15	Trace
259	$CH_2C_6H_5$	CO_2CH_3	38	—	17	—

2.3.8 Other *intermolecular* addition reactions

A base-promoted *tert*-butylation at the aromatic core of either phthalimide (**1**) or *N*-methylphthalimide (**2**) involving a thermal electron transfer step was developed by Russell and co-workers.[79] This radical chain reaction is initiated by photochemical cleavage of alkylmercury halides leading to *tert*-butyl radicals which add to the aromatic ring in a highly regioselective fashion (Figure 91). The yields of the corresponding alkylated phthalimides (**264**) were generally high with 65-93%.

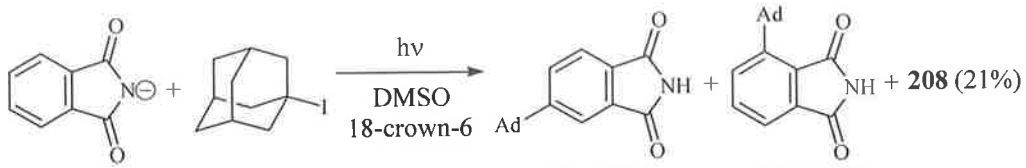


1 R = H
2 R = Me

264 (65-93%)

Figure 91

A similar reaction has been described by Peñéñory *et al.* for 1-iodoadamantane and the phthalimide anion (**3**).[80] In this case, however, the regioselectivity decreased and a mixture of (**265**) and (**266**) was obtained (Figure 92). Additionally, a larger amount of adamantane (**208**) was isolated. The lack of reaction in the dark and inhibition by *p*-nitrobenzene (as radical anion trap), 1,4-cyclohexadiene, and di-*tert*-butylnitroxide (as radical traps) supported a reaction *via* a $S_{RN}1$ mechanism.



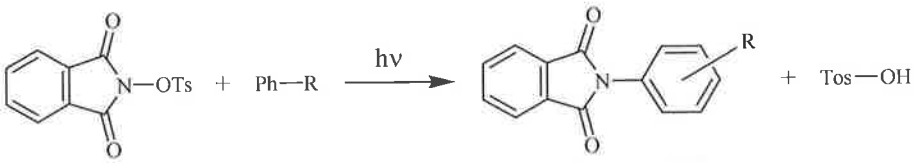
3

265 (45%)

266 (12%)

Figure 92

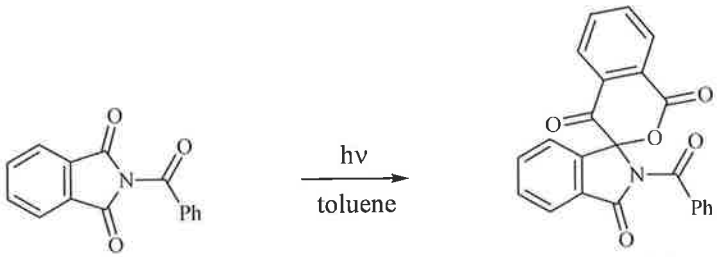
In 1975, Cadogan and Rowley described a radical phthalimidation of aromatic compounds using *N*-tosyloxyphthalimide (**267**).[81] Irradiation in the aromatic solvent gave *N*-arylphthalimides (**268**) in moderate to quantitative yields as mixtures of all three isomers (Figure 93), along with *para*-toluenesulfonic acid. When toluene was used, biphenyl was additionally isolated in 29%, thus indicating a radical mechanism.



267 **268** (12-100%)

Figure 93

Recently, Howie *et al.* have reported on the formation of a *spiro*-benzoyltrione compound (**269**) in 50% yield based on a conversion of 17%, from *N*-benzoylphthalimide (**161**) irradiated in toluene (Figure 94). The compound was thought to be formed from initial photopinacolisation, followed by thermal ring opening and subsequent lactonisation involving the displacement of benzamide.[82]



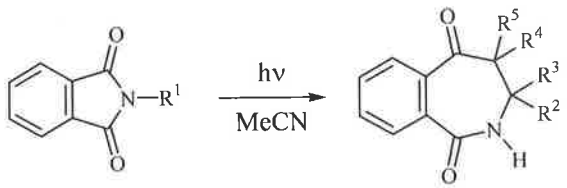
161 **269** (50%)

Figure 94

2.4 *Intramolecular* cyclisation reactions of phthalimides.

2.4.1 Benzazepinedione formation

Kanaoka *et al.*,[17c] have shown that a series of *N*-alkylphthalimides (**173**, **270-278**), which posses both γ- and δ-hydrogens, when irradiated in acetonitrile, *t*-butyl alcohol or acetone, afforded the benzazepindiones (**279-284**) in nearly every case, with yields up to 39%.



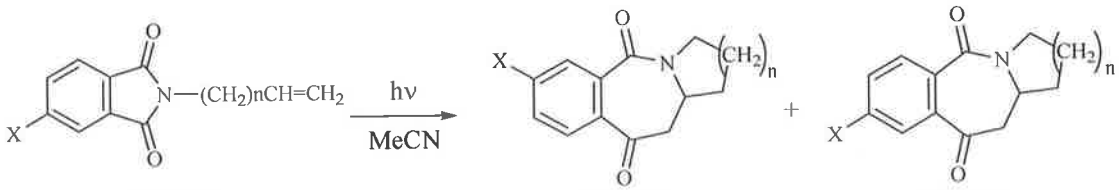
173, 270-278 **279-284** 39%

Figure 95

Table 16

Phthalimide	R^1	Benzazepinedione	R^2	R^3	R^4	R^5	[%]
173	CH_2CH_3	**279**	H	H	H	H	6
270	$CH_2CH_2CH_3$	**280**	H	H	H	CH_3	39
271	$CH(CH_3)_2$	**281**	CH_3	H	H	H	5
272	$CH(CH_3)_3$	**282**	CH_3	CH_3	H	H	20
273	$CH_2CH(CH_3)_2$	**283**	H	H	CH_3	CH_3	8
274	$CH_2CH(CH_3)C_6H_5$	**280**	H	H	H	CH_3	14
275	$CH_2CH_2CH_2CH_3$	**279**	H	H	H	H	18
276	$CH_2CH_2CH(CH_3)_2$	**279**	H	H	H	H	23
277	CH_2cyclopentyl	**284**	H	H	cyclopentyl		1
278	CH_2CH_2cyclohexyl	**279**	H	H	H	H	21

Maruyama and Kubo[31c, 83] reported on an *intramolecular* cycloaddition reaction of *N*-alkenylphthalimides (**285-290**), forming benzazepinediones (**291-296**) and (**297-300**) in poor to excellent yields. This was in sharp contrast to the *N*-alkenylsuccinimides, which give either cyclised oxetanes, or hydrogen abstraction products. Mazzocchi *et al.*[32d,84a] have shown the effect of aryl substituents on a series of phthalimides (**285-290**) (Figure 96; Table 17).



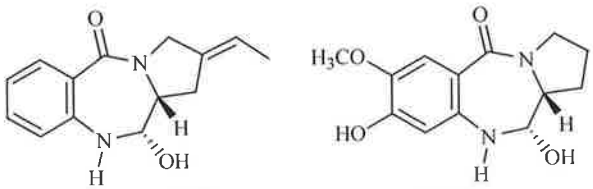
285-290 **291-296** **297-300**

Figure 96

Table 17

Phthalimide			Yield				Yield			
	X	n		[%]	X	n		[%]	X	n
285	H	3	**291**	92	H	1	—	—	—	—
286	OCH_3	3	**292**	68	OCH_3	1	**297**	12	OCH_3	1
287	CH_3	3	**293**	37	CH_3	1	**298**	32	CH_3	1
288	Cl	3	**294**	27	Cl	1	**299**	44	Cl	1
289	$COOCH_3$	3	**295**	6	$COOCH_3$	1	**300**	21	$COOCH_3$	1
290	H	4	**296**	32	H	2	—	—	—	—

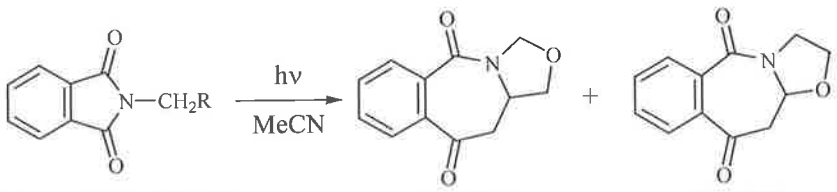
Mazzocchi *et al.*,[84b] have accomplished the total synthesis of the antibiotics *prothracarcin* and *DC81* by the *intra*molecular photochemical ring expansion of *N*-pentenylphthalimides (**285**, X = H, n = 3) to benzazepinediones.



Prothracarcin **DC81**

Figure 97

In a similar manner to (**285-290**), *N*-allyloxymethylphthalimide (**301**) afforded (**303**) in 15% yield, while *N*-(2-vinyloxyethyl)phthalimide (**302**) gave (**304**) in 62% yield.[31c]

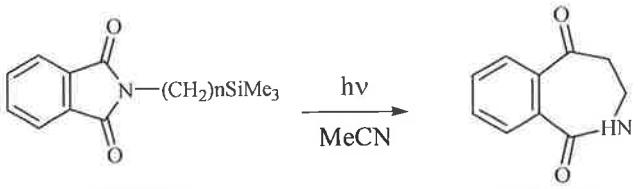


301 R = $OCH_2CH{=}CH_2$
302 R = $CH_2OCH{=}CH_2$

303 15% **304** 62%

Figure 98

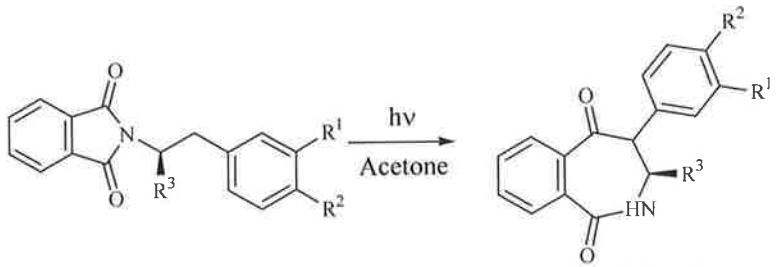
Yoon and Mariano[55d,85] have reported that when *N*-(trimethylsilyl)butyl (**305**; n = 4) or pentylphthalimide (**306**; n = 5) are irradiated in acetonitrile, an *intramolecular* reaction occurs that affords the benzazepinedione (**279**) in poor yield.



305/306 **279** 38%

Figure 99

Castedo *et al.*,[86] have described the cyclisation of *N*-(phenylethyl)phthalimide derivatives (**307-310**) in acetone, to give benzazepinediones (**311-314**) *via* γ-hydrogen abstaction.



307-310 **311-314** 62%

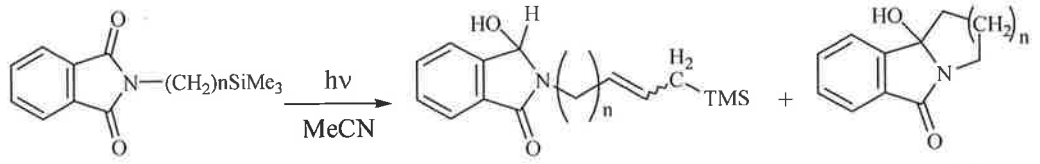
Figure 100

Table 18

	Phthalimide			Yield	
	R^1	R^2	R^3		[%]
307	OCH_3	OCH_3	H	**311**	62
308	-OCH_2O-		H	**312**	64
309	OCH_3	OCH_3	CO_2Et	**313**	42
310	-OCH_2O-		CO_2Et	**314**	25

2.4.2 *Intramolecular* photoreduction.

Yoon and Mariano[85] have reported that when *N*-(4-trimethylsilyl)butyl-(**305**; n = 4) or *N*-(5-trimethylsilyl)pentyl (**306**; n = 5) phthalimides are irradiated in acetonitrile, a photoreduction reaction occurs that affords the reduced phthalimides (**315**; n = 1) and (**316**; n = 2), respectively, in poor yields. The cyclised products (**317**; n = 2; 94%) and (**318**; n = 3; 58%) are formed in excellent yield, based on unreacted starting material, when the irradiation occurs in 35% water: acetonitrile.

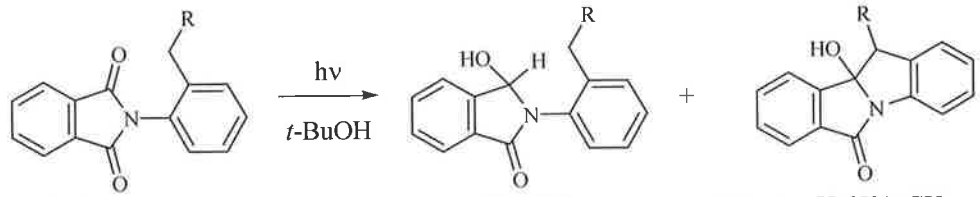


305/306 **315/316** 33% **317** (94%) **318** (58%)

Figure 101

2.4.3 Cyclisations of arenes.

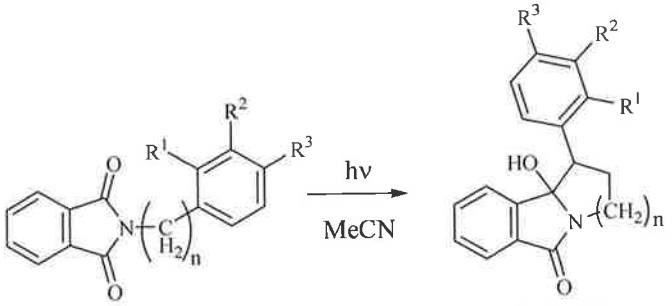
Kanaoka *et al.*,[17a] have shown that irradiation of *N*-arylphthalimides (**319**) in alcoholic solvents, not only gives the photoreduction product (**320**), but also a product resulting from *intramolecular* cyclisation (**321**) in good yields. In effect, the cyclisation occurs *via* δ-hydrogen abstraction, or Norrish type II reaction. Similar results with a variety of substituents on the aromatic rings have also been reported, with yields as good as or better than (**321**) in some cases,[87a,b] while a pyridine derivative of (**320**) and (**321**) has also been synthesised, although in poor yields.[87c]



319 R = H; CH_3 **320** 20% **321** R = H 65%; CH_3 82%

Figure 102

Kanaoka *et al.*,[87d] have also shown that *N*-arylalkylphthalimides (**322-334**) undergo a similar δ-hydrogen abstraction cyclisation to (**335-347**), which is dependant not only on the aromatic substituents but also on the side-chain length, for instance when (n = 2 or 3, R^{1-3} = H) did not yield a product similar to (**335-347**), but instead gave a complex mixture of products. It was also noted that electron-withdrawing groups on the benzene ring appear to promote the cyclisation further. No cyclisation was observed when (n = 6), thus indicating a limiting ring size.



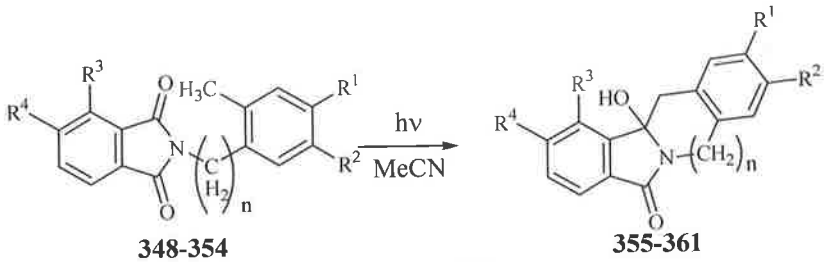
322-334 **335-347**

Figure 103

Table 19

	Phthalimide					Yields				
	n	R^1	R^2	R^3		n	R^1	R^2	R^3	**173** [%]
322	3	OCH_3	H	H	**335**	0	OCH_3	H	H	16
323	3	H	O CH_3	H	**336**	0	H	O CH_3	H	12
324	3	H	O CH_3	OCH_3	**337**	0	H	O CH_3	OCH_3	21
325	4	H	H	H	**338**	1	H	H	H	4
326	4	CH_3	H	H	**339**	1	CH_3	H	H	11
327	4	H	CH_3	H	**340**	1	H	CH_3	H	22
328	4	H	H	CH_3	**341**	1	H	H	CH_3	42
329	4	H	CH_3	CH_3	**342**	1	H	CH_3	CH_3	46
330	4	OCH_3	H	H	**343**	1	OCH_3	H	H	25
331	4	H	OCH_3	H	**344**	1	H	OCH_3	H	47
332	4	H	OCH_3	OCH_3	**345**	1	H	OCH_3	OCH_3	30
333	5	OCH_3	H	H	**346**	2	OCH_3	H	H	Trace
334	5	H	OCH_3	H	**347**	2	H	OCH_3	H	11

Kanaoka *et al.*,[87e] have shown that phthalimides containing an *o*-methylphenyl group in their side chain (**348-354**), gave mainly *tetra*cyclic ring systems (**355-361**), when irradiated in acetonitrile or acetone. Cyclisation occurs at ε or ζ- postitions across the carbons in the benzene rings.



348-354 **355-361**

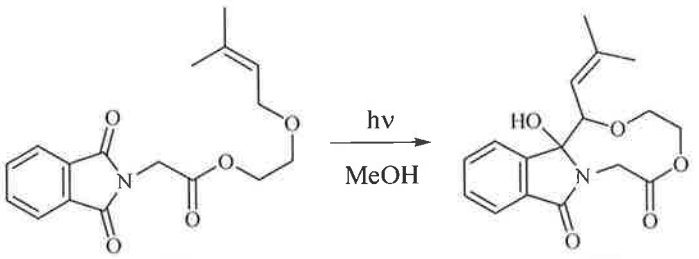
Figure 104

Table 20

Phthalimide						Yields					
	n	R^1	R^2	R^3	R^4		175 [%]	R^1	R^2	R^3	R^4
348	1	H	H	H	H	**355**	18	H	H	H	H
349	1	OCH_3	OCH_3	H	H	**356**	52	OCH_3	OCH_3	H	H
350	1	-OCH_2O-		H	H	**357**	25	-OCH_2O-		H	H
351	2	H	H	H	H	**358**	5	H	H	H	H
352	2	OCH_3	OCH_3	H	H	**359**	27	OCH_3	OCH_3	H	H
353	2	-OCH_2O-		H	H	**360**	17	-OCH_2O-		H	H
354	2	OCH_3	OCH_3	OCH_3	OCH_3	**361**	35	OCH_3	OCH_3	OCH_3	OCH_3

2.4.4 Cyclisations of alkenes

Maruyama and Kubo[38d] have reported on a hydrogen abstraction product (**363**) obtained from the irradiation of (**362**). It is interesting to note that all other products obtained from similar phthalimides were the result of trapping by the solvent.

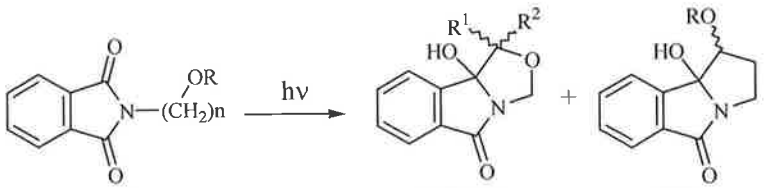


362 **363**

Figure 105

2.4.5 Cyclisations of oxygen containing substituents.

Kanaoka *et al.*,[17b,88a, b] have shown that when *N*-ω-alkyloxyphthalimides (**364-375**) are irradiated in acetone, acetonitrile or *tert*-butyl alcohol, cyclisation by δ-hydrogen abstraction occurs. In the photolysis of (**364**) where no γ-hydrogen is present, cyclisation is to (**376**). (**365**) cyclised to (**377**) in slightly better yield, possibly due to an intermediacy of a secondary radical, while (**366**) gave (**378**), with the *trans* isomer being isolated in reasonable yield. Compound (**374**), which has γ–, δ–, and ε–hydrogens, undergoes δ-hydrogen abstraction to give (**385**) in low yields (Figure 106) and (Table 21).



364-375 376-384 385

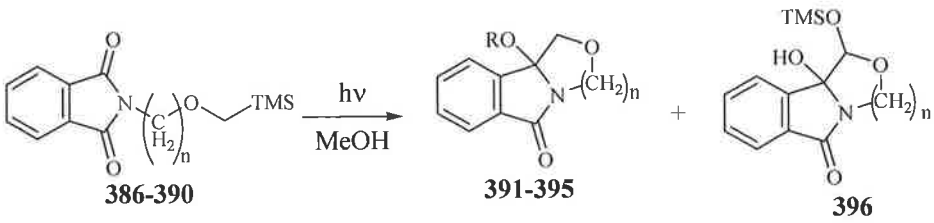
Figure 106

Table 21: Cyclisation of a series of *N*-ω-alkoxyphthalimides

Phthalimide			Yields				Yields	
	n	R		R^1	R^2	[%]	R	**385** [%]
364	1	CH_3	**376**	H	H	12	—	—
365	1	CH_2CH_3	**377**	*cis, trans*-CH_3	H	30	—	—
366	1	$CH_2C_6H_5$	**378**	*cis, trans*-C_6H_5	H	65 (*trans*)	—	—
367	1	$CH(CH_3)_2$	**379**	CH_3	CH_3	39	—	—
368	1	$CH(C_6H_5)_2$	**380**	C_6H_5	C_6H_5	42	—	—
369	1	C_5H_9	**381**	-$(CH_2)_4$-		38	—	—
370	1	C_6H_{11}	**382**	-$(CH_2)_5$-		33	—	—
371	1	C_7H_{13}	**383**	-$(CH_2)_6$-		49	—	—
372	1	C_8H_{15}	**384**	-$(CH_2)_7$-		53	—	—
373	2	CH_3	—	4-Methoxybenzazepinedione		—	—	—
374	3	CH_3	—	—	—	—	CH_3	34
375	3	H	—	—	—	—	H	low

2.4.5.1. Cyclisations of α-Trialkylsilylmethyl-substituted ethers

Yoon and Mariano[89] have shown that irradiation of phthalimide derivatives containing α-trialkylsilylmethyl-substituted ethers (**386-390**) in methanol, exclusively gives rise to the tricyclic structure (**391**; n = 2, R = H) in excellent yields, whereas irradiation in methanol: acetone (2:1) gives (**391**; n = 2, R = H) in reduced yield of 32%, along with (**392**; n = 2, R = TMS) in 19% as well as (**396**). In methanol, the cyclisation occurs with a high degree of chemoselectivity and regioselectivity, while the authors suggest that the reaction occurs *via* the singlet state, forming (**391**; R = H) and the triplet state forming (**392**; R = TMS) and (**396**).[89b] In a similar fashion, Yoon has been able to synthesise large crown ether molecules, with ring sizes up to 21 atoms.[89c]



386-390 **391-395** **396**

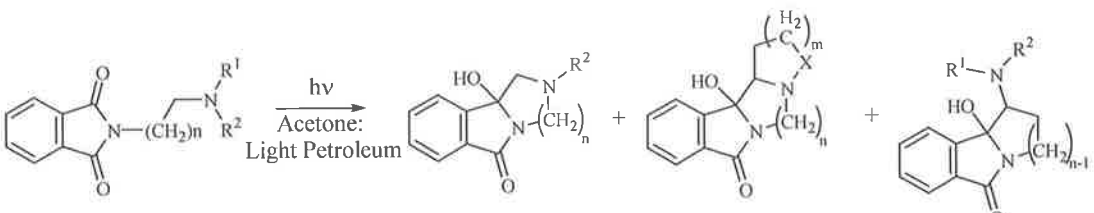
Figure 107

Table 22

			Yields					
	n	Solvent		[%]	n	R	**396** [%]	n
386	2	Methanol	**391**	98	2	H	—	—
387	2	Acetone	**392**	19	2	TMS	16	2
388	3	Methanol	**393**	99	3	H	—	—
389	4	Methanol	**394**	83	4	H	—	—
390	5	Methanol	**395**	83	5	H	—	—

2.4.6 Cyclisations of nitrogen containing substituents.

Kanaoka *et al.*,[90a-c] have reported that a series of *N*-(ω-methylanilino)alkyl-phthalimides (**397-411**), with varying chain lengths have given cyclised products, with up to 22 ring atoms (**420-434**) and (**443-445**), in poor yields, when irradiated in acetone: light petroleum (1:2.7) (Figure 108; Table 23). Coyle and Newport have also reported similar findings with a phthalimide similar to (**397**; n = 0, $R^1 = R^2 = C_6H_5$),[91] however the recovered photoproduct was slightly different. The cyclisation of phthalimides containing *N*-acyl groups (**412-419**),[90d-e] in their side chains, have also been reported, giving (**435-442**), *via* γ, ε, and ζ hydrogen abstractions, in yields up to 87%, with compounds (**439-442**) isolated as *cis/trans* isomers.[90e]



397-419 **420-430/ 435-437** **431-434/ 438-442** **443-445**

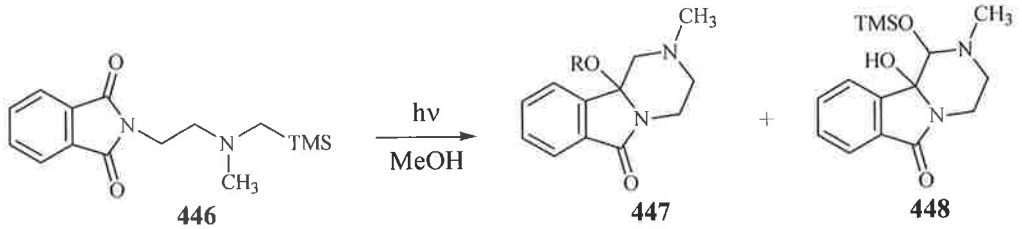
Figure 108

Table 23

Phthalimide				Yields										
	n'	R^1	R^2		[%]	n	X	m	R^2		n-1	[%]	R^1	R^2
397	1	CH_3	C_6H_5	**420**	13	1	—	—	C_6H_5	—	—	—	—	—
398	2	CH_3	C_6H_5	**421**	12	2	—	—	C_6H_5	—	—	—	—	—
399	3	CH_3	C_6H_5	**422**	20	3	—	—	C_6H_5	—	—	—	—	—
400	4	CH_3	C_6H_5	**423**	6	4	—	—	C_6H_5	**443**	2	5	CH_3	C_6H_5
401	5	CH_3	C_6H_5	**424**	15	5	—	—	C_6H_5	—	—	—	—	—
402	6	CH_3	C_6H_5	**425**	10	6	—	—	C_6H_5	—	—	—	—	—
403	10	CH_3	C_6H_5	**426**	8	10	—	—	C_6H_5	—	—	—	—	—
404	12	CH_3	C_6H_5	**427**	9	12	—	—	C_6H_5	—	—	—	—	—
405	18	CH_3	C_6H_5	**428**	9	18	—	—	C_6H_5	—	—	—	—	—
406	2	CH_3	CH_3	**429**	29	2	—	—	CH_3	—	—	—	—	—
407	3	CH_3	CH_3	**430**	13	3	—	—	CH_3	**444**	1	5	CH_3	CH_3
408	2	$-(CH_2)_4-$		**431**	20	2	CH_2	1	—	—	—	—	—	—
409	2	$-(CH_2)_5-$		**432**	33	2	CH_2	2	—	—	—	—	—	—
410	3	$-(CH_2)_4-$		**433**	12	3	CH_2	1	—	—	—	—	—	—
411	3	$-(CH_2)_5-$		**434**	9	3	CH_2	2	—	**445**	1	5	$-(CH_2)_5-$	—
412	1	CH_3	$COCH_3$	**435**	63	1	—	—	—	—	—	—	—	—
413	2	CH_3	$COCH_3$	**436**	24	2	—	—	—	—	—	—	—	—
414	3	CH_3	$COCH_3$	**437**	87	3	—	—	$COCH_3$	—	—	—	—	—
415	1	$-C(O)(CH_2)_3-$		**438**	67	1	C=O	3	—	—	—	—	—	—
416	2	$-C(O)(CH_2)_3-$		**439**	24	2	C=O	3	—	—	—	—	—	—
417	3	$-C(O)(CH_2)_3-$		**440**	78	3	C=O	3	—	—	—	—	—	—
418	1	$-C(O)(CH_2)_4-$		**441**	82	1	C=O	4	—	—	—	—	—	—
419	1	$-C(O)(CH_2)_5-$		**442**	9	1	C=O	5	—	—	—	—	—	—

2.4.6.1. Cyclisations of α-Trialkylsilylmethyl-substituted amines.

Like their ether analogues, the α-trialkylsilylmethyl-substituted amines (**446**) undergo cyclisation giving products *via* the singlet (**447**; R = H) and triplet states (**447** R = TMS), as well as the tricyclic product (**448**).[89a] The mechanism *via* the singlet state is believed to occur by single electron transfer (SET) from the amine-nitrogen centre to the phthalimide, giving a diradical which cyclises to give (**447**).[92]

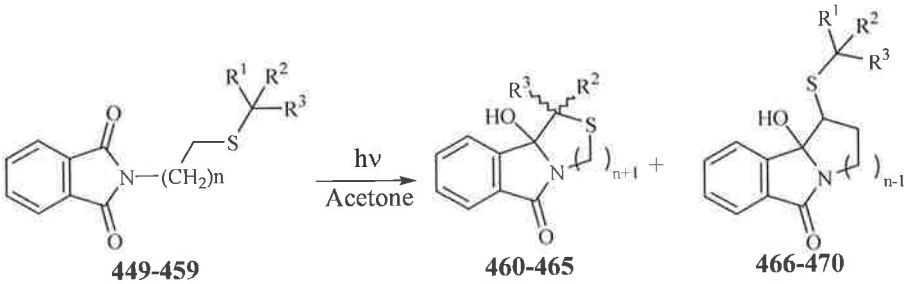


446 447 448

Figure 109

2.4.7 Cyclisations of sulphur containing substituents.

Kanaoka *et al.*,[93a] have reported that a series of *N*-thioalkylphthalimides (**449-459**) undergo cyclisation to (**460-465**), (when $n \leq 1$ and R^1 = H), and (**466-470**) when irradiated in acetone.[20a] Compound (**449**) gave (**460**) in very low yield, with the major product *N*-methylphthalimide (**2**) in 30% yield, while (**466**) was obtained from (**455**) by way of δ-hydrogen abstraction. γ-Hydrogen abstraction results in the formation of (**462-465**) from (**451-454**), mostly in poor yields. It is noteworthy that (**467-470**) are formed from (**456-459**) by way of ε-hydrogen abstraction, in reasonable yields, as it has been established that the order of reactivity is $\gamma > \delta > \varepsilon$.[94] Compounds similar to (**460**) containing up to 15 atoms in the sulphur ring system have been reported.[93b] Sulphur ring systems of up to 27 atoms that also contain ester functions have been reported,[93c] while sulphur ring systems of up to 38 atoms that contain amide functions have been reported.[93d]



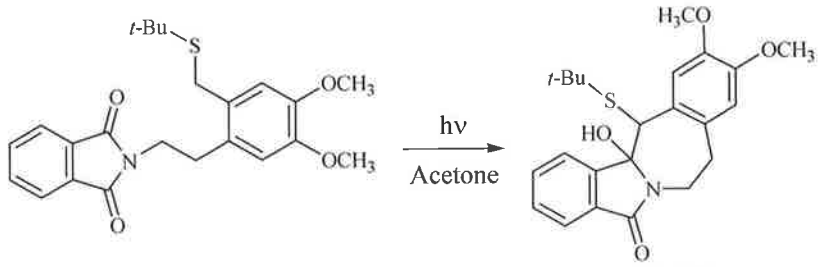
449-459 460-465 466-470

Figure 110

Table 24

Phthalimide					Yields					
	n	R^1	R^2	R^3		n	[%]		n	[%]
449	0	H	H	CH_3	**460**	1	3	—	—	—
450	0	H	H	C_6H_5	**461**	1	27	—	—	—
451	1	H	H	H	**462**	2	47	—	—	—
452	1	H	H	CH_2CH_3	**463**	2	10	—	—	—
453	1	H	CH_3	CH_3	**464**	2	16	—	—	—
454	1	H	H	C_6H_5	**465**	2	19	—	—	—
455	2	CH_3	CH_3	CH_3	—	—	—	**466**	1	47
456	3	H	H	H	—	—	—	**467**	1	68
457	3	H	CH_3	CH_3	—	—	—	**468**	1	40
458	3	CH_3	CH_3	CH_3	—	—	—	**469**	1	76
459	3	C_6H_5	C_6H_5	C_6H_5	—	—	—	**470**	1	39

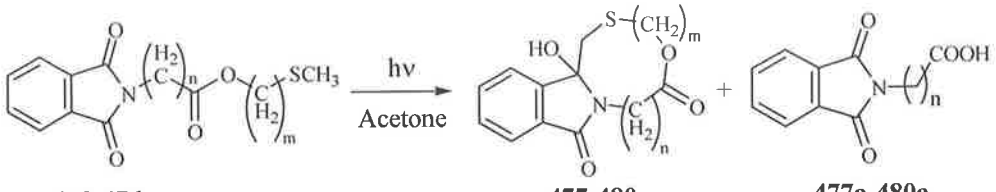
Mazzocchi *et al.*,[95] have described the use of an *intramolecular* photocyclisation in the synthesis of berberine type alkaloids (**472**).



471 **472** 80%

Figure 111

Griesbeck *et al.*,[6] have reported on the cyclisation of a series of methylthioalkyl esters (**473-476**) when irradiated in acetone or acetonitrile, to give the tricyclic systems (**477-480**) as well as (**477a-480a**) which arise from a competing deprotection reaction.



473-476 **477-480** **477a-480a**

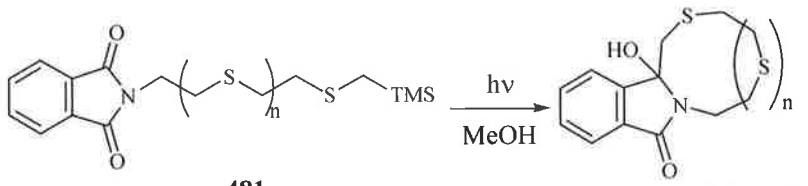
Figure 112

Table 25

Phthalimide			Conversion	Yield			
	m	n	[%]		[%]	m	n
473	1	2	100	**477**	100	1	2
474	1	3	61	**478**	100	1	3
475	1	5	100	**479**	< 10	1	5
476	2	10	—	**480**	82	2	10

2.4.7.1 Cyclisations of α-Trialkylsilylmethyl-substituted thioethers

Yoon and Mariano[96] have reported on the cyclisation of phthalimido-polythioethers (**481**; n = 1, 2), when irradiated in methanol. The cyclised products (**482**; n = 1, 2) are formed in excellent yields, along with low yields of benzazepinediones.

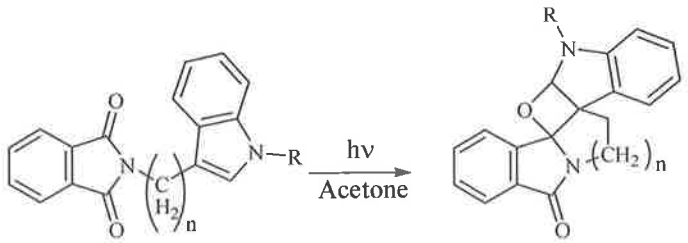


481 **482** 80%

Figure 113

2.4.8 *Intramolecular* Paternò-Büchi reactions

In 1982, Kanaoka *et al.*,[42c] reported on the first example of *intramolecular* oxetane formation. When a series of *N*-(ω-indol-3-ylalkyl)phthalimides (**483-484**) were irradiated in acetone, the phthalimides underwent cycloaddition to give the oxetanes (**485-486**) in poor to reasonable yields.[97a]



483-484 **485-486**

Figure 114

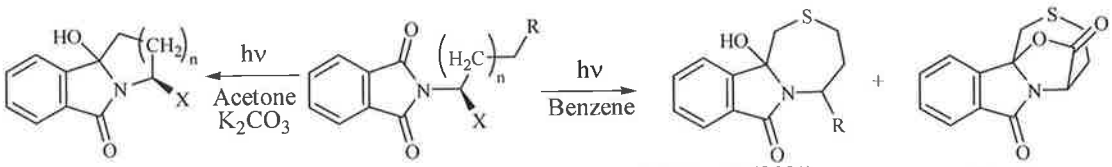
Table 26

Phthalimide			Oxetane			
	n	R		[%]	n	R
483	2	$COCH_3$	**485**	27	1	CH_3CO
484	4	$COCH_3$	**486**	69	3	CH_3CO

Kanaoka *et al.*,[97b] have also shown that a bichromophoric series of phthalimide-*N*-acylindoles, containing a tetrahydrocarbazole in the *N*-alkyl side-chain, when irradiated in acetone, forms oxetanes in poor to reasonable yields.

2.4.9 Decarboxylative photocyclisations.

Griesbeck *et al.*,[98a] have reported that *N*-phthaloylmethionine (**487**) undergoes decarboxylation during irradiation in acetone, acetonitrile or benzene, to give the cyclised products (**496-498**). Similarly, they have also reported that irradiation of the glutamic acid derivative (**488**) in acetone, in the presence of sodium carbonate, affords (**499**) in good yield. (**489**) gave (**500**), the benzyl and methyl derivatives (**490**) and (**491**) afford (**501**) and (**502**),[98b] while rings of up to 13 atoms have been synthesised (**505**) (Figure 115; Table 27).[98c]



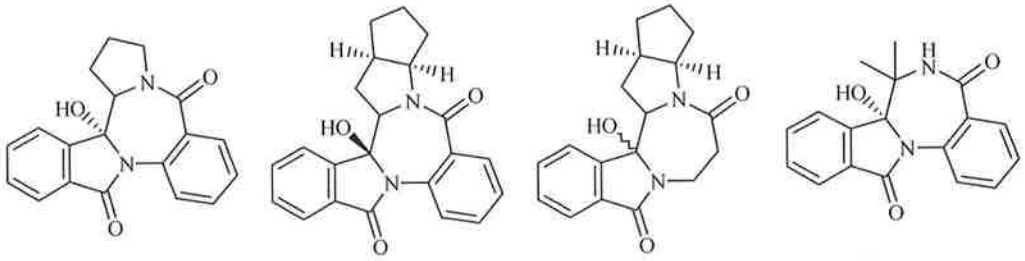
499-505 **487-495** **496** R = H (20%), **497** R = COOH (30%) **498** 50%

Figure 115

Table 27

Phthalimide				Yields				
	n	R	X	**496** [%]		[%]	n	X
487	1	SCH_3	COOH	20	—	—	1	H
488	1	COOH	COOH	—	**499**	76	1	H
489	1	COOH	$COOCH_3$	—	**500**	—	1	$COOCH_3$
490	1	COOH	C_6H_5	—	**501**	74	1	C_6H_5
491	1	COOH	CH_3	—	**502**	81	1	CH_3
492	2	COOH	H	—	**503**	89	2	H
493	3	COOH	H	—	**504**	89	3	H
494	9	COOH	H	—	**505**	81	9	H

A series of macrocyclic systems, containing amide and ester functions, have been photochemically synthesised, as well as more complex tetracyclic structures, from ω-phthalimido carboxylates.[60b]



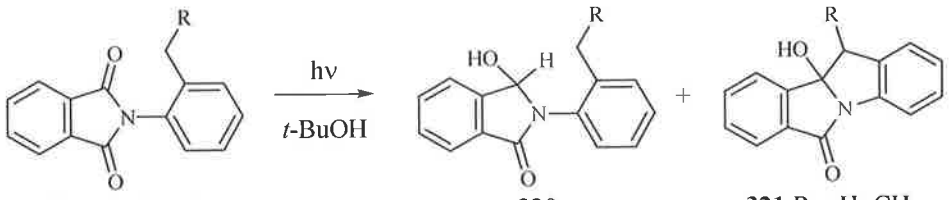
506 **507** **508** **509**

Figure 116

Chapter 3: Photolysis and Thermolysis of 2-Hydroxy and 2-amino-phenyl phthalimides and their acyl derivatives

3.1 Introduction

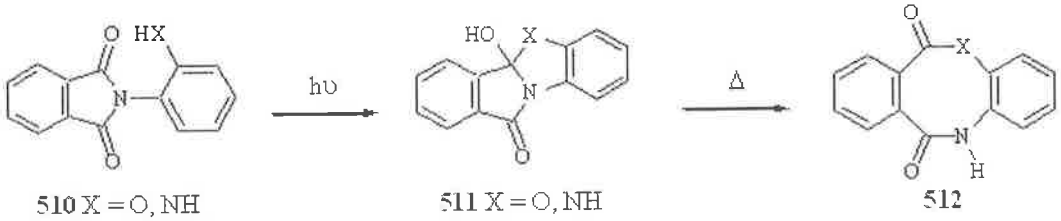
It was known that irradiation of *N*-(2-methylphenyl)phthalimide (**319**; R = H) or *N*-(2-ethylphenyl)phthalimide (**319**; R = CH_3) in alcoholic solvents, not only gives a photoreduction product (**320**), but also a product resulting from *intramolecular* cyclisation (**321**; R = H) in yields up to 82%. The cyclisation occurs by a δ-hydrogen abstraction.[17a] A pyridine derivative has also been reported, although the yields were poor.[87c]



319 R = H; CH_3 **320** **321** R = H; CH_3

Figure 117

However, there was no literature on the analogous 2-hydroxyphenyl (**510,** X = O) or 2-aminophenyl (**510**, X = NH) derivatives. As these compounds also have δ-hydrogens, it was anticipated that they might be photoactive. With that in mind, the initial aim of this project was to see whether a tetra-cyclic system analogous to (**509**) could be photochemically produced, or alternatively, whether an eight membered heterocyclic system (**512**) might be obtained from *N*-(2-hydroxyphenyl) or *N*-(2-aminophenyl)phthalimide (**510**). Attempts to synthesise compounds of the type (**512**) in this research group have proven elusive.[99]

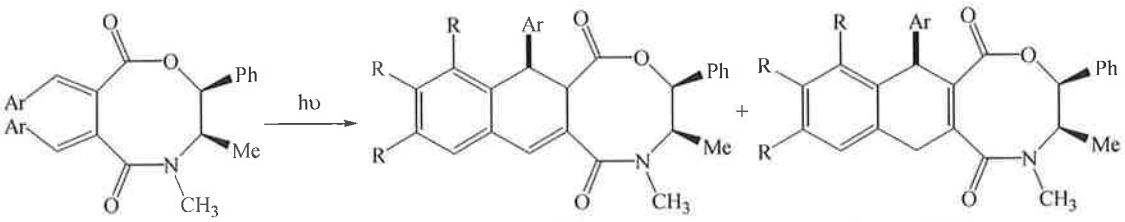


510 X = O, NH 511 X = O, NH 512

Figure 118

While analogues of (**512**) have very recently been synthesized photochemically, they were not, however, derived from a phthalimide system. Assoumatine *et al.*[100] have described the synthesis of (1*S*, 2*R*)-1-(3, 4, 5-trimethoxyphenyl)-6, 7, 8-trimethoxy-1, 2-dihydronaphthalene-2, 3-dicarboxylate (-)-ephedrine cyclic amide ester (**514**) and (1*S*, 2*R*)-1-(3, 4, 5-trimethoxyphenyl)-6, 7, 8-trimethoxy-1, 4-dihydronaphthalene-2, 3-dicarboxylate (-)-ephedrine cyclic amide ester (**515**) from

(*E*, *E*)-2, 3-di (3, 4, 5-trimethoxybenzylidene)succinate (-)-ephedrine cyclic amide ester (**513**) (Figure 119).



513 **514** **515**

Figure 119

3.1.1 General Synthesis of *N*-substituted phthalimides

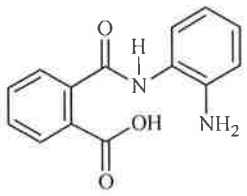
In general, *N*-substituted phthalimides are synthesised by heating phthalic anhydride and the appropriate amine under reflux in glacial acetic acid.

3.1.2 Synthesis of *N*-(2-hydroxyphenyl)phthalimide

The reaction was carried out by heating phthalic anhydride and *o*-aminophenol together under reflux in glacial acetic acid. The crude product was recrystallised from ethyl acetate. ^{1}H NMR spectrum (d_6 DMSO) of the product showed a broad singlet at 9.9ppm and was assigned to the phenol OH, confirmed by an exchange with D_2O. Two hydrogen multiplets at 7.97ppm, 7.93ppm and 7.90ppm along with one hydrogen multiplets at 7.28 and 7.03ppm indicated the eight hydrogens on the two aromatic rings. The ^{13}C NMR spectrum showed ten distinct peaks, with the peak at 167.5 being assigned to the two **C**=O groups, the peak at 154.4ppm being assigned to **C**-OH. The peaks at 134.9, 132.3, 130.8, 130.7, 123.7, 119.5, 119.2 and 116.9ppm were assigned to the remaining aromatic carbons. The IR spectrum showed a peak at 3380cm^{-1} indicating the presence of OH, while a pair of peaks at 1788 and 1702cm^{-1} are suggestive of C=O. The compound exhibited spectral data and melting point in agreement with values reported in the literature.[101, 102]

3.1.3 Synthesis of *N*-(2-aminophenyl)phthalamic acid

Attempts to synthesis *N*-(2-aminophenyl)-phthalimide (**510**, X = NH) by heating phthalic anhydride and 1,2-diaminobenzene together under reflux in glacial acetic acid proved difficult and resulted in very poor yields. A search of the literature indicated that a convenient synthesis could be achieved through the initial formation of *N*-(2-aminophenyl)phthalamic acid (**516**).[103]



516

The required *N*-(2-aminophenyl)phthalamic acid (**516**) was synthesised by dissolving phthalic anhydride in cold chloroform and adding it slowly, with stirring, to a solution of 1,2-diaminobenzene in boiling chloroform. The resulting solution was then allowed to cool and stand at room temperature overnight. The crude product was filtered off, dried and recrystallised from methanol using activated charcoal. The melting point of the compound was obtained and was in agreement with that reported in the literature.[103]

3.1.4 Synthesis of *N*-(2-aminophenyl)phthalimide

The *N*-(2-aminophenyl)phthalamic acid (**516**) was then added to hot dilute hydrochloric acid, and the solution was stirred until clear. After a brief period, a white precipitate formed, and after a further eight minutes, ice was added to lower the temperature. The reaction mixture was neutralised with dilute ammonium hydroxide and the crude product filtered off and recrystallised from ethanol. The ^{1}H NMR spectrum (d_6 DMSO) of the product showed two-hydrogen multiplets at 7.93ppm and 7.87ppm, a one-hydrogen multiplet at 7.13ppm, a two-hydrogen multiplet at 6.76ppm and a one-hydrogen multiplet at 6.57ppm. A broad singlet at 5.34ppm was assigned to the NH_2 and this peak disappeared after addition of D_2O. The ^{13}C NMR spectrum showed ten distinct peaks, with the peak at 167.9 being assigned to the two **C**=O groups and the peaks at 146.8, 134.5, 132.8, 130.4, 130.0, 123.4, 116.3, 115.7, 115.6ppm to the aromatic carbons. The IR spectrum showed peaks at 3459 and 3382cm^{-1}, indicating the presence of NH_2, while a peak at 1707cm^{-1} suggested C=O. The spectral data and melting point were in agreement with values reported in the literature.[103]

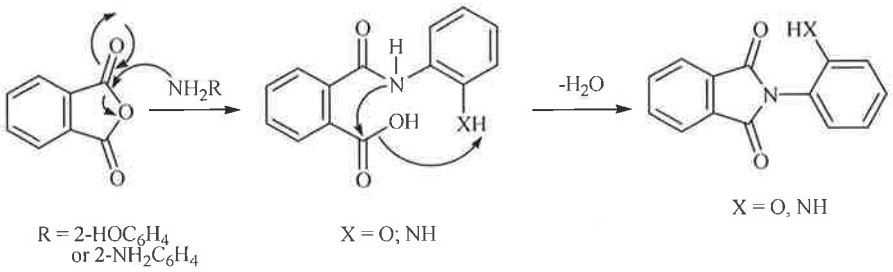


Figure 120

In both cases, the mechanism of reaction involves attack by the nucleophilic amino group on a carboxyl group of the anhydride, forming the phthalamic acid (**516**), followed by subsequent intramolecular attack by the amido nitrogen lone pair on the other carboxyl group, dehydration and formation of phthalimide (**510**).

3.1.4 Photolysis of *N*-substituted phthalimides

As compounds (**510**, X = O, NH) were heteroatom analogues of (**508**, R = H, CH_3) it was decided to determine if they shared similar photochemical properties. A solution of either *N*-(2-hydroxyphenyl)phthalimide or *N*-(2-aminophenyl)phthalimide in one of a number of solvents (methanol, ethanol, iso-propyl alcohol, tert-butyl alcohol, acetone, tetrahydrofuran, acetonitrile or toluene), or a solvent containing a potential electron donor (cyclohexene, styrene, aniline), was irradiated for a prolonged period using a 400 W medium pressure mercury vapour lamp fitted with a Pyrex filter, between six and eight hours. TLC analysis, using 60:40 light petroleum 40-60°: ethyl acetate, showed starting material as well as some baseline product. After solvent evaporation and purification of recovered solid, the starting material was isolated as the major product, in greater than 95% yield, with the remaining solid a mixture of inseparable compounds.

3.1.5 Pyrolysis of *N*-substituted phthalimides

As 2-hydroxyphenyl phthalimide (**510**, X = O) and 2-aminophenyl phthalimide (**510**, X = O), were photochemically inactive, it was decided to investigate their thermal chemistry.

3.1.6 Formation of 2-phenylbenzoxazole (520) from (510 X = O)

Initially, a small amount of *N*-(2-hydroxyphenyl)phthalimide (**510**, X = O) was heated to 250°C, approximately 30°C beyond its melting point, in a melting point

tube for approximately five minutes. The tube was then crushed and the contents analysed by TLC using 95: 5 light petroleum 40-60: ethyl acetate. A highly fluorescent new spot was observed and, as a result of this, the reaction was scaled up. Heating *N*-(2-hydroxyphenyl)phthalimide at 250°C for fifteen minutes, followed by flash chromatography on the resulting black solid gave a white crystalline solid. Further TLC analysis showed that the white crystals and sublimed product were identical.

