# The Synthesis and Reactions of Imidazo-1,2,3-Triazoles Obtained by the Cycloaddition of 1,2,3-Triazolium-N-Imides and Nitrogen-Containing Dipolarophiles

Mairéad Sheridan, B.Sc.

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Supervisor Dr Paraic James
School of Chemical Sciences
Dublin City University

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**Declaration**

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 Mairead Sheridan Date 7 10 02

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## Abstract

In work previously carried out by this group, 3a, 6a-diaryl hexahydropryrrolotriazoles underwent photoinduced disrotatory ring expansion to the new 2,5,6,7-tetrahydro-1,2,3,5 tetrazocines The aim the current work was to introduce a fifth nitrogen atom to this system to form the previously unknown pentazocines

To achieve the addition of a fifth nitrogen atom to the ring system, the 1,3-dipolar cycloadditions of triazolium-1-imides with nitrogen-containing dipolarophiles were investigated Previously the only nitrogen containing dipolarophiles that had been successfully used in addition to triazohum-1-imides were isocyanates and isothiocyanates The reaction of triazohum-1-imides with isocyanates and isothiocyanates was extended, giving a range of imidazo-1,2,3-triazoles with an unsaturated C-5 position

A new range of imidazo-1,2,3-triazoles was synthesised by the cycloaddition of triazolium-1-imides with N-sulfonyl imines, giving for the first time imidazo-1,2,3-triazoles with a saturated C-5 position Subsequent detosylation and decarboxylation gave an N-4-C-5 double bond Reduction of this double bond returned C-5 to the saturated state Novel oxazolo-1,2,3-triazoles were identified as side products of the cycloaddition reaction

The photochemical rearrangements of these cycloadducts were found to depend on the degree of saturation at C-5 and also on the substituent group at the C-5 position The first step in the photochemical reactions of all the imidazo-1,2,3-triazoles is likely to be disrotatory ring-opemng to give the pentazocines as intermediates However these ring systems appear to be unstable and undergo subsequent reactions Irradiation of the saturated compounds with no substituents gave the tetrahydro-1,2,3,5,7-pentazocines as intermediates, but it is believed that these were oxidised to the dihydro pentazocines Transannular ring contraction and rearrangement led to the fragmentation of the molecule Irradiation of the saturated compounds and those with electron-withdrawing substituents also led to ring opening, but again, transannular ring contraction, followed by fragmentation of the molecule led to the formation of substituted 1,2,4-triazoles

## List of Abbreviations

| | |
|---|---|
| AN | Acrylonitrile |
| DEAD* | Diethyl acetylene dicarboxylate |
| DMF* | Dimethyl fumarate |
| DMAD | Dimethyl acetylene dicarboxylate |
| DMM | Dimethyl maleate |
| DMSO | Dimethyl sulfoxide |
| EA | Ethyl acrylate |
| FMO | Frontier molecular orbital theory |
| HMBC | Heteronuclear multiple bond correlation |
| HMO | Huckel molecular orbital theory |
| HMQC | Heteronuclear multiple quantum coherence |
| HO | Highest occupied |
| HOMO | Highest occupied molecular orbital |
| IR | Infra red |
| LUMO | Lowest unoccupied molecular orbital |
| LU | Lowest unoccupied |
| MA | Methyl acrylate |
| MaAn | Maleic anhydride |
| MMA | Methyl methacrylate |
| MO | Molecular orbital |
| MP | Melting point |
| MVK | Methyl vinyl ketone |
| NMR | Nuclear magnetic resonance |
| PIC | Phenyl isocyanate |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| Ts | Tosyl (*p*-toluene sulfonate) |
| UV | Ultraviolet |

*does not refer to the usual meaning

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*This work is dedicated to my parents and my brothers*

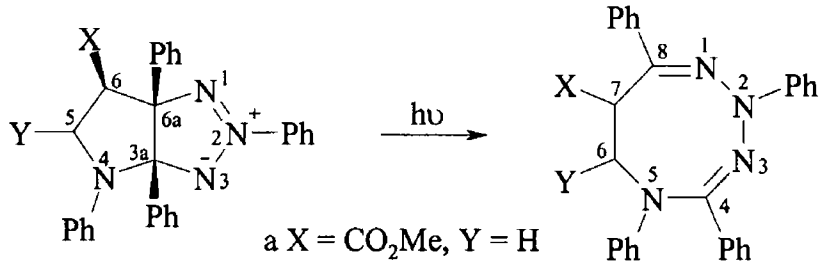
# CHAPTER ONE

# 1,3-DIPOLAR CYCLOADDITIONS OF TRIAZOLIUM-1-IMIDES

## Chapter1 1,3-Dipolar Cycloadditions of Triazolium-1-Imides

### 1.1 Introduction:

In previous work by our group, it was found that the photolysis of substituted 2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazoles, **1** results in the formation of the novel substituted 2,4,5,8-tetraphenyl-2,5,6,7-tetrahydro-1,2,3,5-tetrazocines **2** [1]



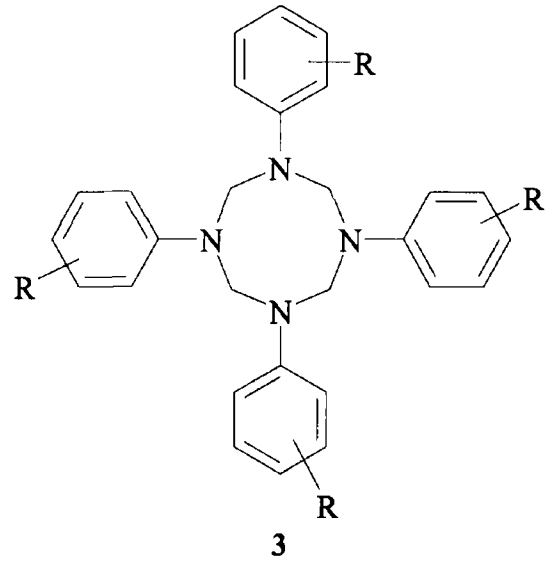

**1** a X = $CO_2Me$, Y = H; b X = $CO_2Et$, Y = H; c X = $CO_2Me$, Y = Me; d X = COMe, Y = H **2**

**Scheme 1.1** *Photochemical rearrangement of substituted 2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole*

It was decided to investigate whether a similar route could be found to yield the previously unknown pentazocine, an eight membered ring containing five nitrogen atoms

There are no known examples of eight membered heterocycles containing five nitrogen atoms within the ring There are many examples of eight membered rings with one, two, three and four nitrogen atoms [2] By far the largest compound class of eight-membered rings containing four or more heteroatoms is 1,3,5,7-tetrazocanes [3] This class includes tetranitrotetrazocane and related compounds, which have found application as propellants and explosives [3]

A number of 1,3,5,7-tetraaryl-1,3,5,7-tetrazocanes **3** have been synthesised by the reaction between aromatic amines and paraformaldehyde [4]

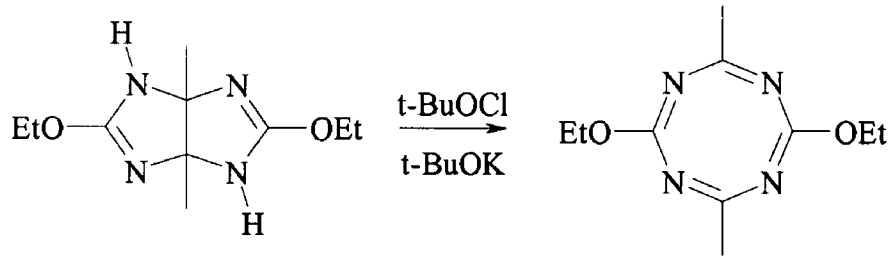


**3**

R = H, *m*Me, *p*Me, *p*$^{t}$Bu, *m*F, *m*Cl, *p*Cl, *p*Br

**Figure 1.1** *1,3,5,7-tetraaryl-1,3,5,7-tetrazocane*

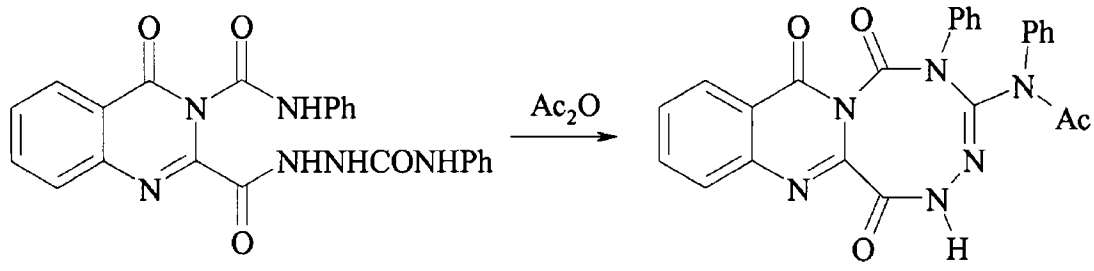
Reaction of dimethylglycoluril derivative with t-butyl hypochlorite and potassium t-butoxide afforded tetrazocine **5** in 50% yield [5]



**4** **5**

**Scheme 1 2** *Synthesis of a 1,3,5,7-tetrazocine*

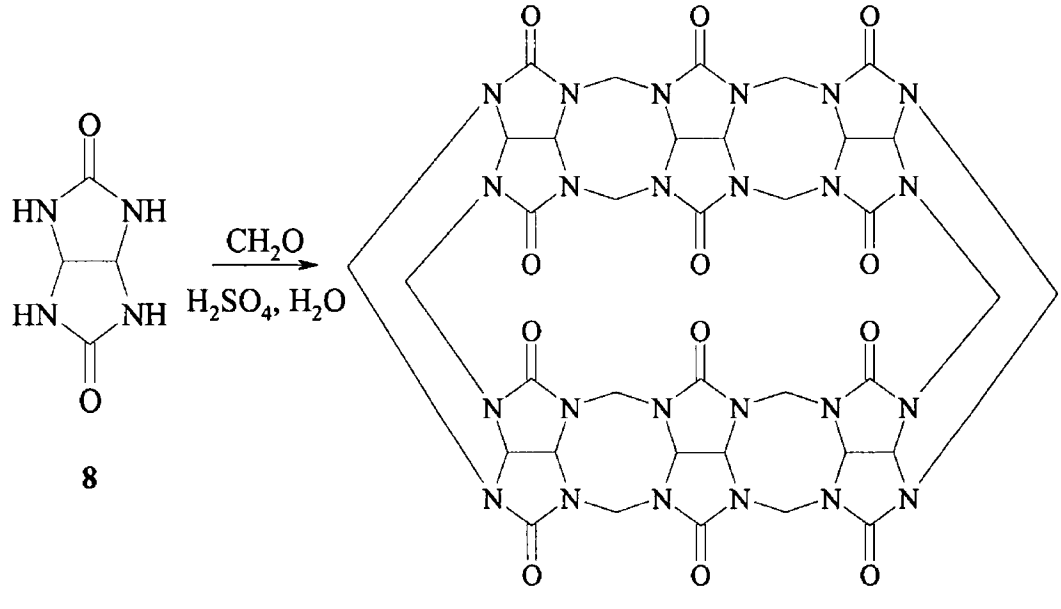
A novel tetrazocine **7** was prepared in 70% yield by boiling **6** in acetic anhydride, which induced ring closure and acetylated the exocyclic amine [6]




6 7

**Scheme 1.3** *Synthesis of tetrazocine*

In 1905, Behrend *et al*[7] reported the synthesis of a white crystalline material in 40-70% yield from the acidic condensation of glycoluril with excess formaldehyde followed by dissolution in concentrated sulfuric acid and precipitation with cold water Freeman *et al* reexamined this reaction in 1981 and the product structure 9 was determined by x-ray analysis of a calcium bisulfate complex [8] The structure consisted of six 1,3,5,7-tetrazocane units fusing the six glycourils The trivial name cucurbituril was coined for the compound for its pumpkm-like shape

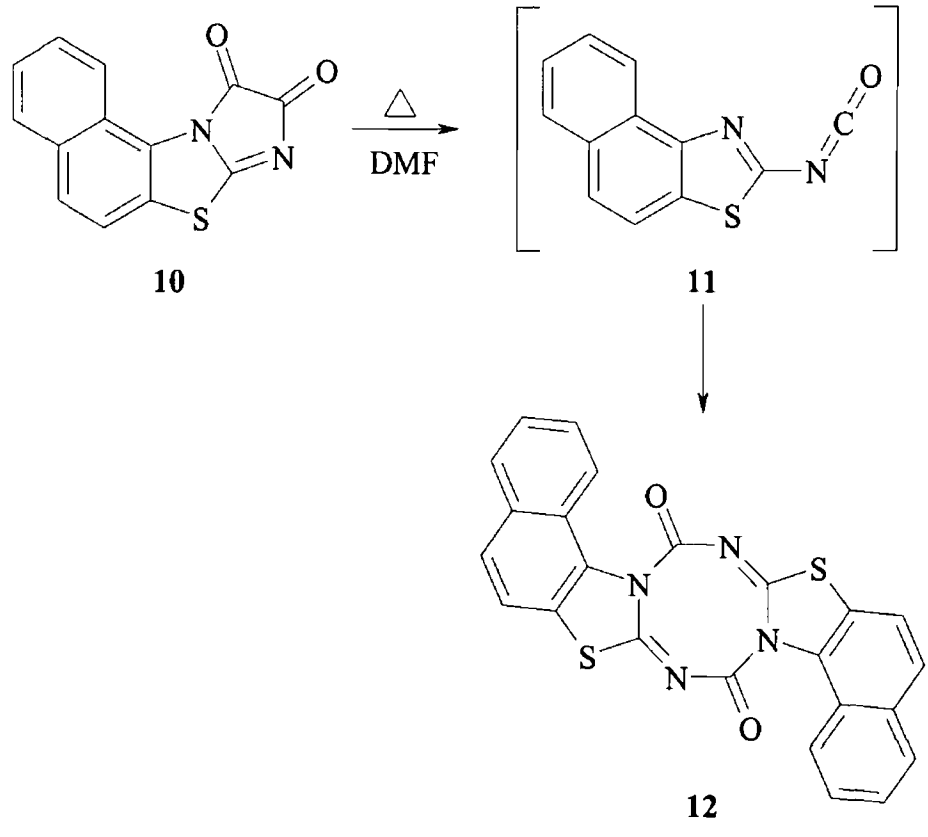



8 9

**Scheme 1.4** *Synthesis of cucurbituril from glycoluril*

Cucurbituril has been used as a catalyst in 1,3-dipolar cycloadditions[9] and a molecular switch has been prepared based on cucurbituril and a triamine [10]

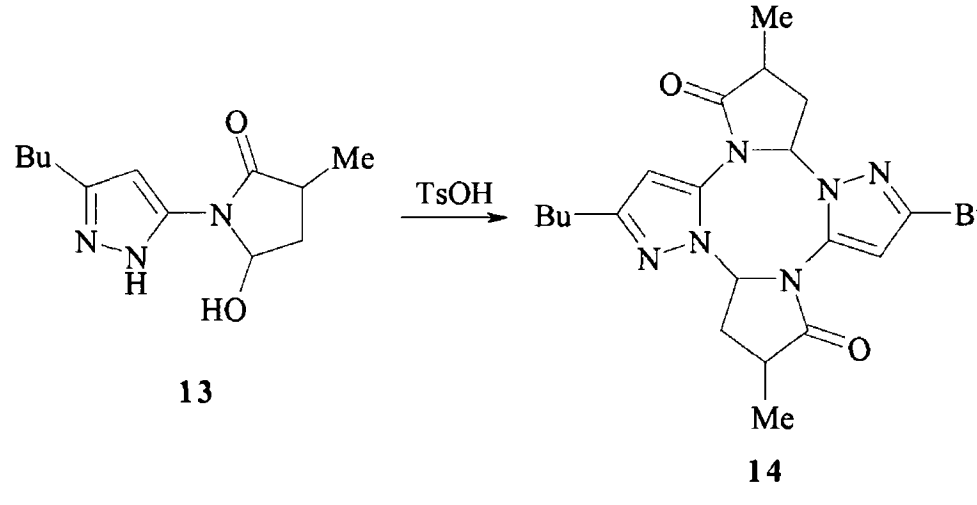
Thermolysis of **10** in DMF gave tetrazocane **12** as yellow crystals in 85% yield, presumably via a [4+4] cycloaddition of intermediate **11** [11]




**10** **11** **12**

**Scheme 1 5** *Thermolysis of 10 to give tetrazocane*

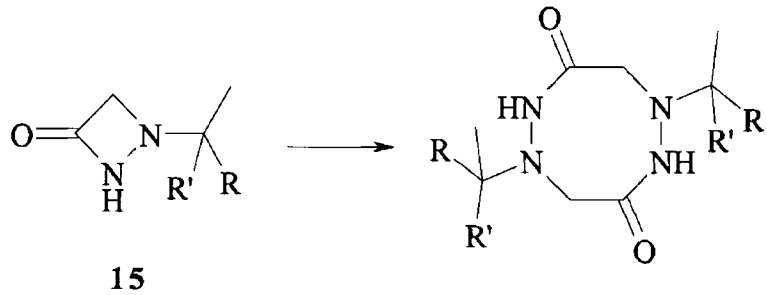
Treatment of 5-hydroxypyrrolidinones with a catalytic amount of *p*-toluene sulfonic acid in refluxing toluene gave tetrazocanes like **14** as white solids [12]




**13** **14**

**Scheme 1 6** *Synthesis of tetrazocanes from pyrrolidinones*

1,2-Diazetidin-3-ones substituted at N-1 dimerised on standing to give materials with the suggested structures **16** and **17** [13]

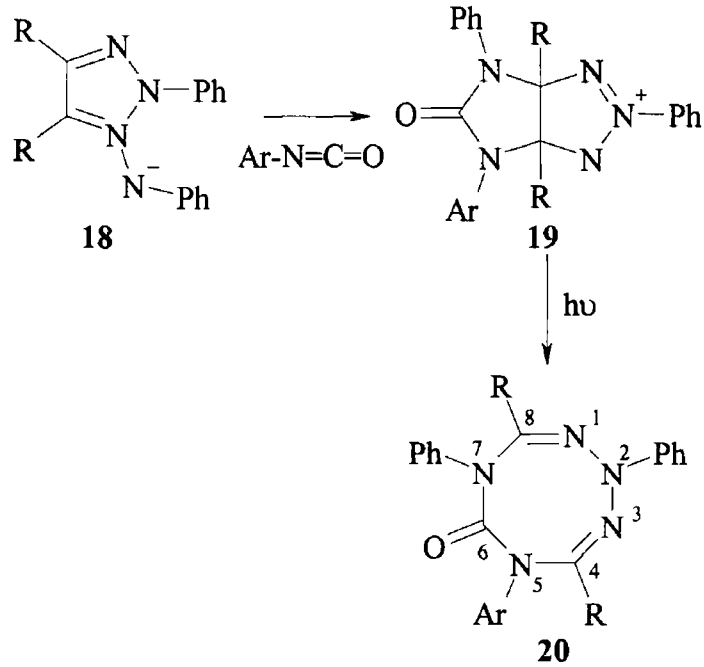


**15**

**16** R= Me, R' = $CH_2CH(OMe)$
**17** R = R' = $-(CH_2)_5-$

**Scheme 1 7** *Synthesis of 1,2,5,6-tetrazocane by dimerisation of diazetidinone*

The planned synthetic route to the novel pentazocine involved the 1,3-dipolar cycloaddition of aryl isocyanate to 1,2,3-triazolium-1-(N-aryl)imides **18** and photochemical ring expansion of the resulting adduct **19** to give the required pentazocine **20**



**18** **19** **20**

**Scheme 1 8** *Proposed synthetic route for the synthesis of a 1,2,3,5,7-pentazocine*

**1 2 1,3-Dipoles.**

1,3-Dipolar compounds are ones in which there is a sequence of three atoms *a-b-c*, of which *a* has a sextet of electrons in the outer shell and *c* an octet with at least one unshared pair Since compounds with six electrons in the outer shell of an atom are usually not stable, the *a-b-c* system is actually one canonical form of a resonance hybrid, for which at least one other form can be drawn 1,3-Dipolar compounds can be divided into two main types

1 *Propargyl-Allenyl Type* those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom

**Figure 1.2** *Canonical forms of the propargyl-allenyl type 1,3-dipoles*

If the atoms are limited to the first row of the periodic table, *b* can only be nitrogen, *c* can be carbon or nitrogen, and *a* can be carbon, oxygen or nitrogen, hence there are six types 1,3-dipoles of this type are usually linear

2 *Allyl Type* those in which the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond

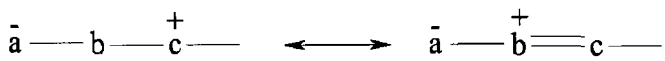


**Figure 1.3** *Canonical forms of the allyl type 1,3-dipoles*

Here *b* can be nitrogen or oxygen, and *a* and *c* can be nitrogen, oxygen or carbon There are twelve types of these 1,3-dipoles and these are bent

The 1,3-dipole can also be defined as 'a species that is represented by zwitterionic octet structures and undergoes 1,3-cycloadditions to a multiple-bond system, the dipolarophile' The formal charges are lost in the [3+2→5] cycloaddition

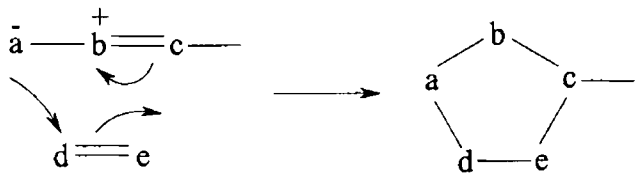


**Figure 1 4** *1,3-dipolar cycloaddition*

The two octet structures of the 1,3-dipole with their allyl anion resonance reveal an ambident nucleophile (both termini of the 1,3-dipole can display nucleophilic character) The two sextet structures (**Figure 1 5**) suggest that both termini may also show electrophilicity

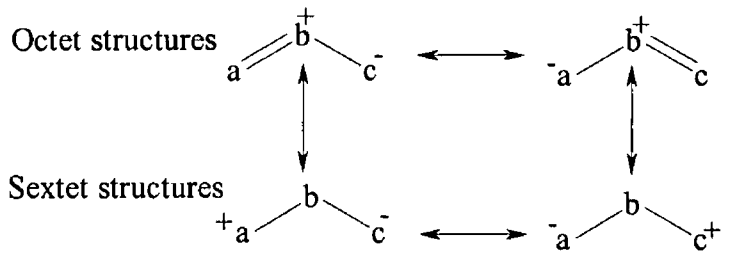



**Figure 1.5** *Octet and sextet structures of 1,3-dipoles*

| Canonical forms | | | Name |
|---|---|---|---|
| —C≡N⁺—C⁻ | ⟷ | —C⁻=N⁺=C | Nitrile ylide |
| —C≡N⁺—N⁻ | ⟷ | —C⁻=N⁺=N | Nitrile imine |
| N≡N⁺—C⁻ | ⟷ | N⁻=N⁺=C | Diazoalkane |
| C=N⁺—N⁻ | ⟷ | C⁻—N⁺=N | Azomethine imine |
| C=N⁺—C⁻ | ⟷ | C⁻—N⁺=C | Azomethine ylide |

**Table 1.1** *Canonical forms of the carbon and nitrogen containing 1,3-dipoles*

### *1.2 1 1,3-Dipolar Cycloadditions*

Cycloadditions involve cyclic electron shifts, they are ring-closure reactions in which the number of σ bonds increases at the expense of π bonds In the largest class of cycloadditions, two new σ bonds are created, whereas those cycloadditions with the net conversion of one π bond into one σ bond can be considered 'electrocyclic reactions'

The cyclic electron shift shown in **Figure 1.4** suggests that the reaction of a 1,3-dipole and a dipolarophile takes place in a planar arrangement of all five centres **Figure 1 6** shows the cycloaddition of an azomethine imine with an ethylemc dipolarophile d=e The substituent R prevents the approach of the dipolarophilic centre *d* to the terminal carbon of the 1,3-dipole Contact with the terminal centres of the azomethine imine can only be achieved after a 90° rotation about the carbon-nitrogen bond axis To reach the planar arrangement, the carbon-nitrogen π bond, and with it, the allyl resonance, must be sacrificed The reaction through this transition state could not be concerted The orbital symmetry treatment cannot be applied to this state because the electrons participating on the side of the 1,3-dipole are not arranged in a proper MO

**Figure 1 6** depicts the orientation complex preceding the transition state for the addition of the azomethine imme to a dipolarophile *d-e* This theory was first published in 1963[14] and is now accepted as the correct mode of interaction of the two reactants As shownin **Figure 1 6** the bending of the linear 1,3-dipole within the horizontal plane preserves the allyl anion orbital which makes contact with the π bond of the dipolarophile The gradual rehybridisation from p to $sp^3$ and $sp^2$ orbitals, which occurs during the reaction, is accompanied by an uplifting of the middle nitrogen until it reaches the plane of the product The arrangement is called the two-plane orientation complex and indicates that (4+2) π electrons are involved in the cycloaddition process exactly as in the Diels Alder reaction The symmetry considerations with the correlation diagrams reveal that the concerted thermal cycloaddition is allowed

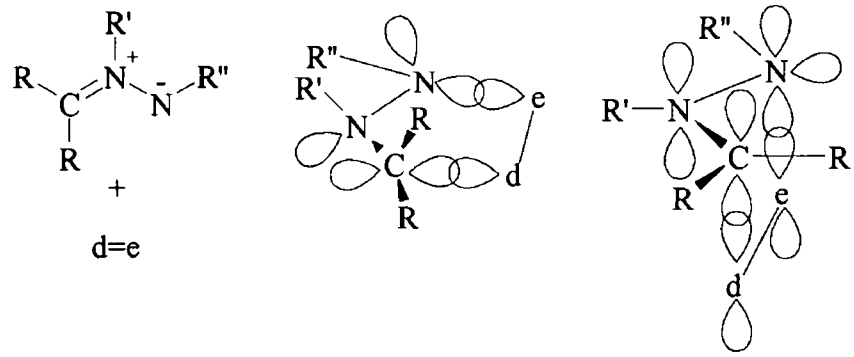



**Figure 1 6** *Two-plane orientation complex of a 1,3-dipolar cycloaddition between an azomethine imine and a dipolarophile d=e*

For the azomethine imine 1,3-dipoles, **(Figure 1 6)** the terminal carbon and nitrogen atoms are ca 2 3Å apart The π orbitals at the termini must bend by a slight twist about the carbon-nitrogen and nitrogen-nitrogen bond axes in order to make contact with the π orbitals of the dipolarophile, which bend outward [15] Gradual rehybridisation converts the two terminal p orbitals of the allyl system as well as the p orbitals of the dipolarophile d=e into $sp^3$ orbitals, which form the new σ bonds This is accompanied by an uplifting and pyramidalising of the middle nitrogen, its former p orbital harbours the unshared electron pair after the process is completed Front and side views of the conceivable transition state are shown in **Figure 1 7**

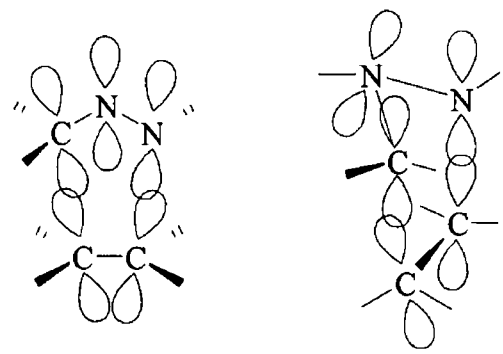



**Figure 1 7** *Front and side views of the concerted cycloaddition transition state*

In the mostly linear 1,3-dipoles of the propargyl-allenyl type, the distance between the terminal centres is greater than in 1,3-dipoles of the allyl type, and the bending must occur early on the reaction coordinate in order to allow σ overlap of the π orbitals of the reactants

The term concerted does not necessarily imply that the two new σ bonds are developed in the transition state to the same extent 1,3-Dipoles that differ in the electrophilic and nucleophilic properties of the termini, and dipolarophiles that are polarised by their substitution pattern, will undergo concerted but not necessarily synchronous cycloadditions The making of one σ bond may lag behind the closure of the second σ bond in the transition state, and partial charges are stabilised at the centres of the weak incipient bond [16]

Since 1965, when Woodward and Hoffmann first proposed the idea, the Principle of Conservation of Orbital Symmetry has become extremely important in understanding and predicting the outcome of concerted reactions The mechanistic scheme of a concerted 1,3-dipole cycloadditions involving the allyl anion system fits precisely the selection rules for concerted cycloadditions according to Woodward and Hoffmann The correlation diagrams of MO and molecular state symmetries were first applied to 1,3-dipolar cycloaddition using the allyl anion and ethylene system as an electronic prototype Introduction of heteroatoms and substituents into the allyl anion and ethylene destroys molecular symmetry, but leaves orbital symmetry sufficiently untouched for the selection rules to be obeyed [17] All the treatments of orbital control indicate that the 1,3-dipolar cycloaddition is allowed to be a thermal concerted process This allowance is shared by all suprafacial cycloadditions that involve $(4n + 2)\pi$ electrons [18]

The ambivalence of 1,3-dipoles as either nucleophilic or electrophilic is of key importance in understanding the mechanism, reactivity sequences, and regiochemistry of 1,3-dipolar cycloadditions The nucleophilic character of the 1,3-dipole may be stronger than its electrophilic quality Compounds such as nitrile ylides or diazomethane will cycloadd to electron-deficient dipolarophiles much faster than to electron-rich multiple bonds The opposite is true for ozone, which combines preferably with electron-rich dipolarophiles In between is a broad range in which nucleophihc and electrophilic character are more or less balanced 1,3-dipoles like diphenylnitrilimine or diazoacetic ester undergo fast cycloadditions with electrophilic and nucleophilic double bonds, resulting in U-shaped reactivity scales of dipolarophiles [19] In the MO model, HOMO and LUMO energies of 1,3-dipole and dipolarophile offer a measure of nucleophilic and electrophilic qualities

For symmetrical 1,3-dipoles it is impossible to assign a nucleophilic or electrophilic end to the dipole However for unsymmetrical dipoles the contribution of some resonance structures carry different weightings in the overall description of the species For azomethine imines the major resonance contributor has the negative charge on the more electronegative nitrogen terminus

### *1.2.2 Stereospecificity.*

The term stereospecificity concerns retention or inversion of reactant stereochemistry during the reaction course Stereospecificity is an important criterion for the concertedness of cycloadditions As long as the 1,3-dipole and dipolarophile are configurationally stable compounds, no rotation about the crucial bonds is conceivable during the concerted formation of the new σ bonds Retention of configuration at the dipolarophile and at the terminal centres of the 1,3-dipole is a necessary consequence

The retention becomes observable when *cis,trans* isomeric reactants produce diastereomeric cycloadducts of sufficient stability, the mutual interconversion of diastereomeric products must be negligible under the conditions of the experiment and analysis The diagnostic value of stereospecificity or nonstereospecificity for concerted and two-step cycloadditions may be discussed for *cis,trans* isomeric dipolarophiles The concerted addition of a 1,3-dipole to a 1,2-*cis* disubstituted ethylene must produce a cycloadduct with *cis*-located substituents [20] This is different for a two-step addition via a zwitterion (**Figure 1.8**) or a biradical Rotation about the former double bond of the dipolarophile can compete with the ring closure of the intermediate Some product with inverted configuration is anticipated If rotation ($k_{rot}$) is fast compared to cyclisation ($k_{cycl}$), the same product mixture is expected from *cis*- and *trans*- configurated dipolarophiles

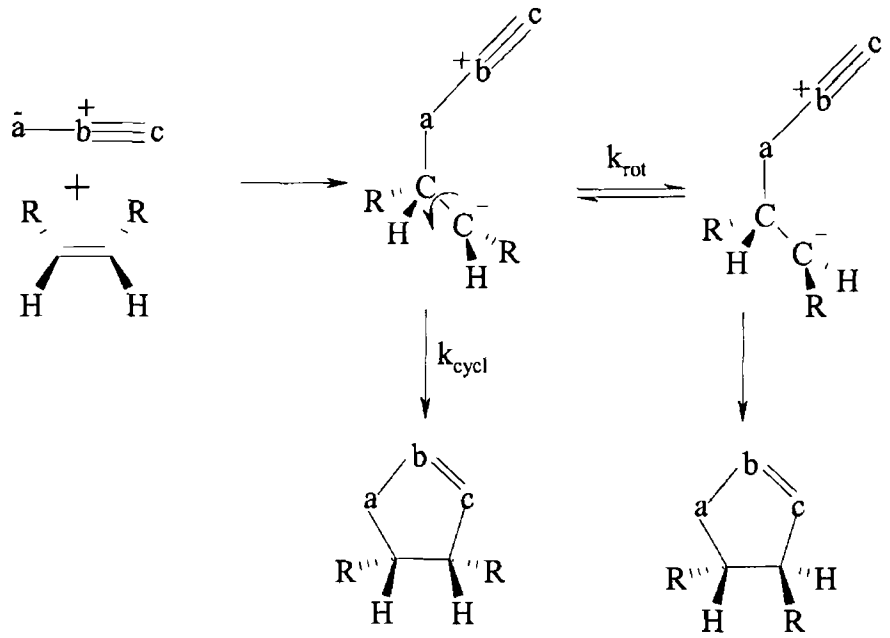


**Figure 1 8** *Stereochemistry of a two-step cycloaddition via a zwitterion*

### *1 2 3. Dipolarophiles.*

Nearly every multiple bond system, including those with heteroatoms can act as a dipolarophile [15] Conjugation with electron-attracting or electron-releasing substituents increases the dipolarophilic activity of a multiple bond Plotting the electron density of an olefinic double bond versus cycloaddition rates, U-shaped curves are obtained which are different for various 1,3-dipoles This phenomenon is explained in two ways

1) conjugation increases the polarisability of the $\pi$ bond of the dipolarophile,

2) concerted formation of the two new $\sigma$ bonds is not necessarily synchronous

Unequal progress of bond formation in the transition state leads to partial charges, which can be stabilised by substituents

Substitution effects in cycloaddition reactions can be explained using HMO-perturbational theory [21] As the 1,3-dipole and dipolarophile approach each other their orbitals begin to interact and orbitals of suitable symmetry are formed Thus the HOMO (highest occupied molecular orbital) of the dipolarophile interacts with the LUMO (lowest unoccupied molecular orbital) of the 1,3-dipole and vice versa A stabilisation of the molecular complex results The magnitude of this stabilisation is a function of the energy difference between the interacting orbitals The closer these energies, the greater

the stabilisation. Substituents will influence the energy of the orbitals and change their relative separation.

### *1.2.4. Regioselectivity:*

Two directions of cycloaddition are conceivable if both the 1,3-dipole and dipolarophile contain non-identical terminal $\pi$ centres. Sometimes pure cycloadducts are isolated and sometimes mixtures of isomers of different orientation are observed.

The experimentally observed regioselectivity (selectivity in direction of addition to an unsymmetrical alkene or alkyne) of most 1,3-dipolar cycloadditions proved to be the most difficult phenomenon to explain. Perturbation theory provided the key to the understanding of regioselectivity in 1,3-dipolar cycloadditions.[22] The unequal magnitudes of the terminal coefficients in the HO and LU $\pi$ orbitals is the key to the explanation of regioselectivity in 1,3-dipolar cycloadditions.

The preferred regioisomeric transition state will be that in which the larger terminal coefficients of the interacting orbitals are united. **Figure 1.9** shows this schematically. Case (a) (large-large, small-small interactions) results in more stabilisation than Case (b) (large-small interactions). A cycloaddition controlled by a strong interaction as in (a) would lead to unequal extents of bond formation in the transition state, bond a-d being more fully developed than bond c-e.

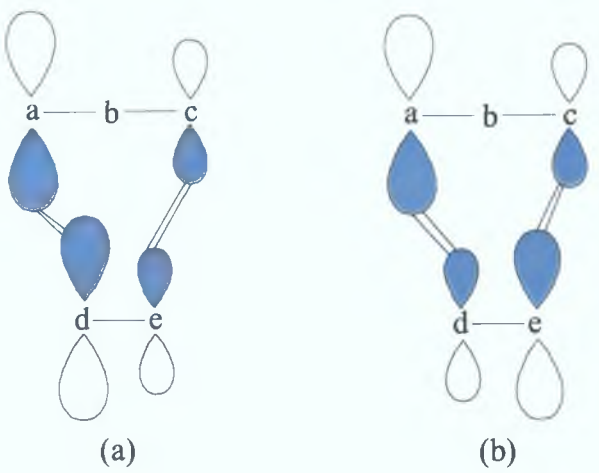



**Figure 1.9** *Schematic representation of greater stabilisation of transition state (a) than (b) due to different coefficient magnitudes.*

**Table 1 2** shows the squares of the products of the CNDO/2 (molecualar mechanic calculation program) calculated frontier orbital coefficients of some 1,3-dipoles

| Dipole | HOMO | LUMO |
|---|---|---|
| $HCN^{+}$-C $H_2$ | 1 07 1 50 | 0 69 0 64 |
| $HCN^{+}$-N H | 0 90 1 45 | 0 92 0 36 |
| $NN^{+}$-C $H_2$ | 0 85 1 57 | 0 56 0 66 |
| $NN^{+}$-N H | 0 72 1 55 | 0 76 0 37 |
| $CH_2$=$N^{+}$-C $H_2$ | 1 28 1 28 | 0 73 0 73 |
| $CH_2$=$N^{+}$-N H | 1 15 1 24 | 0 87 0 49 |
| $CH_2$=$N^{+}$-O | 1 11 1 06 | 0 98 0 32 |

**Table 1.2** *Frontier Orbital Coefficients for terminal atoms[1] of some 1,3-dipoles*

Perturbation theory indicates that reactivity in cycloadditions will increase as the dipole LU orbital is lowered and as the HO orbital is raised in energy The transition states of 1,3-dipolar cycloadditions of linear 1,3-dipoles to alkenes involve appreciable bending of the 1,3-dipole Such a complex would maximise overlap of the p orbitals at the termini of the dipole with those of the dipolarophile The perturbation calculation of regioselectivity based on linear 1,3-dipole MO's could be in serious error were the bent and linear dipole MO's significantly different

Roberts performed Huckel calculations on azides which indicated that bending the NNN angle below 180° would require little energy [23] Calculations carried out by Houk *et al*[24] by the CNDO/2 method for diazomethane using fixed bond lengths, but with variations of the CNN angle in the plane of the molecule from 180° to 120°, show that bending causes only small changes in the coefficients and energies of the HO and LU $\pi$ orbitals In all cases, the relative magnitudes of coefficients remain the same, indicating that the calculations of linear systems are satisfactory for perturbation predictions even if the transition state involves a substantially bent 1,3-dipole

[1] Values are given in the same order as the atoms appear in the left hand column

1,3-Dipolar cycloadditions can be classified into three types,[21] depending on the relative disposition of the 1,3-dipole and dipolarophile frontier orbitals (**Figure 1 10**) These three types are

1) HO-controlled (the interaction of the dipole HO with the dipolarophile LU is greatest),
2) HO,LU-controlled (both frontier orbital interactions are large), and
3) LU-controlled (the interaction of the dipole LU with the dipolarophile HO is greatest)

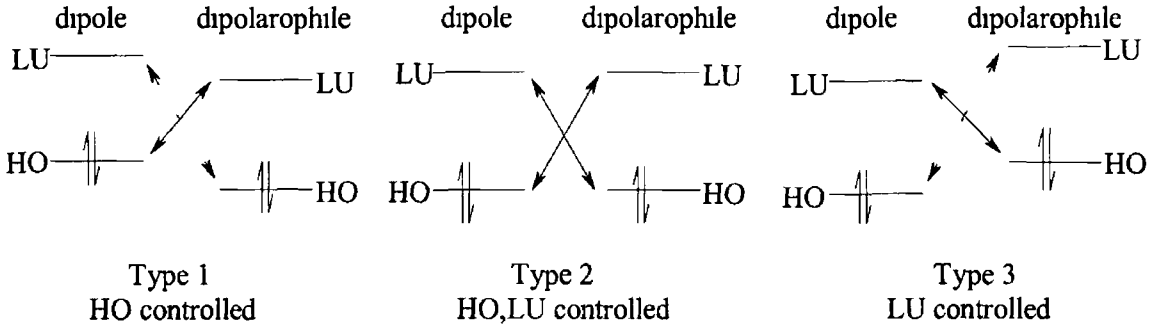



**Figure 1.10** *Sustmann's classification of 1,3-dipolar cycloadditions* [21]

Substituents that raise the dipole HO energy or lower the dipolarophile LU energy will accelerate HO-controlled reactions and decelerate LU-controlled reactions Substituents which lower the dipole LU energy or raise the dipolarophile HO energy will accelerate LU-controlled reactions and decelerate HO-controlled reactions HO,LU-controlled reactions will be accelerated by an increase of either frontier orbital interaction

The discussion of FMO theory is usually limited to reactions of substituted alkenes However, similar consideration may be readily applied to heterodipolarophiles such as ketones, nitriles and imines The HO and LU orbitals of these three types of heterodipolarophiles are shown in **Figure 1 11**, where X represents an oxygen or nitrogen [22] These orbitals will be, in general, located at energies similar to those of electron deficient dipolarophiles With the exception of the nitrile ylides and symmetrical species, all 1,3-dipoles have the larger coefficient at the anionic terminus in the HO and at the neutral terminal in the LU (**Table 1.2**) Both of these interactions as well as the better overlap of carbon with carbon than with oxygen or nitrogen lead to the preferential formation of products **21** [15]

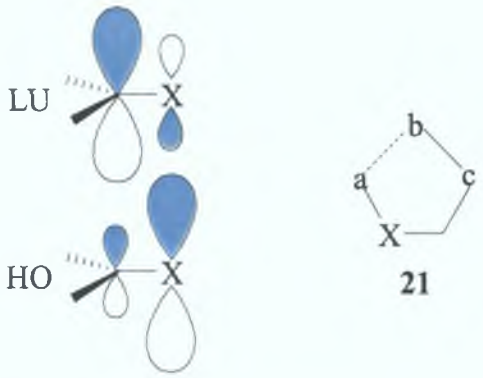



**Figure 1.11** *Frontier orbitals of heterodipolarophiles.*

### *1.2.5. Diastereoselectivity:*

When chiral centres, at least one on the side of each reactant, are generated in the cycloaddition process, diastereomeric adducts may be formed. In 1937 Alder noticed the preferential formation of *endo*-substituted bicyclo[2.2.1]heptenes from cyclopentadiene and π-substituted ethylenes.[25] The diastereoselectivity was later attributed to attractive secondary orbital interactions.

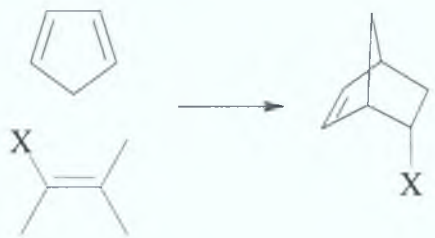


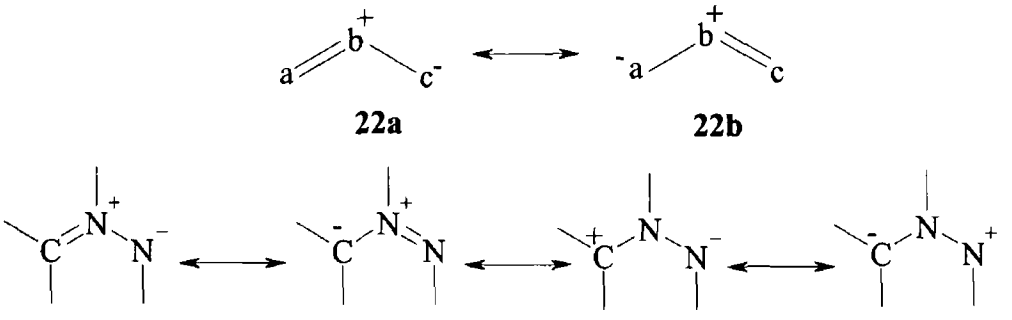

**Figure 1.12** *The favoured formation of endo-substituted bicyclo[2.2.1]heptenes in the Diels-Alder reaction.*

The formation of diastereomeric adducts is very common in 1,3-dipolar cycloadditions.[26] The two adducts (*cis* and *trans*) can be formed via two different two-plane orientation complexes. The ratio of the diastereomers reflects the free-energy difference of the two transition states. This difference comes from repulsive interactions caused by steric hindrance, and attractive forces associated with maximal π overlap. Frequently the latter factor wins in the competition, and the thermodynamically less favoured product is often preferentially formed. More often than the exclusive formation of one diastereomer, is the occurrence of mixtures of cycloadducts. Their composition, nevertheless, reveals that attractive secondary orbital interactions of

conjugated substituents are a powerful antagonist to hindering van der Waals repulsions Conjugated $\pi$ substituents are part of the MOs of the reactants and their interaction is regarded with the proviso that the final product is the five-membered ring although additional weak bonds may occur in the transition state

### 1.3 Azomethine imines:

Azomethine immes belong to the class of 1,3-dipoles of the allyl type with an iminium centre as atom *b* in the general formulation **22** The resonance structures **23a** and **23b** clearly show the allyl anion stabilisation of these 1,3-dipoles The resonance formula **23a** is expected to be more important as a result of the higher electronegativity of nitrogen relative to carbon



**22a** **22b**

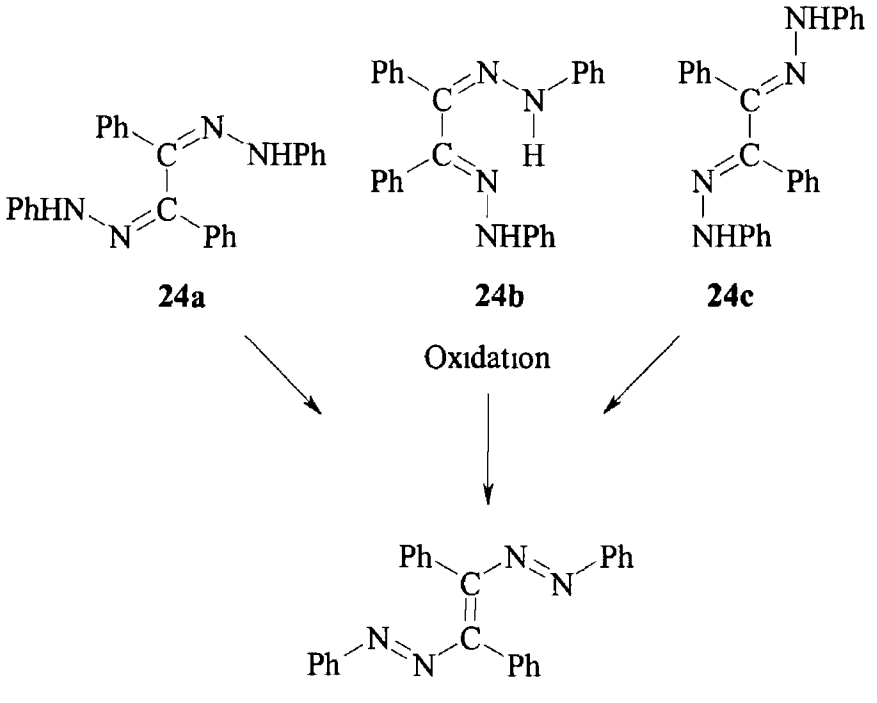
**23a** **23b** **23c** **23d**

**Figure 1 13** *Resonance structures of azomethine imine type 1,3-dipoles 23*

The systematic study of azomethine immes did not begin until 1960, although some examples of this class of compounds, more or less unrecognised, had been known for many years [27]

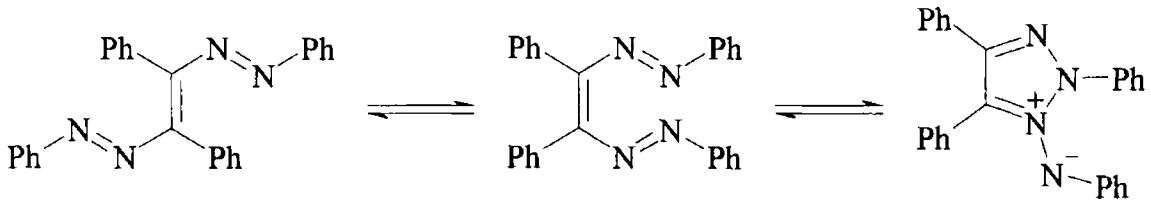
### *1.3.1. Triazolium-1-imides*

The 1,2-bisphenylhydrazone of benzil has three stable isomers, **24a**, **24b**, **24c** (**Scheme 1 9**), discovered by Spassov[28] and investigated by Woodward[29] Oxidation of each or any of them gives the same *trans*-azo compound, **25**, a crystal structure of which has been reported[30]




**Scheme 1.9** *The three isomers of the 1,2-bisphenylhydrazone of benzil and the resulting product of oxidation of each*

The E-form of **25** undergoes a facile E-Z isomerisation in solution followed by the electrocyclisation[31] to give the 1,3-dipole **26** The existence of this dipole form and its potential for cycloaddition was recognised by George *et al*[32] in 1971, although he assigned incorrect structures to the cycloadducts



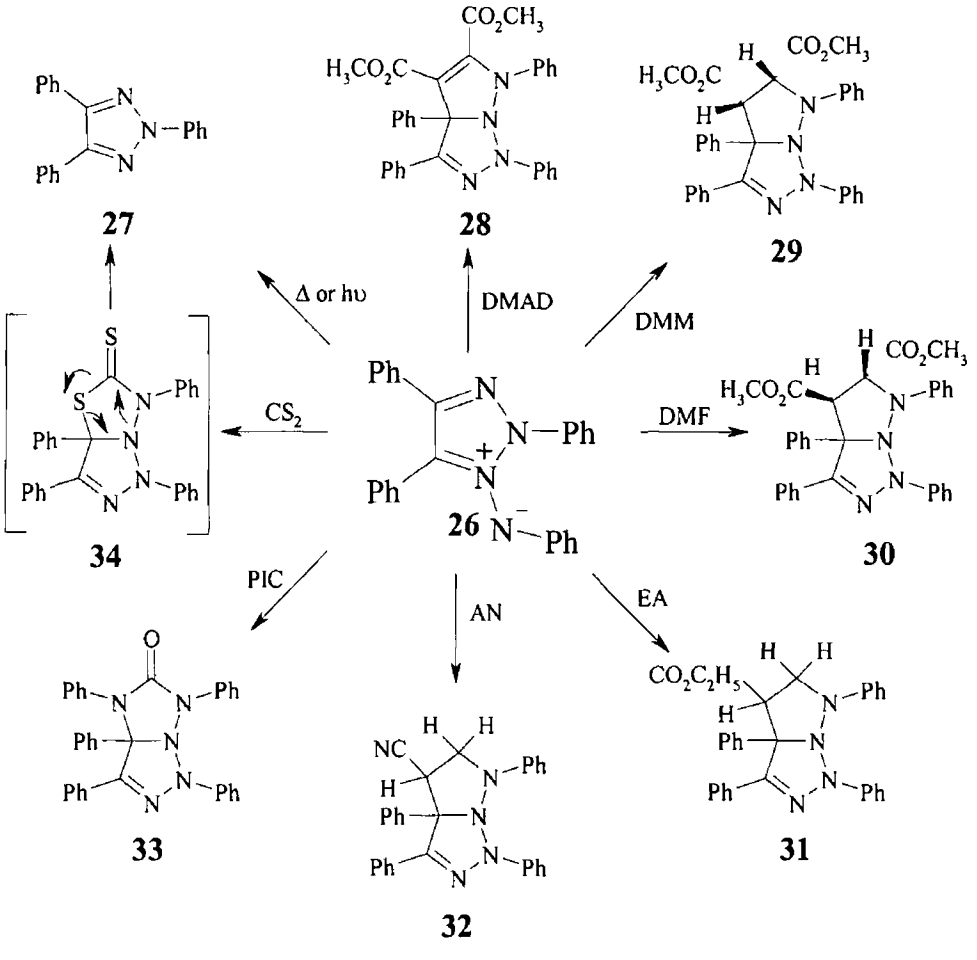
E-form Z-form

**25a** **25b** **26**

**Scheme 1.10** *E-Z isomerisation of the oxidation product of benzil 1,2-bisphenylhydrazone and electrocyclisation to give the 1,3-dipole*

Heating **25** in the absence of any solvent for fifteen minutes around 170°C results in the formation of an 85% yield of 2,4,5-triphenyl-1,2,3-triazole **27** (**Scheme 1 11**) [32] The same triazole was obtained in a 14% yield on photolysis of **25** in benzene The formation of the triazole **27** may be explained in terms of the loss of phenyl nitrene from the mesionic intermediate **26** It was rationalised that **26** exists in equilibrium with **25** under the reaction conditions The equilibrium between the acyclic and cyclic structures was later verified by variable temperature $^{1}$H NMR spectroscopy[33,39]

The reactions of 1,3-dipole **26** with a variety of dipoloarophiles were investigated by George *et al*[32] (**Scheme 1.11**) Treatment of **26** with dimethyl acetylenedicarboxylate in refluxing acetone reportedly gave a 83% yield of the adduct **28** Similarly the reaction of **26** with dimethyl maleate, dimethyl fumarate, ethyl acrylate, acrylonitrile and phenyl isothiocyanate gave the corresponding adducts **29-34** (**Scheme 1.11**)




**Scheme 1 11** *Reaction of dipole **26** with various dipolarophiles*

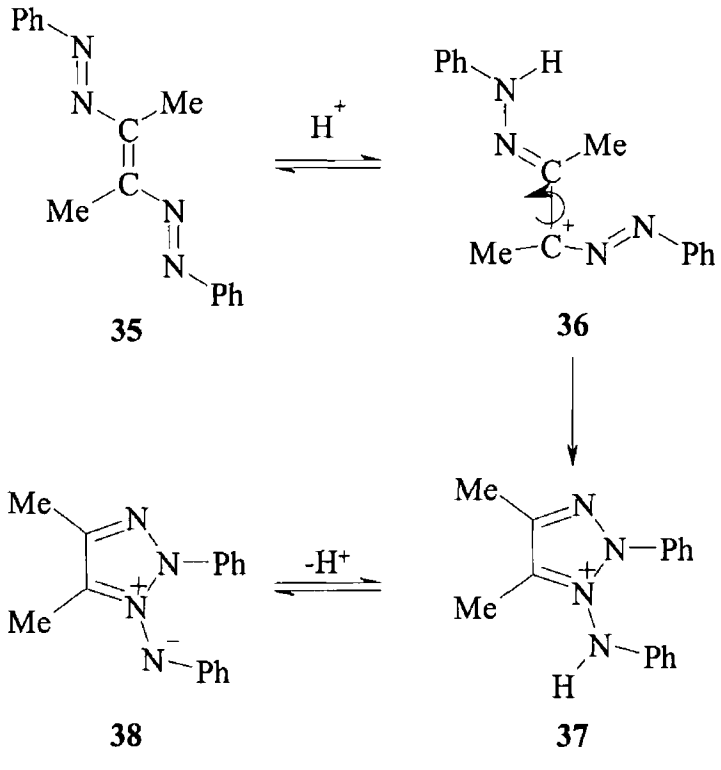
| Abbreviation | Name | Structure |
|---|---|---|
| DMAD | Dimethyl acetylene dicarboxylate | $H_3CO_2C{-}{\equiv}{-}CO_2CH_3$ |
| DMM | Dimethyl maleate | $H_3CO_2C$ (cis) $CO_2CH_3$ |
| DMF | Dimethyl fumarate | $CO_2CH_3$ (trans) $H_3CO_2C$ |
| EA | Ethyl acrylate | $CO_2C_2H_5$ |
| AN | Acrylonitrile | CN |
| PIC | Phenylisocyanate | Ph–N=C=O |

**Table 1.3** *Dipolarophiles used by George et al in the cycloaddition reactions of dipole **26** (**Scheme 1 11**)*

Treatment of **26** with carbon disulphide at room temperature gave a 93% yield of 2,4,5-triphenyl-1,2,3-triazole **27** In addition, elemental sulphur and phenyl isothiocyanate were also isolated from this reaction The formation of these products was rationalised in terms of the fragmentation of the initially formed cycloadduct **34** These structures (**28-34**) were later corrected by Butler *et al*[34] (see **Scheme 1.13**) and later by George [35] In his correction, George did not acknowledge that the correct structure had been reported by Butler some years earlier

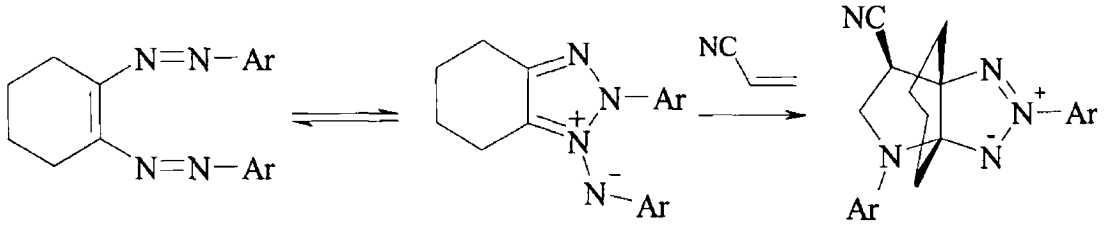
From these and other results it can be deduced that compound **26** is an azomethine imme, Type I 1,3-dipole (HOMO controlled reactions with most dipolarophiles)[36] and is reactive with a wide range of $2\pi$ systems

Although bisazoalkenes are conveniently prepared through the oxidation of the corresponding bisphenylhydrazones, it was found that the nature of the products in these oxidations depends to a large extent on the structure and stereochemistry of the starting bisphenylhydrazones Both azo functions need to be arranged in a *cis* orientation about the C=C bond in order to produce triazolium imides Consequently, *trans*-2,3-bis(phenylazo)-2-butene **35** (the most stable isomer) should not undergo cycloaddition with dipolarophiles Nevertheless, stereoisomerisation followed by electrocyclisation was achieved by the introduction of gaseous hydrogen chloride into an acetone or benzene solution of the azo olefin and dipolarophile[37]