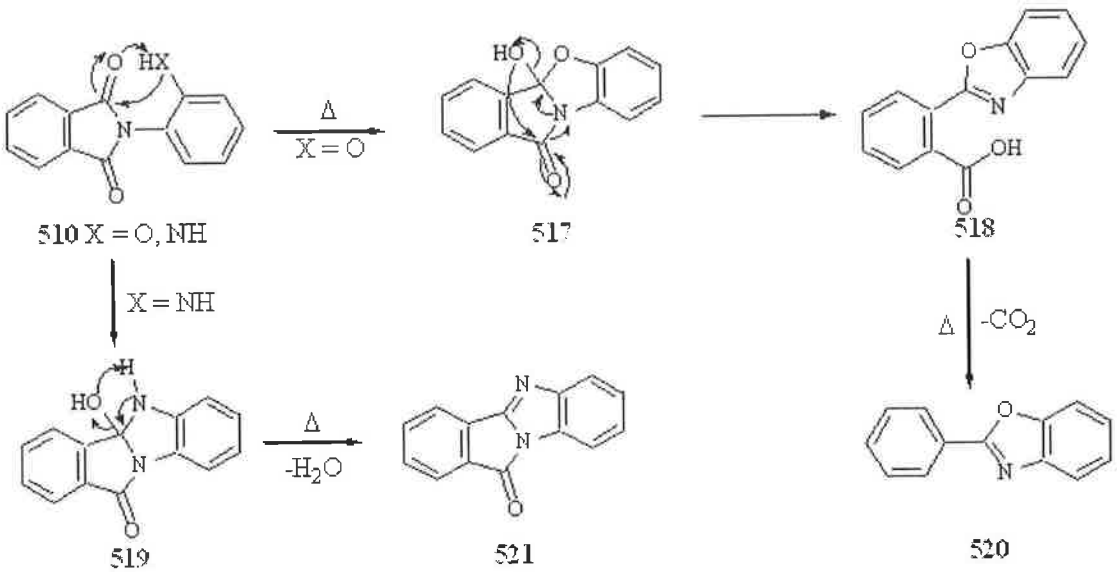
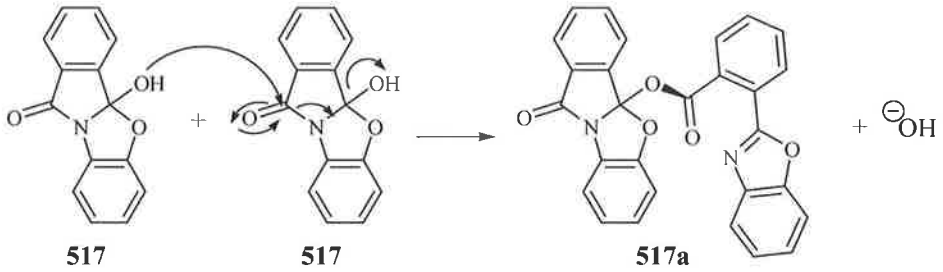


Figure 121

The IR spectrum of the product showed the absence of -OH and C=O groups, while the ^{13}C NMR spectrum ($CDCl_3$) confirmed the absence of C=O groups. The IR spectrum did show a peak at 1618 cm^{-1} assigned to a C=N and a peak at 164 ppm in the ^{13}C NMR spectrum supported this. Two peaks in the IR spectrum at 745 cm^{-1} and 703 cm^{-1} were indicative of a mono-substituted aromatic ring, which was supported by the presence of nine aromatic hydrogens in the ^{1}H NMR spectrum. While there are nine hydrogens in the parent phthalimide, only eight are aromatic, with the ninth being the OH hydrogen. This suggested hydrogen transfer from the phenolic OH group to one of the aromatic rings and requiring either accompanying cleavage of a C-CO bond or of a C-OH bond. From this it was thought that there was hydrogen transfer between the OH of the phthalimide and an aromatic ring, achievable only by breaking one of the two C-C(=O) bonds. Mechanistic considerations (Figure 121) involving phenolic OH attack on a carbonyl group suggest possible formation of a five membered ring intermediate (**517**) containing an O-C-N system. *Intra*molecular

displacement of the oxazolyl unit by the migrating OH via a highly strained pentacyclic intermediate, would yield 2-benzoxazol-2-yl-benzoic acid (**518**). Decarboxylation of (**518**), under the reaction conditions would yield 2-phenylbenzoxazole (**520**), a structure consistent with the spectral data of the isolated product. However, it is more likely that an *inter*molecular process occurs within the melt, initiated by the OH of one molecule of (**517**) attacking at the carbonyl of another, resulting in the cleavage of an (O)C-N bond and the formation of a new C=N bond and liberation of a hydroxide ion. The liberated hydroxide would then propagate the ongoing conversion of (**517**) to (**518**) (Figure 122).



517 **517** **517a**

$HO^{\ominus}$ + **517** ⟶ **518** + $^{\ominus}OH$

Figure 122

An authentic sample of 2-phenylbenzoxazole was prepared according the method described by Hein,[104] whereby equimolar amounts of *o*-aminophenol and benzoic acid were mixed with poly-phosphoric acid and heated at 250°C for four hours. The spectroscopic data and melting point of the isolated 2-phenylbenzoxazole were identical to that of the product from thermolysis of (**510**, X = O).

3.1.7 Formation of benzo[4,5]imidazo[2,1-a]isoindol-11-one (521)

It was anticipated that the 2-aminophenyl derivatve might behave in a similar fashion if heated above its melting point. On heating, *N*-(2-aminophenyl)phthalimide (**510**, X = NH) at 250°C reaction occurred and a yellow crystalline product was isolated. The IR spectrum showed the presence of a carbonyl group (1763cm^{-1}), with a second peak at 1740cm^{-1}, possibly C=N. There was no evidence of any NH being present. The ^{1}H NMR spectrum ($CDCl_3$) showed eight hydrogens, all aromatic. The ^{13}C NMR spectrum showed fourteen carbons, eight of them being aromatic CH units, as confirmed by ^{13}C DEPT experiment. The microanalytical data was consistent with the molecular formula $C_{14}H_8N_2O$, suggesting loss of a water molecule in formation

of the product from *N*-(2-aminophenyl)phthalimide ($C_{14}H_{10}N_2O_2$). Intramolecular ring closure to yield tetracyclic compound (**519**), followed by loss of water made possible by the presence of an NH group, would yield benzo[4,5]imidazo[2,1-a]isoindol-11-one (**521**) (Figure 121). This structure, containing six quaternary carbons, is consistent with the spectral data. Perry[103] and Young[105] have independently prepared (**521**) by heating *N*-(2-aminophenyl)phthalamic acid (**516**) and *N*-(2-aminophenyl)phthalimide (**510**, X = NH) respectively. The IR spectrum and melting point reported by Young[105] are consistent with the IR spectrum and melting point obtained in this work. No NMR spectra are given in either publication.

3.1.8 Synthesis of esters and amides of *N*-substituted phthalimides.

While the thermal reactions of *N*-(2-hydroxyphenyl)phthalimide and *N*-(2-aminophenyl)phthalimide had occurred the photochemical reactions of *N*-(2-hydroxyphenyl)phthalimide and *N*-(2-aminophenyl)phthalimide were unsuccessful. It is possible that the presence of the –OH and $-NH_2$ groups on the *N*-aryl ring of the phthalimide may have changed the lowest excited state from $n \rightarrow \pi^*$ to $\pi \rightarrow \pi^*$, hence reducing the photoactivity. Reducing the availability of the lone pair on the heteroatom to the π-system, might result in raising the energy of the $\pi \rightarrow \pi^*$ state and therefore permit a lowest $n \rightarrow \pi^*$ state. One such way to accomplish this would be to prepare esters and amides from *N*-(2-hydroxyphenyl)phthalimide and *N*-(2-aminophenyl)phthalimide respectively. These ester and amide derivatives might undergo a photochemical change. A series of esters of *N*-(2-hydroxyphenyl)phthalimide and amides of *N*-(2-aminophenyl)phthalimide was synthesised, by the addition of an appropriate acid chloride to an ice-cold solution of pyridine containing either the hydroxy or amino phthalimides (**510**, X = O, NH).

3.1.9 Synthesis of *N*-(2-benzoyloxyphenyl)phthalimide (522)

The ^1H NMR spectrum ($CDCl_3$) of *N*-(2-benzoyloxyphenyl)phthalimide (**522**) showed two-hydrogen multiplets at 7.93, 7.79 and 7.65ppm, a three hydrogen multiplet at 7.45ppm and two-hydrogen multiplets at 7.36 and 7.30ppm, accounting for the expected thirteen aromatic hydrogens. The ^{13}C NMR spectrum showed fifteen signals, with the peaks at 166.9 and 164.3 being assigned as C=O; the peaks at 147.1,

134.8, 134.0, 132.1, 130.5, 130.4, 129.9, 129.2, 128.9, 126.8, 124.3, 124.29 and 123.24ppm were assigned as aromatic carbons. The IR spectrum showed carbonyl peaks at 1787, 1732 and 1721cm^{-1}. Elemental analysis gave satisfactory results for $C_{21}H_{13}NO_4$.

3.1.10 Synthesis of *N*-(2-acetoxyphenyl)phthalimide (523)

The ^{1}H NMR spectrum ($CDCl_3$) of *N*-(2-acetoxyphenyl)phthalimide (**523**) showed two-hydrogen multiplets at 7.89 and 7.73ppm, a one-hydrogen multiplet at 7.40ppm and a three-hydrogen multiplet at 7.30ppm, which were all assigned as aromatic hydrogens, and a three-hydrogen singlet at 2.06ppm which was assigned as CH_3. The ^{13}C NMR spectrum showed twelve signals, with the peaks at 168.5 and 166.9 being assigned as C=O; the peaks at 146.7, 134.9, 132.2, 130.2, 129.8, 126.7, 124.34, 124.30 and 124.0 were assigned as aromatic carbons, with the peak at 21.3ppm assigned to the CH_3. The IR spectrum showed carbonyl peaks at 1777, 1740 and 1721cm^{-1}. Elemental analysis gave satisfactory results for $C_{16}H_{11}NO_4$.

3.1.11 Synthesis of *N*-(2-benzoylamidophenyl)phthalimide (524)

The ^{1}H NMR spectrum ($CDCl_3$) of *N*-(2-benzoylamidophenyl)phthalimide (**524**) showed a broad singlet at 8.34ppm, which exchanged with D_2O and was assigned to the NH. A one hydrogen multiplet was present at 7.95, a two hydrogen multiplet at 7.88, a four hydrogen multiplet at 7.72 and two hydrogen multiplets at 7.45, 7.35 and 7.30ppm, giving in all, thirteen aromatic hydrogens. The ^{13}C NMR spectrum showed fourteen signals, with the peaks at 167.91 and 165.78 being assigned as C=O; the peaks at 134.61, 134.28, 132.33, 132.04, 129.93, 129.14, 128.89, 127.59, 126.68, 126.38, 124.92 and 125.52ppm were assigned as aromatic carbons. The IR spectrum showed a peak at 3349 cm^{-1} assigned to NH, with two carbonyl peaks at 1714 and 1703cm^{-1}. Elemental analysis gave satisfactory results for $C_{21}H_{14}N_2O_3$.

3.1.12 Synthesis of *N*-(2-acetamidophenyl)phthalimide (525)

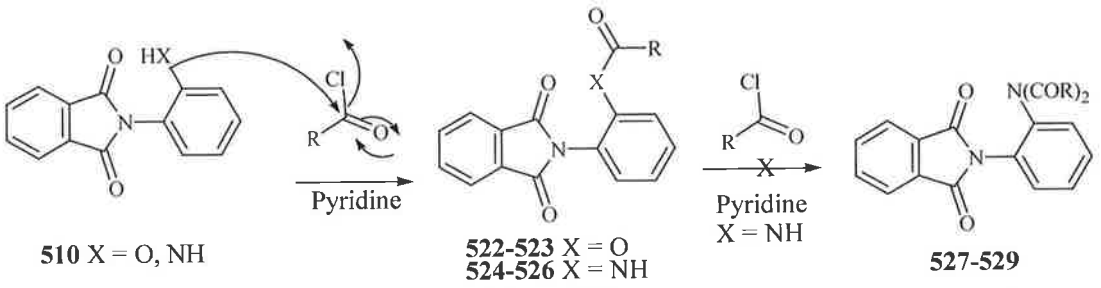
The ^{1}H NMR spectrum ($CDCl_3$) of *N*-(2-acetamidophenyl)phthalimide (**525**) showed a two-hydrogen multiplet at 7.86ppm, a one hydrogen multiplet at 7.82ppm, a one hydrogen multiplet at 7.37ppm, a two-hydrogen multiplet at 7.21ppm and another at 7.14ppm, assigned to the expected eight aromatic hydrogens. A broad singlet, which exchanged with D_2O, was also present at 7.51ppm and assigned as NH and a three-

hydrogen singlet at 1.94ppm which was assigned as CH_3. The ^{13}C NMR spectrum showed twelve signals, with the peaks at 168.87 and 161.72 being assigned as C=O; the peaks at 135.12, 132.14, 129.97, 128.94, 128.93, 126.29, 126.18, 124.45 and 124.39 were assigned as aromatic carbons, with the peak at 24.59ppm assigned to the CH_3. The IR spectrum showed a peak at 3347cm^{-1} attributed to NH, with three carbonyl peaks at 1719, 1707 and 1702cm^{-1}. Elemental analysis gave satisfactory results for $C_{16}H_{12}N_2O_3$.

3.1.13 Synthesis of *N*-(2-propionamidophenyl)phthalimide (526)

The ^1H NMR spectrum ($CDCl_3$) of *N*-(2-propionamidophenyl)phthalimide (**526**) showed the expected eight aromatic hydrogens as a two-hydrogen multiplet at 7.86ppm, a one hydrogen multiplet at 7.83ppm, a two-hydrogen multiplet at 7.73, a one hydrogen multiplet at 7.36ppm, a two hydrogen multiplet at 7.21ppm. A broad singlet, which exchanges with D_2O, at 7.50ppm was assigned as NH. A two-hydrogen quartet at 2.16ppm was assigned as CH_2 and a three hydrogen triplet at 1.00ppm assigned to CH_3. The ^{13}C NMR spectrum showed thirteen signals, with the peaks at 172.51 and 167.70 being assigned as C=O; the peaks at 135.12, 134.53, 132.12, 129.97, 128.94, 126.17, 126.02, 124.41, 124.36 were assigned as aromatic carbons, with the peaks at 30.80ppm and 9.97ppm assigned to $\mathbf{C}H_2CH_3$ and $\mathbf{C}H_3$ respectively. The IR spectrum showed a peak at 3334 cm^{-1} assigned to NH, with carbonyl peaks at 1720 and 1708cm^{-1}. Elemental analysis gave satisfactory results for $C_{17}H_{14}N_2O_3$.

It is worth noting that attempts to synthesise the *di*-amides (**527-529**) under similar conditions (0-5°C), at room temperature or at elevated temperature, either directly from *N*-(2-aminophenyl)phthalimide (**510**, X = NH) or from the previously prepared *mono*-amides, resulted in the recovery of the *mono*-amides. The presence of the electron withdrawing phthalimide group *ortho* to the target nitrogen, and the acetamido carbonyl group, were sufficient to reduce the N nucleophilicity and prevent it reacting with another molecule of an acid chloride. The mechanism for acylation is shown in Figure 123.



510 X = O, NH

522-523 X = O
524-526 X = NH

527-529

Figure 123

Table 28

Phthalimide		Acid Chloride	Ester			Amide		
510	X	R		R	[%]		R	[%]
a	O	C_6H_5	**522**	C_6H_5	54	—	—	—
a	O	CH_3	**523**	CH_3	57	—	—	—
b	NH	C_6H_5	—	—	—	**524**	C_6H_5	62
b	NH	CH_3	—	—	—	**525**	CH_3	53
b	NH	C_2H_5	—	—	—	**526**	C_2H_5	48

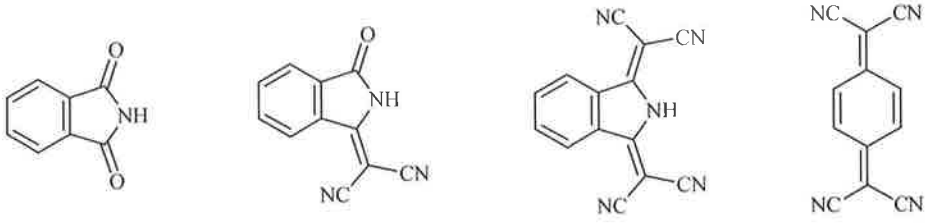
3.1.14 Photolysis and pyrolysis of esters and amides of *N*-(2-hydroxyphenyl) and *N*-(2-aminophenyl)phthalimides

While the *intra*molecular photocyclisation of phthalimides containing esters[86] and amides[90e] was previously known, the esters were β to the phthalimide carbonyl group and the reaction proceeded by γ-hydrogen abstraction, while the amides were at the end of long alkyl chains. The esters and amides studied in this work are δ to the phthalimide carbonyl groups, and δ-hydrogen abstraction from the amide would in principle be possible, in a similar fashion to the δ-hydrogen abstraction reaction undertaken by *N*-(2-alkylphenyl)phthalimides. The photochemical properties of the series (**522-526**) were investigated. Compounds (**523**) and (**525**) were irradiated, using a 400 W medium pressure mercury vapour lamp fitted with a Pyrex filter, in methanol or acetonitrile but only unchanged staring material was recovered. In the absence of any photoreaction with (**523**) and (**525**), (**522**), (**524**) and (**526**) were not irradiated. Attempts to pyrolyse (**522-525**) resulted in charred product that contained starting material and an inseparable mixture of products, possibly polymeric.

Chapter 4: General synthesis of 2-alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones

4.1 Analogues of *N*-substituted phthalimides

As the photochemistry of the *N*-(2-substituted aryl)phthalimides ultimately proved to be unproductive, it was decided to investigate the methylene-malononitrile analogues, $C{=}C(CN)_2$, effectively changing from the phthalimide (**1**) to the structural analogue (**530**). This series is also structurally analogous to (**531**), itself electronically analogous to TCNQ, tetracyanoquinodimethane, (**532**). Compound (**531**) and its *N*-substituted analogues have recently become conveniently accessible due to other work carried out in this research group.[106]



1 **530** **531** **532**

Figure 124

Due to its greater electronegativity, the oxygen in a carbonyl group has a greater share of the electrons than the carbon, resulting in a δ^+ carbon. It was anticipated that the replacement of a carbonyl oxygen by a dicyanomethylene moiety ($C(CN)_2$), would also result in a δ^+ carbon due to the polarising effect of the nitrogens of the CN groups. This change might not significantly impair the photoreactions of these types of compounds. However, the compounds would not have access to the $n \rightarrow \pi^*$ transitions available to phthalimides.

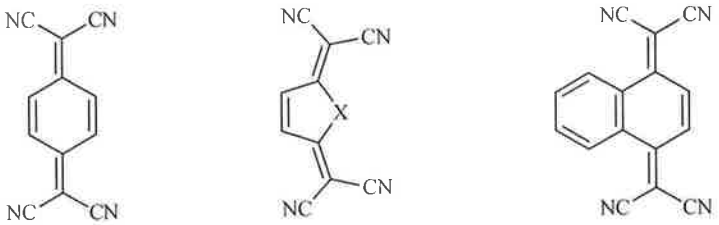
Due to the presence of the carbonyl groups on the strained five-membered ring system, the phthalimide molecule is flat. The carbonyl groups are activated, and the rigid geometrical arrangement allows for effective *intra*molecular interaction between the carbonyl and side chain groups, whereby the symmetrical structure and the presence of two equally reactive carbonyl groups increases the probability of such interaction by a factor of two.

The presence of the dicyanomethylene group will maintain the strained five membered ring system, and therefore maintain the electronic analogy to *N*-substituted phthalimides. However, the introduction of a single dicyanomethylene

group removes the symmetry of the molecule, which could potentially lead to photoreaction at the C=O side, as in phthalimides, or indeed at the dicyanomethylene side, possibly leading to formation of novel families of compounds.

4.1.1 Analogues of tetracyanoquinodimethane (TCNQ).

Tetracyanoquinodimethane, TCNQ, (**532**) a well established electron acceptor, and its derivatives, the majority having π-extended systems, have been the subject of much interest in recent years.[107] Heterocyclic analogues of TCNQ are usually derivatives of (**533**). These compounds are said to be *iso*-π-electronic with TCNQ by virtue of the presence of a heteroatom within the ring system. The lone pair of π electrons on the heteroatom is capable of contributing to the mesomeric bond system.



532 **533** X = S, Se, O, NR **534**

Figure 125

To date, there are no reports of the nitrogen analogue (**533**; X = NR). One and two electron reduction of (**533**) should result in the formation of a 4n + 2π-electron cyclic planar system whose potential aromaticity should result in a lower reduction potential and a stabilizing effect on the anion radical. The degree of aromaticity decreases in the order of thiophene > pyrole > furan (S > N > O), the acceptor ability of (**533**; X = NR) should be expected to be at least midway between that of (**533**; X = S) and (**533**; X = O). An additional advantage to the pyrrole system would be the ability to adjust the properties of the pyrollidine ring by varying the substituents at the nitrogen. This would also allow for the possibility of attaching a variety of functionalities, which might be used to increase the solubility of these compounds, or facilitate the introduction of polymerisable groups, which might increase their applications. In addition, such *N*-substituents might become involved in photoreactions the compounds may undergo.

Our interest in the dicyanomethylene compounds of type (**530**) is due to recent work within this group on the *bis*-dicyanomethylene compounds of the type (**531**), analogues of benzo-TCNQ (**534**).[108] The compounds (**531**) are of interest in that variation of the *N*-substituent would allow fine-tuning of the electron acceptor ability and control of the properties of charge transfer complexes with various electron donors, whose electrical properties would be of interest.

4.1.2 The Knoevenagel Reaction

Originally,[106a] two routes were considered for synthesis of the tetracyano derivatives (**531**). The first involved the Knoevenagel condensation (Figure 126), a classical carbon-carbon double bond forming reaction, which involves treating a carbonyl compound with an active methylene compound, such as malononitrile, in the presence of a catalytic amount of base or sometimes acid. The active methylene group usually contains two electron-withdrawing groups and can include malonates, acetoacetates, acetonitriles, malononitrile, 1,3-diones or barbituric acid. A variety of aldehydes can be used, but the use of ketones is limited due to their reduced reactivity.

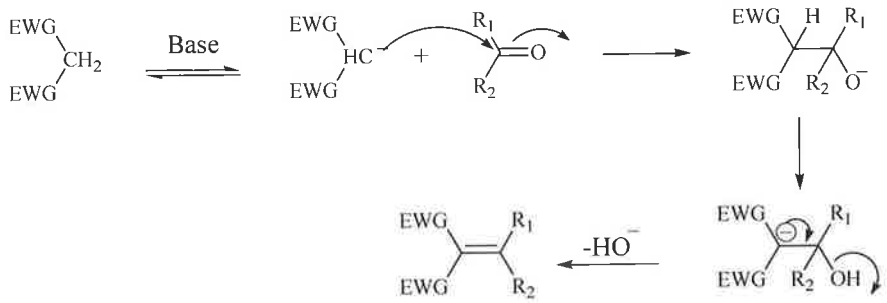
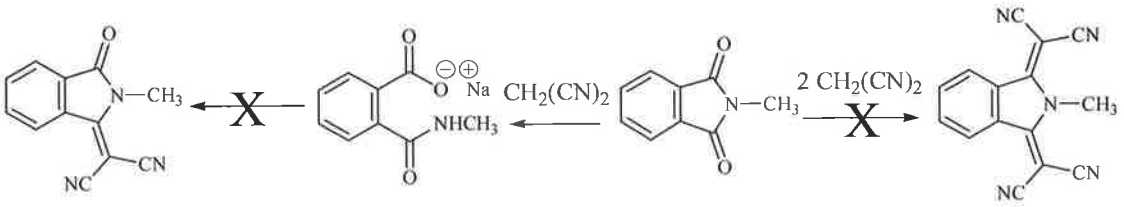


Figure 126: The Knoevenagel Condensation[109]

The catalysts used are also of importance, with the more common ones including primary, secondary and tertiary amines or their corresponding ammonium salts. However pyridine is by far the most widely used catalyst either alone or in the presence of small amounts of piperidine. The ammonium salts can be used with small amounts of ammonium or piperidinium acetate.

The Knoevenagel condensation was initially considered attractive as a readily accessible supply of starting materials, the *N*-substituted phthalimides, could be prepared easily in large quantities. While reports of the Knoevenagel reaction of

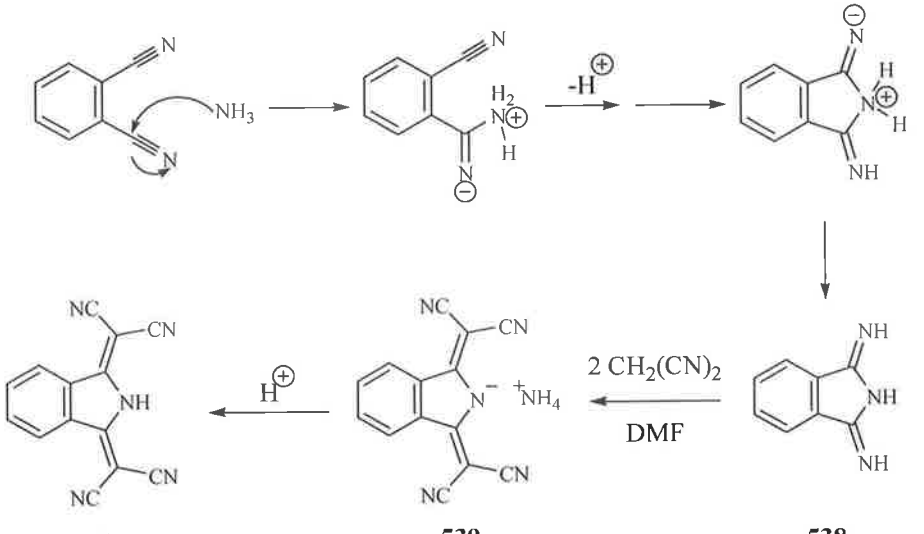
activated methylene compounds with an extensive range of aldehydes and ketones are numerous, such reactions with phthalimides have not been reported. Investigation found that *N*-methylphthalimide (**2**) undergoes ring opening on nucleophilic attack by sodio-malononitile to give a salt (**535**), which failed to undergo ring closure to the desired pseudo phthalimide. Therefore this proved to be a non-viable route for the synthesis of *N*-substituted derivatives of (**530**) or (**531**).[106a]



537 **535** **2** **536**

Figure 127: The Knoevenagel condensation of NMP and malononitrile[106a]

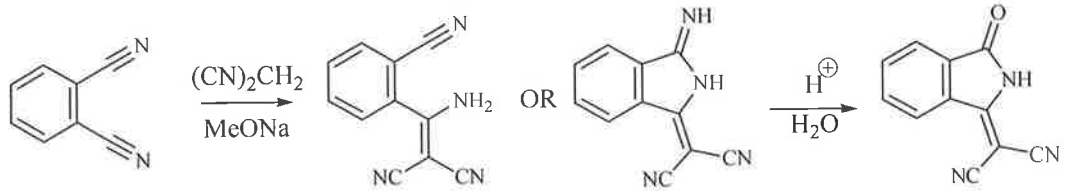
The second route[106a] considered was via (**538**), formed by bubbling ammonia through a methanolic solution of phthalonitrile in DMF. On addition of malononitrile to (**538**) in DMF at room temperature an immediate condensation reaction took place with the elimination of ammonia, to give the ammonium salt (**539**), which was isolated by precipitation with chloroform. The protonation of the ammonium salt was carried out by acidification of a methanolic solution of (**539**) by addition of dilute hydrochloric acid to give (**531**) (Figure 128). Traditional alkylation methods, using alkyl halides or dimethyl sulphate also proved unsuccessful with (**531**) and (**539**), presumably due to the poor nucleophilicity of the ring nitrogen.[106c]



531 **539** **538**

Figure 128: Condensation with imidines.

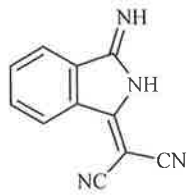
While (**531**) is conveniently synthesised from the method outlined (Figure 128), the method does not provide a route to (**530**). However, it has been independently shown by Conway[106a] and Crean[106c] that by gentle heating of phthalonitrile and malononitrile together in methanol, in the presence of base, they would form either a ring opened product (**540**), which could subsequently be ring closed to (**541**), or give the cyclised product (**541**) directly. Compound (**541**) could then be hydrolysed with acid to yield the required phthalimide analogue (**530**) (Figure 129).



540 **541** **530**

Figure 129

4.1.3 Synthesis of 3-dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine (541)



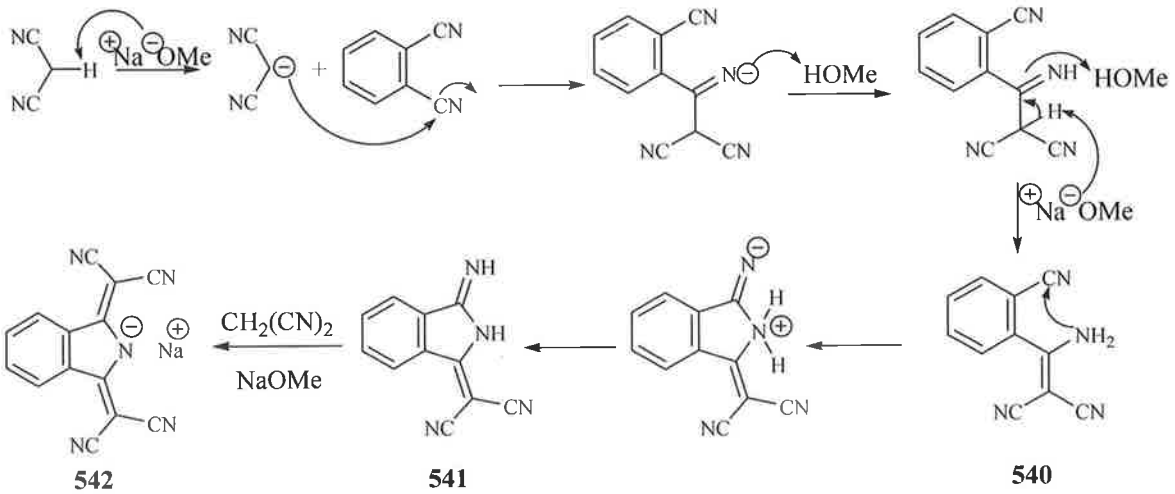
541

When a solution of methanol containing phthalonitrile and malononitrile is heated to about 30°C in the presence of sodium methoxide, a red/ orange solution is obtained. After maintaining the temperature for three hours, an orange precipitate was observed. This was filtered off and recrystallised from methanol, to give an orange compound that did not melt below 350°C, but blackened slowly above 210°C. The compound obtained was identified as (**541**), rather than (**540**), from the ^{13}C NMR and IR spectra. The ^{1}H NMR spectrum (d_6 DMSO) showed a broad singlet at 10.00ppm, corresponding to two hydrogens, this peak was assigned to the two NH groups. The aromatic hydrogens appeared as two-hydrogen multiplets at 8.03 and 7.68ppm. The ^{13}C NMR spectrum showed the presence of **C**=NH at 177.39ppm (or 173.51ppm), (**C**=C(CN)$_2$) at 173.51ppm (or 177.39ppm), and two C≡N peaks at 117.14 and 116.39ppm, consistent with structure (**541**). The IR spectrum showed peaks at 3399cm^{-1} NH and 2982cm^{-1} C=**NH** and 1687cm^{-1} C=N. Mass spectrometric analysis of the product resulted in a molecular ion of 194m/z. There were some ambiguities between the spectral data reported by Conway[106a] Crean[106c] and the data recorded during this work, which made it unclear as to whether compound (**540**) was isolated instead of (**541**). However, if compound

(**540**) had been isolated, a third C≡N peak would be visible and the peak corresponding to **C**=NH would not be present. Presumably (**540**) is formed as an intermediate in the reaction, but is not isolated.

Reaction of (**541**) with malononitrile/ sodium methoxide in boiling methanol provides a convenient route to the sodium salt of (**542**), acidification of which yields (**531**), thus providing an alternative route to (**531**).[106]

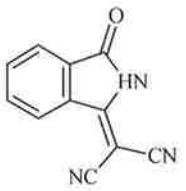
The mechanism for formation of (**541**) (Figure 130) involves removal of a proton from malononitrile by the methoxide anion giving a nucleophilic carbanion, which attacks the electron deficient C in a C≡N bond of phthalonitrile. The nitrogen then can remove a proton from solvent, forming an imine. A second methoxide ion can then remove the hydrogen *alpha* to the cyano groups and the imine, followed by proton transfer from solvent giving the intermediate enamine (**540**). The amino group can then attack *intra*molecularly at the other aromatic C≡N, resulting in the formation of the five membered ring system (**541**).



542 **541** **540**

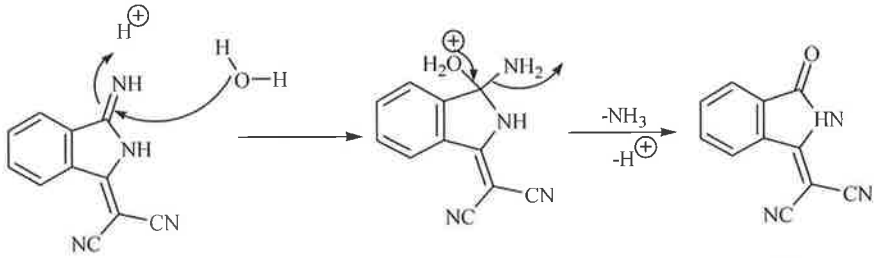
Figure 130

4.1.4 3-Dicyanomethylene-2,3-dihydroisoindol-1-one (530)



530

Compound (**541**) was heated under reflux in an 80:20 mixture of glacial acetic acid: water until a clear yellow solution was obtained. Cooling of this solution overnight in a freezer resulted in the precipitation of a yellow solid, with m.p 249-251°C, in 57% yield. The IR spectra showed two C≡N peaks at 2230 and 2221 cm^{-1}, a carbonyl peak at 1759 cm^{-1} and a broad N-H peak at 3286 cm^{-1}. The ^{1}H-NMR spectrum (D_6 DMSO) showed two multiplets, at 8.27ppm and 7.90ppm, corresponding to four aromatic hydrogens in a ratio of 1:3. A broad N-H peak appeared at 3.40ppm. The ^{13}C NMR spectrum showed two non-aromatic quaternary carbons, at 167.81 and 161.02ppm, either a C=O or **C**=C(CN)$_2$, which had shifted from 177.39 and 173.51ppm in the starting material. A third quaternary carbon with a chemical shift of 58.03ppm was assigned to C=**C**(CN)$_2$. The two C≡N peaks appeared at 114.10 and 112.53ppm. Elemental analysis gave satisfactory results for $C_{11}H_5N_3O$. This spectal data is in agreement with that reported by Conway[106a] and Crean.[106c] A mechanism of the formation of (**530**) is depicted below (Figure 131).



541 **530**

Figure 131: Hydrolysis of (541)

This sequence of reactions, from phthalonitrile to (**541**) and using readily available starting materials, provides a very convenient route to (**530**), the desired phthalimide analogue.

The stability of the anion formed when compound (**531**) dissociates means that (**531**) is acidic and can form salts. The dicyano compound (**530**) should behave in a similar fashion, showing acidic behaviour. Compounds possessing acidic protons can often be readily alkylated using the Mitsunobu reaction,[110] and the Mitsunobu reaction was investigated as a synthetic route to *N*-substituted derivatives of (**530**).

4.1.5 The Mitsunobu Reaction

The Mitsunobu reaction, first reported by Mitsunobu and Yamada in 1967,[110a,b] is one of the most useful and versatile reactions in organic chemistry, enabling the synthetic chemist to convert the hydroxyl group of a primary or secondary alcohol into an excellent leaving group which can be displaced by a number of nucleophiles. The reaction is carried out under mild conditions and uses the redox system of a dialkyl azodicarboxylate, usually diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), and triphenylphosphine. In 1971, Mitsunobu and Eguchi[110c] showed that the reaction with optically pure secondary alcohols proceeded with complete inversion of stereochemistry (Figure 132). As a result, the stereochemistry of a particular alcohol can be inverted by an esterification/hydrolysis procedure.

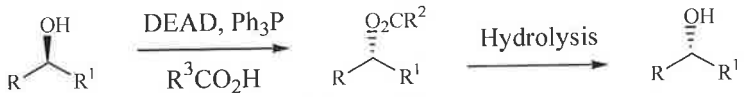


Figure 132

The alcohol component (R-OH) and acidic component (H-Nu) are condensed to form product (R-Nu), while triphenylphosphine is oxidised to triphenylphosphine oxide and the azodicarboxylate is reduced to the corresponding hydrazine. The overall reaction can be summarised as follows (Figure 133).

Figure 133

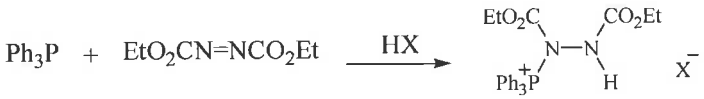
The most established application of the Mitsunobu reaction involves the use of DEAD and triphenylphosphine. In general, the reaction is limited to primary and secondary alcohols, with the reaction of secondary alcohols generally proceeding with complete stereochemical inversion. The acidic component (H-Nu) can be oxygen, nitrogen, carbon or sulphur nucleophiles.

Mitsunobu has proposed that the reactions of alcohols using DEAD and triphenlyphosphine proceeds in three steps.[110d]

1. reaction of DEAD with PPh_3, in the presence of the acid component, to form a salt wherein a phosphorus-nitrogen bond is formed;
2. reaction of the DEAD-PPh_3 adduct with the alcohol to form an activated oxyphosphonium ion intermediate;

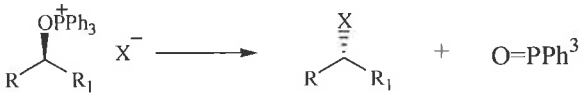
3. displacement by an S_N2 process to form the inverted product and triphenyl phosphine oxide.

The reaction can be shown schematically below, (Figure 134):



Step1: Adduct Formation.

Step 2: Alcohol Activation.



Step 3: S_N2 Reaction

Figure 134

While steps 1 and 3 of the reaction are adequately depicted in Figure 134, the alcohol activation step is not entirely clear. However, Grochowski[111] and Jenkins *et al.*,[112] have independently clarified the situation using ^{31}P NMR. Both these groups have shown that the values of the ^{31}P NMR chemical shifts, which are independent of the dialkylazodicarboxylate used, indicate that the true intermediate is in fact a dialkoxytriphenylphosphorane, $Ph_3P(OR)_2$, which decomposes to products, recycling the second molecule of alcohol in the process (Figure 135).

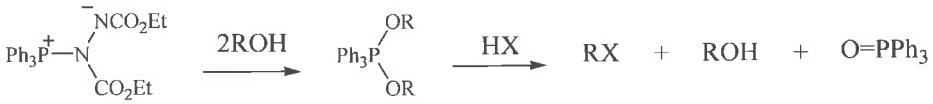


Figure 135

However, both these groups failed to account for an unobserved intermediate, an oxyphosphonium salt, between the dialkoxytriphenylphosphorane and products (Figure 136). However, it has been suggested that the oxyphosphonium salt is a result of the reaction of DEAD with tributylphosphine.[112b]

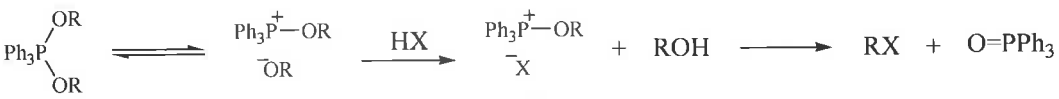


Figure 136

Walker and co-workers[113] have shown that the order in which the reactants are added can have a profound effect on the mechanism of the Mitsunobu reaction. The general procedure is to add the dialkylazodicarboxylate to a solution containing triphenylphosphine, initially forming a betaine, which was originally proposed by Morrsion,[114] and authenticated by Brunn and Huisgen.[115] It is generally assumed that the betaine is formed by the Michael-type nucleophilic attack by the phosphine on the nitrogen, and has been show to be irreversible.[116a, 117]

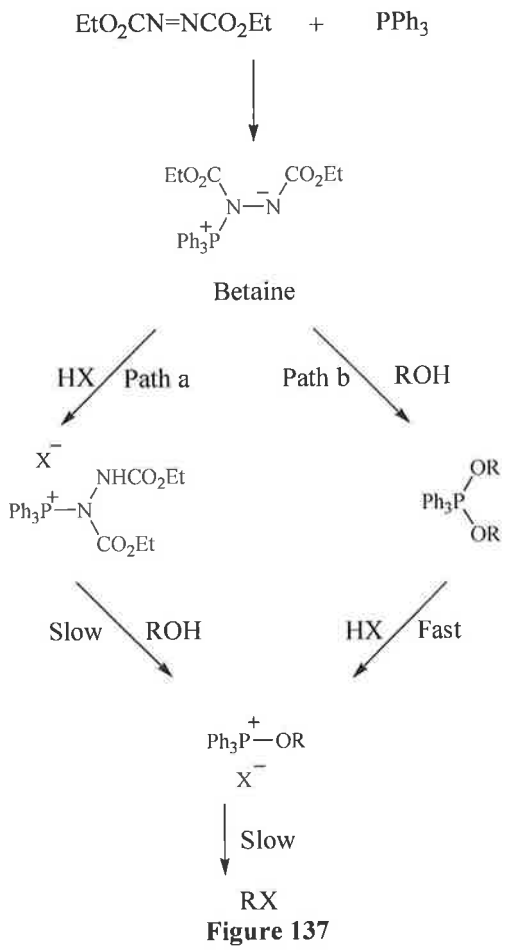


Figure 137

However, if the betaine is formed in the presence of acid, or acid is added subsequently, protonation occurs to give the conjugate acid phosphonium salt (path a). This conjugate acid phosphonium salt undergoes slow conversion to the oxyphosphonium salt after addition of the alcohol component. On the other hand, if the betaine is formed in the absence of acid but in the presence of alcohol, half of the betaine reacts with the alcohol to give the dialkoxytriphenylphosphorane (path b). Addition of the acidic component at this stage protonates the remaining betaine to the conjugate acid phosphonum salt and instantaneously converts the

dialkoxytriphenylphosphorane to the oxyphosphonium salt. The half equivalence of alcohol from dialkoxytriphenylphosphorane is recycled through conjugate acid. Their findings can be shown schematically (Figure 137).

Camp and Jenkins[116b] have shown that the dialkoxytriphenylphosphorane and the oxyphosphonium salt are formed as intermediates, irrespective of the order of addition of reagents. These intermediates are in equilibrium with each other, with the position of the equilibrium being dependant on the pK_a of the acid, as well as the polarity of the solvent.

The use of acids with low pK_a, such as trifluoroacetic acid, results in the oxyphosphonium salt as the only species observed.[116] The use of polar solvents also favours the formation of the oxyphosphonium salt. However, THF ($\varepsilon = 7.6$), the main exception, is a basic solvent and favours the dialkoxytriphenylphosphorane intermediate. In THF any protons are effectively tied up by hydrogen bonding to the solvent and are therefore less available to solvate the X^- of the oxyphosphonium salt species.[118]

Hughes, Reamer and co-workers[119] stated that the main factors governing the rate of formation of the azodicarboxylate-triphenylphosphine adduct to the alcohol are:

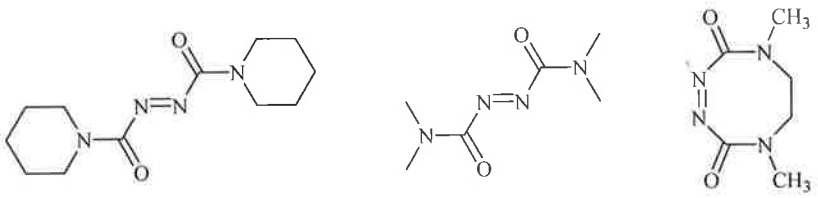
1. the basicity of the counter ion generated in the formation of the dialkylazodicarboxylate-triphenylphosphine adduct;
2. the extent of hydrogen bonding to this counter ion;
3. substituent effects in the triarylphosphine (electron donating substituents on the triarylphosphine diminish the electrophilicity of phosphorus, decreasing the alcohol activation rate).

The Mitsunobu reaction is generally only effective when the pK_a of the acidic component is less than 10. A number of new azo-compounds have been developed in an attempt to widen the pK_a range of acidic components that can be used. Improvements in the redox system used in the Mitsunobu reaction need to:

1. increase the nucleophilicity of the phosphine in the formation of the intermediate betaine;

2. localise the positive charge on the phosphorus of the betaine and in the alkoxyphosphonium salt, the localisation of charge facilitating nucleophilic attack by RO^- on the betaine and X^- on the alkoxyphosphonium salt;
3. localise the negative charge at the azo-nitrogen in order to increase its basicity in the azodicarboxylate anion.

The first two considerations lead to the use of tributylphosphine (TBP) in place of triphenylphosphine (TPP). The third consideration leads to the use of 1,1'-(azodicarbonyl)dipiperidine (ADDP), N,N,N',N'-tetramethylazodicarboxamide (TMAD), and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) (Figure 138).[120]



ADDP TMAD DHTD

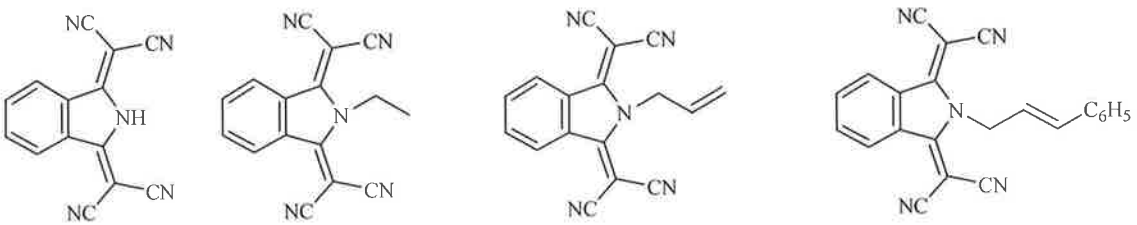
Figure 138

When either TMAD or DHTD are used with tributylphosphine in benzene, alkylated acidic components with pK_a values as high as 13 have been used. DHTD has been shown to be the most versatile compound as it produced the best results with sterically hindered reactants.[120d] While the ADDP – TBP system is more reactive towards primary alcohols, it is less reactive towards secondary alcohols when compared with the DEAD – TPP system. This difference in reactivity can be utilized for regioselective reactions of diols.

Phthalimides were first alkylated using the Mitsunobu reaction in 1971,[121] while other long chain *N*-alkylated phthalimides were obtained from gerianol, citronellol and 10-undecen-1-ol.[122] Alkylated succinimide derivatives have also been synthesised in a similar fashion by the same group.[122b] The syntheses described all followed the standard Mitsunobu reaction, with the reactants being added in the following order: acid (HX), alcohol (ROH), triphenylphosphine and finally azodicarboxylate.

Alternatively a series of *N*-alkyl derivatives of maleimide were made using a different order of addition of the reactants: triphenylphosphine, azodicarboxylate, alcohol and acid.[123] This order of addition pre-forms the reactive betaine and thus eliminates free triphenylphosphine and free azodicarboxylate from the reaction mixture.

If the Mitsunobu reaction were to be applicable to reactions of compounds (**530**) and (**531**) with alcohols, the result would be an *N*-alkylated derivatives of dicyanomethylene compounds and *bis*-dicyanomethylene compounds. Application of the Mitsunobu reaction to the problem of creating *N*-alkyl derivatives of the *bis*-dicyanomethylene compounds (**531**) carried out by Crean[106c] in this research group, proved relatively successful and a number of *N*-alkyl and *N*-alkenyl derivatives have been synthesized (Figure 139).



531

Figure 139: N-substituted derivatives of (531)

Crean[106c] has established the optimum reaction conditions for the Mitsunobu reaction of the unalkylated *bis*-dicyanomethylene compound (**531**) with alcohols:

1. replacement of DEAD with DIAD, which increased the yield;
2. the order of addition of reactants was changed to the following: triphenylphosphine, azodicarboxylate (DIAD), alcohol and acid (**530**), allowing the azodicarboxylate-triphenylphosine adduct to be formed in the absence of the acidic component;
3. varying the stiochiometric ratios of reactants, the best ratio being DIAD: PPh_3: ROH: (**530**) 1.5: 1.5: 1.5: 1.0, increasing yields slightly;
4. increasing the time allowed for reaction to occur, with 3 days being the optimum;
5. changing the temperature at which reaction took place, room temperature being adequate.

These were applied to the unalkylated dicyanomethylene compound (**530**). A reasonable mechanism is shown (Figure 140).

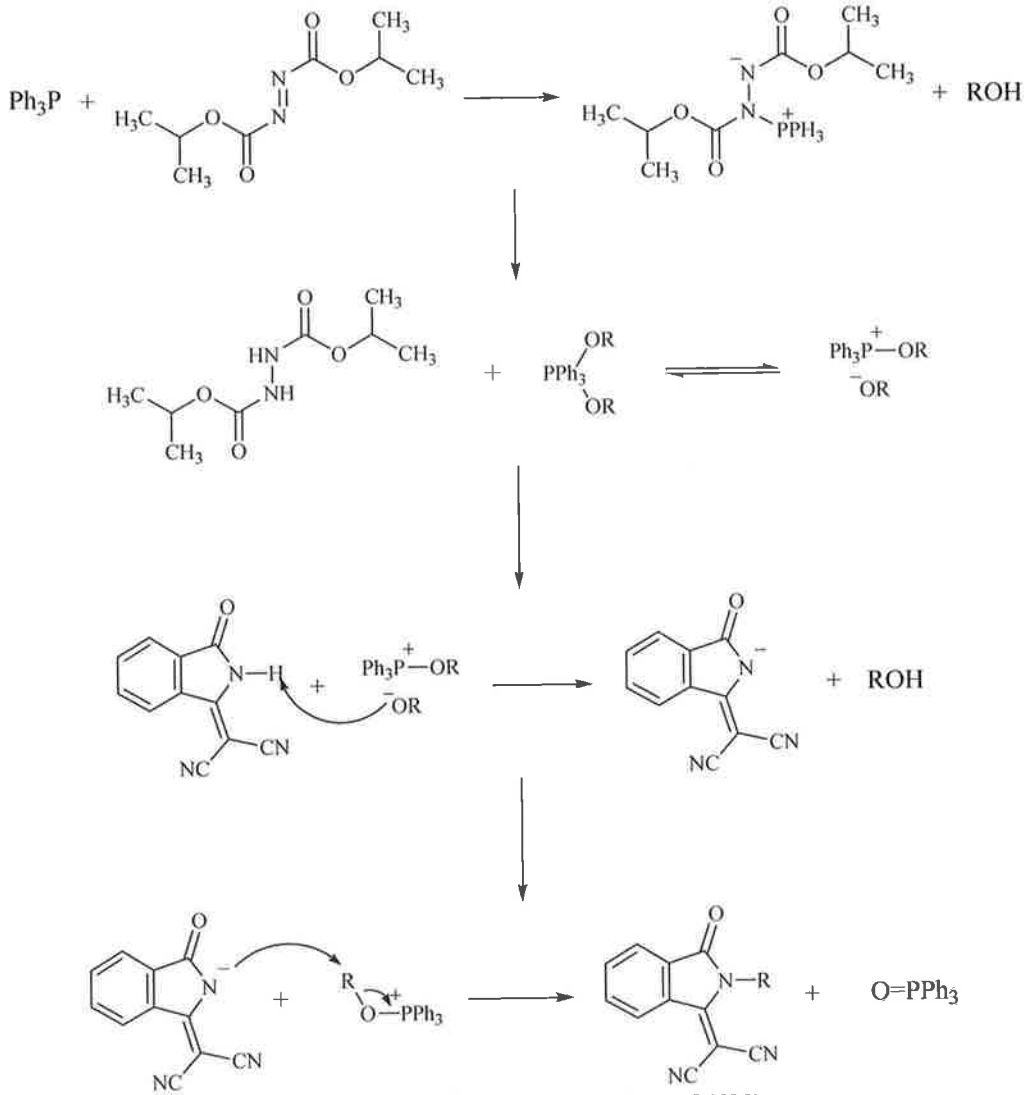


Figure 140: The Mitsunobu Reaction of (530)

In general, the Mitsunobu reaction is limited to primary and secondary alcohols. For secondary alcohols the reaction usually proceeds with clean inversion of stereochemistry.[124] Ahn *et al.*,[125] however, have reported on the retention of stereochemistry with hindered alcohols under Mitsunobu conditions, which involves the intermediacy of an acyloxy-phosphonium salt, followed by acyl transfer to the alcohol.

It is interesting to note that the use of the Hendrickson reagent, triphenylphosphonium anhydride trifluoromethanesulphonate,[126] brings about

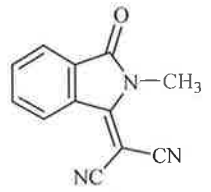
dehydrations in a fashion similar to the Mitsunobu reaction,[127] with the alkoxyphosphonium salt intermediate being involved in both reactions. The similarities between both reactions have gone largely unnoticed. However, when the Hendrickson reagent is used with secondary alcohols, an elimination reaction, rather than inversion, occurs.

Our main area of interest was in the photochemistry of *N*-alkyl derivatives of (**530**), the presence of the carbonyl group making the investigation of their photochemistry more attractive than that of the *N*-alkyl derivatives of the *bis*-dicyanomethylene compounds (**531**). A range of *N*-alkyl derivatives of (**530**) were synthesised using the Mitsunobu reaction with the aim of studying their photochemistry.

4.2 General synthesis of 2-alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543-562)

2-Alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones (**543-563**) were synthesised from (**530**) using the Mitsunobu reaction. 3-Dicyanomethylene-2,3-dihydroisoindol-1-one (**530**), triphenyl phosphine (TPP), diisoproplyazodicarboxylate (DIAD), and the appropriate alcohol were stirred together in dry THF or CH_2Cl_2 under an atmosphere of argon for three days. After this time, the reaction mixture had a brown opaque appearance. The reaction mixture was examined by TLC using dichloromethane as solvent. The starting material (**530**) showed a very low R_f, while the presence of a new yellow spot with high R_f relative to starting material and other polar by-products of the reaction indicated the formation of a new product. The THF was removed under vacuum and the product was isolated by silica chromatography. These compounds, some of which have previously been prepared by Crean,[106c] were prepared in the according to the method described by Crean.[106c]

4.2.1 2-Methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543)



543

The reaction was carried out using methanol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the yellow product showed the anticipated four aromatic hydrogens, with a three hydrogen singlet present at 3.62ppm consistent with the anticipated presence of *N*-methyl group and supported by the presence of a peak at 28.91ppm in the ^{13}C NMR spectrum. In addition to six non-equivalent aromatic carbons, there were also resonances arising from C=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ at 166.56, 159.00 and 60.29ppm with corresponding peaks at 1744 (C=O) and 1600cm^{-1} (C=C) in the IR spectrum. The presence of two non-equivalent cyano groups was supported by peaks at 114.02 and 113.08ppm in the ^{13}C NMR spectrum, in addition to peaks at 2222 and 2211cm^{-1} in the IR spectrum. In addition to the supporting spectral data, the elemental analysis data were consistent with the anticipated molecular formula of $C_{12}H_7N_3O$, supporting the assignment of structure (**543**) to the product.

4.2.2 2-Ethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (544)

544

The reaction was carried out using ethanol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the predicted four aromatic hydrogens as three multiplets. A two hydrogen quartet and a three hydrogen triplet at 4.18 (J = *7Hz*) and 1.32ppm (J = *7Hz*) respectively indicated the presence of the *N*-ethyl group, supported by peaks at 27.02 (N-CH_2) and 15.60ppm in the ^{13}C NMR spectrum. Aside from the six non-equivalent aromatic carbons, the ^{13}C NMR spectrum also showed peaks arising from C=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ at 166.85, 158.26 and 59.94ppm with supporting peaks at 1747 (C=O) and 1577cm^{-1} (C=C) in the IR spectrum. Peaks at 114.44 and 113.29ppm in the ^{13}C NMR spectrum and at 2225 and 2214cm^{-1} in the IR spectrum supported the presence of the expected two non-equivalent cyano groups. The elemental analysis data were consistent with a molecular formula of $C_{13}H_9N_3O$, and the compound was assigned as structure (**544**).

4.2.3 2-Propyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (545)

545

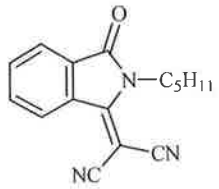
The reaction was carried out using propan-1-ol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the expected four aromatic hydrogens as three multiplets. The *N*-propyl hydrogens appeared as a two hydrogen triplet at 4.15ppm (*J = 7Hz*), a two hydrogen multiplet at 1.80ppm; and a three hydrogen triplet at 1.03ppm (*J = 7Hz*), with corresponding peaks in the ^{13}C NMR spectrum at 42.94 (N-CH_2), 23.33 and 10.89ppm. The ^{13}C NMR spectrum also showed peaks at 166.80, 158.13 and 59.80ppm arising from **C**=O, **C**=$C(CN)_2$ and C=**C**$(CN)_2$ respectively. These were supported by peaks at 1752 (C=O) and 1601cm^{-1} (C=C) from the IR spectrum. The expected cyano peaks appeared at 114.22 and 113.06ppm in the ^{13}C NMR spectrum and 2224 and 2209cm^{-1} in the IR spectrum. The elemental analysis gave satisfactory results for $C_{14}H_{11}N_3O$ and the structure (**545**) was assigned based on these results.

4.2.4 2-Butyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (546)

546

The reaction was carried out using butan-1-ol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the four aromatic hydrogens as three multiplets. The *N*-butyl chain appeared as a two hydrogen triplet at 4.04ppm (*J = 7.7Hz*), a two hydrogen multiplet at 1.64-1.58ppm, a two hydrogen multiplet at 1.29-1.35ppm, and a three hydrogen triplet at 0.87ppm (*J = 7.3Hz*), with the corresponding carbon peaks appearing at 41.35 (N-CH_2), 31.88, 19.88 and 14.07ppm in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also showed six non-equivalent aromatic carbons, as well as **C**=O, **C**=$C(CN)_2$ and C=**C**$(CN)_2$ peaks at 166.66, 158.01 and 59.66ppm. The corresponding C=O and C=C peaks in the IR spectrum appeared at 1752 and 1601cm^{-1}. The two cyano peaks appeared at 114.24 and 113.11ppm in the ^{13}C NMR spectrum, and 2228 and 2213cm^{-1} in the IR spectrum. The elemental analysis results were consistent with the molecular formula $C_{15}H_{13}N_3O$, and the structure (**546**) was assigned to the compound.

4.2.5 2-Pentyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (547)



547

The reaction was carried out using pentan-1-ol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the expected four aromatic hydrogens as three multiplets. The *N*-pentyl chain appeared as a two hydrogen triplet at 4.17ppm (*J = 7.8Hz*), a two hydrogen multiplet at 1.78-1.74ppm, a four hydrogen multiplet at 1.41-1.37ppm and a three hydrogen triplet at 0.93ppm (*J = 6.8Hz*) with the corresponding carbons at 41.63 (N-CH_2), 29.68, 28.62, 22.66 and 14.30ppm in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also showed C=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ peaks at 166.77, 158.07 and 59.80ppm, while the C=O and C=C peaks appeared at 1744 and 1609cm^{-1} in the IR spectrum. The two cyano peaks were visible at 114.24 and 113.07ppm and 2225 and 2215cm^{-1} in the ^{13}C NMR spectrum and IR spectrum respectively. The remaining six peaks in the 13C NMR spectrum were assigned to the non-equivalent aromatic carbons. The elemental analysis results were in agreement with a molecular formula of $C_{16}H_{15}N_3O$ and the compound was assigned as structure (**547**).

4.2.6 2-Hexyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (548)

548

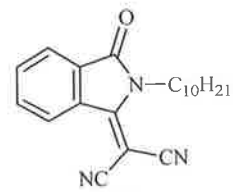
The reaction was carried out using hexan-1-ol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed three anticipated four aromatic hydrogens as three multiplets, and the *N*-hexyl chain as a two hydrogen triplet at 4.14ppm (*J = 7.8Hz*), a two hydrogen multiplet at 1.80-1.70ppm, a broad six hydrogen multiplet at 1.50-1.30ppm along with a three hydrogen triplet at 0.88ppm (*J = 7.0Hz*). The ^{13}C NMR spectrum showed resonances of six corresponding aliphatic carbons at 41.65 (N-**C**H_2), 31.69, 29.93, 26.20, 22.85 and 14.37ppm. Also present in the ^{13}C NMR spectrum were six non-equivalent aromatic carbons, as well as **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ peaks at 166.76, 158.06 and 59.80ppm. The IR spectrum confirmed the presence of C=O and C=C with signals at 1744 and 1609cm^{-1} respectively. The expected non-equivalent cyano groups were visible at 114.25 and 113.08ppm in the ^{13}C NMR spectrum and at 2225 and 2215 cm^{-1} in the IR spectrum. The elemental analysis results were consistent with a molecular formula of $C_{17}H_{17}N_3O$ and the compound was assigned the structure (**548**).

4.2.7 2-Octyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (549)

549

The reaction was carried out using octan-1-ol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the four aromatic hydrogens as three multiplets as was expected. The hydrogens of the *N*-octyl chain appeared as a two hydrogen triplet at 4.09ppm (J = *8Hz*), a two hydrogen multiplet at 1.71-1.63ppm, a broad ten hydrogen multiplet at 1.39-1.13 ppm along with a three hydrogen triplet at 0.80ppm (J = *7Hz*) with the corresponding carbon resonances at 41.66 (N-**C**H_2), 32.11, 29.98, 29.51, 29.47, 26.54, 23.00 and 14.48ppm in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also showed **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ peaks at 166.77, 158.06 and 59.82ppm, with the C=O and C=C being confirmed by peaks at 1742 and 1603cm^{-1} in the IR spectrum. The two cyano peaks were located at 114.24 and 113.06ppm in the ^{13}C NMR spectrum and supported by peaks at 2223 and 2212cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum also showed six non-equivalent aromatic carbons. The elemental analysis results were satisfactory for the molecular formula of $C_{19}H_{21}N_3O$. The structure (**549**) was assigned based on the above results.

4.2.8 2-Decyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (550)

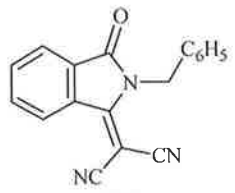


550

The reaction was carried out using decan-1-ol as the alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the four aromatic hydrogens as three multiplets. The aliphatic hydrogens of the *N*-decyl chain were visible as a two hydrogen triplet at 4.12-4.06ppm (J = 7.7*Hz*), a two hydrogen multiplet at 1.72-1.62ppm, a broad fourteen hydrogen mulitplet at 1.36-1.12ppm along with a three hydrogen triplet at 0.81ppm (J = 6.8*Hz*). The ^{13}C NMR spectrum showed the corresponding aliphatic carbons of the *N*-decyl chain at resonances of 41.66 (N-**C**H_2), 32.25, 29.98, 29.87, 29.81, 29.66, 29.56, 26.54, 23.06 and 14.52ppm. The ^{13}C NMR spectrum also showed six non-equivalent aromatic carbons, along with **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ resonances at 166.77 158.06 and 59.82ppm. The presence of C=O and C=C was confirmed by peaks at 1746 1604cm^{-1} respectively in the IR spectrum. Two non-equivalent cyano groups showed peaks at 114.24 and 113.07ppm in the ^{13}C NMR spectrum and 2224 and 2213cm^{-1} in

the IR spectrum. The elemental analysis results were consistent with a molecular formula of $C_{21}H_{25}N_3O$, supporting the assignment of structure (**550**) to the product.

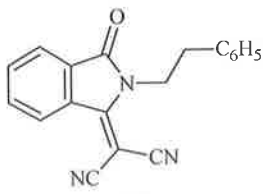
4.2.9 2-Benzyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (551)



551

The reaction was carried out using benzyl alcohol. The ^1H NMR spectrum ($CDCl_3$) of the product showed the anticipated nine aromatic hydrogens. The five aromatic hydrogens of the benzyl moiety appeared as two multiplets at 7.26ppm and 7.16ppm, while the four aromatic hydrogens of the 3-dicyanomethylene-2,3-dihydroisoindol-1-one moiety appeared as three multiplets at 8.54-8.52, 7.96-7.94 and 7.75-7.72ppm. A two-hydrogen singlet at 5.39ppm was assigned as the N-CH_2, supported by a peak at 44.44ppm in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum showed ten aromatic resonances, six were assigned to the 3-dicyanomethylene-2,3-dihydroisoindol-1-one moiety and four to the benzyl moiety. The ^{13}C NMR spectrum showed **C**=O, **C**=$C(CN)_2$ and C=**C**$(CN)_2$ peaks at 167.06, 157.71 and 61.16ppm. The presence of C=O and C=C was confirmed by peaks at 1756 and 1603cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum also showed two cyano peaks at 113.99 and 112.94ppm while peaks at 2228 and 2217cm^{-1} in the IR spectrum confirmed the presence of the cyano peaks. The elemental analysis results were consistent with a molecular formula of $C_{18}H_{11}N_3O$ and the compound was assigned structure (**551**).

4.2.10 2-(2-Phenylethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (552)

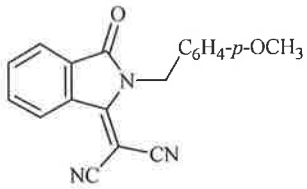


552

The reaction was carried out using 2-phenylethanol. The ^1H NMR spectrum ($CDCl_3$) of the product showed four aromatic hydrogens as three multiplets at 8.54-8.51, 7.86-7.82 and 7.75-7.66ppm assigned to the 3-dicyanomethylene-2,3-dihydroisoindol-1-one moiety and five aromatic hydrogens as two multiplets at 7.26-7.14ppm and 7.17-7.15ppm assigned to the phenyl moiety. A two hydrogen triplet at 4.33ppm (*J = 8.1Hz*) was assigned to N-CH_2 while a two hydrogen triplet at 3.97ppm (*J = 8.1Hz*) was assigned to CH_2Ph. The corresponding carbons were visible at 43.08 (N-**C**H_2) and 35.94ppm (**C**H_2-Ph) respectively in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also showed **C**=O, **C**=$C(CN)_2$ and C=**C**$(CN)_2$ signals at 166.64, 158.11 and

59.97ppm, with the C=O and C=C being confirmed by peaks at 1756 and 1603cm^{-1} in the IR spectrum. Two non-equivalent cyano groups were present at 114.13 and 113.35ppm in the ^{13}C NMR spectrum and supported by peaks at 2228 and 2217cm^{-1} in the IR spectrum. The elemental analysis results were consistent with a molecular formula of $C_{19}H_{13}N_3O$, supporting the assignment of structure (**552**) to the product.

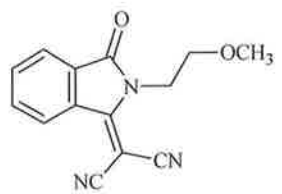
4.2.11 2-(4-Methoxybenzyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (553)



553

The reaction was carried out using 4-methoxybenzyl alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the four aromatic hydrogens of the *p*-methoxybenzyl moiety as multiplets at 7.14-7.12ppm and 6.80-6.77ppm while the four aromatic hydrogens of the 3-dicyanomethylene-2,3-dihydroisoindol-1-one moiety appeared as three multiplets at 8.52-8.50, 7.93-7.91 and 7.73-7.70ppm. A two hydrogen singlet at 5.31ppm was assigned as the N-CH_2 while a three hydrogen singlet at 3.70ppm was assigned as the O-CH_3. The corresponding carbons appeared at 44.44 (N-**C**H_2) and 54.25ppm (O-**C**H_3) in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also showed **C**=O, **C**=$C(CN)_2$, **C**-OCH_3 resonances at 165.71, 158.36 or 156.29ppm as well as a C=**C**$(CN)_2$ peak at 59.52ppm. The presence of O-CH_3, C=O and C=C and were confirmed by peaks at 2840, 1753 and 1577cm^{-1} in the IR spectrum. The two non-equivalent cyano groups were seen at 112.62 and 111.73ppm in the ^{13}C NMR spectrum and 2208cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum also showed ten aromatic carbons. The elemental analysis results were in agreement with a molecular formula of $C_{19}H_{13}N_3O$. The compound was assigned structure (**553**) on the basis of these results.

4.2.12 2-(2-Methoxyethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (554)

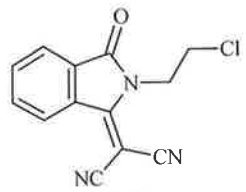


554

The reaction was carried out using 2-methoxyethanol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the expected four aromatic hydrogens as three multiplets. A two hydrogen triplet at 4.39ppm (*J = 5Hz*) was assigned to N-CH_2 while a two hydrogen triplet at 3.64ppm (*J = 5Hz*) was assigned to O-CH_2 with a three hydrogen singlet at 3.28ppm assigned to the O-

CH_3. The ^{13}C and DEPT 135 NMR spectra showed the corresponding carbons at 69.96 (O-**C**H_2), 59.18 (O-**C**H_3) and 40.68ppm (N-**C**H_2). The ^{13}C NMR spectrum also showed **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ peaks at 166.47, 157.94 and 60.01ppm, with the IR spectrum confirming the presence of C=O, C=C and O-CH_3 with peaks at 1756, 1603 and 2822 cm^{-1}. The two cyano peaks were visible at 113.84 and 112.84ppm in the ^{13}C NMR spectrum and supported by peaks at 2228 and 2217cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum also showed six non-equivalent aromatic carbon signals. The elemental analysis gave satisfactory results for $C_{14}H_{11}N_3O$, supporting the assignment of structure (**554**) to the compound.

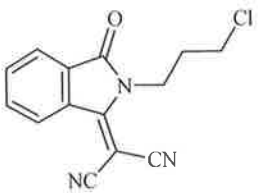
4.2.13 2-(2-Chloroethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (555)



555

The reaction was carried out using 2-chloroethanol. The ^1H NMR spectrum ($CDCl_3$) of the product showed the expected four aromatic hydrogens as three multiplets. The hydrogens on the *N*-(2-chloro)ethyl chain appeared as two hydrogen triplet at 4.55ppm (*J = 6Hz*), assigned to N-CH_2, while a two-hydrogen triplet at 3.78ppm (*J = 6Hz*) was assigned to Cl-CH_2. The ^{13}C NMR spectrum showed the corresponding carbons at 42.43 (N-**C**H_2) and 41.53ppm (Cl-**C**H_2). Six non-equivalent aromatic carbons were also present in the ^{13}C NMR spectrum. Resonances of **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ were present at 166.64, 158.12 and 60.74ppm, supported by C=O and C=C peaks at 1755 and 1600cm^{-1} in the IR spectrum. Two non-equivalent cyano peaks were present at 113.71 and 112.95ppm in the ^{13}C NMR spectrum and supported by peaks at 2229 and 2211cm^{-1} in the IR spectrum. The elemental analysis results were in agreement with a molecular formula of $C_{13}H_8ClN_3O$, thus supporting the assignment of structure (**555**) to the compound.

4.2.14 2-(3-Chloropropyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (556)

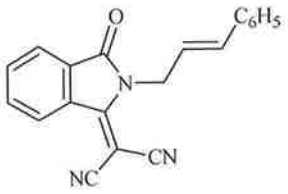


556

The reaction was carried out using 3-chloropropanol. The ^1H NMR spectrum ($CDCl_3$) of the product showed the four aromatic hydrogens as three multiplets, as was anticipated. The hydrogens on the *N*-(2-chloro)propyl chain appeared as a two-hydrogen triplet at 4.36ppm (*J = 7.3Hz*), assigned to N-CH_2, a two hydrogen triplet at 3.78ppm (*J = 6.3Hz*), assigned to Cl-CH_2, and a

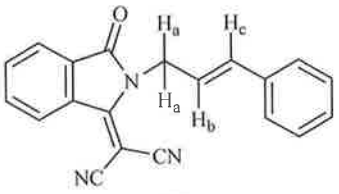
two hydrogen multiplet at 2.31-2.24ppm. The corresponding carbons of the *N*-(2-chloro)propyl chain were found at 41.63 (N-**C**H_2), 39.57 (Cl-**C**H_2) and 32.50ppm (N-CH_2**C**H_2) in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum also showed six non-equivalent aromatic carbon signals; **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ resonances at 166.72, 158.16 and 60.08ppm which were supported by C=O and C=C peaks at 1745 and 1600cm^{-1} in the IR spectrum. The non-equivalent cyano groups were found at 113.92 and 113.11ppm in the ^{13}C spectrum and supported by peaks at 2221 and 2210 cm^{-1} in the IR spectrum. The elemental analysis results supported the molecular formula $C_{14}H_{10}ClN_3O$ and the compound was assigned the structure (**556**).

4.2.15 2-(Phenylallyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (557)



557

The reaction was carried out using *trans*-cinnamyl alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed, as expected, nine aromatic hydrogens. The five aromatic hydrogens of the *N*-(3-phenyl)prop-2-enyl moiety appeared as a five-hydrogen multiplet at 7.29ppm, while the four aromatic hydrogens of the 3-dicyanomethylene-2,3-dihydroisoindol-1-one moiety as three multiplets at 8.53-8.52, 7.92-7.90 and 7.75-768ppm. The N-CH_2 group appeared as a two-hydrogen doublet at 4.90ppm (J = *6Hz*). A doublet (J = 16*Hz*) of triplets (J = 6*Hz*) corresponding to the vinylic hydrogens on C-2 of the side chain was centred at 6.18ppm and the benzylidene hydrogen appeared as a one hydrogen doublet at 6.56ppm (J = 16*Hz*). These hydrogens and their J values are shown in Figure 141 below. The corresponding N-CH_2 carbon of the *N*-prop-2-enyl chain was found at 42.81ppm in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum showed ten non-equivalent aromatic carbons. Peaks at 166.63, 157.70 and 60.63ppm were assigned to **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ respectively, with the presence of C=O and C=C supported by peaks at 1744 and 1601cm^{-1} in the IR spectrum. Two non-equivalent cyano groups were present at 114.06 and 113.19ppm in the ^{13}C NMR spectrum and 2227 and 2216cm^{-1} in the IR spectrum. The elemental analysis results supported the molecular formula $C_{20}H_{13}N_3O$ and the compound was assigned the structure (**557**).

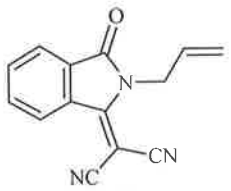


H_a: 4.90ppm (J_{ab} = 6*Hz*)
H_b: 6.18; 6.15ppm (J_{ba} = 6*Hz*, J_{bc} = 16*Hz*)
H_c: 6.56ppm (J_{cb} = 16*Hz*)

557

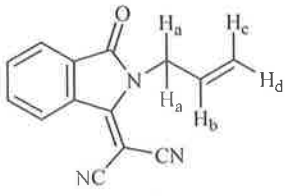
Figure 141: J values of *N*-phenylallyl derivative (557).

4.2.16 2-Allyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (558)



558

The reaction was carried out using allyl alcohol. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed the expected four aromatic hydrogens as three multiplets. The N-CH_2 group appeared as a two-hydrogen doublet at 4.77ppm (J = 4.8*Hz*). A doublet (J = 10.5*Hz*) of doublets (J = 17.1*Hz*) of triplets (J = 4.8*Hz*), centred at 5.88ppm corresponded to the vinylic hydrogen at C-2 of the allyl group and two one-hydrogen doublets, centred at 5.25ppm (J = 10.3*Hz*) and 5.08ppm (J = 17.2*Hz*), corresponded to the vinylic hydrogens at C-3 of the N-allyl group. The typical geminal (J = 1.6*Hz*) coupling constants for were also observed for these hydrogens. The positions of these hydrogens and their coupling constants are shown in Figure 142 below. The ^{13}C NMR spectrum showed the carbons of the N-allyl chain at 43.00 (N-**C**H_2), 131.10 (**C**H=CH_2) and 118.33ppm (CH=**C**H_2). Resonances from **C**=O, **C**=$C(CN)_2$ and C=**C**$(CN)_2$ were found at 166.50, 157.66 and 60.71ppm, with the presence of C=O and C=C confirmed by peaks at 1751 and 1603 in the IR spectrum. The two non-equivalent cyano groups were found at 114.06 and 112.98ppm and supported by peaks at 2226 and 2218cm^{-1} in the IR spectrum. Six non-equivalent aromatic carbons were also shown in the ^{13}C NMR spectrum. The spectral data was in agreement with that reported by Crean[106c].

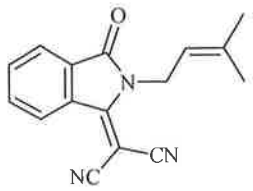


H_a: 4.77ppm (J_{ab} = 4.8*Hz*)
H_b: 5.88ppm (J_{ba} = 4.8*Hz*, J_{bd} = 10.5*Hz*, J_{bc} = 17.2*Hz*)
H_c: 5.08ppm (J_{cb} = 17.2*Hz*)
Hd: 5.25ppm (J_{dc} = 1.6*Hz*)

558

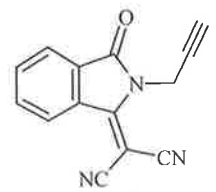
Figure 142: J values of *N*-allyl derivative.

4.2.17 2-(3-Methylbut-2-enyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (559)


559

The reaction was carried out using 3-methyl-2-buten-1-ol. ^{1}H NMR spectrum ($CDCl_3$) of the product showed, as anticipated, three multiplets indicating four aromatic hydrogens at 8.53-8.51, 7.87 and 7.70ppm. A one hydrogen triplet at 5.17ppm (J = 6.5Hz) was assigned to the vinyl hydrogen (C**H**=C(CH_3)$_2$), a two hydrogen doublet at 4.73ppm (J = 6.5Hz) was assigned as (N-C**H**$_2$), and two three hydrogen singlets at 1.74 and 1.68ppm were assigned to the two methyl groups. The ^{13}C NMR spectrum showed the five carbons of the N-butenyl chain at 39.84 (N-**C**H$_2$), 139.64 (CH=**C**(CH$_3$)$_2$) 117.88 (**C**H=C(CH$_3$)$_2$), 26.26 and 18.33ppm (**C**H$_3$). Resonances from **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ were found at 166.63, 157.92 and 60.79ppm, with the presence of C=O and C=C confirmed by peaks at 1745 and 1601 and 1569cm^{-1} in the IR spectrum. The two non-equivalent cyano groups were found at 114.31 and 113.01ppm and supported by a peak at 2223cm^{-1} in the IR spectrum. Six non-equivalent aromatic carbons were also shown in the ^{13}C NMR spectrum. The elemental analysis supported the molecular formula $C_{16}H_{13}N_3O$. The structure (**559**) was assigned based on these results.

4.2.18 2-(Propynyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (560)


560

The reaction was carried out using 2-propyn-1-ol. ^{1}H NMR spectrum ($CDCl_3$) of the product showed the four aromatic hydrogens as three multiplets 8.55, 7.93 and 7.75ppm, as expected. A two hydrogen doublet at 4.92ppm (J = 2.5Hz) was assigned to (N-C**H**$_2$), while a one hydrogen triplet was at 2.41-2.40ppm (J = 2.5Hz) was assigned to (C≡C**H**). The ^{13}C NMR spectrum showed resonances from **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ at 165.66, 156.93 and 61.78ppm, while the C≡CH group was visible as two peaks at 76.32 (C≡**C**H) and 75.17ppm (**C**≡CH), based on the ^{13}C DEPT 135 NMR spectrum. The presence of the C=O and C≡C groups were confirmed by peaks at 1745 and 2127cm^{-1} in the IR spectrum. The two non-equivalent cyano groups were found at 113.38 and 112.06ppm and supported by peaks at 2225 and 2215cm^{-1} in the IR spectrum. A peak at 31.25ppm was assigned to (N-**C**H$_2$). Six non-equivalent aromatic carbons were also shown in

the ^{13}C NMR spectrum. The structure (**560**) was assigned to the compound based on the spectral data.

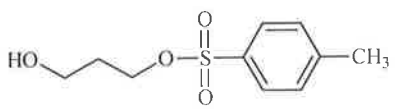
4.2.19 2-(3-Hydroxypropyl)4-methylbenzenesulphonate-3-dicyanomethylene-2,3-dihydroisoindol-1-one (563)

In general, the Mitsunobu reaction is limited to primary and secondary alcohols. In the course of this work, secondary alcohols have been used in order to obtain branched alkyl chains as the R-group. The most obvious choice of secondary alcohols were *iso*-propyl alcohol, cyclohexanol and cyclopentanol. While the reaction of (**530**) with *iso*-propyl alcohol resulted in product (**561**), albeit in very low yield, and will be dealt with separately in Chapter 8. In contrast, the reaction of (**530**) with both cyclopentanol and cyclohexanol resulted in no product formation. However, it should be noted that all attempts to alkylate the tetra cyano analogue (**531**) using secondary cycloalcohols were also unsuccessful.[106c]

As the Mitsunobu reaction is essentially an S_N2 reaction, product formation from secondary alcohols would naturally prove more difficult due to increasing substitution at the alcohol carbon.

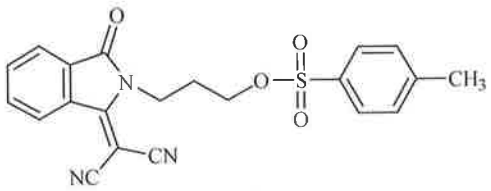
Attempts to synthesise compounds with a terminal amino or hydroxyl in the *N*-substituted side chain, under Mitsunobu conditions using (**530**) and various amino alcohols, such as 2-aminoethanol, 3-aminopropanol, or diols such as 1,3-propanediol or 1,6-hexanediol, also proved to be unsuccessful, with no reaction being observed. The reaction of the amino acids serine and threonine with (**530**) under Mitsunobu conditions again showed no product formation. While it is not known why these reactions were unsuccessful, it was thought that the presence of functional groups other than one OH group may have played a role.

By using a protected derivative such as the tosylate (**562**), it was anticipated that the Mitsunobu reaction with (**530**) would yield the protected alcohol derivative (**563**).



562

The reaction was carried out by preparing 3-hydroxypropyl-4-methylbenzene sulphonate (**562**) according to the procedure described by Burns *et al.*[128] This was then reacted with (**530**) under Mitsunobu conditions to give the a new product. The ^{1}H NMR spectrum ($CDCl_3$) of the product showed eight aromatic hydrogens, three multiplets indicating four aromatic hydrogens at 8.49, 7.89 and 7.81ppm, with two further multiplets at 7.67 and 7.33ppm being assigned to the aromatic hydrogens of the tosyl group. A two hydrogen triplet at 4.23ppm (J = 7*Hz*) and another at 4.14ppm (J = 6*Hz*) were assigned to O-C**H**$_2$ and N-C**H**$_2$ respectively. A three-hydrogen singlet at 2.42ppm was assigned to CH_3, while a two-hydrogen multiplet at 2.10ppm was assigned to the central $NCH_2C\mathbf{H}_2CH_2O$ in the propyl group. The ^{13}C spectrum showed **C**=O, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ signals at 166.61, 158.12 and 59.80ppm, two non-equivalent cyano resonances were found at 113.99 and 113.18ppm, while peaks at 67.77 and 38.50ppm were assigned to O-**C**H$_2$ and N-**C**H$_2$ respectively and peaks at 29.21 and 22.06ppm were assigned to **C**H$_2$ and **C**H$_3$. Ten non-equivalent aromatic carbons were also identified in the spectrum. The presence of C≡N, C=O and C=C were confirmed by signals at 2219, 2208, 1756 and 1600cm^{-1} in the IR spectrum, while a signal at 835cm^{-1} indicated the presence of a para-disubstituted aromatic ring. Elemental analysis gave satisfactory results for a molecular formula of $C_{21}H_{17}N_3O_4S$ and structure (**563**) was assigned to the compound based on these results.

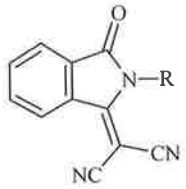


563

4.2.20 General observations

In general, all the compounds with *N*-alkyl substituents contain the same pattern for the aromatic hydrogens in their ^{1}H NMR spectra at approximately 8.50, 7.90 and 7.75ppm in a ratio of 1:1:2. The ^{13}C NMR spectra also show similarities, the **C**=O and **C**=C(CN)$_2$ peaks tend to appear at 166 and 158ppm respectively, the **C**≡N peaks generally appear at 114 and 113ppm, while C=**C**(CN)$_2$ was commonly found in the region of 60ppm, with the N-**C**H$_2$ generally at 41.5ppm. All compounds exhibited the expected peaks in the infrared spectra at approx 2220 and 2210 cm^{-1} for C≡N,

approx. 1750 cm^{-1} for C=O and approximately 1600cm^{-1} for C=C. The UV spectra of some of the compounds were recorded and these show a strong absorption around λ_{max} 230-235nm and a weaker maximum at 300nm, quite similar to the *N*-alkylphthalimides which show relatively simple UV absorption spectra with absorption maxima around 235 nm (π,π^*) and 290 nm (n,π^*).[23a] The yields obtained for each compound are detailed in Table 29. The Mitsunobu reaction was unsuccessful with alcohols containing additional nucleophilic groups such as diols, amino alcohols, or with the amino acids serine and threonine. The general structure is shown below.



General Structure (A)

Table 29

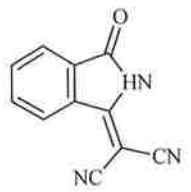
R-OH		Yield		
Alcohol	**R**	**A**	**R**	**[%]**
methanol	CH_3	**543**	CH_3	52
ethanol	C_2H_5	**544**	C_2H_5	47
propan-1ol	CH_2Et	**545**	CH_2Et	20
butan-1-ol	$(CH_2)_3Me$	**546**	$(CH_2)_3Me$	45
pentan-1-ol	$(CH_2)_4Me$	**547**	$(CH_2)_4Me$	51
hexan-1-ol	$(CH_2)_5Me$	**548**	$(CH_2)_5Me$	52
octan-1-ol	$(CH_2)_7Me$	**549**	$(CH_2)_7Me$	45
decan-1-ol	$(CH_2)_9Me$	**550**	$(CH_2)_9Me$	46
benzyl alcohol	$CH_2C_6H_5$	**551**	$CH_2C_6H_5$	45
2-phenylethanol	$CH_2CH_2C_6H_5$	**552**	$CH_2CH_2C_6H_5$	39
4-methoxy benzyl alcohol	$CH_2C_6H_4$-4-OCH_3	**553**	$CH_2C_6H_4$-4-OCH_3	50
2-methoxy ethanol	$CH_2CH_2OCH_3$	**554**	$CH_2CH_2OCH_3$	54
2-chloroethanol	CH_2CH_2Cl	**555**	CH_2CH_2Cl	68
3-chloropropanol	$CH_2CH_2CH_2Cl$	**556**	CH_2 CH_2CH_2Cl	61
trans-cinnamyl alcohol	$CH_2CH{=}CHC_6H_5$	**557**	$CH_2CH{=}CHC_6H_5$	57
allyl alcohol	$CH_2CH{=}CH_2$	**558**	$CH_2CH{=}CH_2$	66
3-methyl-2-buten-1-ol	$CH_2CH{=}C(CH_3)_2$	**559**	$CH_2CH{=}C(CH_3)_2$	46
2-propyn-1-ol	$CH_2C{\equiv}CH$	**560**	$CH_2C{\equiv}CH$	50
propan-2-ol	$CH(CH_3)_2$	**561**	$CH(CH_3)_2$	8
3-tosyl-propan-1-ol	$CH_2CH_2CH_2OTs$	**563**	$CH_2CH_2CH_2OTs$	53
cyclopentanol	C_5H_9	—	C_5H_9	—
cyclohexanol	C_6H_{11}	—	C_6H_{11}	—
1,3-propanediol	C_3H_6OH	—	C_3H_6OH	—
1,6-hexanediol	$C_6H_{12}OH$	—	C_3H_6OH	—
2-aminoethanol	$C_2H_4NH_2$	—	$C_2H_4NH_2$	—
3-aminopropanol	$C_3H_6NH_2$	—	$C_3H_6NH_2$	—
serine	$CH_2CH(NH_2)COOH$	—	CH_2-$CH(NH_2)$-COOH	—
threonine	$CH(CH_3)CH(NH_2)COOH$	—	$CH(CH_3)CH(NH_2)$-COOH	—

Chapter 5: Photochemistry of 2-alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones

5.1 Photochemistry

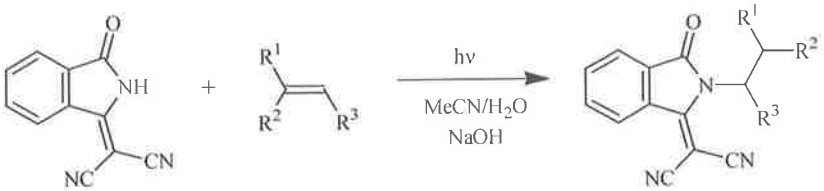
The *N*-substituted 3-dicyanomethylene-2,3-dihydroisoindol-1-ones all show a strong absorption around λ_{max} 230-235nm and a weaker maximum around 300nm, quite similar to the *N*-alkylphthalimides which, in acetonitrile, show relatively unstructured UV absorption spectra with absorption maxima around 235nm ($\pi \rightarrow \pi^*$); and 290 nm ($n \rightarrow \pi^*$) respectively.[23a] As the *N*-substituted 3-dicyanomethylene-2,3-dihydroisoindol-1-ones absorb above 300nm, a pyrex filter (cut-off: 300nm) was used to eliminate shorter wavelength radiation.

5.1.1 Irradiation of 3-dicyanomethylene-2,3-dihydroisoindol-1-one (530)



530

As 3-dicyanomethylene-2,3-dihydroisoindol-1-one (**530**) is an analogue of phthalimide (**1**), it was anticipated that it might share some similar photoreactions. Suau[7,34,49] has extensively researched the photoreactions of the phthalimide anion/ alkene system in acetonitrile/ water, with the reaction outcome being dependant on the HO^- concentration, and has shown that at $[OH^-] > [\text{phthalimide}]$, $[\pi^2+\sigma^2]$-addition predominantly occurs forming benzazepinediones (**62**),[7,34,49] whereas at $[OH^-] < [\text{phthalimide}]$ photoaddition of phthalimide to the double bond of the alkene takes place, resulting in *N*-substituted products. Cyclohexene, cyclopentene, styrene or α-methylstyrene were used in conjunction with various concentrations of NaOH and (**530**). A series of reactions were attempted by irradiating a solution of 3-dicyanomethylene-2,3-dihydroisoindol-1-one, NaOH and the required alkene in acetonitrile/ water. The ratio of (**530**): HO^- was varied from 5:1 to 1: 20. However, all the irradiations resulted in unreacted starting materials. The photoreactions were also attempted in methanol with a similar outcome (Table 30).

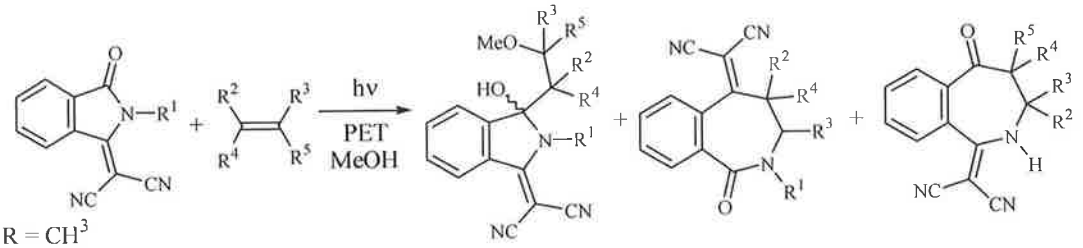


530

Figure 143: Proposed reaction scheme between (530) and alkenes in $MeCN/H_2O$.

5.1.2 Irradiations of 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543), (551) and (553).

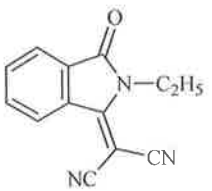
Irradiation of *N*-alkylphthalimides, in the presence of alkenes, in acetonitrile can lead to benzazepinedione formation, whereas irradiation in alcohols leads to a mixture of benzazepinediones and alcohol incorporating photoaddition products. Alcohols,[17a,50] acetone[55d] and amines[58] have been shown to undergo photochemical addition to *N*-alkylphthalimides. As 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**), along with the 2-arylalkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones (**551**) and (**553**) are analogues of *N*-methylphthalimide, they were irradiated in a series of solvents to assess their photoreactivity. In a typical photoreaction, (**543**) was dissolved in methanol, accompanied by the required alkene, filtered and deoxygenated prior to irradiation for between six and eight hours. In all cases, no evidence of any photoproducts was observed and in most cases, the starting material was recovered in nearly quantitative yield (Table 30).



543 R = CH^3
551 R = $CH_2C_6H_5$
553 R = $CH_2C_6H_4$-*p*-OCH_3

Figure 144: Proposed reaction scheme between (543), (551) or (553) and alkenes in MeOH.

5.1.3 Irradiations of 2-ethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (544).

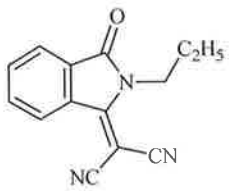


544

Compound (**544**) was dissolved in methanol and irradiated for between six and eight hours. The reaction was also carried out in *iso*-propyl alcohol, acetone and acetonitrile. In all cases, no evidence of any photoproducts was observed and in most cases, the starting material was recovered in nearly quantitative yields.

5.1.4 Irradiations of 2-alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones (545-550).

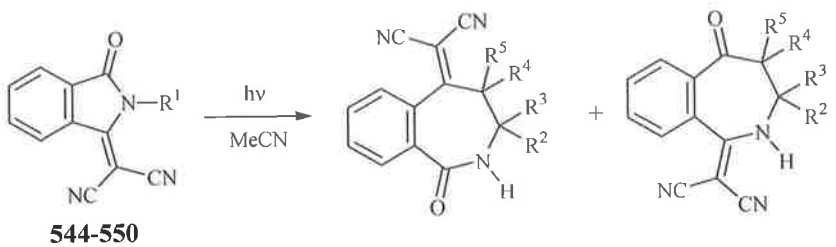
The presence of a γ– and δ–hydrogen on (**545**) increased the potential for photoreactions as the molecule could now undergo an *intra*molecular γ– or δ–hydrogen abstraction. Kanaoka *et al.*[17c] have shown that a series of *N*–alkylphthalimides (**173, 270-278**), which possess both γ– and δ–hydrogens, when irradiated in acetonitrile, *t*-butyl alcohol or acetone, afford benzazepindiones by *intra*molecular hydrogen abstraction in nearly every case, with yields up to 39% (section 2.4.1; *vide supra*).



545

Compound (**545**), 2-propyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one, was irradiated in methanol for eight hours, but only unchanged starting material was recovered. The reaction was also attempted in acetone and acetonitrile, but no evidence of any photoproduct formation was observed and in most cases, the starting material was recovered nearly quantitatively.

In a similar manner, the *N*-butyl (**546**), *N*-pentyl (**547**), *N*-hexyl (**548**), *N*-octyl (**549**) and *N*-decyl (**550**) derivatives also contain a γ– and δ–hydrogen. Irradiation of these compounds in either methanol or acetonitrile for eight hours gave, after column chromatography, unreacted staring material. The *N*-hexyl (**548**) derivative was also irradiated in toluene, in the presence of aniline or *N*, *N*-dimethylaniline as electron donors, or benzophenone as a sensitiser. After eight hours, the unreacted starting material was recovered.

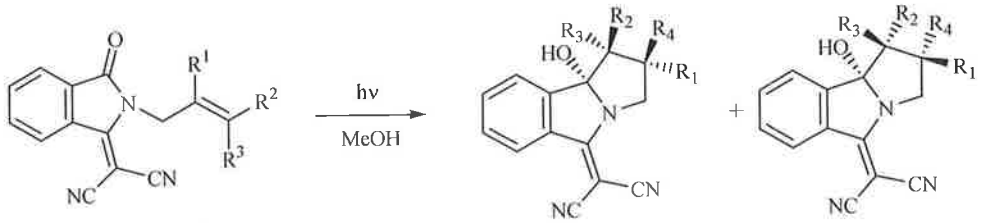


544-550

Figure 145: Proposed reaction scheme of (544-550) in MeCN or Acetone.

5.1.5 Irradiations of 2-alkenyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones (557-559).

Maruyama and Kubo[38] have shown that when *N*-(3-ethyl-2-butenyl)phthalimide (**95**) and *N*-(3-phenyl-2-propenyl)phthalimide (**97**) are irradiated in methanol, they undergo an *intramolecular* photocyclisation which is believed to occur by electron transfer, followed by *anti*-Markovnikov addition of methanol, noting that a small change in the phthalimide influences the reaction. However, they also noted that *N*-allylphthalimide (**94**) did not react under similar conditions (section 2.3.2.5). The *N*-phenylallyl derivative (**557**), is an analogue of *N*-(3-phenyl-2-propenyl)phthalimide (**97**), the *N*-allyl derivative (**558**) is an analogue of *N*-allylphthalimide (**94**) and the *N*-(3-methylbut-2-enyl) derivative (**559**) is an analogue of *N*-(3-methyl-2-butenyl)-phthalimide (**95**). These compounds were irradiated in methanol, to provide comparison as to whether, or not, similar reactions would occur. Similar to *N*-allylphthalimide, which showed no reaction to irradiation, compound (**558**) also showed no reaction after prolonged irradiation in methanol. However, both (**557**) and (**559**) were also unreactive, in contrast to phthalimides (**95**) and (**97**). Irradiation in acetonitrile similarly showed no reaction, while irradiation of (**557**) in acetone also showed no reaction. In all cases, the starting compounds were recovered after column chromatography.



557 $R^1 = R^3 = H$; $R^2 = C_6H_5$
558 $R^1 = R^2 = R^3 = H$
559 $R^1 = H$; $R^2 = R^3 = CH_3$

$R^4 = OCH_3$ $R^4 = OCH_3$

Figure 146: Proposed reaction scheme of (557-559) in MeOH.

5.1.6 Irradiations of 2-arylalkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-ones (552, 554 and 563)

Compound (**552**), which contains a γ-hydrogen, could potentially undergo γ-hydrogen abstraction giving a phenyl stabilised radical intermediate which could then form a benzazepinedione type compound. Irradiation of (**552**) for eight hours in methanol, acetonitrile or acetone gave only unreacted starting material. Compound (**554**), which is an analogue of *N*-ω-alkoxyphthalimides (**373**), contains both γ- and

ε-hydrogen, an intramolecular abstraction of either hydrogen, would result in a radical stabilised by oxygen. The *intra*molecular cyclisation of *N*-ω-alkoxyphthalimides was known to occur by δ-hydrogen abstraction, when irradiation is carried out in acetone, acetonitrile or *tert*-butyl alcohol.[88] When (**554**), was irradiated in methanol, acetone or acetonitrile, however, even after prolonged irradiation no products were observed on TLC and only (**554**) was recovered. Compound (**563**), which contains both γ- and δ-hydrogens, could potentially react via a δ-hydrogen abstraction giving an oxygen stabilised radical, or a γ-hydrogen abstraction might result in the possible elimination of an OTos radical. Irradiation of (**563**) in methanol or acetonitrile similarly led to no product formation. The compound was also irradiated in the same solvents in the presence of cyclohexene, cyclopentene, styrene or α-methylstyrene for a prolonged period, but again no reaction occurred.

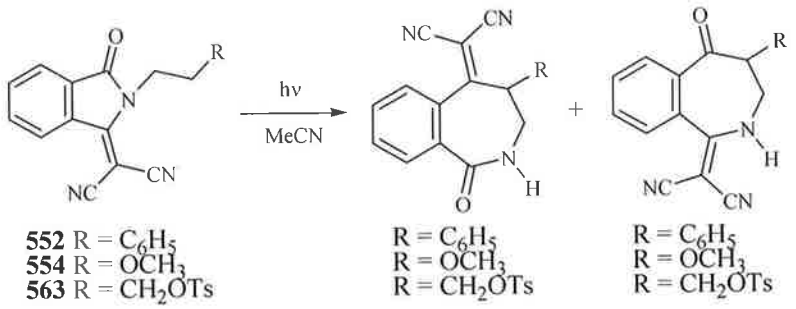
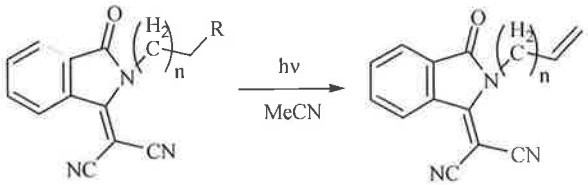


Figure 147: Proposed reaction scheme of (552, 554 or 563) in MeCN.