**Scheme 1 12** *Acid catalysed stereoisomerisation and electrocyclisation of trans-2,3-bis(phenylazo)-2-butene*

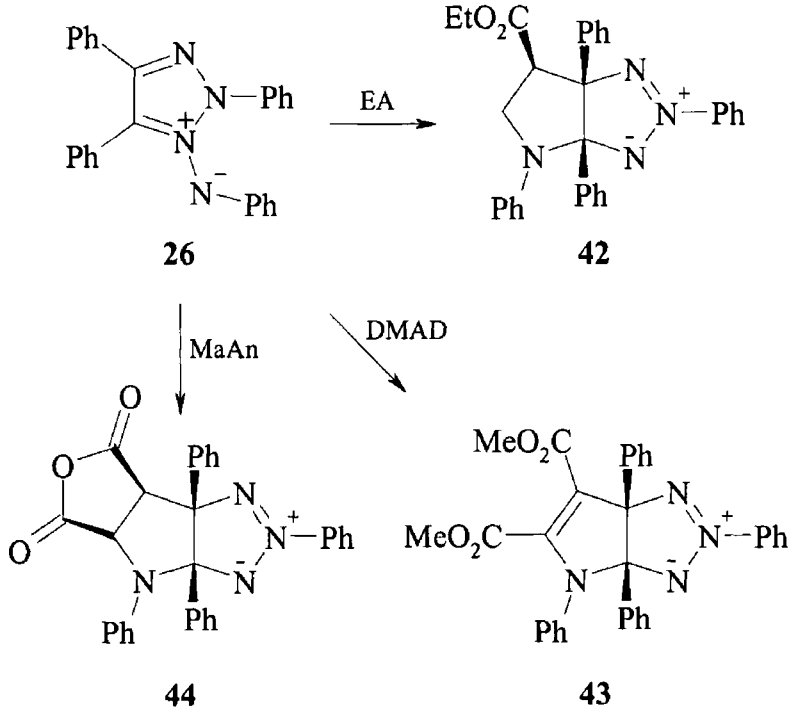
Butler *et al*, in examining the addition reactions of the cyclohexene derivatives with acrylonitrile, obtained the unexpected products **41** [34] **(Scheme 1.13)**



**Scheme 1.13** *The unexpected products from the reaction of the 1,3-dipole with acrylonitrile, confirmed by X-ray analysis*

The $^{13}C$ NMR spectrum of **41** showed two quaternary C-N signals and no C=N signal (as expected with structures **28-34**) X-ray crystallographic analysis showed that a multi-step reaction had occurred involving N-N bond cleavage and N-C bond formation The product had the novel tricyclic structure with a saturated C-C

bridgehead The basic structural unit of the compound is a substituted 3,3a,4,5,6,6a-hexahydropyrrol[2,3-d]-1,2,3-triazole Since these products did not have the expected structure, some of the cycloaddition reactions of a normal acyclic *cis*-bis(areneazo)alkene were reinvestigated The reaction of *cis*-1,2-diphenyl-1,2-bis(benzeneazo)ethylene **26** with different dipolarophiles under various conditions gave the product **42** – **44** (**Scheme 1 14**) Compounds **42** - **44** are analogous to the structure of **41** They showed all of the expected $^{13}C$ NMR signals including the key quarternary bridgehead carbons Attempts to trap the intermediate initial addition compound by carrying out the reaction at lower temperatures gave only the final products at lower yields or no reaction at all

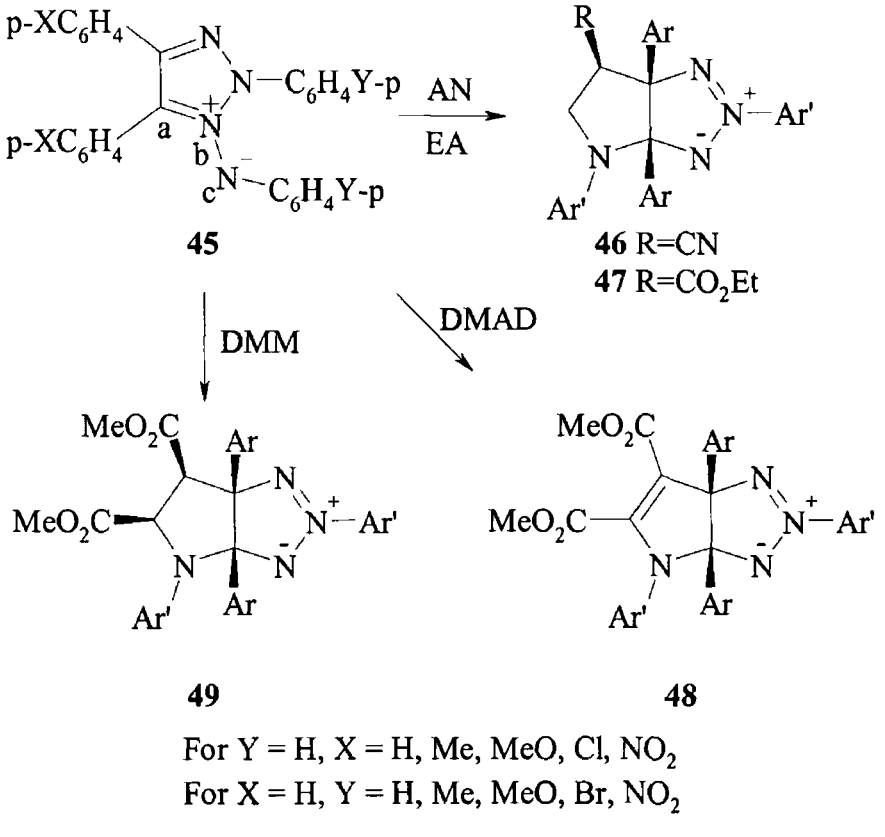



**Scheme 1 14** *Reassignment of the structures of the products of the cycloaddition of the 1,3-dipole with various dipolarophiles*

Further investigations of the previous cycloaddition products showed that all of the previously assigned structures were incorrect and that all of the initial adducts undergo the sigmatropic rearrangement (See **Scheme 1.32** for mechanism) to give the newly assigned structures

### *1.3.2 Kinetics of the Cycloaddition Reaction*

The kinetics of the series of reactions in **Scheme 1 15** was measured by following the disappearance of the dipole **45** at an appropriate UV wavelength[36] In each case the first part of the reaction involved the interaction of the 2π-molecule at atoms *a* and *c* of the molecules **45**




**Scheme 1.15** *Products arising from the cycloaddition of 1,3-dipole with various 2π dipolarophiles*

The final products arise from subsequent reactions of the initial adduct The rates of the initial reaction of dipole **45** with acrylonitrile were measured in four solvents and found to be independent of solvent polarity values They were also similar to values reported for concerted cycloadditions of 1,3-dipoles such as diphenyldiazomethane [38] Hammett plots for the influence of substituents at the carbon terminus *a* and the nitrogen terminus *c* of the dipoles **45** with acrylonitrile in acetone were determined [36] The rates for substituents X at the carbon terminus showed a good linear correlation with Hammett $\sigma_p$ values giving $\rho$=1 51 This behaviour is indicative of a dipole HOMO controlled reaction ie a Type I dipole

Substituents Y at the nitrogen terminus of the dipole surprisingly gave an inverted V-shaped Hammett plot Bent Hammett plots are a common feature of concerted 1,3-dipolar cycloadditions but they are usually V or U shaped and they arise when dipoles show Type II behaviour, i e when the respective HOMO-LUMO energy separations of both pairs of reactants are approximately equal In these situations all substituents enhance the reaction relative to hydrogen The dipoles **45** show the reverse phenomenon where all substituents inhibit the reaction It was suggested that the rate inhibition arises from resonance destruction of the 1,3-dipole character in the substrates **45** as shown in structures **50** (the nitro derivative) and **51** (the methoxy derivative) rather than a change in mechanism

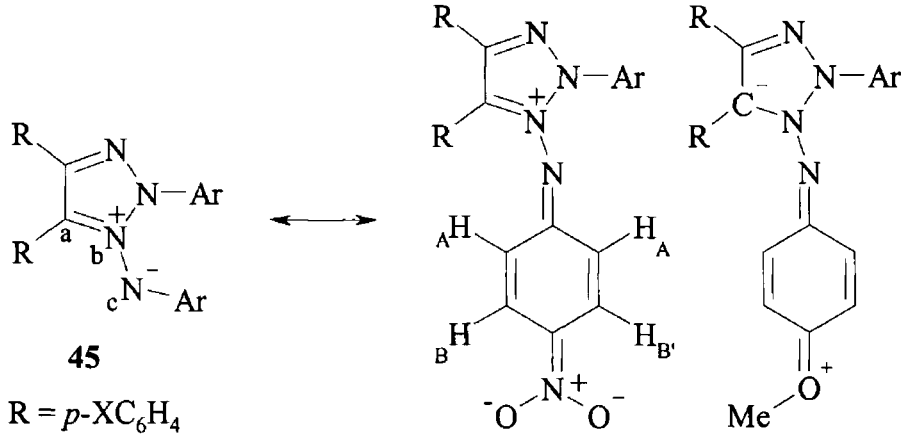



**Figure 1 14** *Resonance destruction of the 1,3-dipole character due to substitution at the nitrogen terminus*

In both of these forms the orthogonal π-electrons on the nitrogen terminus of the dipole are replaced by a π-bond to the aryl substituent and the 1,3-dipole character is lost Strong contribution from structure **50** was detected when at –87°C, the 270 MHz proton NMR spectrum showed severely restricted rotation of the N-C bond at the nitrogen terminus and gave two separate doublet signals from the AA'BB' system, thereby confirming the double bond character of the N-C aryl bond[39] Thus the capacity of the 1,2,3-triazole ring to behave as a source of electrons and an electron sink allows for strong interactions with both electron-donating and electron-withdrawing substituents, thereby increasing the activation energy by stabilising the ground state and reducing the

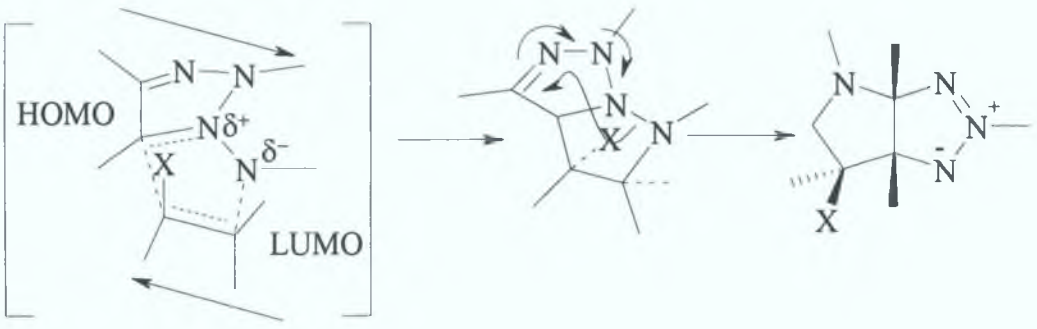
reactive 1,3-dipole character, giving rise to the unusual Hammett plots [40] These rate inhibitions do not affect the synthetic nature of the reaction and all of the reactions of the substrates **45** with acrylonitrile give products **46** in high yields

### *1 3 3. Mechanism and Stereospecificity*

Cycloaddition reactions of these 1,3-dipoles with alkene dipolarophiles gives derivatives of a pyrrolo[2,3-d]-1,2,3-triazole ring system in a general reaction which was eventually established as involving a tandem 1,3-dipolar cycloaddition and sigmatropic rearrangement [41]

Dimethyl maleate and dimethyl fumarate were used as probes for the stereospecificity of the reaction The dipoles and dipolarophiles were heated together in acetone and following recrystallisation from ethanol gave the products in high yields The reactions were found to be stereospecific (>99%) and no traces of mixtures were found

The reaction can be looked upon as a tandem, concerted 1,3-dipolar cycloaddition and 1,4-N→ C sigmatropic rearrangement However, it could also be a multistep Michael reaction involving initial nucleophilic addition of the exocyclic –N terminal of the dipole (which is nucleophilic) to the alkene giving a new N-C single bond followed by subsequent ring closure and cleavage of the N-N bond to give a second intermediate Perusal of such a mechanism shows that it necessitates a loss of stereochemistry due to rotations on the single bonds in a number of intermediates which, because of the substituents, should be sufficiently long-lived for a bond rotation The stereospecificity of the reaction therefore favours a tandem, concerted reaction The *exo*-arrangement of substituents in the products requires an initial *endo*-cycloaddition




52 53 54

**Figure 1.15** *Endo-orientation of the cycloaddition of triazolium imide dipole with dipolarophile followed by 1,4-sigmatropic rearrangement.*

Orbital-controlled regioselectivity gives a transition state **52** where the dipolarophile approaches over the plane of the triazolium imide dipole to give an initial unstable adduct **53** (**Figure 1.14**). The *endo*-orientation could be due to favourable secondary orbital interactions or to favourable alignment of dipoles in the transition state **52** (see arrows).

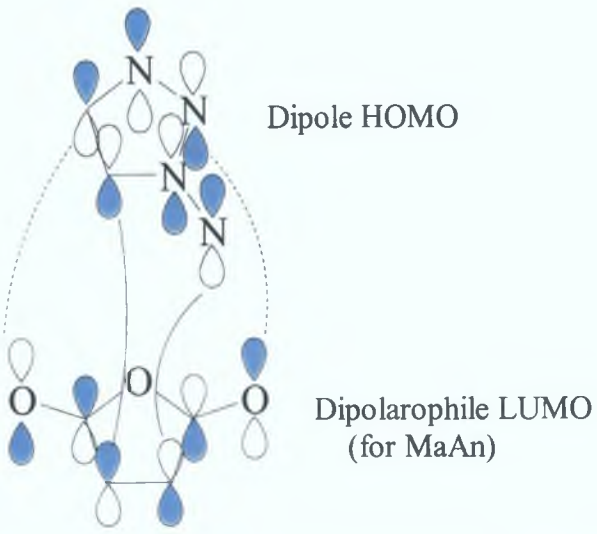
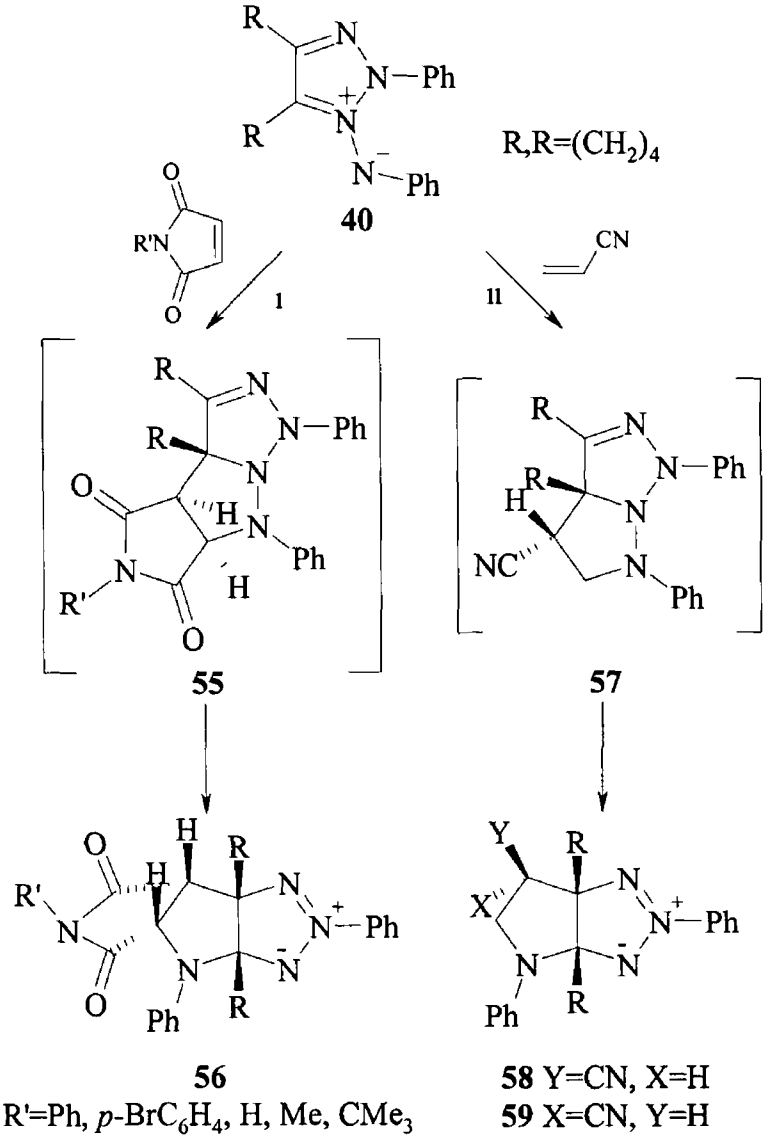



**Figure 1.16** *Favoured endo-transition state. Primary orbital interaction, heavy line; secondary orbital interactions, dashed line.*

In a later study[42] it was discovered that generalisations about the stereospecificity of the cycloadditions could not be made, and that each 1,3-dipole-dipolarophile pair needs to be individually studied. The cycloadditions of maleimides with the dipole **40** unexpectedly gave initial cycloadducts with *exo*-stereochemistry **55** (**Scheme 1.16**).

These subsequently underwent the usual rearrangement to give products **56** where the N-substituted-dicarboximido group was *endo* to the fused 5,5-ring system

In the same study, the cycloadditions using acrylonitrile as dipolarophile were looked at again, giving the same results as previously, i e an initial *endo* addition followed by rearrangement to give the *exo* product **58** A small amount of the *endo* product **59** was also recovered in crude form The fact that the isomer **58** is the major product means that in the initial cycloaddition of acrylonitrile, the *endo* transition state is favoured in contrast to the maleimide dipolarophiles




**Scheme 1 16** *Cycloadditions of triazolium N-imide with i)N-substituted maleimides, resulting in an initial exo-addition to give endo-products and ii) acrylonitrile giving initial endo-addition resulting in exo-products*

It has been suggested that the almost exclusive *exo*-cycloadditions observed with the maleimides are due to a steric effect from the substituents at C-1(dipolarophile) and C-2(dipole) in the developing fused 5,5-ring system With acrylonitrile as the dipolarophile the steric effect is reduced and both stereoisomers are formed with a preference for the *endo*-form

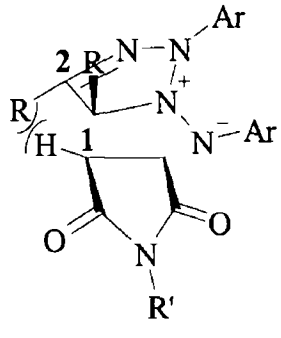
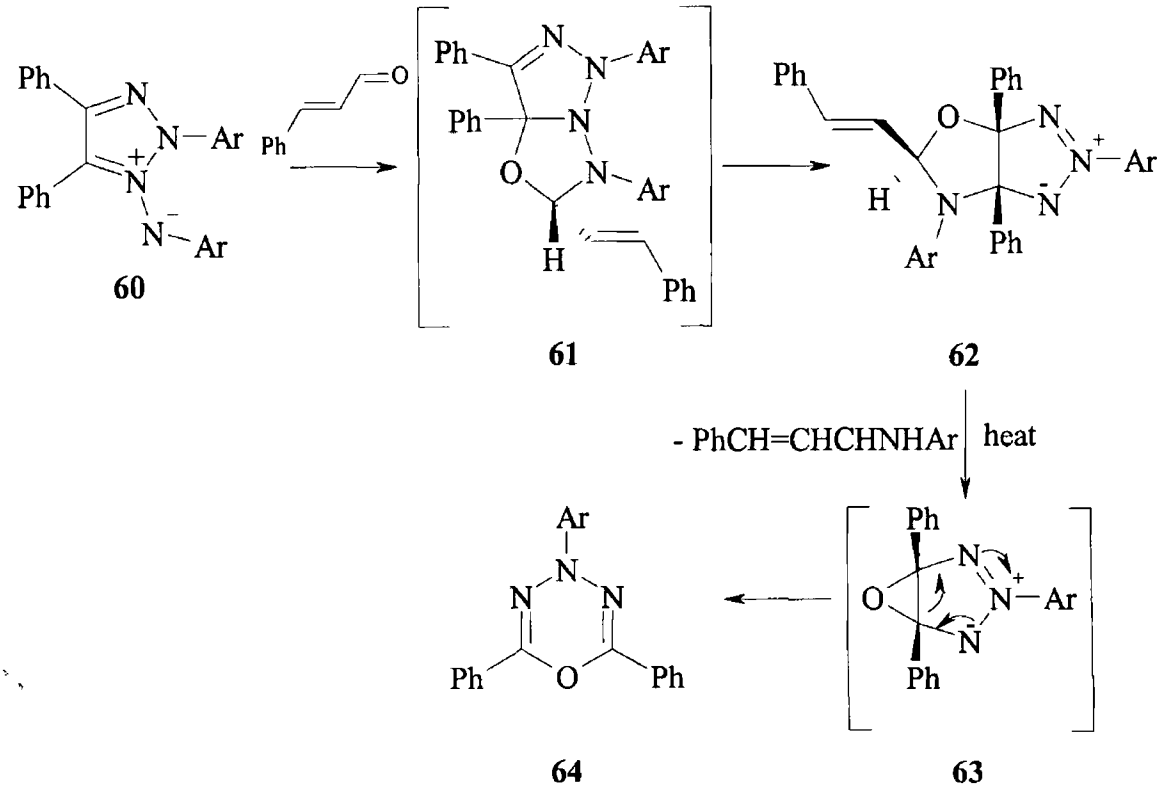



**Figure 1 17** *Proximity of substituents at C-1(dipolarophile) and C-2(dipole) as planar carbons change to tetrahedral in the transition state.*

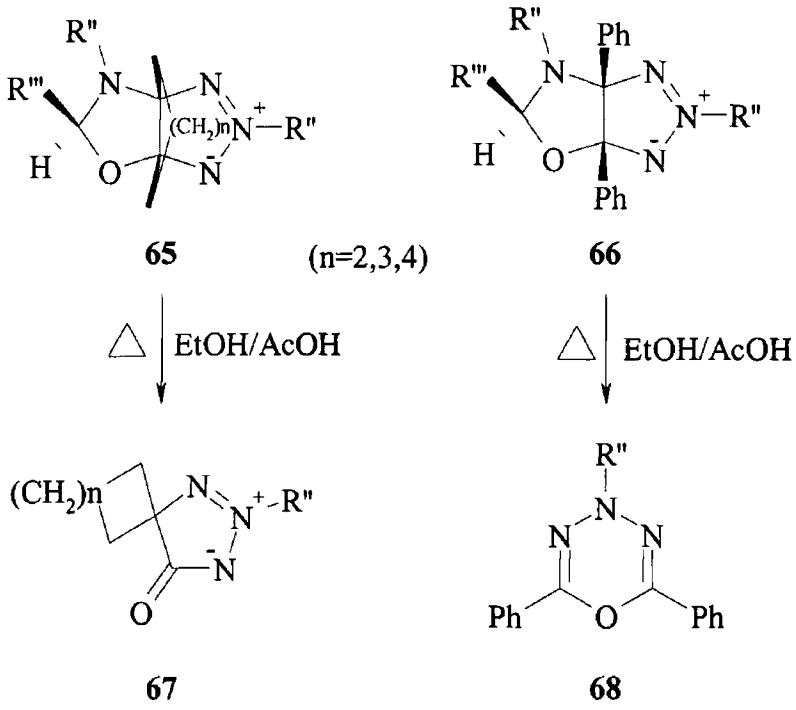
### *1 3 4 Reactions of Triazolium-N-imides·*

When treated with cinnamaldehyde the ultimate products of the cycloaddition were the oxazolo[4,5-d]-1,2,3-triazole derivatives **62** [43] The initial cycloaddition occurs on the carbonyl group, rather than the alkene, giving the unstable *endo*-adduct **61** as a reactive intermediate This sterically unfavoured cycloaddition is thought to be facilitated by secondary orbital interactions in the transition state No other isomer was found and this exclusive stereochemistry supports a 1,3-dipolar cycloaddition rather than a two-step nucleophilic addition to the carbonyl group The compounds are stable under normal conditions but on being heated in ethanol or ethanol/acetic acid for a short time they undergo fragmentation and ring expansion giving substituted 1,3,4,5-oxatriazenes **64** (**Scheme 1.17**) This is thought to be a convenient route to the rare oxatriazene system (a potential $8\pi$ planar system) The only other route known to this system is by the photolysis of a triazole-N-oxide[44]



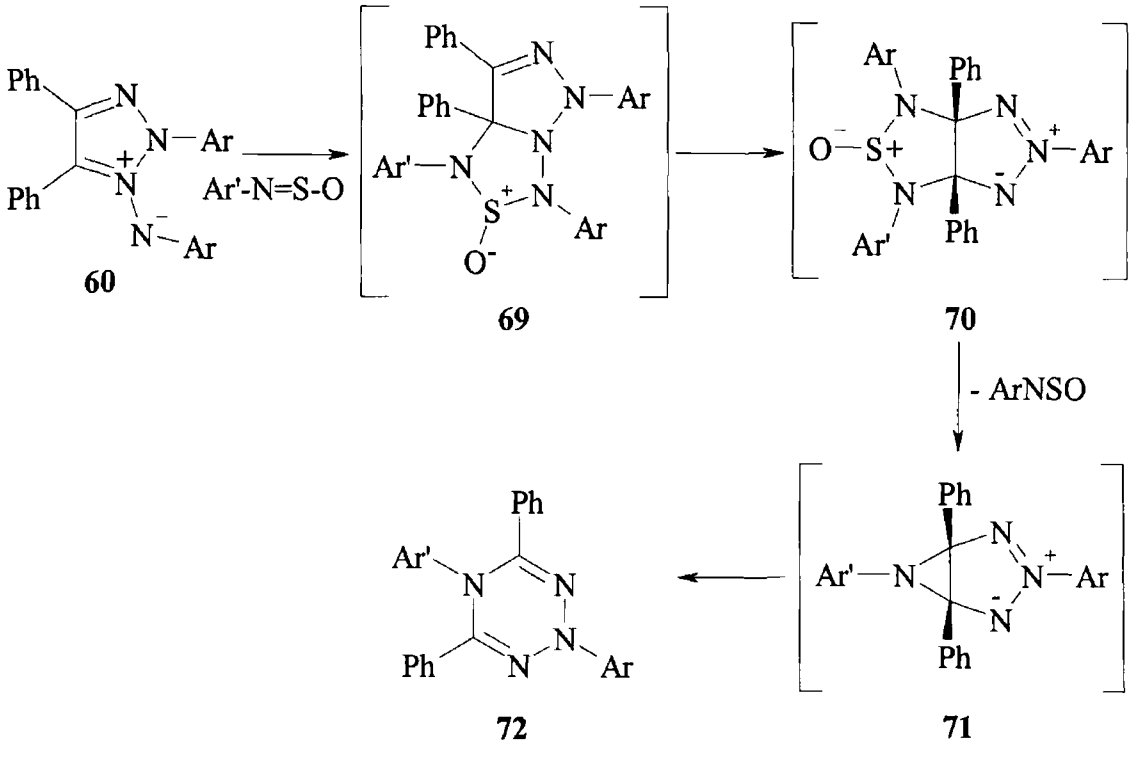

**Scheme 1 17** *Cycloaddition of cinnamaldehyde to 1,3-dipole, followed by 1,4-sigmatropic rearrangement Fragmentation and ring expansion on heating gives the 1,3,4 5-oxatriazine ring*

This reaction was later extended to a range of aldehydes and to a range of cycloalka-1,2,3-triazoliumaminides [R', R' = $(CH_2)_{n+2}$][45] The tricyclic derivatives of the ring system were the first examples of oxatetraazapropellane systems **65** These initial isolated products were then transformed into the 1,3,4,5-oxatriazine system **68** and the new 1,2,3-triazaspiroalkane derivatives **67** by heating in ethanol containing acetic acid




**Scheme 1.18** *Formation of 1,3,4,5-oxatriazine systems and 1,2,3-triazaspiroalkane derivatives following the initial cycloaddition of 1,2,3-triazolium imide with aldehydes*

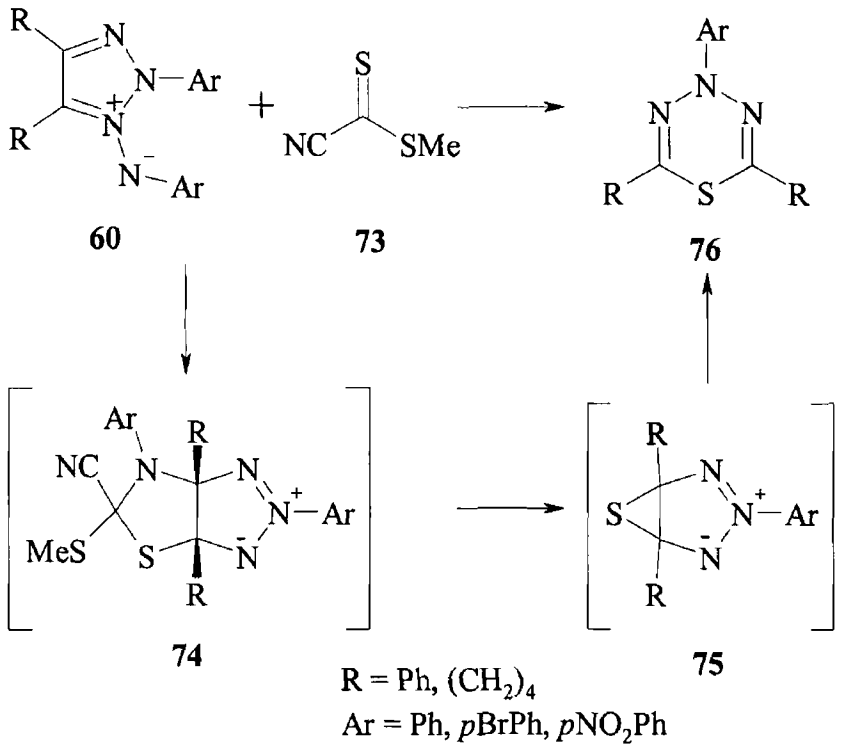
N-sulphinylamines readily undergo 1,3-dipolar cycloadditions and when substituted 1,2,3-triazolium imides were treated with aryl-N-sulphmylammes in benzene the tetrazines **72** were obtained in high yields (**Scheme 1 19**)[46] Loss of a molecule of N-sulphinylamine from **70** may occur in either of two ways when the Ar and Ar' substituents are different, both expected products can be formed, but PhNSO is lost preferentially The ring expansion of **71** is a disrotatory outward electrocyclic process In theory, this could be sterically constricted by bridging the two R substituents When RR = $[CH_2]_5$ the ring expansion was found to still occur, but when the bridging chain was shortened to four carbons the disrotatory outward process was prohibited




60 69 70 71 72

**Scheme 1.19** *Addition of aryl-N-sulphinylamine to 1,2,3-triazolium imides Loss of N-sulphinylamine from resulting adduct, followed by ring expansion gives the 1,2,3,5-tetrazine*

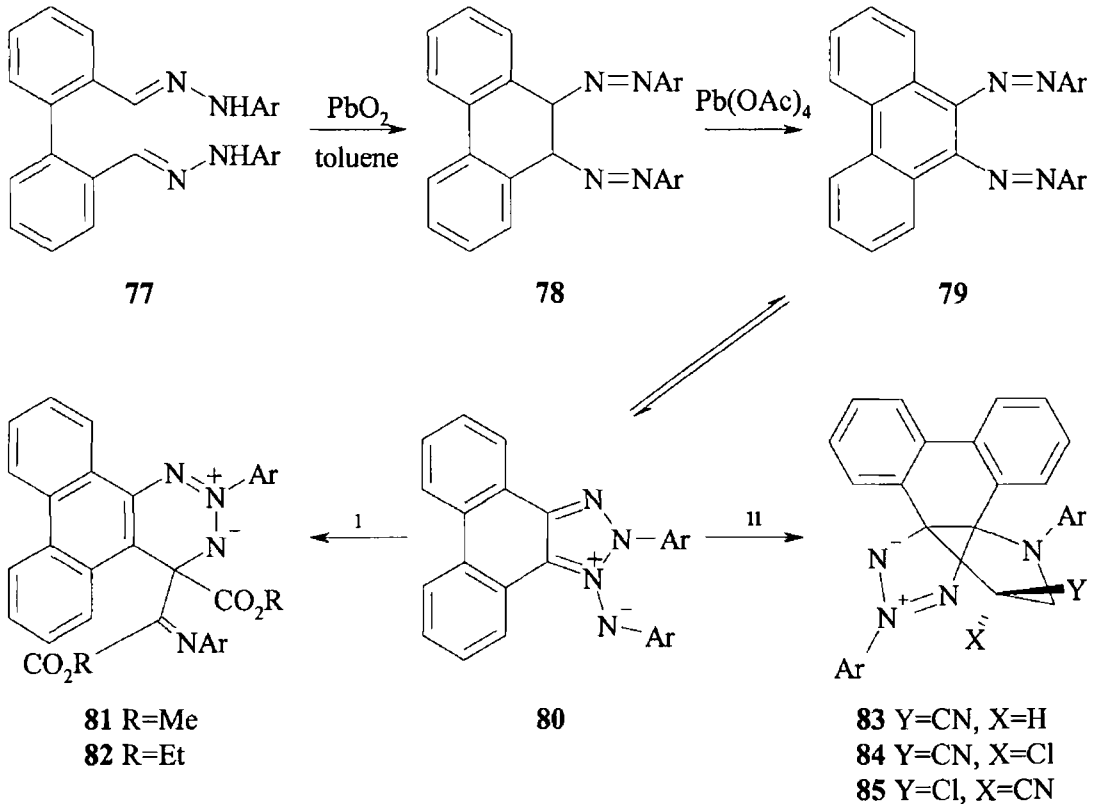
A similar sequence of reactions occurs when methyl cyanodithioformate **73** is used as the dipolarophile in the initial 1,3-dipolar cycloaddition[47,48] The final product, the rare 8π 1,3,4,5-thiatriazine **76**, is produced in high yields (**Scheme 1 20**) None of the intermediates were detected owing to the rapidity of the reaction of the dipole and dipolarophile to give the thiatriazine The fragment which is eliminated in going from **75** to **76** was detected as a small amount of resin and is thought to have derived from the imine MeS(CN)C=NPh




**Scheme 1.20** *Addition of methyl cyanodithioformate to triazolium imide 1,3-dipole, ultimately giving 1,3,4,5-thiatriazines*

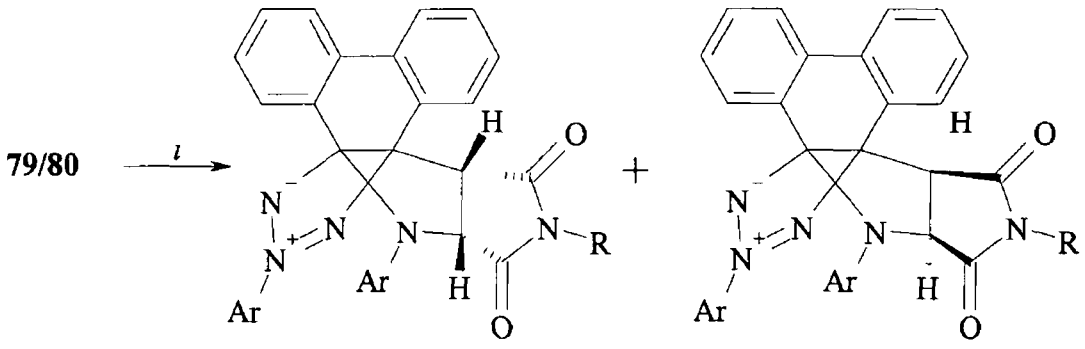
The 2,4,5-triaryl-1,3,4,5-thiatriazines, **76** were unexpectedly obtained in high yields when triazolium imide 1,3-dipole was treated with dry hydrogen sulfide in dichloromethane for 15 minutes at room temperature[49] The mechanism for this reaction does not involve a 1,3-dipolar cycloaddition

A range of new fused ring systems based on phenanthrene were obtained from cycloaddition-rearrangement reactions of 9,10-bisarylazophenanthrenes with alkyne and alkene dipolarophiles[50] Heating compound **79** with dialkyl acetylenedicarboxylates in toluene for 1 – 4 hours gave high yields of the new 1,2,3-triazatriphenylene derivatives **81** and **82** This experimentally simple, one-pot reaction involves a complicated cycloaddition-ring expansion process which appears to be dominated by the need to preserve the phenanthrene structure




**Scheme 1.21** *Reactions of 9,10-bisarylazophenanthrenes with i) dialkyl acetylenedicarboxylates ii) acrylonitrile or 1-chloro-1-cyanoethene*

Similar reactions involving prolonged heating of **79** with the alkene dipolarophiles acrylonitrile, 1-chloro-1-cyanoethene and some N-substituted maleimides gave the series of new tricyclic phenanthrene derivatives **83-89** (**Schemes 1 21** and **1 22**) The reaction with acrylonitrile was regio- and stereoselective, giving the products **83** only With the other alkenes approximately equal mixtures of the *endo-exo* pairs **84/85, 86/87** and **88/89** were obtained These isomeric pairs were not interconvertible under the reaction conditions Normally, the preferred initial cycloaddition follows the *endo* mode giving *exo*-isomers as products, but the presence of the phenanthrene moiety has negated the favourable *endo*-transition state resulting in almost equal mixtures of both isomeric products *Endo* and *exo* isomers were distinguished by $^1$H NMR spectroscopy and X-ray crystallography

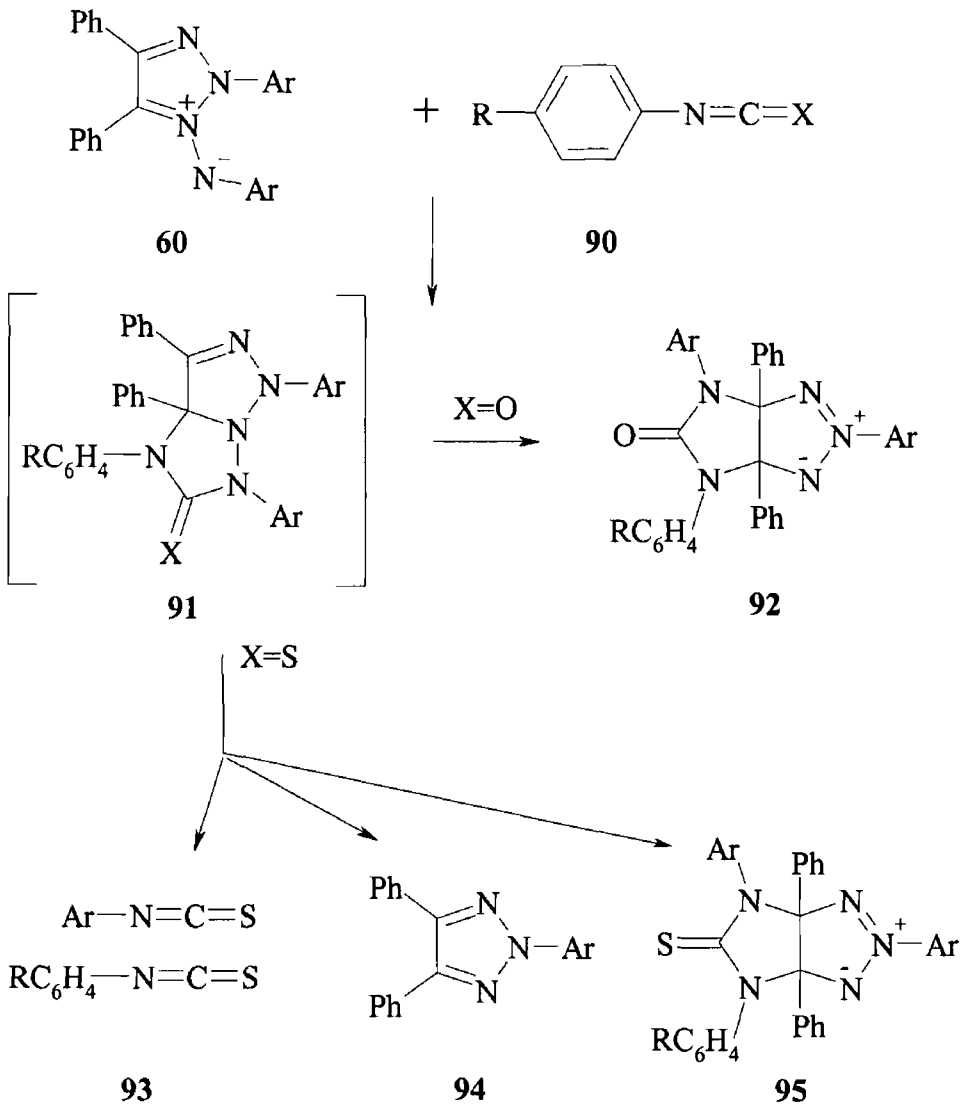



**86** R=Ph
**88** R=Me

**87** R=Ph
**89** R=Me

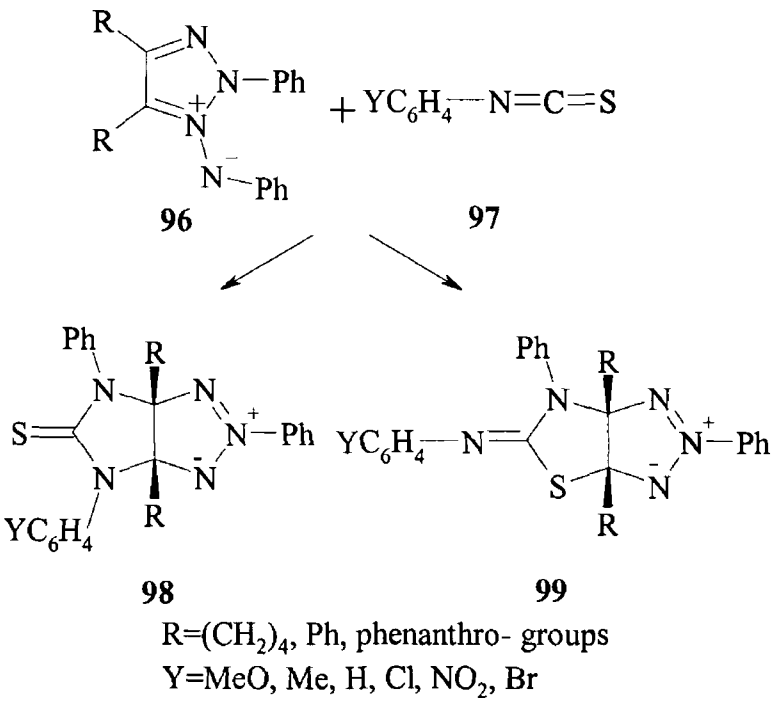
**Scheme 1 22** *Isomeric pairs obtained with the reaction of 9,10-bisarylazophenanthrenes with i) N-substituted maleimides*

George *et al*[32], in the earlier work on triazolium N-imides, used isocyanates and isothiocyanates as dipolarophiles The structures of the adducts were later reassigned in work by Butler *et al* [51] The dipoles reacted with the isocyanates and isothiocyanates at the N=C bond by the usual route, the isocyanates giving high yields of the oxoimidazol-triazolines **92** (**Scheme 1 23**) The reactions with the isothiocyanates gave the corresponding thione products **95** These reactions also gave another insight into the initial adduct **91** which has never been directly detected The sulfur derivatives of the intermediate **91** (X=S) were significantly less stable than the oxygen derivatives (X=O) This instability was found to increase by both electron donating or withdrawing substituents in any of the N-aryl rings of **91** The reactions of dipole **60** with isothiocyanates gave mainly the triazoles **94**, small quantities of the imidazotriazolines **95** and two aryl isothiocyanates, one of which was the original reactant and the other of which had exchanged its aryl group for an aryl group from the dipole **60** The formation of both types of isothiocyanates accompanying the products **94** gives further support for the intermediates **91** which can readily fragment to all these products



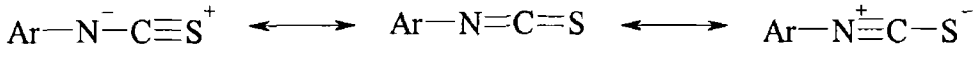

**Scheme 1.23** *Addition of isocyanate (X=O) and isothiocyanate (X=S) to triazolium N-imide 1,3-dipole*

It was later discovered that the triazolium N-imide 1,3-dipoles react with aryl isothiocyanates at both the N=C and C=S sites to give mixtures of substituted imidazolo[4,5-d][1,2,3]triazoles **98** and new thiazolo[4,5-d][1,2,3]triazoles **99** [52] **(Scheme 1 24)**




**Scheme 1 24** *Addition of isothiocyanates to triazolium N-imide 1,3-dipoles Addition can occur at both the N=C and C=S sites*

Substituents on the aryl isothiocyanate have a large influence on the competition between the alternative reaction sites Electron-withdrawing groups at the *para*-position of the phenyl isothiocyanates orientate the reaction strongly towards the C=S site This can be explained by the resonance contributions of forms **100** and **101** to the structure of aryl isothiocyanates (**Figure 1.17**)

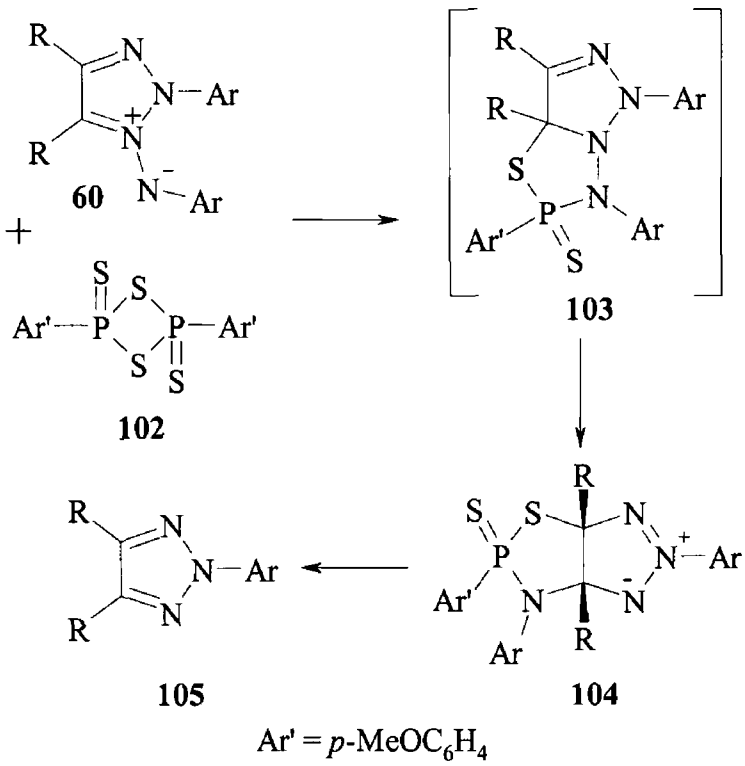



**100** **101**

**Figure 1 18** *Resonance structures of aryl isothiocyanates, explaining their ambident behaviour*

The contribution of **101** is enhanced by electron-donating substituents and that of **100** enchanced by electron-withdrawing groups It can be shown that form **101** reacts with the dipole to favour products **98** while products **99** arise from cycloaddition where form **100** is favoured

The addition of Lawesson's reagent **102** to the triazolium imide 1,3-dipole system proceeds as usual to give the fused nitrogen-phosphorous-sulphur ring system **104** [53] Kinetic studies show that the addition is 2000 times faster than that of acrylonitrile and twice as fast as the C=S dipolarophile of MeSC(S)CN, indicating that Lawesson's reagant is a superdipolarophile However, these products were found to be unstable in solution, breaking down to give the 1,2,3-triazoles **105**



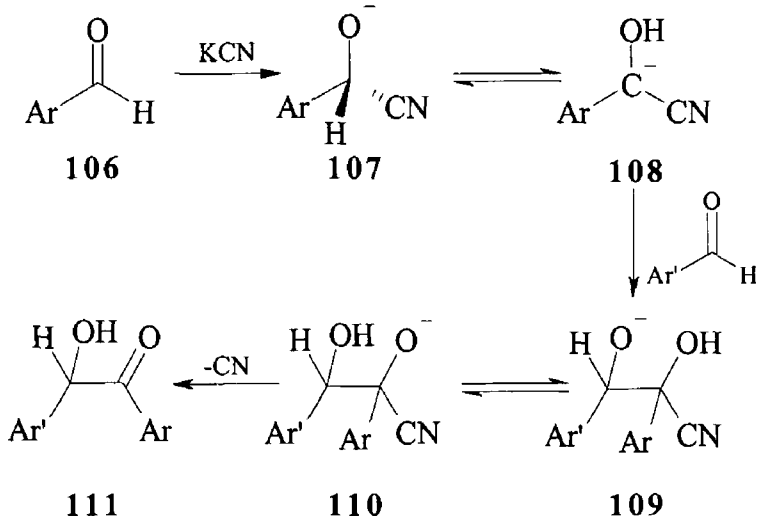

**Scheme 1.25** *The addition of Lawesson's reagent to triazolium N-imide*

## 1.4 Results and Discussion:

### *1.4.1 Synthesis of Triazolium Imide 1,3-Dipoles*

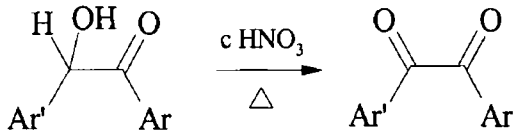
The synthesis of the triazolium imide 1,3-dipole **118a-e** was carried out in two steps 1) the synthesis of the dihydrazone from diketones and hydrazines (**Scheme 1 28**), and 2) the oxidation of the dihydrazone (**Scheme 1.29**) Five different dihydrazones were synthesised – from benzil, 2,3-butanedione and 4,4'-dichlorobenzil, using phenylhydrazine and *p*-nitrophenylhydrazine Of the diketones, benzil and 2,3-butanedione are commercially available 4,4'-dichlorobenzil was synthesised by the potassium cyanide catalysed benzoin condensation of 4-chlorobenzaldehyde (**Scheme 1.26**), followed by oxidation with nitric acid and recrystallisation from water (**Scheme 1.27**)

The general mechanism of the benzoin condensation involves the initial attack of the cyanide on the aldehyde **106** (Ar = *p*ClPh) to form an activated aldehyde carbanion intermediate **108**, which reacts with another molecule of the aldehyde (Ar' = *p*ClPh) Regeneration of the cyanide ion gives the benzoin **111**




**Scheme 1 26** *Benzoin condensation of an aldehyde, catalysed by the cyanide ion*

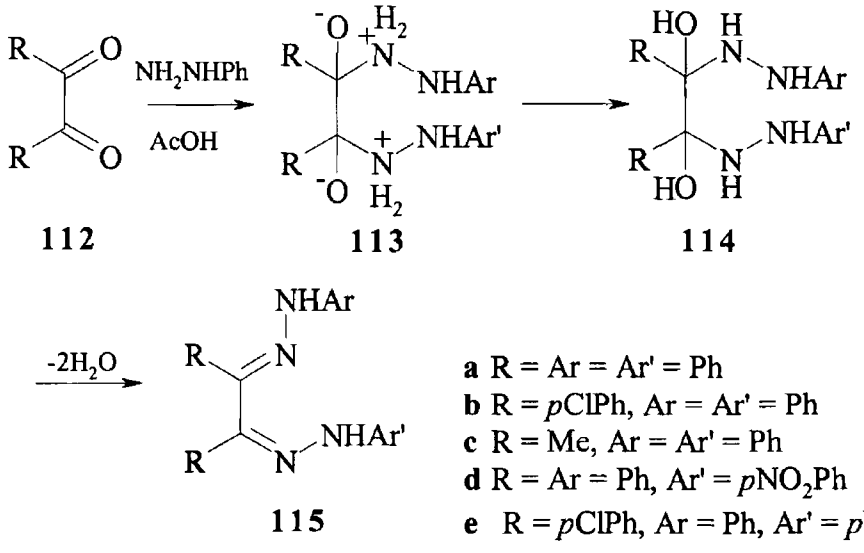
4,4'-Dichlorobenzoin **111** (Ar, Ar' = *p*ClPh) was then oxidised to the corresponding benzil by heating under reflux in concentrated nitric acid During this reaction a brown gas (nitrogen tetroxide) was given off and cessation of this evolution indicated the completion of the reaction (5-6 hours) Recrystallisation from a large volume of water gave high yields of the 4,4'-dichlorobenzil **112** (Ar, Ar' = *p*ClPh) in pure form




111 112

**Scheme 1 27** *General scheme for the nitric acid oxidation of benzoin to benzil, for benzoins derived from aromatic aldehydes*

Reaction of the α-diketone **112**, (R = Ph, pClPh, Me) with phenylhydrazine then gave the bis-phenylhydrazones **115a-c** Reaction conditions varied with the starting α-diketone 2,3-Butadione **112** (R = Me) reacted with the phenylhydrazine at room temperature in glacial acetic acid to give excellent yields of the dihydrazone **115c** The reaction of benzil **112** (R = Ph) with phenylhydrazine required heating under reflux in glacial acetic acid The reaction of 4,4'-dichlorobenzil **112** (R = *p*ClPh) with phenylhydrazine in acetic acid under reflux gave two products the required dihydrazone **115b**(a photochromic compound) and the monohydrazone Extended reaction times improved the yield of the dihydrazone




112 113 114

115

**a** R = Ar = Ar' = Ph
**b** R = *p*ClPh, Ar = Ar' = Ph
**c** R = Me, Ar = Ar' = Ph
**d** R = Ar = Ph, Ar' = *p*$NO_2$Ph
**e** R = *p*ClPh, Ar = Ph, Ar' = *p*$NO_2$Ph

**Scheme 1.28** *Reaction of substituted benzils with phenylhydrazines , giving dihydrazones*

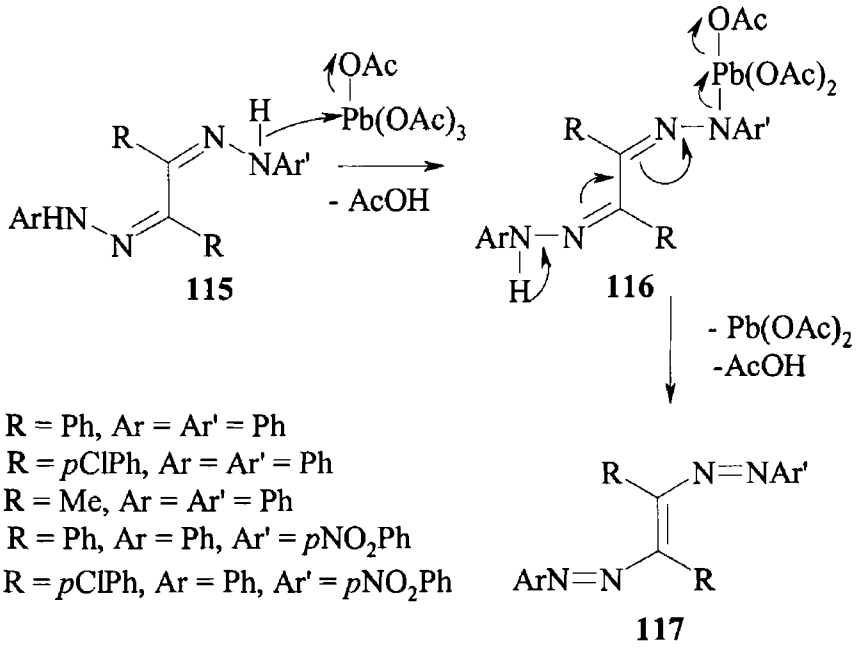
For the 'mixed' dihydrazones **115d-e** it was necessary to first synthesise the monophenyl hydrazone This was easily obtained in the case of dichlorobenzil, the monophenyl hydrazone being a side product of the synthesis of the diphenylhydrazone To synthesise

the benzil monophenylhydrazone, equimolar amounts of benzil and phenylhydrazine were reacted together by heating in ethanol Evaporation of the solvent gave the monohydrazone in good yields

To synthesise the dihydrazone **115d-e**, the monophenylhydrazones were heated with one equivalent of p-nitrophenyl hydrazine in the absence of solvents After melting the mixture was stirred for a further 2 hours at 150-160°C Cooling, and addition of acetic acid afforded the mixed dihydrazones in moderate yields (57%, 42%)

The next step involved the oxidation of the dihydrazones **115** to the bisarylazo analogues **117** The oxidation has been carried out using a number of reagents including nickel peroxide in benzene, sodium dichromate in acetic acid, sodium in ethanol, thallium triacetate in acetic acid, lead dioxide in dichloromethane, lead tetraacetate in acetic acid or dichloromethane and iodobenzene diacetate in acetic acid [41,54]

Stirring the dihydrazones in glacial acetic acid at room temperature with excess lead tetraacetate as the oxidising agent gave the required oxidised products in good yields



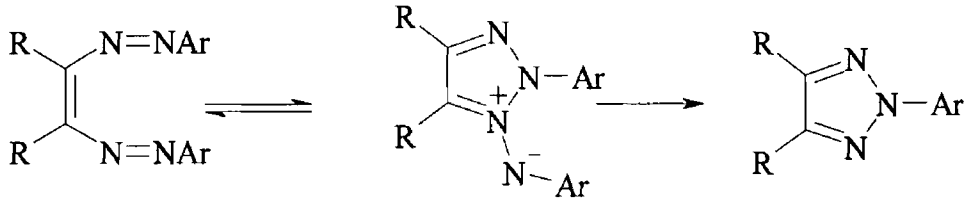

**a** R = Ph, Ar = Ar' = Ph
**b** R = *p*ClPh, Ar = Ar' = Ph
**c** R = Me, Ar = Ar' = Ph
**d** R = Ph, Ar = Ph, Ar' = $pNO_2Ph$
**e** R = *p*ClPh, Ar = Ph, Ar' = $pNO_2Ph$

**Scheme 1.29** *Oxidation of dihydrazones with lead tetraacetate to give bis-arylazostilbenes*

All of the products were deeply coloured due to the extent of conjugation throughout the system *Cis*-1,2-bisphenylazostilbene **117a** and *cis*-1,2-bisphenylazo(4,4'-dichloro)stilbene **117b** have been shown to exist in dynamic equilibrium with the mesoiomc form **118a** and **b** The mesoiomc structure **118** represents an azomethine system, and so, is capable of undergoing 1,3-dipolar cycloadditions

However, 2,3-bisphenylazo-2-butene **117c** does not readily adopt the mesoiomc structure [37] It is probable that the most stable form of 2,3-bisphenylazo-2-butene has a *trans* geometry across the C=C bond, having the bulky azo groups away from each other *Cis-trans* isomerisation can be achieved in the presence of HCl, and the *cis*-isomer then adopts the mesoionic form (See **Scheme 1.12**)

Heating 1,2-bisphenylazostilbene **117a** and 1,2-bisphenylazo(4,4'-dichloro)stilbene **117b** in the absence of solvent gives good yields of the triazole [37]



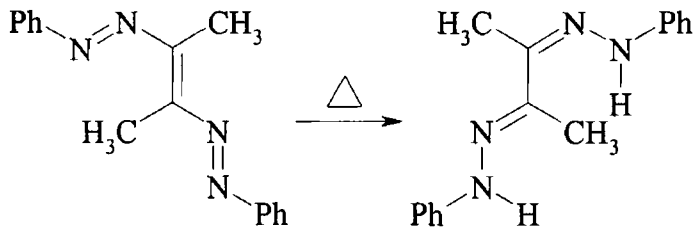

**117** **118** **119**

**Scheme 1 30** *Formation of triazole from the heating and irradiation of bisarylazostilbenes (117a R=Ph,117b R= pClPh)*