5.1.8 Irradiations of 2-(chloroalkyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-ones (555-556)

Compound (**555**) contains a γ-hydrogen which may possibly be stabilised by the chlorine if intramolecular hydrogen abstraction occurs, while compound (**556**) contains both γ- and δ-hydrogens, the δ-hydrogen may be stabilised by the chlorine if δ-hydrogen abstraction were to occur, while γ-hydrogen abstraction might result in the elimination of a chlorine radical. Irradiation of (**555**) in methanol or acetonitrile gave only recovered starting material, while irradiation of (**555**) in methanol or acetonitrile, containing either cyclohexene, cyclopentene, styrene or α-methylstyrene also gave recovered starting material after removal of the solvent and column chromatography. Irradiation of (**556**) in methanol or acetonitrile gave only recovered starting material after removal of the solvent and column chromatography.

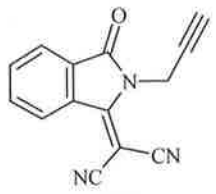


555 n = 1; R = Cl
556 n = 2; R = Cl

n = 0
n = 1

Figure 148: Proposed reaction scheme of (555 or 556) in MeCN.

5.1.7 Photoreactions of 2-propynyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (560)



560

Irradiation of (**560**) in either methanol or acetonitrile, showed after a prolonged period, only starting material on TLC. Following removal of the solvent and column chromatography the starting material was recovered in as the sole product.

It is clear that the *N*-substituted 3-dicyanomethylene-2,3-dihydroisoindol-1-ones compounds are photoinactive compared to their phthalimide analogues. It is reasonable to assume two possibilities for this, the first being the nature of the lowest excited state ie; $\pi \rightarrow \pi^*$ versus $n \rightarrow \pi^*$, the second possibility is whether the excited state is a singlet or a triplet state. The $n \rightarrow \pi^*$ excited state being generally more chemically reactive than $\pi \rightarrow \pi^*$ which suggests that the *N*-substituted 3-dicyanomethylene-2,3-dihydroisoindol-1-one systems have a lowest $\pi \rightarrow \pi^*$ excited states. However, the *N*-substituted phthalimides have shown photoactivity through both excited singlet and triplet states. The order of the excited states of phthalimides has been controversially discussed.[19b] The level of the (n,π) triplet state is either slightly below or above the lowest singlet state, which accounts for the high intersystem crossing rates.

A summary of all irradiations carried out is given, √ - indicates that the photolysis was carried out in just the solvent. Any additions are noted at the bottom of the table (Table 30).

Table 30: Summary of photochemical reactions.

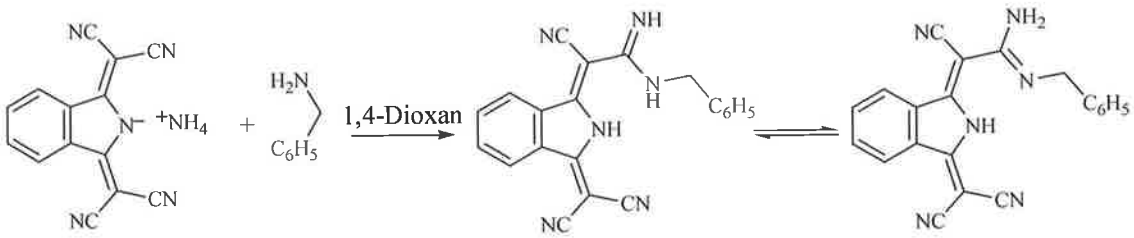
Compound	Solvent							
	MeOH	EtOH	*i*-PrOH	*t*-BuOH	Acetone	THF	MeCN	Toluene
510 (X = O)	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]
510 (X = HN)	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]	√ [a, c, e]
523	√		√	√			√	
525	√		√	√			√	
530	√ [h, i, j, k]				√	√	√ [h, i, j, k]	√ [e, f]
543	√ [a, b, c, d]	√	√	√	√	√	√ [a, b, c, d]	√ [e, f]
544	√		√		√		√	
545	√				√		√	
546	√						√	
547	√						√	
548	√						√	√ [e, f, g]
549	√						√	
550	√						√	
551	√				√		√	
552	√				√		√	
553	√				√		√	
554	√				√		√	
555	√ [a, c, d]						√ [a, c, d]	√ [a, e, f]
556	√						√ [c]	
557	√				√		√	
558	√						√	
559	√						√	
560	√						√	
563	√ [a, b, c, d]						√ [a, b, c, d]	

[a] Cyclohexene; [b] Cyclopentene; [c] Styrene; [d] α-methylstyrene; [e] Aniline; [f] *N*,*N*-Dimethylanaline; [g] Benzophenone; [h] Cyclohexene/ NaOH; [i] Cyclopentene/ NaOH; [j] Styrene/ NaOH; [k] α-methylstyrene/ NaOH.

Chapter 6: Reactions of amines with 3-dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine

6.1 Reactions of nucleophiles with 3-dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine (541).

Conway[106a,108b] has shown that the bis-dicyanomethylene compound (**565**) reacts with benzylamine to give *N*-benzyl-2-cyano-2-(3-dicyanomethylene-2,3-dihydroisoindolylidene)acetamidine (**566**). A benzylammonium salt was also obtained from the reaction, and it is believed that this ammonium salt reacts when heated under reflux to give the product (Figure 149).



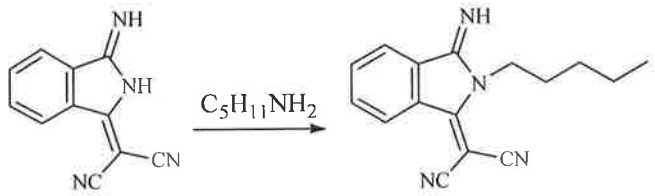
565 **566** **567**

Figure 149

Similar results were obtained by reaction of (**565**) with *n*-propylamine, *iso*-propyl amine, *n*-butylamine, cyclohexylamine, *n*-octylamine and *n*-decylamine, while an X-ray crystal structure of the product from reaction with *N,N*-dibutylamine identified the compound as an amidine. Based on similarities in the spectra of the different products obtained, it was concluded that all the compounds obtained from the reaction of (**565**) with primary amines were amidines. The presence of absorptions due to both an NH proton and NH_2 group in the ^1H NMR spectra of the compounds provided evidence that this series of amidines existed in tautomeric forms (**566**) and (**567**). However, the product from *N,N*-dibutylamine can only occur as a single tautomer.

6.1.1 Reactions of amines with 3-dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine (541).

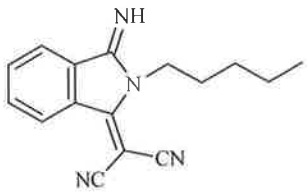
It was anticipated that amines might react in a similar fashion with compounds (**543-561**), however product formation did not occur. Instead, the corresponding imino compound (**541**) did react with alkyl amines such as pentyl amine and decyl amine, but not with aniline or benzylamine.



541 **569**

Figure 150

6.1.1.1 Synthesis of 1-imino-2-pentyl-3-dicyanomethylene-2,3-dihydroiso-indole (569)



569

Pentylamine reacted with (**541**) when heated together under reflux in pyridine. The ^{1}H NMR spectrum of the yellow product , m.p. 191-192°C, showed four aromatic protons. A broad singlet at 6.82ppm was assigned to an N-H, confirmed by exchange with D_2O. Resonances in the 3.8-0.8 region confirmed the presence of an *N*-pentyl group. The ^{13}C NMR spectrum showed signals from **C**=N, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ (175.41, 169.94 and 64.70ppm, respectively) also two non-equivalent C≡N signals (115.55 and 114.81ppm). The five carbons of the *N*-pentyl chain were found at 44.40 (N-**C**H$_2$), 29.38, 29.27, 22.66 (CH$_2$) and 14.33ppm (**C**H$_3$), with the remaining six resonances being assigned to the non-equivalent aromatic carbons. The IR spectrum confirmed the presence of N-H, C≡N and C=C with signal at 3320, 2216 and 1648cm^{-1} respectively. Elemental analysis gave satisfactory results for a molecular formula of $C_{16}H_{16}N_4$, corresponding to replacement of a hydrogen of (**541**) by a pentyl group.

In principle, there are five places (**a-e**) where the amine could attack (Figure 151). Attack by the amine at **a** would result in the loss of a molecule of ammonia and could introduce the alkyl group to either an *exo*-cyclic nitrogen, giving (**568**) or to an *endo*-cyclic ring nitrogen giving (**569**). Attack at **b** would also result in the loss of a molecule of ammonia, and would introduce the alkyl group to the *endo*-cyclic nitrogen (**569**) (Figure 151). Attack at either **a** or **b** would give products consistent with the observed molecular formula $C_{16}H_{16}N_4$. Attack at point **c** seems unlikely as it is not an active centre, while attack at **d** or **e** would not result in loss of a molecule of ammonia, but give addition compounds of molecular formula $C_{16}H_{19}N_5$, inconsistent with the microanalytical data.

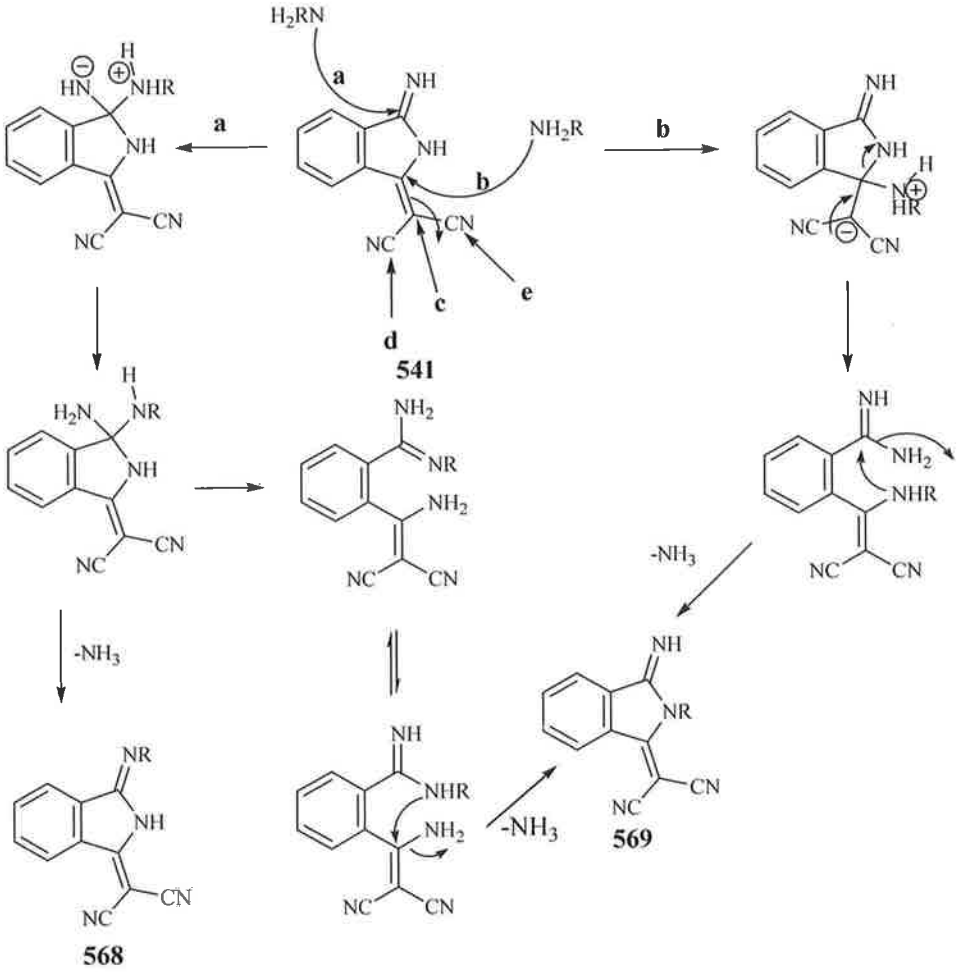


Figure 151

If the product obtained was compound (**568**) the *exo*-cyclic imino functionality would be expected to be lost on hydrolysis (Figure 152), resulting in formation of the known compound (**530**). However, if the product had structure (**569**), hydrolysis would be expected to yield 2-pentyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**547**) (Figure 152).

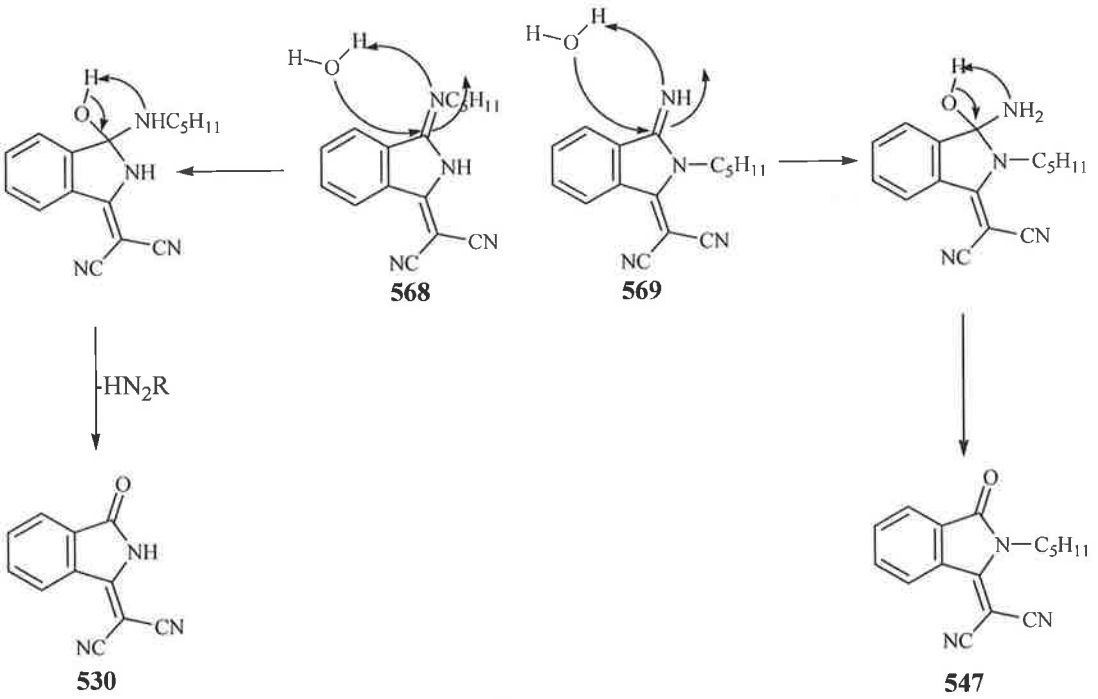
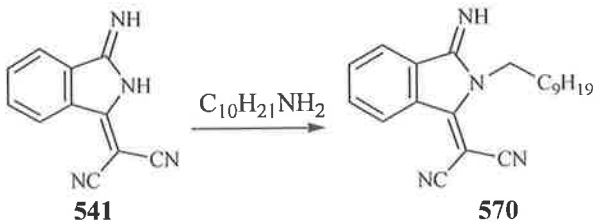


Figure 152

When the yellow compound was heated under reflux in aqueous acetic acid a hydrolysis product with melting point and spectral data identical with those of (**547**) was obtained. Compound (**547**) had previously been obtained by a Mitsunobu reaction. Its formation in the hydrolysis process confirms that reaction of pentylamine with (**541**) gives compound (**569**) rather than (**568**).

6.1.1.2 Synthesis of 1-imino-2-decyl-3-dicyanomethylene-2,3-dihydroiso-indole (570)



Reaction of (**541**) with decylamine similarly gave a yellow solid, m.p. 162-163°C. Its ^{1}H NMR spectrum again showed four aromatic protons and a broad singlet (7.40ppm) which exchanged with D_2O was assigned to the N-H. Peaks in the region 3.8-0.8 were assigned to an *N*-decyl group. The ^{13}C NMR spectrum showed **C**=N, **C**=C(CN)$_2$ and C=**C**(CN)$_2$ signals (175.86, 170.18 and 63.66ppm, respectively), also two non-equivalent C≡N peaks (115.73 and 115.17ppm). Resonances in the 45-14ppm region were due to an *N*-decyl group. Six non-

equivalent aromatic carbons were also present. The IR spectrum supported the presence of N-H, C≡N and C=C with peaks at 3338.9, 2217.2cm^{-1} and 1643.3cm^{-1} respectively. Elemental analysis gave satisfactory results for a molecular formula of $C_{21}H_{26}N_4$.

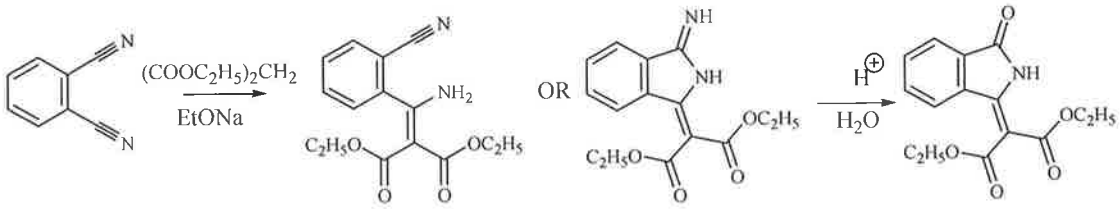
Treatment of this compound with aqueous acetic acid gave a hydrolysis product with melting point and spectral data identical with those of Mitsunobu product (**550**). Reaction of (**541**) with decylamine had therefore produced compound (**570**).

No corresponding reaction occurred with aniline, benzylamine, or phenylethylamine. In the case of aniline, failure to react may possibly be due to decreased nucleophilicity due to delocalisation of the nitrogen lone pair into the aromatic ring, though this would not be the case for benzylamine or phenylethylamine, for which steric factors may possibly play a part.

Chapter 7: Miscellaneous Reactions

7.1 Synthesis of 2-(3-oxo-2,3-dihydro-isoindol-1-ylidene)-malonic acid diethyl ester (564)

It was known that (**564**) the diethyl ester analogue of (**530**), could be prepared from diethylmalonate according to the method (Figure 151) described by Barrett[129] and it was anticipated that it too could also be alkylated under Mitsunobu conditions.



564

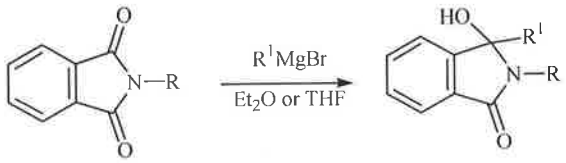
Figure 153

Phthalonitrile and diethylmalonate in the presence of sodium ethoxide, gave 2-(3-oxo-2,3-dihydro-isoindol-1-ylidene)-malonic acid diethyl ester. The ^{1}H NMR spectrum showed seven different types of protons, a broad singlet at 10.07ppm assigned N**H**; aromatic multiplets at 7.91ppm and 7.65ppm; quartets (J = 7*Hz*) at 4.47ppm and 4.33ppm assigned as O-CH_2 and triplets (J = 7*Hz*) at 1.41ppm and 1.35ppm assigned to the CH_3 groups. The ^{13}C NMR spectrum showed three carbonyls at 167.81, 165.92 and 165.61ppm respectively, peaks at 146.89 and 102.60ppm, assigned to **C**=C$(CO_2Et)_2$ and C=**C**$(CO_2Et)_2$ respectively, peaks at 62.66 and 62.14ppm were assigned to O-**C**H_2 with peaks at 14.47 and 14.38ppm assigned to **C**H_3. Six non-equivalent aromatic resonances were also present. This data was consistent with structure (**564**), and the melting point is in agreement with the reported value in the literature.[129] However, the yield was extremely poor, making the synthesis of (**564**) extremely inefficient and no further study was carried out.

7.2 Grignard Reactions

It is well established[130] that *N*-alkylphthalimides can readily react with Grignard reagents, to yield tertiary alcohols in good to excellent yields (Figure 154).[130e] Some of these products are key intermediates in naturally occurring bioactive molecules, some of which show affinity for dopamine D_4 receptor, or are anxiolytic drug candidates.[130b] It was anticipated that 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**), and other *N*-substituted-3-dicyanomethylene-2,3-

dihydroisoindol-1-ones would also react under Grignard conditions and form tertiary alcohols.



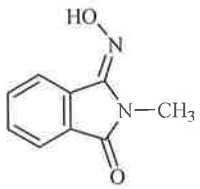
571

Figure 154

7.2.1 Reaction of (543) with Butylmagnesium Bromide

2-Methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**) was added to n-butylmagnesium bromide in anhydrous diethyl ether. However, following aqueous workup, only unchanged starting material was recovered. In a similar manner, reaction was also attempted using phenylmagnesium bromide and benzylmagnesium bromide, also resulting in recovery of unchanged starting material as the only product.

7.2.2 Oxime formation from 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543).



572

When 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**) was heated under reflux in an ethanol solution containing pyridine and hydroxylamine hydrochloride, a pale brown solid, m.p. 216-218°C, was obtained. The IR spectrum showed the presence of an OH and C=O at 3232 and 1705cm^{-1} respectively. However, the complete absence of absorption in the 2220cm^{-1} region revealed the absence of the cyano groups. The ^{1}H NMR spectrum showed six different sets of peaks. a broad singlet at 11.67ppm, which exchanged with D_2O, was assigned to OH. Two one-hydrogen doublets at 8.34 and 7.82ppm and two one-hydrogen triplets at 7.76 and 7.69ppm were assigned as aromatic hydrogens and a three-hydrogen singlet at 3.16ppm was assigned to an N-CH_3. The ^{13}C NMR spectrum showed nine carbon signals. Resonances at 165.70, 148.21 and 25.68ppm were assigned to **C**=O, **C**=N-OH and N-**C**H_3, respectively. The other six peaks were assigned to six non-equivalent aromatic carbons. The spectroscopic data are consistent with structure (**572**). Presumably, the compound is formed by nucleophilic attack of the hydroxylamine nitrogen on the **C**=$C(CN)_2$, rather than on **C**=O as was anticipated,

proton transfer followed by the loss of a molecule of malononitrile. A reasonable mechanism is shown (Figure 155).

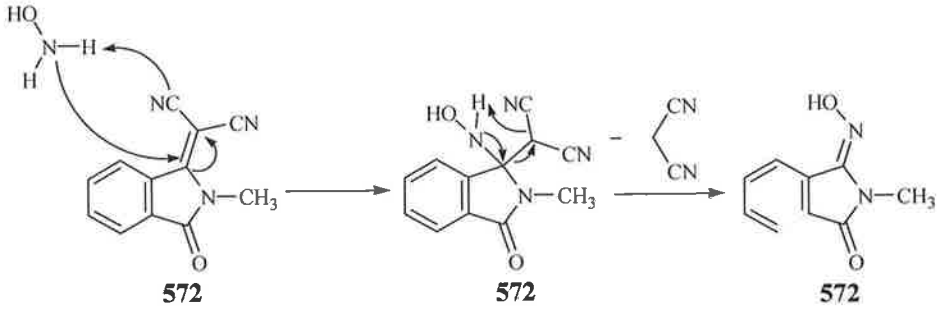
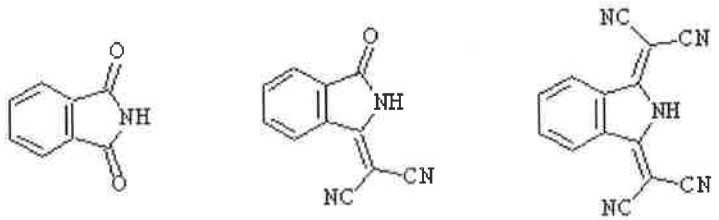


Figure 155: Mechanism of oxime formation

Chapter 8: 2-Isopropyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one

8.1 Introduction

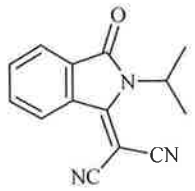
Conway[106a] has shown that, in a series of *N*-substituted derivatives of (**531**), the chemical shift of the **C**=C(CN)$_2$ in the ^{13}C NMR is in the region of 160ppm. Conway has also shown that, in the ^{1}H NMR spectra, the chemical shifts of the aromatic hydrogen *ortho* to the C=**C**(CN)$_2$ groups are in the region 8.6-8.7ppm, while the chemical shifts of the aromatic hydrogens *meta* to the C=**C**(CN)$_2$ groups are in the region 7.8ppm. Independent work carried out by Crean[106c] and also recorded in this thesis have established that, in a series of *N*-substituted derivatives of (**530**), the chemical shift of **C**=C(CN)$_2$ appears in the region 157-159ppm while the chemical shift of the **C**=O is in the region of 165-167ppm. It has also been shown that, in the ^{1}H NMR spectra, the chemical shifts of the aromatic hydrogen *ortho* to the C=**C**(CN)$_2$ group is in the region 8.5ppm, while the chemical shifts of the aromatic hydrogens *ortho* to the C=O group is in the region 7.8ppm. The chemical shift of the C=O groups in the ^{13}C NMR spectra of *N*-substituted derivatives of (**1**) is known to be in the region of 168ppm, while the *ortho* and *meta* aromatic hydrogens appear at 7.8-7.9 and 7.6-7.8ppm respectively.[131] It is clear that the *N*-substituted derivatives of (**530**) share spectroscopic traits with both *N*-substituted derivatives of (**1**) and (**531**). However, when *iso*-propyl alcohol was used as the alcohol component in the Mitsunobu reaction, it appeared as though two compounds were present in the NMR spectra.



1 **530** **531**

Figure 156

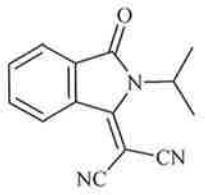
8.2. 2-Isopropyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (561)



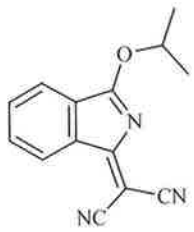
561

The reaction was carried out using *iso*-propyl alcohol. After initial chromatography, both ^{1}H and ^{13}C NMR spectra showed duplication of all the expected peaks in the spectra. The aromatic hydrogens appeared as multiplets at 8.52, 8.17, 7.82, 7.69 and 7.63ppm. One hydrogen multiplets for the *iso*-propyl C-H were visible at 5.62 (minor product) and 5.02ppm (major product), while a six hydrogen doublet appeared at 1.58ppm (major product) with a second six hydrogen doublet at 1.45ppm (minor product). Using the methine and methyl absorptions in the duplicated spectrum, the ratio of the isomers was found to be 1:2.5, corresponding to approximately 70% major isomer and 30% minor isomer.

Two different theories have been considered for this duplication. The first consideration is a competing alkylation reaction at nitrogen and oxygen giving two different compounds (Figure 157), the *iso*-propyl C-H at 5.62ppm possibly due to O-alkylation and that at 5.02ppm possibly due to N-alkylation. Alkylation of oxygen under Mitsunobu conditions has been reported in the literature.[132]



N-alkylation



O-alkylation

Figure 157

Repeated recrystallisation, from methanol, of the initially obtained product mixture afforded only the major compound, mp. 163-165°C. The ^{1}H NMR spectrum showed four aromatic hydrogens as three multiplets at 8.51, 7.82 and 7.69ppm. An *iso*-propyl group was present, as evidenced by a one hydrogen septet at 5.02ppm (J = 6.8*Hz*) and a six hydrogen doublet at 1.62ppm (J = 6.8*Hz*). The ^{13}C NMR spectrum also showed a signal at 167.05ppm which could be assigned to either C=O or C=N. Two other signals at 158.62 and 59.57ppm could be assigned to **C**=C(CN)$_2$ and C=**C**(CN)$_2$ respectively. Peaks at 114.53 and 113.11ppm were consistent with the presence of two non-equivalent cyano groups, while peaks at 49.41 and 21.02ppm

were assigned to **C**H$(CH_3)_2$ and CH$(\mathbf{C}H_3)_2$. Six non-equivalent aromatic resonances were also present. The presence of C≡N and C=O were confirmed by peaks at 2223, 2205 and 1754cm^{-1} in the IR spectrum. Elemental analysis gave satisfactory results for a molecular formula of $C_{14}H_{11}N_3O$. However, it was still not clear as to whether N-alkylation or O-alkylation had occurred.

Examination of the initially formed product mixture by TLC, revealed the presence of two components which were eventually separated by careful column chromatography. The first eluted product, mp 174-175°C, showed four aromatic hydrogens as two multiplets at 8.17 and 7.54ppm. The *iso*-propyl group appeared as a one hydrogen septet at 5.62ppm (J = 6*Hz*) and a six hydrogen doublet at 1.45ppm (J = 6*Hz*). The ^{13}C NMR spectrum showed a signal at 177.97ppm which could be assigned to C=O or C=N. Two signals at 171.52 and 74.40ppm were assigned as **C**=C$(CN)_2$ and C=**C**$(CN)_2$ respectively. Peaks at 112.31 and 111.31ppm were consistent with two non-equivalent cyano groups, while peaks at 71.75 and 20.84ppm were assigned to **C**H$(CH_3)_2$ and CH$(\mathbf{C}H_3)_2$. Six non-equivalent aromatic resonances were also present. It should be noted that the peaks at 71.75 (**C**H$(CH_3)_2$), 74.40 (C=**C**$(CN)_2$) and 177.97ppm (C=O or C=N) were at least 10ppm further downfield than the corresponding signals in any of the other *N*-alkyl derivatives. The presence of C≡N and C=C were confirmed by peaks at 2232 and 1616cm^{-1} in the IR spectrum, however the peak at 1616cm^{-1} could also be assigned to C=N, while there was no peak present in the C=O region of the IR spectrum. Comparison of the ^{1}H NMR spectrum of this component with that of the original mixture, showed it to be the minor product.

The second eluted compound, mp. 163-165°C, had ^{1}H and ^{13}C NMR spectra identical to those of the compound previously obtained by repeated recrystallisation and was the major Mitsunobu product. Elemental analysis confirmed that the compounds were isomers but while they had been separated, it was still unclear as to whether or not competing N-alkylation and O-alkylation had occurred.

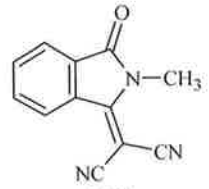
The two-dimensional NMR techniques HMQC (Heteronuclear Multiple Quantum Correlation) and HMBC (Heteronuclear Multiple Bond Correlation) were employed to give a clearer picture of the two isomers. HMQC is an experiment that identifies

protons with their directly bound carbons, while HMBC identifies proton nuclei with carbon nuclei that are separated by more than one bond and can identify carbon resonances that are up to four bonds away. Both experiments are heavily influenced by the concentration of the samples. Similarities in the HMQC and HMBC NMR spectra of the major and minor products would help to determine connectivities within the molecules.

The HMQC NMR spectrum of the major product, mp. 163-165°C, showed coupling of the six hydrogen doublet at 1.62ppm ($CH(C\mathbf{H}_3)_2$) with the carbon at 21.02ppm ($CH(\mathbf{C}H_3)_2$) and the one hydrogen septet at 5.02ppm (C**H**) was coupled to the carbon at 49.41ppm (**C**H), as anticipated for the presence of an *iso*-propyl group. The two aromatic protons at 7.69ppm were coupled to the carbons at 134.57 and 133.90ppm, while the aromatic protons at 7.82 and 8.51ppm were coupled to the carbons at 125.13 and 125.19ppm respectively.

The HMQC NMR spectrum of the minor product, mp 174-175°C, showed coupling of the six hydrogen doublet at 1.45ppm ($CH(C\mathbf{H}_3)_2$) with the carbon at 20.84ppm ($CH(\mathbf{C}H_3)_2$) and the one hydrogen septet at 5.62ppm (C**H**) was coupled to the carbon at 71.75ppm (**C**H), again as anticipated for the presence of an *iso*-propyl group. The three aromatic protons at 7.54ppm were coupled to the carbons at 131.68, 131.63 and 121.31ppm, while the aromatic proton at 8.16ppm was coupled to the carbon at 124.08ppm. The aromatic proton regions of the major and the minor products were significantly different to each other. The major product showed three peaks for the four aromatic hydrogens in a ratio of 1:1:2, while the minor product showed only two peaks for the four hydrogens with a ratio of 1:3. This would suggest that the aromatic ring is influenced by some factor, possible a distortion of the five membered ring system.

The HMBC NMR spectra of *N*-methyl (**543**), *N*-ethyl (**544**) and *N*-(methoxy)ethyl (**554**) compounds were obtained in order to establish a pattern for *N*-alkylation. The HMBC spectrum of the *N*-methyl derivative (**543**) (Figure 158), clearly shows the coupling of the three hydrogen singlet at 3.62ppm coupling to the **C**=C(CN)$_2$ and **C**=O peaks at 159.00 and 166.56 respectively.



543

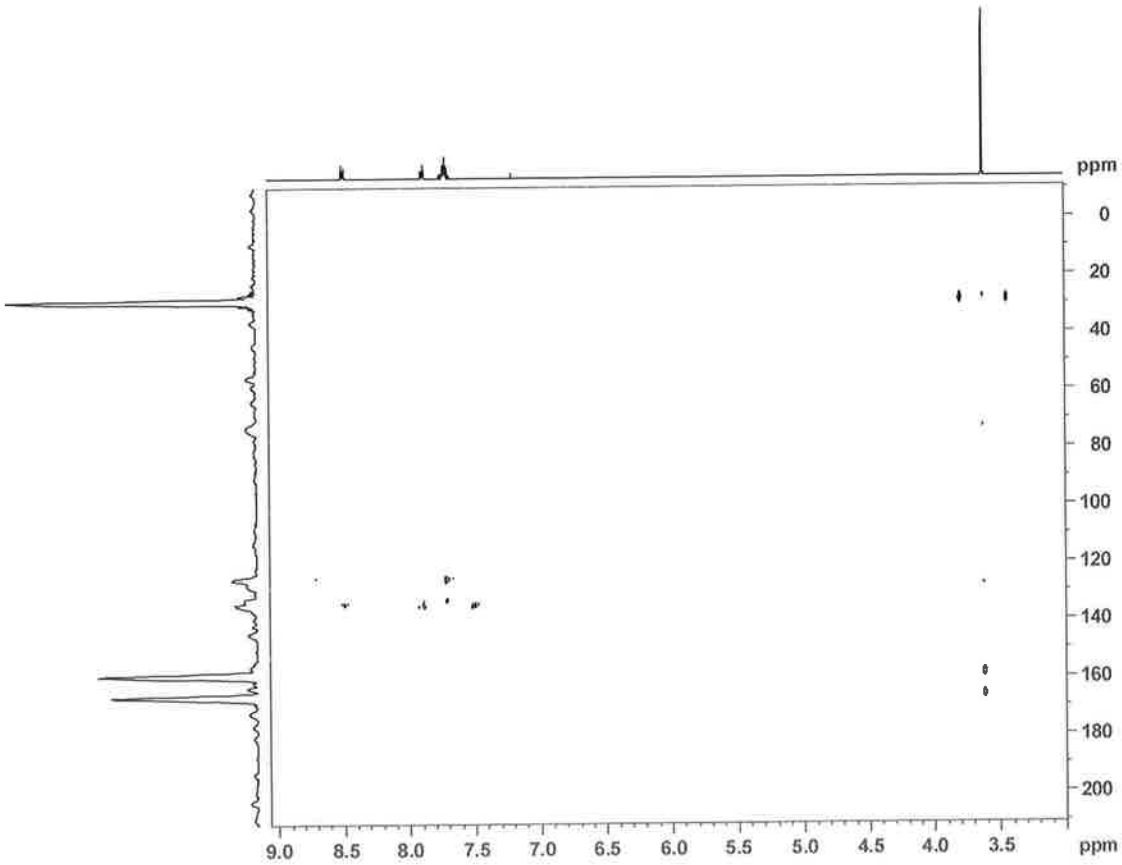
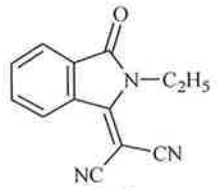


Figure 158: HMBC NMR spectrum of *N*-methyl derivative (543)

The HMBC spectrum of the *N*-ethyl derivative (**544**) (Figure 159), shows the coupling of the two hydrogen quartet at 4.18ppm to the carbon at 15.6ppm (**C**H_3) and also to the carbons at 158.26 (**C**=C$(CN)_2$) and 166.85ppm (**C**=O). It also shows the coupling of the two hydrogen quartet at 4.18ppm to a peak at 113 or 114ppm (**C**N). As a result of sample concentrations, this coupling is not visible in the spectra of the *N*-methyl or *N*-(methoxy)ethyl derivatives.



544

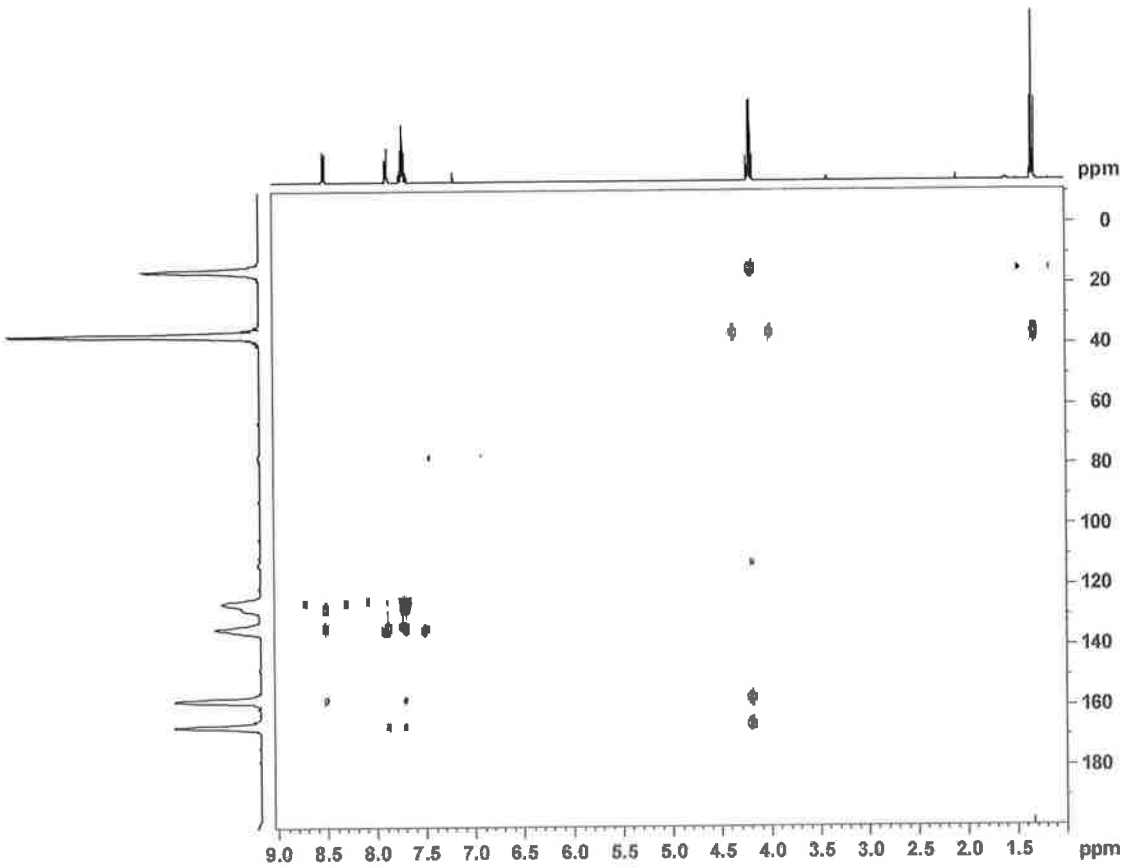
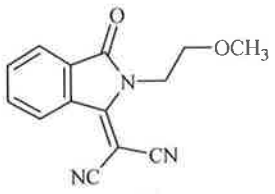


Figure 159: HMBC NMR spectrum of *N*-ethyl derivative (544)

The HMBC spectrum of the *N*-(methoxy)ethyl derivative (**554**) (Figure 160), shows the coupling of the two hydrogen triplet at 4.40ppm to the carbon at 69.96ppm (O-**C**H_2) and also to the carbons at 157.94 (**C**=C(CN)$_2$) and 166.47ppm (**C**=O).



554

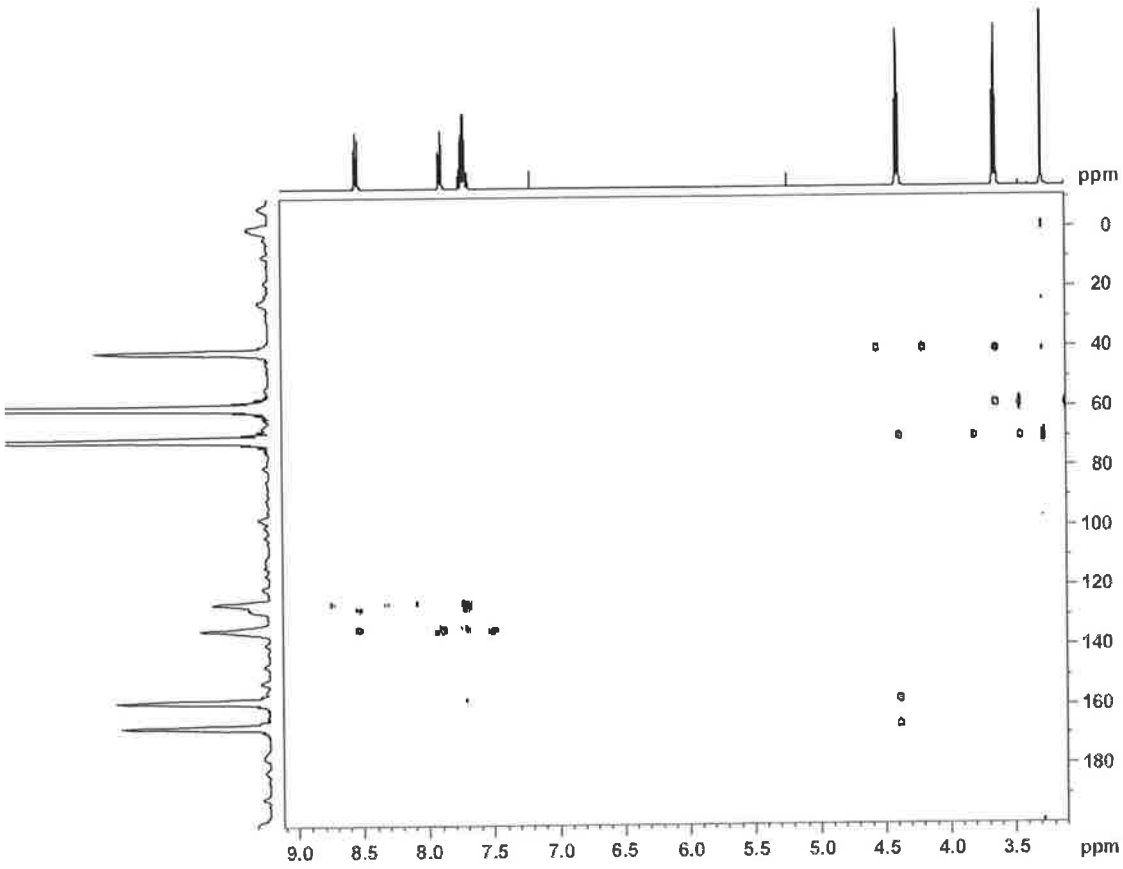
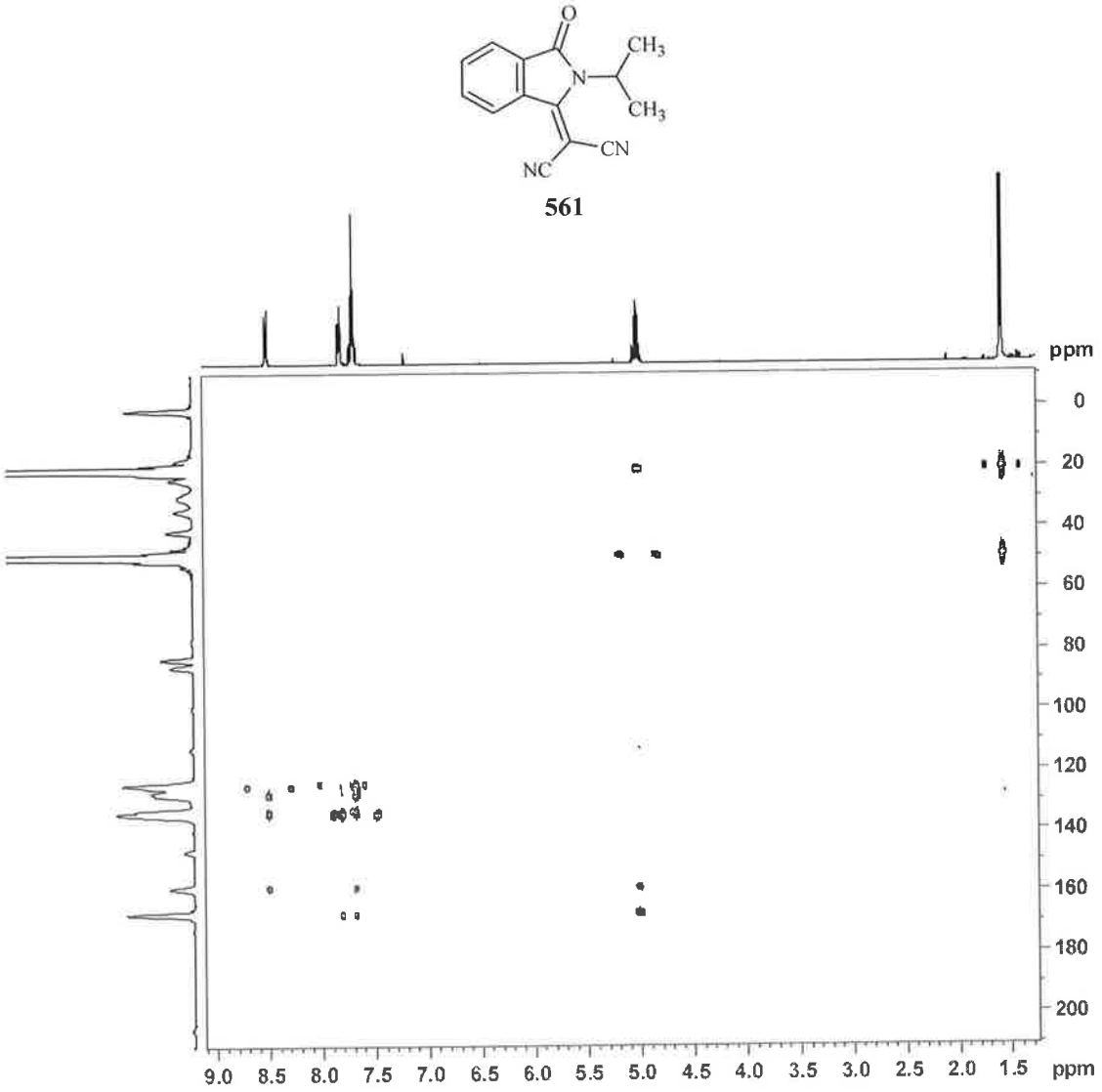


Figure 160: HMBC NMR spectrum of *N*-(methoxy)ethyl derivative (554)

The HMBC NMR spectra of the *N*-methyl (Figure 158), *N*-ethyl (Figure 159) and *N*-(methoxy)ethyl (Figure 160) compounds all show the coupling of a C**H** proton peak to the (**C**=C(CN)$_2$) and (**C**=O). Comparison of these spectra with the HMBC spectra of the major and minor products obtained, would confirm whether or not the analogues were present. If *N*-alkylation had occurred the (C**H**(CH$_3$)$_2$) to (**C**=C(CN)$_2$) and (**C**=O) coupling would be only three bonds away and should be visible along with, depending on concentration, coupling to (**C**N). If *O*-alkylation had occurred, the (C**H**(CH$_3$)$_2$) to (**C**=C(CN)$_2$) coupling is five bonds away and may not be visible,

while the coupling to (**C**N) would be seven bonds away and would, most likely, not be visible.

The HMBC NMR spectrum (Figure 161) of the major product, mp 163-165°C, showed the six hydrogen doublet at 1.62ppm ($CH(C\mathbf{H}_3)_2$) coupling to the carbon at 49.41ppm (N-**C**H), consistent with the presence of an *iso*-propyl group. The one hydrogen septet at 5.02ppm (**C**H) was coupled to the carbons at 21.02 ($CH(\mathbf{C}H_3)_2$), which are two bonds away, also to the carbons at 158.62ppm ($\mathbf{C}{=}C(CN)_2$), at 114.53 (**C**N) and at 167.05ppm. This is consistent with the presence of an *N-iso*-propyl group, but not an *O-iso*-propyl group.

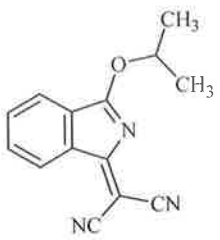


561

Figure 161: HMBC NMR spectra of major product.

The methine hydrogens of an *O-iso*-propyl group would not be expected to couple through five bonds to the **C**=C(CN)$_2$ group, nor through seven bonds to the **C**N. The carbon signal at 167.05ppm was assigned as (**C**=O), consistent with the data observed for the series of *N*-substituted derivatives of (**530**). The aromatic region was quite complex, showing several couplings from aromatic protons to aromatic carbons. However, this could be used, along with the HMQC spectrum, to show the connectivity of the aromatic ring system. From the HMQC spectrum, the hydrogens at 7.69ppm are directly coupled to the carbons 134.57 and 133.90 ppm, and also to the carbons at 167.05 (**C**=O) and 158.62ppm (**C**=C(CN)$_2$) in the HMBC spectrum, indicating that these hydrogens are *beta* to the **C**=O and **C**=C(CN)$_2$ groups. The hydrogen at 7.82ppm is coupled directly to the carbon at 125.13ppm (HMQC) and indirectly coupled to the carbon at 167.05ppm (**C**=O), suggesting it is *gamma* to **C**=O and *delta* to **C**=C(CN)$_2$. The hydrogen at 8.51ppm is directly coupled to the carbon at 125.19ppm (HMQC) and indirectly coupled to the carbon at 158.62ppm (**C**=C(CN)$_2$), suggesting it is *gamma* to **C**=C(CN)$_2$ and *delta* to C=O.

The HMBC NMR spectrum (Figure 162) of the minor product, mp 174-175C^o showed a six hydrogen doublet at 1.45ppm (CH(C**H**$_3$)$_2$) coupling to the carbon at 71.75ppm (**C**H). The one hydrogen septet at 5.62ppm (C**H**) was coupled to the carbon at 20.84 (CH(**C**H$_3$)$_2$), which are two bonds away, and the carbons at 177.97ppm, but not to the carbons at 171.52ppm (**C**=C(CN)$_2$) or 112.31 and 111.31ppm (**C**N). This is more consistent with *O*-alkylation than *N*-alkylation. If that is the case, the peak at 177.97ppm can be assigned as (**C**=N). However, sample concentration may be the reason for the C**H** to (**C**=C(CN)$_2$) and C**H** to **C**N not being visible. Once again, the aromatic region was quite complex, showing several couplings from aromatic protons to aromatic carbons.



573

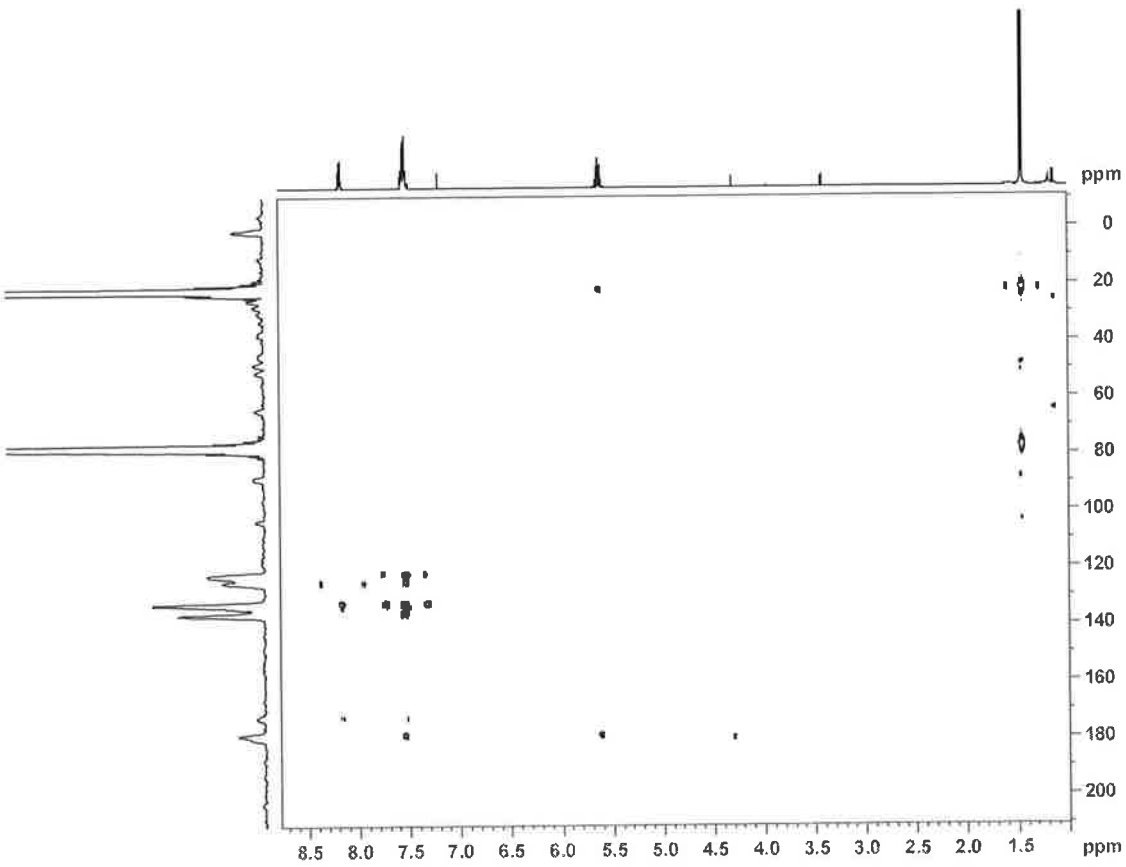
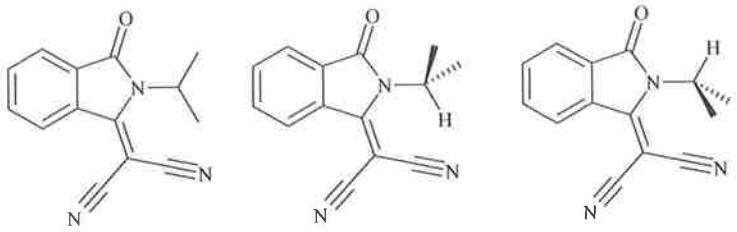


Figure 162: HMBC NMR spectra of minor product.

The second consideration might be that the two isomers are *N-iso*propyl derivatives, they are each of the general structure (**561**). Rotation about the nitrogen-carbon bond of the *N-iso*propyl group should allow for two conformations, which minimise the repulsive interactions between the methyl groups and the remainder of the molecule, and in which there is an in-plane interaction between the isopropyl CH group and the $C(CN)_2$ unit (**561a**) or between the isopropyl CH group and the carbonyl group (**561b**). If the energy barrier to free rotation about the N-C bond were sufficiently high, it might be possible to isolate the rotamers separately as they would be expected to be physically different (Figure 163).



561 **561a** **561b**

Figure 163

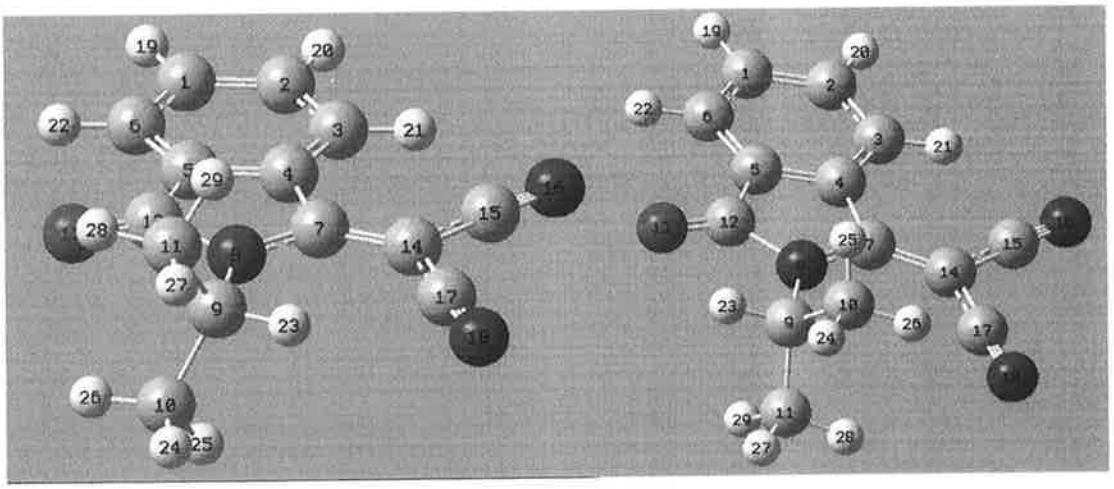


Figure 164: (561a) on left, (561b) on right GaussView.[133]

Compounds that display stereoisomerism resulting from hindered rotation about single bonds, where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers, are known as *atropisomers*.[134] Atropisomerism is significant as it introduces an element of chirality in the absence of a stereogenic carbon. Atropisomerism has been a widely applicable area of stereochemistry from the first resolution of a chiral atropisomeric biaryl, 6,6'-dinitro-2,2'-diphenic acid (Figure 165), by Christie and Kenner in 1922[135] through the discovery of numerous naturally occurring atropisomeric molecules and the development of atropisomeric chiral ligands. A high point in the history of atropisomerism must be the central role played by the atropisomeric ligand BINAP (Figure 165) in Professor Ryoji Noyori's share of the Nobel Prize for Chemistry in 2001.[136]

6,6'-dinitro-2,2'-diphenic acid BINAPs (X = NH_2, OH, PPh_2)

Figure 165

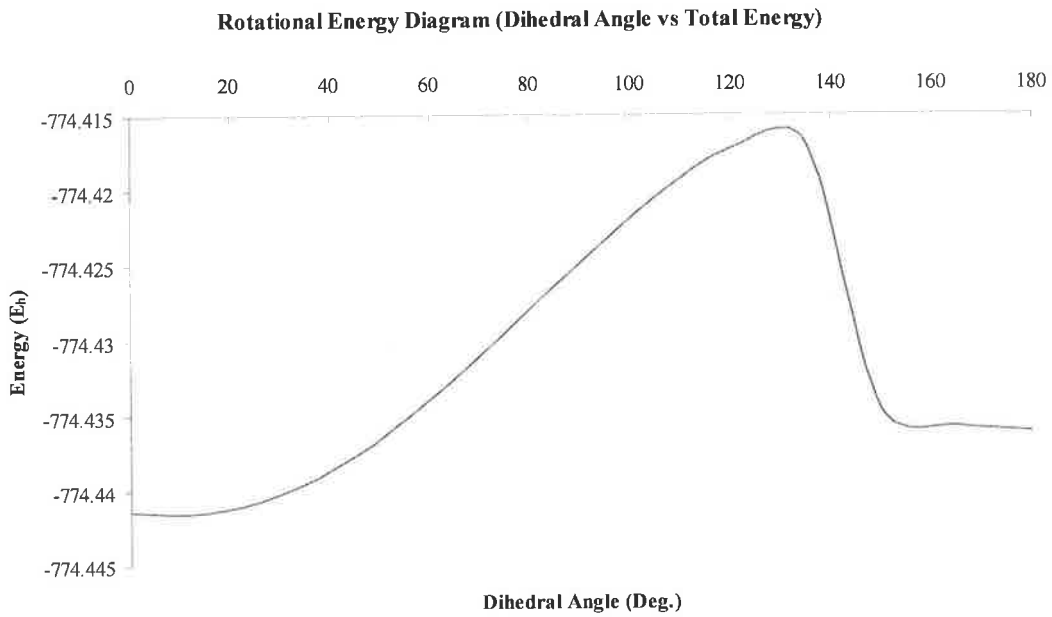
The Gaussian 03 suite of computational chemistry programmes[137] was used to further investigate these conformations and to estimate the rotational barrier separating them. The HC-NCC$(CN)_2$ dihedral angle was set to 0° (**561a**) and this conformation was used as the reference orientation for subsequent calculations.

Calculations at the RHF 6-31G level were carried out for dihedral angles in the range 0°-180° at 15° increments. For each rotational angle, the energy of the relaxed rotamer was calculated by the Hartree Fock (HF) method. The results are listed in Table 31 and show minima at rotational angles of 15° (approx) and 180°, with a maximum in the region of 130°, as seen in Graph 1.

Table 31: Total Energy vs Angle of Rotation around N-CHMe$_2$ bond

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
0°	-774.4414089940
15°	**-774.4414894830**
30°	-774.4402089990
45°	-774.4376394430
60°	-774.4339398210
75°	-774.4295277310
90°	-774.4248770490
105°	-774.4205017610
120°	**-774.4172549630**
135°	**-774.4169337380**
150°	-774.4346822690
165°	-774.4358603240
180°	**-774.4361831030**

Graph 1: Total Energy vs Angle of Rotation around N-CHMe$_2$ bond at the RHF 6-31G level



Further calculations were done at the RHF 6-31G(d) level, a higher computational level, requiring much more lengthy calculation times, to more precisely identify the minimum and maximum energies involved. The rotation angle was increased in 10° increments between 0°-40° (Table 32), in 5° increments between 0°-25° (Table 33) and in 5° increments between 120°-135° (Table 34) and the total energy was calculated for each conformer.

Table 32: Calculations at the RHF 6-31G(d) level 0-40°

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
0°	-774.7757620970
10°	-774.7760084180
20°	-774.7756913830
30°	-774.7749129280
40°	-774.7736141630

Table 33: Calculations at the RHF 6-31G(d) level 0-25°

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
0°	-774.7757620970
5°	**-774.7760097060**
10°	-774.7760084890
15°	-774.7759045380
20°	-774.7756914110
25°	-774.7753630880

Table 34: Calculations at the RHF 6-31G(d) level 120-135°

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
120°	-774.7525376750
125°	-774.7520491680
130°	**-774.7519261970**
135°	-774.7522128310

The resulting data suggest an energy minimum at a dihedral angle of ~5° (Table 33) and a maximum at a dihedral angle of ~130° (Table 34). The energy barrier is thus the difference between the maximum and the minimum. This gives a value of 0.024083509 Hartrees. As one Hartree is equal to 2625.5 kJmol^{-1}, the energy value corresponds to a rotational energy barrier of approximately 63kJmol^{-1}.

The Hartree Fock calculations at both the RHF 6-31G and RHF 6-31G(d) levels suggest that, as rotation around the C-N bond occurs, the 5-membered ring becomes distorted, with the NCHMe$_2$ group twisting out of the plane of the aromatic ring. The dicyanomethylene group also twists about the C=C double bond in an attempt to relieve strain (Figure 166).

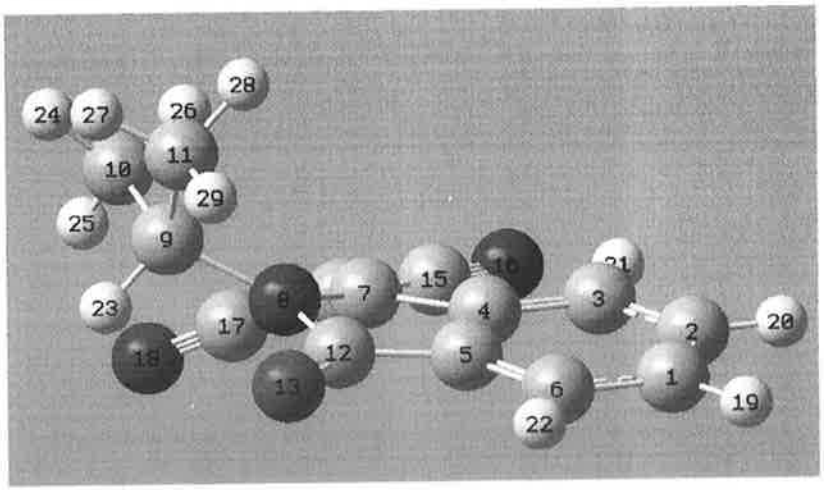


Figure 166: Ring distortion at a dihedral angle of 130°.

Calculations at the more sophisticated DFT B3LYP 6-31G(d) level were undertaken to (a) obtain more reliable measurements of the energy barrier to rotation, (b) to determine whether, using this more refined calculation method, the minimum energy rotamer corresponds to a dihedral angle of 0° or 10° and (c) to calculate the ^{1}H and ^{13}C NMR spectra for each atropisomer.

The calculations at the DFT B3LYP 6-31G(d) level (Table 35 to Table 37) located the lowest energy at 0°, corresponding to (**561a**), in contrast to the RHF 6-31G(d) level calculation which had placed it at ~5/10° (Table 33). The energy maximum calculated corresponded to a dihedral angle of approximately 125° (Table 36), with a higher energy minimum corresponding to a dihedral angle of 180° (**561b**) (Table 37). All of the data in the table 35 to 37 is displayed graphically in (Graph 2)

Table 35: Calculations at the DFT B3LYP 6-31G(d) level 0-25°

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
0°	**-779.5765302830**
5°	-779.5765066470
10°	-779.5764244420
15°	-779.5762551450
20°	-779.5760080800
25°	-779.5756734090

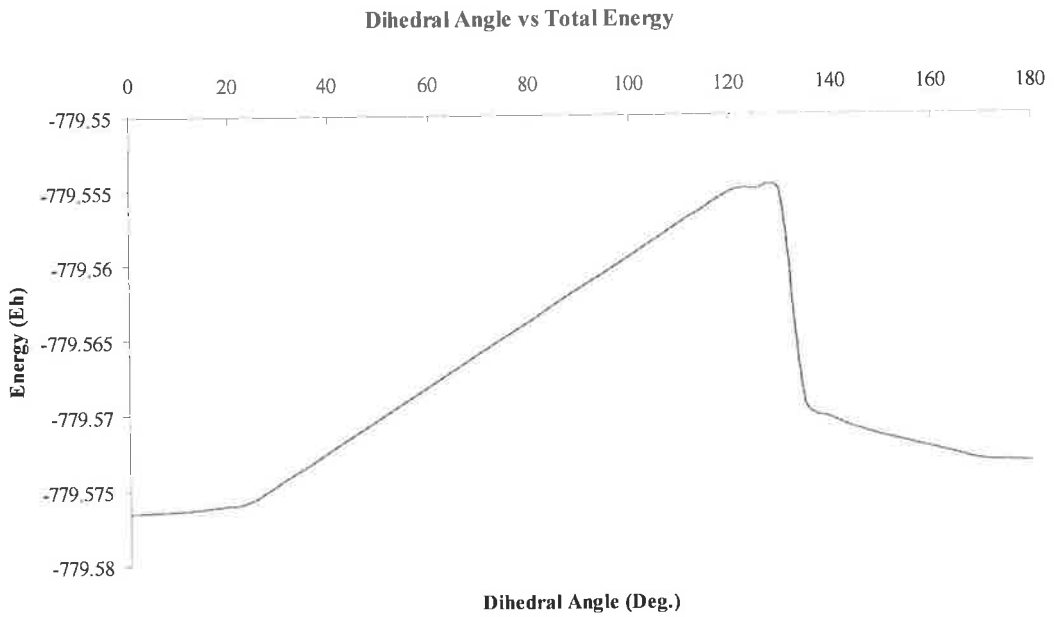
Table 36: Calculations at the DFT B3LYP 6-31G(d) level 120-145°

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
120°	-779.5552415420
125°	**-779.5549822280**
130°	-779.5550880710
135°	-779.5693807220
140°	-779.5702934930
145°	-779.5710645100

Table 37: Calculations at the DFT B3LYP 6-31G(d) level 170-180°

H-C-NC=C(CN)$_2$ Dihedral Angle	Total Energy – Hartree (E_h)
170°	-779.5731562610
175°	-779.5732837450
180°	**-779.5733263040**

Graph 2: Calculations at the DFT B3LYP 6-31G(d) level



The energy barrier is thus the difference between the maximum and the minimum. This gives a value of 0.021548055 Hartrees from the first minimum energy conformation to the maximum, and a value of 0.018344076 Hartrees going from the second minimum energy conformation to the maximum. As one Hartree is equal to 2625.5 $kJmol^{-1}$, the rotational energy barriers are therefore calculated as $57kJmol^{-1}$, from the first minimum energy conformation (**561a**) to the maximum and $48kJmol^{-1}$ from the second minimum energy conformation (**561b**) to the maximum.

The major isomer was heated to 200°C, approximately 35°C above it melting point, to see if any change could be induced in the compound, but after maintaining this temperature for a prolonged period, subsequent TLC analysis showed no change in the major isomer. This suggested that the major isomer was stable to interconversion at elevated temperature.

Gaussian 03 was also used to predict the ^{1}H and ^{13}C NMR spectra of both atropisomers, and these values were compared to the chemical shifts obtained experimentally. They were assigned based on how well the predicted values matched the actual values. In the case of both compounds, the predicted ^{1}H NMR values were closer to the experimentally determined values than the corresponding ^{13}C NMR spectra. The predicted ^{1}H NMR spectrum for compound (**561a**) appeared to be a

better match with the major product, as three of the four aromatic hydrogens were within 0.1ppm of the predicted values, while the *iso*propyl CH (5.1ppm) was within 0.30ppm of the predicted value of 4.82ppm for (**561a**) as opposed to 5.27ppm for (**561b**). The predicted ^{1}H NMR spectrum for compound (**561b**) appeared to be a better match for the minor product, with the two methyls of the *iso*propyl group (1.45ppm) being 0.01ppm from the predicted value (1.46ppm), the *iso*propyl CH (5.6ppm) was within 0.35ppm of the predicted value 5.27ppm for (**561b**) as opposed to 4.82ppm for (**561a**), with two of the aromatic hydrogens being within 0.05ppm of their predicted values. The aromatic hydrogens were assigned based on HMQC and HMBC NMR spectra as discussed previously. The results are tabulated in Table 38.

Table 38: Actual Chemical Shifts vs Gaussian Calculated Chemical Shifts for N-alkylation

Type of Hydrogen	HC-NCC(CN)$_2$ (561a)		HC-NC=O (561b)	
	Gaussian (ppm)	Actual (ppm)	Gaussian (ppm)	Actual (ppm)
Non-aromatic hydrogens				
(C**H**$_3$)$_2$	1.28	1.62	1.46	1.45
N-C**H**	4.82	5.1	5.27	5.6
Aromatic hydrogens				
O=C-CC**H**	7.88	7.82	7.92	7.53
O=C-CC-C**H**	7.57	7.69	7.57	7.53
C=C-CC**H**	8.87	8.51	7.57	7.53
C=C-CC-C**H**	7.69	7.69	8.85	8.17
Type of Carbon	**HC-NCC(CN)$_2$ (561a)**		**HC-NC=O (561b)**	
	Gaussian (ppm)	**Actual (ppm)**	**Gaussian (ppm)**	**Actual (ppm)**
Non-aromatic carbons				
(**C**H$_3$)$_2$	18	21.02	20	20.84
N-**C**H	52.5	49.41	51	71.75
N-C=**C**	59.5	59.57	59	74.4
C≡N	116/113	114.53/113.11	120/116	112.31/111.31
N-**C**=C	160.5	158.62	164	171.52
N-**C**=O	175	167.05	172	177.97
Aromatic carbons				
O=C-C-**C**H	126	125.13	127	121.31
C=C-C-**C**H	128.5	125.19	129	124.08
O=C-**C**	130	128.2	130	131.63
O=C-CC-**C**H	135	133.66	135	131.68
C=C-CC-**C**H	137	133.9	137	132.59
C=C-**C**	140	134.57	140	135.26

Molecular modelling calculations have identified compound (**561a**) as the more stable atropisomer, with compound (**561b**) as the less stable atropisomer. The more stable atropisomer should be the major product, the predicted NMR spectra would support the assignment of (**561a**) as the major isomer and therefore the major product, with (**561b**) as the minor isomer and therefore the minor product.

It should be noted that there is no evidence for the existence of atropisomers in any of the *N*-alkyl derivatives, where the *N*-substituent is a primary alkyl groups, or a more remote bulky group such as C_6H_5. If atropisomerism is a characteristic in dicyanomethylene compounds of the type N-CH_2R, this suggests that there might be a low barrier to rotation around the C-N bond.

Gaussian 03 was also used to predict the ^1H and ^{13}C NMR spectra of the O-alkylated derivative and these values were compared to the chemical shifts obtained experimentally from the minor isomer, as it was more likely to be an O-alkylated product, based on the NMBC NMR spectrum. They were assigned based on how well the predicted values matched the actual values. The predicted ^1H NMR values for the isopropyl group were out by 0.5ppm for both types of proton, however, the corresponding carbon values were a good approximation, particularly for O-**C**H$(CH_3)_2$. The predicted values for the aromatic hydrogens were out by approximately 0.45ppm with one exception being out by 0.7ppm. The predicted values of 179ppm (**C**=C$(CN)_2$) 186ppm (N=**C**-O) were at a higher chemical shift than the corresponding predictions of 164ppm (**C**=C$(CN)_2$) and 172ppm (**C**=O) in the minor atropisomer. This is in agreement with the values observed experimentally, although the values do not agree. The predicted vales for the aromatic carbons are close to the experimentally determined values for the minor isomer.

By comparing the predicted values for the O-alkylated product against the predicted values for (**561b**) (Table 39), it can be seen that the predicted chemical shifts for the ^1H NMR of the *N*-alkylated product are closer to the actual chemical shifts than the predicted chemical shifts for the ^1H NMR of the *O*-alkylated product, with the predicted chemical shift for the two methyls of the *iso*propyl group being identical to the actual value. However, the predicted chemical shifts for the ^{13}C NMR of the

O-alkylated product are closer to the actual values than the predicted chemical shifts for the ^{13}C NMR of the *N*-alkylated product. The predicted chemical shift for peak for O-**C**H$(CH_3)_2$ (73ppm) is a good estimate for the actual value (74ppm), while the predicted chemical shifts of N-C=**C**$(CN)_2$, N-**C**=C$(CN)_2$ and N=**C**-O-CH$(CH_3)_2$ are considerably higher than the observed chemical shifts.

Table 39: Actual Chemical Shifts vs Gaussian Calculated Chemical Shifts for O-alkylation

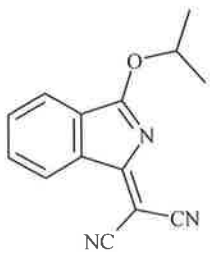
Type of Hydrogen	N=C-O-CH$(CH_3)_2$		HC-NC=O (561b)
	Gaussian (ppm)	Actual (ppm)	Gaussian (ppm)
Non-aromatic Hydrogens			
$(CH_3)_2$	2	1.46	1.46
O-C**H**	6.1	5.6	5.27
Aromatic Hydrogens			
O-C-CC**H**	7.9	7.53	7.92
O-C-CC-C**H**	7.95	7.53	7.57
C=C-CC**H**	8.81	8.1	7.57
C=C-CC-C**H**	7.98	7.53	8.85
Type of Carbon	N=C-O-CH$(CH_3)_2$		HC-NC=O (561b)
	Gaussian (ppm)	Actual (ppm)	Gaussian (ppm)
Non-aromatic Carbons			
$(CH_3)_2$	25.2	20.84	20
O-**C**H$(CH_3)_2$	73	74.4	51
N-C=**C**$(CN)_2$	83.5	71.75	59
C≡N	121	112/111	120/116
N-**C**=C$(CN)_2$	179	171	164
N=**C**-O-CH$(CH_3)_2$	186	177	172
Aromatic Carbons			
O-C-C-**C**H	128	121.31	127
C=C-C-**C**H	132	124.08	129
O-C-**C**	140.5	131.68	130
O-C-CC-**C**H	139	131.63	135
C=C-CC-**C**H	138	132.59	137
C=C-**C**	141	135.26	140

It should be noted that the peaks in the experimentally determined ^{13}C NMR spectrum of the minor isomer at 71.75, 74.40, 171.52 and 177.97ppm, assigned as O-**C**H$(CH_3)_2$, C=**C**$(CN)_2$, **C**=C$(CN)_2$ and C=O, respectively, are at least 10ppm greater than the corresponding signals in any of the other *N*-alkyl derivatives. The peak assigned to N-C**H**R_2 tends to appear in the region of 40ppm in the *N*-alkyl

derivatives, with the peak assigned to C=**C**$(CN)_2$ generally appearing at 60ppm, while the peaks assigned to C=**C**$(CN)_2$ and C=O appear in the region of 158 and 166ppm, respectively.

8.3 Conclusion

By comparison of the spectral data from other *N*-alkylated products, it is clear to see that the spectral data of the major isomer, obtained from the Mitsunobu reaction of (**530**) with *iso*propyl alcohol, are in agreement. As a result, the major isomer has been assigned as an *N*-alkylated product. However, the spectral data of the minor isomer shows significant differences to the spectral data of the major isomer and other *N*-alkylated compounds. There is no carbonyl group in the C=O region of the IR spectrum, while four resonances in the ^{13}C NMR spectrum are also inconsistent with the general trend for the major isomer and other *N*-alkylated compounds. The absence of C=O in the IR spectrum, together with a peak at 177.97ppm in the ^{13}C NMR spectrum is more consistent with the presence of N=C-O rather than N-C=O. The peak at 71.75ppm in the ^{13}C NMR spectrum is also more consistent with *O*-alkylation than with *N*-alkylation. As a result, the minor isomer has been assigned as an O-alkylated product and has been given the structure (**573**), and therefore the two compounds have been assigned as isomers and not rotamers.

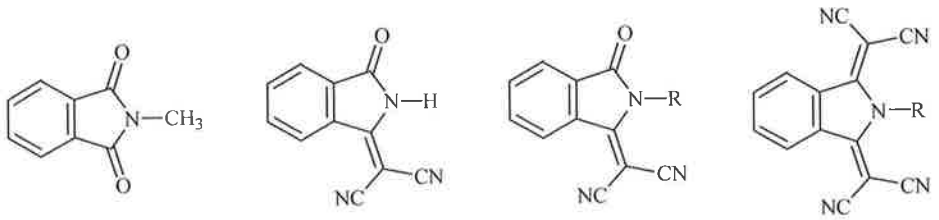


573

Chapter 9: Electrochemistry

9.1 Introduction

In order to compare the electron accepting abilities of the dicyanomethylene compounds prepared in this work, (**530**) and (**543-563**), to a series of tetracyanomethylene (**531**) compounds prepared by other workers in this group,[106] and to other known electron acceptors such as TCNQ, benzo-TCNZ and to some phthalimides (**2**), a series of compounds was chosen and their electrochemical properties were investigated.



2 **530** **543-63** **531**

Figure 167

9.1.1 Linear Sweep Voltammetry and Cyclic Voltammetry

Linear sweep voltammetry (LSV) and cyclic voltammetry (CV), which involve a large potential change imposed on a system, are popular techniques for characterising the electrochemical properties of new species and have proven useful for determining the electron affinity and electron donating ability of compounds. In LSV, a fixed potential range is used, while the voltage is scanned from a lower limit to an upper limit. The current response is plotted as a function of voltage rather than time. However, by changing the time taken to sweep the range, the scan rate (ν) can be altered. Cyclic voltammetry is similar to LSV in that the voltage is swept between two values at a fixed rate, however, when the voltage reaches the upper limit, the scan is reversed and the voltage is swept back to the lower limit (Figure 168).

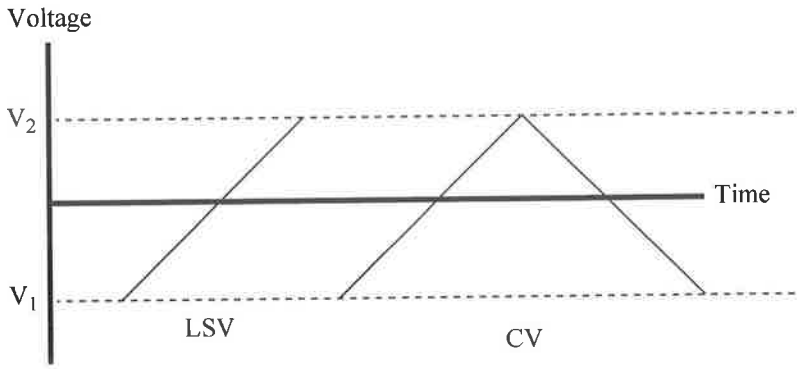


Figure 168

The potential can be swept back and forth between the two chosen limits one or more times and the current monitored continuously. Sweeping the potential in a negative direction can provide information about the reduction of a neutral species to a radical anion, dianion or possibly trianion. When the negative limit is reached a positive potential sweep will provide information about the various oxidative processes that should ultimately lead back to the neutral species.

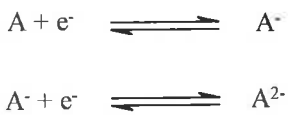


Figure 169

Three key questions can be answered when cyclic voltammetry is applied to potential electron acceptors. Firstly, whether the compound is electrochemically reducible, secondly whether any reduction processes are part of reversible redox couples and finally the potentials at which the electrochemical phenomena occur.

In a typical CV experiment, the standard cell consists of three electrodes immersed in a non-agitated electrolyte. The electrodes are the working electrode (WE), counter electrode (CE) and reference electrode (RE). The applied potential at the working electrode, measured with respect to the reference electrode via a potentiostat, is varied linearly with time at a controlled rate and the resulting current is measured. It is customary to record the current as a function of potential, which is equivalent to recording the current versus time. A typical response curve (cyclic voltammogram) for the reversible reduction of a species A is shown below.

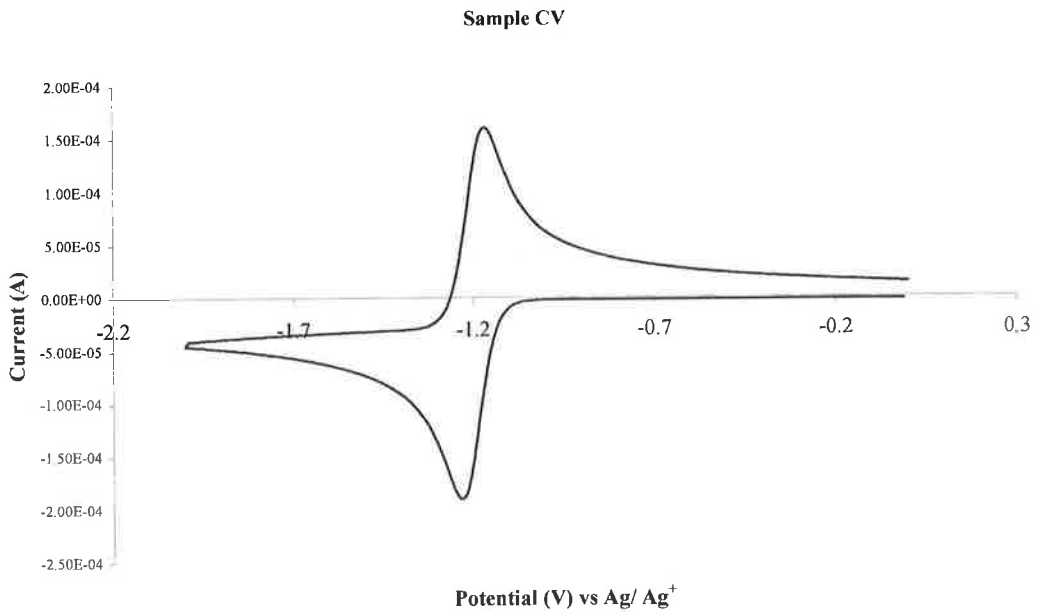


Figure 170: Typical Cyclic Voltammogram for a freely diffusing species. The oxidative process is shown right to left, with the reductive process left to right.

In order to explain the shape of the graph obtained the diagram can be considered to be the amalgamation of two scans, the cathodic scan (reductive process) and anodic scan (oxidative process). Considering the cathodic scan, the sweep is started at a suitably positive potential and at this potential no Faradaic current flows as the only species present is A. When the potential approaches E°' (formal potential of couple) the current begins to rise sharply as the amount of A^- at the electrode surface increases. A maximum current value is achieved when there is no neutral A present at the surface of the electrode. The current then diminishes as the concentration of A in the solution surrounding the electrode decreases. When the negative limit is reached the anodic scan commences. Initially the potential is still negative enough to reduce A even though the potential is scanning in a positive direction. The increasingly positive electrode attracts A^- and the anodic current is generated by its oxidation to neutral A. The current then decays as the solution around the electrode is depleted of A^-.

The system described above is an electrochemically reversible system. This means that the redox couple adheres to the Nernst equation,

$$E = E^{o'} + \frac{RT}{nF} \ln\left(\frac{[A]}{[A^-]}\right)$$

Equation 2: The Nernst Equation.

where E = applied potential difference, E°' = standard electrode potential, R = gas constant, T = temperature (K), F = Faraday constant, n = number of electrons per molecule of oxidised or reduced species, [A] is the concentration of neutral (oxidised) species in mol/cm^3 and [A$^-$] is the concentration of reduced species in mol/cm^3.

In a cyclic voltammogram, the parameters of most importance are the peak potentials $E_{p,c}$ and $E_{p,a}$ (c = cathodic, a = anodic), their difference ΔE_p and the peak currents $i_{p,c}$ and $i_{p,a}$. For a system to be considered electrochemically reversible the difference between the cathodic and anodic peak potentials should be 0.059/n Volts, where n = the number of electrons involved in the electrochemical process (for example one electron is exchanged in going from A to A$^-$ and back again, therefore n = 1). The ratio of the cathodic and anodic peak currents $i_{p,c}/i_{p,a}$ should also be one, since both the oxidised and reduced species are chemically stable. A cause of non-reversibility, which can occur for organic species, is if a chemical reaction occurs at the electrode surface resulting in the generation of a new organic molecule leading to the initial product of electron transfer being lost.

In summary, a system is electrochemically reversible when the forward and backward sweeps are exact mirror images of each other and their peak potentials are within 0.059/n Volts of each other.

9.1.2 Microelectrodes

Microelectrodes, also known as ultramicroelectrodes, may be defined as electrodes whose critical dimensions lie in the micrometer range.[138] These tiny electrodes possess some significant advantages over their macroscopic counterparts, which include small currents, steady state responses and short response times.[139] The current measured at an electrode is a function of the area. Consequently, currents observed at microelectrodes lie in the pA and nA range, which are several orders of magnitude smaller than those observed at conventional macroelectrodes where the radius is several millimeters.[140]

Microelectrodes offer a clear advantage over their macroelectrode counterparts in their rapid mass transport, small double layer capacitance, small ohmic drop and increased signal to noise ratio. Microelectrodes in the form of disks, cylinders and bands are commonly fabricated by sealing a fine wire or foil into a non-conducting electrode body such as glass.[141] The type of electrode used in these electrochemical studies was that of a microdisk electrode containing a platinum wire of radius 1.5mm sealed into a non-conducting glass electrode body, or a glassy carbon electrode.

9.2 Electrochemical Studies

The experimental set-up was as follows; WE = 3mm Pt disc or glassy carbon electrode shrouded in Teflon, RE = Ag/Ag^{+} non-aqueous reference electrode, CE = platinum wire of radius 14μm, solvent = acetonitrile, electrolyte = 0.1M tetrabutyl-ammonium tetrafluoroborate. A blank of the system was obtained before any electrochemical reading was obtained; the blank solution contained only the solvent and the electrolyte.

A typical blank scan is shown (Figure 171). Figures 164 to 171 show the cyclic voltammograms of (**530**), (**545**), (**556**), (**550**), (**552**), (**551**), (**555**) and (**559**) respectively.

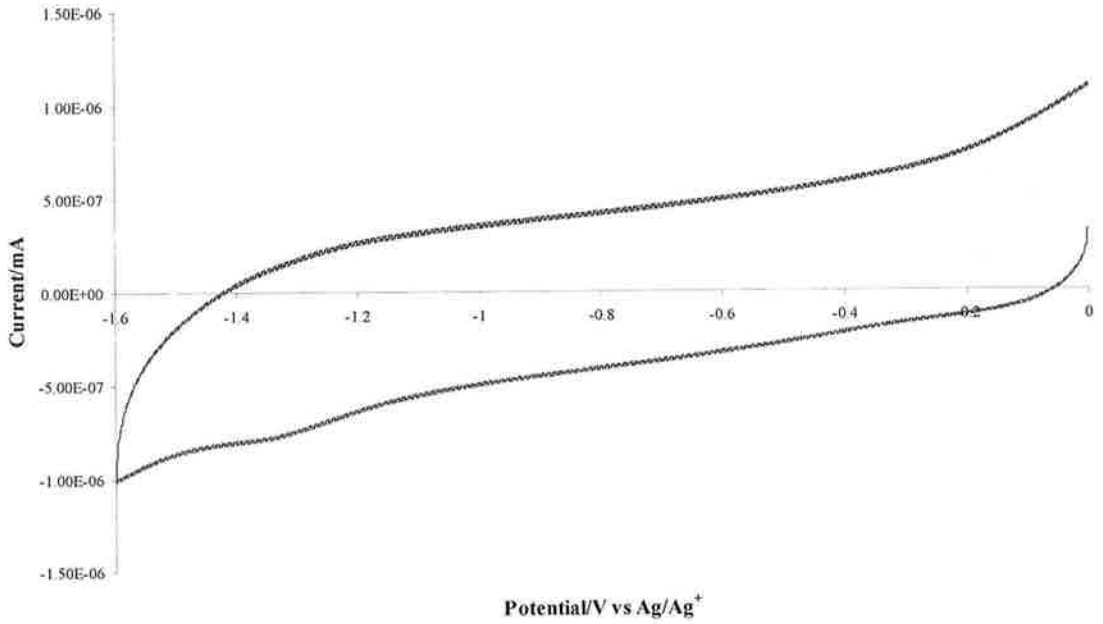
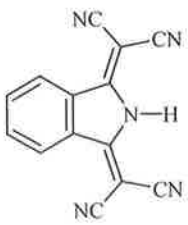
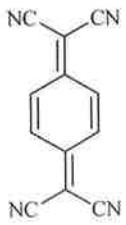


Figure 171: A typical blank scan. The oxidative process is shown right to left, with the reductive process left to right.

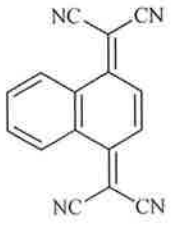
Electrochemical studies of TCNQ (**532**) have shown that it undergoes fully reversible reductions at +0.20V and –0.33V vs SCE in acetonitrile.[142] The electrochemistry of phthalimide (**1**) is complicated by the acidity of the nitrogen proton ($pK_a = 6.96$), but despite the acidity, the initial reduction of phthalimide to its anion is visible at –1.45V, which is non reversible, and a reversible reduction process at –2.29V in DMF.



531

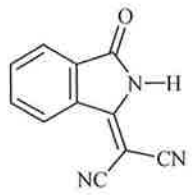


532



534

Figure 172



530

In the CV of (**530**) (Figure 173), the potential was scanned between –1.6 and 0.0 V using a scan rate of 0.1V/s, the compound showed no reactivity outside this range. The resulting voltammogram showed a reductive process at –1.195V with no reciprocal oxidative process, indicating that the process in solution was irreversible. The tetracyano analogue (**531**) showed similar behaviour with an irreversible reductive process at –1.09V in DMF.[106a]

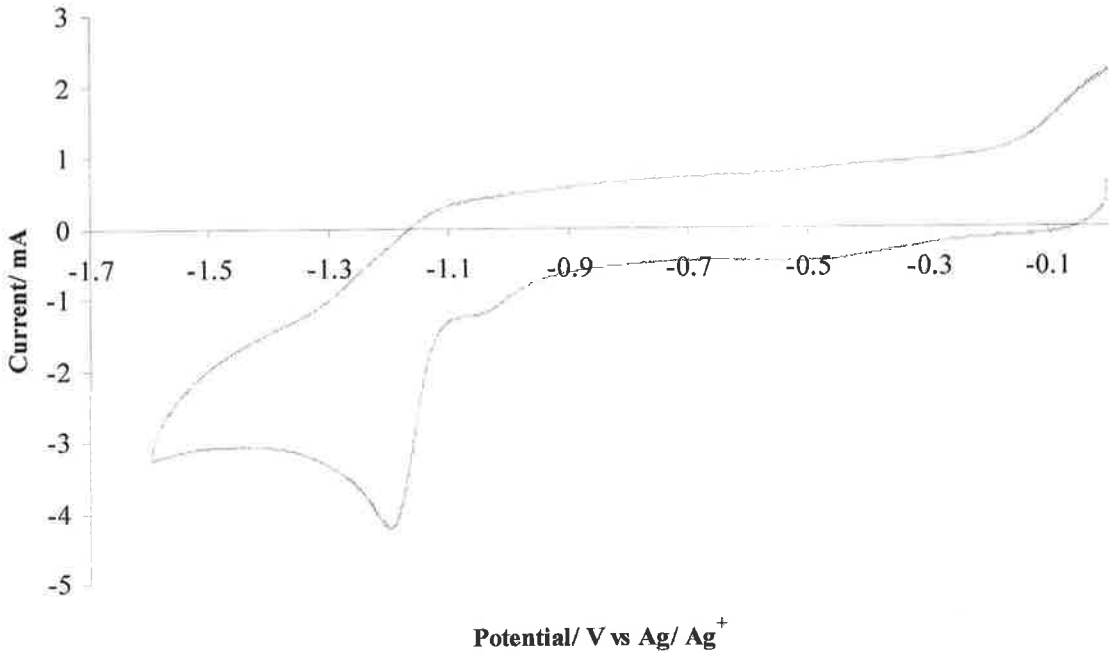
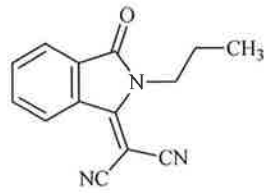


Figure 173: Cyclic voltammogram of di-cyano *N*-H derivative (530) in 0.1M electrolyte in acetonitrile at scan rate (v) = 0.1 V/s, glassy carbon electrode. The oxidative process is shown right to left, with the reductive process left to right.



545

In the CV of the *N*-propyl derivative (**545**), (Figure 174), the potential was scanned between –1.6 and –0.5V using a scan rate of 0.075V/s, and a glassy carbon (GC) electrode, the compound showed no reactivity outside this range. The resulting voltammogram showed only one reductive process at –1.237V, with a corresponding oxidative process at –1.175V (ΔE = 0.062V).

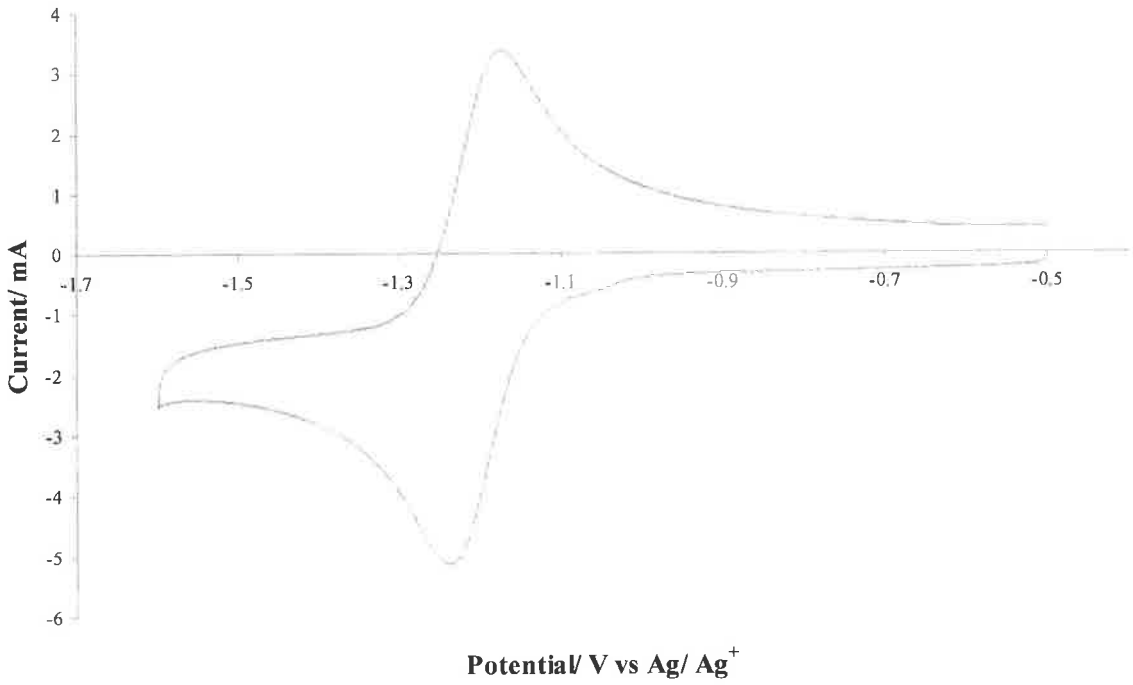
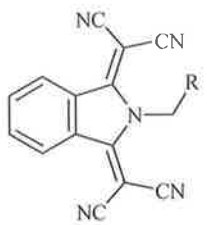


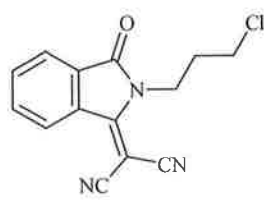
Figure 174: Cyclic voltammogram of di-cyano *N*-propyl derivative (545) in 0.1M electrolyte in acetonitrile at scan rate (ν) = 0.075V/s, glassy carbon electrode. The oxidative process is shown right to left, with the reductive process left to right.



574 R = H
575 R = CH_3

Conway[106a] has shown that the *N*-methyl *tetra*-cyano derivative (**574**) has two nonreversible reduction potentials, at –1.35V and –1.62V, the measurement was carried out using a hanging mercury-drop electrode in DMF containing 0.1M lithium perchlorate. This first reduction is similar to the value reported for *N*-methylphthalimide, which is reversibly reduced to its radical anion at –1.37V vs SCE, and to its dianion at –2.16V vs SCE in DMF.[24a] Crean[106c] has shown that the *N*-ethyl *tetra*-cyano derivative (**575**) has a reductive process at –0.95V with a corresponding oxidative processes at –0.79V (ΔE = 0.16V).

A second non-reversible reductive process was visible at –1.52V. It is interesting to note that there is a considerable difference in the voltage required to initiate reduction in (**574**) and (**575**), which is –0.56V. It is also interesting to note that the ΔE value for the tetra-cyano compound (**575**), ΔE = 0.16V, is more than double that found for the di-cyano compound (**545**), ΔE = 0.062V.



556

Figure 175 shows the overlapped CVs of the *N*-3-chloropropyl derivative (**556**), using a glassy carbon (GC) electrode, in which the potential was scanned between –2.0 and –0.8V and a platinum electrode, in which the potential was scanned between –2.0 and –0.9V. In both cases, a scan rate of 0.1V/s was used. The glassy carbon voltammogram shows reversible reductive processes at –1.218V with a corresponding oxidative process at –1.156V (ΔE = 0.062 V), with a second non-reversible reductive process at –1.670V. The platinum voltammogram shows a reductive process at –1.218V, with the corresponding oxidative process at –1.150V (ΔE = 0.068V). A second non-reversible reductive process is visible at –1.730V.