The same triazole **119** was also formed on irradiation of a benzene solution of the stilbenes The formation of the triazoles can be rationalised in terms of the thermal and photochemical fragmentation of the corresponding phenyhminotriazolium derivatives, resulting in the loss of phenyl nitrene

When 2,3-bisphenylazo-2-butene **117c** is subjected to thermolysis or photolysis under similar conditions, no triazole is produced, due to the stable *trans*-geometry across the C=C bond Katritzky *et al*[55] reported that when heated at 190°C for 2-3 minutes the purple 2,3-bisphenylazo-2-butene is converted to a yellow isomer (mp 230-233°C) It was suggested that this was a *cis-trans* isomerisation However when we carried out the

same reaction it was found that the bisphenylazo compound **117c** gave a yellow product which we identified as the bisphenylhydrazone **115c** (**Scheme 1.31**)



**117c** **115c**

**Scheme 1.31** *Reduction of 2,3-bisphenylazo-2-butene by heating*

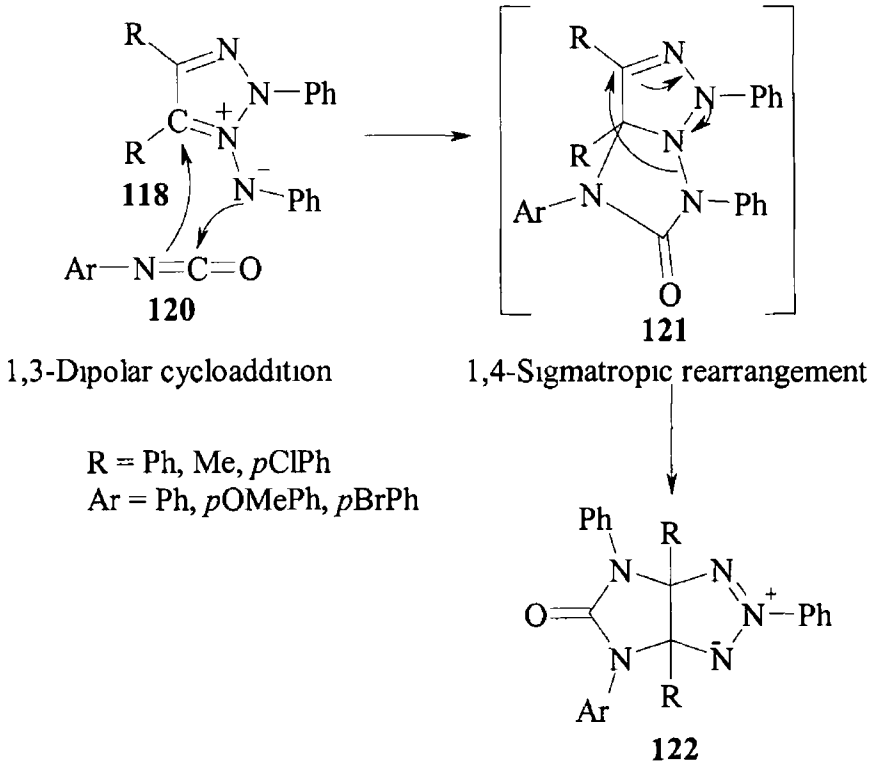
The reaction has also been carried out in an inert atmosphere and in some solvents, those being acidified ethanol, glacial acetic acid and toluene, and under all these conditions the bisphenylhydrazone is obtained

The occurrence of this reduction is both surprising and puzzling Under the reaction conditions, there is no reducing agent present and no source of hydrogen atoms Applying the definition that oxidation is the loss of electrons and reduction is the gain of electrons, and that they occur concurrently, it would be expected to have an accompanying oxidation However there are no obvious compounds present in the reaction mixture and only bisphenylhydrazone is obtained when the reaction is completed

### *1 4.2. Reactions of Triazolium Imide 1,3-Dipoles*

*1 4 2 1 Reactions with Isocyanates*

The reactions of triazolium imide 1,3-dipoles **118** with isocyanates **120** have been extensively studied [32a 51] Isocyanates add to the 1,3-dipole across the C=N bond, followed by a 1,4-sigmatropic rearrangement to give the bicyclic adducts **122** in good yields




**Scheme 1 32** *Mechanism of the 1,3-dipolar cycloaddition and 1,4-sigmatropic rearrangement which gives bicyclic imidazo-1,2,3-triazoles*

The reactions are usually carried out in refluxing acetone, although benzene and toluene can also be used and reach completion in 1-4 hours All adducts **122** show the characteristic bridgehead carbon signals at 90-100ppm and the carbonyl signal at ~170ppm The adduct **122a** obtained from the reaction of phenyl isocyanate and 1,2-bis(phenylazo)stilbene **117a** (R' = H) has a plane of symmetry and so only half of the expected signals are seen on the $^{13}C$ NMR spectrum This plane of symmetry is removed by the use of substituted isocyanates e g 4-methoxyphenyhsocyanate and 4-bromophenylisocyanate For the adducts obtained by the use of these substituted isocyanates in the cycloaddition, all of the expected signals were seen in the $^{13}C$ NMR

spectrum All of the rearranged adducts are crystalline solids, with sharp melting points and white or pale brown in colour (**Table 1 4**)

The cycloadditions of 1,2-bis(phenylazo)butene **117c** were carried out in dry acetone with a steady stream of HCl gas bubbling through the reaction mixture The HCl was required to catalyse the *trans-cis* isomerisation of the oxidised dihydrazone, enabling it to adopt the mesoionic 1,3-dipole formation The yields for this reaction were lower than for the aryl substituted dipoles This is probably due to the fact that isocyanates are easily hydrolysed under acidic conditions, giving primary amines as products

*Reaction with N-tosyl isocyanate*

The tosyl group is a well known protecting group, but is sometimes difficult to remove (see **Chapter 2**) The presence of this functional group on a nitrogen atom in the bicyclic adduct would give scope for different functional groups to be introduced to the molecule

The addition of tosyhsocyanate to the dipole **118a** proceeded in the usual way, a 1,3-dipolar cycloaddition followed by a 1,4-sigmatropic rearrangement Again the reaction was carried out in refluxing acetone and the product required a large volume of ethanol for recrystallisation Yields of **122j** for this reaction were high (77%)

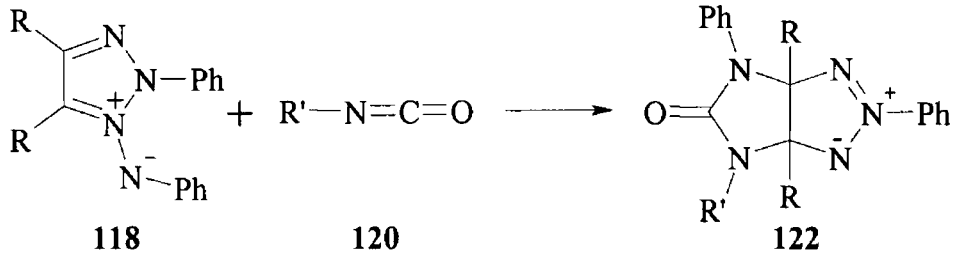
Attempts to remove the tosyl group by treatment with sodium ethoxide in ethanol failed to give the required product After 5 days reflux, no reaction had occurred although similar reactions have been reported to take place at room temperature in two hours [56]

*Reaction with Chlorosulfonyl isocyanate*

Chlorosulfonyl isocyanate has previously been used as a dipolarophile [57] The reaction of the isocyanate with 1,2-bis(phenylazo)stilbene **117a** proceeded as expected, with addition across the C=N bond and 1,4-sigmatropic rearrangement The reaction was carried out in sodium-dried benzene because of the instabilty of the isocyanate in the presence of water

Benzenethiol-pyridine reduction of the chlorosulfonyl group gave the novel adduct **122k** in reasonable yield It was hoped that removal of the proton from nitrogen may

facilitate ring opening to give the required pentazocine However, prolonged heating of the adduct in methanol in the presence of sodium methoxide gave no reaction Heating the adduct in toluene also resulted in no change in the molecule



**118** **120** **122**

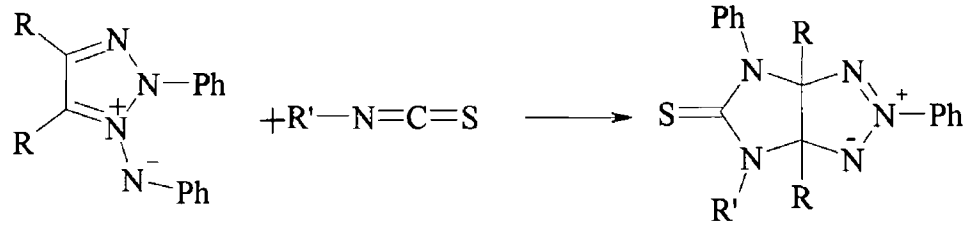
| 122 | R | R' | Yield % | M.p. °C |
|---|---|---|---|---|
| a | $C_6H_5$ | $C_6H_5$ | 61 | 231-232 |
| b | $C_6H_5$ | *p*-$BrC_6H_4$ | 84 | 234-236 |
| c | $C_6H_5$ | *p*-$OMeC_6H_4$ | 76 | 222-224 |
| d | *p*-$ClC_6H_4$ | $C_6H_5$ | 82 | 214-216 |
| e | *p*-$ClC_6H_4$ | *p*-$BrC_6H_4$ | 82 | 286-288 |
| f | *p*-$ClC_6H_4$ | *p*-$OMeC_6H_4$ | 72 | 236-238 |
| g | $CH_3$ | $C_6H_5$ | 58 | 240 |
| h | $CH_3$ | *p*-$BrC_6H_4$ | 47 | 190 |
| i | $C_6H_5$ | Ts | 77 | 249-250 |
| j | $C_6H_5$ | $ClO_2S$ | 46 | 207 |
| k | $C_6H_5$ | H | 60[1] | 263 |

**Table 1.4** *Yields and melting points of the 5-oxo-imidazo-1,2,3-triazoles*

[1] This yield does not refer to the cycloaddition reaction, but to the dechlorosulfonylation reaction

*1 4 2 2 Reactions with Isothiocyanates*

The reactions of triazohum imide 1,3-dipoles **118** with isothiocyanates have also been studied extensively Isothiocyanates can cycloadd to 1,3-dipoles across either the C=S bond or the N=C bond, depending on the substituents on the aryl ring Again, the reaction was carried out in dry acetone followed by removal of the solvent and recrystallisation from ethanol Yields of the cycloadducts **124a-d** were moderate to good but lower than the corresoponding yields for addcuts **122** due to the competing addition across the C=S bond Electron-donating groups like the methoxy group should orientate the reaction towards addition at the C=N bond and yields were expected to be better than those achieved




**118** **123** **124**

| 124 | R | R' | Yield % | M p °C |
|---|---|---|---|---|
| a | $C_6H_5$ | *p*-$BrC_6H_4$ | 30 | 256 |
| b | $C_6H_5$ | *p*-$OMeC_6H_4$ | 18 | 230-232 |
| c | *p*-$ClC_6H_4$ | *p*-$BrC_6H_4$ | 27 | 260 |
| d | *p*-$ClC_6H_4$ | *p*-$OMeC_6H_4$ | 38 | 260 |

**Table 1 5** *Yields and melting points of the 5-thio-imidazo-1,2,3-triazoles*

## 1.5 Conclusion.

The range of imidazo-1,2,3-triazoles, obtained by the cycloaddition of triazolium imide dipoles with isocyanates and isothiocyanates, has been extended by varying the starting materials

Varying the starting benzil derivatives and subsequently the 1,3-dipole, leads to bicyclic adducts with various substitutents at the bridgehead carbons For the first time, imidazo-1,2,3-triazoles with methyl groups at the bridgehead positions have been obtained Synthesis of these molecules was successful despite the fact that the dipolarophiles are hydrolysable in acidic conditions It is necessary to carry out the cycloaddition in the presence of HCl gas in order for the dipole to form

By using different aryl isocyanates and isothiocyanates, the substitution on the N-4 atom was varied Of interest was the use of *p*-toluenesulfonyl isocyanate and chlorosulfonyl isocyanate as dipoles It proved difficult to remove the *p*-toluenesulfonyl group, however the chlorosulfonyl group was easily removed by benzenethiol-pyridine reduction Attempts were made to induce ring opening by base catalysed deprotonation of the N-4 atom However these were not successful

## 1 6 Experimental

Infrared spectra were measured on a Perkin-Elmer System 2000 FT-IR

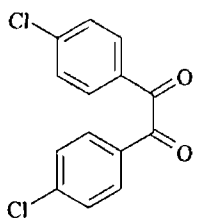
NMR spectra were recorded on a Bruker 400MHz spectrometer

Microanalytical data was provided by the Chemistry Department in University College, Dublin

Melting points were recorded on a Griffin Melting Point Apparatus and are uncorrected

### *1 6.1. Synthesis of 1,3-Dipoles*

#### *1 6 1 1 Synthesis of 4,4'-dichlorobenzil (112)*



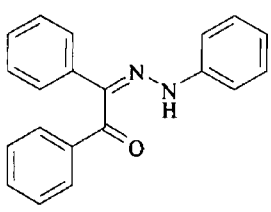
4-Chlorobenzaldehyde (14g, 0 1mol) and 50cm$^3$ aqueous ethanol were placed in round-bottomed flask Potassium cyanide (5g, 0 07mol) in 10cm$^3$ of water was added and the mixture was stirred under reflux for 3 hours The orange solution was diluted with 100cm$^3$ of water and cooled at –4°C overnight The ethanol/water mixture was decanted off, leaving a viscous orange oil 60cm$^3$ of concentrated nitric acid was added and the mixture was stirred under reflux until the emission of brown fumes of nitric oxides had ceased (approx 10 hours) The mixture was cooled to room temperature, poured into 350cm$^3$ of cold water, and crystallisation of a yellow solid occurred immediately The mixture was left to further crystallise overnight and the solid was removed by filtration, yielding 12 92g (0 046mol, 92%) of 4,4'-dichlorobenzil

**M p** 198-199°C (lit 198-199°C)

**$^1$H (CDCl$_3$) (ppm)**· 7 56 (4H, d, J=8Hz), 7 69 (4H, d, J=8Hz), (all phenyl H)

**$^{13}$C (CDCl$_3$) (ppm)** 128 84, 129 72 (phenyl CH), 131 24, 131 75 (phenyl C), 137 87 (C=O)

#### *1 6 1 2 Synthesis of benzil monophenylhydrazone*



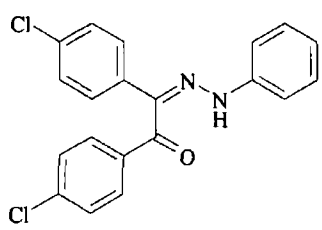
Benzil (5g, 0 0238mol) and phenylhydrazine (2 5cm$^3$, 0 0254mol) were stirred under reflux in 75cm$^3$ of ethanol and 1cm$^3$ of acetic acid for 2 hours Concentration of the solvent yielded 3 75g (0 0125mol 53%) of the monohydrazone which was removed by filtration and washed with hexane

**M.p.:** 134°C (lit 135°C)

**$^1$H (DMSO-d$_6$) (ppm).** 6 90 (1H, t), 7 21 (4H, m), 7 40 (2H, d), 7 56 (6H, m), 7 90 (2H, d) (all aromatic protons), 10 11 (1H, s) (N-H)

**$^{13}$C (DMSO-$d_6$) (ppm):** 114 87, 122 07, 127 99, 129 17, 129 29, 129 37, 129 31, 131 23, 131 55, 139 67, 141 41, 144 16 (C=N and aromatic Cs), 191 65 (C=O)

*1 6 1 3 Synthesis of 4,4'-dichlorobenzil- monophenylhydrazone*



4,4'-Dichlorobenzil (2 5g, 009mol) and phenylhydrazine (2cm$^3$, 0 02mol) were stirred under reflux in glacial acetic acid for 2 hours The red solution was cooled to room temperature, during which time a yellow solid formed This was removed by filtration and washed with pet ether 40-60

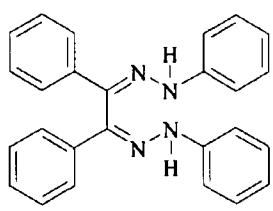
It was found to be the mono-hydrazone

**M p** 170-172°C

**$^1$H (DMSO-$d_6$) (ppm).** 6 91 (2H, t, J=8Hz), 7 16-7 26 (5H, m), 7 40 (2H, d, J=8Hz), 7 58 (2H, d, J=8Hz), 7 90 (2H, d, J=8Hz) (all phenyl H), 10 24 (1H, s) (N-H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 114 60, 122 01, 127 76, 128 93, 129 11, 129 68, 131 67, 131 87, 133 72, 136 04, 137 45, 143 58 (C=N and aromatic Cs), 189 65 (C=O)

*1 6 1 4 Synthesis of 1,2-bis(phenylhydrazone)stilbene (115a)*



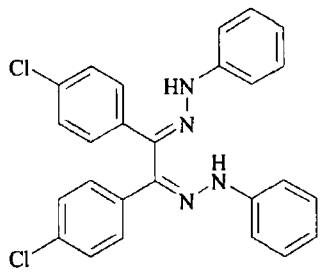
Benzil (5g, 0 024mol) and phenylhydrazine (5 0cm$^3$, 0 05mol) were stirred under reflux in 50cm$^3$ glacial acetic acid for 1 hour The solution was cooled in ice, and a yellow solid formed This was removed by filtration and washed with pet ether 40-60, yielding 7 24g (0 018mol, 75%) of 1,2-bis(phenylhydrazone)stilbene

**M p** 222-224°C (lit 234°C)[29]

**$^1$H (DMSO-$d_6$) (ppm):** 6 79 (2H, t, J=8Hz), 7 20 (4H, t, J=8Hz), 7 27 (2H, t, J=8Hz), 7 32-7 37 (8H, m), 7 60 (4H, d, J=8Hz) (all phenyl CH), 9 62 (2H, s) (N-H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 113 77, 120 02, 125 7, 128 16, 128 99, 129 14, 135 87, 135 94 (all phenyl C and CH), 145 52 (C=N)

*1 6 1 5 Synthesis of 1,2-bis(phenylhydrazone)-4,4'-dichlorostilbene (115b)*



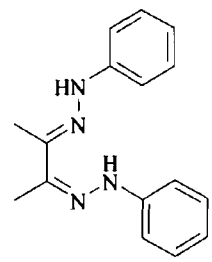
The solvent was removed from the filtrate under vacuum and the residue was recrystallised from ethanol yielding 1 34g (0 003mol, 33%) of the yellow 1,2-bis(phenylhydrazone)-4,4'-dichlorostilbene

**M.p** 190-192°C (lit 205°C)

**$^1$H (DMSO-$d_6$) (ppm).** 6 80 (2H, t, J=8Hz), 7 20 (4H, t, J=8Hz), 7 32 (4H, d J=8Hz), 7 41 (4H, d, J=12Hz), 7 56 (4H, d, J=12Hz) (all phenyl H), 9 78 (2H, s) (N-H)

**$^{13}$C (DMSO-$d_6$) (ppm).** 113 50 (phenyl CH), 119 99 (phenyl C), 126 85, 128 73, 128 84, 132 25 (all phenyl CH), 133 79 134 34 (phenyl C), 144 93 (C=N)

*1 6 1 6 Synthesis of 1,2-bis(phenylhydrazone)butene (115c)*



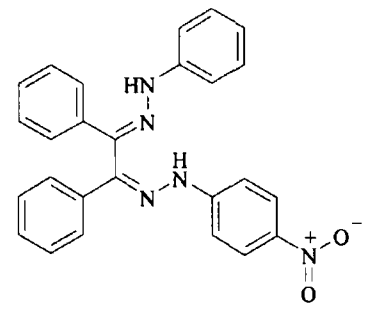
2,3-Butadione (3 5cm$^3$, 0 04mol) and phenylhydrazine (10cm$^3$, 0 10mol) were stirred in 30cm$^3$ of glacial acetic acid at room temperature for 45 minutes The resulting yellow crystals were removed by filtration and washed with pet ether 40-60, yielding 9 45g (0 035mol, 89%) of 1,2-bis(phenylhydrazone)butene

**M p** 242-244°C (lit 245°C)

**$^1$H (DMSO-$d_6$) (ppm)** 2 20 (6H, s) ($CH_3$), 6 75 (2H, t, J=4Hz), 7 215 (8H, d, J=4Hz) (all phenyl CH), 9 25 (2H, s) (N-H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 10 94 ($CH_3$), 113 03, 119 18, 129 23, 143 09 (all phenyl C and CH), 146 18 (C=N)

*1 6 1 7 Synthesis of 1-(phenylhydrazone)-2-(p-nitrophenylhydrazone)stilbene (115d)* [1]



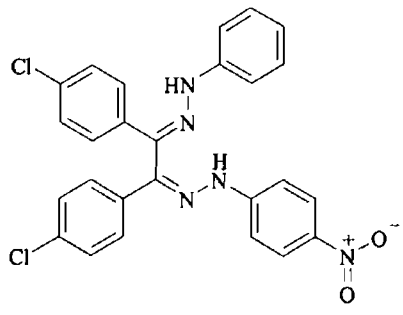
Benzil-monophenylhydrazone (3g, 0 01mol) and *p*-nitrophenylhydrazine (1 53g, 0 01mol) were heated at 150°C for 2 hours On cooling and the addition of acetic acid, the dihydrazone fell out of solution The mixture was heated and on cooling the pure dihydrazone was formed This was removed by filtration, yielding 2 48g (0 0057mol, 57%)

[1] Procedure take from Alexandrou, N E *Tetrahedron,* **1966,** *22,* 1309

**M p..** 253°C(ht 255°C)[58]

Spectroscopic analysis was not carried out on this compound

*1 6 1 8 Synthesis of 1-(phenylhydrazone)-2-(p-nitrophenylhydrazone)-4,4'-dichlorostilbene (115e)*



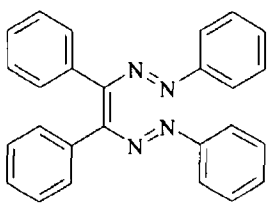
4,4'-Dichlorobenzil- monophenylhydrazone (2 39g, 0 0065mol) and p-nitrophenylhydrazine (1g, 0 0065mol) were heated at 150-160°C for 2 hours The mixture was cooled and then stirred under reflux in glacial acetic acid for a further 2 hours After cooling, the dihydrazone was removed by filtration It was recrystallised from ethanol yielding 1 36g (0 0027mol, 42%)

**M p** 236°C

**$^1$H (DMSO-$d_6$) (ppm):** 7 20-7 69 (19H, m) (all aromatic H), 9 63 (1H, s), 10 52 (1H, s) (both N-H)

**$^{13}$C (DMSO-$d_6$) (ppm):** 113 28, 113 82 (C=N), 125 57, 125 71, 125 99, 126 42, 128 14, 128 29, 128 99, 129 09, 129 18, 129 30, 129 37, 135 06, 135 71, 135 89, 139 57, 141 52 (all aromatic CH)

*1 6 1 9 Synthesis of 1,2-bis(phenylazo)stilbene (117a)*



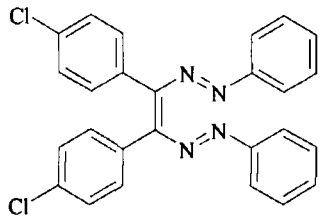
1,2-Bis(phenylhydrazone)stilbene (2 0g, 0 005mol) was stirred in 25cm$^3$ glacial acetic acid Lead tetraacetate (4 5g, 0 01mol) was added and the mixture stirred for 30 minutes, after which time the brown 1 68g (0 004mol, 90%) 1,2-bis(phenylazo)stilbene was removed by filtration and washed with petroleum ether 40-60

**M p** 165-167°C (lit 179°C)[32b]

**$^1$H ($CDCl_3$) (ppm)** 6 85 (1H, t, J=7 2Hz), 7 02 (2H, d, J=7 6Hz), 7 12 (2H, d, J=7 6Hz), 7 26-7 35 (5H, m), 7 38 (1H, t, J=7 6Hz), 7 48 (2H, d, J=6 4Hz), 7 52-7 55 (1H, q) (all aromatic CH)

**$^{13}$C ($CDCl_3$) (ppm):** 119 10, 123 88, 127 50, 128 84, 129 12, 129 26, 129 32, 129 40, 130 37, 131 80, 132 75

*1 6 1 10 Synthesis of 1,2-bis(phenylazo)-4,4'-dichlorostilbene (117b)*



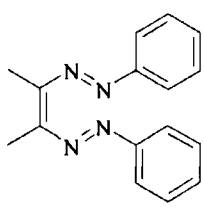
1,2-Bis(phenylhydrazone)-4,4'-dichlorostilbene (2 0g, 0 004mol) was stirred in 25cm$^3$ glacial acetic acid Lead tetraacetate (3 5g, 0 07mol) was added and the mixture stirred for 30 minutes, after which time 1 26g (0 0027mol, 67%) of the brown 1,2-bis(phenylazo)stilbene was removed by filtration and washed with petroleum ether 40-60

**M.p.** 196-198°C (lit 205°C)[37]

**$^1$H (CDCl$_3$) (ppm):** 6 95 (1H, d, J=7 6Hz), 7 40 (2H, d, J=8 0Hz), 7 15-7 22 (4H, m), 7 30 (2H, d, J=8 8Hz), 7 36 (5H, m), 7 42 (2H, d, J=8 8Hz) 7 53-7 55 (2H, q)

**$^{13}$C (CDCl$_3$) (ppm):** 123 92, 127 83, 129 57, 129 69, 130 61, 133 96

*1 6 1 11 Synthesis of 1,2-bis(phenylazo)butene (117c)*



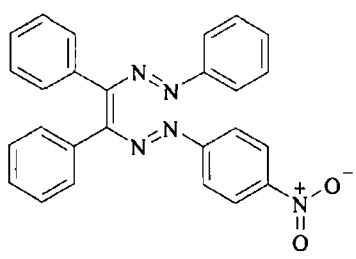
1,2-Bis(phenylhydrazone)butene (2 0g, 0 0075mol) was stirred in 25cm$^3$ glacial acetic acid Lead tetraacetate (6 0g, 0 013mol) was added and the mixture stirred for 30 minutes, after which time 1 59g (0 006mol, 80%) of the brown 1,2-bis(phenylazo)butene was removed by filtration and washed with petroleum ether 40-60

**M p** 158-159°C (lit 159°C)[37]

**$^1$H (DMSO-d$_6$) (ppm)** 1 25 (6H, s) ($CH_3$), 7 27 (4H, d, J=4Hz), 7 64-7 70 (2H m), 7 99 (4H, d) (all phenyl CH)

**$^{13}$C (DMSO-d$_6$) (ppm)** 11 34 ($CH_3$), 123 62, 129 53, 131 58, 153 95, 157 48

*1 6 1 12 Synthesis of 1-(phenylazo)-2-(p-nitrophenylazo)stilbene (117d)*

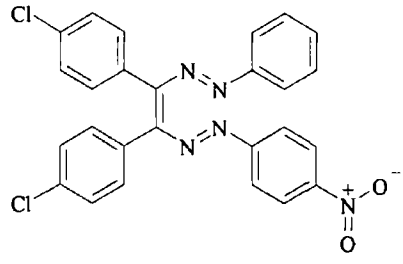


1-(Phenylhydrazone)-2-(*p*-nitrophenylhydrazone) stilbene (2g, 0 0045mol) and lead tetraacetate (3g, 0 0068mol) were stirred for 30 minutes in 25cm$^3$ of glacial acetic acid The mixture was filtered yielding 1 6g (0 0037mol, 82%) of 1-(phenylazo)-2-(*p*-nitrophenylazo)stilbene, which was washed with petroleum ether or hexane

**M.p..**90°C (lit 89-91°C)[59]

Spectroscopic analysis was not carried out on this compound

*1 6 1 13 Synthesis of 1-(phenylazo)-2-(p-nitrophenylazo)-4,4'-dichlorostilbene (117e)*



1-(Phenylhydrazone)-2-(*p*-nitrophenylhydrazone)-4,4'-dichlorostilbene (2g, 0 0040mol) and lead tetraacetate (3g, 0 0068mol) were stirred for 30 minutes in 25cm$^3$ of glacial acetic acid The mixture was filtered, yielding 1 3g (0 0026mol, 65%) of 1-(phenylazo)-2-(p-nitrophenylazo)-4,4'-dichlorostilbene which was washed with petroleum ether or hexane

**M.p .** 132°C

**$^1$H (DMSO-d$_6$) (ppm):** 7 20-7 70 (15H, m), 8 14 (2H, d) (all aromatic CH)

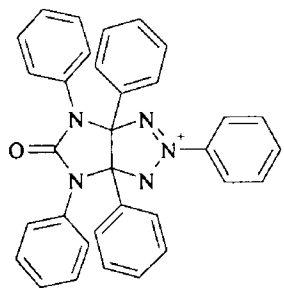
*1 6 1 14 Thermolysis of 1,2-bis(phenylazo)butene (117c)*

1,2-Bis(phenylazo)butene (0 23g, 0 87mmol) was heated in a stoppered flask at 200-210°C for 5 minutes The purple compound melted and yellow fumes were given off 5cm$^3$ of ethanol was added and a yellow powder appeared This was removed by fitration, yielding 0 22g (0 83mmol, 95%) of 1,2-bis(phenylhydrazone)butene ***(115c)***

*NMR spectra were identical to those of* **(115c)**

*1 6 2 Cycloadditions with Isocyanates as Dipolarophiles:*

*1 6 2 1 Synthesis of 2,3a,4,6,6a-pentaphenyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo [4,5-d]-1,2,3-triazole (122a)*



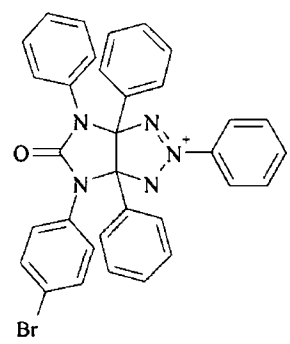
1,2-Bis(phenylazo)stilbene (0 5g, 0 0013mol) and phenyhsocyanate (0 5cm$^3$, 0 46mol) were stirred under reflux in dry acetone for 3 hours The acetone was removed under vacuum, and the residue recrystallised from ethanol, yielding 0 41g (0 0008mol, 61%) of 2,3a,4,6,6a-pentaphenyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p** 231-232°C (lit 232-233°C)[51]

**$^1$H (DMSO-$d_6$) (ppm)** 6 94-6 99 (6H, m), 7 07-7 10 (6H, m), 7 28 (4H, t, J=8Hz), 7 73-7 84 (7H, m), 8 49 (2H, d, J=8Hz) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm)**· 96 07 (C-3a, C-6a), 122 72, 124 41, 125 02, 127 47, 127 71, 128 14, 128 37, 129 82, 133 04 (all phenyl CH), 134 41, 137 10, 139 57 (all phenyl C), 155 49 (C=O)

*1 6 2 2 Synthesis of 2,3a,6,6a-tetraphenyl-4-(4-bromophenyl)-5-oxo-3,3a,4,5,6,6a hexahydroimidazo-[4,5-d]-1,2,3-triazole (122b)*



1,2-Bis(phenylazo)stilbene (0 5g, 0 0013mol) and 4-bromophenyhsocyanate (0 26g, 0 0013mol) were stirred under reflux in dry acetone for 3 hours The acetone was removed under vacuum, and the residue recrystallised from ethanol, yielding 0 63g (0 0011mol, 84%) of 2,3a,6,6a-tetraphenyl-4-(4-bromophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

**M.p** 234-236°C (lit 236°C)[51]

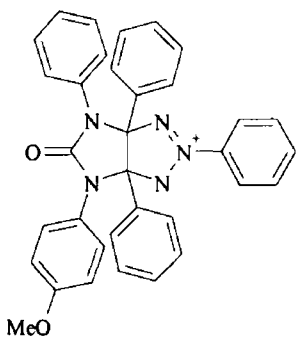
**I R (KBr) (cm$^{-1}$)** 1717 (C=O stretch), 1588, 1491, 1448 (aromatic C-C stretch), 825 (*p*-substituted Ph, C-H vibration), 698, 758 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm)**· 6 94-7 08 (11H, m), 7 25 (2H, t, J=8Hz), 7 34 (2H, d J=8Hz), 7 60, (2H, t, J=8Hz), 7 66, (1H, t, J=4Hz), 7 73-7 80 (4H, m), 8 46 (2H, d, J=8Hz) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm):** 96 38, 96 62 (C-3a, C-6a), 117 61, 122 89, 124 08, 124 94, 127 99, 127 41, 127 48, 127 75, 127 86, 128 10, 128 19, 128 39, 129 24, 131 32 (all

phenyl CH), 132 26, 134 59, 137 63, 136 61, 137 13, 140 07(all phenyl C), 155 98 (C=O)

*1 6 2 3 Synthesis of 2,3a,6,6a-tetraphenyl-4-(4-methoxyphenyl)-5-oxo-3,3a,4,5,6,6a hexahydroimidazo-[4,5-d]-1,2,3-triazole* ***(122c)***




1,2-Bis(phenylazo)stilbene (0 5g, 0 0013mol) and 4-methoxyphenylisocyanate (0 17cm$^3$, 0 0013mol) were stirred under reflux in dry acetone for 3 hours The acetone was removed under vacuum, and the residue recrystallised from ethanol, yielding 0 52g (0 0010mol, 76%) of 2,3a,6,6a-tetraphenyl-4-(4-methoxyphenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

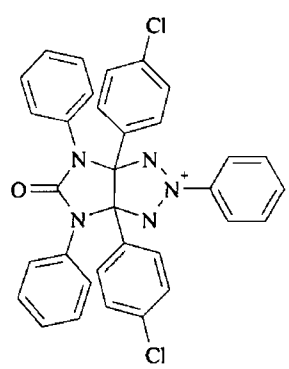
**M p** 222-224°C (lit 222-223°C)[51]

**I R (KBr) (cm$^{-1}$)** 1713 (C=O stretch), 1513, 1449 (aromatic C-C stretch), 822 (*p*-disubstituted Ph), 689, 747 (monosubstituted Ph)

**$^1$H (DMSO-d$_6$) (ppm):** 3 69 (3H, s) ($OCH_3$), 6 87 (2H, d, J=12Hz), 6 95-7 02 (6H, m), 7 06-7 13 (5H, m), 7 28 (2H, t, J=8Hz), 7 62 (2H, d, J=12Hz), 7 74-7 82 (5H, m), 8 50 (2H, d, J=8Hz) (all phenyl CH)

**$^{13}$C (DMSO-d$_6$) (ppm)** 55 44 ($OCH_3$), 96 42, 96 50 (C-3a, C-6a), 113 98, 123 08, 124 51, 125 14, 127 22, 127 82, 127 97, 128 03, 128 08, 128 49, 128 70, 130 06, 130 19, 133 36, 134 89, 137 65, 140 00 (all phenyl C and CH), 157 20 (C=O)

*1 6 2 4 Synthesis of 2,4,6-triphenyl-3a,6a-bis(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(122d)***




1,2-Bis(phenylazo)-4,4'-dichlorostilbene (0 5g, 0 0011mol) and phenylisocyanate (0 15cm$^3$, 0 0014mol) were stirred under reflux in acetone for 4 hours The acetone was removed under vacuum and the residue was recrystallised from ethanol, yielding 0 52g (0 0009mol, 82%) of 2,4,6-triphenyl-3a,6a-bis-(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

**M.p.** 214-216°C

**I R (KBr) (cm$^{-1}$)** 1700 (C=O), 1560 (aromatic C-C stretch), 802 (*p*-substituted Ph, C-H vibration), 773, 752 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm):** 7 09-7 14 (6H, m), 7 18 (4H, d, J=8Hz), 7 31 (4H, t, J=8Hz), 7 76 (6H, t, J=8Hz), 7 83, (1H, t, J=8Hz), 8 51 (2H, d, J=8Hz) (all phenyl CH)

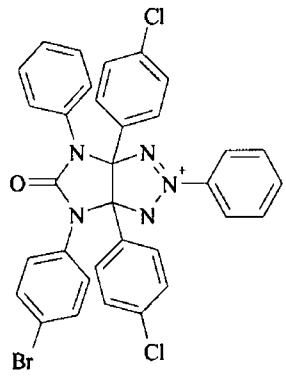
**$^{13}$C (DMSO-$d_6$) (ppm)** 95 93 (C3a, C6a), 123 19, 124 88, 125 69, 128 29, 128 86, 129 93, 130 19, 133 39, 133 54, 133 94, 137 11, 139 82 (all phenyl C and CH), 155 56 (C=O)

**M W.** 576 49gmol$^{-1}$, $C_{33}H_{23}Cl_2N_5O$

**Microanalysis.** Theory C 68 75%, H 4 03%, N 12 15%

Found C 69 02%, H 4 23%, N 11 95%

*1 6 2 5 Synthesis of 2,6-bisphenyl-4(4-bromophenyl)-3a,6a-bis(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole (122e)*




1,2-Bis(phenylazo)-4,4'-dichlorostilbene (0 5g, 0 0011mol) and 4-bromophenylisocyanate (0 26g, 0 0013mol) were stirred under reflux m acetone for 3 5 hours The acetone was removed under vacuum and the residue was recrystallised from ethanol, yielding 0 59g (0 0009mol, 82%) of 2,6-bisphenyl-4(4-bromophenyl)-3a,6a-bis(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p** 286-288°C

**I R (KBr) (cm$^{-1}$):** 1718 (C=O), 1560 (aromatic C-C stretch), 843 (p-substituted Ph, C-H vibration), 771, 752 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm).** 6 95-7 01 (8H, m), 7 09 (1H, t, J=8Hz), 7 27 (2H, t, J=8Hz), 7 36 (2H, d, J=8Hz), 7 62 (2H, t, J=8Hz), 7 685 (3H, d, J=12Hz), 7 73 (2H, d, J=8Hz), 8 45 (2H, d, J=8Hz) (all phenyl H)

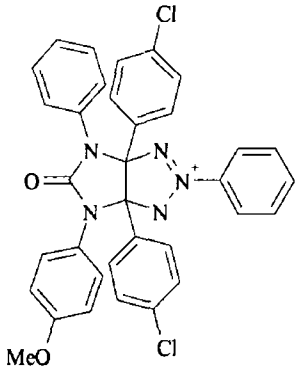
**$^{13}$C (DMSO-$d_6$) (ppm)** 95 82, 96 06 (C-3a, C-6a), 118 06 (phenyl C), 122 84, 124 10, 125 02, 125 31, 128 24, 128 36, 128 56, 128 73, 128 80, 129 35, 131 50, 132 84 (all phenyl CH), 133 17, 133 20, 134 44, 134 56, 136 17, 136 69, 139 81 (all phenyl C), 155 63 (C=O)

**M W** 655 39gmol$^{-1}$, $C_{33}H_{22}BrCl_2N_5O$

**Microanalysis:** Theory C 60 48%, H 3 38%, N 10 69%

Found C 60 18%, H 3 30%, N 10 28%

*1 6 2 6 Synthesis of 2,6-bisphenyl-4(4-methoxyphenyl)-3a,6a-bis(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole (122f)*




1,2-Bis(phenylazo)-4,4'-dichlorostilbene (0 5g, 0 0011mol) and 4-methoxyphenylisocyanate (0 18cm$^3$, 0 0014mol) were stirred under reflux in acetone for 2 5 hours The acetone was removed under vacuum and the residue was recrystallised from ethanol, yielding 0 48g (0 0008mol, 72%) of 2,6-bisphenyl-4(4-methoxyphenyl)-3a,6a-bis(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p** 236-238°C

**I R (KBr) (cm$^{-1}$)** 1743 (C=O), 1595 (aromatic C=C stretch), 860 (p-substituted Ph, C-H vibration), 771, 705 (monosubstituted Ph)

**$^1$H (DMSO-d$_6$) (ppm)** 3 68 (3H, s) ($OCH_3$), 6 87 (2H, d, J=8Hz), 7 07-7 11 (5H, m), 7 14 (2H, d, J=8Hz), 7 19 (2H, d, J=8Hz), 7 27-7 34 (2H, m), 7 59 (2H, d, J=8Hz), 7 71-7 77 (4H, q, J=8Hz), 7 82 (1H, t, J=8Hz), 8 49 (2H, d, J=8Hz) (all phenyl H)

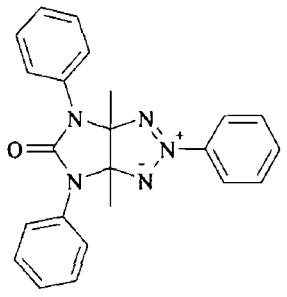
**$^{13}$C (DMSO-d$_6$) (ppm).** 55 45 ($OCH_3$), 95 00, 95 90 (C3a, C6a), 114 08, 114 30, 120 27, 123 15, 124 61, 125 44, 127 35, 128 29, 128 82, 129 67, 129 89, 130 05, 130 15, 133 30, 133 35, 133 48, 134 04, 137 29, 139 87, 155 92 (all phenyl C and CH), 157 40 (C=O)

**M.W.** 606 52gmol$^{-1}$, $C_{34}H_{25}Cl_2N_5O_2$

**Microanalysis:** Theory C 67 33%, H 4 15% N 11 55%

Found C 66 87%, H 4 15%, N 11 38%

*1 6 2 7 Synthesis of 2,4,6-triphenyl-3a,6a-dimethyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole (122g)*



1,2-Bis(phenylazo)butene (0 5g, 0 0019mol) and phenylisocyanate (0 3cm$^3$, 0 0027mol) were stirred under reflux in dry acetone in the presence of dry HCl gas[1] for 45 minutes The acetone was removed under vacuum and the residue was dissolved in ethyl acetate This was washed with 3 20cm$^3$ aliquots of saturated sodium hydrogen carbonate, followed by 3 20cm$^3$ aliquots of distilled water The organic layer was dried over anhydrous magnesium sulphate and the ethyl acetate removed under vacuum The residue was recrystallised from ethanol, yielding 0 42g (0 0011mol, 58%) of the pale yellow 2,4,6-triphenyl-3a,6a-dimethyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M.p.** 240°C

**I.R. (KBr) (cm$^{-1}$):** 1702 (C=O stretch), 1600, 1472 (aromatic C-C stretch), 690, 757 (monosubstituted Ph)

**$^1$H (DMSO-d$_6$) (ppm):** 1 60 (6H, s) ($CH_3$), 7 31 (2H, t, J=7 2, 7 6Hz), 7 47 (4H, t, J=7 6, 8 0Hz), 7 60 (4H, d, J= 7 6Hz), 7 65 (2H, t, J=8 0, 7 2Hz), 7 72 (1H, t, J=7 2), 8 24 (2H, d, J= 8 0Hz) (all phenyl CH)

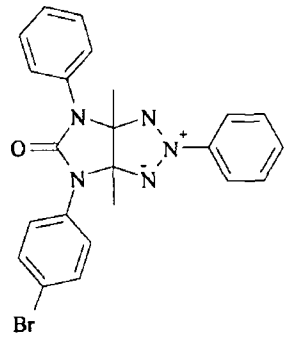
**$^{13}$C (DMSO-d$_6$) (ppm).** 18 17 ($CH_3$), 90 15 (C-3a, C-6a), 118 10, 122 38, 126 19, 126 41, 128 82, 129 40, 136 35, 139 65 (all aromatic Cs), 154 71 (C=O)

**M.W.** 384 46gmol$^{-1}$, $C_{23}H_{22}N_5O$

| **Microanalysis** | Theory | C 71 85%, H 5 77%, N 18 22% |
|---|---|---|
| | Found | C 72 04%, H 5 49%, N 18 53% |

[1] Dry HCl is produced by dropping conc sulphuric acid onto ammonium chloride moistened by a small amount of hydrochloric acid The gas is then allowed to pass through two Dreschel bottles, one containing sulphuric acid which acts as a drying agent The second Dreschel is empty, preventing 'suckback' of the reaction mixture

*1 6 2 8 Synthesis of 2,6-bisphenyl-4(4-bromophenyl)-3a,6a-dimethyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole (122h)*



1,2-Bis(phenylazo)butene (0 5g, 0 0019mol) and 4-bromophenylisocyanate (0 27g, 0 0014mol) were stirred under reflux in dry acetone in the presence of dry HCl gas for 1 hour The acetone was removed under vacuum and the residue was dissolved in ethyl acetate This was washed with 3 20cm$^3$ aliquots of saturated sodium hydrogen carbonate, followed by 3 20cm$^3$ aliquots of distilled water The organic layer was dried over anhydrous magnesium sulphate and the ethyl acetate removed under vacuum The residue was recrystallised from ethanol, yielding 0 41g (0 0009mol, 47%) of 2,6-bisphenyl-4(4-bromophenyl)-3a,6a-dimethyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p.** 190°C

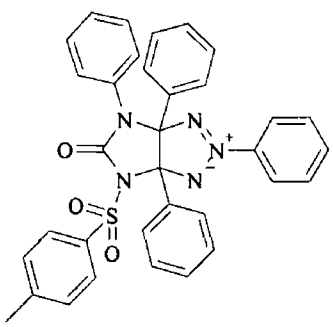
**I R (KBr) (cm$^{-1}$):** 1702 (C=O stretch), 1490, 1474 (aromatic C-C stretch),

**$^1$H (DMSO-d$_6$) (ppm).** 1 64 (6H, s) ($CH_3$), 7 27 (1H, t, J=8Hz), 7 41 (2H, t, J=8Hz), 7 50-7 54 (4H, m), 7 58-7 65 (5H, m), 8 22 (2H, d, J=8Hz) (all phenyl H)

**$^{13}$C (DMSO-d$_6$) (ppm).** 18 60, 18 68 ($CH_3$), 90 36, 90 58 (C-3a, C6a), 119 38, 122 57 (all phenyl C), 126 48, 126 56, 127 50, 128 79, 128 98, 131 79, 132 00 (all phenyl CH), 135 70, 136 17 (all phenyl C), 155 20 (C=O)

**M W** 465 38gmol$^{-1}$, $C_{23}H_{23}BrN_5O$

*1 6 2 9 Synthesis of 2,3a,6,6a-tetraphenyl-4-tosyl-5-oxo-3,3a,4,5,6,6a-hexahydro imidazo-[4,5-d]-1,2,3-triazole (122i)*



1,2-Bis(phenylazo)stilbene (0 5g, 0 0013mol) and tosylisocyanate (0 2cm$^3$, 0 0013mol) were stirred under reflux in dry acetone for 24 hours The acetone was removed under vacuum and the residue recrystallised from ethanol yielding 0 58g (0 0010mol, 77%) of 2,3a,6,6a tetraphenyl-4-tosyl-5-oxo3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

**M.p** 249-250°C

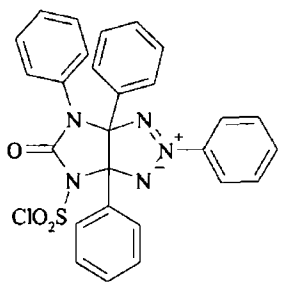
**I.R. (KBr) (cm$^{-1}$)** 1734 (C=O stretch), 1596, 1492, 1450 (aromatic C-C stretch), 841 (p-disubstituted Ph), 747, 690 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm).** 2 31 ($CH_3$), 6 88-6 92 (5H, m), 6 99-7 12 (6H, m), 7 19 (2H, t, J=8Hz), 7 73 (1H, t, J=7 2Hz), 8 05 (2H, d, J=8 4Hz), 8 52 (2H, d, J=8Hz) (all aromatic CH)

**$^{13}$C (DMSO-$d_6$) (ppm)** 22 01 ($CH_3$), 97 11, 98 33 (C3a, C6a), 123 27, 124 64, 126 09, 128 05, 128 18, 128 76, 128 78, 128 93, 129 43, 129 69, 133 22, 133 85, 136 34, 136 43, 136 58, 140 10, 145 15 (all phenyl C and CH), 153 65 (C=O)

**M W** 585 69gmol$^{-1}$, $C_{34}H_{27}N_5O_3S$

*1 6 2 10 Synthesis of 2,3a,6,6a-tetraphenyl-4-chlorosulfonyl-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole **(122j)***



1,2-Bis(phenylazo)stilbene (2 0g, 0 005moles) and sulfonylisocyanate (0 43cm$^3$, 0 005moles) were stirred under reflux in 50cm$^3$ sodium-dried benzene for 3 hours The solvent was removed under vacuum and the residue heated in ethanol The hot mixture was filtered yielding 1 2g (0 0023moles, 46%) of 2,3a,6,6a-tetraphenyl-4-sulfonyl-5-oxo-3,3a,4,5,6,6a-hexahydro imidazo-[4,5-d]-1,2,3-triazole as a white powder

**M p** 207°C

**I R (KBr) (cm$^{-1}$):** 1755 (C=O stretch), 1492, 1450 (aromatic C-C stretch) 691, 752 (monosubstituted Ph)

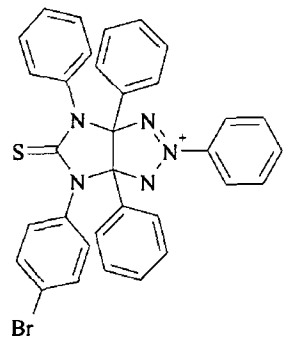
**$^1$H (DMSO-$d_6$) (ppm).** 6 96-6 98 (4H, m), 7 10-7 13 (5H, m), 7 21-7 25 (2H, t, J=7 2Hz, J=7 6Hz), 7 36 (2H, t, J=8 0Hz), 7 2 (2H, d, J=7 6Hz), 7 79 (2H, t, J=7 2Hz), 7 86 (1H, d, J=7 2Hz), 8 50 (2H, d, J=7 6Hz), (all aromatic H)

**$^{13}$C (DMSO-$d_6$) (ppm).** 97 72, 97 99 (C3a, C6a), 123 32, 126 13, 126 94, 127 57, 128 18, 128 22, 129 23, 130 33, 132 59, 133 95, 134 69, 135 29, 139 59 (all phenyl C and CH), 150 86 (C=O)

**M W** 445 53gmol$^{-1}$, $C_{28}H_{23}N_5O$

### *1.6.3 Cycloadditions with Isothiocyanates as Dipolarophiles.*

*1 6 3 1 Synthesis of 2,3a,6,6a-tetraphenyl-4-(4-bromophenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole (124a)*




1,2-Bis(phenylazo)stilbene (0 5g, 0 0013mol) and 4-bromophenylisothiocyanate (0 28g, 0 0013mol) were stirred under reflux in dry acetone for 3 5 hours The acetone was removed under vacuum, and the residue recrystallised from ethanol, yielding 0 22g (0 0004mol, 30%) of 2,3a,6,6a-tetraphenyl-4-(4-bromophenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

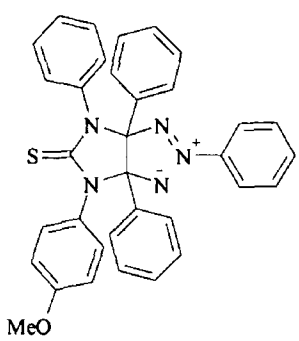
**M p** 259°C (lit 261°C)[51]

**I R (KBr) ($cm^{-1}$)**· 1490, 1449 (aromatic C-C stretch), 692, 749 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm)** 7 00 (6H, t, J=4Hz), 7 10-7 16 (4H, m), 7 23 (1H, t, J=8Hz), 7 31 (2H, t, J=8Hz), 7 42 (2H, d, J=8Hz), 7 58 (2H, d, J=8Hz), 7 62-7 67 (4H, q), 7 73 (1H, t, J=8Hz), 8 50 (2H, d, J=8Hz) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 100 60, 100 79 (C3a, C6a), 120 67, 123 18, 127 89, 128 11, 128 17, 128 26, 128 72, 128 97, 129 42, 130 32, 131 35, 131 64, 133 66, 133 70, 133 82, 138 00, 138 42, 139 63 (all phenyl C and CH), 183 98 (C=S)

*1 6 3 2 Synthesis of 2,3a,6,6a-tetraphenyl-4-(4-methoxyphenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole (124b)*




1,2-Bis(phenylazo)stilbene (0 5g, 0 0013mol) and 4-methoxyphenyhsothiocyanate (0 25$cm^3$, 0 0018mol) were stirred under reflux in dry acetone for 3 5 hours The acetone was removed under vacuum, and the residue recrystallised from ethanol The solution was filtered while still hot and the filtrate left to cool overnight The crystals were removed by filtration, yielding 0 13g (0 00023mol, 18%) of 2,3a,6,6a-tetraphenyl-4-(4-methoxyphenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

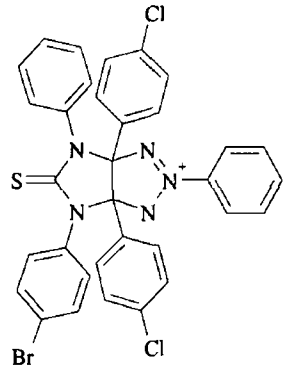
**M.p.** 230-232°C (lit 231-232°C)[51]

**I.R. (KBr) ($cm^{-1}$):** 1498, 1471 (aromatic C-C stretch), 704, 749 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm)**· 3 74 (3H, s) ($OCH_3$), 6 82 (2H, d, J=8Hz), 6 98-7 03 (6H, m), 7 12-7 14 (2H, m), 7 20 (3H, t, J=8Hz), 7 30 (2H, t, J=8Hz), 7 50 (2H, d, J=8Hz), 7 63-7 73 (5H, m), 8 51 (2H, d, J=8Hz) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm):** 55 49 ($OCH_3$), 100 64, 100 70 (C3a, C6a), 113 83, 123 12, 127 59, 128 09, 128 14, 128 60, 128 79, 128 86, 129 27, 130 32, 130 84, 131 16, 133 57, 133 99, 134 07, 138 73, 139 70, 158 52, (all phenyl C and CH) 184 57 (C=S)

*1 6 3 3 Synthesis of 2,6-bisphenyl-4(4-bromophenyl)-3a,6a-bis(4-chlorophenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(124c)***




1,2-Bis(phenylazo)-4,4'-dichlorostilbene (0 5g, 0 0011mol) and 4-bromophenyhsothiocyanate (0 29g, 0 0013mol) were stirred under reflux in acetone for 1 hour The acetone was removed under vacuum and the residue recrystallised from ethanol, yielding 0 20g (0 0003mol, 27%) of 2,6-bisphenyl-4-(4-bromophenyl)-3a,6a-bis-(4-chlorophenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

**M p** 260°C

**I R (KBr) (cm$^{-1}$)**· 1560, 1472 (aromatic C-C stretch), 1092 (C=S), 755, 706 (monosubstituted Ph)

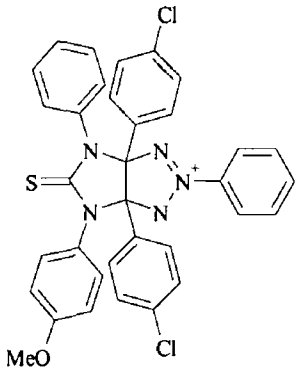
**$^1$H (DMSO-$d_6$) (ppm).** 7 15 (4H, d, J=8Hz), 7 23-7 30 (5H, m), 7 35 (2H, t, J=8Hz), 7 47 (1H, t, J=8Hz), 7 54-7 65 (4H, m), 7 78 (2H, t, J=8Hz), 7 86 (1H, t, J=8Hz), 8 11 (1H, d, J=8Hz), 8 52 (2H, d, J=8Hz) (all phenyl CH)

**$^{13}$C (DMSO-$d_6$) (ppm)** 100 01, 100 23 (C-3a, C-6a), 118 86, 120 91, 123 27, 128 36, 128 46, 128 82, 128 99, 129 38, 130 17, 130 30, 131 33, 131 76, 132 83, 132 92, 133 83, 134 23, 137 69, 138 14, 139 15, 139 52 144 99 (all phenyl C and CH), 183 91 (C=S)

**M W** 671 45gmol$^{-1}$, $C_{33}H_{22}BrCl_2N_5S$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 59 03%, H 3 30%, N 10 43% |
| | Found | C 59 54%, H 3 76%, N 10 04% |

*1 6 3 4 Synthesis of 2,6-bisphenyl-4(4-methoxyphenyl)-3a,6a-bis(4-chlorophenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(124d)***




1,2-Bis(phenylazo)-4,4'-dichlorostilbene (0 5g, 0 0011mol) and 4-methoxyphenylisothiocyanate (0 2cm$^3$, 0 0014mol) were stirred under reflux in acetone for 1 5 hours The acetone was removed under vacuum The residue was not very soluble in hot ethanol, but when cooled and collected by filtration the white solid was found to be 2,6-bisphenyl-4(4-methoxyphenyl)-3a,6a-bis(4-chlorophenyl)-5-thio-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole The yield was 0 26g (0 0004mol, 38%)

**M.p.** 260°C

**I R (KBr) (cm$^{-1}$)**· 1617, 1568, 1534, 1472 (aromatic C-C stretch), 1249 (C-O stretch in Ar-O-$CH_3$), 1091 (C=S)

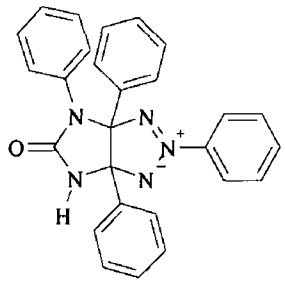
**$^1$H (DMSO-$d_6$) (ppm).** 3 70 (3H, s) ($OCH_3$), 6 88 (2H, d, J=12Hz), 7 11-7 16 (4H, t, J=8Hz, J=12Hz), 7 20-7 23(3H, m), 7 25 (2H, d, J=8Hz), 7 33 (2H, t, J=8Hz), 7 45 (2H, d, J=8Hz), 7 62 (2H, d, J=8Hz), 7 77 (2H, d, J=8Hz), 7 84 (1H, d, J=8Hz), 8 50 (2H, d, J=8Hz) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 55 33 ($OCH_3$), 100 36, 100 43 (C-3a, C-6a), 113 98, 122 94, 127 79, 128 34, 128 63, 128 97, 129 23, 129 61, 130 48, 132 76, 133 08, 135 00, 138 35, 139 81, 158 89 (all phenyl CH and C), 185 68 (C=S)

**M W** 623 59gmol$^{-1}$, $C_{34}H_{26}Cl_2N_5OS$

### *1 6 4 Reactions of Cycloadducts:*

#### *1 6 4 1 Synthesis of 2,3a,6,6a-tetraphenyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (122k)*



2,3a,6,6a-Tetraphenyl-4-sulfonyl-5-oxo-3,3a,4,5,6,6a-hexahydro imidazo-[4,5-d]-1,2,3-triazole (1g, 0 002moles) was dissolved in 80cm$^3$ of acetone and thiophenol (0 41cm$^3$, 0 004moles) added A mixture of pyridine (0 2cm$^3$, 0 0024moles) in 20cm$^3$ acetone was added to the reaction at –30°C over 20 minutes [1] The reaction mixture was stirred at –30°C for a further 30 minutes after which TLC analysis showed that all of the starting material had disappeared 100cm$^3$ of cold water was added with constant stirring and a precipitate formed This was removed by filtration and NMR analysis showed it to be the required product (0 5g, 0 0012moles, 60%)