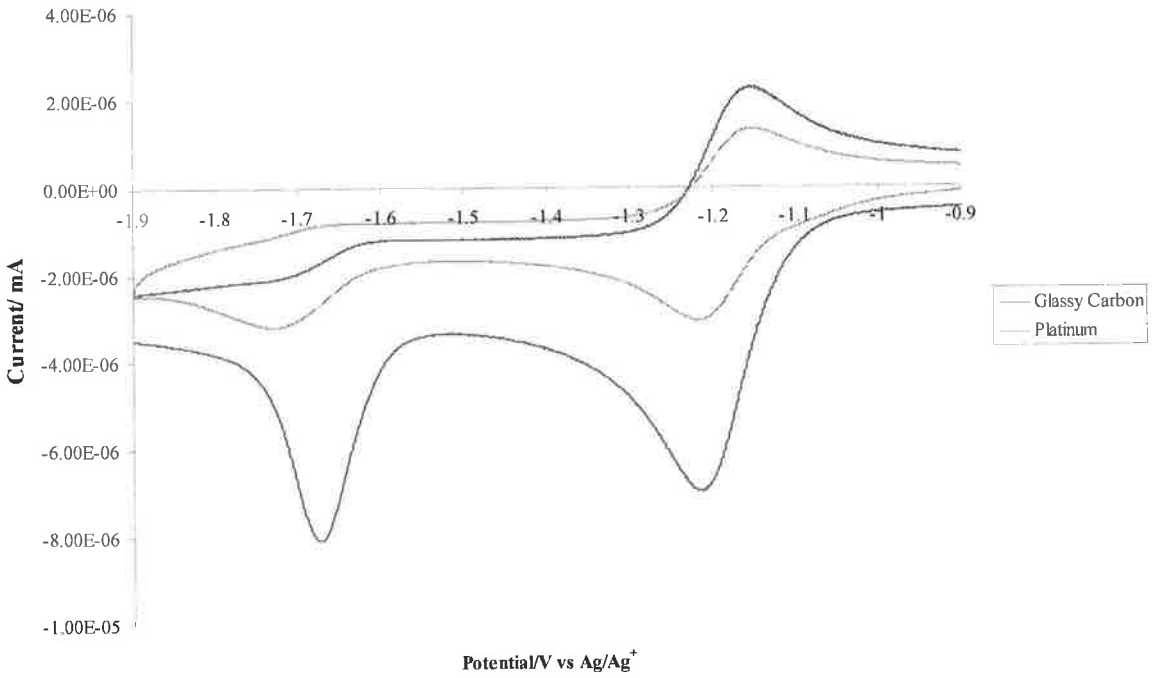
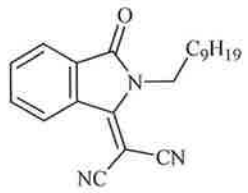


Figure 175: Cyclic voltammogram of di-cyano *N*-(3-chloro)propyl derivative (556) in 0.1M electrolyte in acetonitrile at scan rate (ν) = 0.1 V/s, glassy carbon electrode and platinum electrode. The oxidative process is shown right to left, with the reductive process left to right.



550

Figure 176 shows the overlapped CVs of the *N*-decyl derivative (**550**), using a glassy carbon electrode and a platinum electrode. In both cases, the potential was scanned between –2.0 and –0.8V using a scan rate of 0.1V/s. The glassy carbon electrode voltammogram shows a reductive peak at –1.240V with an oxidative peak at –1.179V (ΔE = 0.061 V), there is also a second, non-reversible reductive peak at –1.717V. The platinum electrode voltammogram shows only one reductive process at –1.245V with the corresponding oxidative process at –1.175 (ΔE = 0.070V).

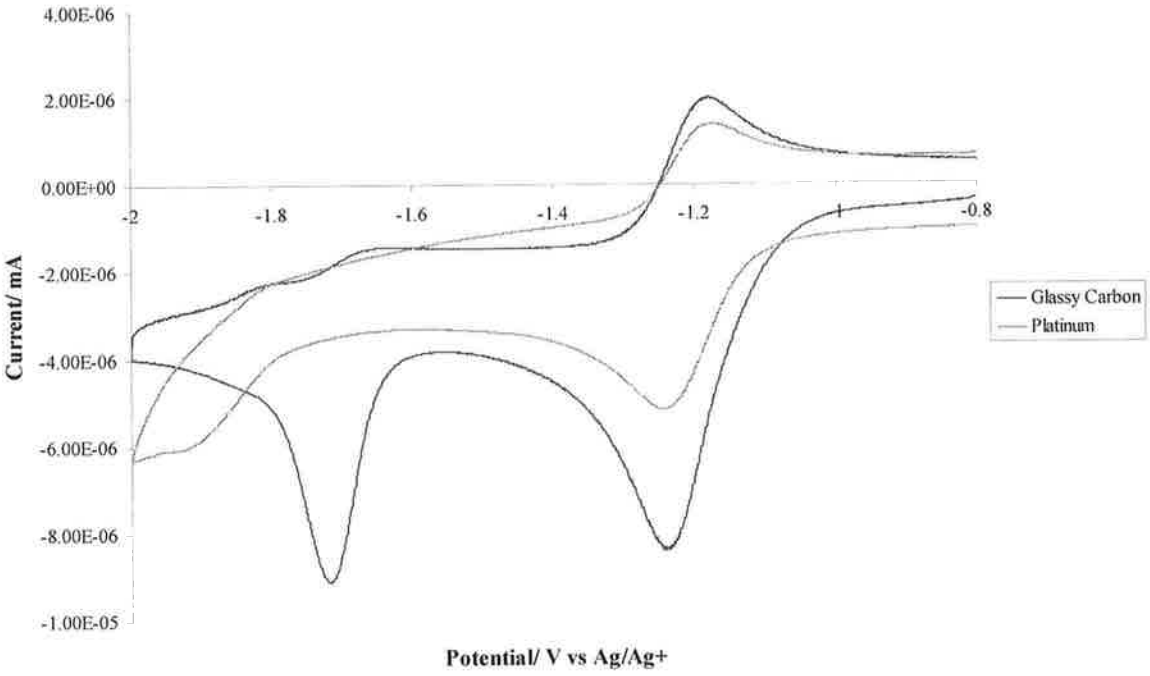
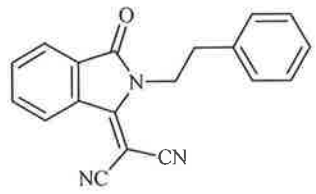


Figure 176: Cyclic voltammogram of di-cyano *N*-decyl derivative (550) in 0.1M electrolyte in acetonitrile at scan rate (ν) = 0.1 V/s, glassy carbon electrode and platinum electrode. The oxidative process is shown right to left, with the reductive process left to right.



552

Figure 177 shows the overlapped CVs of the *N*-phenylethyl derivative (**552**), using a glassy carbon electrode with the potential being scanned from –2.0 and –0.6V and a platinum electrode where the potential was scanned from 1.9 and –0.7 V, using in both cases a scan rate of 0.1V/s. The glassy carbon electrode voltammogram shows a reductive peak at –1.240V with a corresponding oxidative peak at –1.179V (ΔE = 0.061V) a second reductive peak is visible at –1.717V, which has no corresponding oxidative process. The platinum electrode voltammogram shows a reversible reductive processes at –1.221V with the corresponding oxidative process at –1.156V (ΔE = 0.065V) and a second reductive process at –1.701V with no corresponding oxidative process.

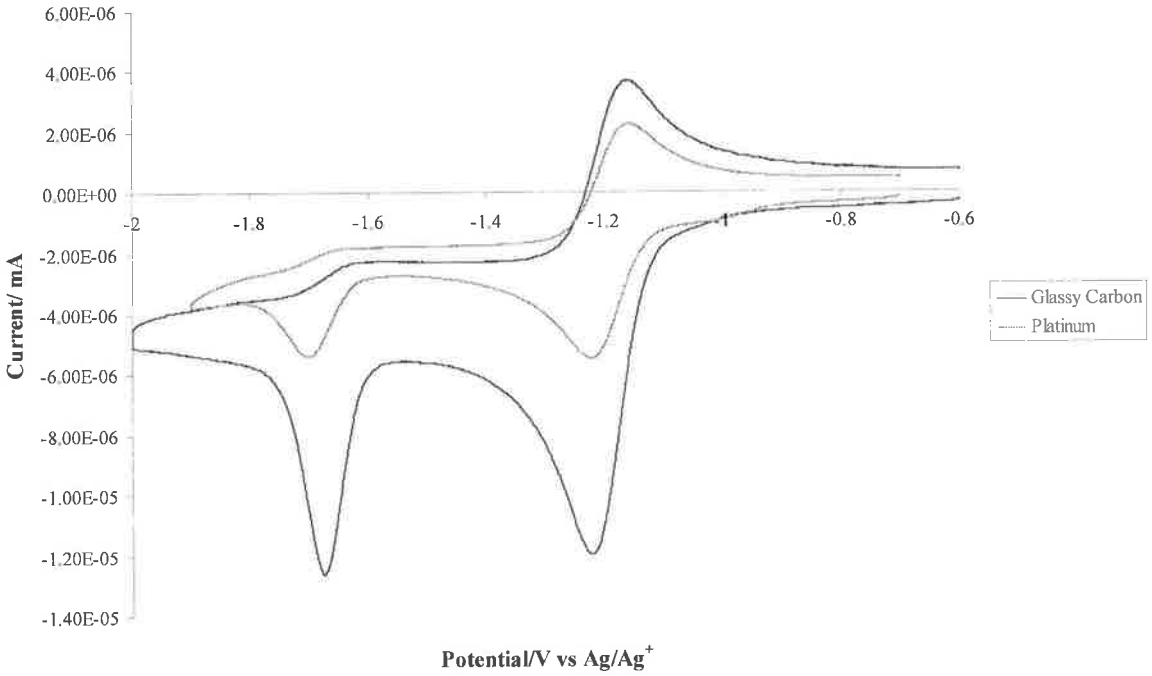
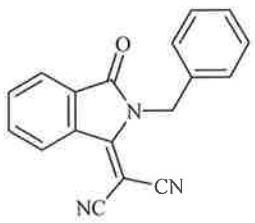
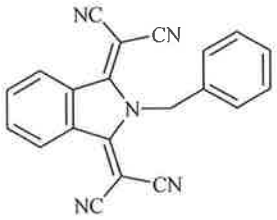


Figure 177: Cyclic voltammogram of di-cyano *N*-phenylethyl derivative (552) in 0.1M electrolyte in acetonitrile at scan rate (v) = 0.1 V/s, glassy carbon electrode and platinum electrode. The oxidative process is shown right to left, with the reductive process left to right.



551



575

As can be seen in Figure 178 the *N*-benzyl derivative (**551**), which was scanned between –1.6 and –0.6V using a platinum electrode and a scan rate of 0.1V/s and showed no reactivity outside this range, has one reductive process occurring at –1.213V, with a corresponding oxidative process occurring at –1.112V (ΔE = 0.101V). The tetra-cyano *N*-benzyl derivative (**576**), synthesised by Crean,[106c] shows a reductive process at –0.92V with a reciprocal oxidative process at –0.71V (ΔE = 0.21V) and a second reductive process at –1.54V, but without a corresponding oxidative process.

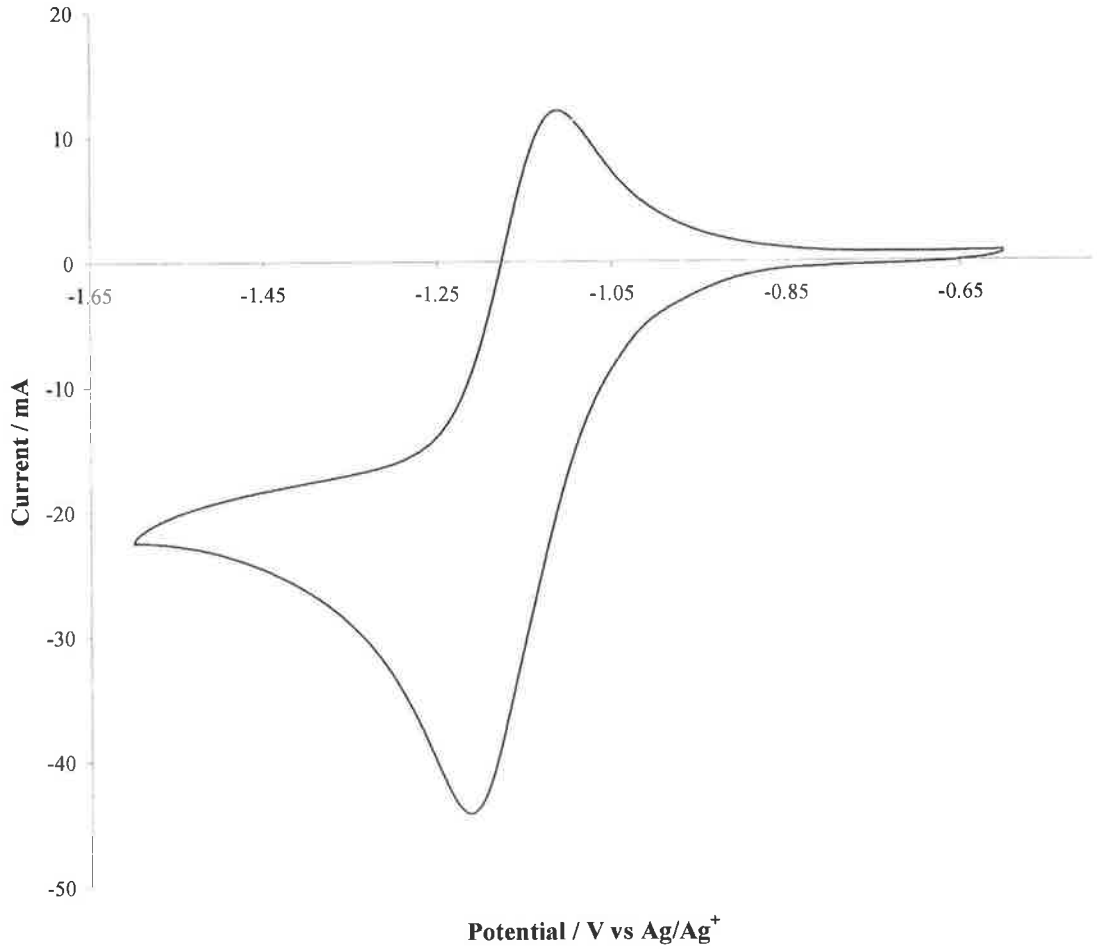
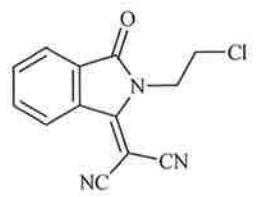


Figure 178: Cyclic voltammogram of di-cyano *N*-benzyl derivative (551) in 0.1M electrolyte in acetonitrile at scan rate (ν) = 0.1 V/s, Platinum electrode. The oxidative process is shown right to left, with the reductive process left to right.



555

As can be seen in Figure 179, the *N*-2-chloroethyl derivative (**555**), which was scanned between –1.5 and–0.6V using a platinum electrode and a scan rate of 0.1V/s, the compound showed no reactivity outside this range, shows a reductive process at –1.168V with the oxidative process at –1.095V (ΔE = 0.073V). This is in stark contrast to the N-(3-chloro)propyl derivative (**556**) which shows a similar reversible reductive process at –1.218V, with the corresponding oxidative process at –1.150V (ΔE = 0.068V) but also shows a non-reversible reductive process at –1.730V. It is not known why *N*-(3-chloro)propyl derivative (**556**) displays this second non-reversible process, while the *N*-(2-chloro)ethyl derivative (**555**) does not.

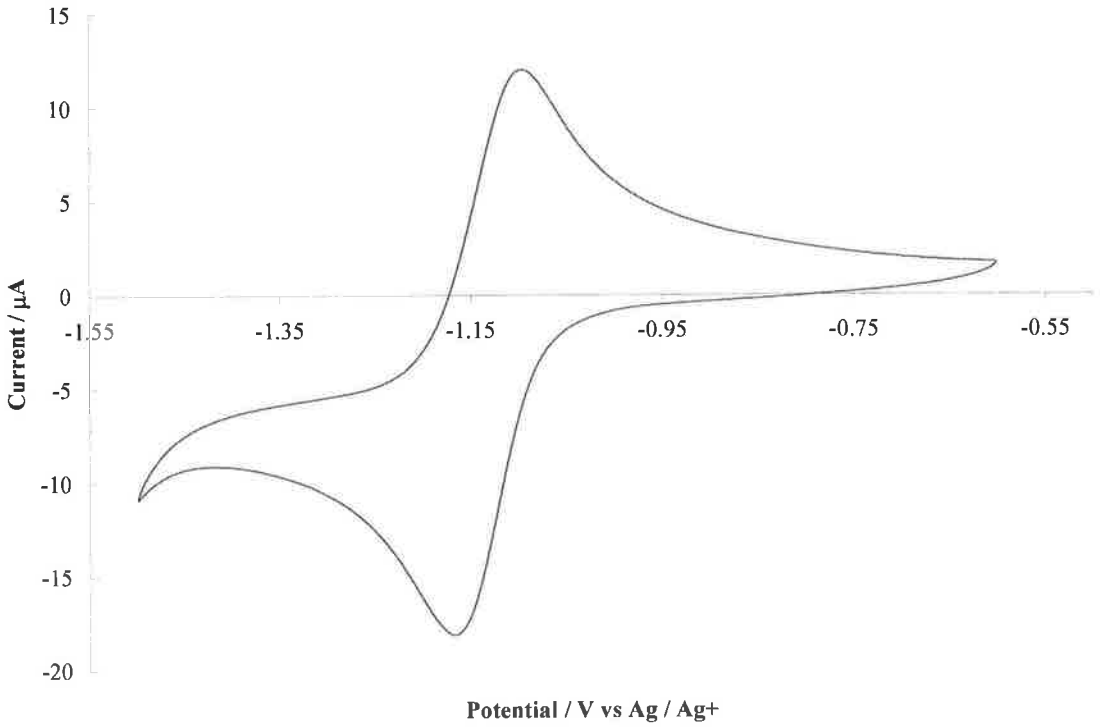
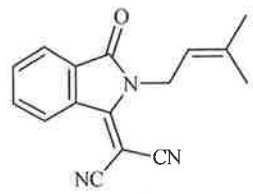


Figure 179: Cyclic voltammogram of *N*-(2-chloro)ethyl derivative (555), in 0.1M electrolyte in acetonitrile at scan rate (ν) = 0.1 V/s, Platinum electrode. The oxidative process is shown right to left, with the reductive process left to right.



559

Figure 180 shows the overlapped CVs of the *N*-(3-methylbut-2-enyl) derivative (**559**), using a glassy carbon and platinum electrodes. In both cases with the potential was scanned from –2.0 and –0.5V using a scan rate of 0.1V/s. The glassy carbon electrode voltammogram shows a reversible reductive peak at –1.224V with a corresponding oxidative peak at –1.159V (ΔE = 0.065V). There is a second reductive peak at –1.679V, but this peak has no corresponding oxidative peak. The platinum electrode voltammogram shows a reversible reductive process at –1.227V with the corresponding oxidative process at –1.155 (ΔE = 0.072V) and a second reductive process occurring at –1.739V but without a corresponding oxidative process.

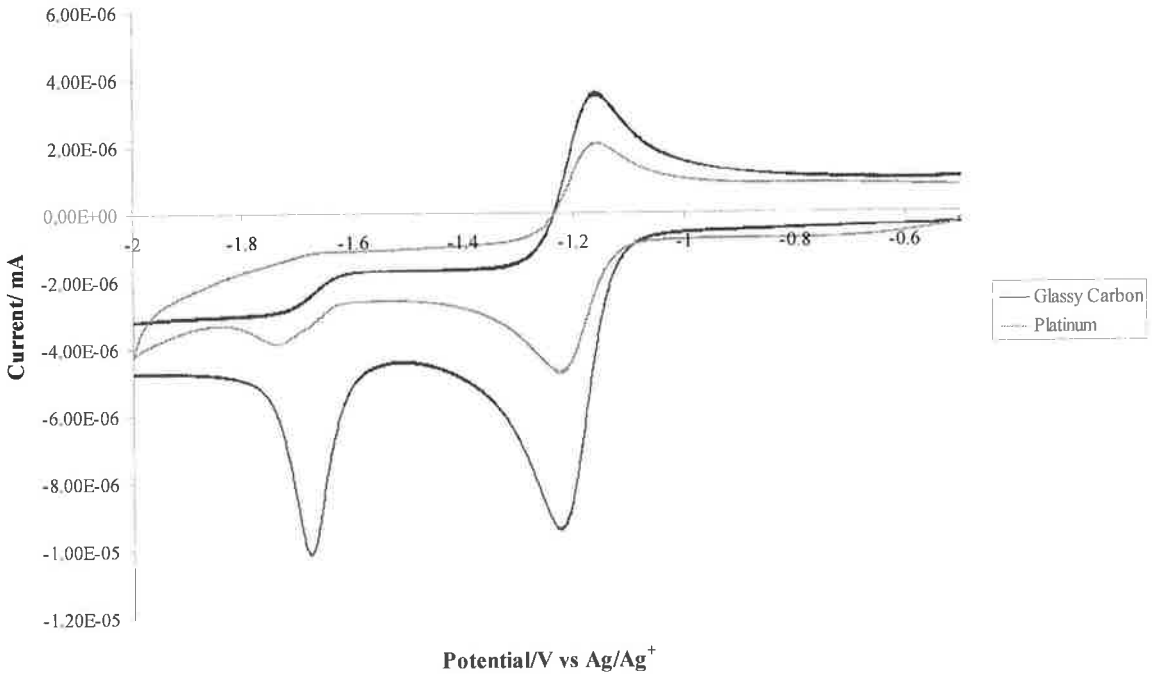
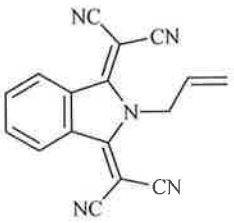
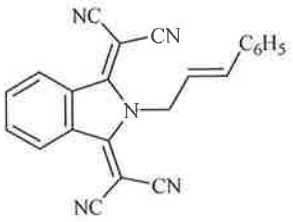


Figure 180: Cyclic voltammogram of di-cyano *N*-(3-methylbut-2-enyl) derivative (559) in 0.1M electrolyte in acetonitrile at scan rate (ν) = 0.1 V/s, glassy carbon electrode and platinum electrode. The oxidative process is shown right to left, with the reductive process left to right.

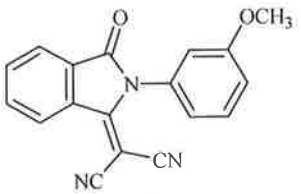


577

The tetracyano *N*-allyl derivative (**577**) synthesised and examined electrochemically by Crean,[106c] showed similar results with two reductive processes. The first was at –0.93V with the corresponding oxidative process at –0.73 ($\Delta E = 0.20V$), and the second at –0.158V and was non-reversible. The tetra-cyano *N*-cinnamyl derivative (**578**) behaved in a similar manner showing two reductive process. One at –0.95V had a reversible oxidative peak at –0.71V ($\Delta E = 0.20V$), whereas the second at –1.53V, was non-reversible.



578



579

Cyclic voltammetric analysis of the related compound (**579**) by Carloni *et al.*[143] was carried out with slightly different results. The reduction peak potentials for (**579**) were at –0.92V and –1.43V, which would suggest that this compound is easier to reduce than any of the *N*-alkyl derivatives prepared in this work, therefore making it a better electron acceptor. However the redox couple corresponding to the reduction of (**579**) to its radical anion and oxidation back to the neutral species was fully reversible while the reduction of the radical anion to the dianion had no significant oxidation peak. The reduction peak potentials for the related *N*-phenylphthalimide were –1.31V and –2.09V in DMF and were fully reversible.

The electrochemical results obtained are summarised below:

Table 40

Compound	Scan Rate V/s	Electrode	Cathodic Potential		Anodic Potential		ΔE/ V
			Ep_{c1}/ V	Ep_{c2}/ V	Ep_a/ V	Ep_{a2}/ V	Ep_a-Ep_c/ V
530	0.075	Glassy Carbon	–1.195	N/A	N/A	N/A	N/A
545	0.075	GC	–1.237	N/A	–1.175	N/A	0.062
550	0.1	GC	–1.240	–1.717	–1.179	N/A	0.061
550	0.1	Platinum	–1.245	N/A	–1.175	N/A	0.070
551	0.1	Pt	–1.213	N/A	–1.112	N/A	0.101
552	0.1	GC	–1.240	–1.717	–1.179	N/A	0.061
552	0.1	Pt	–1.221	–1.701	–1.156	N/A	0.065
559	0.1	GC	–1.224	–1.679	–1.159	N/A	0.065
559	0.1	Pt	–1.227	–1.739	–1.155	N/A	0.072
555	0.1	Pt	–1.168	N/A	–1.095	N/A	0.073
556	0.1	GC	–1.218	–1.670	–1.156	N/A	0.062
556	0.1	Pt	–1.218	–1.730	–1.150	N/A	0.068

9.3 Conclusion

Cyclic voltammetric analysis has shown that the reductive and oxidative processes for the tetra-cyano compounds synthesised by Conway[106b] and Crean[106c] occur at higher voltages than the same processes in the di-cyano compounds synthesised in this work, thus making the tetracyano compounds better electron acceptors. The ΔE for the dicyano compounds in this work are considerably lower than those values obtained by Conway[106a] and Crean[106c] for the tetracyano compounds. It could be concluded that the di-cyano compounds are more reversible, however, diffusion factors could influence the difference in ΔE values.

Results indicate that the dicyano compounds are as good as, if not slightly better electron acceptors than their corresponding phthalimide analogues, however the phthalimide anion and dianion reductions are fully reversible, while only the dicyano anion reduction is reversible. All of the *N*-alkylated compounds appear to be reducible electrochemically, however none of the redox couples observed for any of the compounds are completely reversible, making calculation of the half wave potentials impossible.

The observed reduction peak potentials show that both the tetracyano and dicyano compounds are poor electron acceptors relative to TCNQ (**532**) or its isoelectronic equivalent benzo-TCNQ (**534**), but are equivalent or better than their corresponding phthalimide analogues.

Chapter 10: Experimental

10.1 General Techniques

Nuclear magnetic resonance spectra were recorded on a Brucker 400 Ultrashield instrument operating at 400 M*Hz* for ^{1}H NMR (δH) and 100M*Hz* for ^{13}C NMR (δC). All spectra were recorded in the solvent stated (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; quat = quaternary carbon).

Infrared spectra (υ_{max}) were recorded on a Perkin Elmer system 2000 FT-IR spectrophotometer and were obtained for solid dispersion in compressed KBr disks.

Ultraviolet spectra were recorded on a Hewlett Packard 8452A diode array UV-vis spectrophotometer, using spectrophotometric grade methanol as solvent unless otherwise stated.

Melting points (m.p.) were recorded using a Griffin melting point apparatus and are uncorrected.

Elemental analyses were carried out by the Microanalytical Laboratory, University College Dublin, Belfield, Dublin 4.

Thin layer chromatography (TLC) was carried out on silica gel coated on aluminium strips, and containing a fluorescent indicator. Plates were examined using an ultra-violet lamp operating at 254nm or 366nm.

Preparative scale photochemistry was carried out in a cylindrical reaction vessel, approximately 30 cm in length and 8cm in diameter. The vessel was fitted with a water-cooled quartz immersion well containing a 400 W medium pressure mercury vapour lamp – Photochemical Reactors Limited model 3040 – fitted with a Pyrex filter. The immersion well was fitted with a teflon tube and a syringe, which allowed sampling without interrupting the photolysis. The selected compounds were dissolved in solvents of spectrophotometric grade purity and the solutions were gravity filtered and deoxygenated prior to photolysis using a stream of argon for a

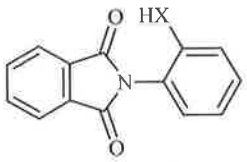
period of thirty minutes. Argon bubbling was continued for the duration of the reaction. TLC was used to follow the progress of the reaction.

In order to remove *tert*-butyl catechol stabiliser from styrene and α-methylstyrene, they were stirred with an equal volume of 50 % NaOH solution for 2 hours, during which time the mixture turned purple. The styrene was then separated from the aqueous alkaline phase, and washed with water (4 x 50 cm^3), followed by drying over anhydrous magnesium sulphate before being filtered. The styrene was then distilled using a rotary evaporator fitted with a cold finger apparatus.

Cyclic voltammetry was performed using a CH Instruments Model 660 Electrochemical Workstation and a conventional three-electrode cell. Experiments were carried out in spectrophotometric grade acetonitrile, and the solutions were deoxygenated thoroughly using argon, with a blanket of argon being maintained over the solution during all experiments. Potentials are quoted with respect to Ag/AgCl reference electrode. All experiments were carried out at room temperature (22±3°C). Platinum wire and an Ag/AgCl reference electrode were combined to form a counter electrode.

10.2 Syntheses of phthalimides

10.2.1 Synthesis of N-(2-hydroxyphenyl)phthalimide (510)



510 X = O

Phthalic anhydride (14.8g, 100mmol) was dissolved in glacial acetic acid (100cm^3) in a 250cm^3 round bottom flask. To this, 2-aminophenyl (10.9g, 100mmol) was added slowly. The mixture was heated under reflux for 1 hour, filtered hot and allowed to cool, the solid was filtered off and washed with 3 x 20cm^3 light petroleum. The crude product (**510**, X = O) was recrystallised from ethyl acetate to give off-white crystals in 73% yield, (17.45g, 73mmol), with m.p. 223-224°C. (lit. 223°C[101]).

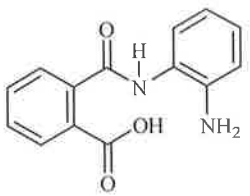
The title compound was also synthesized according to the method described by Sandhu.[102] Phthalic anhydride (7.4g, 50mmol) was mixed with 2-aminophenyl (5.45g, 50mmol) using a mortar and pestle. The combined solid was then placed in a conical flask and heated using an 800W microwave oven at about 600W for 3 minutes. The reaction mixture was then dissolved in chloroform to remove unreacted starting material and the insoluble product was filtered off and recrystallised from ethyl acetate. Yields were similar (71%) to the procedure described above.

ν_{max} KBr: 3380 (OH); 1788 and 1702 (C=O) cm^{-1}.

δH DMSO-d_6: 9.9 (s, 1H, OH); 7.97 (m, 2H, aromatic); 7.94 (m, 2H, aromatic); 7.90 (m, 2H, aromatic); 7.33 (m, 1H, aromatic); 7.29 (m, 1H, aromatic) ppm; 7.03 (m, 1H, aromatic) ppm.

δC DMSO-d_6: 167.5 (**C**=O); 154.4 (**C**-OH), 134.9, 132.3, 130.8, 130.7, 123.7, 119.5, 119.2 and 116.9 (aromatic **C**) ppm.

10.2.2 Synthesis of *N*-(2-aminophenyl)phthalamic acid (516)



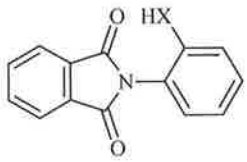
516

Phthalic anhydride (14.8g, 100mmol) was dissolved in cold chloroform (200cm^3) with stirring. 1,2-Diaminobenzene (12.08g, 100mmol) was dissolved in boiling chloroform (200cm^3). The amine solution was removed from the heat source and the temperature recorded as 60°C. Then the

anhydride solution was added in 20 cm^3 aliquots with thorough stirring between additions. After addition of the anhydride solution, the temperature was recorded as 45°C and the solution was allowed to cool and to stand at room temperature overnight. The crude product was filtered off and washed well with diethyl ether and air dried to constant weight (18.6g, 72.6mmol). Purification was carried out by dissolving the total product in boiling methanol (125cm^3), treating it with activated charcoal, filtering and allowing the filtrate to cool to room temperature by standing for two hours, after which time the product was filtered off and air dried to give pure product (5.1g). A further portion (4.0g) was recovered by adding diethyl ether (130cm^3) and standing the solution overnight at room temperature. In total *N*-(2-aminophenyl)phthalamic acid (**516**) was recovered in 35% yield (9.1g, 35.5mmol), with m.p. 149–152°C with decomposition (lit. 147-150°C[103] and 151-152°C[144]).

C, H, N analysis was reported by Perry.[103]

10.2.3 Synthesis of *N*-(2-aminophenyl)phthalimide (510)



510 X = NH

Dilute 2 M HCl (20cm^3) was heated to 65–70°C in a 50cm^3 conical flask with magnetic stirring. Solid *N*-(2-aminophenyl)phthalamic acid (1.30g, 5mmol) was added directly to the flask and stirring continued until a clear solution was obtained. After a few minutes more stirring, a white precipitate appeared and after eight minutes ice was added to bring the temperature to 25°C. The solution was neutralised with 0.880 M aqueous NH_3. The crude product was filtered off and recrystallised from ethanol to give yellow crystals of *N*-(2-aminophenyl)phthalimide (**510**, X = NH) in 77 % yield (0.92g, 3.86mmol), with m.p. 193–194°C (lit. 192-193°C).[103]

ν_{max} KBr: 3459 and 3382 (NH_2); 1707 (C=O) cm^{-1}.

δH DMSO-d_6: 7.93 (m, 2H, aromatic); 7.87 (m, 2H, aromatic); 7.13 (m, 1H, aromatic); 6.76 (m, 2H, aromatic); 6.57 (m, 1H, aromatic); 5.34 (s, 2H, NH_2) ppm.

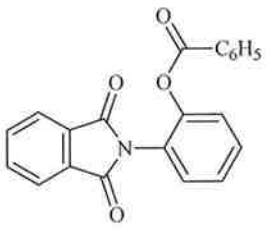
δC DMSO-d_6: 167.9 (C=O); 146.8, 134.5, 132.8, 130.4, 130.0, 123.4, 116.3, 115.7, 115.6 (aromatic C) ppm.

C, H, N analysis was reported by Perry.[103]

10.3 General synthesis of esters of *N*-(2-hydroxyphenyl)phthalimide and amides of *N*-(2-aminophenyl)phthalimide

N-(2-Hydroxyphenyl)phthalimide (**510,** X = O) or *N*-(2-aminophenyl)phthalimide (**510,** X = NH) (1.0g, 4.2mmol) was dissolved in pyridine (15cm^3) and placed in an ice bath. The appropriate acid chloride (4.2mmol) was added dropwise and the solution was stirred for 20 minutes. Ice water (20cm^3) was added and a precipitate was formed. This was filtered off, dissolved in chloroform, washed with 3M HCl (10cm^3) followed by saturated $NaHCO_3$ (10cm^3) and finally with brine (10cm^3). The organic portion was then dried over $MgSO_4$, filtered and concentrated under vacuum.

10.3.1 Synthesis of *N*-(2-benzoyloxyphenyl)phthalimide (522)



522

Benzoyl chloride (0.45cm^3, 5mmol) was added to N-(2-hydroxyphenyl)phthalimide (**510,** X = O). The crude product (**522**) was recrystallised from methanol to yield a white solid (0.78g, 2.3 mmol) with m.p. 169-170°C. in 54% yield. A recent literature search revealed the compound was previously unknown.

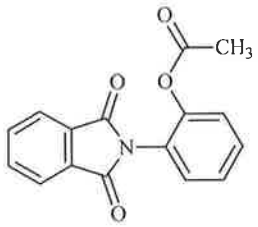
ν_{max} KBr: 1787, 1732 and 1721 (C=O) cm^{-1}.

δH $CDCl_3$: 7.94 (m, 2H, aromatic); 7.79 (m, 2H, aromatic); 7.65 (m, 2H, aromatic); 7.45 (m, 3H, aromatic); 7.36 (m, 2H, aromatic); 7.30 (m, 2H, aromatic) ppm.

δC $CDCl_3$: 166.9 and 164.3 (C=O); 147.1, 134.8, 134.0, 132.1, 130.5, 130.4, 129.9, 129.2, 128.9, 126.8, 124.3, 124.29 and 123.24 (aromatic C) ppm.

C, H, N Analysis: Found: C, 73.36; H, 3.85; N, 4.00%. Calculated for $C_{21}H_{13}NO_4$: C, 73.46; H, 3.82; N, 4.08%.

10.3.2 Synthesis of N-(2-acetoxyphenyl)phthalimide (523)



523

Acetyl chloride (0.28cm^3, 4mmol) was added to N-(2-hydroxyphenyl)phthalimide (**510,** X = O). The crude product (**523**) was recrystallised from ethanol to yield a white solid in 57% yield (0.67 g, 2.4 mmol), with m.p. 161-163°C. A recent literature search revealed the compound was previously unknown.

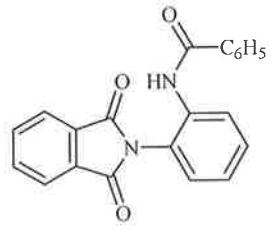
ν_{max} KBr: 1777, 1740 and 1721 (C=O) cm^{-1}.

δH $CDCl_3$: 7.89 (m, 2H, aromatic); 7.73 (m, 2H, aromatic); 7.41 (m, 1H, aromatic); 7.30 (m, 3H, aromatic); 2.06 (s, 3H, CH_3) ppm.

δC $CDCl_3$: 168.5 and 166.9 (C=O); 146.7, 134.9, 132.2, 130.2, 129.8, 126.7, 124.34, 124.30 and 124.0 (aromatic C); 21.3 (CH_3) ppm.

C, H, N Analysis: Found: C, 68.06; H, 3.86; N, 4.96 %. Calculated for $C_{16}H_{11}NO_4$: C, 68.33; H, 3.94; N, 4.98 %.

10.3.3 Synthesis of N-(2-benzoylaminophenyl)phthalimide (524)



524

Benzoyl chloride (0.45cm^3, 5mmol) was added to N-(2-aminophenyl)phthalimide (**510,** X = NH). The crude product (**524**) was recrystallised from methanol to yield a white solid in 62% yield (0.89g, 2.6mmol), with m.p. 211-213°C (lit. 220-222°C,[145] 204-205°C[146]).

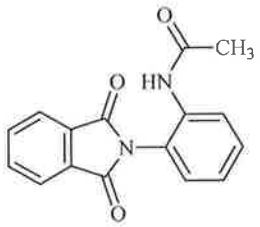
ν_{max} KBr: 3349 (NH), 1714 and 1703 (C=O) cm^{-1}.

δH $CDCl_3$: 8.34 (s, broad, 1H, N**H**); 7.95 (m, 1H, aromatic); 7.88 (m, 2H, aromatic); 7.72 (m, 4H, aromatic); 7.45 (m, 2H, aromatic); 7.35 (m, 2H, aromatic); 7.30 (m, 2H, aromatic) ppm.

δC $CDCl_3$: 167.91 and 165.78 (C=O); 134.61, 134.28, 132.33, 132.04, 129.93, 129.14, 128.89, 127.59, 126.68, 126.38, 124.92 and 125.52 (aromatic C) ppm.

C, H, N Analysis: Found: C, 73.53; H, 4.16; N, 8.18%. Calculated for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18%.

10.3.4 Synthesis of 2-(2-acetamidophenyl)phthalimide (525)



525

Acetyl chloride (0.28cm^3, 4mmol) was added to *N*-(2-aminophenyl)phthalimide (**510,** X = NH). The crude product (**525**) was recrystallised from ethanol to give a white solid in 53% yield (0.62g, 2.2mmol), with m.p. 200-201°C (lit.[147] 202-203°C).

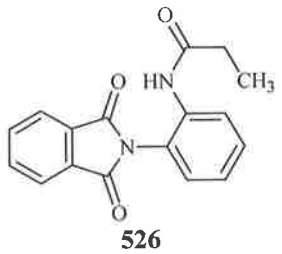
ν_{max} KBr: 3347 (N-H stretch), 1719, 1707, 1702 (C=O) cm^{-1}.

δH $CDCl_3$: 7.86 (m, 2H, aromatic); 7.82 (m, 1H, aromatic); 7.51 (s, broad, N**H**); 7.37 (m, 1H, aromatic); 7.21 (m, 2H, aromatic); 7.14 (m, 2H, aromatic); 1.94 (s, 3H, CH_3) ppm.

δC $CDCl_3$:, 168.87 and 161.72 (**C**=O); 135.12, 132.14, 129.97, 128.94, 128.93, 126.29, 126.18, 124.45 and 124.39 (aromatic C); 24.59 (**C**H_3) ppm.

C, H, N Analysis: Found: C, 68.51; H, 4.25; N, 9.99%. Calculated for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99%.

10.3.5 Synthesis of 2-(2-propionamidophenyl)phthalimide (526)



526

Propionyl chloride (0.36cm^3, 4mmol) was added to *N*-(2-aminophenyl)phthalimide (**510,** X = NH). The crude product (**526**) was recrystallised from ethanol to yield a white solid in 48 % yield (0.56 g, 1.9 mmol), with m.p. 140-141°C. A recent literature search revealed the compound was previously unknown.

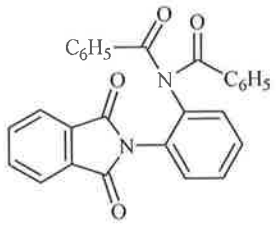
ν_{max} KBr: 3334 (NH), 1720 and 1708 (C=O) cm^{-1}.

δH $CDCl_3$: 7.86 (m, 2H, aromatic); 7.83 (m, 1H, aromatic); 7.73 (m, 2H, aromatic); 7.50 (s, broad, N**H**); 7.36 (m, 1H, aromatic); 7.21 (m, 2H, aromatic); 2.16 (q, 2H, *J* = *8Hz*, CH_2CH_3) and 1.00 (t, 3H, *J* = *8Hz*, CH_2CH_3) ppm.

δC $CDCl_3$: 172.51 and 167.70 (**C**=O); 135.12, 134.53, 132.12, 129.97, 128.94, 126.17, 126.02, 124.41, 124.36 (aromatic C); 30.80 (CH_2CH_3) and 9.97 (CH_3) ppm.

C, H, N Analysis: Found: C, 69.23; H, 4.81; N, 9.48%. Calculated for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52%.

10.3.6 Attempted synthesis of *N*-(2-N,N-dibenzoylaminophenyl)phthalimide (527)

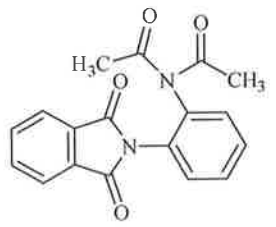


527

Benzoyl chloride (0.90cm^3, 10mmol) was added to N-(2-aminophenyl)phthalimide (**510,** X = NH). The crude product was recrystallised from methanol to yield a white solid in 66% yield (0.94g, 2.8mmol), with m.p. 211-213°C.

The spectral data and elemental analysis data for this compound were identical to those of N-(2-benzoylaminophenyl)phthalimide (**524**). As a result, it was concluded that *mono*-substitution only had occurred. This reaction was repeated at room temperature and at 40°C. In both cases the spectral data were identical to those of the *mono*-substituted product (**524**).

10.3.7 Attempted synthesis of *N*-(2-N,N-diacetamidophenyl)phthalimide (528)

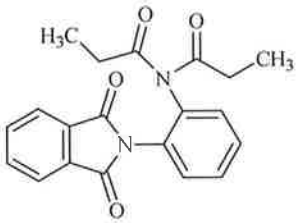


528

Acetyl chloride (0.56cm^3, 8mmol) was added to *N*-(2-aminophenyl)phthalimide (**510,** X = NH). The crude product was recrystallised from ethanol to give a white solid in 58% yield (0.68g, 2.4mmol), with m.p. 200-201°C.

As the spectral data and elemental analysis data for this compound were identical to that of 2-(2-acetamidophenyl)phthalimide (**525**), it was concluded that *mono*-substitution only had occurred. This reaction was repeated at room temperature and at 40°C. In both cases, the spectral data were identical to those of the *mono*-substituted product (**525**).

10.3.8 Attempted synthesis of *N*-(2-dipropionamidoaminophenyl)phthalimide (529)



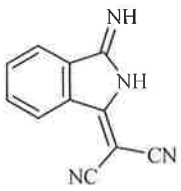
529

Propionyl chloride (0.36cm^3, 4mmol) was added to N-(2-aminophenyl)phthalimide (**510,** X = NH). The crude product was recrystallised from ethanol to yield a white solid in 55 % yield (0.68 g, 2.3 mmol), with m.p. 140-141°C.

As the spectral data and elemental analysis data for this compound were identical to that of 2-(2-propionamidophenyl)phthalimide (**526**). As a result, it was concluded that *mono*-substitution only had occurred. This reaction was repeated at room temperature and at 40°C and in both cases, the spectral data were identical to those of the *mono*-substituted product (**526**).

10.4 Synthesis of phthalimide analogues.

10.4.1 Synthesis of 3-dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine (541)



541

1,2-Dicyanobenzene (phthalonitrile) (9.15g, 71.5mmol) was added to methanol (180.00cm^3). Sodium metal (4.14g 180.0mmol) was added with extreme caution to methanol (100.0cm^3). When the sodium was dissolved and the solution had cooled to room temperature, it was added slowly to the 1,2-dicyanobenzene/ methanol mixture. The resultant brownish solution was stirred continuously. Malononitrile (5.94 g/5.66 cm^3, 90.0 mmol) was then added dropwise. The solution turned a bright orange colour. This solution was then stirred at 30°C for 3 hours. An orange solid (**541**) was then isolated by vacuum filtration (10.2g, 52.5 mmol) in 73% yield and recrystallised from methanol. No melt was observed below 350°C, while a slow decomposition was noted above 210°C. The spectral data is in agreement with the data reported by Conway,[106a] who also reported the elemental analysis: Found: C, 67.84; H, 3.11; N, 28.87%, Calculated for $C_{11}H_6N_4$: C, 68.03; H, 3.11; N, 28.85%.

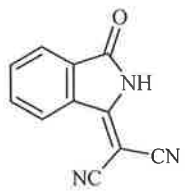
M/Z: M^+ 194.

ν_{max} **KBr:** 3399cm^{-1} (broad, NH), 2982cm^{-1} (broad, C=**NH**), 2222 and 2213cm^{-1} (C≡N), 1687cm^{-1} (C=N).

δH DMSO: 9.90 (s, broad, 2H, N**H**); 8.03 (m, 2H, aromatic); 7.68 (m, 2H, aromatic) ppm.

δC DMSO: 175.73 and 172.39 (**C**=C(CN)$_2$) and (**C**=NH); 137.61 (quat), 134.99 (quat), 132.70, 132.02, 123.35 and 123.02 (aromatic C); 116.64 and 115.76 (**C**N); 57.28 (C=**C**(CN)$_2$) ppm.

10.4.2 Synthesis of 3-dicyanomethylene-2,3-dihydroisoindol-1-one (530)



530

3-Dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine (**541**) (5.10g, 26.4mmol) was heated under reflux in glacial acetic acid (120cm^3) containing water (30cm^3) until it had fully dissolved, which took approximately 1 hour. TLC analysis of the reaction mixture showed the formation of a new spot faster moving compared to the starting material. The reaction mixture was then allowed to cool overnight. The resulting yellow solid was vacuum filtered and washed with 3 x 20 cm^3 light petroleum. 3-dicyanomethylene-2,3-dihydroisoindol-1-one (**530**) was isolated as a yellow solid and recrystallised from methanol (2.94g, 15mmol) in 57% yield, m.p. 249-251°C (lit.[106c] 249-251°C)

ν_{max} **KBr:** 3286 (NH), 2230, 2221 (C≡N), 1759 (C=O) cm^{-1}.

λ_{max}**:** 230 (ε = 9875), 302 (ε = 7842), 342 (ε = 6963) nm.

δH DMSO: 8.27 (m, 1H, aromatic), 7.90 (m, 3H, aromatic); 3.40 (s, broad, 1H, N**H**) ppm.

δC DMSO: 167.85 and 161.12 (**C**=O) and (**C**=C(CN)$_2$); 134.98, 134.81, 133.24 (quat), 129.55 (quat), 124.86, 124.64 (aromatic C); 114.18 and 112.60 (**C**N); 58.03 (C=**C**(CN)$_2$) ppm.

C, H, N Analysis: Found: C, 67.42; H, 2.61; N, 21.26%. Calculated for $C_{11}H_5N_3O$: C, 67.69; H, 2.58; N, 21.53%.

10.4.3 General procedure for the Mitsunobu Reaction

Triphenylphosphine (2.02g, 7.70mmol) was dissolved in sodium dried THF ($40cm^3$) and diisopropyl azodicarboxylate, DIAD, (1.55g, 7.70mmol) was then added. The mixture was stirred in the flask for about one minute. The appropriate alcohol (7.7mmol) was then added and the solution was stirred for another minute and 3-dicyanomethylene-2,3-dihydroisoindol-1-one (**530**) (1.00g, 5.12mmol) was finally added. The reaction flask was then sealed with a rubber septum. A balloon was filled with argon and attached to a syringe that had been cut in half. A needle was attached then placed through the septum, and the reaction was stirred under argon for three days. TLC analysis, using dichloromethane as solvent, was used to check the formation of product. Following completion of the reaction, the THF was removed by rotary evaporation, the resulting paste was dissolved in dichloromethane, to which a small amount of silica was then added. The dichloromethane was then removed by rotary evaporation and the silica added to the top of a silica chromatography column. The products were isolated by column chromatography, as a yellow band, which eluted after triphenyl phosphine oxide, using dichloromethane as solvent.

10.4.4 Synthesis of 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543)

543

Methanol (0.25g, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from a mixture of dichloromethane/ hexane to give 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**530**) as pale yellow crystals in 52 % yield, (0.56g, 2.66mmol) with m.p. 202-203°C (Lit.[106c] 200-202°C).

ν_{max} KBr: 2222, 2211 (CN); 1744 (C=O); 1600 (C=C); 1570, 1437, 1383, 1260, 1205, 1048, 954, 916, 799, 782, 704 (o-disubstituted aromatic) cm^{-1}.

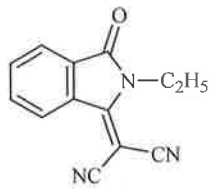
λ_{max}: 206 (ε = 9095), 232 (ε = 16305), 302 (ε = 11068) and 354 (ε = 8217) nm.

δH $CDCl_3$: 8.49 (m, 1H aromatic); 7.89 (m, 1H aromatic); 7.72 (m, 2H aromatic); 3.62 (s, 3H, CH_3) ppm.

δC $CDCl_3$: 166.56 and 159.00 (**C**=O) and (**C**=C(CN)$_2$); 135.15, 134.44, 133.23, 127.83, 125.59, 125.38 (aromatic C); 114.02 and 113.08 (**C**N); 60.29 (C=**C**(CN)$_2$); 28.91 (N-**C**H$_3$) ppm.

C, H, N analysis: Found: C, 68.63; H, 3.44; N, 20.02%. Calculated for $C_{12}H_7N_3O$: C, 68.89; H, 3.37; N, 20.09%.

10.4.5 Synthesis of 2-ethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (544)



544

Ethanol (0.44mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from a mixture of dichloromethane/ hexane to give 2-ethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**544**) as pale yellow crystals in 47 % yield (0.53g, 2.4mmol) with m.p. 171-173°C (Lit.[106c] 172-174°C).

ν_{max} KBr: 2225 and 2214 (CN), 1747cm^{-1} (C=O), 1577 (C=C), 1457, 1402, 1329, 1215, 1063, 922 and 709cm^{-1}

λ_{max}: 230 (ε = 17459), 292 (ε = 11936), 354 (ε = 7563) nm.