**M p** 263°C

**I R. (KBr) (cm$^{-1}$)** 1709 (C=O stretch), 1598, 1500, 1450 (aromatic C-C stretch), 751, 688 (monosubstituted Ph)

**$^1$H (DMSO-d$_6$) (ppm)**· 6 94-7 11 (11H, m), 7 21 (2H, t, J=8 0Hz, J=7 6Hz), 7 62 (2H, d, J=8 0Hz), 7 73 (2H, t, J=7 2Hz, J=8Hz), 7 78 (1H, d, J=7 2Hz), 8 38 (2H, d, J=7 6Hz), (all phenyl C and CH), 9 06 (1H, s) (N-H)

**$^{13}$C (DMSO-d$_6$) (ppm).** 92 73, 97 67 (C3a, C6a), 122 90, 123 59, 124 41, 127 18, 127 45, 128 04, 128 27, 128 54, 130 06, 133 06, 135 69, 137 86 (all phenyl C and CH), 158 40 (C=O)

**M.W.** 431 50gmol$^{-1}$, $C_{27}H_{21}N_5O$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 75 16%, H 4 91%, N 16 23% |
| | Found | C 75 44%, H 5 03%, N 15 99% |

[1] Procedure taken from Moriconi & Kelly, *J Org Chem* **1968**, 33, 8, 3036

*1 6 4 2 Thermolysis of 2,3a,6,6a-tetraphenyl-4-tosyl-5-oxo-3,3a,4,5,6,6a-hexahydro imidazo-[4,5-d]-1,2,3-triazole (122i)*

2,3a,6,6a-Tetraphenyl-4-tosyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (300mg, 0 512mmol) was dissolved in 30cm$^3$ of toluene and stirred under reflux for 5 days TLC analysis indicated that no reaction had taken place The solvent was removed and the residue was analysed by NMR The spectra were identical to those of the starting material

*1 6 4 3 Treatment of 2,3a,6,6a-tetraphenyl-4-tosyl-5-oxo-3,3a,4,5,6,6a-hexahydro imidazo-[4,5-d]-1,2,3-triazole (122i) with base*

2,3a,6,6a-Tetraphenyl-4-tosyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (250mg, 0 427mmol) was dissolved in 100cm$^3$ of anhydrous methanol Sodium methoxide (250mg, 4 6mmol) in 30cm$^3$ of methanol was added and the mixture was stirred under reflux for 4 days TLC analysis indicated that no reaction had occurred The solvent was removed, the residue dissolved in 20cm$^3$ of dichloromethane and washed with 3 20cm$^3$ aliquots of water It was then dried over $MgSO_4$, the solvent removed and the residue analysed by NMR The spectra were identical to those of the starting material

*1 6 4 4 Thermolysis of 2,3a,6,6a-tetraphenyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (122k)*

2,3a,6,6a-Tetraphenyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (200mg, 0 463mmol) was dissolved in 25cm$^3$ of toluene and heated under reflux for 3 days TLC analysis indicated that no reaction had taken place The solvent was removed and the residue analysed by NMR The spectra were identical to those of the starting material

*1 6 4 5 Treatment of 2,3a,6,6a-tetraphenyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (122k) with base*

2,3a,6,6a-Tetraphenyl-5-oxo-3,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (300mg, 0 695mmol) was dissolved in 100cm$^3$ of anhydrous methanol Sodium methoxide (0 4g, 7 4mmol) in 50cm$^3$ was added dropwise and the mixture was stirred under reflux for 7 days TLC analysis indicated that no reaction had occurred The solvent was removed and the residue was dissolved in 20cm$^3$ of dichloromethane This

was washed with 3 x 20cm$^3$ aliquots of water, dried over $MgSO_4$ and the solvent was removed NMR spectra of the residue were identical to those of the starting material

## 1.7 References·


1 Byrne, C , Draper, S M , James, J P , Long, C *J Chem Res* **1995**, 2501

2 Katritzky, A R , Rees, C W *'Comprehensive Heterocyclic Chemistry'*, Vol 7, pg 653

3 Katritzky, A R , Rees, C W *'Comprehensive Heterocyclic Chemistry'*, Vol 7, pg 687

4 Giumanini, A G , Verardo, G , Zangrando, E , Lassiam, L *J Prakt Chem* **1987**, 1087

5 Gompper, R , Schwarzensteiner, M-L *Angew Chem Int Ed Engl* **1983**, 543

6 Amine, M S , El-Hashas, M A , Attia, I A *Indian J Chem* **1993**, 577

7 Behrend, R , Meyer, E , Rusche, F *Liebigs Ann Chem* **1905**, 339

8 Freeman, W A , Mock, W L , Shih, N-Y *J Am Chem Soc* **1981**, 7367

9 Mock, W L , Shih, N-Y *J Org Chem* **1983**, 3619

10 Mock, W L , Pierpont, J *J Chem Soc Chem Commun* **1990**, 1509

11 Liu, K-C , Shih, B-J *J Heterocycl Chem* **1986**, 1265

12 Brinkmeyer, R S , Terando, N H *J Heterocycl Chem* **1989**, 1713

13 Taylor, E C , Davies, H M L *J Org Chem* **1984**, 4415

14 Huisgen, R. *Angew Chem , Int Ed Engl* , **1963**, *2*, 633

15 Huisgen, R *J Org Chem* **1968**, *33*, 2291

16 Padwa, A *'1,3-Dipolar Cycloadditions Chemistry- Volume* 1' Wiley Interscience, **1984**, pg 37

17 Eckell, A , Huisgen, R , Sustmann, G , Wallbilhch, G , Grashey, D , Spindler, E *Chem Ber* **1967**, *100*, 2192

18 Hoffmann, R , Woodward, R B *J Am Chem Soc* **1965**, *87*, 2046, 4388

19 Padwa, A *'1,3-Dipolar Cycloadditions Chemistry- Volume 1'* Wiley Interscience, **1984**, pg 31

20 Padwa, A *'1,3-Dipolar Cycloadditions Chemistry- Volume 1'* Wiley Interscience, **1984**, pg 61

21 Sustmann, R *Tetrahedron Lett* **1971**, *29*, 2717

22 Houk, K N , Sims, J , Duke, R E Jr , Strozier, R W , George, J K *J Am Chem Soc* **1973**, *95*, 7287

23 Roberts, J D *'Notes on Molecular Orbital Calculations'* W A Benjamin, New York, N Y , **1962**, pg131

24 Houk, K N , Sims, J , Watts, C R , Luskus, L J *J Am Chem Soc* **1973**, *95*, 7301

25 Alder, K , Stein, G *Angew Chem* **1937**, *50*, 510

26 Padwa, A *'1,3-Dipolar Cycloadditions Chemistry- Volume 1'* Wiley Interscience, **1984**, pg 145

27 a) Huisgen, R *Naturwiss Rundschau*, **1961**, *14*, 43

b) Huisgen, R , Grashey, R , Sauer J in S Patai, Ed , *'The Chemistry of Alkenes'*, Interscience, London, **1964**, pg 739, 848

c) Huisgen, R *Angew Chem* **1964**, *75*, 604

d) Huisgen, R *Angew Chem Int Ed Engl* **1963**, *2*, 565

28 Spassov, A V , *Bulgarska Akademiia na Naukite, Sofia, Khimicheski Institut Izvestiia* **1951**, *1*, 217

29 Woodward, R B , Wintner, C *Tetrahedron Lett* , **1969**, 2697

30 Chesick, J P *Acta Cryst* , **1973**, *B29*, 2309

31 George, M V , Mitra, A , Sukumaran, K B *Angew Chem Int Ed Engl* , **1980**, *19*, 973

32 a) Angadiyavar, C S , Sukumaran, K B , George, M V *Tetrahedron Lett* , **1971**, 633

b) Sukumaran, K B , Angadiyavar, C S , George, M V *Tetrahedron*, **1972**, *28*, 3987

33 Butler, R N , James, J P *J Chem Soc Chem Commun* , **1983**, 627

34 Butler, R N , Cunningham, D , James, J P , McArdle, P *J Chem Soc , Chem Commun* , **1983**, 762

35 Ramaiah, D , Rath, N P , George, M V *Acta Cryst* **1998**, *C54*, 872

36 Butler, R N , Lysaght, F A , Burke, L A *J Chem Soc , Perkin Trans 2*, **1992**, 1103

37 Sukumaran, K B , Satish, S , George, M V *Tetrahedron*, **1974**, *30*, 445

38 Padwa, A *'1,3-Dipolar Cycloadditions Chemistry- Volume 1'* Wiley Interscience, **1984**, pg 86

39 Butler, R N , Gillan, A M , Collier, S , James, J P , *J Chem Res (S)*, **1987**, 332

40 Butler, R N , Grogan, D C , Burke, L A *J Heterocyclic Chem* , **1997**, 1825

41 Butler, R N , Evans, A M , Gillan, A M , James, J P , McNeela, E M , Cunningham, D , McArdle, P *J Chem Soc Perkin Trans 1*, **1990**, 2537

42 Butler, R N , Wallace, L M *J Chem Soc , Perkin Trans 1*, **2001**, 1778

43 Butler, R N , Evans, A M , McArdle, P , Cunningham, D *J Chem Soc Chem Commun* **1987**, 1090

44 Gainsford, G J , Woolhouse, A D *Aust J Chem* **1980**, *33*, 2447

45 Butler, R N , O'Shea, D F *J Chem Soc , Perkin Trans 1*, **1994**, 2797

46 Butler, R N , Cunningham, D , McArdle, P , O'Halloran, G A *J Chem Soc Chem Commun* , **1988**, 232

47 Butler, R N , O'Shea, P D , Cunningham, D , McArdle, P *J Chem Soc Perkin Trans 1*, **1989**, 371

48 Butler, R N , Evans, A M , McNeela, E M , O'Halloran, G A , O'Shea, P D , Cunningham, D , McArdle, P *J Chem Soc , Perkin Trans 1*, **1990**, 2527

49 Butler, R N , O'Shea, D F *J Chem Res (S)*, **1994**, 350

50 Butler, R N , Lysaght, F A , McDonald, P D , Pyne, C S , McArdle, P , Cunningham, D *J Chem Soc , Perkin Trans 1*, **1996**, 1623

51 Butler, R N , Colleran, D M *J Chem Soc , Perkin Trans 1*, **1992**, 2159

52 Butler, R N , Grogan, D C , McDonald, P D , Burke, L A *J Chem Soc , Perkin Trans 1*, **1997**, 3587

53 Butler, R N , McKenna, E C , Grogan, D C *J Chem Soc Chem Commun* , **1997**, 2149

54 James, J P , PhD Thesis UCG **1983**, 45

55 Bauer, H , Boulton, A J , Fedeli, W , Katritzky, A R , Majid-Hamid, A , Mazza, F , Vaciago, A *J Chem Soc Perkin Trans II* **1972**, 663

56 Ito, K , Saito, K Takeuchi, S , Takahashi, K *Heterocycles*, **1992**, *34*, 1415

57 a) Moriconi, E J , Kelly, J F , *J Org Chem* **1968**, *33*, 3036

b) Nakatsuka, T , Iwata, H , Tanaka, R , Imajo, S , Ishiguro, M *J Chem Soc , Chem Commun* **1991**, 662

58 Roy, S , Sen, H *J Ind Chem* **1933**, *10*, 347

59 Alexandrou, N E *Tetrahedron*, **1966**, *22*, 1309

# CHAPTER TWO

# N-SULFONYL IMINES AS DIPOLAROPHILES

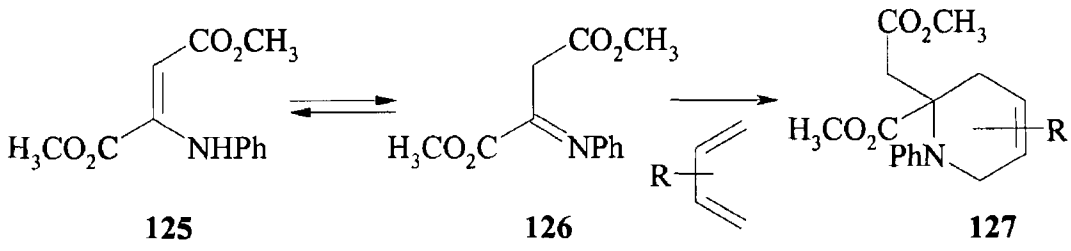
## Chapter 2 N-Sulfonyl Imines·

### 2.1 Introduction·

For several years, the Diels-Alder reaction was the only widely used example of cycloaddition reactions The extensive work by Huisgen and co-workers[1] on the concept of 1,3-dipolar cycloadditions opened new avenues for these reactions In contrast with the tremendous number of studies which characterised cycloadditions to olefins in the earlier literature, cycloadditions to imines seemed almost insignificant This can be traced to several factors

The greatly reduced stability of imines made their use as synthetic reagents less practical, since upon standing, many of them deteriorated Thus, the more stable partners of cycloadditions such as alkenes, alkynes and nitriles were chosen in preference to imines Furthermore, the possibility of tautomerism in imines created additional difficulties However m more recent years, the study of the synthesis and use of imines in cycloadditions other than the Diels-Alder reaction has developed

Alder briefly mentioned the initial example of an imino compound acting as a dienophile in 1943 [2] Reaction of amino diester **125** with various aliphatic dienes did not give the carbocyclic adducts which were presumably expected (**Scheme 2.1**), but instead gave the tetrahydropyridines **127** via imino tautomer **126** This initial observation stimulated very little research until nearly 40 years later




**125** **126** **127**

**Scheme 2.1** *First example of an imino-type dienophile in the Diels-Alder reaction*

Not all imino compounds are effective dienophiles Simple Schiff bases have proven to be unreactive in [4+2]-cycloadditions unless exceptionally reactive dienes such as quinone methides are used In general, electron-deficient imines are the most reactive dienophiles, particularly those of the *N*-sulfonyl, *N*-acyl and iminium salt types Other imino-type compounds have been used as dienophiles but are not as generally reliable

as the aforementioned types It should also be noted that some imino Diels-Alder reactions are catalysed by Lewis acids [3]

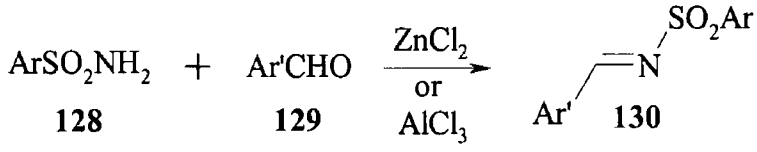
N-Sulfonyl imines have been increasing in importance because they are one of the few types of electron-deficient imines that are stable enough to be isolated but reactive enough to undergo addition reactions They have been used as electron-deficient 1,3-azabutadiene equivalents in inverse electron demand Diels-Alder chemistry[4], as electrophilic aza-aldehyde equivalents in addition reactions[5], as reactive olefin equivalents in ene reactions,[6,7] or as precursors to N-sulfonyloxaziridines which have utility as chiral oxidants [8]

## 2 2 Synthesis of N-Sulfonyl Imines:

The synthesis of imines can be achieved by a wide variety of methods, some of those being addition of ammonia or amines to aldehydes and ketones, reduction of oximes, treatment of nitriles with enamine salts, and addition of Grignard reagents to nitriles [9] However the methods used for generating N-sulfonyl imines were very limited until the last 15 years when a lot of interest in this area developed A number of procedures now exist for direct synthesis of N-sulfonyl imines, in particular those derived from non-enolisable aldehydes There is still a lack of good procedures for producing N-sulfonyl imines from enolisable aldehydes and ketones

### *2.2.1. From Sulfonamides and Aldehydes/Ketones/Acetals*

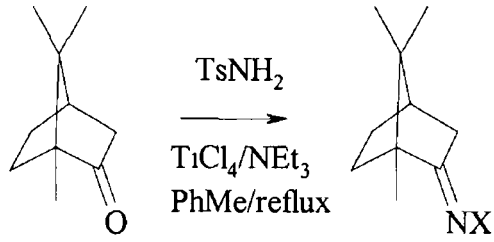
Lichtenburger *et al* first reported the synthesis of N-sulfonyl imines by the Lewis acid ($ZnCl_2$) catalysed condensation of aromatic aldehydes and *p*-toluene sulfonamide [10] **(Scheme 2.2)** Yields of 20-70% of crystalline products were improved by the use of $AlCl_3$ as the catalyst [11]




Ar = Ph, *p*ClPh
Ar' = Ph, *m*$NO_2$Ph, *p*$Me_2$NPh

**Scheme 2.2** *Lewis acid catalysed condensation of aromatic aldehydes and sulfonamides*

Jennings and Lovely[12] have developed a milder version of this reaction by using titanium tetrachloride and triethylamine at 0°C Yields of crude imine were generally 50- 90%, recrystalhsation lowered these by 10-20% The extension of this reaction to readily enolisable ketones failed to give the desired imines, the aldol condensation products were obtained instead In the case of ketones which are not readily enolisable, (e g camphor **131**), the reaction proceeds at higher temperatures, giving moderate yields of the imine **132 (Scheme 2.3)** This imine is unusual in that it can be purified by column chromatography, those derived from aldehydes and ketones decompose on silica gel to the parent carbonyl compound and sulfonamide

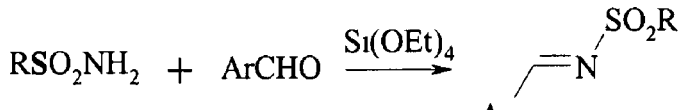



**131** **132** X=Ts

**Scheme 2.3** *Condensation of (+)-camphor with p-toluene sulfonamide yielding (-)-camphor sulfonyl imine*

This method was also developed by Davis *et al*[13] and was used to prepare the closely related camphor sulfonamides (**Scheme 2 3** $X=SO_2CH_2R$, R=Me/Ph) in good yields This group also condenses aromatic aldehydes and *p*-toluenesulfonamide in the presence of an acid ion exchange resin and molecular sieves with the azeotropic distillation of water [14] Yields are high, but the reaction times are longer than those for the titanium tetrachloride procedure

The synthesis of a number of aryl N-sulfonyl imines under neutral conditions can be achieved by heating the aldehyde **129** and *p*-toluenesulfonamide **128** in the presence of tetraethyl orthosilicate [15] The reaction times are short (N-sulfonyl imines form within 1hour) and the yields are high (70-90%)



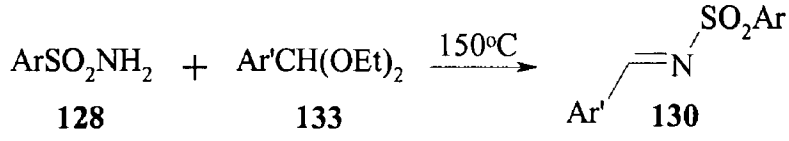

**128** **129** **130**

R = *p*MePh
Ar = Ph, *p*MeOPh, *p*$NO_2$Ph,
*o*ClPh, *o*HOPh

**Scheme 2 4** *Condensation of aromatic aldehydes and p-toluenesulfonamide in the presence of tetraethyl orthosilicate*

This method shares the common limitation of not being applicable to the synthesis of N-sulfonyl imines from enolisable aldehydes and ketones, products derived from aldol condensations being obtained instead

It has been reported that heating a neat mixture of an aryl sulfonamide and an ethyl or methyl acetal from an aromatic aldehyde gives the N-sulfonyl imine in good yields[16] No indication was given if this procedure was carried out with acetals of aliphatic aldehydes



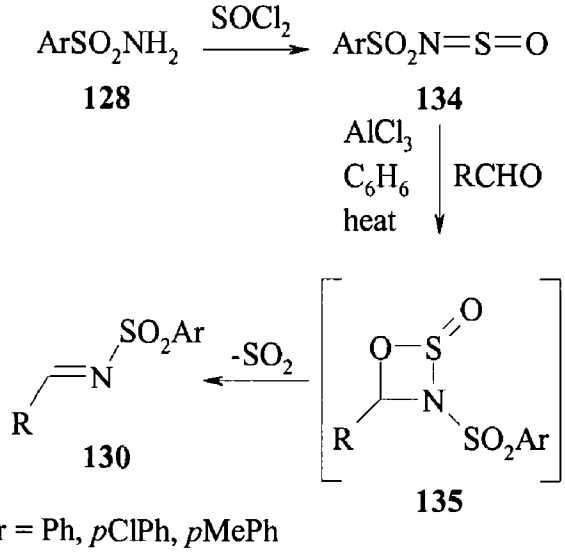

**128** **133** **130**

Ar = *p*MePh, Ph, *p*$NO_2$Ph, *p*ClPh
Ar' = Ph, *m*$NO_2$Ph, *p*MeOPh, *p*$NO_2$Ph

**Scheme 2 5** *Condensation of aryl sulfonamides and acetals of aromatic aldehydes*

### *2.2.2 From 'Activated' Sulfonamides and Aldehydes/Ketones*

In 1964 Kresze and co-workers showed that non-enolisable aldehydes could be converted to the corresponding N-sulfonyl imines using N-sulfinyl-*p*-toluene sulfonamide **134** in the presence of a Lewis acid [16 17] **(Scheme 2 6)**




**128** **134** **130** **135**

Ar = Ph, *p*ClPh, *p*MePh
R = Ph, *p*$NO_2$Ph, $CCl_3$, $CO_2$Bu, 2-furyl, 2-pyridyl

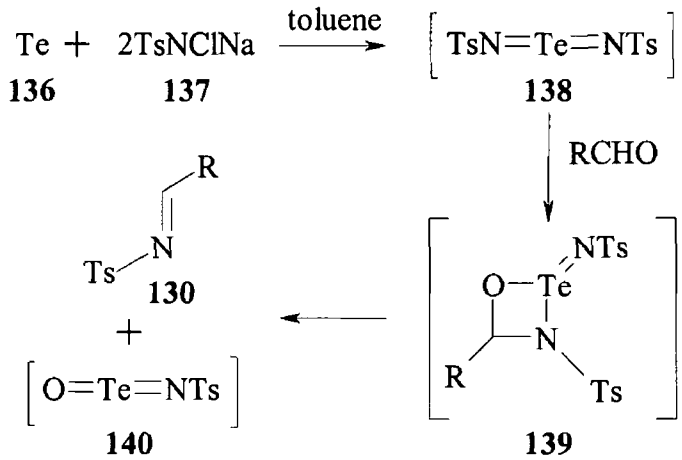
**Scheme 2 6** *The use of N-sulfinyl-sulfonamides in the synthesis of N-sulfonyl imines*

The N-sulfinyl-*p*-toluene sulfonamides **134** are generated from the parent sulfonamide and thionyl chloride[18] and are usually used *in situ* They can be isolated but purification

is difficult and time-consuming Heating the aldehydes and sulfonamide in benzene with a catalytic amount of aluminium chloride produces the N-sulfonyl imines

The reaction is likely to involve an initial [2+2]-cycloaddition of the aldehyde and N-sulfinyl sulfonamide to produce the adduct **135** which loses sulfur dioxide to yield the N-sulfonyl imme In the case of the enolisable aldehyde dichloroacetaldehyde, only a low yield of N-sulfonyl imme was produced However the method was later extended to generate N-sulfonyl immes from several enolisable aliphatic aldehydes [5,7 19] Boron trifluoride etherate is used as a catalyst and the reaction proceeds in dichloromethane at low temperatures (-30°C) In the absence of the Lewis acid catalyst, the reaction can take place at room temperature, but with slower reaction times The *in situ* produced N-sulfonyl imines are efficiently trapped by 1,3-dienes in [4+2]-cycloadditions

In a related method, a wide variety of aryl and aliphatic N-tosyl imines have been synthesised in high yields by the reaction of N,N'-ditosyl telluordiimide **138** and the corresponding aldehyde [20] **(Scheme2 7)** The reaction, involving the *in situ* formation of the imido tellurium reagent from tellurium metal and chloramine T, proceeds in a variety of refluxing solvents, toluene being the most effective The order of reactivity is aliphatic (30min) > electron rich aromatic (1-2hr) > electron poor aromatic (~ 5hr)



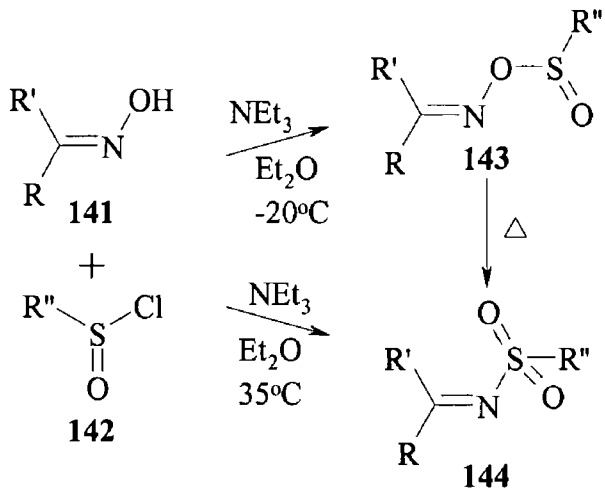

R = Ph, *p*OMePh, *o*ClPh, *m*$NO_2$Ph, *t*-butyl

**Scheme 2 7** *Synthesis of N-tosyl imines using the bis-imido tellurium reagent generated from tellurium metal and chloramine T*

As with other methods of forming N-sulfonyl imines, some enolisable aldehydes undergo the transformation, but enolisation is generally a problem

### *2 2 3 From Oximes*

Hudson *et al*[21] have reported that aldoximes and ketoximes **141** react rapidly with sulfinyl chlorides **142** to give derivatives which rearrange at low temperatures via radical pathways to the corresponding sulfonyl imines **144**, and in the case of aldoximes, to imines, aldehydes and sulfonyl imines



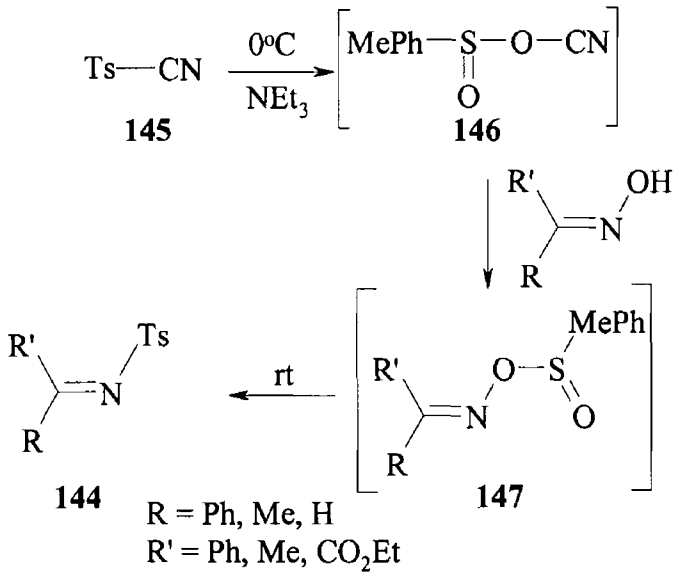

R,R' = Ph, Me, *p*MePh, $CHPh_2$
R" = Me, *p*MePh

**Scheme 2.8** *Rearrangement of O-sulfinyl oxime to give N-sulfonyl imine*

The O-sulfinyl ketoximes are prepared by the treatment of the ketoxime with a sulfinyl chloride in the presence of triethylamine in ether at –20°C The sulfonyl imine may also be obtained by carrying out the reaction at room temperature Heating the N-sulfinyl imine, either neat or in a solution of carbon tetrachloride results in the quantitative formation of the N-sulfonyl imine

This method has proven general and applicable to the preparation of a wide range of N-sulfonyl imines including enolisable $\alpha,\beta$-unsaturated N-sulfonyl imines However the use of the unstable and reactive sulfinyl chloride reagents detracts from the technical convenience of this procedure A convenient modification of the original Hudson

procedure is based on the preparation and *in situ* rearrangement of oxime O-sulfinates employing the commercially available and stable sulfonyl cyanides as reagents [22]

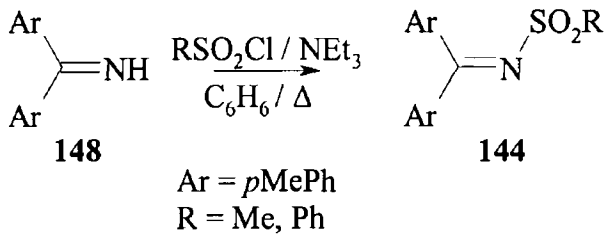



**Scheme 2 9** *Synthesis of N-sulfonyl imines by the homolytic rearrangement of oxime O-sulfinates*

A range of reaction conditions was examined for the isomerisation of *p*-toluenesulfonyl cyanide to *p*-toluenesufinyl cyanate and its subsequent reaction with the oxime of benzophenone The reaction requires the use of a tertiary amine, triethylamine the best of those examined Carbon tetrachloride was found to be the best solvent

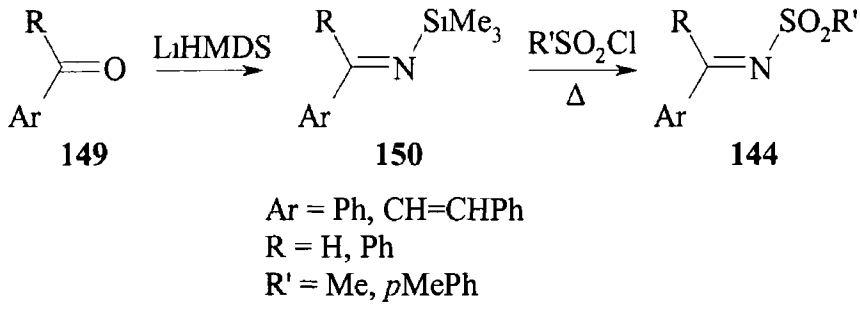
### *2 2 4 From Imines and N-Silyl Imines*

The direct N-sulfonylation of simple NH imines has not been studied to any significant degree despite the availability of these precursors However Hudson and co-workers[23] have reported two examples of N-sulfonylation of ditolyl imine **148** to give N-sulfonyl imines (**Scheme 2 10**)




**Scheme 2 10** *Sulfonylation of simple imines to give N-sulfonyl imines*

More recently, a conversion of N-trimethylsilyl imines **150** to N-sulfonyl imines, using the appropriate sulfonyl chloride, has been reported [24] The aldehydes and ketones are initially converted to their N-trimethylsilyl imines by the Hart procedure using lithium hexamethyldisilazide [25] **(Scheme 2 11)**

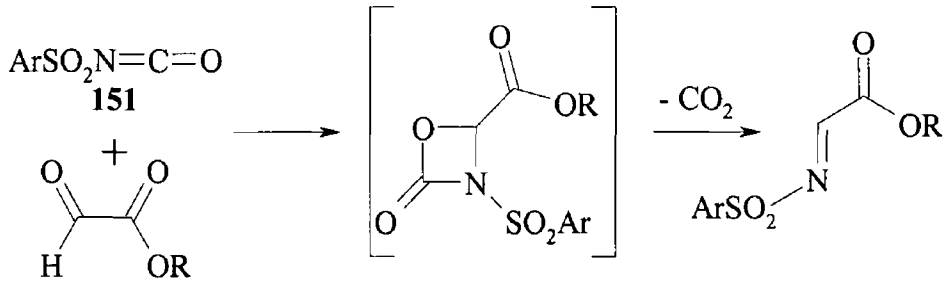



**Scheme 2 11** *Conversion of N-trimethylsilyl imines to N-sulfonyl imines*

The N-trimethylsilyl imines are easily purified by vacuum distillation and then reacted stoichiometrically with the sulfonyl chloride to give the N-sulfonyl imines and the volatile by-product, trimethylsilyl chloride Removal of the solvent and TMSCl gives the pure N-sulfonyl imines in quantitative yields This method cannot be applied to forming N-sulfonyl imines from enolisable aldehydes and ketones

### *2 2 5 From p-Toluenesulfonyl Isocyanate and Aldehydes/Glyoxylic Esters*

The use of the commercially available p-toluenesulfonyl isocyanate **151** in the synthesis of N-sulfonyl imines derived from aromatic aldehydes was first reported in 1966 [26] The method was later developed to synthesise N-sulfonyl imines from gloxylic esters[27 28] and is now one of the simplest and most widely used methods of preparing these compounds The reaction proceeds through the cyclic intermediate **153** which then loses carbon dioxide to give the N-sulfonyl immes in good yields (**Scheme 2 12**)




**152a** R=Me, Ar=*p*MePh
**152b** R=Et, Ar=*p*MePh
**152c** R=Bu, Ar=*p*MePh

**153**

**154a** R=Me, Ar=*p*MePh
**154b** R=Et, Ar=*p*MePh
**154c** R=Bu, Ar=*p*MePh

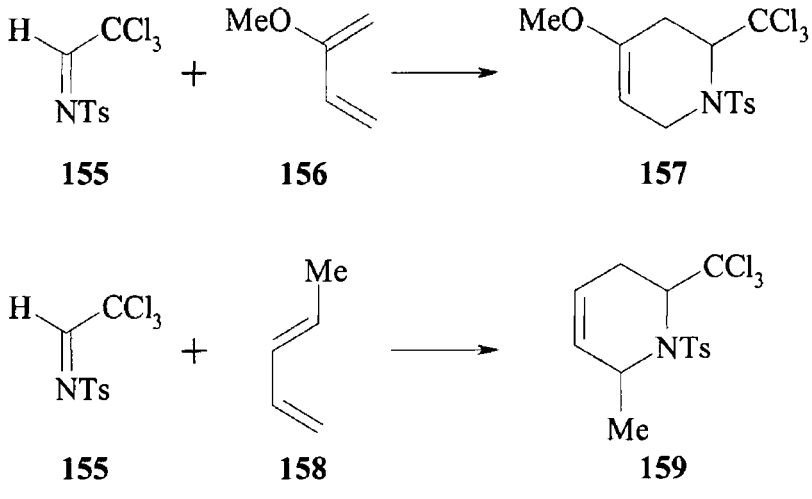
**Scheme 2 12** *Synthesis of N-sulfonyl imines derived from glyoxylic esters using p-toluenesulfonyl isocyanate*

## 2.3 Reactions of N-Sulfonyl Imines

### *2 3 1 Diels-Alder Reactions.*

#### *2 3 1 1 N-Sulfonyl Imines of Chloral and Fluoral*

Albrecht and Kresze reported the first examples of N-sulfonyl imines acting as dienophiles in [4+2]-cycloadditions [4] The N-sulfonyl imines derived from chloral and fluoral reacted with a number of 1,3-dienes to give cycloadducts in high yields [29] The regioselectivity of these reactions is excellent, with trichloromethyl-N-sulfonyl imine **155** giving only adduct **159** when reacted with *E*-piperylene and adduct **157** with 2-methoxybutadiene **156** (**Scheme 2 13**) This selectivity has been explained by assuming that these imines are highly polarised which is reflected in the transition state of the cycloaddition

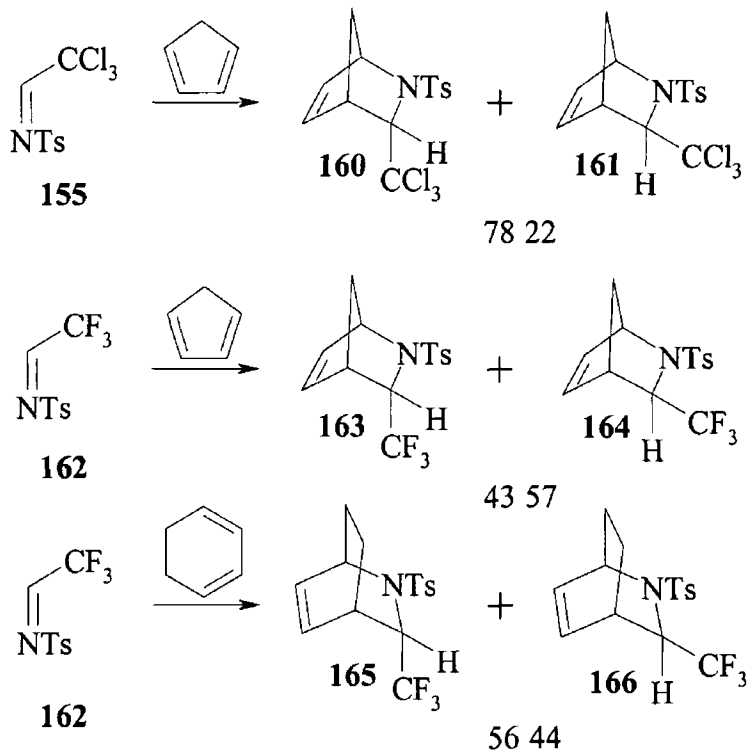



**Scheme 2 13** *Regioselectivity of the Diels-Alder cycloaddition of trichloromethyl-N-sulfonyl imine to 1,3-dienes*

A later investigation of the addition of these N-sulfonyl imines to cyclopentadiene and 1,3-cyclohexadiene established the stereochemistry of the cycloadducts [30] Addition of trichloromethyl-N-sulfonyl imine to cyclopentadiene yields a 78 22 ratio of *endo* adduct **160** to *exo* **161** but with trifluoromethyl-N-sulfonyl imine **162** the *exo* isomer **164** is favoured over the *endo* **163** adduct by 57 43 However with the fluoral derivative and 1,3-cyclohexadiene, a 56 44 ratio of *endo* **165** to *exo* **166** was produced

These were results were rationalised by the assumption that the *E*-imine is the reactive species and that steric interactions between the trihalomethyl and/or tosyl groups with

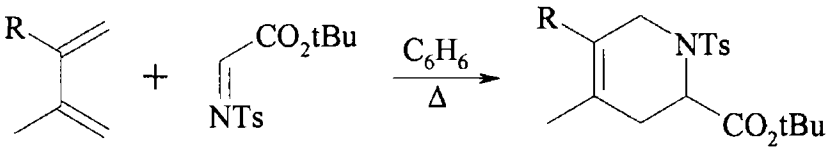
the 1,4-substituents on the diene are important in determining the stereochemistry of the products




**Scheme 2.14** *Stereoselectivity of the Diels-Alder reaction of trihalomethyl-N-sulfonyl imines and cyclic dienes*

*2 3 1 2 N-Sulfonyl Imines of Glyoxylic Esters*

The vast majority of examples of Diels-Alder reactions of N-sulfonyl imines involve those compounds derived from glyoxyhc esters The first of these was again reported by Albrecht and Kresze[17] and involved the addition of the imine of glyoxylic butyl ester **154c** to butadienes



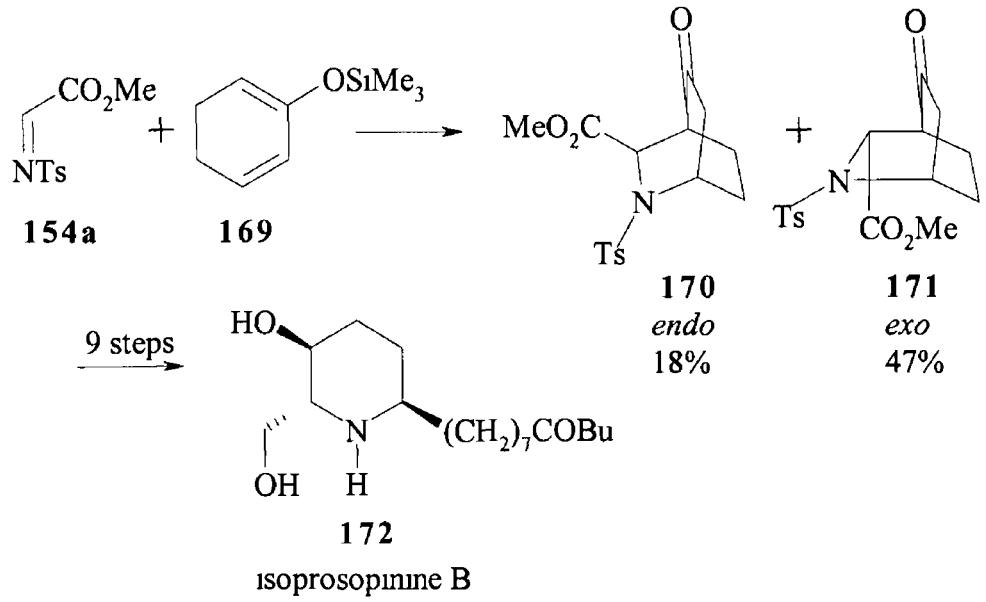

**167** **154c** **168**

R = H, Me

**Scheme 2.15** *Diels-Alder addition of N-sulfonyl imine derived from butyl glyoxylate to butadienes*

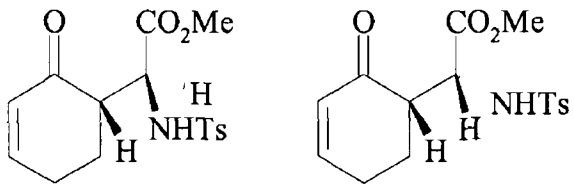
The butyl glyoxylate imine has been used in other cycloadditions,[31] but it was after the discovery of the synthesis of these imines using *p*-toluenesulfonyl isocyanate[27] that the use of these compounds in Diels-Alder reactions increased remarkably [29,32,33]

The Holmes group in particular, have used the N-sulfonyl imine **154a** derived from methyl glyoxylate in a wide range of reactions [34-37] The major *exo* product **171** from siloxydiene was used in the total synthesis of the piperidine alkaloids isoprosopinmes A and B[35] and deoxyprosopimne [36]




**Scheme 2 16** *The cycloaddition of methyl glyoxylate N-sulfonyl imine to siloxydiene, used in the total synthesis of Isoprosopinine B*

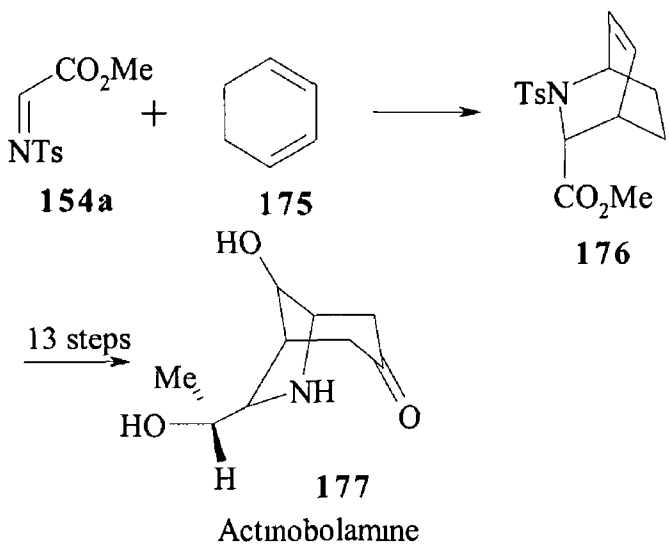
During the course of their work they also found that the reaction of the imine **154a** with 2-trimethylsilyloxycyclohexadiene followed by acidic work-up shows a divergence in pathways at low temperatures in polar solvents the cyclohexanones **173** and **174** are favoured, while at higher temperatures the bicyclic ketones are the predominant products [37]




**173** **174**

**Figure 2 1** *Cyclohexanones produced when the reaction between methyl glyoxylate N-sulfonyl imine and 2-trimethylsilyloxycyclohexadiene is carried out at low temperatures in polar solvents*

The addition of the methyl glyoxylate imine **154a** to cyclohexa-1,3-diene has been used in the first step of the stereoselective synthesis of (±)-actmobolamine, the main degradation product of the antitumour compound actinobolin [38]



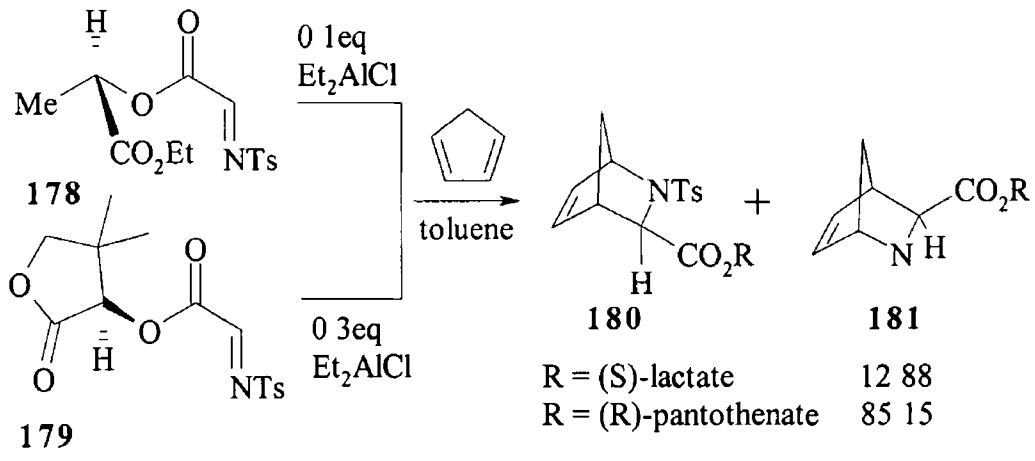

**154a** **175** **176**

**177**

Actinobolamine

**Scheme 2 17** *Addition of methyl glyoxylate N-sulfonyl imine to cyclohexa-1,3-diene in the first step of the total synthesis of Actinobolamine*

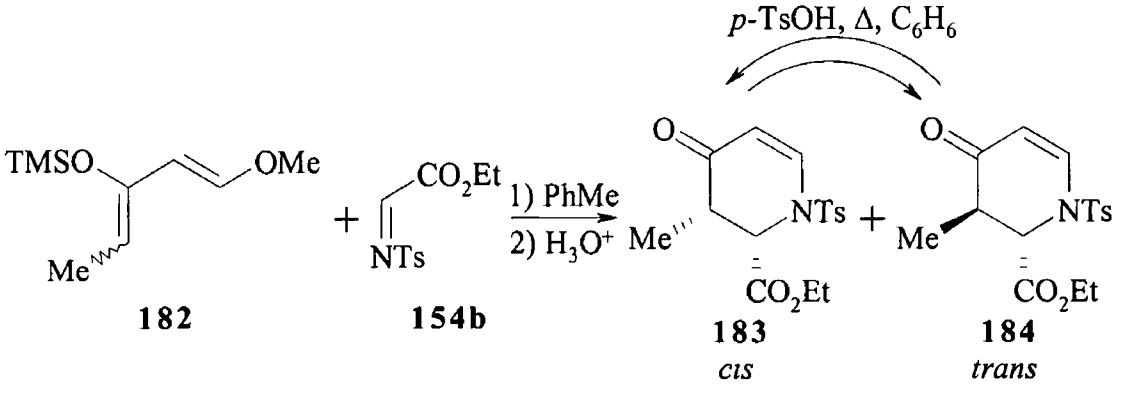
More recently, this group has studied the stereoselectivity of the Diels-Alder reaction of N-sulfonyl imines derived from glyoxylate carrying an ester chiral auxiliary [39] Thermal reactions of the (S)-lactate **178** and (R)-pantothenate **179** derived imines with cyclopentadiene showed relatively low facial diastereoselectivity, but the introduction of a Lewis acid catalyst improved the selectivity significantly




**Scheme 2 18** *Stereoselectivity in the Diels-Alder reaction, induced by N-sulfonyl imines of chiral glyoxylic esters*

Diethylaluminium chloride proved to be the best catalyst, whereas other strong Lewis acids, such as $TiCl_4$, $SnCl_4$ and $BF_3 OEt_2$ caused decomposition The weaker Lewis acids, $Al(OEt)_3$, $MgBr_2$, $ZnCl_2$ and $Me_2AlCl$ gave lower selectivities

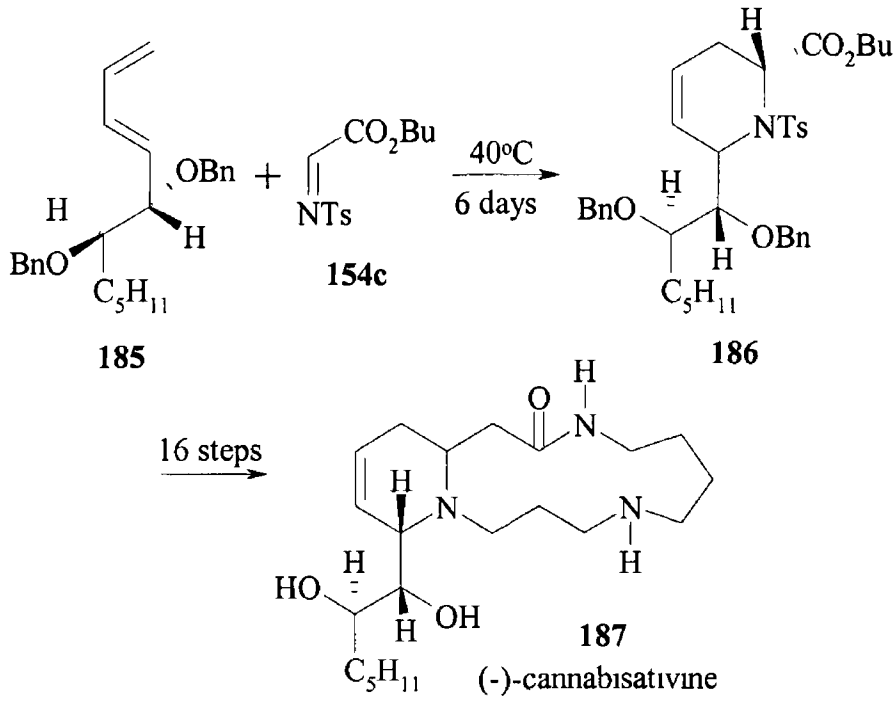
Weinreb *et al* have used the N-sulfonyl imine derived from ethyl glyoxylate **154b** in a Diels-Alder reaction with oxygenated diene **182** [40] The resulting *trans* enone was then used to construct a piperidine ring unit with the view to using it in the total synthesis of the marine hepatotoxin *Cylindrospermopsin*




**Scheme 2 19** *Diels Alder reaction of ethyl glyoxylate N-sulfonyl imine with oxygenated diene The trans isomer has potential for the synthesis of Cylindrospermopsin*

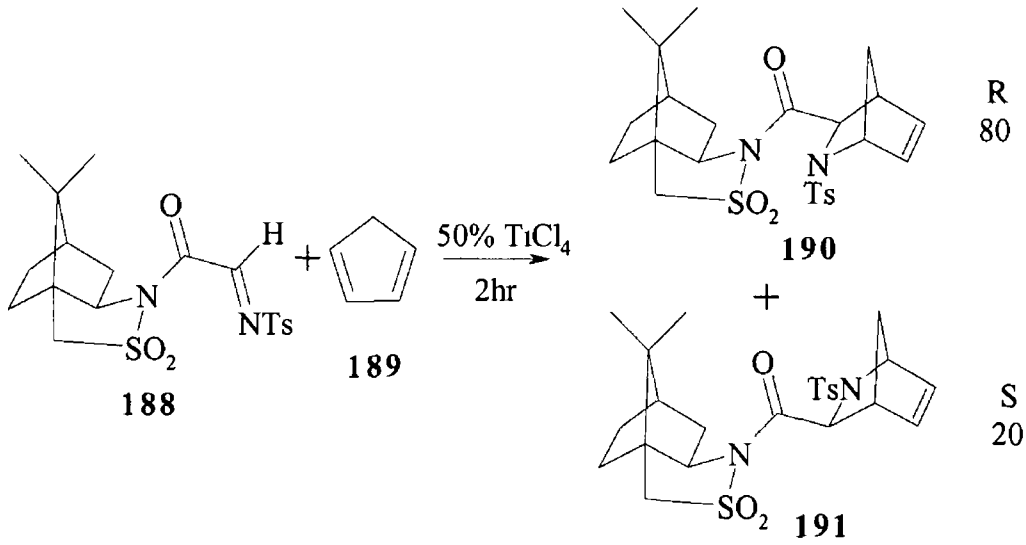
Hamada and co-workers have studied the face selectivity of the glyoxylate N-sulfonyl imine cycloadditions with acyclic dienes bearing a stereogenic centre [41] They subsequently used the hetero Diels-Alder reaction of the chiral diene **185** and butyl

glyoxylate N-sulfonyl imine **154c** in the synthesis of (-)-cannabisativine **187** [42] In this key step, regio- and diastereo-face selectivities were completely controlled and only one diastereomer was isolated in high yield



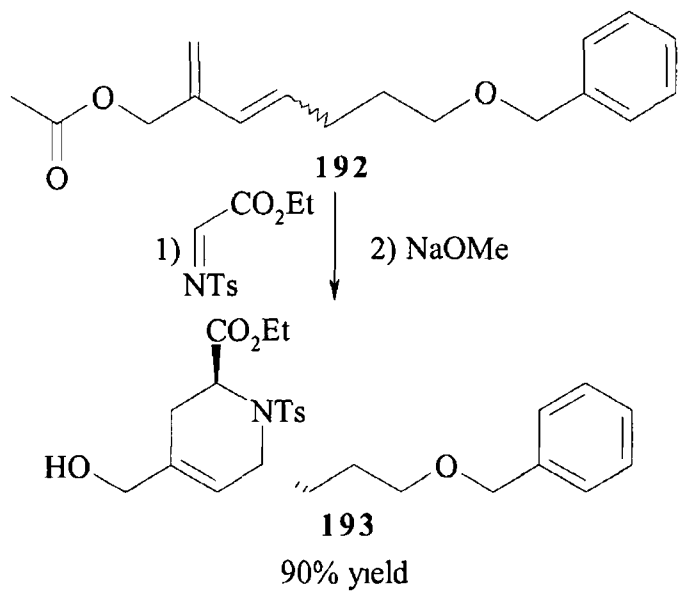

**Scheme 2 20** *Diels-Alder addition of butyl glyoxylic N-sulfonyl imine to chiral diene, a key step in the total synthesis of (-)-cannabisativine*

Good diastereoisomeric excess is also obtained in the Diels Alder reaction of the N-sulfonyl imine of N-glyoxyloyl-(2R)-bornane-10,2-sultam **188** with cyclopentadiene [43] Under ambient conditions without any catalyst the two *exo* diastereomers are obtained in a ratio of 36 64 Application of high pressure techniques and the introduction of Lewis acid catalysts resulted in a change of the direction of asymmetric induction, namely the major diastereomer **190** possessed the (R) absolute configuration on the new stereogenic centre In all cases studied the yield was low and the diastereoisomeric excess of the major cycloadduct was in the region of 80 20




**Scheme 2 21** *The asymmetric [4+2] cycloaddition of cyclopentadiene to chiral glyoxylate N-sulfonyl imine, resulting in good diastereoisomeric excess of the (R)-diastereoisomer*

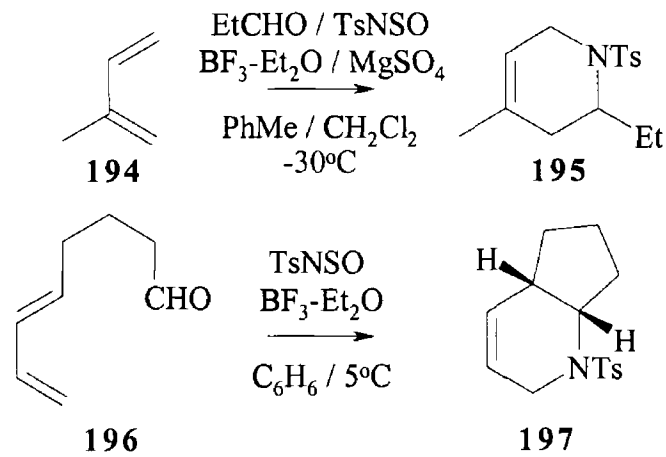
Recently, N-sulfonyl imines derived from chloral and ethyl glyoxylate have been used in a combination of enyne cross methathesis and Diels-Alder reaction under high pressure to synthesise substituted tetrahydropyridines [44] The ethyl glyoxylate imine was reacted with diene **192** to give a pipecolic derivative, which was then equilibrated using sodium methoxide in methanol to give **193** as a single diastereomer in high yield




**Scheme 2 22** *Stereoselective synthesis of a pipecolic acid derivative*

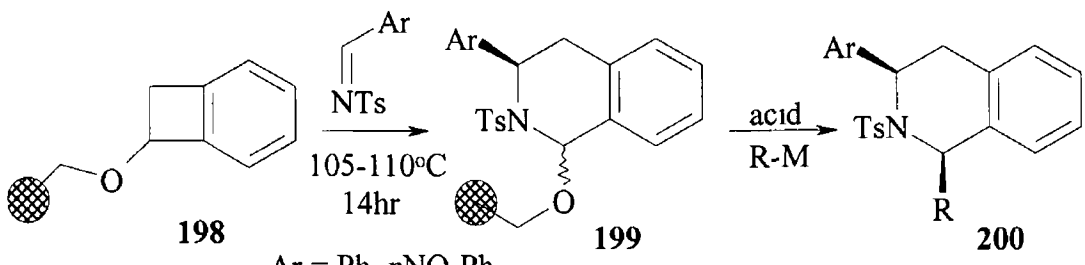
*2 3 1 3 Other N-Sulfonyl Imines*

Weinreb and Sisko have reported the first examples of Diels-Alder reaction of N-sulfonyl imines derived from enohsable aldehydes [19a] Treatment of the aldehyde with N-sulfinyl-*p*-toluenesulfonamide and boron trifluoride etherate followed by the diene gives the cycloadduct **195** in good yield Intramolecular additions were also achieved by this procedure Yields and reproducibility are greatly improved by the suspension of anhydrous magnesium sulfate in the reaction mixture Molecular sieves are also effective, but less so than magnesium sulfate




**Scheme 2 23** *Diels-Alder reactions of N-sulfonyl imines derived from enolisable aldehydes*

Recently, the hetero Diels-Alder reaction of N-sulfonyl imines with *o*-quinodimethane has been carried out on solid-support benzocyclobutene ether resin [45] The heterocyclic polymer supported products **199** were then subjected to reaction with Bronsted or Lewis acid-nucleophile combinations providing substituted tetrahydroisoquinolines **200**, whilst leaving no trace of attachment to the polymer support




Ar = Ph, $p$NO$_2$Ph
R = H, Me, -CH$_2$CH=CH$_2$
M = Sn, Al

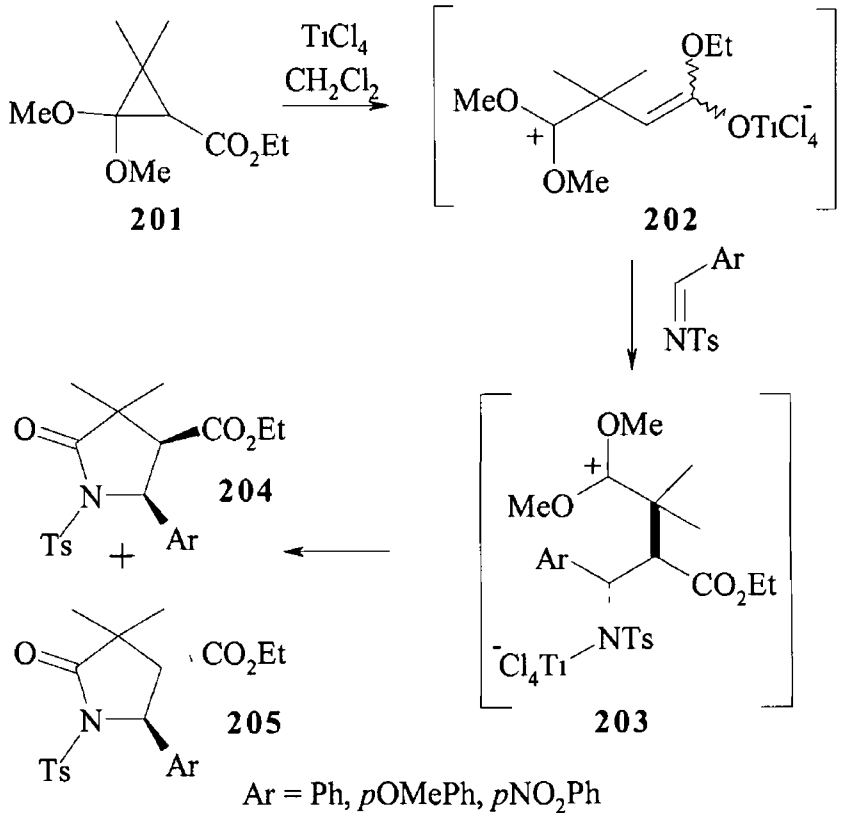
**Scheme 2 24** *Diels-Alder reaction of N-sulfonyl imines and o-quinodimethane on a polymer support*

### *2 3.2. Synthesis of Five-Membered Rings.*

As shown, the early cycloadditions of N-sulfonyl imines were very much based on the Diels-Alder reaction and the synthesis of 6-membered heterocycles It has only been in the past decade that these compounds have been found useful in the synthesis of 5-membered heterocycles

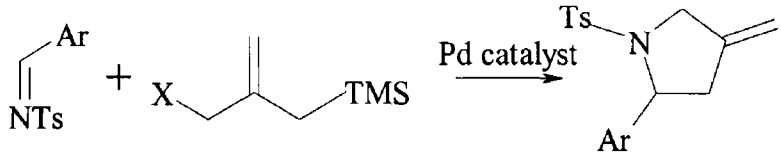
#### *2 3 2 1 Five-Membered Rings Containing One Heteroatom*

A highly stereoselective reaction of ethyl 2,2-dialkoxycyclopropane carboxylates **201** with some aromatic N-sulfonyl imines[46] was one of the first examples of the use of N-sulfonyl imines in the synthesis of 5-membered heterocycles In the presence of $TiCl_4$, the cyclopropane derivative condenses with the imines to stereoselectively produce γ-lactams in good yields (70-90%), with the *cis* isomer **204** being the major product It is likely that the mechanism involves addition of the imine to the intermediate zwitterionic ester enolate **202** **(Scheme 2.25)**




**Scheme 2.25** *Condensation of aromatic N-sulfonyl imines with cyclopropane derivative, producing 3 4-disubstituted lactams with high stereoselectivity*

Trost *et al* have reported that aromatic and aliphatic N-sulfonyl imines undergo palladium catalysed cycloadditions to trimethylenemethane (TMM) precursors, giving substituted pyrrolidines **207** in high yields [47,48] Simple imines fail to react, but imines possessing an electron withdrawing group at either the carbon or nitrogen enhance the electrophilicity of the imine sufficiently to make it an excellent acceptor Aliphatic N-sulfonyl imines, derived from both enolisable and non-enolisable aldehydes require higher temperatures to react and yields are not as high as those of the aromatic N-sulfonyl imines This was because the aliphatic imines were not purified but used directly in the cycloaddition

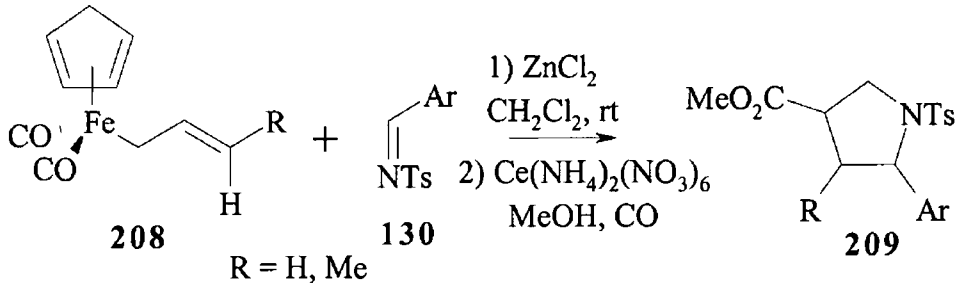



**130** **206** **207**

Ar = Ph, *o*ClPh, *m*$NO_2$Ph, *p*OMePh
X = OAc, $OCO_2CH_3$

**Scheme 2.26** *Palladium catalysed cycloaddition of N-sulfonyl imines with ((trimethylsilyl)methyl)allyl acetates*

Substituted pyrrolidines **209** can also be produced by the reaction of aromatic N-sulfonyl imines with allyl(cyclopentadienyl)iron dicarbonyl complexes [49] The reaction is carried out at room temperature in dichloromethane with $ZnCl_2$ as the Lewis acid catalyst However if $TiCl_4$ or $BF_3$-$Et_2O$ is used as the catalyst, none of the expected [3+2]-adduct is obtained The reaction is worked up with a methanolic solution of ceric ammonium nitrate under a carbon monoxide atmosphere, and yields are moderate (30-55%)

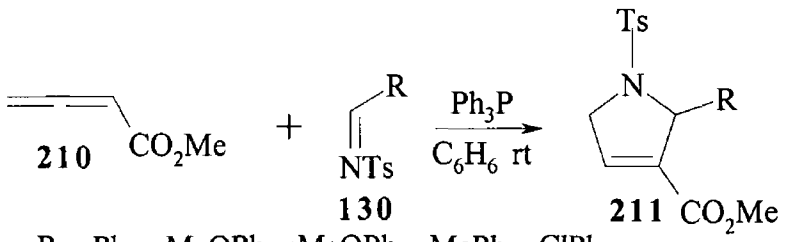



**208** **130** **209**

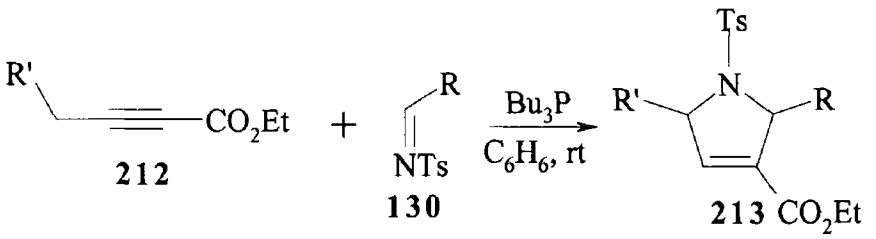
R = H, Me
Ar = Ph, *p*$NO_2$Ph

**Scheme 2.27** *Synthesis of substituted pyrrolidines using N-sulfonyl imines derived from aromatic aldehydes*

Lu and Xu have carried out extensive work on the cycloaddition of aromatic N-sulfonyl imines to 2,3-butadienoates **210** and 2-alkynoates **212** [50,51 52] This is an efficient route to the pyrrolidine rings **211** and **213**, which are examples of the important structural unit existing in a large number of natural products and pharmaceutical molecules The reactions are catalysed by triphenylphosphine or tributylphosphine and work well with both electron withdrawing and electron releasing substituents on the phenyl ring The addition of N-sulfonyl imines derived from aliphatic aldehydes (trace amounts of products) does not give as good results as those from aromatic aldehydes (90-98%)



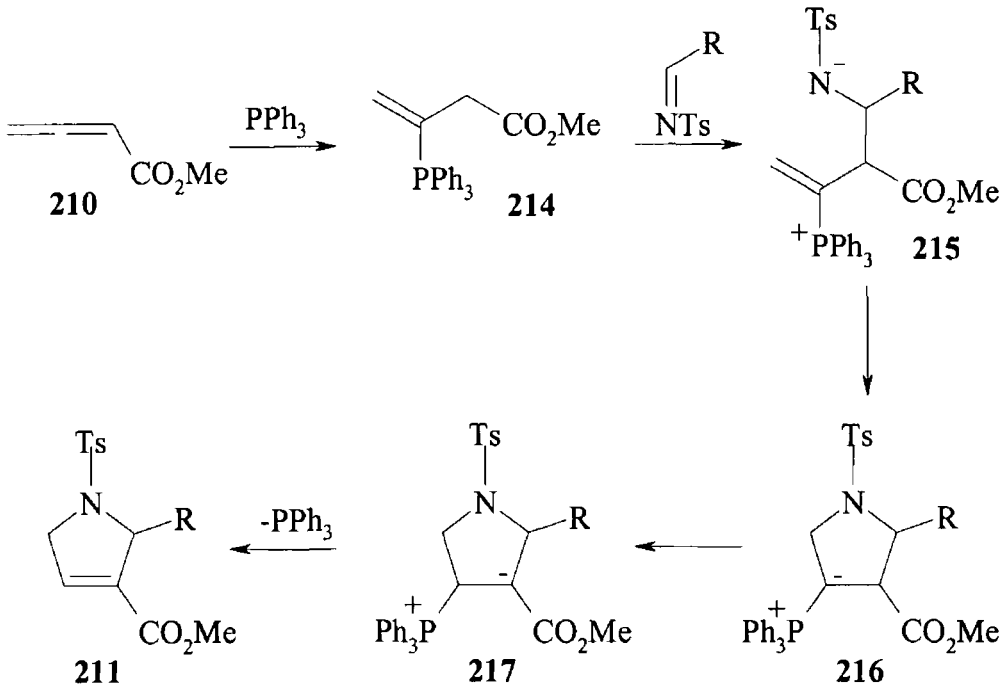

R = Ph, *m*MeOPh, *p*MeOPh, *p*MePh, *p*ClPh, *p*$NO_2$Ph, 1-napthyl, 2-furyl, $^t$-Bu




R' = H, R = Ph, *p*MeOPh, *p*MePh, *p*ClPh, *p*$NO_2$Ph etc
R' = n-Pr, Et, R = Ph, 2-furyl, piperonyl, 1-naphthyl,

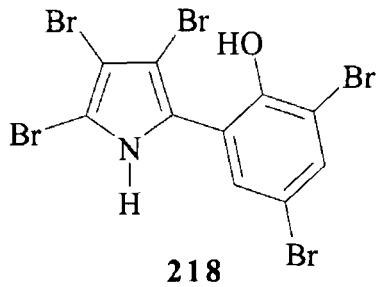
**Scheme 2 28** *1,3-Dipolar Cycloaddition of N-sulfonyl imines to 2,3-butadienoates and 2-alkynoates, yielding substituted pyrrolidines*

The mechanism is thought to involve the nucleophilic attack of the phosphine catalyst on the allenoates or alkynoates to generate a reactive dipolar intermediate, which is then trapped by the dipolarophilic imine, forming an open chain intermediate **215** Subsequent intramolecular nucleophilic addition gives a cyclic intermediate **216**, hydrogen transfer forms the intermediate **217** which then produces the pyrrolidine




**Scheme 2 29** *Proposed mechanism for the phosphine-catalysed cycloaddition of N-sulfonyl imines to methyl 2,3-butadienoate*

This group has used this [3+2] cycloaddition (**Scheme 2.29**, R = *o*-MeOPh) as the first step in the synthesis of *pentabromoaseudilin* **218**, a potent marine antibiotic which has stronger antibiotical properties than penicillin and exhibits antitumour, antimicrobial and phytotoxic activities



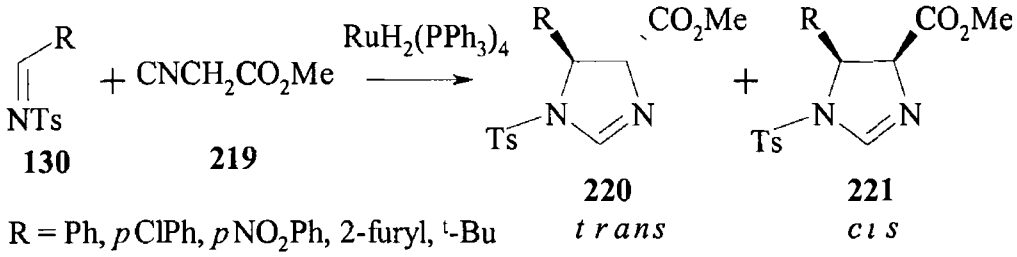

**218**

**Figure 2 2** *Pentabromopseudilin, the marine antibiotic synthesised using the cycloaddition of N-tosyl 2-methoxybenzaldimine and methyl 2,3-butadienoate as the first step*

*2 3 2 2 Five Membered Rings Containing Two Heteroatoms*

*2 3 2 2 1 Two Nitrogen Atoms*

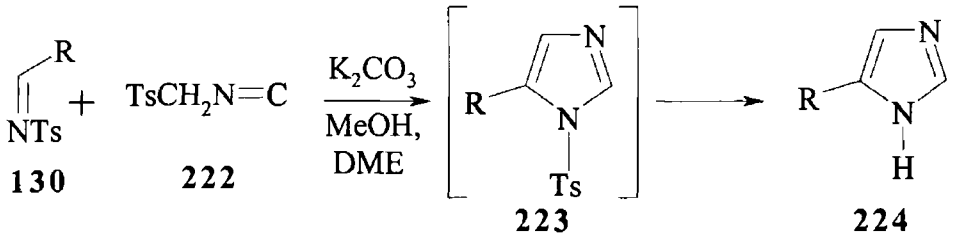
The synthesis of 2-imidazolines **220** and **221** can be achieved by the transition metal complex catalysed reaction of N-sulfonyl imines with isocyanoacetate (**Scheme 2 30**)The Ru(II)-catalysed aldol reaction gave *trans*-2-imidazolines stereoselectively,[53] whereas an Au(I) complex catalysed similar reaction gave *cis*-2-imidazohne as the major product [54] Hydrolysis of these imidazolines yields 2,3-diamino acids which are constituents of some peptidic antibiotics and other biologically active compounds




**Scheme 2 30** *The ruthenium catalysed aldol reaction of N-sulfonyl imines with isocyanoacetate, giving the trans isomer as the major product*

The extension of this work to using a chiral $Me_2SAuCl$-ferrocenylphosphine catalyst results in an efficient enantioselective synthesis of optically active 2-imidazolines [55] As with the previous gold-catalysed reactions, the *cis* isomer was the major product with enantiomeric excess of 99% achieved for some of the products

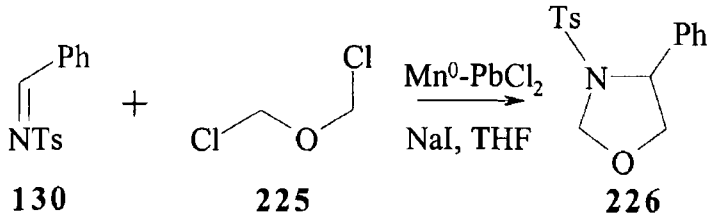
When N-sulfonyl aldimines are reacted with tosylmethyl isocyanide **222** in the presence of a base, cycloaddition occurs to give 4(5)-monosubstituted imidazoles **224** [56] The tosyl group of the initially formed 1-tosyl imidazole **223** is spontaneously lost under the reaction conditions




**Scheme 2.31** *4(5)-monosubstituted imidazoles from N-tosylaldimines and tosylmethyl isocyanide*

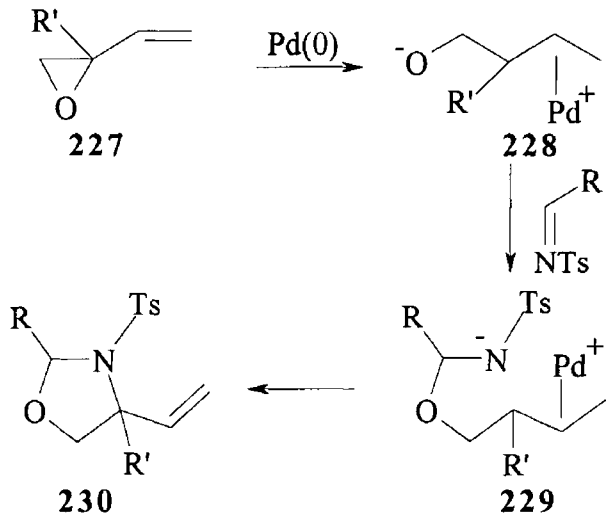
*2 3 2 2 2 One Nitrogen Atom, One Oxygen Atom*

The N-sulfonyl imine derived from benzaldehyde has been used as an electron deficient dipolarophile in a cycloaddition with a carbonyl ylide [57] Manganese metal was used to generate the carbonyl ylide from bis-(chloromethyl)ether The use of other N-sulfonyl imines was not reported




**Scheme 2.32** *Substituted oxazolidine from the cycloaddition of N-tosyl benzaldimine and carbonyl ylide*

1,3-oxazolidines **230** can also be synthesised by the palladium catalysed reaction of N-sulfonyl immes with vinylic oxiranes **227** in what is essentially a regioselective [3+2] cycloaddition Imines possessing a phenyl or furyl substituent reacted well, as did aromatic imines containing electron-donating substituents at the *para* position Imines having sterically crowding substituents as the R group gave slightly lower yields of oxazolidines




R = Ph, 2-furyl, *p*MePh, *p*OMePh, 1-naphthyl, $^{t}$-Bu

**Scheme 2 33** *Mechanism of the palladium catalysed reaction of N-sulfonyl imines with vinylic oxiranes, give 1,3-oxazolidines*

## 2.4 Results and Discussion:

### *2 4 1 Introduction*

As shown in Chapter 1, the reaction of triazolium imide 1,3-dipoles with a wide range of dipolarophiles has been investigated In general, the reactions proceed as a 1,3-dipolar cycloaddition followed by a 1,4-sigmatropic rearrangement To date, the only nitrogen-containing dipolarophiles which ultimately give the imidazo[4 5-d]-1,2,3-triazoles as the final products, are isocyanates and isothiocyanates However these reactants limit the substituent at C-5 to carbonyl and thionyl groups In order to enable variation of the substituent at C-5 it was decided to investigate whether N-sulfonyl imines could be used as nitrogen-containing dipolarophiles If these imines successfully added to the triazolium imide 1,3-dipoles, this would provide a new class of imidazo[4,5-d]-1,2,3-triazoles, containing an $sp^3$ hybridised C-5 There would also be the possibility of removing the N-sulfonyl group from N-4 and introduction of new substituents at this site

Conjugation with electron-attracting or electron-releasing substituents increases the dipolarophilic activity of a multiple bond, and as would be expected, this effect is observed with N-sulfonyl imines Sulfonyl imines containing an aromatic group do not form adducts when heated in benzene with dienes, despite the electron-withdrawing effect of the sulfonyl group However, if the carbon atom of the C=N bond also carries an electron-withdrawing group as in $CO_2R$, $CF_3$, of $CCl_3$, adducts are formed under the above conditions [18] For this reason, four immes were chosen to use as dipolarophiles Of these, three had an electron-withdrawing group attached to the carbon atom, i e $CO_2CH_3$, $CO_2C_2H_5$, $CCl_3$, and the fourth had a phenyl group attached to the carbon atom

### *2.4 2 Synthesis of N-Sulfonyl Imines.*

*2 4 2 1 N-p-Toluenesulfonyl Trichloroimine*

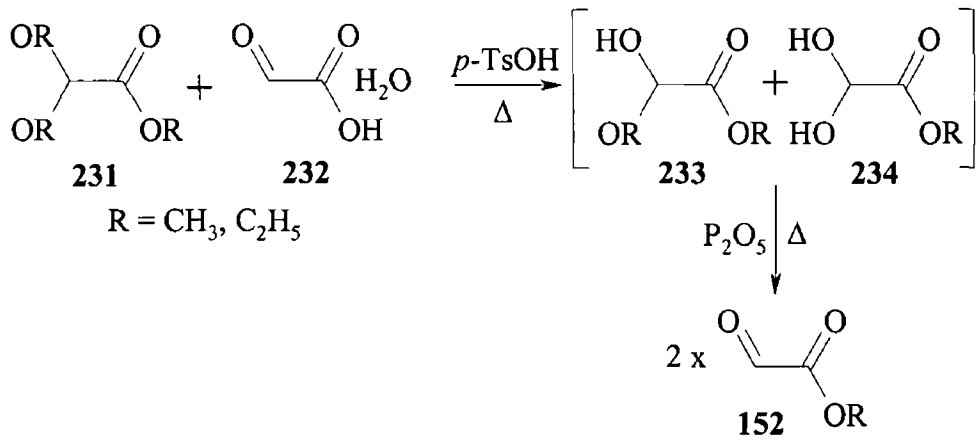
The synthesis of N-*p*-toluenesulfonyl trichloroimine was carried out by the method of Albrecht and Kresze [16] This involved the Lewis acid catalysed reaction of N-sulfinyl-*p*-toluene sulfonamide with chloral, with benzene as the solvent N-sulfinyl-*p*-toluene sulfonamide was first prepared from *p*-toluene sulfonamide and thionyl chloride The thionyl chloride, used in excess, was removed by vacuum distillation The crude N-sulfinyl-*p*-toluene sulfonamide was then reacted with chloral in refluxing benzene in the presence of a catalytic amount of aluminium trichloride Addition of petroleum ether gave the required imine in moderate yields

*2 4 2 2 N-p-Toluenesulfonyl Benzaldimine*

The synthesis of N-*p*-toluenesulfonyl benzaldimine was carried out by the method reported by Love *et al* [15] The reaction involved heating benzaldehyde, *p*-toluenesulfonamide and tetraethylorthosilicate for six hours Treatment of the reaction mixture with ethyl acetate followed by n-pentane gave excellent yields of the imme in a high state of purity

*2 4 2 3 N-p-Toluenesulfonyl Imino-2 Acetic Acid Esters*

The synthesis of the starting aldehydes (methyl and ethyl glyoxylate)[58] involves an acid catalysed exchange of one equivalent of alcohol between acetal ester **231** and glyoxylic acid monohydrate **232** The resulting syrup which consists of hemi-acetal ester **233** and ester hydrate **234**, is then treated with phosphorus pentoxide Distillation of this mixture gives good yields of the alkyl glyoxylate **152**



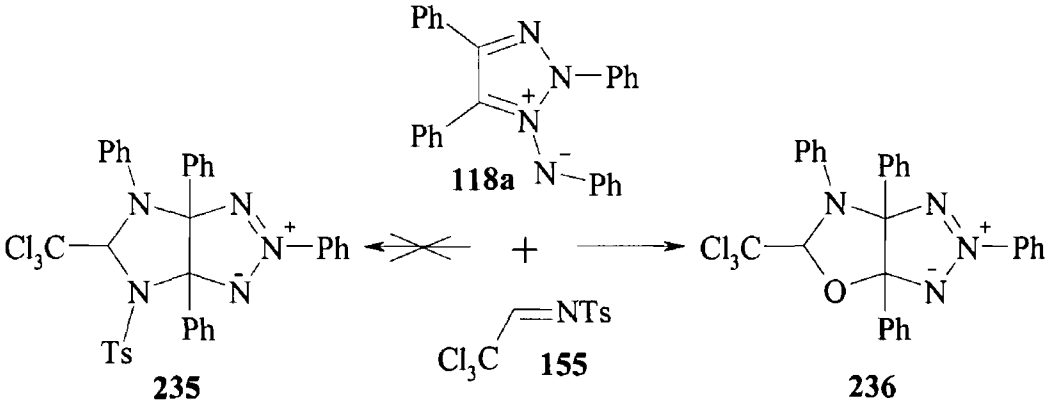

**Scheme 2.34** *The Hook Synthesis of alkyl glyoxylates*

The alkyl glyoxylate is then used immediately to synthesise the N-sulfonyl imine **154** [27] Glyoxylic acid esters **152** and tosylisocyanate **151** react as shown in **Scheme 2.12** through the intermediate **153**, leading, after decarboxylation to the imine The reaction is carried out in refluxing benzene, the use of aluminium chloride as a catalyst has been reported but was found to have little effect on the yield of imme In fact, the reaction usually gave better yields of imme if the catalyst was omitted from the reaction mixture The methyl ester analogue **154a** has never been isolated until now, it has always been reported as being used *in situ* However, for our purposes it was more productive to isolate the imme as white crystals and then proceed with the cycloaddition reaction

### *2 4 3 Cycloaddition Reactions of N-Sulfonyl Imines*

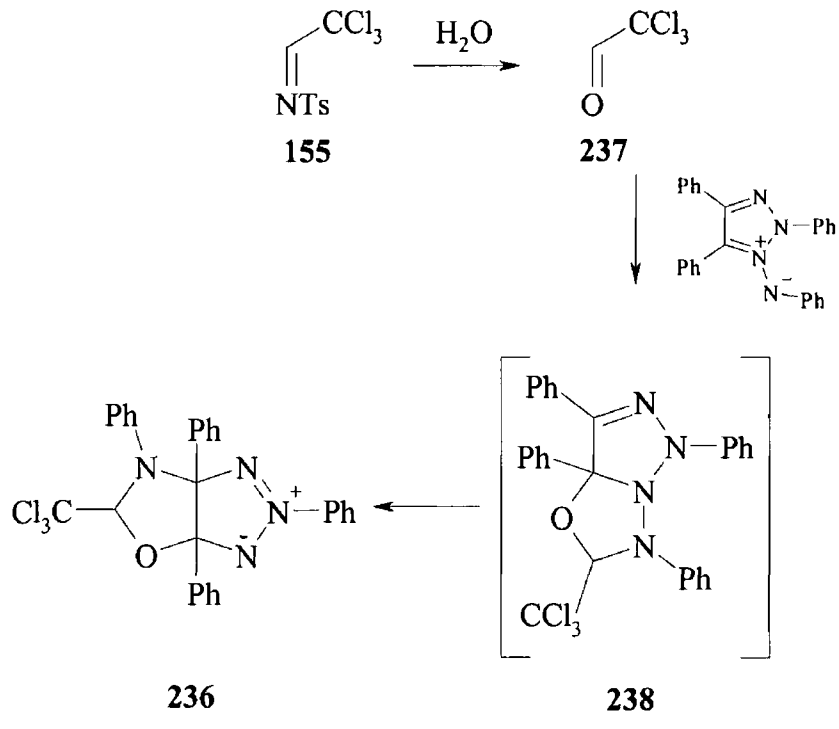
#### *2 4 3 1 N-p-Toluenesulfonyl Trichloroimine*

The addition of N-*p*-toluenesulfonyl trichloroimine **155** to the triazolium imide 1,3-dipole **118a** was initially carried out under the usual conditions for this type of reaction i e equimolar amounts of the two reactants were stirred under reflux in dry acetone for 7 hours The reaction was monitored by TLC, which indicated when the reaction had reached completion The solvent was removed and the residue recrystalhsed from ethanol $^{1}H$ and $^{13}C$ NMR spectra of the pure product indicated that a cycloaddition-rearrangement reaction had indeed occurred The doublet at 8 23ppm in the $^{1}H$ spectrum, and the bridgehead signals at 102 04 and 102 30ppm in the $^{13}C$ spectrum, are characteristics of the bicyclic adduct products of these types of reactions However, the absence of a methyl signal and some aromatic signals in the spectra indicated that the N-*p*-toluenesulfonyl group was not present in the molecule as expected Microanalysis proved that the product was in fact 2,3a,6,6a-tetraphenyl-5-trichloromethyl-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole **236**




**Scheme 2 35** *Reaction of triazolium imide 1,3-dipole with N-p-toluenesulfonyl trichloroimine did not give the expected imidazo-1,2,3-triazole, but the oxazolo-1,2,3-triazole*

The formation of this molecule can be explained by the hydrolysis of the N-sulfonyl imine to *p*-toluenesulfonamide and the corresponding aldehyde, chloral **237**, and the subsequent cycloaddition of chloral with the triazolium imide 1,3-dipole As is usual for the addition of aldehydes to these dipoles, the addition occurs across the carbon-oxygen double bond The hydrolysis of imines is easy and can be carried out with water [59] The source of water in this reaction is probably the solvent, acetone being difficult to dry and particularly susceptible to absorbing atmospheric moisture




**Scheme 2.36** *Hydrolysis of N-sulfonyl trichloroimine by the presence of water in the solvent results in cycloaddition of the resulting aldehyde, chloral, with triazolium imide 1,3-dipole*

To combat the hydrolysis, sodium-dried benzene was used as the solvent, but again the oxazolo-1,2,3-triazole was obtained, although in lower yields than the use of acetone afforded None of the required imidazo-1,2,3-triazole was produced in the reaction This led to the conclusion that the trichloromethyl group does not sufficiently activate the N-sulfonyl imine to allow it to act as a dipolarophile in the cycloaddition

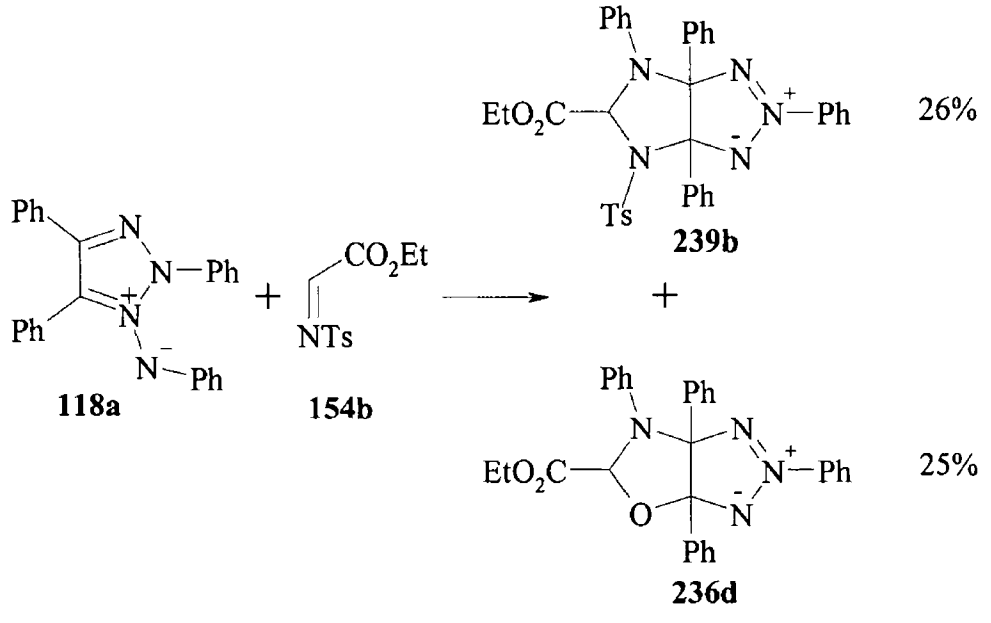
*2 4 3 2 N-p-Toluenesulfonyl Benzaldimine*

After the results of the reaction of the trichloromethyl imine with the dipole, the reaction of N-*p*-toluenesulfonyl benzaldimine **134** with the triazolium imide 1,3-dipole was not expected to give the imidazo-1,2,3-triazole It is unlikely that the phenyl group on the carbon atom would sufficiently activate the imine to enable it to add to the dipole However, the reaction was carried out with dry benzene as the solvent As with the trichloromethyl imine, one of the compounds isolated was the cycloaddition product of the dipole with an aldehyde, in this case, benzaldehyde The other isolated product of

the reaction was *p*-toluenesulfonamide, which fell out of solution in the reaction mixture This is a product of the hydrolysis of N-sulfonyl imines

*2 4 3 3 N-p-Toluenesulfonyl Imino-2 Acetic Acid Esters*

The reaction of N-*p*-toluenesulfonyl imino-2-acetic acid ethyl ester **154b** with 1,2-bis(phenylazo)stilbene **118a** was carried out in the usual manner, i e equimolar amounts of reactants were stirred under reflux in sodium-dried benzene The reaction was monitored by TLC and after 10 hours 1,2-bis(phenylazo)stilbene could still be detected A 20% excess of the imine was added and the reaction allowed to continue for a further 10 hours TLC analysis also showed the presence of two products, and a small amount of *p*-toluenesulfonamide was recovered from the reaction mixture Separation of the products by column chromatography gave two yellow crystalline compounds $^{1}H$ and $^{13}C$ NMR spectra identified these as bicyclic adducts, one being the imidazo-1,2,3-triazole **239b** obtained by the addition of the N-sulfonyl imine, the other being the oxazolo-1,2,3-triazole **236d**




**118a** **154b** **239b** 26% **236d** 25%

**Scheme 2.37** *The two products obtained from the reaction of triazolium imide 1,3-dipole with N-p-toluenesulfonyl imino-2-acetic acid ethyl ester*

Proof that the imine reacted as required with the dipole can be seen from the methyl signals in the NMR spectra (2 16ppm in the $^{1}H$, 14 53ppm in the $^{13}C$, **Figure 2 3**) These indicate the presence of the tosyl group in the adduct Other peaks of interest are

the multiplet at 4 37-4 47ppm and the singlet occurring at 5 15ppm The multiplet represents the $CH_2$ of the ester group and the splitting pattern is not the expected quartet, but rather a multiplet with 7 peaks This complicated splitting pattern occurs because the two protons of the $CH_2$ group are diastereotopic, and therefore have a splitting effect on each other, as well as being split by the three protons of the $CH_3$ group The singlet occurring at 5 15ppm represents the proton bonded to C-5 This occurs more upfield than the corresponding C-H (5 65ppm) peak of the oxazolo-triazole This is due to the effect of the neighbouring oxygen atom as compared to the neighbouring nitrogen atom Oxygen is more electronegative than nitrogen and so, has a deshielding effect on protons in close proximity This deshielding effect causes the proton signal to be shifted downfield Nitrogen, while still electronegative, has less of a deshielding effect and so the proton signal is shifted upfield

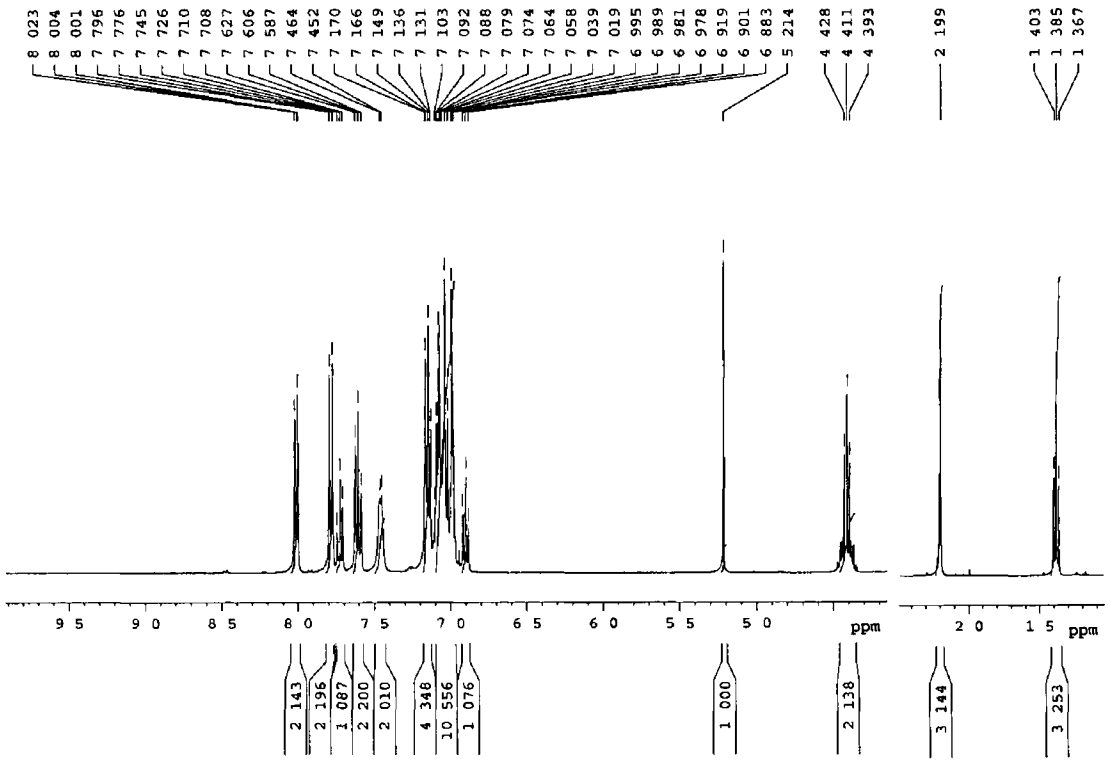



**Figure 2 3** *$^1H$ NMR of 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(239b)***

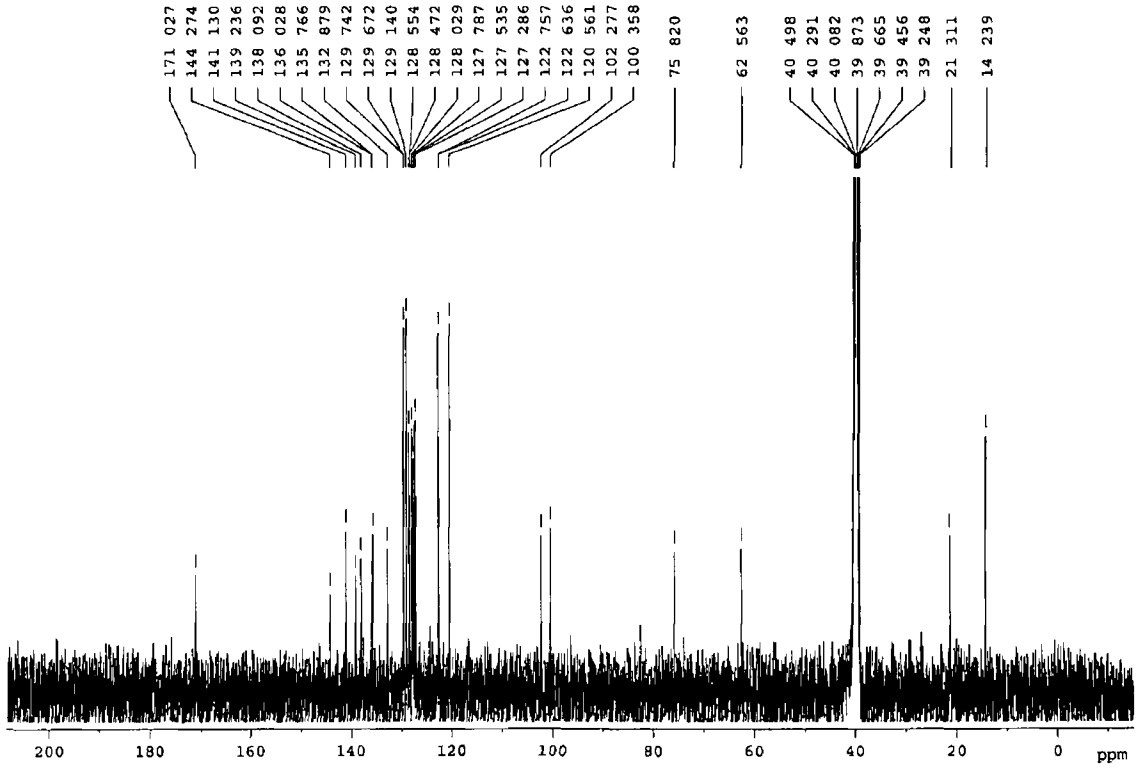
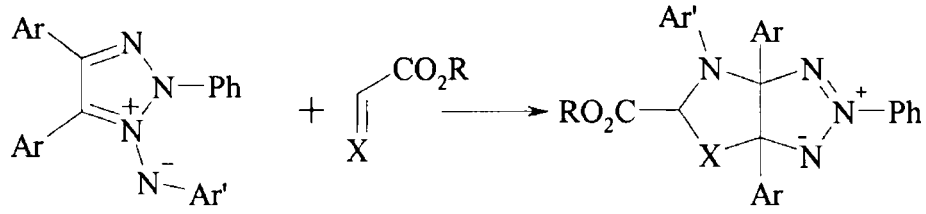



**Figure 2 4** *13C NMR of 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(239b)***

Microanalysis confirmed that the molecule obtained was the novel 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a-4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole **(239b)** This adduct represents a new group of hexahydroimidazo[4,5-d]-1,2,3-triazoles, in which the C-5 is $sp^3$ hybridised rather than $sp^2$ hybridised

It should also be noted that this reaction was attempted by using the imine *in situ*, as has been done in numerous Diels-Alder cycloadditions It was not successful, the ethyl glyoxylate was the only compound recoverable from the reaction mixture The reaction was also attempted using dry THF as the solvent, but in this instance, only the oxazolo-1,2,3-triazole was produced

The addition of the methyl ester analogue to the dipole was also successful This reaction was initially carried out using the N-sulfonyl imine *in situ*, giving low yields (10%) of the imidazo-1,2,3-triazole adduct Yields were improved by first isolating the N-sulfonyl imme and subsequently using it in the cycloaddition



**118** **236** X = O
**239** X = NTs

| | X | Ar | Ar' | R | Yield | M P |
|---|---|---|---|---|---|---|
| 239a | NTs | Ph | Ph | $CO_2Me$ | 15% | 197-198 |
| 239b | NTs | Ph | Ph | $CO_2Et$ | 26% | 206-208 |
| 239c | NTs | *p*ClPh | Ph | $CO_2Et$ | 10% | 228-230 |
| 239d | NTs | Ph | *p*$NO_2$Ph | $CO_2Et$ | 18% | 243-244 |
| 239e | NTs | *p*ClPh | *p*$NO_2$Ph | $CO_2Et$ | 20% | 168-170 |
| 236a | O | Ph | Ph | Ph | 50% | 170-172 |
| 236b | O | Ph | Ph | $CCl_3$ | 46% | 163-164 |
| 236c | O | Ph | Ph | $CO_2Me$ | 22% | 220 |
| 236d | O | Ph | Ph | $CO_2Et$ | 25% | 154-156 |
| 236e | O | *p*ClPh | Ph | $CO_2Et$ | 21% | 181-182 |
| 236f | O | Ph | *p*$NO_2$Ph | $CO_2Et$ | 30% | 179-180 |
| 236g | O | *p*ClPh | *p*$NO_2$Ph | $CO_2Et$ | 26% | 178-180 |

**Table 2 1** *Yields and melting points of the novel imidazo-1,2,3-triazoles and oxazolo-1,2,3-triazoles*

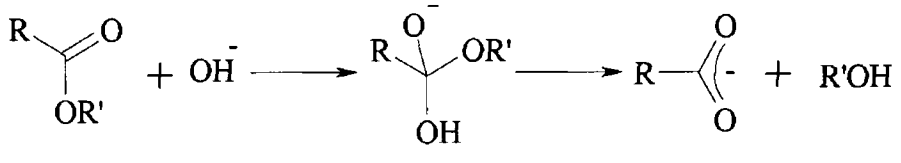
### *2 4 4. Reactions of Imidazo-1,2,3-Triazoles*

#### *2 4 4 1 Removal of the N-p-Toluenesulfonyl Group*

Aryl sulfonyl substituents are highly effective protecting groups for the amino functional group They are stable to most reaction conditions, but unfortunately these protecting groups have frequently proved troublesome to remove A variety of deprotection methods have been used These include a sodium/liquid ammonia reductive detosylation,[60] (lithium can also be used[61]) the use of magnesium in methanol,[62] hydrobromic acid and phenol,[63] or acetic acid,[64] sodium naphthalanide,[65] sodium amalgam in methanol,[35 66] and sodium methoxide in methanol [67] The tosyl group has also been cleaved from nitrogen by photolysis[68] and electrolysis [69]

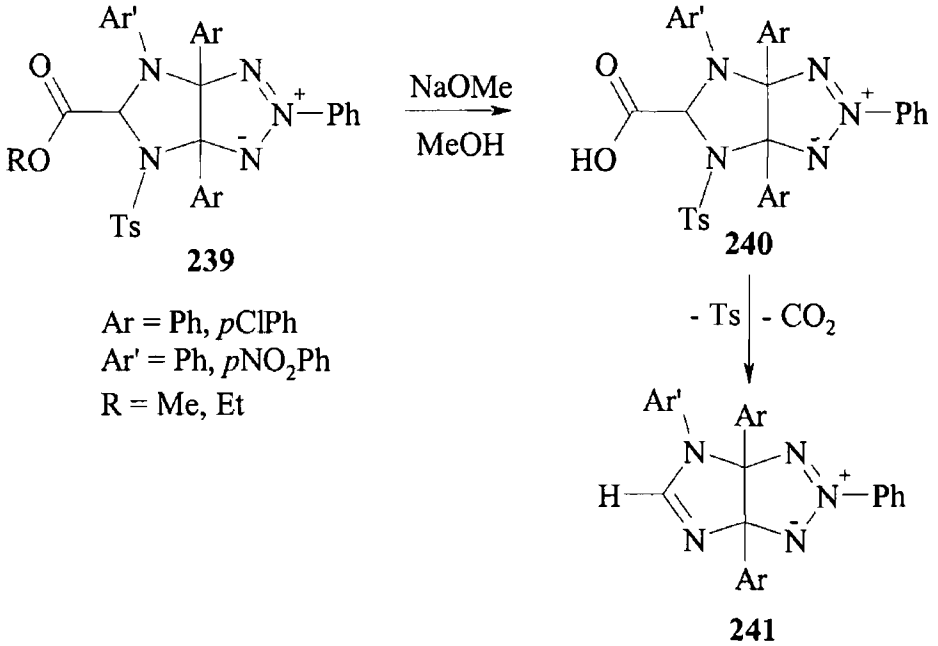
Treatment of the imidazo-1,2,3-triazole with an excess of sodium methoxide (20 molar excess) in boiling methanol resulted in the initial formation of two new products, one of those being an intermediate which disappeared after longer reaction times (up to 24 hours) After work-up and purification on a silica gel column, the resulting $^{1}H$ and $^{13}C$ NMR spectra showed that the bicychc skeleton of the molecule had remained intact, and that the tosyl group had successfully been removed from the molecule The results also indicated that the carboxylate group had been cleaved from C-5 Of interest in the $^{1}H$ spectrum is the singlet at 8 64ppm which represents the proton attached to the now $sp^{2}$-hybridised C-5 The signal peak for the C-5 atom appears at 154 90ppm in the $^{13}C$ spectrum

The mechanism for this reaction is thought to involve base catalysed hydrolysis of the ester moiety A carboxylic ester is hydrolysed to a carboxylic acid and an alcohol when heated with aqueous acid or aqueous base Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH This reaction is essentially irreversible, since a resonance-stabilised carboxylate anion shows little tendency to react with an alcohol




**Scheme 2 38** *Base catalysed hydrolysis of a carboxylic ester*

To confirm the mechanism of the detosylation, the reaction was stopped before it reached completion and the intermediate was isolated The identification of the carboxylic acid derivative **240** as the intermediate serves to support the theory that hydrolysis of the ester is the first step in the removal of the ester and tosyl groups from the 1,3-dipolar cycloaddition product Elimination of carbon dioxide followed by cleavage of the tosyl group gives the novel tetrahydro-imidazo-1,2,3-triazole **241** in good yields




**239**

Ar = Ph, *p*ClPh
Ar' = Ph, *p*$NO_2$Ph
R = Me, Et

**240**

**241**

**Scheme 2 39** *Removal of the tosyl group by treatment with sodium methoxide in methanol The carboxylate group is also removed, yielding a tetrahydro-imidazo-1,2,3-triazole*

Similar reactions have been reported in which treatment of a Diels Alder adduct of the butyl ester N-sulfonyl imine with sodium ethoxide in ethanol or potassium hydroxide gave the detosylated carboxylic acid derivative [17 31] In these instances the sulfinic acid residue is eliminated first, leaving the acid functional group in the product

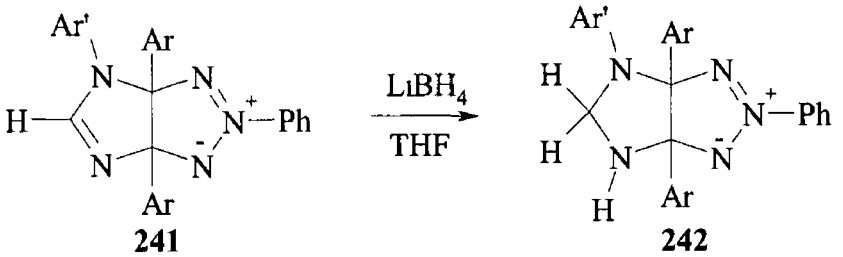
The removal of the tosyl group was also attempted with magnesium in methanol, but was not successful

*2 4 4 2 Reduction of the Carbon-Nitrogen Double Bond*

The removal of the carboxylate and tosyl groups from the adducts of triazolium N-imide and N-sulfonyl imines gave new tetrahydro-imidazo-1,2,3-triazoles **241** These derivatives possess a $sp^2$ hybridised C-5 atom as a result of the carbon-nitrogen double bond Reduction of this bond would give a $sp^3$ hybridised atom at C-5, and provide a hexahydro-imidazo-1,2,3-triazole with non-electron withdrawing groups at C-5

Imines, Schiff bases, hydrazones and other C=N compounds can be reduced with lithium aluminium hydride, sodium borohydride, sodium/ethanol, hydrogen and a catalyst, as well as other reducing agents [70]

In this case, the reduction of the carbon-nitrogen double bond was achieved by stirring a solution of the tetrahydro imidazo-triazole in dry THF in the presence of a large excess of lithium borohydride Lithium borohydride is intermediate in activity as a reducing agent between lithium aluminium hydride and sodium borohydride The reaction usually reached completion in 24 hours, and was then quenched with water The product was easily purified by recrystallisation from ethanol or by flash chromatography




**241** **242**

Ar = Ph, *p*ClPh
Ar' = Ph, *p*$NO_2$Ph

**Scheme 2 40** *Reduction of the carbon-nitrogen double bond with lithium borohydride*

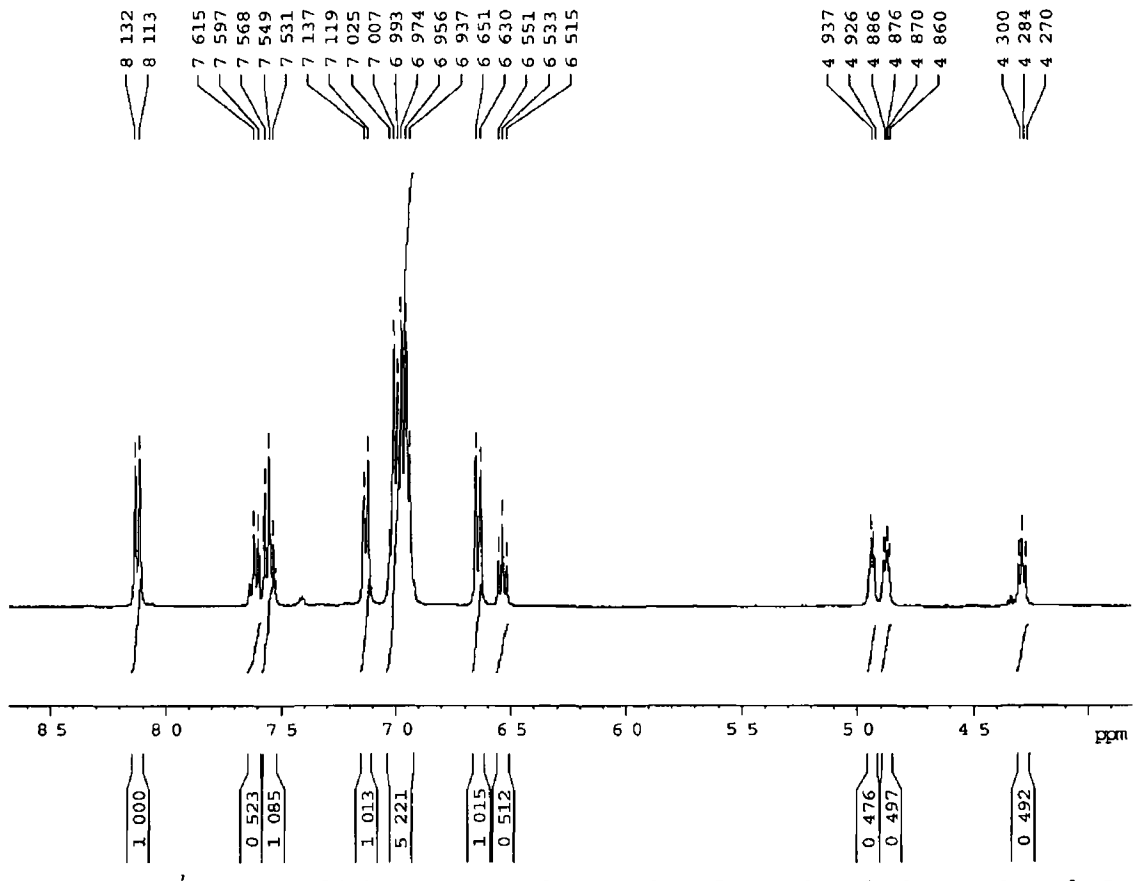



**Figure 2 5** *$^{1}H$ NMR of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole* ***(242a)*** *(Integrals are twice the shown values)*

The $^{1}H$ and $^{13}C$ NMR spectra of the product are shown (**Figures 2 5** and **2 6**) Of interest in the $^{1}H$ spectrum is the difference in the shifts of the two diastereotopic protons attached to the prochiral C-5 These triplets occur at 4 28 and 4 94ppm The chemical shift differences ($\Delta\delta$) between Hs on the same carbon atom tend to be small – usually less than 1ppm – and the coupling constants, *J*, tend to be large In this case $\Delta\delta$ is 0 66ppm and the coupling constant is 5 6Hz The effect of the neighbouring electronegative nitrogen atoms, as well as the five-membered ring, explains the small coupling constant The signal for the N-H proton occurs at 4 87ppm, HMQC and a $D_2O$ shake confirmed this

In the $^{13}C$ spectrum, the bridgehead carbon signals are clearly seen at 96 04 and 102 22ppm The peak at 64 26ppm is due to the $sp^3$ hybridised C-5 The HMQC spectrum shows that the four most downfield peaks (137 96, 738 80, 140 54, 143 46ppm) are those of the four phenyl carbons attached to the bicyclic ring structure

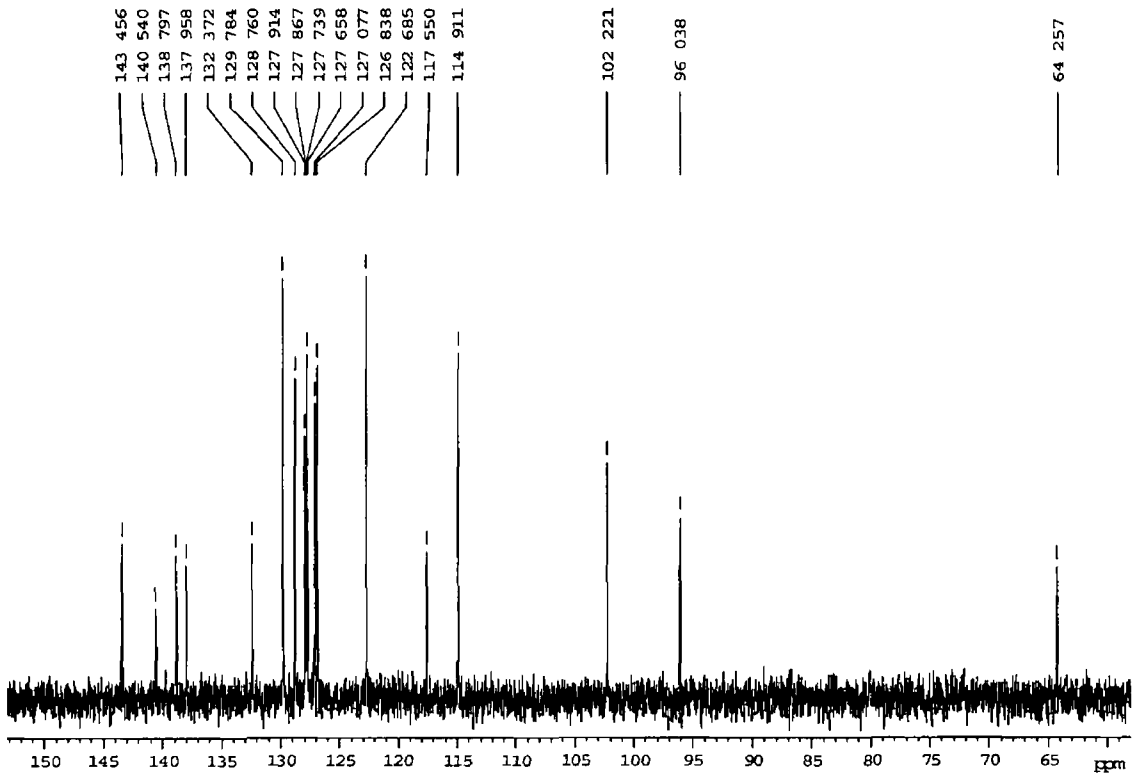



**Figure 2.6** *$^{13}C$ NMR of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole* ***(242a)***

The HMQC and HMBC spectra of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole are discussed in **Chapter 3** and shown in **Figure 3.6**

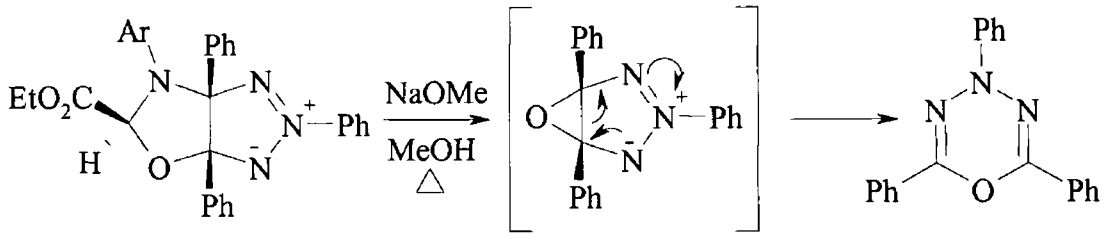
### *2 4 5 Reactions of Oxazolo-1,2,3-Triazoles*

#### *2 4 5 1 Reaction with Sodium Methoxide/Methanol*

The reaction of imidazo-1,2,3-triazoles with sodium methoxide in methanol proceeded with the initial hydrolysis of the ester group attached to C-5 Loss of carbon dioxide and elimination of the tosyl group followed giving tetrahydro imidazo-1,2,3-triazoles Further proof for this mechanism could be obtained if the treatment of oxazolo-1,2,3-triazoles with sodium methoxide in methanol also resulted in hydrolysis of the ester