δH $CDCl_3$: 8.50 (m, 1H aromatic); 7.87 (m, 1H aromatic); 7.72 (m, 2H aromatic); 4.19 (q, 2H, *J* = *7Hz*, C**H**$_2$); 1.32 (t, 3H, *J* = *7Hz*, C**H**$_3$) ppm.

δC $CDCl_3$: 166.85 and 158.26 (**C**=O) and (**C**=C(CN)$_2$); 135.73, 134.63, 133.85, 128.05, 125.95, 125.54 (aromatic C); 114.44 and 113.29 (**C**N); 59.94 (C=**C**(CN)$_2$); 27.02 (N-**C**H$_2$); 15.60 (C-**C**H$_3$) ppm.

C, H, N analysis: Found: C, 69.79; H, 4.20; N, 18.84%. Calculated for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82%

10.4.6 Synthesis of 2-propyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (545)

545

Propan-1-ol (0.57mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-propyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**545**) as pale yellow crystals in 20 % yield (0.22g, 1 mmol), with m.p. 138-139°C. This compound had not been previously reported.

ν_{max} KBr: 2224 and 2209 (CN); 1752 (CO); 1601 (C=C) cm^{-1}.

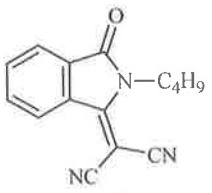
λ_{max}: 234 (ε = 23201), 303 (ε = 16466) and 355 (ε = 11714) nm.

δH $CDCl_3$: 8.61 (m, 1H, aromatic); 7.97 (m, 1H, aromatic); 7.80 (m, 2H, aromatic); 4.15 (t, 2H, *J = 7Hz*, N-C**H_2**); 1.80 (m, 2H, *J = 7Hz*, N-CH_2-C**H_2**); 1.04 (t, 3H, *J = 7Hz,* C**H_3**) ppm.

δC $CDCl_3$: 166.80 and 158.13 (**C**=O) and (**C**=$C(CN)_2$); 135.12, 134.36, 133.55, 127.71, 125.71, 125.36 (aromatic C); 114.22 and 113.06 (**C**N); 59.80 (C=**C**$(CN)_2$); 42.94 (N-**C**H_2); 23.33 (N-CH_2-**C**H_2); 10.89 (C-**C**H_3) ppm.

C, H, N analysis: Found: C, 70.57; H, 4.75; N, 17.74%. Calculated for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71%.

10.4.7 Synthesis of 2-butyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (546)



546

Butan-1-ol (0.70mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-butyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (**546**) as yellow crystals in 45% yield (0.87g, 3.5mmol), with m.p. 94-96°C (Lit.[106c] 97-99°C).

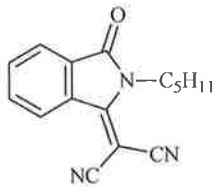
ν_{max} KBr: 2976, 2962, 2942, 2872 cm^{-1} (C-H stretching), 2228.5, 2213.5 (CN), 1752, 1749 cm^{-1} (C=O), 1576 (Aromatic), 1400 (C-H bend), 1330, 1298 (C-N) cm^{-1}.

δH $CDCl_3$: 8.44 (m, 1H, aromatic); 7.83 (m, 1H, aromatic); 7.69 (m, 2H, aromatic); 4.04 (t, 2H, *J* = *7.7Hz*, N-CH_2); 1.61 (m, 2H, NCH_2-CH_2); 1.32 (m, 2H, $CH_2CH_2CH_3$); 0.89-0.85 (t, 3H, *J* = *7.3Hz*, CH_2CH_3) ppm.

δC $CDCl_3$: 166.66 and 158.01 (C=O) and (C=$C(CN)_2$); 135.09, 134.36, 133.51, 128.65, 125.56, 125.24 (aromatic C); 114.24 and 113.11 (CN); 59.66 (C=$C(CN)_2$); 41.35 (N-CH_2); 31.88 (NCH_2-CH_2-CH_2); 19.88 (CH_2-CH_2-CH_3); 14.07 (C-CH_3) ppm.

C, H, N analysis: Found: C, 71.76; H, 5.31; N, 16.81%. Calculated for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72%.

10.4.8 Synthesis of 2-pentyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (547)



547

Pentan-1-ol (0.83mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-pentyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**547**) as yellow crystals in 51% yield (1.04g, 3.9mmol), with m.p. 88-90°C (Lit.[106c] 90-92°C). The elemental analysis was reported by Crean;[106c] as **C, H, N analysis:** Found: C, 72.13; H, 5.74; N, 15.71%. Calculated for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84%.

λ_{max}: 235 (ε = 21132) and 276 (ε = 43316) nm.

ν_{max} **KBr:** 2225 and 2215 (CN), 1744 (C=O), 1609 (C=C) cm^{-1}.

δH $CDCl_3$: 8.60 (m, 1H, aromatic); 7.96 (m, 1H, aromatic); 7.79 (m, 2H, aromatic); 4.17 (t, 2H, *J* = *7.8Hz*, NCH_2); 1.76 (m, 2H, NCH_2-CH_2); 1.39 (m, 4H, $CH_2CH_2CH_3$); 0.93 (t, 3H, *J* = *6.8Hz*, CH_3) ppm.

δC $CDCl_3$: 166.77 and 158.07 (C=O) and (C=$C(CN)_2$); 135.09, 134.34, 133.58, 127.73, 125.70 and 125.32 (aromatic C); 114.24 and 113.07 (CN); 59.80 (C=$C(CN)_2$); 41.63 (N-CH_2), 29.68 (NCH_2-CH_2-CH_2); 28.62 (CH_2-CH_2-CH_2); 22.66 (CH_2-CH_2-CH_3); 14.30 (CH_2-CH_3) ppm.

10.4.9 Synthesis of 2-hexyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (548)

548

Hexan-1-ol (0.97mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-hexyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**548**) as yellow crystals in 52% yield (1.11 g, 4mmol), with m.p. 77-79°C. This compound had not been previously reported.

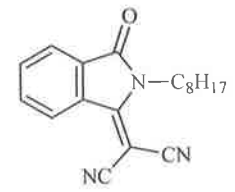
ν_{max} **KBr:** 2961, 2916, 2858 (C-H stretching); 2225, 2215 (C≡N); 1744 (C=O); 1609 (C=C); 1583, 1458 (aromatic C-C stretching) cm^{-1}.

δH $CDCl_3$: 8.52 (m, 1H, aromatic); 7.91 (m, 1H, aromatic); 7.72 (m, 2H, aromatic); 4.14 (t, *J = 7.8Hz*, 2H, CH_2); 1.75ppm (m, 2H, CH_2); 1.40ppm (m, 6H, $(CH_2)_3$); 0.88ppm (t, *J = 7.0Hz*, 3H).

δC $CDCl_3$: 166.76 and 158.06 (**C**=O) and (**C**=C(CN)$_2$); 135.09, 134.34, 133.58, 127.73, 125.69, 125.32 (aromatic C); 114.25 and 113.08 (**C**N); 59.80 (C=**C**(CN)$_2$) and 41.65 (N-**C**H_2); 31.69 (N-CH_2-**C**H_2); 29.93 (N-$(CH_2)_2$-**C**H_2); 26.20 (N-$(CH_2)_3$-**C**H_2); 22.85 (N-$(CH_2)_4$**C**H_2-CH_3); 14.37ppm (**C**H_3) ppm.

C, H, N analysis: Found: C, 73.06; H, 6.14; N, 15.09%. Calculated for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13%; N, 15.04%.

10.4.10 Synthesis of 2-octyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (549)



549

Octan-1-ol (1.2cm^3, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-octyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (**549**) as yellow crystals in 39% yield (0.92 g, 3 mmol), with m.p. 61-63°C. This compound had not been previously reported.

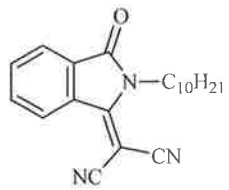
ν_{max}: 2952, 2924, 2854 (C-H stretching); 2223, 2212 (C≡N); 1742 (C=O); 1603 (C=C); 1572, 1467 (aromatic C-C stretching) cm^{-1}.

δH $CDCl_3$: 8.54 (m, 1H, aromatic); 7.88 (m, 1H, aromatic); 7.71 (m, 2H, aromatic); 4.09 (t, 2H, J = 8*Hz*, N-CH_2); 1.67 (m, 2H, J = 8*Hz*, N-CH_2CH_2); 1.26 (m, 10H, broad); 0.80 (t, 3H, J = 7*Hz*, CH_3)ppm.

δC $CDCl_3$: 166.77 and 158.06 (**C**=O) and (**C**=$C(CN)_2$); 135.08, 134.32, 133.59 (quat), 127.74 (quat), 125.71, 125.32 (aromatic); 114.24 and 113.06 (**C**N); 59.82 (C=**C**$(CN)_2$); 41.66 (N-**C**H_2); 32.11, 29.98, 29.51, 29.47, 26.54, 23.00 (CH_2**C**H_2); 14.48 (CH_2**C**H_3) ppm.

C, H, N analysis: Found: C, 73.99; H, 6.91; N, 13.61%. Calculated for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67%.

10.4.11 Synthesis of 2-decyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (550)



550

Decan-1-ol (1.47mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-decyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**550**) as yellow crystals in 46% yield (1.18g, 3.5mmol), with m.p. 53-54°C (lit.[106c] 49-51°C).

ν_{max} KBr: 234 (ε = 27182) and 276 (ε = 75697) nm.

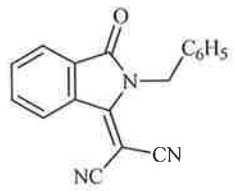
ν_{max}: 2958, 2921, 2852 (C-H stretching); 2224, 2213 (C≡N); 1746 (C=O); 1604, 1576 (aromatic C-C stretching); 1467, 1403 (C-H bending); 1084, 1073 (aliphatic C-N stretch) cm^{-1}.

δH $CDCl_3$: 8.52 (m, 1H, aromatic); 7.88 (m, 1H, aromatic); 7.71 (m, 2H, aromatic); 4.09 (t, 2H, J = 7.7*Hz*, N**C**H_2); 1.67 (m, 2H, NCH_2**C**H_2); 1.24 (m, 14H); 0.81 (t, 3H, J = 6.8*Hz*, C**H**$_3$) ppm.

δC $CDCl_3$: 166.77 and 158.06 (**C**=O) and (**C**=$C(CN)_2$); 135.09, 134.32, 133.58, 127.74, 125.70 and 125.32 (aromatic C); 114.24 and 113.07 (**C**N); 59.82 (C=**C**$(CN)_2$); 41.66 (N-**C**H_2); 32.25, 29.98, 29.87, 29.81, 29.66, 29.56, 26.54 (CH_2**C**H_2); 23.06 (CH_2**C**H_3); 14.52 (CH_2**C**H_3) ppm.

C, H, N analysis: Found: C, 75.23; H, 7.48; N, 12.54%. Calculated for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53%.

10.4.12 Synthesis of 2-benzyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (551)



551

Benzyl Alcohol (0.80mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-benzyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**551**) as yellow crystals in 45 % yield (0.98g, 3.4mmol), with m.p. 163-165°C (lit.[106c] 160-162°C).

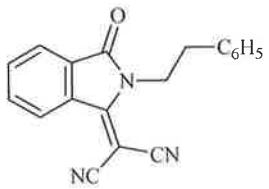
ν_{max} KBr: 2228 and 2217 (CN), 1756 (C=O), 1603 (C=C) cm^{-1}.

δH $CDCl_3$: 8.53 (m, 1H aromatic); 7.95 (m, 1H aromatic); 7.74 (m, 2H aromatic); 7.26 (m, 3H aromatic); 7.16 (m, 2H aromatic); 5.39 (s, 2H, CH_2).

δC $CDCl_3$: 167.06 and 157.71 (**C**=O) and (**C**=C(CN)$_2$); 135.38, 134.96, 134.56, 133.67, 129.47, 128.60, 127.54, 127.11, 125.89 and 125.66 (aromatic C); 113.99 and 112.94 (**C**N); 61.16 (C=**C**(CN)$_2$); 44.44 (N-**C**H$_2$).

C, H, N analysis: Found: C, 75.64; H, 3.88; N, 14.68%. Calculated for $C_{18}H_{11}N_3O$: C, 75.78%; H, 3.89; N, 14.73%.

10.4.13 Synthesis of 2-(2-phenylethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (552)



552

2-Phenylethanol (0.92cm^3, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-phenylethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**552**) as yellow crystals in 39% yield (0.89g, 3mmol), with m.p. 149-151°C. This compound had not been previously reported.

ν_{max} KBr: 3026, 2959, 2938 (C-H); 2223, 2251 (CN); 1750 (C=O); 1603, 1575, 1455, 1405, 1361, 1330, 1247, 1116, 1090, 1073, 1004, 960; 776, 754 (ortho disubstituted benzene); 705 (monosubstituted benzene) cm^{-1}.

δH $CDCl_3$: 8.53 (m, 1H aromatic); 7.84 (m, 1H aromatic); 7.71 (m, 2H aromatic); 7.20 (m, 5H aromatic); 4.34 (t, 2H, J = *8.1Hz*, N-**C**H$_2$), 2.97 (t, 2H, J = *8.1Hz*, **C**H$_2$Ph).

δC $CDCl_3$: 166.64 and 158.11 (**C**=O) and (**C**=C(CN)$_2$); 136.91, 135.22, 134.46, 133.54, 129.54, 129.19, 127.59, 125.77, 125.38 (aromatic); 114.13, 113.35 (**C**N); 59.97 (C=**C**(CN)$_2$); 43.08 (N-**C**H$_2$-CH$_2$); 35.94 (CH$_2$-**C**H$_2$-Ph) ppm.

C, H, N analysis: Found: C, 76.27; H, 4.48; N, 13.95%. Calculated for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04%.

10.4.14 Synthesis of 2-(4-methoxybenzyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (553)

553

4-Methoxybenzyl alcohol (0.96mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-(4-methoxy)benzyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**553**) as bright yellow crystals in 50 % yield (1.21g, 3.85mmol), with m.p. 135-137°C. This compound had not been previously reported.

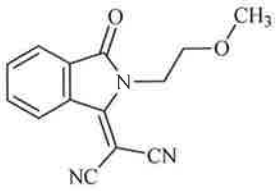
ν_{max} KBr: 2840 (OCH_3); 2208 (C≡N); 1753 (C=O); 1602 (C=C) cm^{-1}

δH $CDCl_3$: 8.51 (m, 1H, aromatic); 7.92 (m, 1H, aromatic); 7.72 (m, 2H aromatic); 7.13 (m, 2H, aromatic); 6.79 (m, 2H, aromatic); 5.31 (s, 2H, N-C**H**$_2$); 3.70 (s, 3H, O-C**H**$_3$).

δC $CDCl_3$: 165.71 and 158.36 (**C**=O) or (**C**=C(CN)$_2$); 156.29 (quat), 133.87, 133.06, 132.29 (quat), 127.42, 126.13 (quat), 125.41 (quat), 124.40, 124.14 and 113.33 (aromatic C); 112.62 and 111.73 (**C**N); 59.52 (C=**C**(CN)$_2$); 54.25 (O-**C**H$_3$); 44.44 (N-**C**H$_2$) ppm.

C, H, N analysis: Found: C, 72.07; H, 4.14; N, 13.22%. Calculated for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33%.

10.4.15 Synthesis of 2-(2-methoxyethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (554)



554

2-Methoxy ethanol (0.61g, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from dichloromethane/ hexane to give 2-methoxyethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**554**) as pale yellow crystals in 54% yield (1.05g, 4.1mmol) with mp. 134-136°C. This compound had not been previously reported.

ν_{max} **KBr:** 2937, 2908 (C-H stretching); 2822 (CH of OCH_3); 2221 (C≡N); 1763 (C=O), 1602 (C=C), 1566 (aromatic C-C stretching) cm^{-1}.

δH $CDCl_3$: 8.54 (m, 1H, aromatic); 7.93 (m, 1H, aromatic); 7.72 (m, 2H, aromatic); 4.40 (t, 2H, $J = 5Hz$, N-C**H**$_2$); 3.64 (t, 2H, $J = 5Hz$, C**H**$_2$-O); 3.28 (s, 3H, -OC**H**$_3$).

δC $CDCl_3$: 166.47 and 157.94 (**C**=O) or (**C**=C(CN)$_2$); 134.76, 133.99, 133.26 (quat), 127.27 (quat), 125.37 and 125.07 (aromatic); 113.84 and 112.84 (**C**N); 69.96 (O-**C**H$_2$); 60.01 (quat, C=**C**(CN)$_2$); 59.18 (O-**C**H$_3$); 40.68 (N-**C**H$_2$) ppm.

C, H, N analysis: Found: C, 66.27; H, 4.36; N, 16.50%. Calculated for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59%.

10.4.16 Synthesis of 2-(2-chloroethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (555)

555

2-Chloroethanol (0.52cm^3, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from dichloromethane/ hexane to give 2-(2-chloroethyl)-3-dicyanomethylene-2,3-dihydro-isoindol-1-one (**555**) as yellow crystals in 68% yield (1.34g, 5.2mmol) with mp. 181-182°C. This compound had not been previously reported.

ν_{max} **KBr**: 206 (ε = 10712), 232 (ε = 16963) and 292 (ε = 13098) nm.

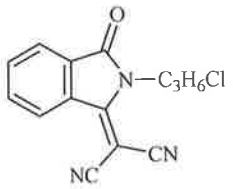
ν_{max}**:** 3114, 3040 (CH); 2229, 2211 (C≡N); 1755 (C=O); 1600 (C=C) cm^{-1}.

δH $CDCl_3$: 8.56 (m, 1H, aromatic); 7.93 (m, 1H, aromatic); 7.75 (m, 2H, aromatic); 4.55 (t, 2H, *J* = 6*Hz*, N-C**H**$_2$); 3.78 (t, 2H, *J* = 6*Hz*, C**H**$_2$Cl).

δC $CDCl_3$: 166.64 and 158.12 (**C**=O) or (**C**=C(CN)$_2$); 135.74, 134.70, 133.44, 127.27, 125.92 and 125.67 (aromatic); 112.95 and 113.71 (**C**N); 60.74 (C=**C**(CN)$_2$); 42.43 (N**C**H$_2$); 41.53 (**C**H$_2$Cl).

C, H, N analysis: Found C, 60.48; H, 3.08; N, 16.02%. Calculated for $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31%.

10.4.17 Synthesis of 2-(3-chloropropyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (556)



556

3-Chloropropanol (0.64cm^3, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from dichloromethane/ hexane to give 2-(-3chloropropyl)-3-dicyanomethylene-2,3-dihydro-isoindol-1-one as yellow crystals in 61% yield (1.27g, 4.7mmol) with mp. 119-120°C. This compound had not been previously reported.

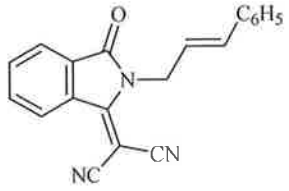
ν_{max} KBr: 2971 (CH); 2221 and 2210 (C≡N); 1745 (C=O); 1600 (C=C) cm^{-1}

δH $CDCl_3$: 8.62 (m, 1H, aromatic); 7.99 (m, 1H, aromatic); 7.82 (m, 2H, aromatic); 4.36 (t, 2H, *J* = 7.3*Hz*, N-C**H**$_2$); 3.78 (t, 2H, *J* = 6.3*Hz*, C**H**$_2$Cl); 2.28 (m, 2H, C**H**$_2$).

δC $CDCl_3$: 166.72 and 158.16 (**C**=O) or (**C**=C(CN)$_2$); 135.32, 134.58, 133.49, 127.53, 125.80, 125.51 (aromatic); 113.11 and 113.92 (**C**N); 60.08 (C=**C**(CN)$_2$); 41.63 (N-**C**H$_2$); 39.57 (**C**H$_2$Cl); 32.5 (N-CH$_2$**C**H$_2$) ppm.

C, H, N analysis: Found: C, 61.68; H, 3.74; N, 15.38%. Calculated for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.71; N, 15.47%.

10.4.18 Synthesis of 2-phenylallyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (557)



557

t-Cinnamyl alcohol (0.99mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-phenylallyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**557**) as pale yellow crystals in 57% yield (1.36g, 4.39mmol) in 57 % yield, with m.p. 152-153°C (lit.[106c] 156-158°C).

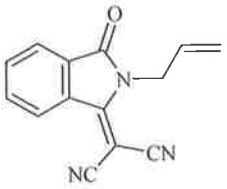
ν_{max} KBr: 2227, 2216 (CN), 1744 (C=O), 1601, 1575 (C=C) cm^{-1}.

δH $CDCl_3$: 8.53 (m, 1H, aromatic); 7.91 (m, 1H, aromatic); 7.72 (m, 2H aromatic); 7.29 (m, 2H, aromatic); 7.30 (m, 3H, aromatic); 6.56 (d, 1H, J = 16*Hz*, CH=C**H**Ph); 6.17ppm (d of t, 1H, J_t=6*Hz* and J_d = 16*Hz*, C**H**=CHPh); 4.90 (d, 2H, J = 6*Hz*, NC**H**$_2$) ppm.

δC $CDCl_3$: 166.63 and 157.70 (**C**=O) and (**C**=C(CN)$_2$); 136.09, 135.27, 134.90, 134.48, 133.61, 129.05, 128.76, 127.06, 125.83, 125.50, 127.69 and 122.10 (aromatic and vinylic C); 114.06 and 113.19 (**C**N); 60.63 (C=**C**(CN)$_2$); 42.81ppm (N-**C**H$_2$) ppm.

C, H, N analysis: Found: C, 76.86; H, 4.24; N, 13.63%. Calculated for $C_{20}H_{13}N_3O$: C, 77.16; H, 4.21; N, 13.50%.

10.4.19 Synthesis of 2-allyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (558)



558

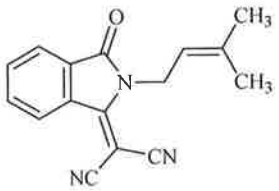
Allyl alcohol (0.52mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-allyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**558**) as yellow crystals in 66% yield (1.19g, 5 mmol), with m.p. 153-155°C (lit.[106c] 154-156°C). The elemental analysis was reported by Crean;[106c] as **C, H, N analysis:** Found: C, 71.36; H, 3.96; N, 17.67%. Calculated for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86%.

ν_{max} KBr: 2226.0 and 2218.0 (C≡N), 1751.4 (C=0), 1741 and 1603.0 (C=C) cm^{-1}.

δH $CDCl_3$: 8.54 (m, 1H, aromatic); 7.92 (m, 1H, aromatic); 7.74 (m, 2H, aromatic); 5.89 (d of d of t, 1H, $CH_2C\mathbf{H}=CH_2$); 5.25 (d, 1H, J = 10.3*Hz* (*cis*), $CH_2CH=C\mathbf{H}_2$); 5.08 (d, 1H, J = 17.2*Hz* (*trans*), $CH_2CH=C\mathbf{H}_2$); and 4.77 (d, 2H, J = 4.8*Hz*, $NC\mathbf{H}_2$) ppm.

δC $CDCl_3$: 166.50ppm (**C**=O); 157.66ppm (**C**=$C(CN)_2$); 135.28, 134.50, 133.46, 127.59, 125.81 and 125.53ppm (aromatic C); 131.10ppm (**C**H=CH_2); 118.33ppm (CH=**C**H_2); 114.06 and 112.98ppm (**C**N); 60.71ppm (C=**C**$(CN)_2$); 43.00ppm (N-**C**H_2).

10.4.20 Synthesis of 2-(3-Methylbut-2-enyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (559)



559

3-Methyl-2-buten-1-ol (0.78mls, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-(3-methylbut-2-enyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**559**) as yellow crystals in 46% yield (0.93g, 3.5mmol), with m.p. 136-138°C. This compound had not been previously reported.

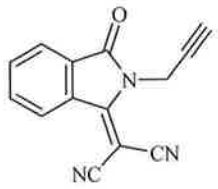
ν_{max} KBr: 2223 (CN); 1745 (C=O); 1601 and 1569 (C=C).

δH $CDCl_3$: 8.52 (m, 1H, aromatic); 7.87 (m, 1H, aromatic); 7.70 (m, 2H, aromatic); 5.17 (t, 1H, J = 6.5*Hz*, vinyl H); 4.73 (d, 2H, J = 6.5*Hz*, NCH_2); 1.74 (s, 3H, $C\mathbf{H}_3$); 1.68 (s, 3H, $C\mathbf{H}_3$) ppm.

δC $CDCl_3$: 166.63 and 157.92 (**C**=O) or (**C**=$C(CN)_2$); 135.06, 134.28, 133.71, 127.87, 125.70 and 125.31 (aromatic C); 139.64 (CH=**C**$(CH_3)_2$), 117.88 (**C**H=$C(CH_3)_2$); 114.31 and 113.01 (**C**N); 60.79 (C=**C**$(CN)_2$); 39.84 (N-**C**H_2); 26.26 and 18.33 ($C(\mathbf{C}H_3)_2$) ppm.

C, H, N analysis: Found: C, 72.52; H, 4.94; N, 15.88%. Calculated for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96%.

10.4.21 Synthesis of 2-propynyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (560)



560

2-Propyn-1-ol (0.45cm^3, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from methanol to give 2-prop-2-ynyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**560**) as pale yellow crystals in 50% yield (0.89g, 3.85mmol), with m. p. 184-186°C. This compound had not been previously reported.

λ_{max}: 232 (ε = 13699), 292 (ε = 11400), 344 (ε = 6266) nm.

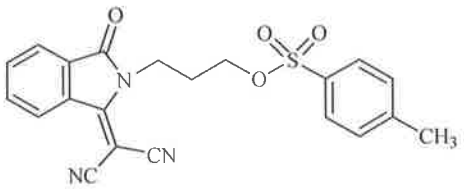
ν_{max} KBr: 3270 (C-H); 2215, 2225 (C≡N); 2127 (C≡C); 1754 (C=O); 1602 (C=C) cm^{-1}.

δH $CDCl_3$: 8.55 (m, 1H, aromatic); 7.93 (m, 1H, aromatic); 7.75 (m, 2H, aromatic); 4.92ppm (d, 2H, *J* = 2.5*Hz*, N-C**H**$_2$); 2.41ppm (t, 1H, *J* = 2.5*Hz*, CH).

δC $CDCl_3$: 165.66 and 156.93 (C=O) or (**C**=C(CN)$_2$); 135.11 134.28, 133.05 (quat), 127.06 (quat), 125.53 and 125.34 (aromatic); 113.38 and 112.06 (**C**N); 76.32 (C≡**C**H); 75.17 (quat, **C**≡CH); 61.38 (C=**C**(CN)$_2$); 30.87 (N-**C**H$_2$) ppm.

C, H, N analysis: Found C, 71.22 (70.66); H, 3.10 (3.22); N, 17.71 (17.05)%. Calculated for $C_{14}H_7N_3O$: C, 72.10; H, 3.03; N, 18.02%.

10.4.22 Synthesis of 2-propyl-(4-methylbenzenesulphonate)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (563)



563

3-Hydroxypropyl 4-methylbenzene sulphonate (1g, 7.7mmol) was added as the alcohol. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, which was recrystallised from dichloromethane/ hexane to give 2-propyl-(4-methylbenzenesulphonate)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**563**) as pale crystals in 53% yield (1.66g, 4mmol), with m.p. 113-115°C. This compound had not been previously reported.

λ_{max}: 206 (ε = 17773), 230 (ε = 29797) and 302 (ε = 13599).

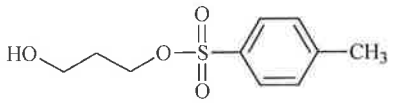
ν_{max} **KBr:** 2219, 2208 (C≡N); 1756 (C=O); 1600 (C=C); 835 (*p*-disub aromatic)cm^{-1}

δH $CDCl_3$: 8.49 (m, 1H, aromatic); 7.89 (m, 1H, aromatic); 7.82 (m, 2H, aromatic); 7.67 (m, 2H, *J* = 8*Hz*, aromatic); 7.33 (m, 2H, *J* = 8*Hz*, aromatic); 4.23 (t, 2H, *J* = 7*Hz*, O-C**H**$_2$); 4.14 (t, 2H, *J* = 6*Hz*, N-C**H**$_2$); 2.42 (s, 3H, C**H**$_3$); 2.10 (m, 2H, *J* = 7*Hz*, C**H**$_2$) ppm.

δC $CDCl_3$: 166.61 and 158.12 (**C**=O) or (**C**=C(CN)$_2$); 145.52, 135.24, 134.57, 133.39, 132.84, 130.37, 128.20, 127.42, 125.61 and 125.43 (aromatic); 113.99 and 113.18 (**C**N); 67.77 (O-**C**H$_2$); 59.80 (C=**C**(CN)$_2$); 38.50 (N-**C**H$_2$); 29.21 (CH_2**C**H_2CH_2); 22.06 (CH_3) ppm.

C, H, N analysis: Found: C, 61.63; H, 4.22; N, 10.09%. Calculated for $C_{21}H_{17}N_3O_4S$: C, 61.91; H, 4.21; N, 10.31%.

10.4.23 Synthesis of 3-hydroxypropyl 4-methylbenzenesulphonate (562)



562

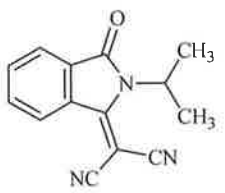
This compound was prepared according to the procedure described by Burns *et al.*[128] A mixture of 1,3-propanediol (14.66g, 192.5mmol), a catalytic amount of 4-dimethylaminopyridine, pyridine (10.4cm^3, 128.5mmol) and CH_2Cl_2 (55cm^3) was cooled to –5 °C using ice water/ NaCl. *p*-Toluenesulfonyl chloride (6.15g, 31.1mmol) was added over a period of 30 minutes. The reaction mixture was then stirred for three hours, then quenched with ice water (100cm^3) and extracted with CH_2Cl_2 (4 x 50cm^3). The organic extracts were combined and washed with 3M HCl (100cm^3) followed by saturated $NaHCO_3$ (100cm^3) and finally with brine (100cm^3), dried over $MgSO_4$ and concentrated under vacuum. The crude product (6.82g) was purified by column chromatography using hexane/ethyl acetate 50:50, to yield 3-hydroxypropyl 4-methylbenzenesulphonate (**562**) as a clear oil (5.00g) (lit.[128] b.p. 166-168°C and were obtained with a micro boiling point apparatus). NMR spectroscopy confirmed that the product was of good purity and it was used in the next step without further purification. All spectral data were in agreement with those reported by Burns *et al.*[128]

δH $CDCl_3$: 7.69 (m, 2H, aromatic); 7.27 (m, 2H, aromatic); 4.08 (t, 2H, J = 7.5*Hz*, CH_2-OTs); 3.58 (t, 2H, J = 7.5*Hz*, CH_2-OH); 2.47 (s, 1H, OH); 2.35 (s, 3H, CH_3); 1.78 (m, 2H, $CH_2CH_2CH_2$) ppm.

δC $CDCl_3$: 145.37, 133.13, 130.3 and 128.20 (aromatic); 68.12, 58.48 and 31.99 (CH_2); 21.99 (CH_3) ppm.

However, it should be noted that attempts to make similar products from 1,4-butanediol and 1,6-hexanediol failed to give the desired products under identical conditions, although both compounds have been reported in the literature.[128]

10.4.24 Synthesis of 2-isopropyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (561a)



561

Propan-2-ol (0.59mls, 7.7mmol) was added as the alcohol. The reaction was stirred at room temperature for seven days instead of three days as a secondary alcohol was being used. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, in 73% yield. Initial NMR analysis showed duplication of all peaks in the ^1H NMR and ^{13}C NMR spectra, indicating the presence of two compounds in a ratio of 1:2.5. TLC analysis, using a 50:50 diethyl ether: light petroleum, showed that there were two products present. Further TLC analysis showed that these compounds could be sufficiently separated using a mobile phase of 10:90 diethyl ether: light petroleum. Following column chromatography, on 200mg of product mixture, using the previously determined mobile phase, the major product was isolated as the second product as a pale yellow solid in 64% yield (0.128g, 0.54mmol) with m.p. 163-165°C (Lit.[106c] 167-169°C). The product was recrystallised from methanol to give 2-isopropyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**561a**).

λ_{max}: 232 (ε = 33577), 277 (ε = 42036), 302 (ε = 23392) and 350 (ε = 17811) nm.

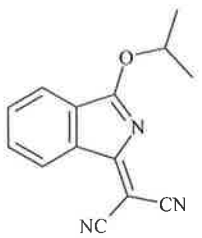
ν_{max} KBr: 2223 and 2205 (C≡N), 1754 (C=O) cm^{-1}.

δH $CDCl_3$: 8.51 (m, 1H, aromatic); 7.82 (m, 1H, aromatic); 7.69 (m, 2H, aromatic); 5.02 (sept, 1H, J = 6.8*Hz*, N-CH$(CH_3)_2$); 1.62 (d, 6H, J = 6.8*Hz*, N-CH$(CH_3)_2$) ppm.

δC $CDCl_3$: 167.05 and 158.62 (**C**=O) or (**C**=C(CN)$_2$); 134.57, 133.90, 133.66, 128.20, 125.19 and 125.13 (aromatic C); 114.53 and 113.11 (**C**N); 59.57 (C=**C**(CN)$_2$); 49.41 (N-**C**H(CH$_3$)$_2$); 21.02 (N-CH(**C**H$_3$)$_2$) ppm.

C, H, N analysis: Found: C, 70.65; H, 4.68; N, 18.01 %. Calculated for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71%.

10.4.25 Synthesis of 2-(3-isopropoxy-isoindol-1-ylidene)-malononitrile (573)



573

Propan-2-ol (0.59mls, 7.7mmol) was added as the alcohol. The reaction was stirred at room temperature for seven days instead of three days as a secondary alcohol was being used. Following chromatography, the dichloromethane was removed by rotary evaporation to give a pale yellow solid, in 73% yield. Initial NMR analysis showed duplication of all peaks in the ^{1}H NMR and ^{13}C NMR spectra, indicating the presence of two compounds in a ratio of 1:2.5. TLC analysis, using a 50:50 diethyl ether: light petroleum, showed that there were two products present. Further TLC analysis showed that these compounds could be sufficiently separated using a mobile phase of 10:90 diethyl ether: light petroleum. Following column chromatography, on 200mg of product mixture, using the previously determined mobile phase, the minor product was isolated as the first product as a yellow solid in 24% yield () with m.p. 174-175°C. The product was recrystallised from methanol, to give 2-(3-isopropoxy-isoindol-1-ylidene)-malononitrile (**573**). This product had not been previously reported.

λ_{max}: 238 (ε = 12738), 291 (ε = 7906.6), 302 (ε = 8169.3) and 339 (ε = 6939.1)nm.

ν_{max} KBr: 2232 and 2205 (C≡N), 1616 (C=N) cm^{-1}.

δH $CDCl_3$: 8.17 (m, 1H, aromatic); 7.54 (m, 3H, aromatic); 5.61 (sept, 1H, *J* = 6.0*Hz*, N-C**H**(CH$_3$)$_2$); 1.45 (d, 6H, *J* = 6.0*Hz*, N-CH(C**H$_3$**)$_2$) ppm.

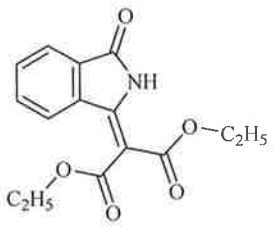
δC $CDCl_3$: 177.97 and 171.52 (**C**=O) or (**C**=C(CN)$_2$); 135.26, 132.59, 131.68, 131.63, 124.08 and 121.31 (aromatic C); 112.31 and 111.31 (**C**N); 74.41 (N-**C**H(CH$_3$)$_2$); 71.75 (C=**C**(CN)$_2$); 20.84 (N-CH(**C**H$_3$)$_2$) ppm.

C, H, N analysis: Found: C, 70.57; H, 4.66; N, 17.69%. Calculated for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71%.

10.4.26 Attempted syntheses using other alcohols with (530).

A series of other alcohols were used in the Mitsunobu reaction with (**530**) that contained a ring system, such as cyclopentanol and cyclohexanol, an amino functionality, such as 2-aminoethanol, 3-aminopropanol, serine and threonine, or a second alcohol group, such as 1,3-propanediol and 1,6-hexanediol. The reactions were carried out according to the general procedure. In each case, the desired product, 2-substituted alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one, was not obtained. Instead starting material (**530**) was recovered, along with a series of complex mixtures that were not purified further.

10.4.27 Synthesis of 2-(3-oxo-2,3-dihydro-isoindol-1-ylidene)-malonic acid diethyl ester (564).[129]



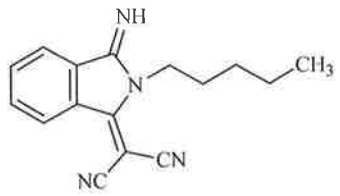
564

Sodium metal (2.3g, 100mmol) was added slowly to ethanol (50cm^3) of and allowed to cool. With constant stirring diethyl malonate (16g, 100mmol) was added dropwise, followed by phthalonitrile (12.8g, 100mmol). The mixture was heated to boiling, allowed to cool and poured onto a mixture of ice and 1M HCl (100cm^3). It was then washed with toluene (25cm^3). Overnight, the aqueous layer deposited a purple solid, which was vacuum filtered. 2-(3-oxo-2,3-dihydro-isoindol-1-ylidene)-malonic acid diethyl ester (**564**) was isolated by flash chromatography, using 80:20 light petroleum ether and ethyl acetate, in the first fraction, which was isolated as a light brown solid. The product was recrystallised from methanol to yield white needles in 1% yield (0.31g, 1mmol), with mp 107-108°C (lit.[129] 108°C).

δH $CDCl_3$: 10.07 (broad s, 1H, N**H**); 7.91 (m, 1H, aromatic); 7.65 (m, 3H, aromatic); 4.47 (q, 2H, *J* = *7Hz,* C**H**$_2$); 4.33 (q, 2H, *J* = *7Hz*, C**H**$_2$); 1.41 (t, 3H, *J* = *7Hz*, C**H**$_3$); 1.35 (t, 3H, *J* = *7Hz* C**H**$_3$) ppm.

δC $CDCl_3$: 167.81, 165.92 and 165.61 (**C**=O); 146.89 (**C**=C(CO$_2$Et)$_2$); 134.88, 133.5, 132.51, 130.3, 124.66 and 124.35 (aromatic); 102.60 (C=**C**(CO$_2$Et)$_2$); 62.66 and 62.14 (O-**C**H$_2$); 14.47 and 14.38ppm (**C**H$_3$) ppm.

10.4.28 Synthesis of 1-imino-2-pentyl-3-dicyanomethylene-2,3-dihydroiso-indole (569)



569

3-Dicyanomethylene-2,3-dihydroisoindol-1-ylidene-amine (**541**) (1.0g, 5.22mmol) was dissolved in pyridine (40cm^3). Pentylamine (1.0cm^3) was added and the solution was heated under reflux for 4 hours. The solution was allowed to cool and the product was precipitated by the addition of water, filtered off and washed with copious amounts of water. The filter cake was dried at the pump overnight. It was then dissolved in chloroform and the solution dried over magnesium sulphate, filtered and the filtrate condensed under vacuum. The resulting orange solid was purified by column chromatography using a 60:40 light petroleum: ethyl acetate. 1-Imino-2-pentyl-3-dicyanomethylene-2,3 dihydroisoindole (**569**) was recovered as a yellow powder in 54% yield, (0.74g, 2.8mmol) with melting point 191-192°C.

ν_{max} KBr: 3320.5 (NH), 2216.3 (CN), 1648.4 (C=C) cm^{-1}.

δH $CDCl_3$: 8.20 (m, 1H, aromatic); 7.53 (m, 3H, aromatic); 6.82 (s, broad, 1H, NH, exchanges with D_2O); 3.77 (q, 2H, J = 6.8*Hz*, N-CH_2); 1.66 (quin, 2H, J = 7*Hz*, CH_2); 1.29-1.34 (m, 4H, $(CH_2)_2$); 0.86 (t, 3H, J = 6.9*Hz*, CH_3) ppm.

δC $CDCl_3$: 175.41 (quat, **C**=N); 169.94 (quat, **C**=$C(CN)_2$); 137.94 (quat), 134.38 (quat), 132.77, 131.88, 125.24, 120.58 (aromatic); 115.55, 114.81 (quat, **C**N); 64.70 (quat, C=**C**$(CN)_2$); 44.40 (N-**C**H_2), 29.38, 29.27, 22.66 (**C**H_2); 14.33 (**C**H_3) ppm.

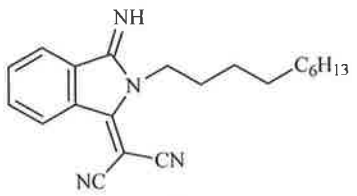
C, H, N analysis: Found: C, 74.49; H, 5.88; N, 20.93%. Calculated for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20%.

10.4.29 Hydrolysis of 1-imino-2-pentyl-3-dicyanomethylene-2,3-dihydroiso-indole (569)

1-Imino-2-pentyl-3-dicyanomethylene-2,3-dihydroisoindole (**569**) was heated under reflux in a solution of glacial acetic acid (12cm^3) containing water (3cm^3) for one hour. The solution was allowed to cool, and a pale yellow solid precipitated out and was filtered off and recrystallised from methanol to give 2-pentyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (**547**). NMR and IR spectra of this compound, along with its melting point, were compared with those of 2-pentyl-3-

dicyanomethylene-2,3-dihydroisoindol-1-one (**547**) (section 5.4.5) prepared by way of the Mitsunobu reaction, and were found to be identical.

10.4.30 Synthesis of 1-imino-2-decyl-3-dicyanomethylene-2,3-dihydroisoindole (570)



570

3-Dicyanomethylene-2,3-dihydroisoindol-1-ylidene-amine (**541**) (1.0g, 5.22mmol) was dissolved in pyridine (40cm^3). Decylamine (1.0cm^3) was added and the solution was heated under reflux for 4 hours. The solution was allowed to cool and the product was precipitated by the addition of water, filtered off and washed with copious amounts of water. The filter cake was dried at the pump overnight. It was then dissolved in chloroform and the solution dried over magnesium sulphate, filtered and the filtrate condensed under vacuum. The resulting orange solid was purified by column chromatography using a 60:40 light petroleum: ethyl acetate. 1-Imino-2-decyl-3-dicyanomethylene-2,3-dihydroisoindole (**570**) was recovered as a yellow solid in 58% yield (1.03g, 3.1mmol) with melting point 162-163°C.

ν_{max} KBr: 3338.9 (NH); 2922 and 2852 (CH); 2217.2 (CN), 1643.3 (C=C)cm^{-1}.

δH $CDCl_3$: 8.26 (m, 1H, aromatic); 7.76 (m, 1H, aromatic) 7.61 (m, 2H, aromatic); 7.40 (s, broad, 1H, NH, exchanges with D_2O); 3.84 (q, 2H, J = 6.8*Hz*, N-CH_2); 1.78 (m, 2H, J = 7*Hz*, CH_2); 1.33 (m, 14H, $(CH_2)_7$); 0.89 (t, 3H, J = 6.8*Hz*, CH_3) ppm.

δC $CDCl_3$: 175.86 (quat, aromatic **C**N); 170.18 (quat, **C**=C$(CN)_2$); 137.91 (quat), 134.51 (quat), 132.73, 132.00, 125.04, 121.15 (aromatic); 115.73, 115.17 (quat, **C**N); 63.66 (quat, C=**C**$(CN)_2$); 44.49 (N-**C**H_2); 32.26, 29.92, 29.69, 29.62, 27.25, 23.06 (**C**H_2); 14.52 (**C**H_3) ppm.

C, H, N analysis: Found: C, 75.32; H, 7.80; N, 16.52%; Calculated for $C_{21}H_{26}N_4$: C, 75.41; H, 7.84; N, 16.75%.

10.4.31 Hydrolysis of 1-imino-2-decyl-3-dicyanomethylene-2,3-dihydroisoindole (570)

1-Imino-2-decyl-(3-dicyanomethylene)-2,3 dihydroisoindole (**570**) was heated under reflux in a solution of glacial acetic acid (12cm^3) containing water (3cm^3) for one

hour. The solution was allowed to cool, and a pale yellow solid precipitated out and was filtered off and recrystallised from methanol to give 2-decyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**550**). NMR and IR spectra of this compound, along with its melting point, were compared with those of (**550**) (section 5.4.8) prepared by way of the Mitsunobu reaction, and were found to be identical.

10.4.32 Attempted syntheses using other amines with 3-dicyanomethylene-2,3-dihydroisoindol-1-ylideneamine (541).

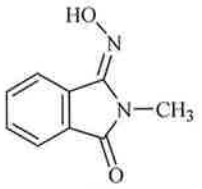
A series of other amines were used in an attempt to make other 1-imino-2-substituted-3-dicyanomethylene-2,3-dihydroiso-indole compounds similar to (**568**) (**569**), such as aniline, benzylamine. The reactions were carried out as described in section 5.4.24 and 5.4.26, however desired products, 1-imino-2-substituted-3-dicyanomethylene-2,3-dihydroiso-indole, were not obtained. Instead starting material (**541**) was recovered, along with a series of complex mixtures that were not purified further.

10.4.33 Grignard Reactions of 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543).

Magnesium turnings (0.048g, 2mmol) and dry diethyl ether ($10cm^3$) of were placed in a dry $100cm^3$ 3-necked round bottom flask. 1-Bromobutane ($0.16cm^3$, 1.5mmol) was dissolved in dry diethyl ether ($10cm^3$) in a dropping funnel. An iodine crystal was then added to the flask, turning the solution brown, followed by about $1cm^3$ of the 1-bromobutane solution, which was added very slowly. As the reaction began, the solution became cloudy and white. The remaining 1-bromobutane solution was added to the flask slowly over a period of fifteen minutes. The flask was then heated under reflux for thirty minutes in order to complete the Grignard reagent formation. The reaction mixture was allowed to cool, and dry diethyl ether ($10cm^3$) was added through the dropping funnel. 2-Methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**) (0.3188g, 1.52mmol) was dissolved in dry diethyl ether ($10cm^3$) and added over a fifteen minute period. The reaction was heated under reflux for twenty minutes and allowed to cool to room temperature. A solution of 3M ammonium chloride ($10cm^3$) was added, followed by diethyl ether ($10cm^3$) and saturated salt solution ($10cm^3$). The solution was separated into three layers, with the white emulsion further washed with diethyl ether ($10cm^3$). The aqueous phase was also

further washed with diethyl ether (15cm^3). The organic portions were combined and washed with 5% aqueous sodium bicarbonate (10cm^3), dried over anhydrous magnesium sulphate, and filtered. Removal of the diethyl ether by rotary evaporation yielded a solid which was shown by TLC, NMR and IR analysis to be unchanged 2-Methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**). Bromobenzene and benzyl bromide were also used and in both cases, the starting material was recovered unchanged.

10.4.34 Oxime synthesis from Grignard Reactions of 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543).



572

2-Methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**) (2.0 mmol), was added to an ethanol solution (40 cm^3) of pyridine (2.5 g, 3.0 mmol) and hydroxylamine hydrochloride (2.1 g, 3.0 mmol). The solution was heated under reflux for twenty-four hours and allowed to cool. The ethanol was removed by rotary evaporation and iced water (20 cm^3) was added to the solution, which was then stirred for a further hour. Dilute HCl (10 cm^3) was then added and the product was extracted using chloroform. Removal of the chloroform by rotary evaporation gave 2-methyl-phthalimide monooxime which was recrystallised from aqueous methanol to yield a pale brown solid (0.125g, 0.7mmol, 35 % yield) m.p. 216-218 °C.

ν_{max} **KBr:** 3232 (OH), 1705 (C=O), 1682 (C=N) cm^{-1}.

δH DMSO: 11.67 (s, 1H, N-OH); 8.34 (m, 1H, aromatic, *J* = 7.6*Hz*); 7.82 (m, 1H, aromatic, *J* = 7.4*Hz*); 7.76 (t, 1H, aromatic, *J* = 7.6*Hz*); 7.74 (t, 1H, aromatic, *J* = 7.6*Hz*); 3.16 (s, 3H, N-C**H**$_3$);

δC DMSO: 165.70 (**C**=O); 148.21 (**C**=N-OH); 133.673, 131.81, 130.97 (quat), 128.23 (quat), 127.23 and 123.02 (aromatic); 25.68 (N-**C**H3) ppm.

C, H, N analysis: Found: C, 60.78 (60.70); H, 4.56 (4.57); N, 15.73 (15.70)%; Calculated for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90%.

10.5 Photochemistry of Phthalimides

10.5.1 Irradiations of *N*-(2-hydroxyphenyl)phthalimide (510, X = O)

N-(2-Hydroxyphenyl)phthalimide (**510,** X = O) (0.50g, 2.1mmol) was dissolved in a number of different solvents (methanol, ethanol, *iso*-propyl alcohol, *tert*-butyl alcohol, acetone, THF, acetonitrile or toluene) and irradiated. After eight hours irradiation in each solvent, (**510,** X = O) showed no evidence of reaction on TLC. The reaction was also carried out in the presence of an excess of cyclohexene, styrene or aniline which was added to the reaction vessel and the photolysis was continued for another eight hours. Once again, (**510,** X = O) showed no evidence of reaction on TLC. In all cases, after removal of the solvent and purification of the recovered solid, the NMR and IR spectra of the recovered material were compared to those of the starting material and were found to be identical.

10.5.2 Irradiations of *N*-(2-aminophenyl)phthalimide (510, X = NH)

N-(2-Aminophenyl)phthalimide (**510,** X = NH) (0.50g, 2.1mmol) was dissolved in irradiated in a number of different solvents (methanol, ethanol, *iso*-propyl alcohol, *tert*-butyl alcohol, acetone, THF, acetonitrile or toluene). After eight hours irradiation in each solvent, (**510,** X = NH) showed no evidence of reaction on TLC. The reaction was also carried out in the presence of an excess of cyclohexene, styrene or aniline which was added to the reaction vessel and the photolysis was continued for another eight hours. Once again, (**510,** X = NH) showed no evidence of reaction on TLC. In all cases, after removal of the solvent and purification of the recovered solid, the NMR and IR spectra of the recovered material were compared to those of the starting material and were found to be identical.