Treatment of 2,3a,6a-triphenyl-6-(4-nitrophenyl)-5-ethylcarboxylate-3,3a,5,6 tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole **236f** with an excess of sodium methoxide for three days resulted in the formation of two products These were separated by column chromatography and identified by NMR spectroscopy as 4-nitroaniline and 2,4,6-triphenyl-4H-1,3,4,5-oxatriazene **244** Melting points also concurred with literature values

Butler *et al* have reported similar results [71] The products of the cycloaddition of triazolium N-imide 1,3-dipoles with aldehydes rearrange on heating in ethanol or ethanol/acetic acid to give a range of 1,3,4,5-oxatriazenes These results are explained by a fragmentation and ring expansion mechanism, which probably involves the key intermediate **243** Ring expansion occurs by a preferred distotatory outward electrocychc process, relieving strain at the tetrahedral bridgehead carbons This is a convenient route from simple precursors to the rare oxatriazene system




**236f**
Ar = *p*$NO_2$Ph

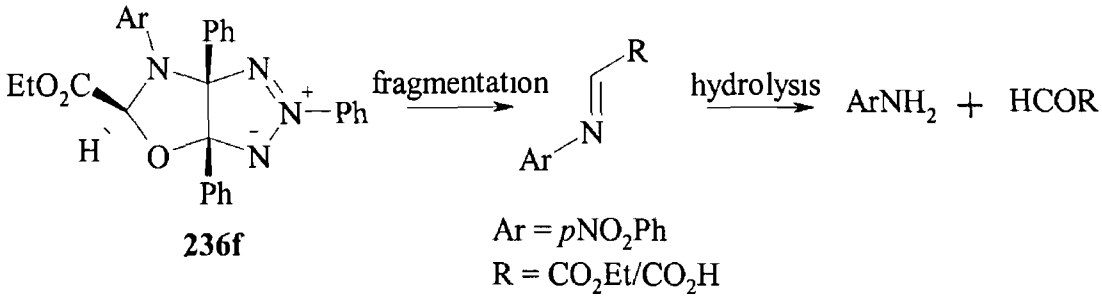
**243**

**244**

**Scheme 2.41** *Thermal induced fragmentation and ring expansion of oxazolo-1,2,3-triazole to give 2,4,6-triphenyl-4H-1,3,4,5-oxatriazene (244)*

The only compound of this unusual class (a potential 8π planar system) known previously was prepared in 1980 by photolysis of a relatively inaccessible triazole-N-oxide [72]

The other compound isolated from the reaction mixture was *p*-nitroaniline This is a possible product of the initial fragmentation reaction Butler's group has not reported the isolation of anilines from this or similar reactions The only secondary products they obtained were in the form of resins and could not be characterised, although they have postulated that the resins may be derived from imines It is likely that this is the case and that the *p*-nitroanihne isolated is the hydrolysis product of the fragmented imine




**236f**

Ar = *p*$NO_2$Ph
R = $CO_2$Et/$CO_2$H

**Scheme 2.42** *Hydrolysis of fragmentation imine giving p-nitroaniline and unknown carbonyl compound*

It cannot be shown from these results if the ester group on C-5 of the initial adduct was hydrolysed during the reaction It is very likely that under these conditions, hydrolysis did occur and, that the carbonyl product from the hydrolysis of the imme was glyoxylic acid (R = $CO_2$H)

## 2 5 Conclusion

The cycloadditions of N-sulfonyl imines to triazolium imide 1,3-dipoles are limited by the substituent on the carbon atom of the imine Electron-donating groups such as phenyl are not useful substituents in the Diels Alder reactions of N-sulfonyl immes, and this group was also found to be ineffective in the 1,3-dipolar cycloaddition Surprisingly, the electron-withdrawing trichloromethyl group was also ineffective in this reaction However, the methyl and ethyl carboxylate substituents sufficiently activated the N-sulfonyl imine to successfully add to the 1,3-dipole, giving novel hexahydro imidazo-1,2,3-triazoles, saturated at the C-5 position, after 1,4-sigmatropic rearrangement of the initial adduct It is thought that favourable secondary orbital interactions are responsible for the successful cycloaddition of the carboxylate substituted N-sulfonyl imines In all cases hydrolysis of the imine occurred and the resulting carbonyl compounds took part in a 1,3-dipolar cycloaddition with the triazolium imide Subsequent 1,4-sigmatropic rearrangement yields a range of novel oxazolo-1,2,3-triazoles

The reaction of these imidazo-1,2,3-triazoles with sodium methoxide and methanol served to remove both the carboxylate and tosyl substituents, giving new tetrahydro imidazo 1,2,3-triazole derivatives Reduction of the carbon-nitrogen double bond gave further novel hexahydro derivatives

The treatment of oxazolo-1,2,3-triazole with sodium methoxide and methanol yielded the rare oxatriazene and *p*-nitro aniline This is explained by a fragmentation and ring-opening process, in which an imme is eliminated as the other fragment The *p*-nitroanihne is believed to be the hydrolysis product of that imme

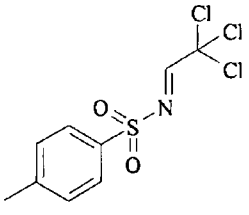
## 2 6 Experimental·

### *2 6 1 Synthesis of N-sulfonyl imines.*

#### *2 6 1 1 Synthesis of N-sulfinyl-p-toluenesulfonamide[1] (134)*

*p*-Toluenesulfonamide (20g, 0 117mol) and thionyl chloride (36cm$^3$) were stirred under reflux for 8 hours The excess thionyl chloride was removed under vacuum and the crude product was used in the synthesis of N-*p*-toluenesulfonyl trichloroimine

#### *2 6 1 2 Synthesis of N-p-toluenesulfonyl trichloroimine (155)*



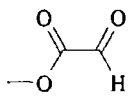
N-sulfinyl-p-toluenesulfonamide (5g, 0 023mol) and chloral (4cm$^3$, 0 041mol) were stirred under reflux in 20cm$^3$ of benzene for 15 minutes Aluminium chloride was used to catalyse the reaction After 15 minutes the red solution was allowed to cool to room temperature Addition of pet ether 40-60 resulted in crystallisation of white crystals Filtration of these gave 3 45g (0 0115mol, 50%) of N-*p*-toluenesulfonyl trichloromethyl imine

**M p** 113°C (lit 113°C)[16]

**$^1$H (DMSO-d$_6$) (ppm)** 2 40 (3H, s) ($CH_3$), 7 35 (2H, d), 7 75 (2H, d), (aromatic C-H), 8 80 (1H, d) (imino H)

**$^{13}$C (DMSO-d$_6$) (ppm)**· 21 34 (CH3), 86 00 (C=N), 102 71 ($CCl_3$), 127 07, 129 67, 139 33, 143 06 (all aromatic C)

#### *2 6 1 3 Synthesis of methyl glyoxylate (152a)*



Methyl dimethoxyacetate (10g, 0 075mol), glyoxylic acid monohydrate (7 0g, 0 075mol) and *p*-toluenesulphonic acid monohydrate (50mg) were heated at 80°C for 18hours The resultant syrup was cooled (ice-methanol) and treated portionwise with vigorous stirring with phosphorus pentoxide (8 0g) The mixture was heated at 80°C for a further additional 4hours [2] The mixture was then distilled under vacuum to give 10 56g (0 12mol, 80%) of the methyl glyoxylate

**$^1$H ($CDCl_3$) (ppm).** 3 79 (3H, s) ($OCH_3$), 9 38 (1H, s) (aldehydic H)

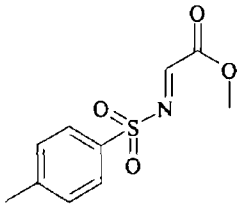
**$^{13}$C ($CDCl_3$) (ppm):** 53 31 ($OCH_3$), 160 13 (C=O, ester), 184 08 (C=O, aldehyde)

---

[1] Kresze, G , Wucherpfennig, W *Angew, Chem Internat Edit* **1967**, 6, *149*

[2] The reaction mixture at this stage may be conveniently stored in a refrigerator under argon indefinitely, and distilled to yield glyoxylic ester as required

*2 6 1 4 Synthesis of N-tosyl imino-2 acetic acid methylester **(154a)***



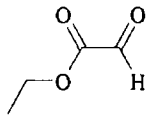
Methyl glyoxylate (5 17g, 0 059mol) and p-toluenesulfonyl isocyanate (11 62g, 0 059mol) were stirred under reflux in sodium dried toluene for 36 hours The product was isolated by removal of the solvent and recrystallisation from ethyl acetate

**M.p.** 175-176°C

**$^1$H (DMSO-$d_6$) (ppm).** 2 33 (3H, s) ($CH_3$), 3 32 (3H, s) ($OCH_3$), 7 29 (2H, d), 7 53 (2H, d) (aromatic C-H), 8 75 (1H, d) (imino H)

**$^{13}$C (DMSO-$d_6$) (ppm)**· 21 22 ($CH_3$), 53 02 ($OCH_3$), 63 66 (C=N), 116 65, 129 72, 138 07, 167 43 (all aromatic C), 167 73 (C=O)

*2 6 1 5 Synthesis of ethyl glyoxylate **(152b)***

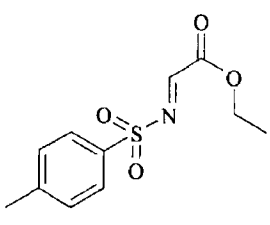


Ethyl diethoxyacetate (17 8cm$^3$, 0 10mol), glyoxylic acid monohydrate (8 84g, 0 097mol) and *p*-toluenesulphonic acid monohydrate (136mg) were combined and heated at 90°C for 27 hours in a flask fitted with an air condenser The resultant clear homogeneous syrup was cooled (ice-methanol), stirred vigorously while phosphorus pentoxide (12 25g) was added portionwise, and then heated at 90-100°C for an additional 2 hours The mixture was then distilled under vacuum to give 8 67g (0 085mol, 85%) of ethyl glyoxylate

**$^1$H (d-acetone) (ppm).** 1 36 (3H, d) ($OCH_2\mathbf{C}H_3$), 4 32 (2H, q) ($OC\mathbf{H}_2CH_3$), 9 37 (1H, s) (aldehydic H)

**$^{13}$C(d-acetone) (ppm)** 14 89 ($OCH_2\mathbf{C}H_3$), 62 53($O\mathbf{C}H_2CH_3$), 160 86 (C=O, ester), 185 84 (C=O, aldehyde)

*2 6 1 6 Synthesis of N-tosyl imino-2 acetic acid ethylester **(154b)***



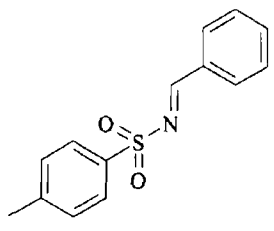
Anhydrous glyoxylic acid ethyl ester (10 2g, 0 1mol) and p-toluenesulfonyl isocyanate(16cm$^3$, 0 1mol) were stirred under reflux in sodium-dried benzene in the presence of a catalytic amount of aluminium chloride for 3hours The benzene was removed under vacuum and the gum-like residue was stirred under reflux in pet ether 60-80 to remove the remaining benzene Under these conditions the residue solidified, and after removal of the solvent, was recrystallised from ethyl acetate, yielding 18 38g (0 072mol, 72%) of N-tosyl imino-2 acetic acid ethylester

**M.p** 196-198°C (lit 198 5°C)[27]

**$^1$H (DMSO) (ppm)** 0 90 (3H, t) ($OCH_2C\mathbf{H_3}$), 2 37 (3H, s) ($CH_3$), 3 76 (2H, m) ($OC\mathbf{H_2}CH_3$), 7 32 (2H, d), 7 61 (2H, d) (aromatic CH), 8 85 (1H, d) (imino H)

**13C (DMSO) (ppm)** 13 67 ($CH_3$), 21 26 ($OCH_2\mathbf{C}H_3$), 62 02 ($O\mathbf{C}H_2CH_3$), 63 83 (C=N), 126 77, 129 63 (phenyl CH), 138 61, 143 20 (phenyl C), 166 92 (C=O)

*2 6 1 7 Synthesis of N-p-toluenesulfonyl benzaldimine* ***(130)***



Benzaldehyde (3 89g, 36 7mmol), *p*-toluenesulfonamide (6 28g, 36 7mmol) and tetraethyl orthosilicate (8 04g, 38 6mmol) were placed in a round-bottom flask equipped with a still head and heated at 160°C under nitrogen for 6 hours, during which time ethanol was collected in the receiving flask The mixture was cooled and dissolved in warm ethylacetate The mixture was treated with n-pentane and allowed to crystallise at room temperature overnight The crystals were collected by filtration, and washed with n-pentane, yielding 6 20g (65%, 23 9mmol) of N-*p*-toluenesulfonyl benzaldimine

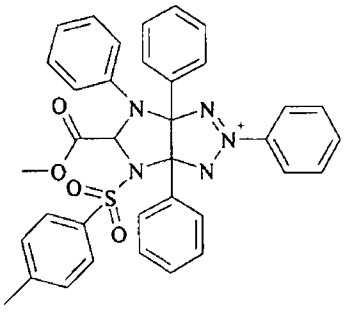
**M p** 108-109°C (lit 111-113°C)[15]

**$^1$H (DMSO-$d_6$) (ppm)** 2 40 (3H, s) ($CH_3$), 7 45, 7 47 (2H, d), 7 54, 7 56, 7 58 (2H, t), 7 69, 7 71, 7 73 (1H, t), 7 84, 7 86 (2H, d), 8 01, 8 03 (2H, d) (all phenyl CH), 9 15 (1H, s) (imino H)

**$^{13}$C (DMSO-$d_6$) (ppm).** 21 44 ($CH_3$), 125 96, 128 02, 129 66, 130 43, 131 60, 132 48, 135 18, 135 59, 171 90 (phenyl C and CH, C=N)

***2.6 2 Synthesis of Hexahydroimidazo-1,2,3-triazoles by 1,3-Dipolar Cycloaddition·***

*2 6 2 1 Synthesis of 2,3a,6,6a-tetraphenyl-4-tosyl-5-methylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole* ***(239a)***



1,2-bis(phenylazo)stilbene (0 5g, 0 0013mol) and N-*p*-toluenesulfonyl-2-acetic acid methyl ester (0 35g, 0 0015mol) were stirred under reflux in 25cm$^3$ sodium dried benzene for 24 hours The hot solution was filtered and the filtrate evaporated to dryness The residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 123mg (0 195mmol, 15%) of 2,3a,6,6a-tetraphenyl-4-tosyl-5-methylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo -[4,5-d]-1,2,3-triazole

**M p** 197-198°C

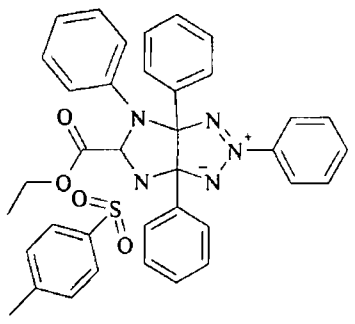
**I.R (KBr) (cm$^{-1}$)**

**$^1$H (CDCl$_3$) (ppm)** 1 49 (3H, s) ($CH_3$), 3 47 (3H, s) ($OCH_3$), 5 22 (1H, s) (C-H), 6 80-6 84 (5H, m), 6 94, 6 96, 6 98 (1H, t), 7 03, 7 05 (2H, d), 7 10, 7 12, 7 14 (2H, t), 7 22, 7 24 (3H, d), 7 55-7 59 (6H, m), 7 64, 7 66 (1H, d), 7 97, 7 99 (2H, d), 8 44, 8 46 (2H, d) (all phenyl CH)

**$^{13}$C (CDCl$_3$) (ppm)** 21 60 ($CH_3$), 53 00 ($OCH_3$), 76 70 (C-5), 97 87, 97 92 (C-3a, C-6a), 122 87, 124 24, 125 52, 127 30, 127 65, 127 78, 128 52, 129 03, 129 29, 129 69, 132 81, 136 02, 144 45 (all phenyl C and CH), 164 37 (C=O)

**M.W** 629 74gmol$^{-1}$, $C_{36}H_{31}N_5O_4S$

*2 6 2 2 Synthesis of 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(239b)***



1,2-bis(phenylazo)stilbene (0 5g, 0 0013mol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (0 33g, 0 0013mol) were stirred under reflux in sodium-dried benzene for 10 hours Inspection by TLC (mobile phase 5 1pet ether 40-60 ethyl acetate) showed that all of the 1,2-bis(phenylazo)stilbene had not been used A further 0 05g (20% excess) of the imine was added and the reaction allowed to continue for a further 10hours The benzene was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 0 22g (0 0003mol, 26%) of 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole

**M.p** 206-208°C

**I.R (KBr) ($cm^{-1}$)**·1745 (C=O stretch), 1597, 1505, 1449 (aromatic C-C stretch), 1306, 1263, 1168, 1090 (ester C-O stretch), 839 (*p*-disubstituted Ph), 750, 690 (monosubstituted Ph)

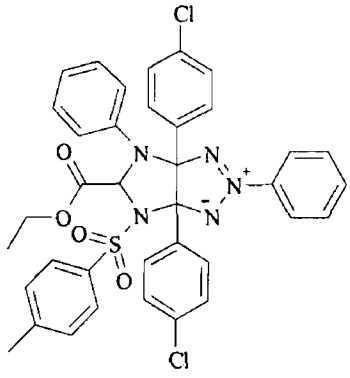
**$^1$H (DMSO-$d_6$) (ppm)** 1 39 (3H, t, J=7 2Hz) ($OCH_2\mathbf{CH_3}$), 2 20 (3H, $\mathbf{CH_3}$), 4 39-4 43 (2H, m) ($OC\mathbf{H_2}CH_3$), 5 21 (1H, s) (C5-H), 6 90 (1H, t, J=7 2Hz), 6 98-7 10 (10H, m), 7 13-7 17 (4H, m), 7 45 (2H, d, J=4 8Hz), 7 61 (2H, t, J=8 4, 7 6Hz), 7 3 (1H, t, J=7 6, 6 4Hz), 7 79 (2H, d, J=8 0Hz), 8 01 (2H, d, J=7 6Hz) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 14 24 ($CH_3$), 21 31 ($OCH_2\mathbf{C}H_3$), 62 56 ($O\mathbf{C}H_2CH_3$), 75 82 (C-5), 100 35, 102 27 (C-3a, C-6a), 120 56, 122 64, 122 76, 127 29, 127 54, 127 79, 128 03, 128 47, 128 55, 129 14, 129 67, 129 74, 132 88, 135 77, 136 02, 138 09, 139 24, 141 13, 144 27 (all phenyl C, CH), 171 02(C=O)

**M W** 643 77gmol$^{-1}$, $C_{37}H_{33}N_5O_4S$

| **Microanalysis** | Theory | C 69 03%, H 5 17%, N 10 88% |
|---|---|---|
| | Found | C 69 79%, H 5 30%, N 11 16% |

*2 6 2 3 Synthesis of 2,6-diphenyl-3a,6a-di-(4-chlorophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(239c)***



1,2-bis(phenylazo)-4,4'-dichlorostilbene (0 46g, 0 0010mol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (0 31g, 0 0012mol) were stirred under reflux in sodium-dried benzene for 24 hours The solvent was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 71mg (99μmol, 10%) of 2,6-diphenyl-3a,6a-di-(4-chlorophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p** 228-230°C

**I R (KBr) ($cm^{-1}$).** 1749 (C=O stretch), 1598, 1492, 1469 (aromatic C-C stretch), 1168, 1092 (ester C-O stretch), 855 (*p*-disubstituted Ph), 669, 768 (monosubstituted Ph)

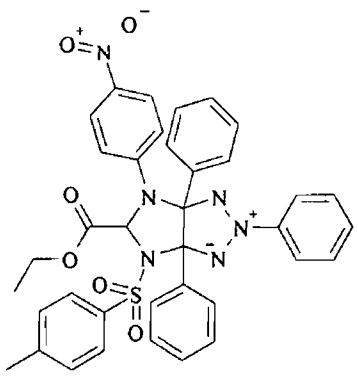
**$^1$H (DMSO-$d_6$) (ppm)** 1 37 (3H, t, J=7 2Hz) (($OCH_2\mathbf{CH_3}$), 2 19 (3H, s) ($CH_3$), 4 38-4 43 (2H, m) ($O\mathbf{CH_2}CH_3$), 5 21 (1H, s) (C5-H), 6 93 (1H, t, J=7 2Hz), 7 01 (2H, d, J=7 6Hz), 7 07 (2H, d, J=8 8Hz), 7 12-7 20 (6H, m), 7 23, (2H, d, J=8 8Hz), 7 49 (2H, d, J=6 4Hz), 7 60 (2H, t, J=7 6Hz, J=8 4Hz), 7 74 (1H, t, J=7 6Hz, J=7 2Hz), 7 78 (2H, d, J=8 4Hz), 8 05 (2H, d, J=7 6Hz), (all phenyl CH)

**$^{13}$C (DMSO-$d_6$) (ppm)** 14 21 ($CH_3$), 21 31 ($OCH_2\mathbf{CH_3}$), 62 77 ($O\mathbf{CH_2}CH_3$), 75 67 (C5), 99 70, 101 77 (C3a,C6a), 120 67, 122 83, 123 01, 127 58, 128 33, 128 54, 129 31, 129 48, 129 67, 129 84, 133 08, 133 44, 134 98, 135 56, 137 19, 139 08, 140 65, 144 49 (all phenyl C and CH), 171 05 (C=O)

**M.W.** 712 66gmol$^{-1}$, $C_{37}H_{31}Cl_2N_5O_4S$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 62 36%, H 4 38%, N 9 83% |
| | Found | C 62 26%, H 4 47%, N 9 80% |

*2 6 2 4 Synthesis of 2,3a,6a-triphenyl-6-(4-nitrophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(239d)***



1-phenyl-2-(4-nitrophenyl) azostilbene (0 5g, 1 2mmol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (0 38g, 1 5mmol) were stirred under reflux in 25cm$^3$ sodium-dried benzene for 3½ hours The solvent was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 149mg (0 216mmol, 18%) of 2,3a,6a-triphenyl-6-(4-nitrophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p** 243-244°C

**I.R (KBr) (cm$^{-1}$)**· 1739 (C=O stretch), 1597, 1472, 1450 (aromatic C-C stretch), 1540, 1310 ($NO_2$ asym and sym N-O stretch), 1175 (ester C-O stretch), 859 (*p*-disubstituted Ph)

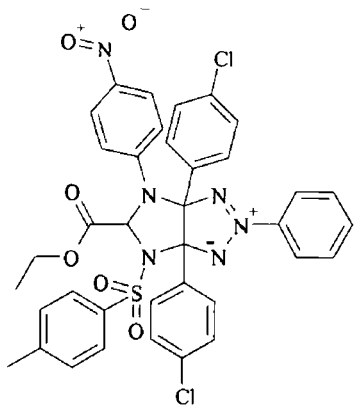
**$^1$H (DMSO-d$_6$) (ppm)** 1 45 (3H, t) ($OCH_2\mathbf{CH_3}$), 1 99 (1H, s) ($CH_3$), 4 48 (2H, m) ($\mathbf{OCH_2}CH_3$), 5 55 (1H, s) (C5-H), 6 93-6 97 (3H, m), 7 03-7 07 (2H, m), 7 12 (2H, t), 7 29 (2H, t), 7 61 (2H, t), 7 78 (2H, t), 7 85-7 94 (4H, m), 8 03 (2H, t), 8 14 (2H, dd), 8 48 (2H, d) (all phenyl CH)

**$^{13}$C (DMSO-d$_6$) (ppm)** 14 44 ($CH_3$), 21 42 ($OCH_2\mathbf{CH_3}$), 60 12 ($\mathbf{OCH_2}CH_3$) 73 15 (C-5), 96 65, 97 43 (C3a,C6a), 123 12, 124 39, 124 57, 127 40, 127 63, 127 87, 128 31, 128 41, 128 81, 129 00, 129 70, 130 23, 139 22, 144 45 (all aromatic C), 173 26 (C=O)

**M W** 690 78gmol$^{-1}$, $C_{37}H_{32}N_6O_6S$,

| **Microanalysis**· | Theory | C 64 51%, H 4 69%, N 12 20% |
|---|---|---|
| | Found | C 64 08%, H 4 51%, N 12 47% |

*2 6 2 5 Synthesis of 2-phenyl-3a,6a-di-(4-chlorophenyl)-6-(4-nitrophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole* ***(239e)***



1-phenyl-2-(4-nitrophenyl)-azo-4,4'-dichlorostilbene (500mg, 1mmol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (380mg, 1 5mmol) were stirred under reflux in 25cm$^3$ sodium-dried benzene for 24 hours The solvent was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 152mg (0 2mmol, 20%) of 2-phenyl-3a,6a-di-(4-chlorophenyl)-6-(4-nitrophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole

**M p** 168-170°C

**I R (KBr) (cm$^{-1}$)**· 1763 (C=O stretch), 1598, 1470 (aromatic C-C stretch), 1509, 1323 ($NO_2$ asym and sym N-O stretch), 1173, 1115, 1092 (ester C-O stretch), 834 (*p*-disubstituted Ph), 685, 749 (monosubstituted Ph)

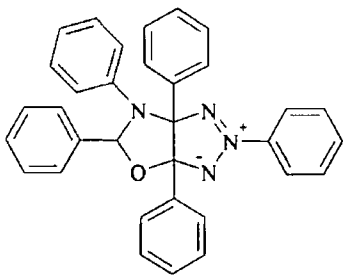
**$^1$H (DMSO-d$_6$) (ppm)** 1 45 (3H, t), ($OCH_2CH_3$), 2 28 (3H, s), ($CH_3$), 4 48-4 51 (2H, m), ($OCH_2CH_3$), 5 57 (1H, s), (C5-H), 6 92 (2H, d), 7 05-70 9, (2H, m), 7 21 (3H, d), 7 30-7 35 (5H, m), 7 61 (2H, d), 7 72 (1H, t), 7 91 (2H, d), 8 02-8 06 (4H, m), (all aromatic CH)

**$^{13}$C (DMSO-d$_6$) (ppm)**· 14 23 ($CH_3$), 21 37($OCH_2CH_3$), 63 44 ($OCH_2CH_3$), 73 21 (C5), 100 77, 101 25 (C3a, C6a), 115 96, 123 03, 125 21, 127 64, 128 58, 129 22, 129 41, 129 55, 129 74, 129 98, 133 18, 133 29, 133 84, 134 99, 135 12, 136 87, 139 16, 139 96, 144 95, 146 13 (all aromatic C and CH), 170 78 (C=O)

**M W** 760 68gmol$^{-1}$, $C_{37}H_{30}Cl_2N_6O_6S$

### *2 6 3 Synthesis of Oxazolo-1,2,3-Triazoles*

#### *2 6 3 1 Synthesis of 2,3a,5,6,6a-pentaphenyl-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole (236a)*



1,2-bis(phenylazo)stilbene (0 4g, 0 001mol) and N-*p*-toluenesulfonyl benzaldimine (0 26g, 0 001mol) were stirred under reflux in sodium-dried benzene for 6 hours After 6hours a further 0 026g (0 0001mol, 10% excess) of N-p-toluenesulfonyl benzaldimine was added and the mixture allowed to reflux for a further 12 hours The benzene was removed under vacuum and the residue was recrystallised from ethanol, yielding 0 24g (0 0005mol, 50%) of 2,3a,5,6,6a-pentaphenyl-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d] 1,2,3-triazole

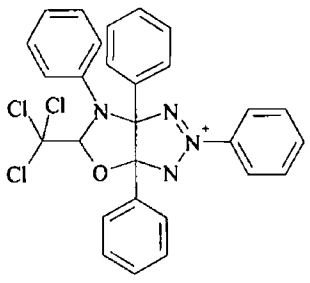
**M p** 171-173°C (lit 174-175°C)[73]

**I R (KBr) ($cm^{-1}$)** 1602, 1501, 1450 (aromatic C-C stretch), 763, 691 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm)** 6 28 (1H, s) (C-H), 6 77, 6 78, 6 79 (3H, t), 6 97, 6 99, 7 01 (2H, t), 7 12, 7 14, 7 15 (6H, t), 7 19, 7 21, 7 23 (2H, t), 7 47-7 57 (5H, m), 7 66, 7 68, 7 70 (2H, t), 7 75, 7 76, 7 78 (1H, t), 7 92, 7 94 (2H, d), 8 24, 8 26 (2H, d) (all phenyl H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 91 25 (C-H), 98 45, 98 49 (C-3a, C-6a), 112 24, 120 53, 121 70, 122 96, 126 95, 127 56, 127 77, 128 29, 129 44, 129 28, 129 86, 129 97, 132 89, 137 19, 138 28, 138 89, 140 33, 143 33 (all phenyl C's)

*2 6 3 2 Synthesis of 2,3a,6,6a-tetraphenyl-5-trichloromethyl-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole (236b)*



1,2-bis(phenylazo)stilbene (0 5g, 0 0013mol) and N-*p*-toluenesulfonyl trichloroimine (0 5g, 0 0016mol) were stirred under reflux in acetone[3] for 5 hours after which time there was no colour change in the reaction mixture A further 0 2g (0 0007mol) of N-*p*-toluensulfonyl trichloroimine were added and the reaction was allowed to continue for another 15 hours The acetone was removed under vacuum and the residue recrystalhsed from ethanol, yielding 0 32g (0 0006mol, 46%) of 2,3a,6,6a-tetraphenyl-5-trichloromethyl-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole

**M.p** 163-164°C

**I.R. (KBr) ($cm^{-1}$).** 1589, 1487, 1461 (aromatic C-C stretch), 767, 697 (monosubstituted Ph)

**$^1$H (DMSO-$d_6$) (ppm)**· 6 28 (1H, s) (C-H), 7 05-7 28 (13H, m), 7 49, 7 51 (2H, d), 7 66, 7 68, 7 70 (2H, d), 7 74, 7 76, 7 78 (1H, t), 8 23, 8 25 (2H, d)

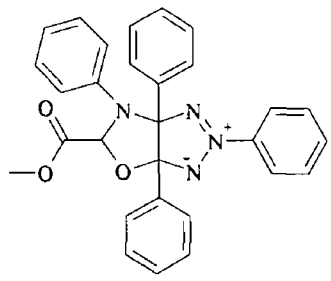
**$^{13}$C (DMSO-$d_6$) (ppm)** 97 15 (C-H), 102 04, 102 30 (C-3a, C-6a), 112 50 ($CCl_3$), 124 09, 127 87, 128 63, 128 77, 129 32, 129 55, 130 11, 130 74, 133 86 (all phenyl C-H), 137 87, 138 74, 141 35, 144 28 (all phenyl C)

**M W** 535 86gmol$^{-1}$, $C_{28}H_{21}Cl_3N_4O$

| **Microanalysis** | Theory | C 62 76%, H 3 95%, N 10 46% |
|---|---|---|
| | Found | C 62 58%, H 3 93%, N 10 34% |

[3] This reaction was also carried out using sodium-dried benzene as the solvent, with the same result

*2 6 3 3 Synthesis of 2,3a,6,6a-tetraphenyl-5-methylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole* ***(236c)***



1,2-bis(phenylazo)stilbene (0 5g, 0013mol) and N-*p*-toluenesulfonyl-2-acetic acid methyl ester (0 35g, 0 0015mol) were stirred under reflux in 25cm$^3$ sodium dried benzene for 24 hours The hot solution was filtered and the filtrate evaporated to dryness The residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 136mg (0 286mmol, 22%) of 2,3a,6,6a-tetraphenyl-5-methylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole

**M p** 220°C

**I R (KBr) (cm$^{-1}$)·** 1753 (C=O stretch), 1598, 1505, 1449 (aromatic C-C stretch), 752, 698 (monosubstituted Ph)

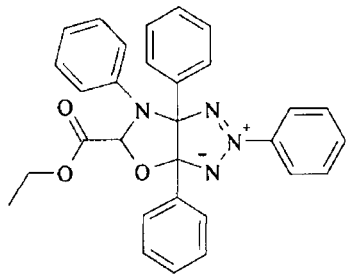
**$^1$H (DMSO-d$_6$) (ppm).** 3 97 (3H, s) ($OCH_3$), 5 69 (1H, s) (C5-H), 6 61 (2H, d, J=8 4Hz), 6 77 (1H, t, J=7 2Hz, J=7 6Hz), 7 05-7 15 (10H, m), 7 45 (2H, d, J=6 4Hz), 7 64 (2H, t, J=7 2Hz, J=8 0Hz), 7 73 (1H, t, J=7 2Hz, J=7 6Hz), 8 22 (2H, d, J=7 6Hz) (all phenyl H)

**$^{13}$C (DMSO-d$_6$) (ppm)** 53 73 ($OCH_3$), 86 76, 97 08 (C3a, C6a), 114 78, 115 76, 119 94, 123 01, 126 89, 127 23, 127 85, 128 35, 128 48, 128 79, 129 07, 129 89, 133 04, 136 02, 137 26, 140 22, 141 34 (all phenyl C and CH, also C5), 170 40 (C=O)

**M.W.** 476 54gmol$^{-1}$, $C_{29}H_{24}N_4O_3$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 73 09%, H 5 08%, N 11 76% |
| | Found | C 72 79%, H 5 17%, N 11 65% |

*2 6 3 4 Synthesis of 2,3a,6,6a-tetraphenyl-5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole* ***(236d)***



1,2-bis(phenylazo)stilbene (0 5g, 0 0013mol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (0 33g, 0 0013mol) were stirred under reflux in sodium-dried benzene for 10 hours Inspection by TLC (mobile phase 5 1 pet ether 40-60 ethyl acetate) showed that all of the 1,2-bis(phenylazo)stilbene had not been used A further 0 05g (20%excess) of the imine was added and the reaction allowed to continue for a further 10hours The benzene was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 159mg (0 325mmol, 25%) of 2,3a,6,6a-tetraphenyl-5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole

**M p** 154-156°C

**I.R (KBr) ($cm^{-1}$).** 1754, (C=O stretch), 1600, 1505, 1449 (aromatic C-C stretch), 1232, 1203, 1180 (ester C-O stretch), 753, 699 (monosubstituted Ph)

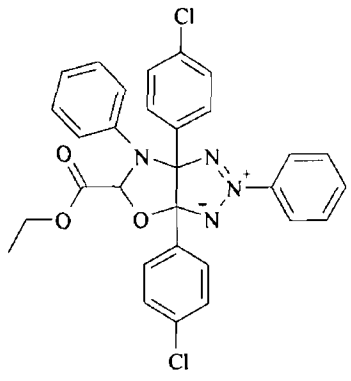
**$^1$H (DMSO-$d_6$) (ppm)** 1 37 (3H, t, J=7 2Hz) ($OCH_2\mathbf{CH_3}$), 4 41-4 46 (2H, m) ($OCH_2CH_3$), 5 65 (1H, s) (C5-**H**), 6 29 (2H, d, J=8 0Hz), 6 77 (1H, t, J=7 6Hz), 7 08-7 13 (10H, m), 7 46 (2H, d, J=5 2Hz), 7 64 (2H, t, J=8 0Hz), 7 73 (1H, d, J=7 2Hz), 8 22 (2H, d, J=7 2Hz), (all phenyl CH)

**$^{13}$C (DMSO-$d_6$) (ppm)** 14 32 ($OCH_2\mathbf{CH_3}$), 62 65 ($\mathbf{O}CH_2CH_3$), 86 96, 97 11 (C3a, C6a), 114 79, 115 73, 119 91, 123 02, 126 91, 127 25, 127 82, 128 31, 128 47, 128 78, 129 05, 129 89, 133 02, 136 09, 137 25, 140 23, 141 33 (all phenyl C and CH), 169 86 (C=O)

**M W** 490 57gmol$^{-1}$, $C_{30}H_{26}N_4O_3$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 73 45%, H 5 34%, N 11 42% |
| | Found | C 73 08%, H 5 69%, N 10 74% |

*2 6 3 5 Synthesis of 2,6-diphenyl-3a,6a-di-(4-chlorophenyl)-5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole* ***(236e)***



1,2-bis(phenylazo)-4,4'-dichlorostilbene (0 46g, 0 0010mol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (0 31g, 0 0012mol) were stirred under reflux in sodium-dried benzene for 24 hours The solvent was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 117mg (0 21mmol, 21%) of 2,6-diphenyl-3a,6a-di-(4-chlorophenyl)-5-ethylcarboxylate-3,3a,5,6,-tetrahydro-[1,3]-oxazolo-[4,5-d]-1,2,3-triazole

**M p** 181-182°C

**I R (KBr) ($cm^{-1}$)** 1741 (C=O stretch), 1598, 1492, 1468 (aromatic C-C stretch), 1305, 1236, 1092 (ester C-O stretch), 832 (p-disubstituted Ph), 746, 685 (monosubstituted Ph)

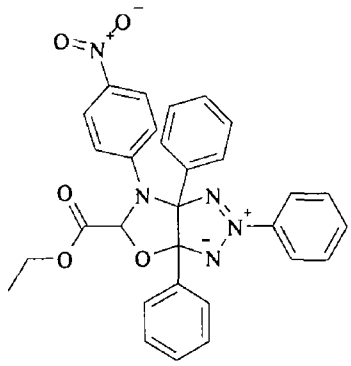
**$^1$H (DMSO-$d_6$) (ppm).** 1 35 (3H, t, J=6 8Hz, J=7 2Hz) ($OCH_2\mathbf{CH_3}$) 4 37-4 48 (2H, m) ($\mathbf{OCH_2}CH_3$), 5 68 (1H, s) (C5-H), 6 61 (2H, d, J=8 8Hz), 6 80 (1H, t, J=7 2Hz), 7 11-7 16 (4H, m), 7 23-7 26 (4H, m), 7 48 (2H, d, J=7 6Hz), 7 64 (2H, t, J=8 0Hz), 7 73 (1H, t, J=6 8Hz), 8 22 (2H, d, J=7 6Hz)

**$^{13}$C (DMSO-$d_6$) (ppm):** 14 29 ($OCH_2\mathbf{CH_3}$), 31 05 (C5), 62 81($\mathbf{OCH_2}CH_3$), 86 97, 96 73 (C3a, C6a), 114 35, 115 89, 120 28, 123 11, 128 12, 128 58, 128 88, 129 20, 129 87, 133 16, 133 28, 133 71, 135 09, 136 29, 140 12, 140 94 (all phenyl C and CH), 169 83 (C=O)

**M.W** 559 46gmol$^{-1}$, $C_{30}H_{24}Cl_2N_4O_3$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 64 41%, H 4 32%, N 10 01% |
| | Found | C 64 35%, H 4 44%, N 9 76% |

*2 6 3 6 Synthesis of 2,3a,6a-triphenyl-6-(4-nitrophenyl)--5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole* ***(236f)***



1-phenyl-2-(4-nitrophenyl)-azo-stilbene (0 5g, 0 0012mol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (0 38g, 0 0015mol) were stirred under reflux in 25cm$^3$ sodium-dried benzene for 24 hours The solvent was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 193mg (0 360mmol, 30%) of 2,3a,6a-triphenyl-6-(4-nitrophenyl)-5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole

**M p.** 179-180°C

**I R (KBr) (cm$^{-1}$).** 1754 (C=O stretch), 1597, 1449 (aromatic C-C stretch), 1505, 1385 ($NO_2$ asym and sym N-O stretch), 1314, 1211, 1160, 1134, 1114 (ester C-O stretch), 834 (*p*-disubstituted Ph), 758, 702 (monosubstituted Ph)

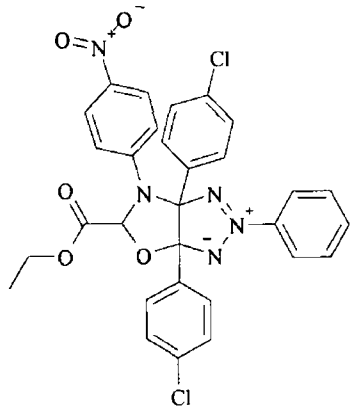
**$^1$H (DMSO-d$_6$) (ppm).** 1 41 (3H, t, J=7 2Hz) ($OCH_2CH_3$), 4 48 (2H, m) ($OCH_2CH_3$), 5 95 (1H, s) (C5-**H**), 6 73 (2H, d, J=9 2Hz), 7 03-7 15 (9H, m), 7 65 (t, 2H, J=8 0Hz), 7 73 (1H, d, J=6 8Hz), 8 05 (2H, d, 9 2Hz), 8 25 (2H, d, J=8 0Hz) (all phenyl C**H**)

**$^{13}$C (DMSO-d$_6$) (ppm)**· 18 90 ($OCH_2CH_3$), 56 38 ($OCH_2CH_3$), 63 15 (C5), 86 34, 96 91 (C3a, C6a), 114 99, 115 20, 123 13, 125 41, 126 77, 127 12, 128 01, 128 58, 128 93, 129 91, 133 23, 135 29, 135 84, 139 51, 140 10, 146 80 (all phenyl C and CH), 168 90 (C=O)

**M W** 535 56gmol$^{-1}$, $C_{30}H_{25}N_5O_5$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 67 28%, H 4 71%, N 13 08% |
| | Found | C 67 00%, H 4 79%, N 12 87% |

*2 6 3 7 Synthesis of 2-phenyl-3a,6a-di-(4-chlorophenyl)-6-(4-nitrophenyl)-5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole* ***(236g)***



1-phenyl-2-(4-nitrophenyl)-azo-4,4'-dichlorostilbene (500mg, 1mmol) and N-*p*-toluenesulfonyl-2-acetic acid ethyl ester (380mg, 1 5mmol) were stirred under reflux in 25cm$^3$ sodium-dried benzene for 24 hours The solvent was removed under vacuum and the residue was purified on a silica gel column (mobile phase, 5 1 pet ether 40-60 ethyl acetate) yielding 157mg (0 26mmol, 26%) of 2-phenyl-3a,6a-di-(4-chlorophenyl)-6-(4-nitrophenyl)-5-ethylcarboxylate-3,3a,5,6-tetrahydro-[1,3]-oxazolo-[5,4-d]-1,2,3-triazole

**M p.** 178-180°C

**I R. (KBr) (cm$^{-1}$)** 1747 (C=O stretch), 1600, 1466 (aromatic C-C stretch), 1509, 1326 ($NO_2$ asym and sym N-O stretch), 1173, 1137, 1115, 1094 (ester C-O stretch), 752, 690 (monosubstituted Ph)

**$^1$H (DMSO-d$_6$) (ppm)** 1 39 (3H, t) ($OCH_2CH_3$), 4 46-4 50 (2H, m) ($OCH_2CH_3$), 5 98 (1H, s) (C5-H), 6 71 (2H, d), 7 08-7 15 (4H, m), 7 25-7 30 (4H, m), 7 65 (2H, t), 7 74 (1H, t), 8 09 (2H, d), 8 24 (2H, d) (all phenyl H)

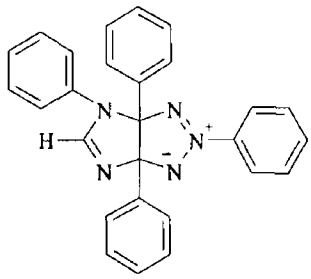
**$^{13}$C (DMSO-d$_6$) (ppm)**· 14 29 ($OCH_2CH_3$), 58 21 ($OCH_2CH_3$), 62 79 (C5), 86 97, 96 74 (C3a,C6a), 114 36, 115 89, 120 25, 123 12, 128 11, 128 58, 128 89, 129 19, 129 85, 133 14, 133 27, 133 70, 135 11, 136 30, 140 13, 140 95 (all aromatic C), 169 83 (C=O)

**M W** 604 45gmol$^{-1}$, $C_{30}H_{23}Cl_2N_5O_5$

| **Microanalysis**· | Theory | C 59 60%, H 3 84%, N 11 59% |
|---|---|---|
| | Found | C 59 72%, H 4 05%, N 11 12% |

### *2.6 4 Detosylation of Hexahydroimidazo-1,2,3-Triazoles*

*2 6 4 1 Synthesis of 2,3a,4,6a-tetraphenyl-1,3a,4,6a-tetrahydro-imidazo[4,5-d]-1,2,3-triazole (241a)*



2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole (500mg, 0 777mmol) and sodium methoxide (839mg, 15 54mmol, 20 molar excess) were stirred under reflux in 150cm$^3$ anhydrous methanol for 24 hours The solvent was removed and the residue dissolved in dichloromethane The organic layer was washed with water and then dried with magnesium sulphate The magnesium sulphate and dichloromethane were removed and the residue recrystalhsed from ethanol to yield 251mg (604mmol, 78%) of 2,3a,4,6a-tetraphenyl-1,3a,4,6a-tetrahydro-imidazo[4,5-d]-1,2,3-triazole

**M p** 168°C

**I.R (KBr) (cm$^{-1}$).**

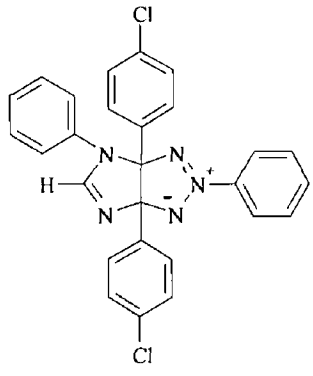
**$^1$H (DMSO-$d_6$) (ppm).** 6 93-7 06 (11H, m), 7 20 (2H, t, J=8 0Hz), 7 33 (2H, d, J=8 0Hz), 7 68 (2H, t, J=8 0Hz), 7 74 (1H, d, J=7 2Hz), 8 35 (2H, d, 7 6Hz) (all phenyl CH), 8 64 (1H, s) (C5-H)

**$^{13}$C (DMSO-$d_6$) (ppm)** 99 38, 110 52 (C3a, C6a) 118 07, 122 96, 123 00, 127 36, 127 43, 127 61, 127 78, 127 87, 128 11, 129 43, 129 92, 132 77, 135 87, 138 02, 138 26, 140 20 (all phenyl C and CH), 154 90 (C5)

**M.W** 415 50gmol$^{-1}$, $C_{27}H_{21}N_5$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 78 04%, H 5 10%, N 16 86% |
| | Found | C 77 74%, H 5 13%, N 16 85% |

*2 6 4 2 Synthesis of 2,4,-diphenyl-3a,6a-(4-chlorophenyl)-1,3a,4,6a-tetrahydro-imidazo[4,5-d]-1,2,3-triazole* ***(242b)***



2,6-diphenyl-3a,6a-di-(4-chlorophenyl)-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo[4,5-d]-1,2,3-triazole (400 mg, 0 56mmol) and sodium methoxide (605mg, 11 2mmol, 20 molar excess) were stirred under reflux in 150cm$^3$ anhydrous methanol for 24 hours The solvent was removed and the residue dissolved in dichloromethane The organic layer was washed with water and then dried with magnesium sulphate The magnesium sulfate and dichloromethane were removed and the residue recrystallised from ethanol to yield 217mg (0 448mmol, 80%) of 2,4,-diphenyl-3a,6a-(4-chlorophenyl)-1,3a,4,6a-tetrahydro-imidazo[4,5-d]-1,2,3-triazole

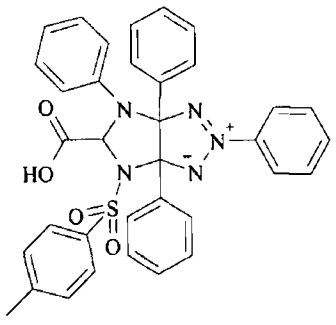
**M p** 145°C

**$^1$H (DMSO-d$_6$) (ppm)** 6 88 (1H, t, J=7 6Hz), 6 98 (2H, d, J=8 4Hz), 7 02 (2H, d, J=6 8Hz), 7 09-7 17 (5H, m), 7 24 (2H, d, J=7 6Hz), 7 51 (1H, t, J=8Hz), 7 60 (2H, t, J=7 2Hz), 7 67 (1H, t, J=7 6Hz), 8 26 (2H, d, J=8Hz) (all aromatic CH), 8 55 (1H, s), (C5-H)

**$^{13}$C (DMSO-d$_6$) (ppm)** 98 24, 109 64 (C3a, C6a) 118 24, 123 02, 123 38, 127 35, 127 56, 127 69, 127 85, 128 33, 129 35, 129 55, 129 94, 132 65, 135 76, 137 64, 137 03, 139 81(all phenyl C and CH), 155 12 (C5)

**M W** 484 39gmol$^{-1}$, $C_{27}H_{19}Cl_2N_5$

*2 6 4 3 Synthesis of 2,3a,6,6a-tetraphenyl-4-tosyl-5-carboxylate-3,3a,4,5,6,6a hexahydroimidazo-[4,5-d]-1,2,3-triazole* ***(240)***



2,3a,6,6a-tetraphenyl-4-tosyl-5-methylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole (500mg, 0 777mmol) and sodium methoxide (839mg, 15 54mmol, 20 molar excess) were stirred under reflux in 150cm$^3$ anhydrous methanol TLC analysis during the reaction showed the presence of a second product The solvent was removed and the residue dissolved in dichloromethane The organic layer was washed with water and then dried with magnesium sulphate The magnesium sulphate and dichloromethane were removed and the two products separated on a silica gel column (mobile phase 5 3 pet ether (40-60) ethyl acetate) The second product was found to be 2,3a,6,6a-tetraphenyl-4-tosyl-5-carboxylate-3,3a,4,5,6,6a hexahydroimidazo-[4,5-d]-1,2,3-triazole

**M p** 259-260°C

**I R. (KBr) (cm$^{-1}$).** 3209 (O-H stretch), 1708 (C=O stretch), 1597, 1499, 1450 (aromatic C-C stretch), 851 (*p*-disubstituted Ph), 751, 688 (monosubstituted Ph)

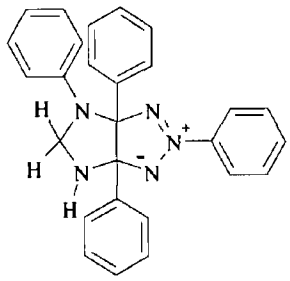
**$^1$H (DMSO-d$_6$) (ppm).** 2 31 (3H, s), ($CH_3$), 6 87-6 99 (7H, m), 7 01-7 04 (6H, m), 7 14 (2H, t, J=8Hz), 7 22 (1H, s) (C5-H), 7 30 (1H, d, J=8Hz), 7 56 (2H, d, J=8Hz), 7 66 (3H, t, J=7 6Hz), 7 71 (1H, d, J=7 2Hz), 8 32 (2H, d, J=8Hz), (all phenyl H), 8 99 (1H, s) (COOH)

**$^{13}$C (DMSO-d$_6$) (ppm):** 21 26 ($CH_3$), 92 74, 97 67 (C3a, C6a), 122 90, 123 59, 124 41, 125 97, 127 18, 127 45, 128 03, 128 08, 128 27, 128 53, 129 65, 130 05, 133 05, 135 69, 136 80, 137 86, 140 14, 141 77, 142 20, 158 41 (COOH)

**M W** 615 72gmol-1, $C_{35}H_{29}N_5O_4S$

### *2 6 5 Reduction of Tetrahydroimidazo-1,2,3-Triazoles*

2 6 5 1 *Synthesis of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6,6a-hexahydro-imidazo[4,5-d]-1,2,3-triazole* ***(242a)***



2,3a,4,6a-tetraphenyl-1,3a,4,6a-tetrahydro-imidazo[4,5-d]-1,2,3-triazole (250mg, 0 602mmol) was dissolved in 20cm$^3$ of dry THF Lithium borohydride (65mg, 3 01mmol) was added and the mixture was stirred for 12 hours, using a calcium chloride guard tube to prevent the introduction of atmospheric moisture The reaction was quenched with water and the solvent removed under vacuum The residue was dissolved in dichloromethane and the purified on a silica gel column (mobile phase, 5 3 pet ether 40-60 ethyl acetate) yielding 156mg (0 373mmol, 62%) of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6,6a-hexahydro-imidazo[4,5-d]-1,2,3-triazole

**M.p.** 160-162°C

**I.R (KBr) (cm$^{-1}$)** 3408 (N-H stretch), 1598, 1500, 1448 (aromatic C-C stretch), 749, 688 (monosubstituted Ph)

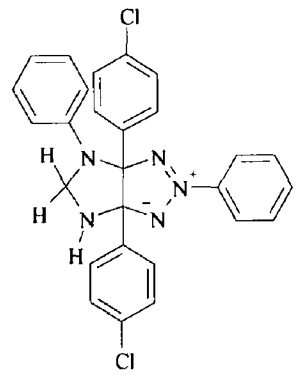
**$^1$H (DMSO-d$_6$) (ppm)** 4 28 (1H, t, J=5 6Hz, J=6 4Hz) (C5-H), 4 87 (1H, t, J=4Hz, J=6 4Hz) (N-H), 4 93 (1H, t, J=4 4Hz) (C5-H), 6 53 (1H, t, J=7 2Hz), 6 64 (2H, d, J=8 4Hz), 6 94-7 03 (10H, m), 7 13 (2H, d, J=7 2Hz), 7 50 (2H, t, J=7 2Hz, J=7 6Hz), 7 61 (1H, d, J=7 2Hz), 8 12 (2H, d, J=7 6Hz) (all phenyl CH)

**$^{13}$C (DMSO-d$_6$) (ppm).** 64 26 (C5), 96 04, 102 22 (C3a, C6a), 114 91, 117 55, 122 69, 126 84, 127 08, 127 66, 127 74, 127 87, 127 91, 128 76, 129 78, 132 37, 137 96, 138 80, 140 54, 143 46 (all phenyl C and CH)

**M W** 417 52gmol$^{-1}$, $C_{27}H_{23}N_5$

| | | |
|---|---|---|
| **Microanalysis** | Theory | C 77 67%, H 5 55%, N 16 77% |
| | Found | C 77 67%, H 5 63%, N 16 68% |

2 6 5 2 *Synthesis of 2,4-di-phenyl-3a,6a-di-(4-chlorophenyl)-1,3a,4,5,6,6a-hexahydro-imidazo[4,5-d]-1,2,3-triazole* ***(242b)***



2,4-di-phenyl-3a,6a-di-(4-chlorophenyl)-1,3a,4,6a-tetrahydro imidazo [4,5-d]-1,2,3-triazole (300mg, 0 62mmol) was dissolved in 20cm$^3$ of dry THF Lithium borohydride (65mg, 3 01mmol) was added and the mixture was stirred for 12 hours, using a calcium chloride guard tube to prevent the introduction of atmospheric moisture The reaction was quenched with water and the solvent removed under vacuum The residue was dissolved in dichloromethane and the purified on a silica gel column (mobile phase, 5 3 pet ether 40-60 ethyl acetate) yielding 199mg (0 41mmol, 66%) of 2,4-di-phenyl-3a,6a-di-(4-chlorophenyl)-1,3a,4,5,6,6a-hexahydro-imidazo[4,5-d]-1,2,3-triazole

**M p** 159-161°C

**$^1$H (DMSO-$d_6$) (ppm).** 4 39 (1H, t), (C5-H), 5 05 (1H, t), 5 11 (1H, t) (C5-H), 6 69 (1H, t), 6 75 (2H, d), 7 11 (2H, t), 7 17 (2H, d), 7 21-7 28 (5H, m),

**$^{13}$C (DMSO-$d_6$) (ppm)** 64 11 (C5), 95 67, 101 62 (C3a, C6a), 114 96, 117 92, 122 73, 127 96, 128 89, 128 97, 129 41, 129 83, 130 33, 132 37, 132 56, 132 72, 137 04, 137 90, 140 36, 143 14 (all aromatic Cs)

**M.W** 486 41gmol$^{-1}$, $C_{27}H_{21}Cl_2N_5$

## 2 7 References.


1 a) Huisgen, R *Angew Chem , Int Ed Engl* **1963**, *2*, 633

b) Huisgen, R *J Org Chem* **1968**, *33*, 2291

c) Huisgen, R *J Org Chem* **1976**, *41*, 403

2 Alder, K Neuer Methoden der Praerative Organischen Chemie, 1943, Verlag Chemie, Weinheim

3 For an early review of the imino Diels Alder reaction, see

Weinreb, S M , Levin, J I *Heterocycles*, **1979**, *12*, 949

4 For the first Diels-Alder reaction with N-sulfonyl imines, see

a) Albrecht, R , Kresze, G *Chem Ber* **1964**, *97*, 490

For a review on early work, see

b) Boger, D L , Weinreb, S N *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic San Diego, **1987**

c) Boger, D L , Kasper, A M *J Am Chem Soc* **1989**, *111*, 1517

d) Boger, D L , Corbett, W L , Curran, T T , Kasper, A M *J Am Chem Soc* **1991**, *113*, 1713

For assymetric version, see

e) McFarlane, A K , Thomas, G , Whiting, A *Tetrahedron Lett* **1993**, *34*, 2379

5 Sisko, J , Weinreb, S M J *Org Chem* **1990**, *55*, 393

6 Tschaen, D M , Turos, E , Weinreb, S M *J Org Chem* **1984**, *49*, 5058

7 Melnick, M J , Freyer, A J , Weinreb, S M *Tetrahedron Lett* **1988**, *29*, 3891

8 Davis, F A , Reddy, R T , Reddy, R E *J Org Chem* **1992**, *57*, 6387

9 March, J *Advanced Organic Chemistry, Reactions, Mechanisms and Structure* 4th Edition, Wiley **1992**

10 Lichtenburger, J , Fleury, S , Barrett, B *Bull Soc Chim Fr* **1955**, 669

11 Kretow, A J , Abrazhanova, E A *J Gen Chem USSR (Engl Trans )* **1957**, *27*, 1993

12 a) Jennings, W B , Lovely, C J *Tetrahedron Lett* **1988**, *29*, 3725

b) Jennings, W B , Lovely, C J *Tetrahedron* **1991**, *47*, 5561

13 Davis, F A , Zhou, P , Lal, G S *Tetrahedron Lett* **1990**, *31*, 1653

14 Vishwakarma, L C , Stringer, O D , Davis, F A *Org Synth* **1987**, *66*, 203

15 Love, B E , Raje, P S , Wılliams, T C *Synlett* **1994**, 493

16 Albrecht, R , Kresze, G , Mlakar, B *Chem Ber* **1964**, *97*, 483

17 Albrecht, R , Kresze, G *Chem Ber* **1965**, *98*, 1431

18 Kresze, G , Wucherpfennıg, W *Angew Chem Int Edıt* **1967**, *6*, 149

19 a) Sısko, J , Weınreb, S M *Tetrahedron Lett* **1989**, *30*, 3037

b) Alexander, M D , Anderson, R E , Sısko, J , Weınreb, S M *J Org Chem* **1990**, *55*, 2563

c) Ralbovsky, J L , Kınsella, M A , Sısko, J , Weınreb, S M *Synth Commun* **1990**, *20*, 573

20 Trost, B M , Marrs, C *J Org Chem* **1991**, *56*, 6468

21 a) Hudson, R F , Record, K A F *J Chem Soc Chem Commun* **1976**, 831

b) Hudson, R F , Brown, C , Record, K A F *J Chem Soc Chem Commun* **1977**, 540

22 Boger, D L , Corbett, W L *J Org Chem* **1992**, *57*, 4777

23 Brown, C , Hudson, R F , Record, K A F *J Chem Soc Perkın Trans 2* **1978**, 822

24 Georg, G I , Harrıman, G C B , Peterson, S A *J Org Chem* **1995**, *60*, 7366

25 Hart, D J , Kanaı, K , Thomas, D G , Yang, T K J *J Org Chem* **1983**, *48*, 289

26 Nıwa, E , Aokı, H , Tanoka, H , Munakata, K , Namıkı, M *Chem Ber* **1966**, *99*, 3932

27 Baıllargé, M , Le Goffic, F *Synth Commun* **1987**, *17*, 1603

28 Hamley, P , Holmes, A B , Kee, A , Ladduwahetty, T , Smıth, D F *Synlett*, **1991**, 29

29 a) Rıjsenbrıj, P P M , Loven, R , Wıjnberg, J B P A , Speckamp, W N , Huısmam, H O *Tetrahedron Lett* **1972**, *15*, 1425

b) Loven, R P , Zunnebeld, W A , Speckamp, W N *Tetrahedron*, **1975**, *31*, 1723

c) Shı, G , Schlosser, M *Tetrahedron*, **1993**, *49*, 1445

30 a) Krow, G , Rodebaugh, R , Marakowskı, J , Ramey, K C *Tetrahedron Lett* **1973**, 1899

b) Krow, G , Pyun, C , Rodebaugh, R , Marakowskı, J *Tetrahedron* **1974**, *30*, 2977

31 Zunnebeld, W A , Speckamp, W N *Tetrahedron*, **1975**, *31*, 1717

32 Edwards, M L , Matt, J E , Wenstrup, D L , Kemper, C A , Persichetti, R A , Margolin, A L *Org Prep Proced Int* **1996**, *28*, 193

33 Craig, D , Gordon, R S *Tetrahedron Lett* **1998**, *39*, 8337

34 Holmes, A B , Raithby, P R , Thompson, J , Baxter, A J G , Dixon, J *J Chem Soc Chem Commun* **1983**, 1490

35 Holmes, A B , Birkinshaw, T N *Tetrahedron Lett* **1987**, *28*, 813

36 Holmes, A B , Thompson, J , Baxter, A J G , Dixon, J *J Chem Soc Chem Commun* **1985**, 37

37 a) Birkinshaw, T N , Tabor, A B , Holmes, A B , Kay, P , Mayne, P M , Raithby, P *J Chem Soc Chem Commun* **1988**, 1599

b) Birkinshaw, T N , Tabor, A B , Holmes, A B , Kay, P , Mayne, P M , Raithby, P *J Chem Soc Chem Commun* **1988**, 1601

38 Holmes, A B , Kee, A , Ladduwahetty, T, Smith, D F J *Chem Soc Chem Commun* **1990**, 1412

39 Hamley, P , Helmchen, G , Holmes, A B , Marshall, D R , MacKinnon, J W M , Smith, D F , Ziller, J W *J Chem Soc Chem Commun* **1992**, 786

40 Heintzelman, G R , Weinreb, S M *J Org Chem* **1996**, *61*, 4594

41 Hamada, T , Sato, H , Hikota, M , Yonemitsu, O *Tetrahedron Lett* **1989**, *30*, 6405

42 Hamada, T , Zenkoh, T , Sato, H , Yonemitsu, O *Tetrahedron Lett* **1991**, *32*, 1649

43 Bauer, T , Szymanski, S , Jezewski, A , Gluzinski, P , Jurczak, J *Tetrahedron Assym* **1997**, *8*, 2619

44 Schurer, S C , Blecher, S *Tetrahedron Lett* **1999**, *40*, 1877

45 Craig, D , Robson, M J , Shaw, S J *Synlett*, **1998**, 1381

46 Saigo, K , Shimada, S , Hasegawa, M *Chem Lett* **1990**, 905

47 Trost, B M , Matelich, M C *J Am Chem Soc* **1991**, *113*, 9007

48 Trost, B M , Marrs, C M *J Am Chem Soc* **1993**, *115*, 6636

49 Chen, T , Jiang, S , Turos, E *Tetrahedron Lett* **1994**, *35*, 8325

50 Xu, Z , Lu, X *Tetrahdron Lett* **1997**, *38*, 3461

51 Xu, Z , Lu, X *J Org Chem* **1998**, *63*, 5031

52 Xu, Z , Lu, X *Tetrahedron Lett* **1999**, *40*, 549

53 Lin,Y -R , Zhou, X -T , Dai, L -X , Sun, J *J Org Chem* **1997**, *62*, 1799

54 Hayashi, T , Kishi, E , Soloshonok, V A , Uozumi, Y *Tetrahedron Lett* **1996**, *37*, 4969

55 Zhou, X T , Lin, Y -R , Dai, L -X Sun, J , Xia, L -J , Tang, M -H *J Org Chem* **1999**, *64*, 1331

56 ten Have, R , Huisman, M , Meetsma, A , van Leusen, A M *Tetrahedron*, **1997**, *53*, 11355

57 Hojo, M , Aihara, H , Suginohara, Y , Sakata, K , Nakamura, S , Murakami, C , Hosomi, A *J Org Chem* **1997**, *62*, 8610

58 Hook, J M *Synthetic Commun* **1984**, *14*, 83

59 March, J *Advanced Organic Chemistry, Reactions, Mechanism and Structure 4th Ed* **1992**, pg 884

60 a) Ponzo, V L , Kaufman, T S *Tetrahdron Lett* **1995**, *36*, 9105

b) Kovacs, J , Ghatak, U R *J Org Chem* **1966**, *31*, 119

c) Rudinger, J , van den Brink-Zimmermannova H M *Helv Chim Acta* **1973**, 2216

d) Schultz, A G McCloskey, P J , Court, J J *J Am Chem Soc* **1987**, *109*, 6493

61 Heathcock, C H , Smith, K M , Blumenkopf, T A *J Am Chem Soc* **1986**, *108*, 5022

62 a) Yokoyama, Y , Matsumoto, T , Murakami, Y *J Org Chem* **1995**, *60*, 1486

b) Nyasse, B , Grehn, L , Ragnarsson, U *Chem Commun* **1997**, 1017

c) Grehn, L , Ragnarsson, U *Tetrahedron*, **1999**, *55*, 4843

63 Snyder, H R , Heckert, R E *J Am Chem Soc* **1952**, *74*, 2006

64 Haskell, B E , Bowlus, S B *J Org Chem* **1976**, *41*, 159

65 a) Trost, B M , Sudhakar, A R , *J Am Chem Soc* **1987**, *109*, 3792

b) Henry, J R , Marcin, L R , McIntosh, M C , Scola, P M , Harris, G D , Weinreb, S M , *Tetrahedron Lett* **1989**, *30*, 5709

66 Vriesema, B K , Buter, J , Kellog, R M *J Org Chem* **1984**, *49*, 110

67 Attanasi, O A , Santeusanio, S , Serra-Zanetti, F *Synthesis* **1994**, 372

68 a) Yuan, W , Fearon, K , Gelb, M H *J Org Chem* **1989**, *54*, 906

b) Corrie, J E T , Papageorgiou, G *J Chem Soc , Perkin Trans 1* **1996**, 1583

69 a) Civitello, E R , Rapoport, H *J Org Chem* **1992**, *57*, 834

b) Peterli-Roth, P , Maguire, M P , Leon, E , Rapoport, H *J Org Chem* **1994**, *59*, 4186

70 For a review, see

Harada, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*, Ref 40, p276-293

71 a) Butler, R N , Evans, A M , McArdle, P , Cunningham, D *J Chem Soc Chem Commun* **1987**, 1090

b) Butler, R N , Evans, A M , McNeela, E M , O'Halloran, G A , O'Shea, P D , Cunningham, D , McArdle, P *J Chem Soc Perkin Trans 1* **1990**, 2527

72 Gainsford, G J , Woolhouse, A D *Aust J Chem* **1980**, **33**, 2447

73 Butler, R N , O'Shea, D F *J Chem Soc Perkin Trans 1* **1994**, 2797

# CHAPTER THREE

# PHOTOCHEMISTRY OF IMIDAZO-1,2,3-TRIAZOLES

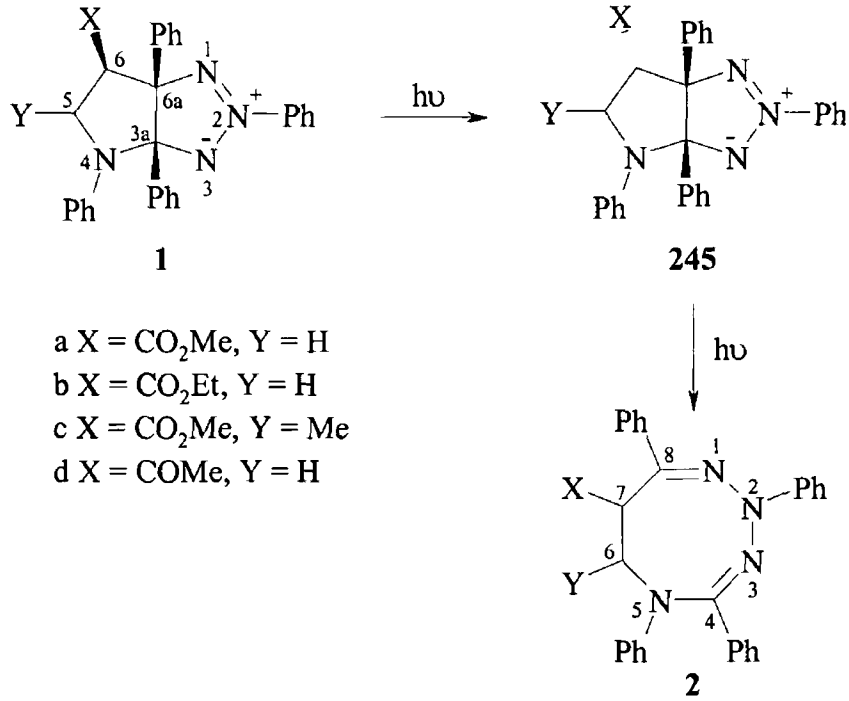
## Chapter 3 Photochemistry of Imidazo-1,2,3-Triazoles

### 3.1 Photochemistry of Pyrrolo-1,2,3-Triazoles.

In previous work by our group,[1] the photochemistry of a range of pyrrolo-1,2,3-triazoles was investigated The photochemistry of this group of compounds was found to be dependent on the bridgehead substituents, on the degree of saturation between C5 and C6, and on the substituents at C5 and C6

#### *3.1.1 Photorearrangements of Substituted 2,3a,4,6a-Tetraphenyl-3,3a,4,5,6,6a-Hexahydropyrrolo[2,3-d]-1,2,3-Triazoles.*

As mentioned in **Chapter One**, irradiation of hexahydropyrrolo[2,3-d]-1,2,3-triazoles **1** led to the formation of 2,5,6,7-tetrahydro-1,2,3,5-tetrazocines **2** by a photochemically allowed 4π disrotatory electrocyclic ring expansion [2] X-ray crystallography analysis of the tetrazocines formed revealed that the stereochemistry of the ester substituent on C7 was not as expected It was discovered that the first step in the photochemical electrocyclic ring opening was an *exo-endo* epimerisation of the ester group This epimerisation gives a more sterically favourable tetrazocine, in which the ester group is further away from the bulky phenyl groups of C-8 and N-5



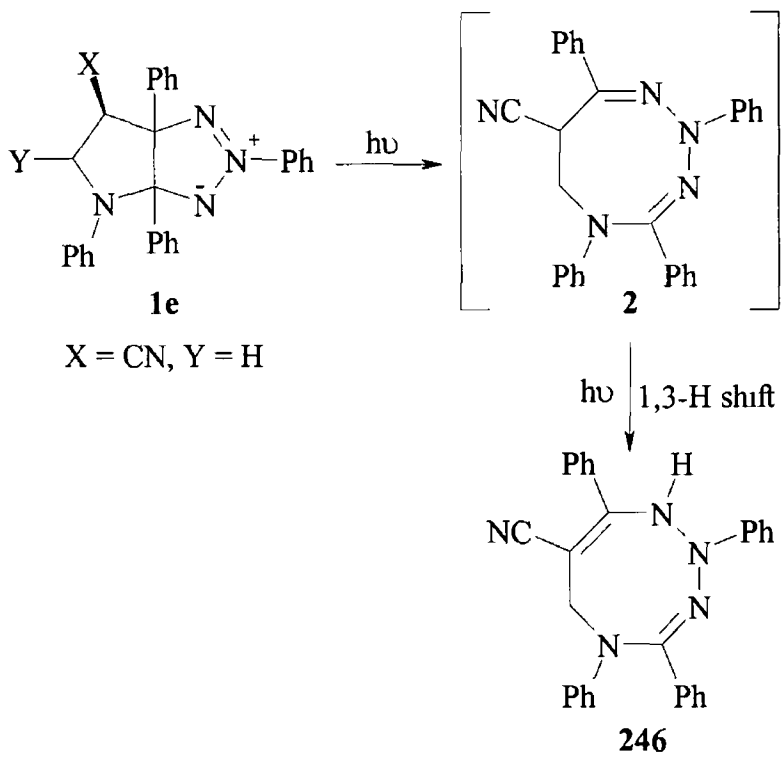

**1** **245** **2**

a X = $CO_2Me$, Y = H
b X = $CO_2Et$, Y = H
c X = $CO_2Me$, Y = Me
d X = COMe, Y = H

**Scheme 3 1** *Formation of novel 1,2,3,5-tetrazocine from bicyclic precursors*

However substitution of electron-donating groups on C5 and C6 (X=Y=$CH_2OH$) gave no reaction on irradiation This is due to the *exo*-orientations of the C6 subsitituent and not the required *endo*-orientation

When X = CN the resulting 2,5,6,7-tetrahydro-1,2,3,5-tetrazocine **2** subsequently underwent a 1,3-H sigmatropic shift to give the 1,2,5,6-tetrahydro-1,2,3,5-tetrazocine **246** [1] The mechanism of this reaction is shown in **Scheme 3.2** The fact that the 1,3-H shift was only observed for the cyano derivative was attributed to the fact that the nitrile α-CH bond is more labile than the α-CH bond of the ester and ketone analogues




**1e**

X = CN, Y = H

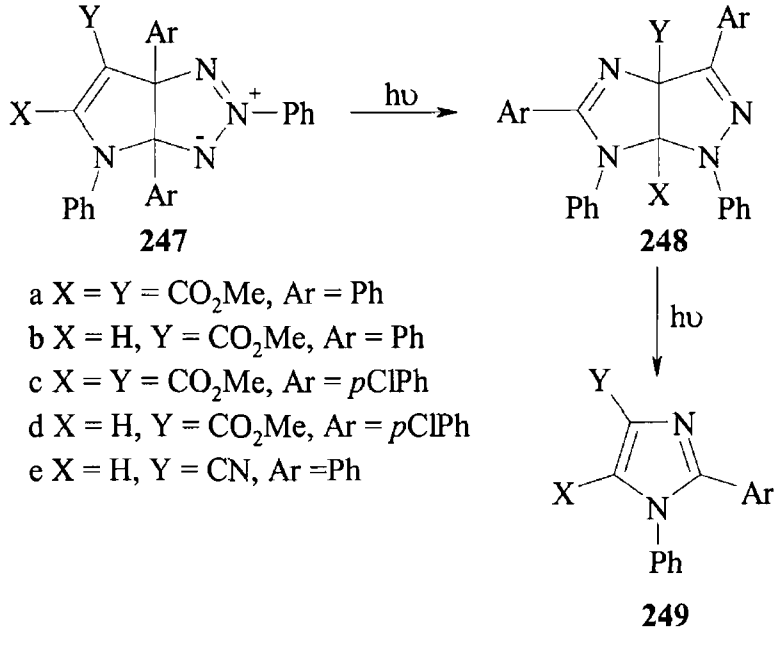
**2**

**246**

**Scheme 3.2** *1,3-H sigmatropic shift of the initially formed 2,5,6,7-tetrahydro-1,2,3,5-tetrazocine, giving the 1,2,5,6-tetrahydro-1,2,3,5-tetrazocine*

### *3.1.2. Photorearrangements of Substituted 3a,6a-diaryl-2,4-diphenyl-3,3a,4,6a-Tetrahydropyrrolo[2,3-d]-1,2,3-Triazoles*

Photolysis of tetrahydropyrrolo-1,2,3-triazoles **247** led to the rearrangement of the molecule to give imidazo[4,5-c]pyrazoles **248**, which on further photolysis fragmented to give imidazoles **249** This result was also reported by Butler *et al*[3] who confirmed the structure of the imidazo[4,5-c]pyrazoles by X-ray crystallography




**247**

a X = Y = $CO_2Me$, Ar = Ph
b X = H, Y = $CO_2Me$, Ar = Ph
c X = Y = $CO_2Me$, Ar = *p*ClPh
d X = H, Y = $CO_2Me$, Ar = *p*ClPh
e X = H, Y = CN, Ar =Ph

**248**

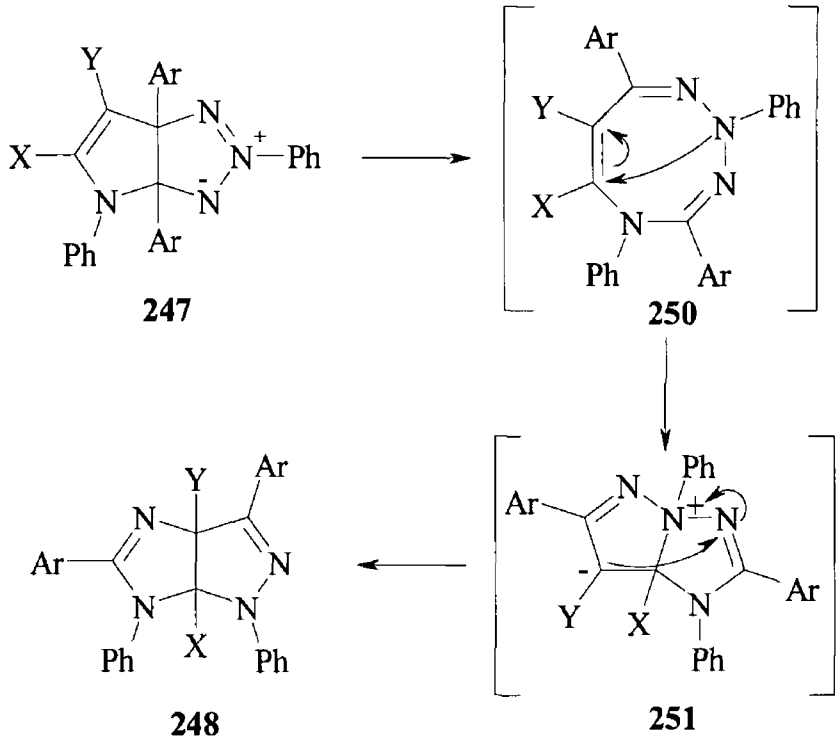
**249**

**Scheme 3.3** *Photolysis of tetrahydropyrrolo-1,2,3-triazoles results in rearrangement of the molecule to imidazo[4,5-c]pyrazoles Further irradiation causes fragmentation, giving substituted imidazoles*

The mechanism proposed by Butler *et al*[3] for this complex rearrangement involves an initial disrotatory outward electrocyclic ring expansion to the 10π-tetrazocine **250** (**Scheme 3 4**) This is followed by a transannular ring contraction to the intermediate **251** and a 1,4-sigmatropic rearrangement involving N-N bond cleavage and C-N bond formation to yield the stable bicyclic products **248**

The intermediate tetrazocine ring **250** undergoes transannular ring contraction by nucleophilic attack of the N-2 lone pair on the electron deficient C-6 The 1,4-sigmatropic rearrangement of **251** to **248** is a thermally allowed suprafacial process It involves six electrons, two of which come from the negative charge of the zwitterionic

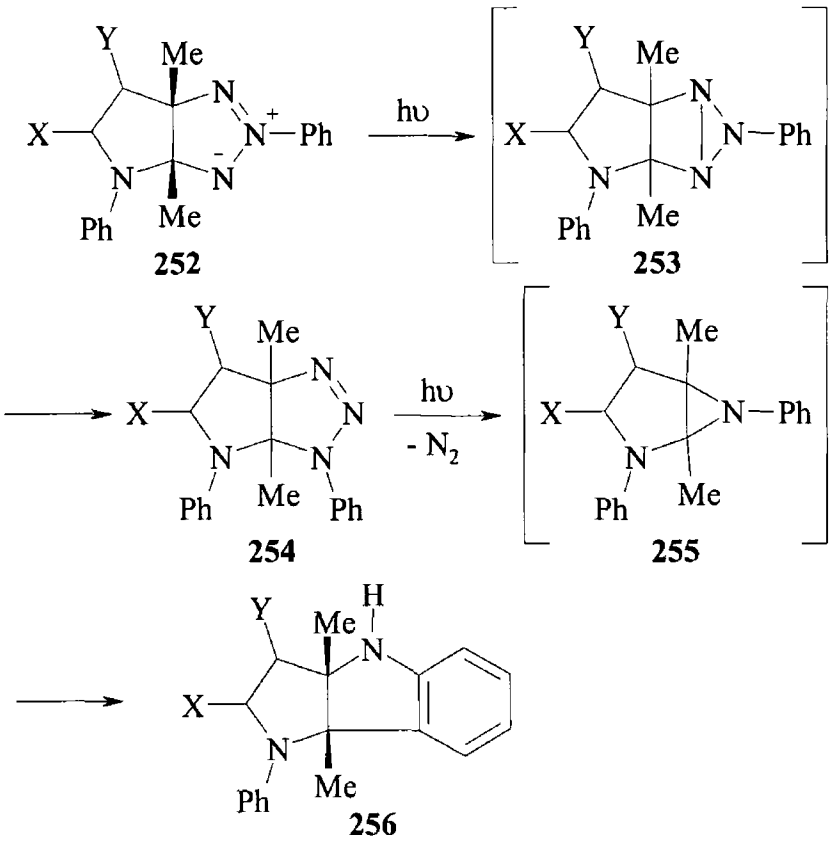
intermediate **251** The migration dissipates the formal charges of **251** and is also favourable as it involves the breaking of a N-N bond and the formation of a C-N bond




**Scheme 3 4** *Mechanism of formation of imidazo[4,5-c]pyrazoles by the irradiation of substituted tetrahydropyrrolo-1,2,3-triazoles (Ar, X and Y as in* ***Scheme 3 3)***

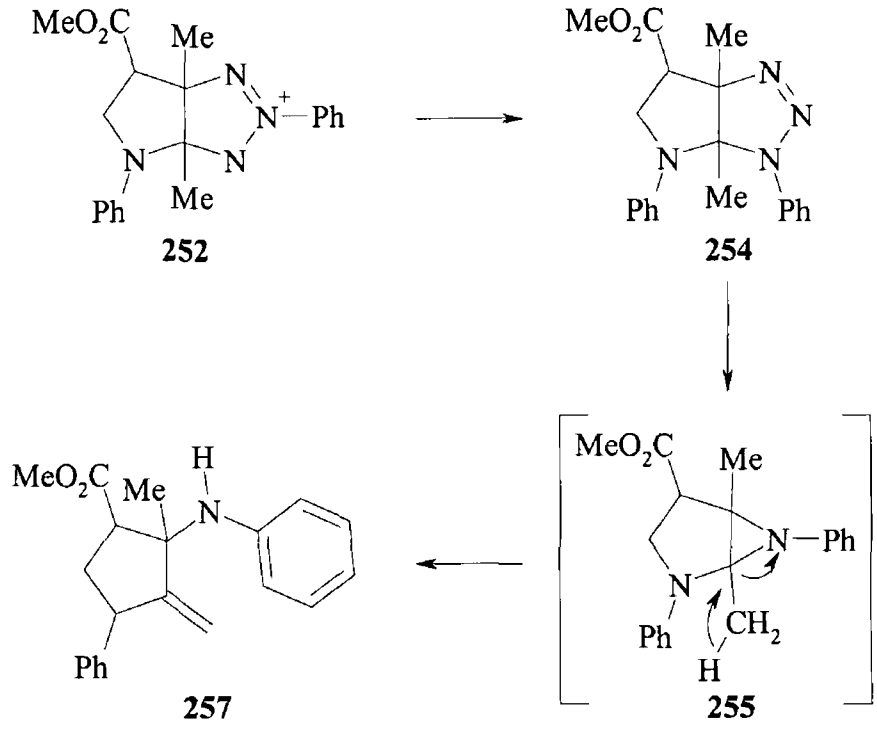
### *3.1.3 Photorearrangements of Substituted 3a,6a-Dimethyl-3,3a,4,5,6,6a-Hexahydropyrrolo[2,3-d]-1,2,3-Triazoles*[1]

The irradiation of 3a,6a-dimethyl hexahydropyrrolo[2,3-d]-1,2,3-triazoles **252** with a medium pressure mercury lamp yielded the stable hexahydropyrrolo[3,2-b]-indole **256** The mechanism shown in **Scheme 3 5** is explained in terms of a series of photoinduced sequential transformations The initial intermdiate is the tricyclic fused triaziridine **253** which then yields the 1-substituted fused 1,2,3-triazole **254** by a tandem ring opening and 1,3-sigmatropic rearrangement This rearrangement is favoured as it relieves the ring strain of the triaziridine Further irradiation of the isolated 1,2,3-triazole yields the pyrroloindole by loss of nitrogen and intramolecular cyclisation




**Scheme 3 5** *Mechanism of photochemical reaction of substituted 3a,6a-dimethyl hexahydropyrrolo[2,3-d]-1,2,3-triazoles, yielding pyrrolo[3,2-b]indoles*

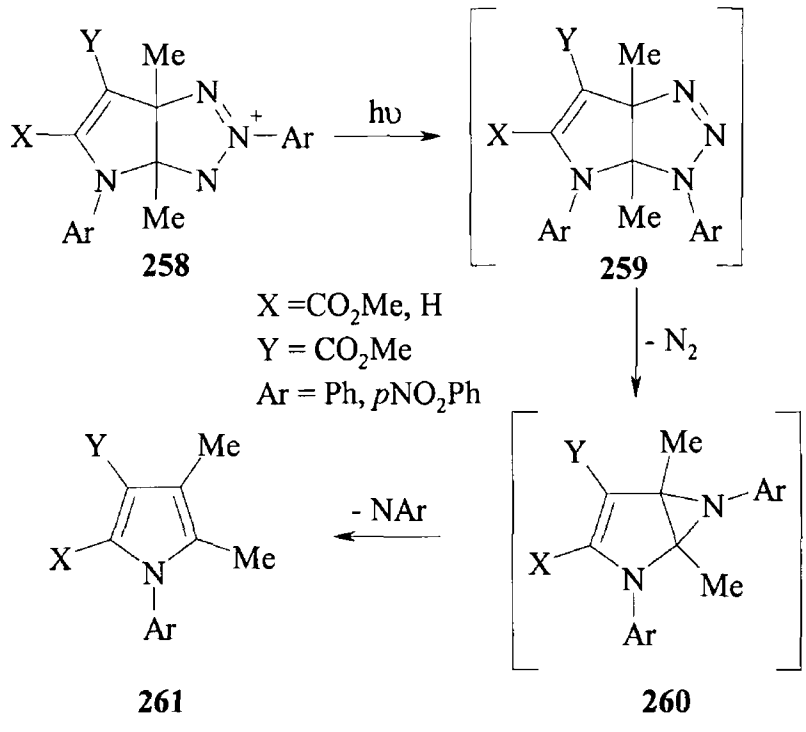
However on irradiation of 6-methoxycarbonyl 3a,6a-dimethyl-2,4-diphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole **252** (X=$CO_2$Me, Y=H), two products were isolated [1] The minor product was the pyrroloindole **256** (X=$CO_2$Me, Y=H) The major product was found by X-ray crystallography to be **257** The mechanism of formation of **257** is shown in **Scheme 3 6** On further irradiation by pyrex filtered UV light, **257** undergoes ring closure to give the pyrroloindole




**Scheme 3 6** *Mechanism of formation of 257 on photolysis of 3a,6a-dimethyl-2,4-diphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole*

### *3.1 4 Photorearrangements of Substituted 3a,6a-Dimethyl-3,3a,4,6a-Tetrahydropyrrolo[2,3-d]1,2,3-Triazoles* [1]

On irradiation of **258** in acetonitrile solution using a medium pressure mercury lamp two products were isolated (**Scheme 3 7**) The major product was identified as the substituted pyrrole **261** The formation of this five-membered ring is explained by a mechanism similar to that proposed for the hexahydro analogues Initial photorearrangement to **259** followed by loss of nitrogen and subsequent loss of aryl nitrene from the fused aziridine intermediate **260** yields the substituted pyrrole The driving force for the elimination of aryl nitrene is the formation of the aromatic five-membered ring The other photoproduct isolated was azoarene, formed on dimerisation of the aryl nitrene eliminated during the reaction process




**Scheme 3 7** *Formation of substituted pyrroles by the irradiation of 3a,6a-dimethyl tetrahydropyrrolo-1,2,3-triazoles*

### 3 2 Woodward-Hoffmann Rules and Photochemistry

The use of light to bring about chemical change has been recognised for many years, but it was in 1970, when Woodward and Hoffmann published their application of the Principle of Conservation of Orbital Symmetry,[4] that the understanding of photochemical processes began to develop

Concerted reactions, which proceed through a cyclic transition state, e g electrocyclic, sigmatropic, cheletropic and cycloaddition, are termed pericyclic reactions The Principle of Conservation of Orbital Symmetry predicts which types of cyclic transition states are energetically feasible The Woodward-Hoffmann orbital symmetry rules are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction

An electrocyclic rearrangement is a pericyclic reaction in which one new σ bond is formed (or broken) across the ends of a single conjugated π system Stereochemical

studies show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or by light There are four stereochemically distinguishable ways in which an electrocychc reaction can take place (**Figure 3 1**), two are distrotatory (one group rotates clockwise and one anticlockwise) and two are conrotatory (the two groups rotate in the same way, both clockwise or both anticlockwise)

The application of frontier molecular orbital theory, the aromatic transition state theory and orbital correlation diagrams all result in the same predictions for electrocyclic reactions These are summarised in **Table 3 1**

| Number of π electrons | Reaction | Motion |
|---|---|---|
| 4n | thermal | conrotatory |
| 4n | photochemical | disrotatory |
| 4n + 2 | thermal | disrotatory |
| 4n + 2 | photochemical | conrotatory |

**Table 3 1** *Woodward Hoffmann rules for electrocyclic reactions*

Woodward and Hoffmann state the general rule for pericyclic reactions as follows

> *'A ground state pericyclic change is symmetry allowed when the total number of (4n + 2) suprafacial and 4n antarafacial components is odd '*

This can also be written as

> *Thermal pericyclic reactions occur via aromatic transitions states*
> *Photochemical pericyclic reactions occur via antiaromatic transition states*

These generalisations are based on the fact that in principle, there are two types of aromatic systems, the Huckel aromatic system which has (4n + 2)π electrons and the Mobius type aromatic system which has (4n)π electrons

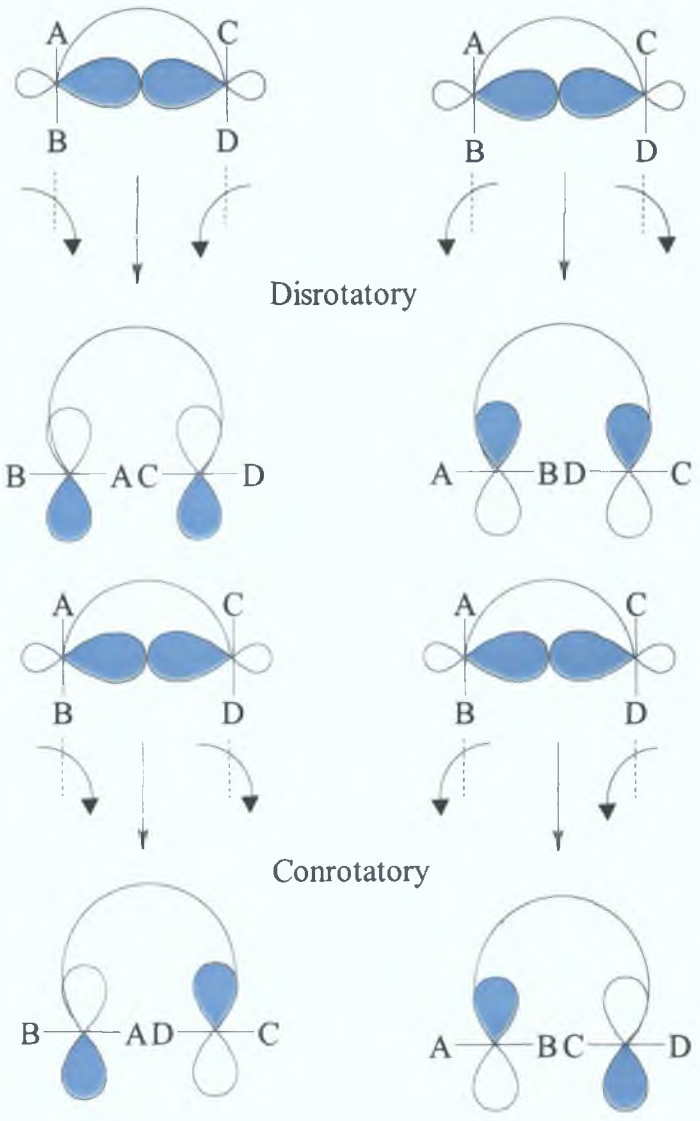


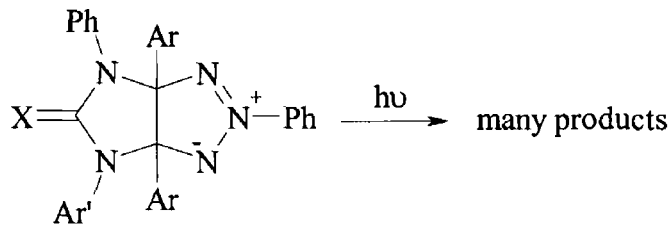

**Figure 3.1** *Four possible stereochemical outcomes of an electrocyclic ring opening reaction.*

The initial photochemical ring-opening of pyrrolo-1,2,3-triazoles is a disrotatory outward electrocyclic process, involving the 4π electrons of the triazole ring.[3] Because of the presence of the lone pairs in the conjugated system, the electrocyclic process **1** → **2** can be viewed as either 4π or 4π + 2 but if it is confined to the terminal bond involved it is a 4π process requiring irradiation for disrotation. As it is the triazole half of the molecule which is involved in the ring opening, imidazo-1,2,3-triazoles should also undergo this disrotatory electrocyclic process.

## 3.3 Results and Discussion:

### *3.3 1 Photochemistry of $sp^2$-C5 Imidazo-1,2,3-Triazoles.*

The initial attempts to synthesise a 1,2,3,5,7-pentazocine involved the irradiation of the adducts derived from triazolium-N imides and isocyanates and isothiocyanates (adducts **122a-k** and **124a-d**) These adducts possess a carbonyl or thionyl group at the C-5 position, but it was hoped that the presence of this group would not affect the photochemical behaviour of the ring opening The 4n π system involved is contained in the triazole functionality of the bicyclic adduct, and the imidazo functionality should play no part in the photochemically induced ring-opening



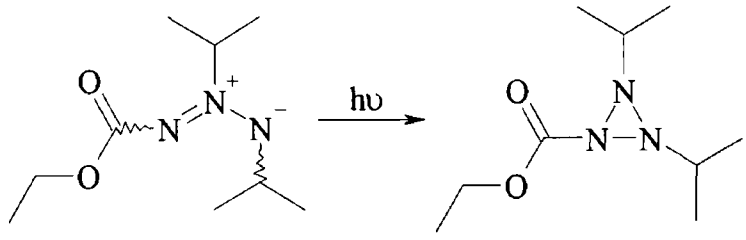

**122** X = O
**124** X = S

**Scheme 3.8** *Irradiation of imidazo-1,2,3-triazoles with a thionyl or carbonyl group at C-5*

However, the irradiation of imidazo-1,2,3-triazoles derived from the cycloaddition of triazolium-N-imides with isocyanates and isothiocyanates resulted in a large number of photoproducts The separation and identification of these products proved to be extremely difficult Variation of experimental conditions, such as concentration of photolysis solution, length of time of irradiation, solvents, and degassing before and during photolysis, gave little improvement Short periods of irradiation time gave fewer products, but extremely low yields of unstable compounds, which proved impossible to identify Longer reaction times gave more products that were difficult to separate by column chromatography The separation of these products was attempted using preparative TLC plates, but to no avail The use of different solvents, and solid-state photolysis had no effect on the reaction

Breaking the imidazo-1,2,3-triazole into it's constituent functional groups, and examining the photochemical reactions of each, it is easy to see why so many photoproducts were formed

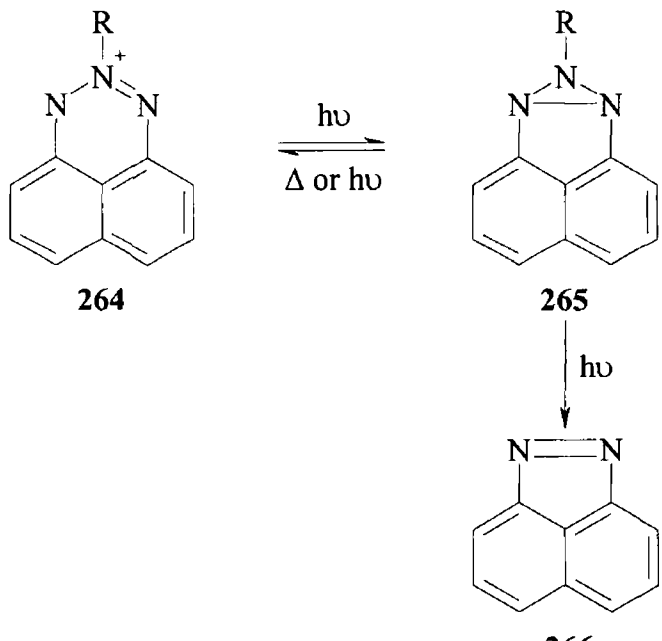
The azimine group, a three-nitrogen 4π dipolar system undergoes photoisomerisation to give triaziridines [5]



**262** **263**

**Scheme 3 9** *The first triaziridine was synthesised by the U V irradiation of azimine*

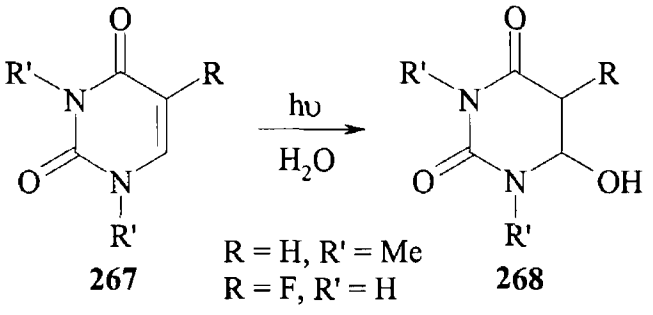
The blue azimine **264**, of interest as an inhibitor in the photo-oxidation of polymers and as a trapping reagent for the detection of free radicals, proved to be stable on long and short wavelength irradiation [6] However, multiple excitation with excimer laser pulses led to a disappearance of the blue colour and the product was assigned the isomeric structure **265** Further irradiation of **265** using a low pressure lamp led to the reformation of **264**, along with a number of other compounds, the major by-product being **266**, formed by loss of methyl nitrene



**264** **265** **266**

**Scheme 3 10** *Irradiation of the blue azimine led to the formation of a triaziridine, which on loss of methyl nitrene gave* ***266***

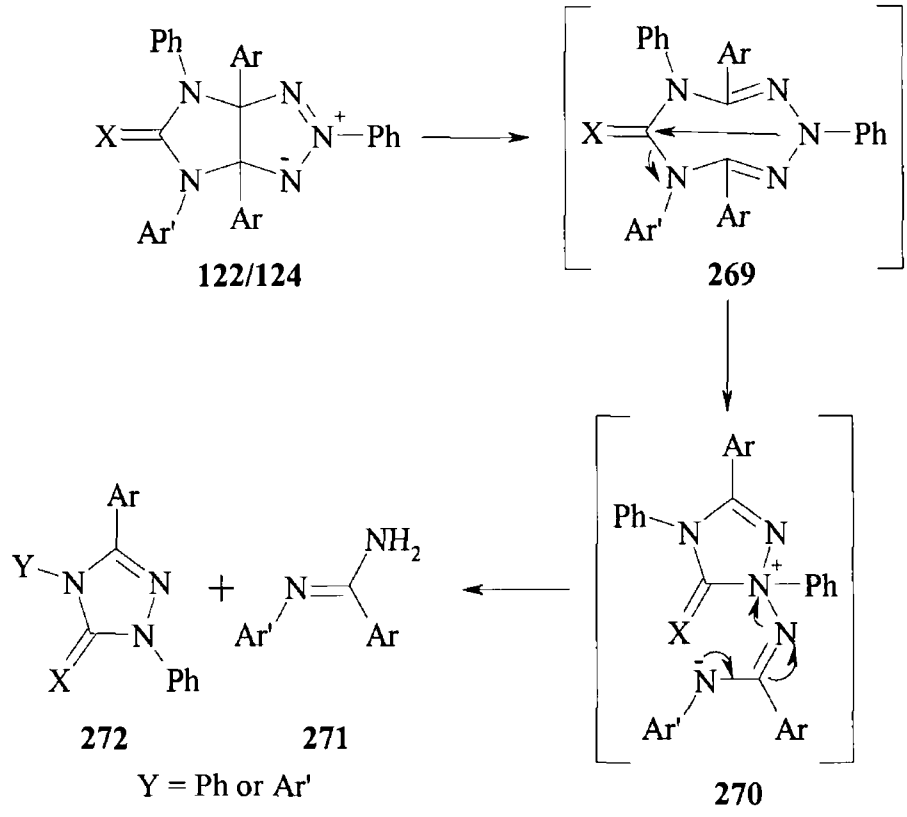
The photochemistry of the carbonyl group has been extensively studied, more so than the thionyl group, but both groups seem to undergo similar photochemical reactions The presence of the carbamide functionality seems to prevent the usual photoreactions of the carbonyl bond The UV irradiation of an aqueous solution of 1,3-dimethyluracil **267** resulted in a photoadduct, 6-hydroxy-1,3-dimethylhydrouracil **268**[7] The carbamide group remained intact during the photolysis




**267** **268**

**Scheme 3 11** *Photoaddition of water to a double bond UV irradiation has no effect on the carbamide functional group*

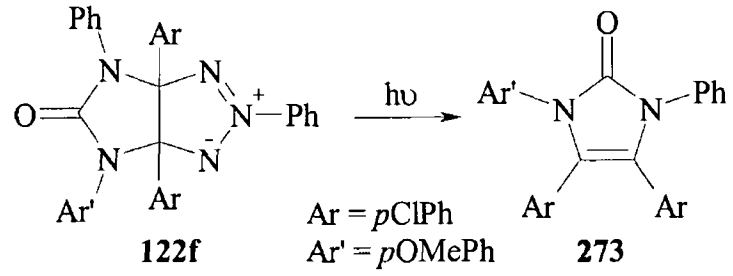
Of course, the possibility that the required electrocyclic ring-opening of the imidazo-1,2,3-triazole did occur, cannot be discounted, in fact it is highly likely that it did take place However, the susceptibility of the carbonyl group to attack by nucleophiles would result in further rearrangement and probable fragmentation of this molecule One of the products which was isolated and analysed by NMR, is possibly the 2,4,5-triaryl-2,4-dihydro-[1,2,4]-triazol-3-one **272** It is likely that this molecule is formed as shown in **Scheme 3.12** After electrocyclic ring-opening, the carbonyl carbon is attacked by the lone pair of nitrogen This type of transannular interaction is well known in eight-membered rings containing an exocyclic carbonyl bond [8] Cleavage of the carbon-nitrogen bond and the nitrogen-nitrogen bond would give the triazolone and N-phenyl benzamidine **271**




**Scheme 3 12** *Possible photoreaction of imidazo-1,2,3-triazoles with a carbonyl or thionyl group at C-5*

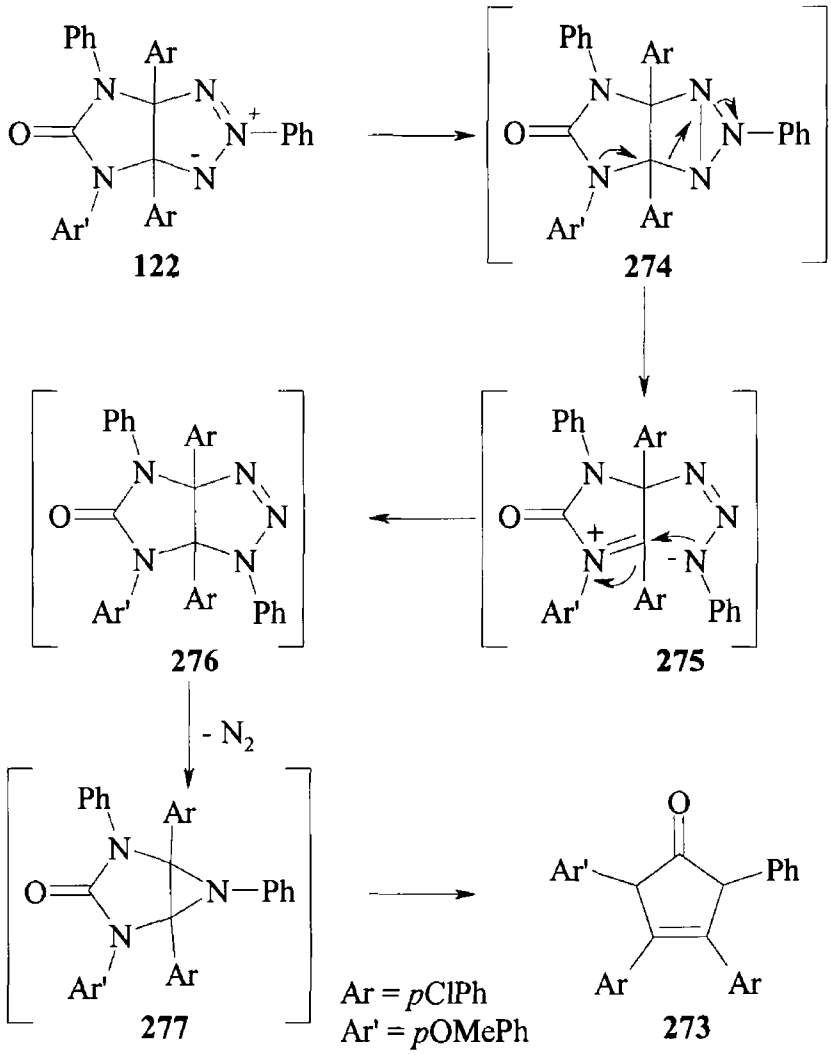
The substituent Y on N-4 could be either the phenyl ring or substituted phenyl ring, depending on which carbon-nitrogen bond is broken after transannular interaction

Of all of the imidazo-1,2,3-triazoles derived from isocyanates **122a-k**, and isothiocyanates **124a-d**, the cleanest product was obtained from the irradiation of 2,6-diphenyl-4(4-methyoxyphenyl)-3a,6a-bis(4-chlorophenyl)-5-oxo-3,3a,4,5,6,6a-hexahydroimidazo [4,5-d]-1,2,3-triazole **122f** 500mg of the cycloadduct were irradiated with a medium pressure mercury lamp for 2 hours Separation of the products by flash chromatography yielded a small amount of a yellow compound $^1$H NMR analysis of this compound showed a singlet peak at 3 69ppm, with an integration of 3 protons This indicated that the methoxy group was still present in the product The product also showed 17 aromatic protons, with a very defined splitting pattern This led to the conclusion that the molecule was the substituted imidazolone The splitting pattern of the $^1$H NMR fits this structure very well, showing 7 doublets, integrating as 2 protons each, and two triplets, integrating as one proton and two protons




**Scheme 3 13** *Irradiation of cycloadduct led to the novel imidazolone*

The mechanism (**Scheme 3 14**) is likely to involve the photoisomerisation of the azimine moiety to give the triaziridine **274** Loss of molecular nitrogen followed by loss of phenyl nitrene would give the imidazolone **273** This compound has not previously been reported, but was not stable enough to fully characterise

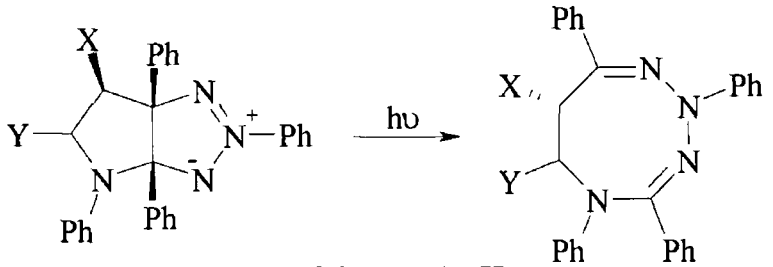



**Scheme 3 14** *Possible mechanism for the formation of the novel imidazolone 273*

### *3.3 2 Photochemistry of $sp^3$-C5 Imidazo-1,2,3-Triazoles*

*3 3 2 1 No Substituents at C5*

As mentioned previously, the irradiation of hexahydropyrrolo-[2,3-d]-triazoles with ultraviolet light (wavelength >385nm) led to the stable 2,5,6,7-tetrahydro-1,2,3,5-tetrazocines [2] **(Scheme 3.15)**

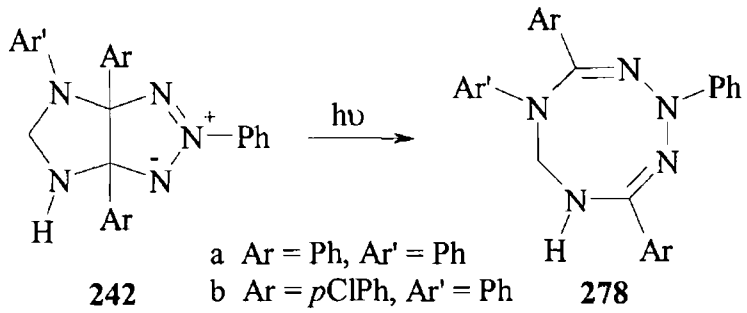



**1** a X = $CO_2Me$, Y = H **2**
b X = COMe, Y = H
c X = $CO_2Et$, Y = H
d X = $CO_2Me$, Y = Me

**Scheme 3 15** *Synthesis of novel 1,2,3,5-tetrazocines by the irradiation of hexahydropyrrolo-1,2,3-triazoles*

The success of this reaction is due to the absence of substituents on the $sp^3$-hybridised C5 atom of the bicyclic precursor Both electron withdrawing at the C5 position and electron donating substituents at both the C5 and C6 positions were found to prevent the formation of stable tetrazocines The initial step in the reaction is an *exo-endo* epimerisation (**Scheme 3 1**) which reduces steric crowding and facilitates the ring-opening Attempts to form tetrazocines from precursors with alkoxy substituents at C5 and C6 failed, due to the C6 substituent being in the *exo*-orientation

Hexahydroimidazo-1,2,3-triazoles with no substituents at C5 would hopefully provide suitable precursors for the previously unknown pentazocine molecule Irradiation of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole **242** with white light for 24 hours led to the formation of one major product, as shown by TLC Separation of this product and initial $^1H$ and $^{13}C$ NMR studies indicated that the system had undergone distrotatory ring opening and that the required pentazocine **278** had been formed (**Scheme 3 16**) (See **Figure 3 2** for $^1H$ NMR spectrum )




242 a Ar = Ph, Ar' = Ph; b Ar = *p*ClPh, Ar' = Ph 278

**Scheme 3 16** *Photolysis of hexahydroimidazo-1,2,3-triazoles to give the novel 1,2,3,5,7-pentazocines*

Unfortunately, crystals suitable for X-ray diffraction could not be obtained This led to the search for a suitable method of proving that the novel pentazocine had been synthesised

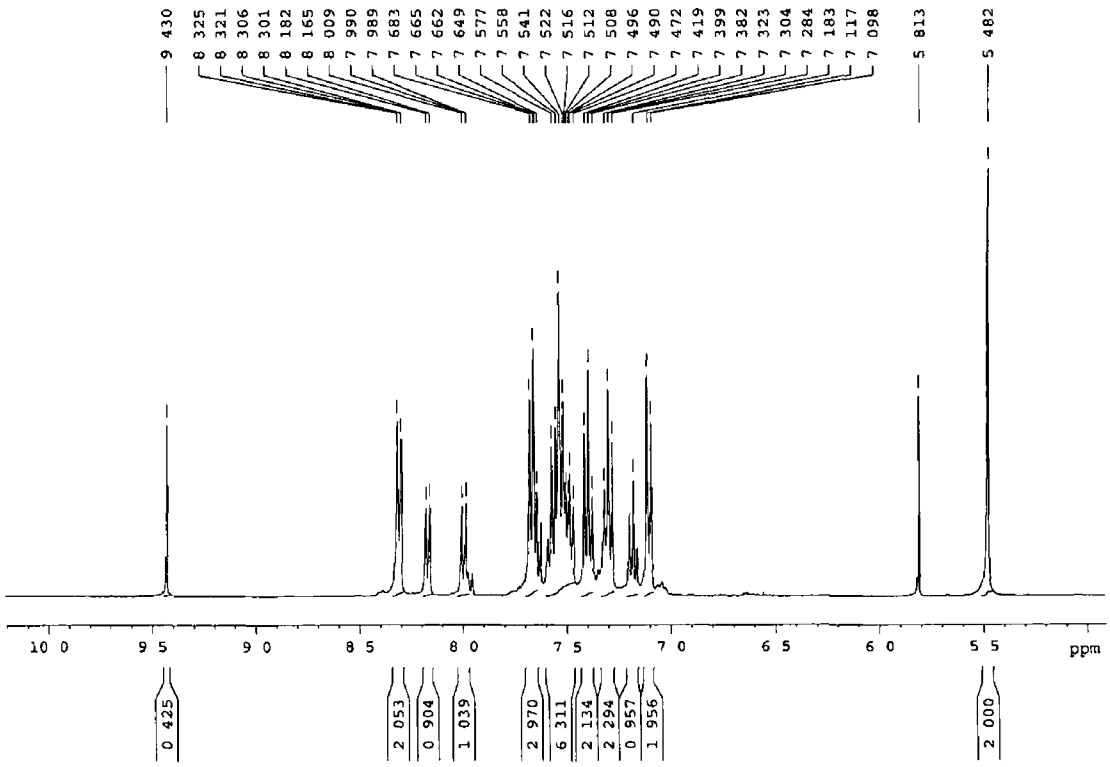



**Figure 3 2** *$^1$H NMR of product from photolysis of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole* ***242a*** *(The peak at 5 813ppm is due to dichloromethane)*

*3 3 2 2 2D NMR Experiments*

HMQC (heteronuclear multiple quantum correlation) and HMBC (heteronuclear multiple bond correlation) are inverse detection two-dimensional NMR techniques that show both short range and long range coupling HMQC experiments show one bond C-H connections while HMBC shows 2 and 3 bond C-H connections

A comparison of the HMQC and in particular, the HMBC of the proposed pentazocine and it's immediate precursor should provide enough information to prove the structure of the eight-membered ring

As a control experiment, the HMQC and HMBC spectra of a known tetrazocine, 7-ethoxycarbonyl-2,3,4,8-tetraphenyl-2,5,6,7-tetrahydro-1,2,3,5-tetrazocine **2b** and its immediate precursor **1b** were also obtained The HMQC (**Figure 3 3a**) of the precursor indicates the difference in chemical shifts of the two diastereotopic protons attached to C-5 However, differentiation between the other diastereotopic proton, the proton attached to C-6 and the $OCH_2$ of the ester group cannot be achieved as all of these protons appear as a multiplet between 3 73 and 3 88 ppm Moving on to the HMBC (**Figure 3 3b**), the more downfield diastereotopic proton shows 2-bond coupling with C-6, and 3-bond coupling with one of the bridgehead carbons, as well as the carbonyl carbon of the ester group The 4-proton muliplet shows coupling with a number of carbon atoms, including both bridgeheads, C-5 and C-6, and the carbonyl carbon, but it is difficult to definitively assign these couplings

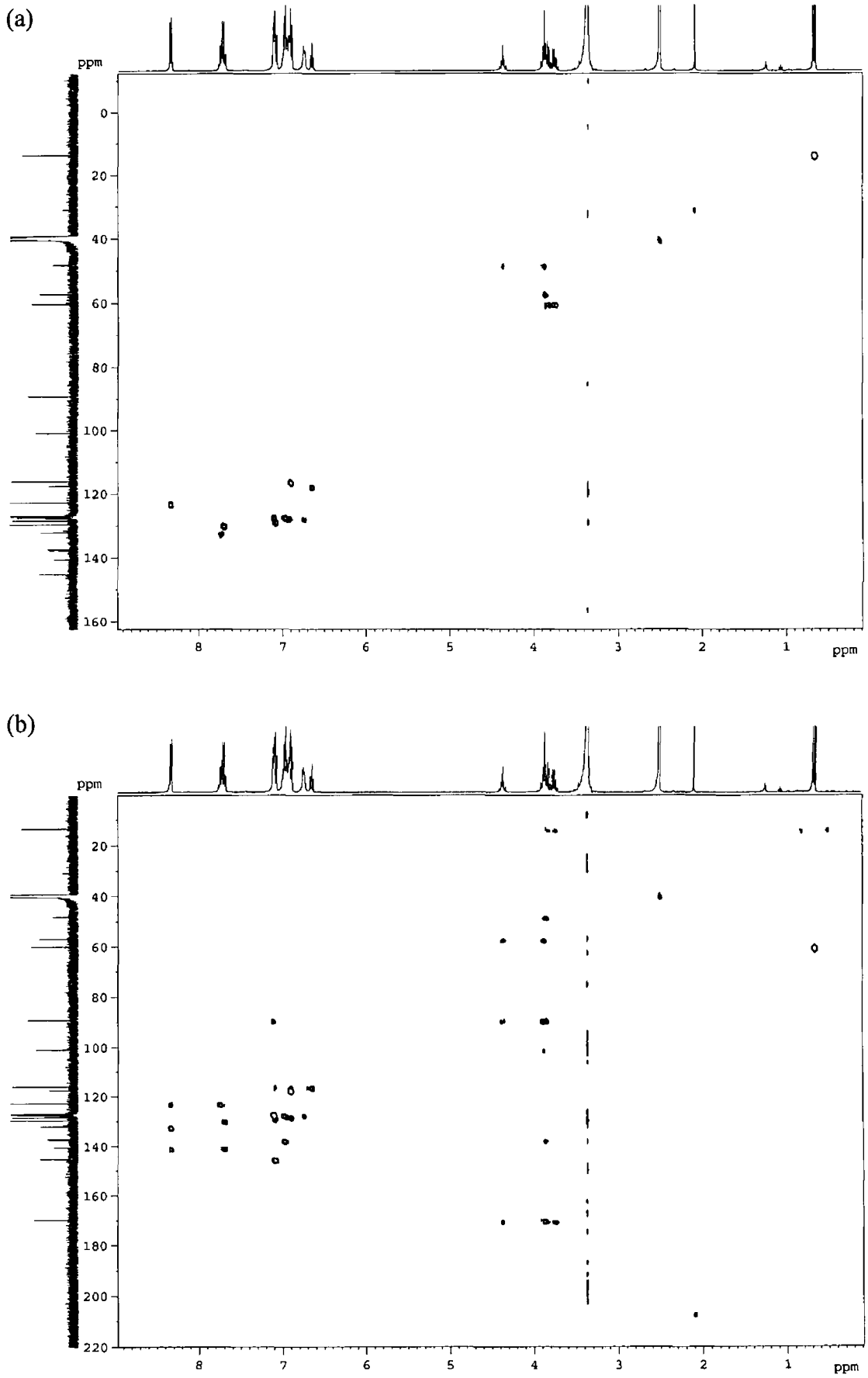



**Figure 3 3** *HMQC (a) and HMBC (b) spectra of the tetrazocine precursor* ***1b***

The HMQC spectrum (**Figure 3 4a**) of the tetrazocine gave some unexpected results and lead to a reassignment of some peaks in both the $^{1}H$ and $^{13}C$ spectra The signals that appear at 3 68 and 3 88ppm in the $^{1}H$ spectrum and couple to the peak at 61 19ppm in the $^{13}C$ spectrum were assigned as the $CH_2$ of the ester group This appearance of two peaks for apparently equivalent protons was confirmed by the HMBC spectrum (**Figure 3 4b**), in which $^{2}J_{HC}$ coupling with the $CH_3$ of the ester group and $^{3}J_{HC}$ coupling with the carbonyl carbon are seen No other protons in the molecule could display these interactions