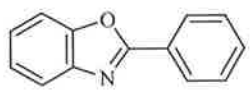
10.5.3 Irradiations of phenyl esters and amides (523 and 525)

N-(2-Acetoxyphenyl)phthalimide (**523**) (0.50g, 1.8mmol) was irradiated in methanol, *iso*-propyl alcohol, *tert*-butyl alcohol or acetonitrile. After eight hours irradiation (**523**) showed no evidence of reaction on TLC. After removal of the solvent and purification of the recovered solid, NMR and IR analysis showed identical spectra to the starting material. Similarly, *N*-(2-acetamidophenyl)phthalimide (**525**) (0.50g, 1.79mmol) was also irradiated in methanol, *iso*-propyl alcohol, *tert*-butyl alcohol or acetonitrile. After eight hours, TLC showed no reaction. After removal of the solvent and purification of the

recovered solid, NMR and IR analysis showed identical spectra to the starting material.

10.6 Pyrolysis of Phthalimides

10.6.1 Pyrolysis of *N*-(2-hydroxyphenyl)phthalimide (510, X = O).



520

N-(2-Hydroxyphenyl)phthalimide (0.1g, 0.4mmol) was placed in a 50cm^3 beaker and heated to its melting point on an electric hotplate. The temperature was gradually raised until sublimation occurred at 250°C. The product was collected by covering the beaker with a clock glass filled with ice. After 15 minutes, the heating was stopped and the beaker was allowed to cool. A white crystalline substance was observed on the clock-glass and the contents of the beaker had blackened. TLC analysis (95: 5 light petroleum 40-60: ethyl acetate) of the white crystals and of the blackened mixture showed the formation of a new faster moving spot, compared to *N*-(2-hydroxyphenyl)phthalimide. The blacked mixture was dissolved in chloroform (20cm^3) and filtered. A small amount of silica was then added. The chloroform was removed by rotary evaporation and the silica, with its absorbed reaction products, added to the top of a silica chromatography column. The products were isolated by column chromatography, using 95: 5 light petroleum 40-60: ethyl acetate as solvent. Using TLC (95: 5 light petroleum 40-60: ethyl acetate) as a comparison, the fractions containing the same spot as the white crystals were collected and the solvent removed to afford more white crystals. The combined white product was recrystallised from methanol to give white crystals of 2-phenylbenzooxazole (**520**) in 16% yield (0.016g) with m.p. 104-106°C, (lit.[148] 103-105°C).

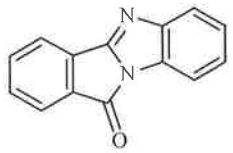
ν_{max} **KBr**: 1618 (C=N), 1553, 745, 703 and 688 cm^{-1}.

δH $CDCl_3$: 8.16-8.19 (m, 2H, aromatic); 7.68-7.70 (m, 1H, aromatic); 7.48-7.51 (m, 1H, aromatic); 7.43-7.44 (m, 3H, aromatic); 7.25-7.27 (m, 2H, aromatic) ppm.

δC $CDCl_3$: 163.4 (C=N), 151.2, 142.5, 131.9, 129.3, 128.0, 127.6, 125.5, 124.9, 120.4 (aromatic C), 111.0 (**C**(-O)=N) ppm.

An authentic sample of 2-phenylbenzooxazole (**520**) was prepared according the method described by Hein,[104] and was shown to be identical to the pyrolysis product.

10.6.2 Pyrolysis of *N*-(2-aminophenyl)phthalimide (510, X = NH)



521

N-(2-Aminophenyl)phthalimide (**510**, X = NH) (0.1g, 0.4mmol) was placed in a 50cm^3 beaker and heated to its melting point on an electric hotplate. The temperature was gradually raised until sublimation occurred at 250°C. The product was collected by covering the beaker with a clock glass filled with ice. After 15 minutes, the heating was stopped and the beaker was allowed to cool. A yellow crystalline substance was observed on the clock-glass and the contents of the beaker had blackened. TLC analysis (95: 5 light petroleum 40-60: ethyl acetate) of the yellow crystals and the blackened mixture showed the formation of a new faster moving spot, compared to N-(2-aminophenyl)phthalimide. The blackened mixture was dissolved in chloroform (20cm^3) and filtered. A small amount of silica was then added. The chloroform was then removed by rotary evaporation and the silica added to the top of a silica chromatography column. The products were isolated by column chromatography, using 95: 5 light petroleum 40-60: ethyl acetate as solvent. Using TLC (95: 5 light petroleum 40-60: ethyl acetate) as a comparison, the fractions containing the same spot as the yellow crystals were collected and the solvent removed to afford more yellow crystals. The combined yellow product was recrystallised from methanol to give yellow crystals of benzo[4,5]imidazo[2,1-a]isoindol-11-one (**521**) in 11% yield (0.011g), with m.p. 212-213°C (lit.[105] 214-215°C).

ν_{max} KBr: 1763 (C=O), 1740, 1619 (C=N), 1467, 1377, 873, and 713cm^{-1}.

δH $CDCl_3$: 7.75-7.78 (m, 2H, aromatic); 7.70-7.72 (m, 1H, aromatic); 7.60-7.62 (m, 1H, aromatic); 7.55-7.59 (m, 1H, aromatic); 7.43-7.47 (m, 1H, aromatic); 7.25-7.29 (m, 1H, aromatic) and 7.21-7.23 (m, 1H, aromatic) ppm.

δC $CDCl_3$: 161.35 (**C**=O); 157.06 (**C**=N); 149.53, 135.43, 135.16, 132.71, 132.04, 130.19, 126.86, 126.28, 125.49, 122.73, 121.67 and 113.11 (aromatic C) ppm.

C, H, N Analysis: Found: C, 76.26; H, 3.51; N, 12.59%. Calculated for $C_{14}H_8N_2O$: C, 76.35; H, 3.66; N, 12.72%

10.7 Photochemistry of phthalimide analogues

10.7.1 Irradiations of 3-dicyanomethylene-2,3-dihydroisoindol-1-one (530).

A typical irradiation of 3-dicyanomethylene-2,3-dihydroisoindol-1-one (**530**) in the presence of alkene/ NaOH is described below using a (**530**): NaOH ratio of 5:1. Other ratios used were 2:1, 1:1, 1:2, 1:5, 1:10 and 1:20. In order to obtain other ratios, the amount of NaOH added was varied as required. Cyclopentene, styrene and α-methylstyrene were also used as alkenes.

A solution of 3-dicyanomethylene-2,3-dihydroisoindol-1-one (1.17 g, 6mmol), NaOH (1.5cm3 of a 1M solution) and cyclohexene (0.779g, 8.6mmol) were dissolved in acetonitrile or methanol (140cm^3) and water (20 cm^3). The clear yellow solution was irradiated and followed by TLC. After six hours no evidence of reaction was visible on TLC and the reaction was stopped and the solution neutralized with dilute HCl. The solvent was removed and the residue was extracted with CH_2Cl_2. The organic layer was dried and the solvent was removed, the residue was column-chromatographed using methanol as mobile phase to afford a compound that had NMR and IR spectra identical to the starting material. The compound was also irradiated in acetone and THF without the addition of alkene or base, and in toluene with the addition of aniline or *N*,*N*-dimethyl aniline. In all cases, the spectral data of the recovered soild was identical to the starting material.

10.7.2 Irradiations of 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (543).

In a typical irradiation, 2-methyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**543**) (0.43g, 2mmol) was dissolved in methanol (400cm^3) to which cyclohexene (10mmol) was added. The clear yellow solution was irradiated, while being followed by TLC, for six-eight hours at which time TLC analysis indicated that no reaction had occurred. The solvent was removed and the residue was column chromatographed using dichloromethane to yield unchanged starting material as the sole product. NMR and IR analysis confirmed the presence of starting material. The reaction was also carried out using cyclopentene, styrene and α-methylstyrene as the alkene component with methanol as solvent, while (**543**) was also irradiated in acetonitrile in the presence of all four alkenes. The reaction was also carried out in

toluene, using aniline and *N*,*N*-dimethylaniline as electron donors. In all cases, the sole product obtained after column chromatography was the starting material.

In a similar manner, (**543**) (0.43g, 2mmol) was dissolved in ethanol (400cm^3), the solution was irradiated for six hours and the solvent was removed. After column chromatography, using dichloromethane, the starting material was recovered as the sole product. The reaction was repeated using *iso*-propyl alcohol and *tert*-butyl alcohol, as well as acetone and tetrahydrofuran and in all cases, the starting material was recovered as the sole product.

10.7.3 Irradiations of 2-ethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (544).

In a similar manner to the procedure described above, 2-ethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**544**) (0.45g, 2mmol) was dissolved in methanol (400cm^3), the solution was irradiated while being followed by TLC. After six hours, TLC analysis showed no product formation. The solvent was removed by rotary evaporation. After column chromatography, using dichloromethane, the starting material was recovered as the sole product. The reaction was repeated using *iso*-propyl alcohol, acetone and acetonitrile and in all cases, the starting material was recovered as the solitary product.

10.7.4 Irradiations of 2-alkyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (545-550).

In a similar manner to the procedure described in section 10.8.2, one of (**545-550**) (2mmol) was dissolved in methanol (400cm^3), the solution was irradiated for six to eight hours while being followed by TLC, which indicated that no reaction had occurred. The solvent was removed by rotary evaporation. After column chromatography, using dichloromethane, the starting material was recovered as the sole product. The reaction was repeated using acetone or acetonitrile and in all cases, the starting material was recovered as the only product. Compound (**548**) was also irradiated in toluene, for six hours, in the presence of either benzophenone, aniline or *N*,*N*-dimethylaniline, but only unreacted (**548**) was recovered.

10.7.5 Irradiations of 2-arylalkyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-ones (551-553, 563)

2-Benzyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**551**) (0.57g, 2mmol), 2-phenylethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**552**) (0.60g, 2mmol) or the 2-(4-methoxy)benzyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**553**) (0.63g, 2mmol) was dissolved in either methanol ($400cm^3$), acetone ($400cm^3$) or acetonitrile ($400cm^3$), and irradiated and the reaction followed by TLC. After eight hours, TLC analysis showed no product formation. After removal of solvent by rotary evaporation and subsequent column chromatography, using dichloromethane, the starting material was recovered as the sole product. In a similar manner, (**563**) (0.81g, 2mmol) was dissolved in methanol ($400cm^3$) or acetonitrile ($400cm^3$) and irradiated for six to eight hours. Starting material was recovered after column chromatography. The compound was also irradiated for six hours in methanol or acetonitrile in the presence of an excess of one of cyclohexene, cyclopentene, styrene or α-methylstyrene (10mmol). After column chromatography using dichloromethane, the starting material remained unchanged.

10.7.6 Irradiations of 2-methoxyethyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (554)

2-Methoxyethyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**554**) (0.51g, 2mmol) was dissolved methanol, acetone or acetonitrile ($400cm^3$) and irradiated for six hours. At this time, TLC analysis indicated no product formation and the reaction was stopped. After removal of solvent and subsequent column chromatography using dichloromethane, the starting material was recovered unchanged.

10.7.7 Irradiations of 2-chloroalkyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-ones (555-556)

2-(2-Chloroethyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**555**) (0.51g, 2mmol) was dissolved in either methanol, acetonitrile or toluene ($400cm^3$) and irradiated and the reaction followed by TLC. After six hours, TLC analysis indicated that no reaction had occurred. After removal of solvent and subsequent column chromatography using dichloromethane, the starting material was recovered unchanged. The compound was also irradiated in methanol or acetonitrile in the

presence of an excess of cyclohexene, cyclopentene or α-methylstyrene (10mmol), it was also irradiated in toluene in the presence of an excess of cyclohexene, aniline or *N*,*N*-dimethylaniline (10mmol). In all cases the starting material was recovered unchanged after column chromatography, using dichloromethane.

Similarly, 2-(3-chloropropyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**556**) (0.54g, 2mmol) was dissolved in either methanol or acetonitrile (400cm^3) and irradiated for six hours. TLC analysis at this time indicated that no reaction had taken place. It was also irradiated in acetonitrile in the presence of an excess of styrene (10mmol). The starting material was recovered unchanged after column chromatography using dichloromethane.

10.7.8 Irradiations of 2-alkenyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (557-559).

2-Phenylallyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**557**) (0.62g, 2mmol) was dissolved in methanol (400cm^3) and irradiated. After 8 hours, TLC analysis indicated that no reaction had occurred. The solvent was removed by rotary evaporation. The reaction was also carried out in acetone and acetonitrile with similar results. In a similar manner, 2-Allyl-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**558**) (0.47g, 2mmol) was also irradiated in methanol (400cm^3) and acetonitrile (400cm^3) and in both cases the starting material remained unchanged, even after prolonged irradiation. Similarly, 2-(3-Methylbut-2-enyl)-3-dicyanomethylene-2,3-dihydroisoindol-1-one (**559**) (0.53g, 2mmol) was also irradiated in methanol (400cm^3) and acetonitrile (400cm^3) giving only the starting material after column chromatography, using dichloromethane.

10.7.9 Irradiations of 2-propynyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (560)

2-Propynyl-(3-dicyanomethylene)-2,3-dihydroisoindol-1-one (**560**) (0.46g, 2mmol) was dissolved in either methanol or acetonitrile (400cm^3) and irradiated for six hours. When TLC analysis indicated that no reaction had occurred, the reaction was stopped. After removal of solvent and subsequent column chromatography using dichloromethane, the starting material was recovered unchanged.

Chapter 11: References

11.1 References

1 Vogel, *Textbook of Practical Organic Chemistry,* 5th ed., Longman Scientific and Technical, New York, p. 106-110, **1989**.

2 Kanaoka, Y. *Acc. Chem. Res.,* 11, 407-413, **1978**.

3 Mazzocchi, P.H., in *Organic Photochemistry*, ed. A. Padwa, Marcel Dekker, New York, vol. 5, p. 421, **1981**.

4 Yoon, U.C.; Mariano, P.S., *Acc. Chem. Res.*, 34, 7, 523-533, 2001.

5 McDermott, G.; Yoo, D. J.; Oelgemöller, M., *Heterocycles*, 65, 9, 2221-2257, **2005**.

6 Griesbeck, A.G.; Oelgemöller, M.; Lex, J., *J. Org. Chem.*, 65, 9028-9032, **2000**.

7 Suau, R.; Garcia-Segura, R.; Sanchez-Sanchez, C.; Perez-Inestrosa, E.; Pedraza, A.M., *Tetrahedron*, 59, 2913-2919, **2003**.

8 Neckers, D.C., *Mechanistic Organic Photochemistry*, Reinhold Publishing Company, New York, p. 8, **1967**.

9 Gilbert, A.G.; Baggott, J., *Essentials of Molecular Photochemistry*, Blackwell Scientific Publications, Oxford, p. 287-353, **1991.**

10 A.C. Pratt, *4th year notes*, DCU, **1998**.

11 Chasteen, T.G., Sam Houston State University, Huntsville, Texas. http://www.shsu.edu/~chemistry/chemiluminescence/JABLONSKI.html

12 Stone, P.G., Cohen, S. *J. Am. Chem. Soc.*, 104, 3435-3440, **1982**.

13 Vogel, *Textbook of Practical Organic Chemistry,* 5th ed., Longman Scientific and Technical, New York, p. 528, **1989**.

14 Wagner, P. *Acc. Chem. Res.*, 16, 461, **1983**.

15 Arnold, D. R; Hinman, R. G.; Glick, A. H., *Tetrahedron Lett.*, 1425-1430, **1965**.

16 Coyle, J. D., *Introduction to Organic Photochemistry*, John Wiley & Sons, **1986.**

17 a) Kanaoka, Y.; Koyama, K. *Tetrahedron Letters*, 12, 4517-4520, **1972**; b) Kanaoka, Y.; Migita, Y. *Tetrahedron Letters*, 13, 51-54, **1973**; c) Kanaoka, Y.; Migita, Y.; Koyama, K.; Sato, Y.; Nakai, H.; Mizoguchi, T. *Tetrahedron Letters*, 14, 1193-1196, **1973**; d) Sato, Y.; Nakai, H.; Mizoguchi, T.; Kawanishi, M.; Kanaoka, Y. *Chem. Pharm. Bull.*, 21. 1164-1166, **1973.**

18 For early reviews, see: a) Kanaoka, Y. *Kagaku no Ryoiki Zokan*, 123, 41-, **1979**; b) Kanaoka, Y. *J. Synth. Org. Chem. Jpn.*, 33, 949-959, **1975**.

19 a) Oelgemöller, M.; Griesbeck, A. G. 'CRC Handbook of Organic Photochemistry and Photobiology,' 2nd ed., ed. by Horspool, W. M.; Lenci, F. CRC Press, Boca Raton, Fl, Chapter 84, 1-19, **2004**; b) Oelgemöller, M.; Griesbeck, A. G. *J. Photochem. Photobiol. C: Photochem. Rev.*, 3, 109-127, **2002**; c) Griesbeck, A. G.; Mauder, H. 'CRC Handbook of Organic Photochemistry and Photobiology,' ed. by Horspool, W. M.; Song, P.-S. CRC Press, Boca Raton, Fl, 513-521, **1995**; d). Coyle, J. D 'Synthetic Organic Photochemistry', ed. by Horspool, W. M. Plenum Press, New York, 259-284, **1984**.

20 a) Sato, Y.; Nakai, H.; Ogiwara, H.; Mizoguchi, T; Migita, Y; Kanaoka, Y. *Tetrahedron Letters*, 4565-4568, **1973**; b) Sato, Y.; Nakai, H.; Mizoguchi, T.; Kawanishi, M.; Hatanaka, Y.; Kanaoka, Y. *Chem. Pharm. Bull.*, 30, 1263-1270, **1982.**

[21] Maruyama, K.; Kubo, Y, *J. Org. Chem.*, 46, 3612-3622, **1981.**

[22] a) Mazzocchi, P.H.; Minamikawa, S.; Bowen, M.J. *J. Org. Chem.*, 43, 15, 3079-3080, **1978**; b) Mazzocchi, P.H.; Bowen, M.; Narian, N. *J. Am. Chem. Soc.*, 99, 7063-7064, **1977**; c) Mazzocchi, P.H.; Minamikawa, S.; Wilson, P.; Bowen, M.; Narian, N. *J. Org. Chem.*, 46, 4846-4851, **1981.**

[23] a) Wintgens, V.; Valat, P.; Kossanyi, J.; Biczok, L.; Demeter, A.; T. Bérces, T. *J. Chem. Soc., Faraday Trans.*, 90, 411-421, **1994**; b) Griesbeck, A. G.; Görner, H. *J. Photochem. Photobiol. A: Chem.*, 129, 111, **1999**; c) Hayashi, H.; Nagakura, S.; Kubo, Y.; Maruyama, K. *Chem. Phys. Lett.*, 72, 291-294, **1980**; d) Coyle, J. D.; Harriman, A.; Newport, G. L. *J. Chem. Soc., Perkin Trans. 2*, 799, **1979**; e) Filho, P. B.; Toscano, V. G.; Politi, M. J. *J. Photochem. Photobiol. A: Chem.*, 43, 51-58, **1988**; *J. Photochem. Photobiol. A: Chem.*, 45, 265, **1988.**

[24] a) Leedy D. W.; Muck D. L. *J. Am. Chem. Soc.*, 93, 4264-4270, **1971**; b) Farnia, G.; Romanin, A.; Capobianco, G.; Torzo, F. *J. Electroanal. Chem.*, 33, 31-, **1971**; c) Capobianco, G.; Farnia, G.; Torzo, F. *Ric. Sci.*, 38, 842-, **1968.**

[25] a) Oelgemöller, M.; Griesbeck, A. G.; Lex, J.; Haeuseler, A.; Schmittel, M.; Niki, M.; Hesek, D.; Inoue, Y. *Org. Lett.*, 3, 1593-1596, **2001**; b) Oelgemöller, M.; Haeuseler, A.; Schmittel, M.; Griesbeck, A. G.; Lex, J.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2*, 676-686, **2002.**

[26] a) Rehm D.; Weller, A. *Isr. J. Chem.*, 8, 259-271, **1970**; b) Rehm D.; Weller, A. *Ber. Bunsenges. Phys. Chem.*, 73, 834-, **1969.**

[27] Kanaoka, Y.; Sakai, K.; Murata, R.; Hatanaka, Y. *Heterocycles*, 3, 719-722, **1975.**

[28] Sánchez-Sánchez, C.; Pérez-Inestrosa, E.; García-Segura, R.; Suau, R. *Tetrahedron*, 58, 7267-7274, **2002.**

[29] Freccero, M.; Fasani, E.; Albini, A. *J. Org. Chem.*, 58, 1740-1745, **1993.**

[30] a) Somich, C.; Mazzocchi, P. H.; Edwards, M.; Morgan, T.; Ammon, H. L. *J. Org. Chem.*, 55, 2624-2630, **1990**; b) Mazzocchi, P. H.; Somich, C.; Edwards, M.; Morgan, T.; Ammon, H. L. *J. Am. Chem. Soc.*, 108, 6828-6829, **1986**; c) Weidner-Wells, M. A.; Oda, K.; Mazzocchi, P. H. *Tetrahedron*, 53, 3475-3486, **1997**; d) Mazzocchi, P. H.; Minamikawa, S.; Wilson, P. *J. Org. Chem.*, 50, 2681-2684, **1985**; e) Mazzocchi P. H.; Klinger, L. *J. Am. Chem. Soc.*, 106, 7567-7572, **1984.**

[31] a) Maruyama K.; Kubo,Y. *J. Org. Chem.*, 50, 1426-1435, **1985**; b) Maruyama, K.; Kubo, Y. *Chem. Lett.*, 851-845, **1978.** c) Maruyama, K.; Kubo, Y. *Chem. Lett.*, 769-772, **1978.**

[32] a) Mazzocchi, P.H.; Minamikawa, S.; Wilson, P. *J. Org. Chem.*, 44, 1186-1188, **1979**; b) Mazzocchi, P.H.; Khachik, F. *Tetrahedron Letters*, 22, 4189-4192, **1981**; c) Mazzocchi, P.H.; Khachik, F.; Wilson, P. *J. Am. Chem. Soc.*, 103, 6498-6499, **1981**; d) Mazzocchi, P.H.; Wilson, P.; Khachik, F.; Klinger L.; Minamikawa, S. *J. Org. Chem.*, 48, 2981-2989, **1983**; e) Mazzocchi, P.H.; Minamikawa, S.; Bowen, M. *Heterocycles*, 9, 1713-1716, **1978.**

[33] Zimmerman, H.E.; Sandel, U.R. *J. Am. Chem. Soc.*, 85, 915-922, **1963.**

[34] a) Suau Suarez, R.; García-Segura, R. *Tetrahedron Letters*, 29, 1071-1074, **1988**; b) Suau, R.; Sánchez-Sánchez, C.; García-Segura, R.; Pérez-Inestrosa, E. *Eur. J. Org. Chem.*, 1903-1911, **2002.**

[35] Kanaoka Y.; Hatanaka, Y. *Chem. Pharm. Bull.*, 22, 2205-2206, **1974**.

[36] a) Mazzocchi, P.H.; Khachik, F. *Tetrahedron Letters*, 24, 1879-1882, **1983**; b) Mazzocchi, P.H.; Minamikawa, S.; Wilson, P. *Tetrahedron Letters*, 45, 4361-4364, **1978**; c) Mazzocchi, P. H.; Shook, D.; Liu, L. *Heterocycles*, 26, 1165-1167, **1987.**

[37] a) Yoon, U. C.; Kim, D. U.; Kim, J. C.; Lee, J. G.; Mariano, P. S.; Lee, Y. J.; Ammon, H. L. *Tetrahedron Letters*, 34, 5859-5862, **1993**; b) Yoon, U. C.; Kim, D. U.; Lee, C. W.; Choi, Y. S.; Lee, Y. J.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.*, 117, 2698-2710, **1995**.

[38] a) Maruyama, K.; Kubo, Y.; Machida, M.; Oda, K.; Kanaoka, Y.; Fukuyama, K. *J. Org. Chem.*, 43, 2303-2304, **1978**; b) Maruyama, K.; Kubo, Y.; Ogawa, T., *Kokagahu Tovoukai Koen Yoshishu*, 268-269, **1979**; c) Machida, M.; Oda, K.; Maruyama, K.; Kubo, Y.; Kanaoka, Y., *Heterocycles*, 14, 779-782, **1980**; d) Maruyama, K.; Kubo, Y., *J. Am. Chem. Soc.*, 100, 7772-7773, **1978**.

[39] a) Machida, M.; Oda, K.; Kanaoka, Y., *Chem. Pharm. Bull.*, 32, 75-84, **1984**; b) Machida, M.; Oda, K.; Kanaoka, Y., *Tetrahedron*, 41, 4995-5001, **1985**.

[40] Xue, J.; Zhu, L.; Fun, H.-K.; Xu, J.-H.. *Tetrahedron Lett.*, 41, 8553-8557, **2000**.

[41] Mazzocchi, P. H.; Klingler, L.; Edwards, M.; Wilson, P.; Shook, D. *Tetrahedron Letters,* 24, 143-146, **1983**.

[42] a) Takechi, H.; Machida M.; Kanaoka, Y. *Chem. Pharm. Bull.*, 36, 3770-3779, **1988**; b) Takechi, H.; Machida, M.; Kanaoka, Y. *Heterocycles*, 23, 1373-1376, **1985**; c) Machida, M.; Takechi, H.; Kanaoka, Y. *Tetrahedron Letters*, 23, 4981-4982, **1982**.

[43] Kubo Y.; Umehara, T. *Bull. Chem. Soc. Jpn.*, 66, 282-286, **1993**.

[44] Fu, H. P.; Zhang, M.; Shi, H. G.; Xu, J. H., *Res. Chem. Intermed.*, 30, 383-395, **2004**.

[45] Schwack, W., *Tetrahedron Letters*, 28, 1869-1872, **1987**.

[46] Suau, R.; García-Segura, R.; Sosa Olaya, F., *Tetrahedron Letters*, 30, 3225-3228, **1989**.

[47] Kubo, Y.; Taniguchi, E.; Araki, T., *Heterocycles*, 29, 1857-1860, **1989**.

[48] a) McSweeney, N.; Pratt, A. C.; Long, C.; Howie, R. A., *Acta Cryst.*, E61, o547-o549, **2005**; b) McSweeney, N.; Pratt, A. C.; Long, C.; Howie, R. A., *Acta Cryst.*, E61, o1904-o1906, **2005**; c) Grimley, F. M.; O'Donnell, C.; Pratt, A. C.; Long, C.; Howie, R. A.; *Acta Cryst.*, C61, o369-o372, **2005**.

[49] a) Suau, R.; García-Segura, R.; Sánchez, C.; Pedraza, A. M., *Tetrahedron Letters*, 40, 2007-2010, **1999**.

[50] Roth, H. J.; Hundeshagen, G., *Arch. Pharm.*, 309, 58-, **1976**.

[51] Kanaoka, Y.; Sato, E., *Chem. Pharm. Bull.*, 26, 989-992, **1978**.

[52] a) Kanaoka, Y.; Hatanaka, Y.; Deusler, E. N.; Karle, I. L.; Witkop, B., *Tetrahedron*, 41, 5370-5370, **1985**; b) Kanaoka Y.; Hatanaka, Y., *Heterocycles*, 21, 693, **1984**; c) Kanaoka, Y.; Hatanaka, Y.; Deusler, E. N.; Karle, I. L.; Witkop, B., *Chem. Pharm. Bull.*, 30, 3028-3031, **1982**.

[53] Roth, H. J.; Schwarz, D. *Arch. Pharm.*, 309, 52-, **1976**.

[54] Tanabe, M.; Dehn, R. L.; Bramhall, R. R.; *J. Arg. Food Chem.*, 22, 54-, **1974**.

[55] a) Yoon, U. C.; Mariano, P. S., 'CRC Handbook of Organic Photochemistry and Photo-biology,' 2nd ed., ed. by Horspool, W. M.; Lenci, F., CRC Press, Boca Raton, Fl, Chapter 85, pp. 1-15, **2004**; b) Yoon, U. C.; Mariano, P. S., *J. Photosci.*, 10, 89-96, **2003**; c) Yoon, U. C.; Kim, H. J.; Mariano, P. S. *Heterocycles*, 29, 1041-1064, **1989**; d) Lee, Y. J.; Ling, R.; Mariano, P. S.; Yoon, U. C.; Kim, D. U.; Oh, S. W., *J. Org. Chem.*, 61, 3304-3314, **1996.**

[56] a) Gutenberger, G.; Meggers, E.; Steckhan, E., 'Novel Trends in Electroorganic Synthesis', ed. by Torii, S., Springer, Tokyo, pp. 367-369, **1998**; b) Yoshida, J., *Top. Curr. Chem.*, 170, 39-, **1994**.

[57] a) Lee, Y. J.; Lee, C. P.; Jeon, Y. T.; Mariano, P. S.; Yoon, U. C.; Kim, D. U.; Kim, J. C.; Lee, J. G. *Tetrahedron Letters*, 34, 5855-5858, **1993**.

[58] Cohen, S. G.; Parola, A.; Parsons, G. H., *Chem. Rev.*, 73, 141, **1973**.

[59] a) Hatanaka, Y.; Sato, Y.; Nakai, H.; Wada, M.; Mizuguchi, T.; Kanaoka, Y., *Liebigs Ann. Chem.*, 1113-, **1992**; b) Sato, Y.; Wada, M.; Nakai, H.; Hatanaka, Y.; Kanaoka, Y. *Heterocycles*, 20, 173, **1983**.

[60] a) Bartoschek, A.; Griesbeck, A. G.; Oelgemöller, M., *J. Inf. Recording*, 119-, **2000**; b) Griesbeck, A. G.; Kramer, W.; Oelgemöller, M., *Synlett*, 1169-1178, **1999**; c) Griesbeck, A. G.; Henz, A.; Kramer, W.; Lex, J.; Nerowski, F.; Oelgemöller, M.; Peters, K.; Peters, E.-M., *Helv. Chim. Acta*, 80, 912-, **1997**.

[61] a) Griesbeck, A. G.; Oelgemöller, M.; *Synlett*, 492-494, **1999**; b) Oelgemöller, M.; Cygon, P.; Lex, J.; Griesbeck, A. G., *Heterocycles*, 59, 669-684, **2003**; c) Yoo, D. J.; Kim, E. Y.; Oelgemöller, M.; Shim, S. C., *Photochem. Photobiol. Sci.*, 3, 311-316, **2004**.

[62] a) Griesbeck, A. G.; Kramer, W.; Oelgemöller, M.; *Green Chem.*, 1, 205-208, **1999**; b) Griesbeck, A. G.; Maptue, N.; Bondock, S.; Oelgemöller, M., *Photochem. Photobiol. Sci.*, 2, 450-451, **2003**.

[63] a) Farcas, S.; Namy, J.-L.; *Tetrahedron Letters*, 42, 879-881, **2001**; b) Ang, W. S.; Halton, B. *Aust. J. Chem.*, 24, 851-, **1971**; c) Heidenbluth, K.; Tönjes, H.; Scheffler, R.; *J. Prakt. Chem.*, 30, 204-, **1965**; d) Wittig, G.; Streib, H., *Liebigs Ann. Chem.*, 584-, 1, **1953**; e) Flynn, G. A., *J. Chem. Soc., Chem. Comm.*, 862-, **1980**.

[64] Eberson, L., 'Electron Transfer Reactions in Organic Chemistry (Reactivity and Structure-Concepts in Organic Chemistry)', ed. by Hafner, K., Springer-Verlag, Berlin, Vol. 25, **1987**.

[65] a) Görner, H.; Griesbeck, A. G.; Heinrich, T.; Kramer, W.; Oelgemöller, M.; *Chem. Eur. J.*, 7, 1530-1538, **2001**; b) Görner, H.; Oelgemöller, M.; Griesbeck, A. G., *J. Phys. Chem. A*, 106, 1458-1464, **2002**.

[66] Yokoi, H.; Nakano, T.; Fujita, W.; Ishiguro, K.; Sawaki, Y., *J. Am. Chem. Soc.*, 120, 12453-12458, **1998**.

[67] a) Kubo, Y.; Imaoka, T.; Egusa, C.; Araki, T., *Chem. Express*, 4, 527-, **1989**; b) Kubo, Y.; Egusa, C.; Araki, T., *Chem. Lett.*, 1213-, **1985**.

[68] a) Griesbeck, A. G.; Mauder, H.; Müller, I., *Chem. Ber.*, 125, 2467-, **1992**; b) Griesbeck, A. G.; Mauder, H., *Angew. Chem. Int. Ed. Engl.*, 31, 73-, **1992**.

[69] The *d.e.* values were, however, incorrectly reported in the original article.[61a]

[70] Griesbeck, A. G.; Gudipati, M. S.; Hirt, J.; Lex, J.; Oelgemöller, M.; Schmickler, H.; Schouren, F., *J. Org. Chem.*, 65, 7151-7157, **2000**.

[71] Griesbeck, A. G.; Warzecha, K.-D.; Neudörfl, J. M.; Görner, H., *Synlett*, 2347-2350, **2004**.

[72] Castedo, L.; Guitián, E.; Saá, J. M.; Suau, R., *Heterocycles*, 19, 279-, **1982**.

[73] Pienta, N. J., 'Photoinduced Electron Transfer', ed. by Fox, M. A.; Chanon, M., Elservier, Amsterdam, 421-486, **1988**.

[74] a) Griesbeck A. G.; Oelgemöller, M., *Synlett*, 71-72, **2000**; b) Kim, A. R.; Lee, K.-S.; Lee, C.-W.; Jin Yoo, D.; Hatoum, F.; Oelgemöller, M., *Tetrahedron Letters*, 46, 3395-3398, **2005**; c) Griesbeck, A. G.; Oelgemöller, M.; Lex, J.; Haeuseler, A.; Schmittel, M., *Eur. J. Org. Chem.*, 1831-1843, **2001**.

[75] Fox, M. A., *Adv. Photochem.*, 13, 237-, **1986**.

[76] Griesbeck, A. G.; Oelgemöller, M.; Lex, J., *Synlett*, 1455-1457, **2000**.

[77] a) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I., *Chem. Rev.*, 99, 1991-, **1999**; b) Caronna, T.; Minisci, F., *Rev. React. Species Chem.*, 1, 263-, **1976**.

[78] Sato, Y.; Nakai, H.; Wada, M.; Mizoguchi, T.; Hatanaka, Y.; Migita, Y.; Kanaoka, Y., *Liebigs Ann. Chem.*, 1099-1118, **1985**.

[79] Russell, G. A.; Chen, P.; Kim, B. H.; Rajaratnam, R., *J. Am. Chem. Soc.*, 119, 8795-8801, **1997**.

[80] Maquieira, M. B.; Peñéñory, A. B.; Rossi, R. A., *J. Org. Chem.*, 67, 1012-1015, **2002**.

[81] Cadogan, J. I. G.; Rowley, A. G.; *J. Chem. Soc., Perkin Trans. 1*, 1069-, **1975**.

[82] McSweeney, N.; Pratt, A. C.; Creaven, B. S.; Long, C.; Howie, R. A., *Acta Cryst.*, E60, o2025-o2028, **2004**.

[83] Maruyama, K.; Ogawa, T.; Kubo, Y.; Araki, T., *J. Chem. Soc. Perkin Trans I.*, 2025-, **1985**.

[84] a) Mazzocchi, P. H.; DeCamp Schuda, A., *Heterocycles*, 23, 1603-1606, **1985**; b) Weidner-Wells, M. A.; DeCamp, A.; Mazzocchi, P. H., *J. Org. Chem.*, 54, 5746-5758, **1989**.

[85] Yoon, U. C.; Oh, S. W.; Lee, S. M.; Cho, S. J.; Gamlin, J.; Mariano, P. S., *J. Org. Chem.*, 64, 4411-4418, **1999.**

[86] a) Paleo, M. R.; Domínguez, D.; Castedo, L., *Tetrahedron Letters*, 34, 2369-2370, **1993**; b) Paleo, M. R.; Domínguez, D.; Castedo, L., *Tetrahedron*, 50, 3627-3638, **1994**.

[87] a) Kanaoka, Y.; Nagasawa, C.; Nakai, H.; Sato, Y.; Ogiwara, H.; Mizoguchi, T., *Heterocycles*, 3, 553-556, **1975**; b) Terashima, M.; Koyama, K.; Kanaoka, Y., *Chem. Pharm. Bull.*, 26, 630-632, **1978**; c) Terashima, M.; Seki, K.; Koyama, K.; Kanaoka, Y., *Chem. Pharm. Bull.*, 25, 1591-1595, **1977**; d) Kanaoka, Y.; Migita, Y., *Tetrahedron Letters*, 3693-3696, **1974**; e) Machida, M.; Nakamura, M.; Oda, K.; Takechi, H.; Ohno, K.; Nakai, H.; Sato, Y.; Kanaoka, Y., *Heterocycles*, 26, 2683-2690, **1987**.

[88] a) Nakai, H.; Sato, Y.; Ogiwara, H.; Mizoguchi, T.; Kanaoka, Y., *Heterocycles*, 2, 621-624, **1974**; b) Sato, Y.; Nakai, H.; Wada, M.; Ogiwara, H.; Mizoguchi, T.; Migita, Y.; Hatanaka, Y.; Kanaoka, Y., *Chem. Pharm. Bull.* 30, 1639-1645, **1982**.

[89] a) Yoon, U. C.; Cho, S. J.; Oh, J. H.; Lee, J. G.; Kang, K. T.; Mariano, P. S., *Bull. Korean. Chem. Soc.*, 12, 241-354, **1991**; b) Yoon, U. C.; Oh, J. H.; Lee, S. J.; Kim, D. U.; Lee, J. G.; Kang, K.

T.; Mariano, P. S., *Bull. Korean. Chem. Soc.*, 166-172, **1992**; c) Yoon, U. C.; Oh, S. W.; Lee, C. W., *Heterocycles*, 41, 2665-2682, **1995**.

90 a) Machida, M.; Takechi, H.; Kanaoka, Y., *Heterocycles*, 7, 273-276, **1977**; b) Machida, M.; Takechi, H.; Kanaoka, Y., *Heterocycles*, 14, 1255-1258, **1980**; c) Machida, M.; Takechi, H.; Kanaoka, Y., *Chem. Pharm. Bull.*, 30, 1579-1589, **1982**; d) Machida, M.; Takechi, H.; Shishido, Y.; Kanaoka, Y., *Synthesis*, 1078-1080, **1982**; e) Takechi, H.; Machida, M.; Kanaoka, Y., *Liebigs Ann. Chem.*, 859-868, **1986**.

91 a) Coyle, J. D.; Newport, G. L., *Tetrahedron Letters*, 11, 899-902, **1977**; b) Coyle, J. D.; Newport, G. L., *J. Chem. Soc. Perkin I*, 93-96, **1980**; c) Coyle, J. D.; Smart, L. E.; Challiner, J. F.; Haws, E. J., *J. Chem. Soc. Perkin Trans I*, 121-129, **1985**.

92 Su, Z.; Mariano, P. S.; Falvey, D. E.; Yoon, U. C.; Oh, S. W., *J. Am. Chem. Soc.*, 120, 10676-10686, **1998**.

93 a) Sato, Y.; Nakia, H.; Mizoguchi, T.; Kanaoka, Y., *Tetrahedron Letters*, 1889-1890, **1976**; b) Wada, M.; Nakai, H.; Sato, Y.; Kanaoka, Y., *Tetrahedron Letters*, 23, 3077-3080, **1982**; c) Wada, M.; Nakai, H.; Aoe, K.; Kotera, K.; Sato, Y.; Hatanaka, Y.; Kanaoka, Y., *Tetrahedron*, 39, 1273-1279, **1983**; d) Sato, Y.; Nakai, H.; Wada, M.; Mizoguchi, T.; Hatanaka, Y.; Kanaoka, Y., *Chem. Pharm. Bull.*, 40, 3174-3180, **1992**.

94 Wagner, P.J., *Acc. Chem. Res.*, 4, 168-177, **1971**.

95 Mazzocchi, P. H.; King, C. R.; Ammon, H. L., *Tetrahedron Letters*, 28, 2473-2476, **1987**.

96 Yoon, U. C.; Oh, S. W.; Lee, J. H.; Park, J. H.; Kang, K. T.; Mariano, P. S., *J. Org. Chem.*, 66, 939-943, **2001**.

97 a) Takechi, H.; Machida, M.; Kanaoka, Y., *Chem. Pharm. Bull.*, 36, 2853-2863, **1988**; b) Takechi, H.; Machida, M.; Nishizono, N.; Kanaoka, Y., *Chem. Pharm. Bull.*, 42, 188-196, **1994**.

98 a) Griesbeck, A. G.; Mauder, H.; Müller, I.; Peters, E.-M.; Peters; K.; von Schnering, H. G., *Tetrahedron Letters*, 34, 453-456, **1993**; b) Griesbeck, A. G.; Nerowski, F.; Lex, J., *J. Org. Chem.*, 64, 5213-5217, **1999**; c) Griesbeck, A. G.; Henz, A.; Peters, K.; E.-M.; Peters; von Schnering, H. G., *Angew. Chem. Int. Ed. Engl.*, 34, 474-476, **1994**.

99 McCormac, P. B.; Pratt, A. C.; Long, C.; Howie, R. A.; *Acta Crystallogaphica.* E61, o2047-o2049, **2005**.

100 Assoumatine, T.; Datta, P. K.; Hooper, T. S.; Yvon, B. L.; Charlton, J. L., *J. Org. Chem.*, 69, 4140-4144, **2004**.

101 Wanag, Veinbergs, *Chem. Berichte*, 75, 1558-1567, **1942**.

102 Borah, H.N.; Boruah, R.C.; Sandhu, J.S. *J. Chem. Research (S)*, 5, 272 – 273, **1998**.

103 Perry, C.J.; *J. Chem. Soc., Perkin Trans. 2*, 5, 977-982, **1997**.

104 Hein, D.W.; Alheim, R.J.; Leavitt, J.J., *J. Am. Chem. Soc.* 79, 427-429, **1957**.

105 Young, P.R., *J. Heterocyclic Chemistry*, 9, 371-378, **1972.**

106 a) Conway, S.; Ph.D. Thesis, D.C.U., **1996**; b) Delaney, J.; Ph. D. Thesis, D. C. U., **1997**; c) Crean, C.; Ph.D. Thesis, D.C.U., **2002**.

107 Gonzalo Rodríguez, J.; Martín-Villamil, R.; Lafuente, A., *Tetrahedron,* 59, 7, 1021-1032, **2003**.

[108] a) Crean, C.; Gallagher, J. F.; Pratt, A.C., *Acta Crystallogaphica*, C58, o36-o38, **2002**; b) Conway, S. P.; Pratt, A. C.; Long, C.; Howie, R. A., *Acta Crystallogaphica*, E61, o2258-o2260, **2005**.

[109] Jenner, G., *Tetrahedron Letters,* 42, 2, 243-245, **2001**.

[110] a) Mitsunobu, O.; *Bull. Chem. Soc. Jpn.,* 40, 935, **1967**; b) Mitsunobu, O., Yamada, M., *ibid.,* 40, 2380, **1967**; c) Mitsunobu, O., Eguchi, M., *ibid.,* 44, 3427, **1971**; d) Mitsunobu, O., *Synthesis,* 1-28, **1981**.

[111] Growchowski, E.; Hilton, B.D.; Kupper, R.J.; Michejda, C.J., *J. Am. Chem. Soc.,* 104, 6876-6877, **1982**.

[112] a) Guthrie, R.D.; Jenkins, I.D., *Aust. J. Chem.*, 35, 767-774, **1982**. b)Von Itzstein, M.; Jenkins, I.D., *Aust. J. Chem.,* 36, 557-563, **1983**.

[113] Varasi, M.; Walker, K.A.M.; Maddox, M.L., *J. Org. Chem.,* 52, 4235-4238, **1987**.

[114] Morrison, D.C., *J. Org. Chem.*, 1072-1074, 23, **1958.**

[115] Brunn, E.; Huisgen, R., *Angew. Chem., Int. Ed. Eng.*, 8, 513-515, **1969**.

[116] a) Camp, D.; Hanson, G.R.; Jenkins, I.D., *J. Org. Chem.*, 60, 2977-2980, **1995**. b) Camp, D.; Jenkins, I.D., *J. Org. Chem.,* 54, 3045-3049, **1989**.

[117] Crich, D.; Dyker, H.; Harris, R.J., *J. Org. Chem.*, 54, 257-259, **1989**.

[118] March, J., *Advanced Organic Chemistry,* 2nd ed., 232.

[119] Hughes, D.L.; Reamer, R.A.; Bergan, J.J.; Grabowski, E., *J. Am. Chem. Soc.,* 110, 6487-6491, **1988**.

[120] a) Tsunoda, T.; Yamamiya, Y.; Ito, S., *Tetrahedron Letters,* 34, 1639-1642, **1993**; b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S., *Chem. Lett.*, 539, **1994**; c) Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Ito, S., *Tetrahedron Letters,* 36, 2531-2534, **1995**; d) Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Ito, S., *Tetrahedron Letters,* 36, 14, 2529-2530, **1995**.

[121] Mitsunobu, O.; Wada, M.; Sano, T., *J. Am. Chem. Soc.,* 94, 679-680, **1971**.

[122] a) Vig, O.P.; Trehan, I.R.; Kad, G.L.; Ghose, J., *Indian J. Chem.,* 22B, 515, **1983**; b) Vig, O.P.; Trehan, I.R.; Kad, G.L.; Kumari, S.; Bedi, A.L., *Indian J. Chem.,* 62, 238, **1985**.

[123] Walker, M.A., *J. Org. Chem.* 60, 5352-5355, **1995**.

[124] Hughes, D.L., *Organic Reactions*, 42, 335, **1992**.

[125] Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.*, 67, 1751-1753, **2002**.

[126] Hendrickson, J.B.; Singer, M.; Hussoin, Md. S. *J. Org. Chem.*, 58, 6913-6914, **1993**.

[127] Elson, K.E.; Jenkins, I.D.; Loughlin, W.A., *Org. Biomol. Chem.*, 1, 2985-2965, **2003**.

[128] Burns, D.H.; Chan, H-.K.; Miller, J.D.; Jayne, C.L; Eichorn, D.M., *J. Org. Chem.*, 65, 5185-5196, **2000**.

[129] Barrett, P.A.; Linstead, R.P.; Leavitt, J.J.; Rowe, G.A., *J. Chem. Soc.*, 1076-1079, **1940**.

[130] a) Ruan, Y.-P.; Chen, M.-D.; He, M.-Z; Zhou, X.; Huang, P.-Q., *Synthetic Communications*, 34, 853-862, **2004**; b) Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q., *Tetrahedron*, 60, 1651-1657, **2004**; c) Chihab-Eddine, A.; Daich, A.; Jilale, A.; Decroix, B., *Heterocycles*, 58,

449-456, **2002**; d) Pigeon, P.; Othman, M.; Decroix, B., *J. Heterocyclic Chem.*, 1, 35-40, **2001**; e) Denieu, E.; Enders, D., *Tetrahedron Letters*, 41, 2347-2350, **2000**.

[131] Yoon, U.C.; Kwon, H.C.; Hyung, T.G.; Choi, K. H.; Oh, S.W.; Yang, S.; Zhao, Z.; Mariano, P.S., *J. Am. Chem. Soc.*, 126, 1110-1124, **2004.**

[132] a) Takahashi, H., *J. Pharm. Soc. Jpn.*, 122, 755-771, **2002**; b) Takahashi, H.; Iwai, Y.; Hitomi, Y.; Ikegami, S., *Org. Lett.*, 4, 2401-2403, **2002**; c) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S., *J. Am. Chem. Soc.*, 122, 2995-3000, **2000**.

[133] GaussView, Version 3.09, Dennington II, Roy; Keith, Todd; Millam, John; Eppinnett, Ken; Hovell, W. Lee; and Gilliland, Ray; Semichem, Inc., Shawnee Mission, KS, 2003.

[134] Bringmann, G.; Price Mortimer, A.J.; Keller, P.A.; Gresser, M.J.; Garner, J.; Breuning, M., *Angew. Chemie Int. Ed.*, 44, 5384-5427, **2005.**

[135] Christie, G.H.; Kenner, J., *J. Chem. Soc., Trans.*, 121, 614-620, **1922.**

[136] Claydon, J., *Tetrahedron*, 60, 4335, **2004.**

[137] Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

[138] "*Principles and Applications if Electrochemistry*"; 4th Ed., Crow, D.R.; Blackie Academic and professional, **1994.**

[139] "*Electrode Dynamics*"; Fisher, A.C.; Oxford Chemistry Primers, Oxford University Press, **1996.**

[140] Lehmann, M.W.; Evans, D.H., *J. Phys. Chem. B.*, 102, 9928, **1998.**

[141] Moiroux, J.; Elving, P.J., *Anal. Chem.*, 50, 1056, **1978.**

[142] Suchanski, M.R.; Van Duyne, R.P. *J. Am. Chem. Soc.*, 98, 250-252, **1976.**

[143] Carloni, P.; Greci, L.; Stipa, P.; Dopp, D.; El-Din, A.; Hafeez Hassan, A.; Alberti, A., *Tetrahedron Letters,* 51, 27, 7451-7458, **1995.**

[144] Colson, J. G.; Michel, R. H.; Paufler, R. M., *J. Polym. Sci., Polym. Chem. Ed.*, 4, 59, **1966**.

[145] Fahmy, A.F.M.; Aly, N.F.; Mohammed, M.M.; Arief, M.M.H., *Indian J. Chem. Sect B.*, 25, 308-311, **1986.**

[146] a) Valter, R.E.; Batse, A.E.; Valter, S.P., *Chem. Heterocycl. Compd. (Engl. Transl.)*, 18, 70-74, **1982**; b) Valter, R.E.; Batse, A.E.; Valter, S.P., *Khim. Geterotsikl. Soedin.*, 18, 83-87, **1982.**

[147] a) Rupe, H.; Thiess, K. G. Chem. Ber., 42, 4290, **1909**; b) Arcoria; Bottino, *Ann. Chim. (Rome)*, 51, 426-433, **1961**; c) Cul, A.; Daïch, A.; Decroix, B.; Sanz, G.; Van Hijfte, L., *Tetrahedron*, 60, 11029-11039, **2004.**

[148] Prager, R.H.; Smith, J.A.; Weber, B.; Williams, C.M., *J. Chem. Soc. Perkin Trans. 1*, 17, 266-2672, **1997.**