The multiplet that appears at 4 76ppm was then assigned as the two protons bonded to C-6, which appears at 47 80ppm These assignments are confirmed by the coupling that is seen in the HMBC spectrum Here $^{2}J$ coupling with C-7 appears, as well as $^{3}J$ interaction with the carbonyl carbon On the basis that the C-6 protons are the only non-aromatic protons in the molecule that would have 2 or 3 bond interactions with C-4, the peak at 176 84 was reassigned as the $sp^2$-hybridised carbon The remaining two couplings of these protons were assigned as $^{3}J$ to C-8 at 154 24ppm and $^{3}J$ to the quaternary carbon of the phenyl group attached to N-5

The C-7 proton appears as a double doublet at 4 11ppm and couples with the carbon peak at 48 91ppm in the HMQC spectrum Correlation signals for this proton show $^{2}J$ interactions with C-6, C-8 and the carbonyl carbon, and $^{3}J$ interaction with the quaternary carbon of the phenyl group bonded to C-8

The peak at 168 90ppm must be the carbonyl carbon as it couples with the $-OCH_2$, the C-6 protons and the proton bonded to C-7, and is the only atom with which all five protons can interact

It can be seen that the $CH_3$ of the ester group has $^{2}J$ coupling to the $CH_2$ carbon, but also has two further correlation peaks that correspond to $^{1}J$ coupling Peaks like these, for directly bonded hydrogen and carbon atoms should be suppressed, but this does not always happen for all the protons in the molecule In such cases, a doublet is obtained in the 2D spectrum, corresponding to the positions of the $^{13}C$ satellites in the $^{1}H$ NMR spectrum

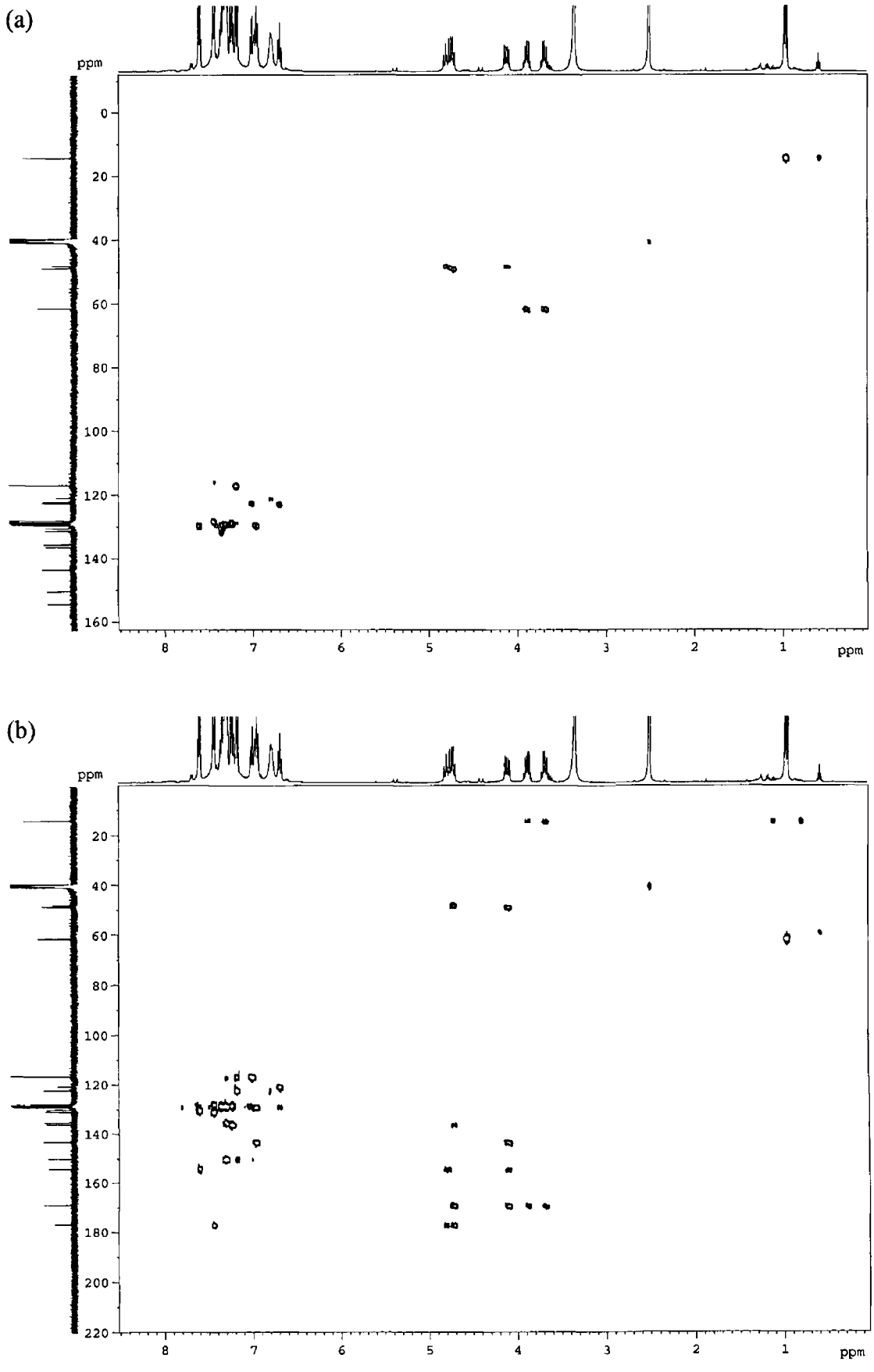



**Figure 3 4** *HMQC (a) and HMBC (b) spectra of the known tetrazocine (**2b**)*

The HMQC (**Figure 3 6a**) of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole **242** clearly shows the C-H coupling of the diastereotopic protons attached to C-5, as well as the various aromatic C-H couplings However it is the HMBC (**Figure 3 6b**) of this compound that is of more interest It was predicted that both diastereotopic protons would show 3-bond couplings to both of the bridgehead carbons The spectrum showed only one of these protons coupling to the bridgehead carbons Increasing the number of scans of the experiment showed coupling of the proton attached to N-4 with both of the bridgehead carbons It is thought that the more intense signal is due to 2-bond coupling while the signal of lesser intensity is due to 3-bond coupling The increased number of scans also showed weak coupling of the N-H with an aromatic carbon, presumably due to 3-bond coupling with a phenyl ring attached to the adjacent bridgehead

The fact that only one of the diastereotopic protons showed coupling to the bridgehead carbons can be explained by the Karplus curve (**Figure 3 5**), in which the vicinal coupling constant is related to the dihedral angle

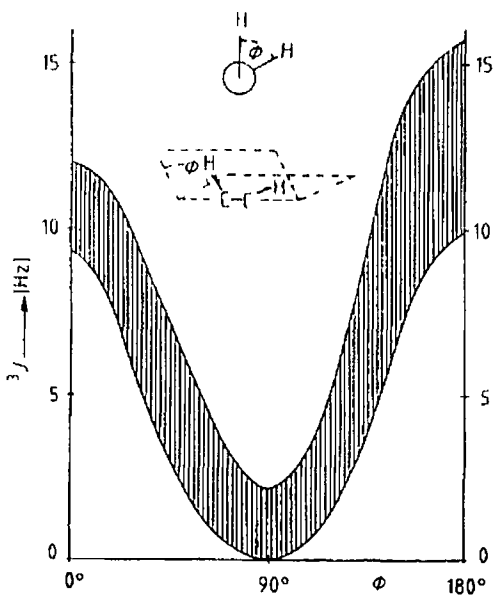



**Figure 3 5** *Range of observed vicinal coupling constants for different values of the dihedral angle Φ (Karplus curve)*

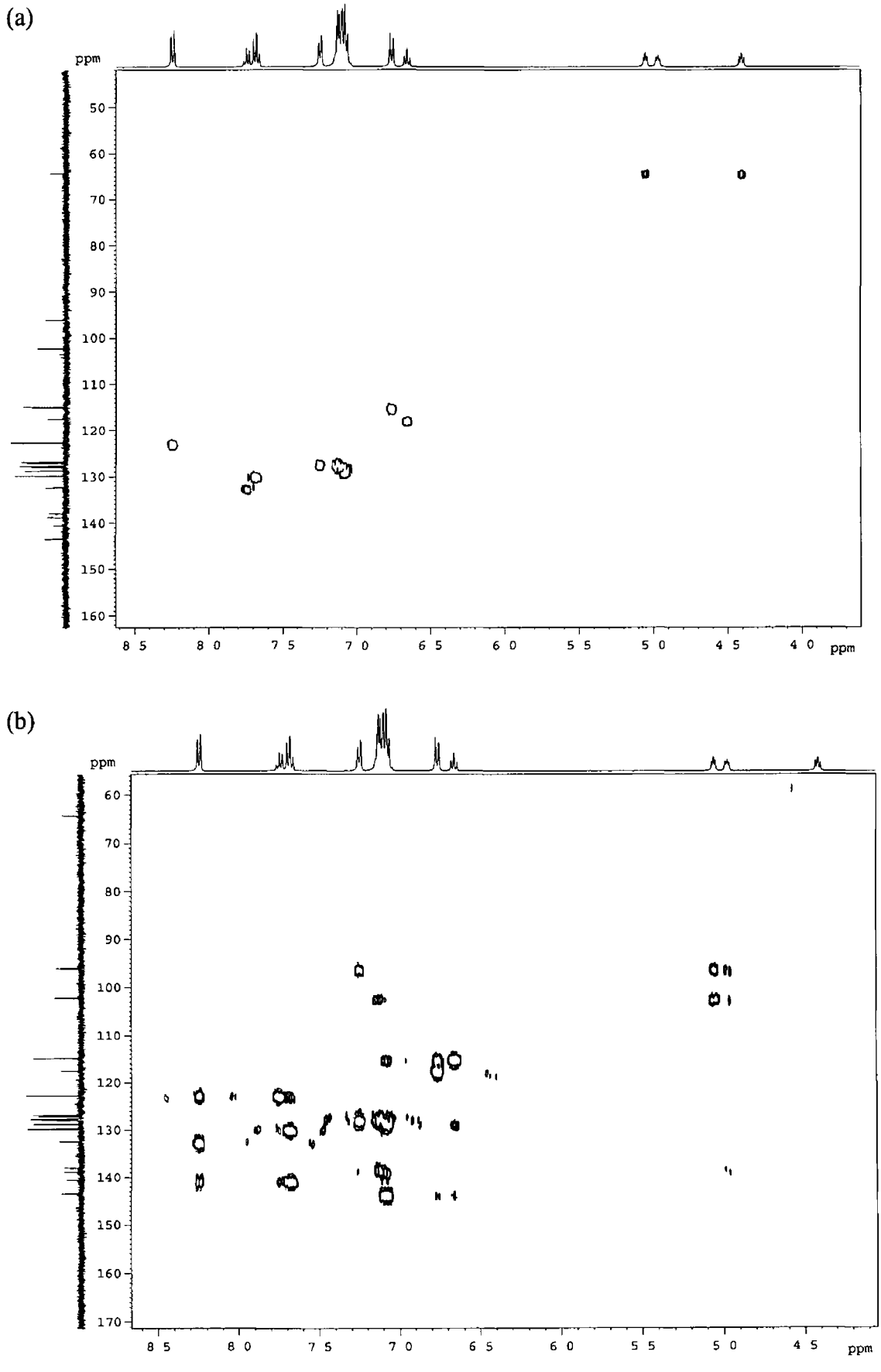



**Figure 3.6** *HMQC (a) and HMBC (b) spectra of the hexahydroimidazo-1,2,3-triazole* ***(242a)***

Simple molecular modelling indicates that the molecule could adopt a slightly twisted conformation which gives a ~90° dihedral angle between one of the diastereotopic protons and each of the bridgehead carbons The Karplus curve predicts a coupling constant of zero with a dihedral bond angle of 90°, which would explain the absence of a signal in the HMBC In the twisted conformation, the other diastereotopic proton would have a ~180° dihedral bond angle with each of the bridgehead carbons A coupling constant of 10-16Hz is predicted by the Karplus curve as the dihedral bond angle approaches 180° In the HMBC spectrum, strong $^{3}J_{HC}$ coupling appears between one of the diastereotopic protons and both of the bridgehead carbons

HMBC experiments are designed to detect long range couplings at a coupling constant of 12Hz By varying the $D_6$ parameter of the pulse sequence, the value of $J$ can be optimised HMBC spectra were obtained with $J$-values of 8Hz, 6Hz, 4Hz and 2Hz, in the hope that the $^{3}J_{HC}$ coupling of the diastereotopic proton with the bridgehead carbons could be detected However these changes in the experimental parameters did not serve to detect the required interaction

Moving onto the product of the photolysis of hexahydroimidazo-1,2,3-triazoles, the HMQC (**Figure 3 7a**) and HMBC (**Figure 3.7b**) spectra gave some very surprising results The peak at 9 43ppm in the $^{1}$H spectrum was originally thought to be the N5-H peak of the pentazocine However the 2D spectra showed $^{1}J$ coupling of this proton with the carbon peak at 143 80ppm and $^{2}J$ or $^{3}J$ coupling with the peak at 162 21ppm Obviously then, this was not an N-H peak, but a C-H signal

On repeating the photolysis reaction, the $^{1}$H NMR of the isolated product was not as expected, but showed only four proton signals, all of which were present in the original spectra, including the C-H peak at 9 43ppm This product was identified as a diphenyl-1,2,4-triazole

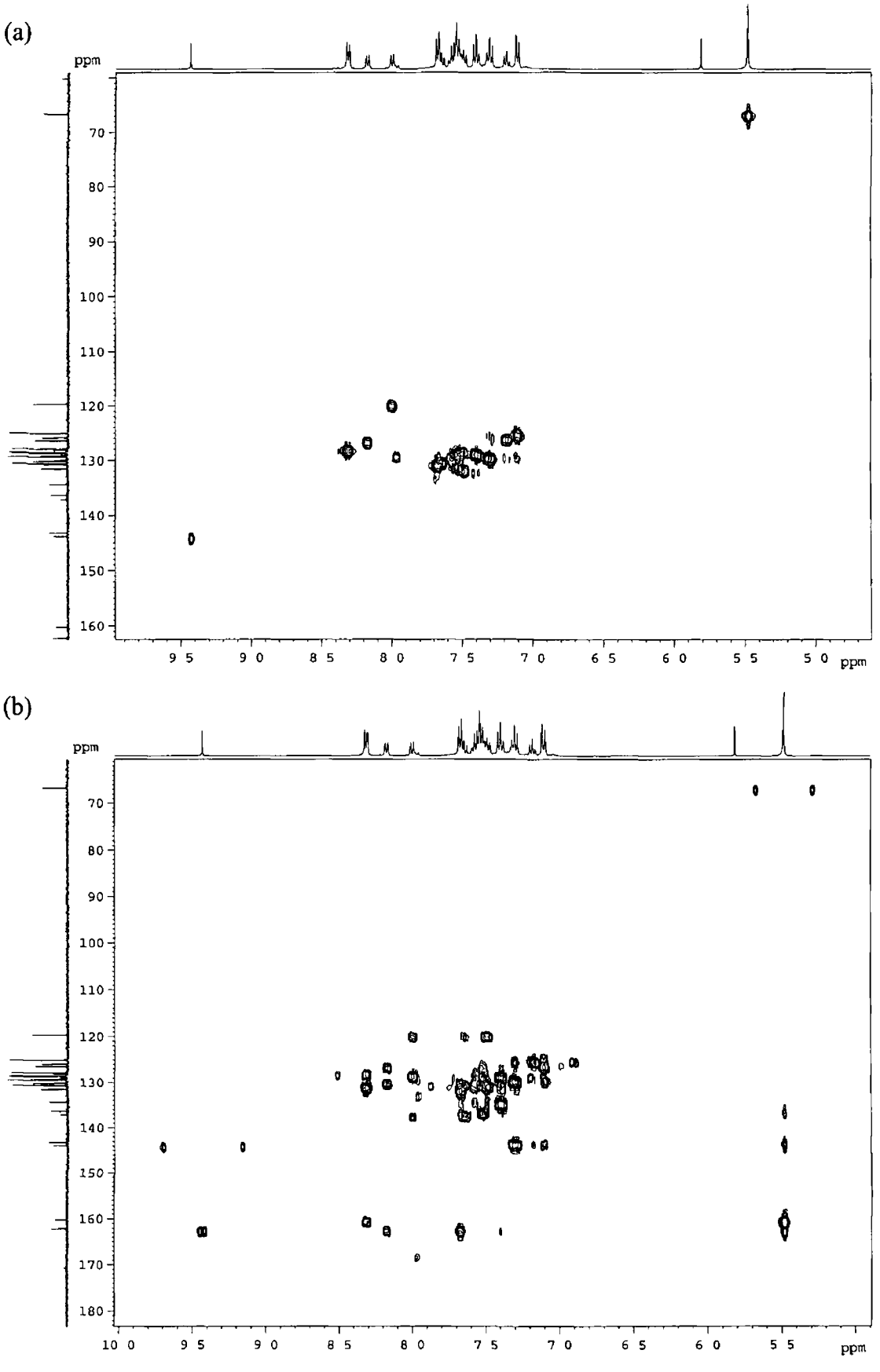
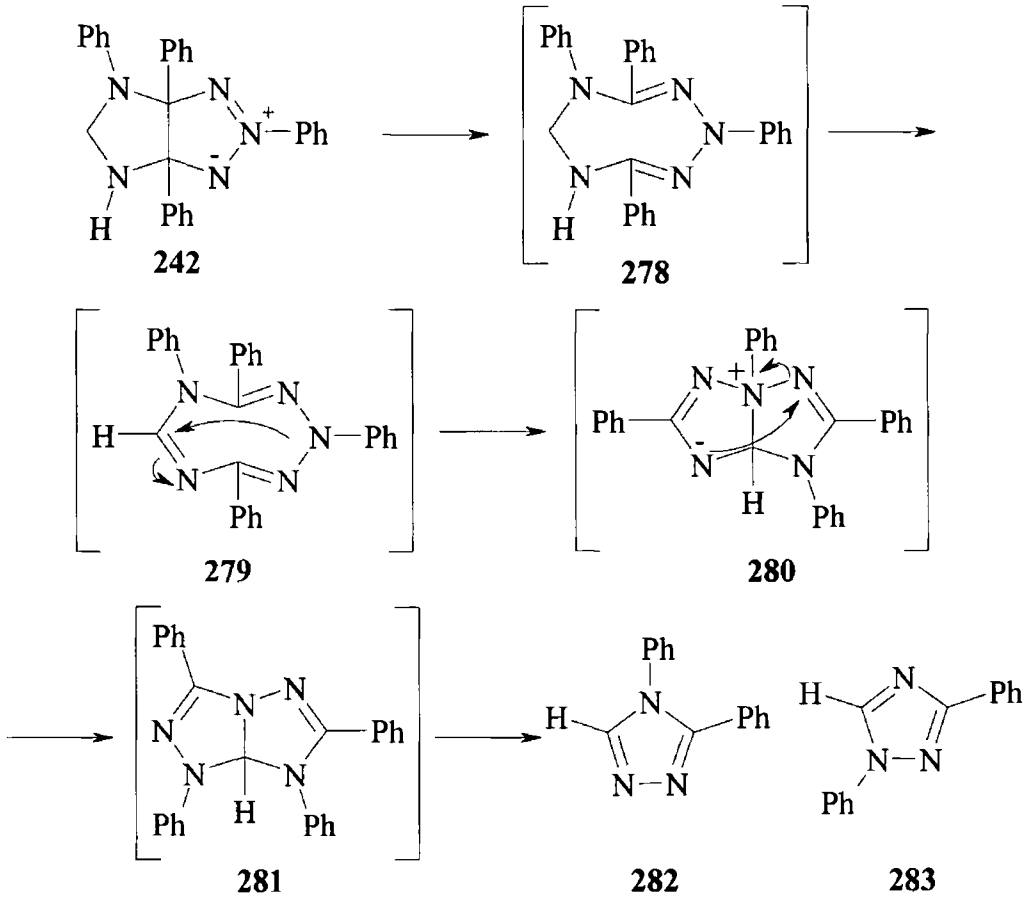



**Figure 3.7** *HMCQ (a) and HMBC (b) spectra of the mixture of products obtained by the photolysis of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole* ***242a***

This identification led to the conclusion that the original isolated product was in fact a mixture of the 1,2,4-triazole (**282** or **283**) and another photoproduct Mass spectrometry confirmed the presence of a diphenyl-1,2,4-triazole with a peak appearing at *m/z* 222 The mechanism of formation of the 1,2,4-triazole is similar to that seen for pyrrolo-1,2,3-triazoles as reported previously by both our group[1] and Butler *et al*[3] (**Scheme 3 17**)

On photolysis of the hexahydroimidazo-1,2,3-triazole, the tetrahydropentazocine **278** is initially formed by disrotatory ring opening However this ring system appears to be susceptible to oxidation by the air and forms the dihydropentazocine **279** The $sp^2$-hybridised C-6 is now electrophilic and is attacked by the nucleophilic N-2, causing transannular ring contraction and subsequent fragmentation of the bicyclic system **281**, to give one of the two 1,2,4-triazoles **282** or **283**



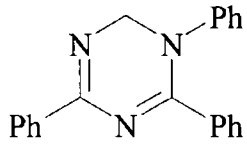

**Scheme 3 17** *Photolysis of hexahydroimidazo-1,2,3-triazoles led to the formation of substituted 1,2,4-triazoles through the initial formation of a pentazocine, subsequent oxidation, transannular ring contraction and fragmentation*

It is impossible to tell from the spectroscopic data which of the two triazoles are present in the mixture A literature search revealed that both of the triazoles had been synthesised previously NMR data for the 1,3-diphenyl-1,2,4-triazole **283** reports that the C-H peak occurs at 8 57ppm in $CDCl_3$ (200MHz spectrometer) and at 8 35ppm when run in $CD_3CN$(60MHz) Our C-H peak occurs at 8 52ppm in $CDCl_3$ and at 8 75ppm in $CD_3CN$ For the 3,4-diphenyl-1,2,4-triazole **282**, the C-H peak is reported to occur at 8 58ppm when run in deuterated acetone and gives a broad signal in the range of 8 28-8 35ppm when run in $CDCl_3$ These results are summarised in **Table 3 2**

| Solvent | 1,3-diphenyl-1,2,4-triazole, 283 | 3,4-diphenyl-1,2,4-triazole, 282 | Photolysis product |
|---|---|---|---|
| $CDCl_3$ | 8 57ppm | 8 28-8 35ppm | 8 52ppm |
| $CD_3CN$ | 8 35ppm | - | 8 75ppm |
| $(CD_3)_2O$ | - | 8 58ppm | 8 98ppm |
| DMSO | - | - | 9 43ppm |

**Table 3 2** *Effects of different solvents on the chemical shift of the –C-H peak and comparisons with the chemical shifts of the C-H peak of the two 1,2,4-triazoles **282** and **283***

As mentioned previously, a mixture of two compounds was obtained from the photolysis of the hexahydroimidazo-1,2,3-triazoles **242** Evidence clearly points to the presence of a diphenyl-1,2,4-triazole in the mixture, however the other molecule is not so easily identified A peak at *m/z* 312 suggests that the starting material has a lost a phenyl ring, two nitrogen atoms and a proton, and the NMR spectra indicate that a $CH_2$ group is present in the mixture Based on this data, we suggest that the other compound in the photolysis mixture is the previously unknown 1,4,6-triphenyl-1,2-dihydro-[1,3,5]triazine **284**

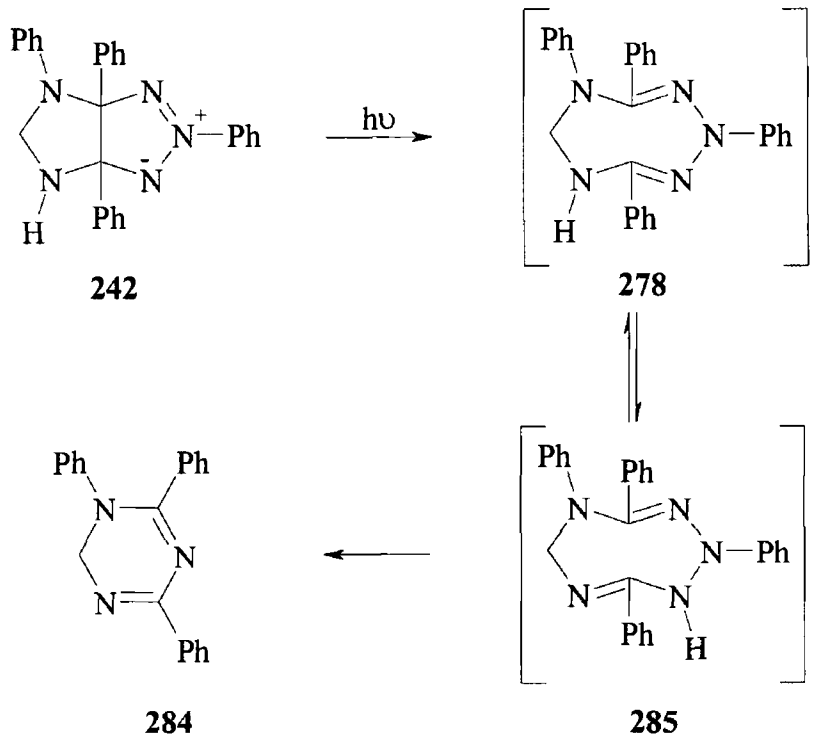



**284**

**Figure 3 8** *1,4,6-Triphenyl-1,2-dihydro-[1,3,5]triazine*

This structure fits all of the spectroscopic data, including the 2D NMR data In the HMQC spectrum there is very clear $^{1}J$ coupling between the protons at 5 48ppm and the carbon at 66 63ppm In the HMBC spectrum, these protons show coupling with five other carbons, probably $^{3}J$ coupling with both of the $sp^2$-hybridised ring carbons, and weaker $^{3}J$ and $^{4}J$ interactions with each of the phenyl rings

A mechanism for the formation of the triazine is tentatively proposed as follows the initial step is the usual photochemically allowed disrotatory ring opening The 2,5,6,7-tetrahydro pentazocine **278** then undergoes tautomerism to the 1,2,5,6-tetrahydro analogue **285** Subsequent fragmentation, with loss of the PhNNH group, and ring closure leads to the 1,3,5-triazine **284**




**Scheme 3 18** *Proposed mechanism for the formation of 1,4,6-triphenyl-1,2-dihydro-[1,3,5]triazine*

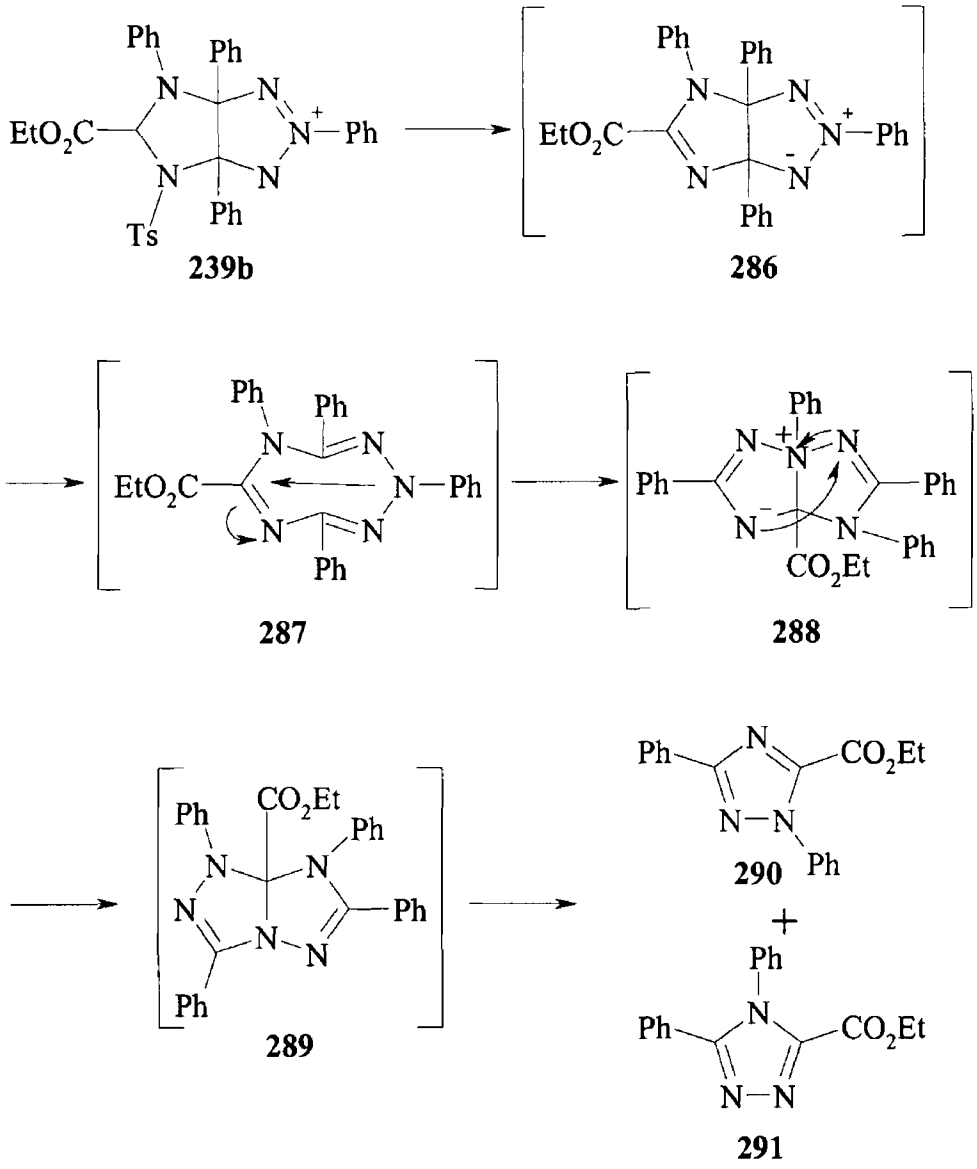
*3 3 2 3 Electron-Withdrawing Substituents at C5*

The degree of saturation at C5, and the substituents on C5 had previously been determined as the key factor in the success of obtaining eight-membered heterocycles by the irradiation of bicyclic precursors

On irradiation of 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a-hexahydroimidazo-[4,5-d]-1,2,3-triazole **239b**, two products were isolated and identified as 1,3-diphenyl-1H-[1,2,4]triazole-5-carboxyhc acid ethyl ester **290** and 4,5-diphenyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester **291**

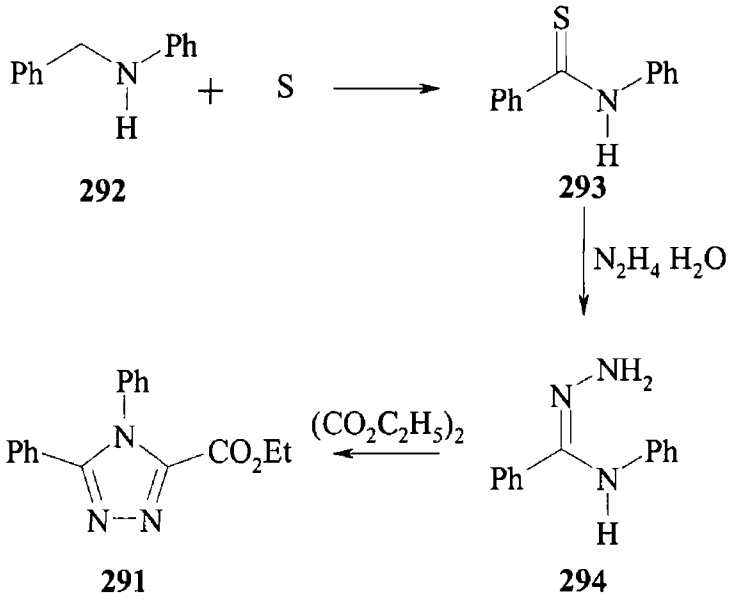
The formation of these molecules in the photolysis reaction can be explained by the initial loss of the tosyl group from N-4, giving an unsaturated C-5 in the bicyclic system **286** The photoinduced cleavage of the tosyl group from both nitrogen[9] and oxygen[10] has been reported, the initial step being a transfer of an electron from an electron donor to the excited *p*-toluensulfonate In our case, the cleavage was not reductive, in that the proton from C-5 was also removed, giving a carbon-nitrogen double bond

The mechanism then proceeds in a similar way to that described previously The disrotatory ring-opening of the bicyclic compound gives the 1,2,3,5,7-pentazocine, **287** Attack of the N-2 lone pair on the electrophilic C-5, followed by rearrangement gives the bicyclic intermediate **289**, which fragments into the two 1,2,4-triazoles (**Scheme 3 19**)



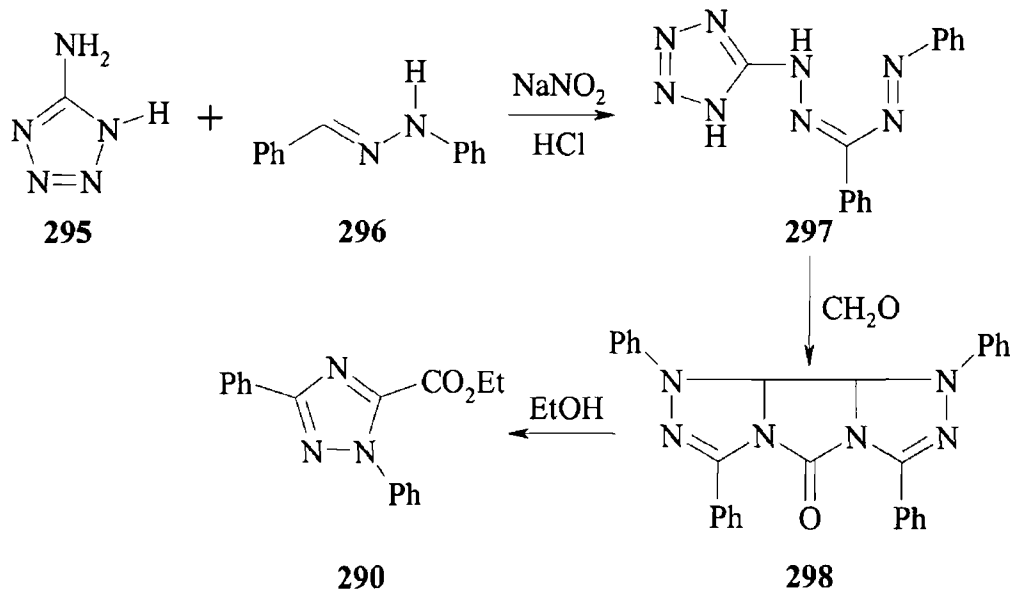
**Scheme 3 19** *Irradiation of substituted imidazo-1,2,3-triazoles results in loss of the tosyl group, followed by electrocyclic ring opening, transannular ring contraction and fragmentation of the resulting molecule, giving two substituted triazoles*

4,5-Diphenyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester has previously been synthesised by the reaction of phenylbenzamidrazone **294** with diethyl oxalate [11] The starting amidrazone is obtained by the treatment of the thiobenzanilide **293** with hydrazine hydrate[12] and the thiobenzanilide is synthesised by the reaction of sulfur with N-phenylbenzylamine **292** [13] This reaction was carried out to prove the compound obtained from the photolysis reaction was the 3,4,5-substituted 1,2,4-triazole **291**



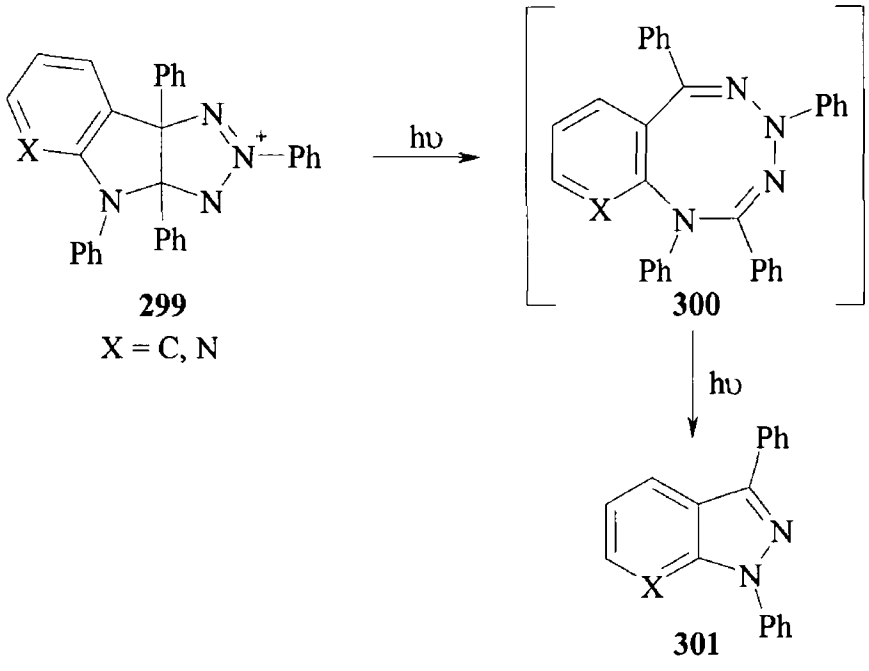

**Scheme 3 20** *Alternative synthesis of 4,5-diphenyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester*

The synthesis of 1,3-diphenyl-1H-[1,2,4]triazole-5-carboxylic acid ethyl ester **290** has also previously been reported [14] To prove that the compound we isolated was the 1,3,5-substituted-1,2,4-triazole, the synthesis was carried out according to the method of Shchipanov and Klyuev [11c] This involved the initial formation of 1,3-diphenyl-5-(5-tetrazolyl)-formazan **297** and it's reaction with formaldehyde in an alkaline solution The resulting 1,3,7,9-tetraphenyl-5-oxo-5H-1,2,4-triazolo-[3',4' 5,1]- imidazo-[4,3-c]-1,2,4-triazole **298** was then refluxed in ethanol which gave the tri-substituted 1,2,4-triazole




**Scheme 3 21** *Alternative synthesis of 1,3-diphenyl-1H-[1,2,4]triazole-5-carboxylic acid ethyl ester*

In unpublished work by our group,[15] this photoreaction has been extended to the adducts of triazolium-N-imide and benzyne and pyridyne **295** The photoreaction then yields 1,3-diaryl-1H-indazoles and 1,3-diaryl-1H-pyrazolo[3,4-b]pyridines




**Scheme 3 22** *Irradiation of tricyclic adducts gives indazoles or pyrazolo-pyridines*

### 3.4 Conclusion

The irradiation of imidazo-1,2,3-triazoles containing a C=O or C=S at the C-5 position failed to yield the required 1,2,3,5,7-pentazocine Instead, a large number of photoproducts were obtained, which proved impossible to separate and identify The reason for the production of so many photoproducts is due to the various photoreactive fragments of the bicyclic molecule The possibility that the pentazocine did form cannot be discounted However it is likely that this molecule, once formed would undergo transannular ring contraction and fragmentation Conclusive proof of this has not been found, although one of the products that was isolated from the photoreactions is possibly a triazolone which would be a product of the ring contraction and fragmentation sequence

Photolysis of hexahydroimidazo-1,2,3-triazole with no substituents at C5 gave an inseparable mixture of two products, believed to be a diphenyl 1,2,4-triazole and a 1,3,5-triazine Because the compounds could not be isolated, these structures have been proposed on the basis of NMR spectroscopic data and mass spectrometry The 1,2,4-triazole is obtained after oxidation of the intermediate pentazocine, transannular ring contraction, rearrangement and fragmentation This is a well known reaction for eight-membered heterocycles The formation of the triazine is unusual, but is also believed to occur through the pentazocine intermediate

Photolysis of hexahydroimidazo-1,2,3-triazoles with carboxylate substituents at the C-5 position yielded two substituted 1,2,4-triazoles The reaction proceeds by the initial loss of the tosyl group from N-4, giving a C=N between N-4 and C-5 The resulting compound then undergoes the known ring opening, transannular ring contraction, rearrangement and fragmentation sequence to give the two 1,2,4-triazoles

**3 5 Future work:**

It is clear from this work that it is not only the degree of saturation of the C-5 atom in the imidazo-1,2,3-triazoles which is important in the photochemistry of these molecules The substituents on this carbon atom also affect the stability of the pentazocine that is formed on irradiation of the bicyclic systems

It is likely that a stable 1,2,3,5,7-pentazocine will be achieved by the irradiation of these systems when the C-5 atom is fully saturated and has two electron-donating groups as substituents These types of systems may be achieved by the use of triacylimino dipolarophiles in the initial 1,3-dipolar cycloaddition If these systems successfully added to the 1,3-dipole, there would be scope to convert these groups into electron donating groups By using triacylimino dipolarophiles the possibility of oxidation of the carbon-nitrogen bond would also be diminished

## 3.6 Experimental

Photochemistry was carried out using

- a 400W medium pressure mercury lamp fitted with a pyrex filter The samples were degassed with nitrogen prior to, and during photolysis
- a white light projector lamp The samples were degassed with nitrogen prior to photolysis

Mass spectrometry was carried out on a Bruker Esquire spectrometer

### *3 6 1 Photochemistry of $sp^2$-C5 Imidazo-1,2,3-Triazoles (122 and 124)*

The typical procedure for the photolysis of imidazo-1,2,3-triazoles derived from triazolium N-imide and aryl isocyanates or aryl isothiocyanates is given below

*Photolysis of 2,3a,4,6,6a-pentaphenyl-5-oxo-hexahydroimidazo-[4,5-d]-1,2,3-triazole (122a)*

2,3a,4,6,6a-Pentaphenyl-5-oxo-hexahydroimidazo-[4,5-d]-1,2,3-triazole (500mg, 0 98mmol) was dissolved in 200$cm^3$ of dry dichloromethane and degassed with nitrogen for 30 minutes It was irradiated with a medium pressure mercury lamp with constant bubbling of nitrogen Samples were taken every 30 minutes and analysed by TLC (5 1 pet ether 40-60 ethyl acetate) Irradiation times ranged from 1-4 hours The solvent was then removed under vacuum and the residue separated on a silica gel column or silica preparative TLC plates, using the same eluent as used for TLC

One product was isolated from the photolysis of 2,3a,6,6a-tetraphenyl-4-(4-methoxyphenyl)-5-oxo-hexahydroimidazo-[4,5-d]-1,2,3-triazole Based on the $^1$H NMR data, we propose that this compound is

*4,5-bis(4-chlorophenyl)-1-(4-methoxyphenyl)-3-phenyl-1,3-dihydro-imidazolo-2-one (273)*

**$^1$H (DMSO-$d_6$) (ppm)**· 3 69 (3H, s) (OC**H**$_3$), 6 47 (2H, d, J=7 4Hz), 6 67 (2H, d, J=8 88Hz), 6 78 (2H, d, J=8 84Hz), 7 00 (1H, t, J=7 36, 7 4Hz), 7 12 (2H, t, J=7 88), 7 48 (2H, d, J=8 84Hz), 7 54 (2H, d, J=8 84Hz), 7 74 (2H, d, J=8 84Hz), 7 79 (2H, d, 8 36Hz)

### *3 6 2. Photochemistry of $sp^3$-C5 Imidazo-1,2,3-Triazoles*

#### *3 6 2 1 Photochemistry of 2,3a,4,6a-tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (242)*

1 2,3a,4,6a-Tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole (200mg, mmol) was dissolved in 80cm$^3$ of HPLC grade dichloromethane and degassed with argon The solution was then irradiated with white light for 20 hours TLC analysis showed the formation of one major product The solvent was removed under vacuum and the residue was separated on a silica gel column (5 2 pet ether ethyl acetate) The major product was an oily yellow substance, which was difficult to solidify This has been identified as an inseparable mixture of two compounds

**$^1$H NMR (DMSO-$d_6$) (ppm):** 5 48 (2H, s) ($CH_2$), 7 11 (2H, d, J=7 6Hz), 7 18 (1H, t, J=7 6Hz), 7 30 (2H, t, J=7 6Hz), 7 40 (2H, t, J=8Hz), 7 47-7 59 (6H, m), 7 63-7 68 (3H, m), 7 99 (1H, d, J=7 6Hz), 8 17 (1H, d, J=6 8Hz), 8 31 (2H, d, J=6 0Hz) (all aromatic CH), 9 43 (1/2H, s) (C-H)

**$^{13}$C NMR (DMSO-$d_6$) (ppm).** 66 63 ($CH_2$), 119 64, 125 03, 125 91, 126 40, 127 89, 128 15, 128 51, 128 61, 128 73, 128 99, 129 23, 129 34, 129 96, 130 17, 130 56, 130 74, 130 79, 131 55, 134 37, 136 35, 137 13, 143 21, 143 79 (triazole C-H), 160 21, 162 78, 162 21 (triazole C-Ph)

**M S data (m/z).** 312(Cmpd **284**), 222 (Cmpd **282** or **283**), 197, 180, 106

2 2,3a,4,6a-Tetraphenyl-1,3a,4,5,6a-hexahydro-imidazo-[4,5-d]-1,2,3-triazole was irradiated as above, but for a period of 30 hours Separation of the products gave an orange solid which was identified as a 1,2,4-triazole **282** or **283**

**$^1$H NMR (DMSO-$d_6$) (ppm)** 7 49-7 66 (6H, m), 7 99 (2H, d, J=7 6Hz), 8 16 (2H, d, J=6 8Hz) (all aromatic protons), 9 42 (1H, s) (C-H)

**$^{13}$C NMR (DMSO-$d_6$) (ppm)** 119 64, 126 40, 128 16, 129 23, 129 96, 130 17, 130 73, 137 12 (all aromatic C and CH), 143 81 (C-H), 162 20 (C-Ph)

*3 6 2 2 Photochemistry of 2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6a hexahydroimidazo[4,5-d]-1,2,3-triazole (**239b**)*

2,3a,6,6a-tetraphenyl-4-tosyl-5-ethylcarboxylate-3,3a,4,5,6,6ahexahydroimidazo[4,5-d]-1,2,3-triazole (200mg, 0 311mmol) was dissolved in 200cm$^3$ of dry dichloromethane and degassed with nitrogen for 30minutes It was then subjected to irradiation with a medium pressure mercury lamp for a total of 3 hours The solvent was removed and the residue was loaded onto a silica prep TLC plate and developed with 5 1 pet ether ethyl acetate Two products were isolated and identified as

*1,3-diphenyl-1H-[1,2,4]triazole-5-carboxylic acid ethyl ester (**290**)*

**$^1$H NMR (dmso-$d_6$)(ppm)** 1 24 (3H, t, J=7 2Hz) ($OCH_2\mathbf{CH_3}$), 4 33 (2H, q, J=7 2Hz) ($OCH_2CH_3$), 7 58 (2H, d, J=7 2Hz), 7 61-7 64 (4H, m), 7 69-7 72 (2H, m), 8 14 (2H, d, J=6Hz) (all aromatic CH)

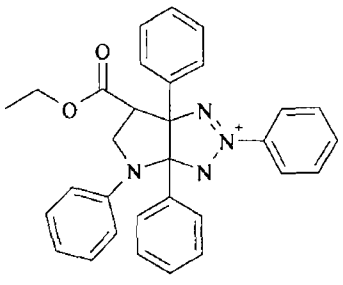
**$^{13}$C NMR (dmso-$d_6$)(ppm).** 14 02 ($OCH_2CH_3$), 62 43($OCH_2CH_3$), 126 27, 126 43, 127 99, 128 96, 129 23, 129 37, 129 95, 130 37, 138 32, 157 17, 161 05 (C3, C5, aromatic C and CH)

*and*

*4,5-diphenyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester (**291**)*

**$^1$H NMR (dmso-$d_6$)(ppm)** 1 15 (3H, t, J=6 8Hz) ($OCH_2\mathbf{CH_3}$), 4 19 (2H, q, J=6 8Hz) ($OCH_2CH_3$), 7 28-7 37 (10H, m) (aromatic protons)

*3 6 2 3 Synthesis of 6-ethoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (1b)*



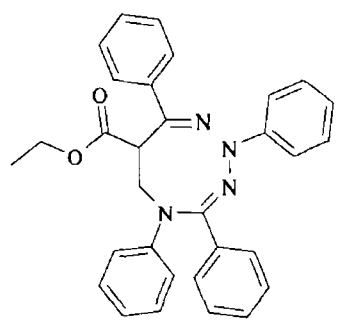
1,2-bis(phenylazo)stilbene (0 5g, 0 0013mol) and ethyl acrylate (0 5g, 0060mol) were stirred under reflux in 30cm$^3$ of dry acetone for 3 hours The solvent was removed under vacuum and the residue was recrystallised from ethanol, yielding 0 36g (0 0007mol, 54%) of the yellow compound

**M.P** 200°C (lit 201-203°C)[1]

**$^1$H NMR (DMSO-d$^6$) (ppm).** 0 66 (3H, t, J=7 2Hz) ($OCH_2CH_3$), 3 73-3 88 (4H, m) ($OCH_2CH_3$, C-6-**H**, C-5-**H**), 4 36 (1H, m) (C-5-**H**), 6 65 (1H, t, J=7 2Hz), 6 74 (2H, d, J=6 8Hz), 6 88-7 00 (8H, m), 7 07-7 11 (4H, m), 7 68-7 74 (3H, m), 8 33 (2H, d, J=7 2Hz) (all aromatic **CH**)

**$^{13}$C NMR (DMSO-d$^6$) (ppm)** 13 66 ($OCH_2CH_3$), 48 32 (**C**-5), 57 21 (**C**-6), 60 33 ($OCH_2CH_3$), 89 39, 101 08 (**C**-3a, **C**-6a), 116 27, 117 68, 122 97, 127 14, 127 19, 127 35, 127 44, 127 70, 127 85, 128 63, 129 81, 132 33, 137 53, 137 82, 140 76, 145 42 (all aromatic **C** and **CH**), 170 10 (**C**=O)

*3 6 2 4 Synthesis of 7-ethyoxycarbonyl-2,4,5,8-tetraphenyl-2,3,6,7-tetrahydro-1,2,3,5-tetrazocine (2b)*



6-ethoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (250mg, 0 511mmol) was dissolved in 80cm$^3$ of dry dichloromethane and degassed with nitrogen The solution was irradiated with white light for a total of 20 hours TLC analysis showed the formation of one new compound This was separated on a silica gel column (5 2 pet ether 40-60 ethyl acetate), yielding 150mg (0 307mmol, 60%) of the yellow tetrazocine

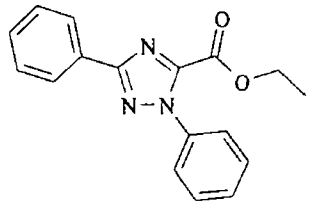
**M.p** 101-102°C (lit 101-103°C)[2]

**$^1$H NMR (DMSO-d$^6$) (ppm).** 0 96 (3H, t, J=6 8, 7 2Hz) ($OCH_2CH_3$), 3 68 (1H, m), 3 88 (1H, m) ($OCH_2CH_3$), 4 11 (1H, dd J=7 2, 14 4Hz) (C-7-**H**), 4 76 (2H, m) (C-6-**H**), 6 69 (1H, t, J=7 2Hz), 6 80 (2H, d), 6 94-7 02 (3H, m), 7 17 (2H, d, J=8 0Hz), 7 23 (2H,

t, J=8Hz), 7 28-7 37 (6H, m), 7 44 (2H, d, J= 7 2Hz), 7 60 (2H, d, J=7 2Hz) (all aromatic CH)

**$^{13}$C NMR (DMSO-d$^6$) (ppm)** 13 94 ($OCH_2CH_3$), 47 80, 48 49 (C-7, C-6), 61 19 ($OCH_2CH_3$), 116 68, 120 74, 122 11, 122 41, 127 81, 128 31, 128 49, 128 59, 129 07, 129 20, 130 23, 130 99, 135 38, 136 16, 143 26, 150 12 (all aromatic C and CH), 154 24 (C-8), 168 90 (C=O), 176 84 (C-4)

*3 6 2 5 Synthesis of 1,3-diphenyl-1H-[1,2,4]triazole-5-carboxylic acid ethyl ester (290)*



Benzaldehyde (3 18g) and phenylhydrazine (3 57g, 10%excess) were stirred under reflux in glacial acetic acid for 2 hours The solution was cooled and the resulting pale yellow needle-like crystals of benzaldehyde phenylhydrazone were removed by filtration (4g)

5-Aminotetrazole monohydrate (1 55g) in 10cm$^3$ of 20% NaOH was added to sodium nitrite ($NaNO_2$) in 10cm$^3$ of water, containing 15g of ice The mixture was cooled to 0°C and poured onto a stirred mixture of 8cm$^3$ of conc HCl in 50g of ice The mixture was stirred for 20 minutes at 0°C and then sodium acetate trihydrate (10g) was added

Meanwhile benzaldehyde phenylhydrazone (2 93g) was dissolved in 400cm$^3$ of ethanol and cooled to 0°C The diazonium salt solution was added to the hydrazone solution with constant stirring, forming a red solution This solution was cooled overnight at –4°C 200cm$^3$ of water was then added and the solution was left to stand for a further 4 hours, after which time it was filtered, yielding the formazan as a very dark red powder in low yield (0 25g)

A solution of formazan (3g) and 37% formaldehyde (2cm$^3$) in 90cm$^3$ of 1% sodium hydroxide were stirred under argon for 24 hours The mixture was filtered and the precipitate washed with water, dried and recrystallised from ethanol, yielding 0 25g of **298**

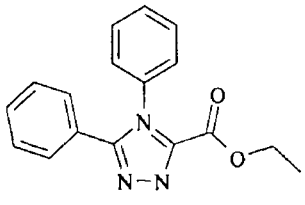
**298** was stirred under reflux in 15cm$^3$ of ethanol for 2 hours The solvent was removed under vacuum and the residue was recrystallised from heptane, giving the triazole

**M.p.** 112-113°C (lit 114 5-115 5°C)[14c]

**$^1$H NMR (dmso-$d_6$)(ppm)** 1 27 (3H, t, J=7 2Hz) ($OCH_2CH_3$), 4 30 (2H, q, J=7 2Hz) ($OCH_2CH_3$), 7 57 (2H, d, J=7 2Hz), 7 62-7 65 (4H, m), 7 72-7 73 (2H, m), 8 13 (2H, d, J=6Hz) (all aromatic CH)

**$^{13}$C NMR (dmso-$d_6$)(ppm)** 14 02 ($OCH_2CH_3$), 62 43($OCH_2CH_3$), 126 27, 126 43, 127 99, 128 96, 129 23, 129 37, 129 95, 130 37, 138 32, 157 17, 161 05 (C3, C5, aromatic C and CH)

*3 6 2 6 Synthesis of 4,5-diphenyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester (291)*



N-Phenylbenzylamine (30g) and sulfur (8 6g) were heated under reflux in pyridine (16 5cm$^3$) for 24 hours, giving a red solution This was cooled slightly and added to 670cm$^3$ of water containing 50cm$^3$ of conc HCl A red oil fell to the bottom and was removed by filtration and was washed with a little water The oil solidified on standing but melted on heating and was transferred to a separating funnel, to which 660cm$^3$ of 2 5% NaOH was added The mixture was shaken well and then filtered The alkaline filtrate was neutralised with conc HCl and the required yellow thiobenzanilide fell out of solution and was removed by filtration

Thiobenzanilide (3g) was stirred under reflux in 25cm$^3$ of ethanol with hydrazine monohydrate (3cm$^3$) until the evolution of $H_2S$ had stopped (approx 2 5 hours) Water was added to the mixture and left standing overnight after which time a pink solid had formed This was removed by filtration and on standing the required amidrazone fell out of the ethanohc filtrate

Amidrazone (0 15g) and diethyl oxalate (0 5cm$^3$) was stirred under reflux in 10cm$^3$ of ethanol for 2 hours The ethanol was reduced and on addition of pet ether 40-60 the triazole fell out of solution

**M p** 151°C (lit 151-152°C)[11]

**$^1$H NMR (DMSO-$d_6$) (ppm)** 1 12 (3H, t, J=6 8Hz) ($OCH_2CH_3$), 4 20 (2H, q, J=7 2Hz) ($OCH_2CH_3$), 7 35-7 52 (10H, m) (all aromatic CH)

**$^{13}$C NMR (DMSO-$d_6$) (ppm)** 13 99 ($OCH_2CH_3$), 61 95($OCH_2CH_3$), 126 36, 128 13, 128 88, 129 05, 129 53, 130 03, 130 62, 135 16, 146 74, 156 05 (C3, C5, and aromatic C), 156 99 (C=O)

## 3 7 References.


1 Byrne, C PhD Thesis, D C U **1996**

2 Byrne, C , Draper, S M , James, J P Long, C *J Chem Res* **1995**, 2501

3 Butler, R N , Colleran, D M , O'Shea, D F , Cunningham, D , McArdle, P , Gillan, A M *J Chem Soc Perkin Trans 1* **1993**, 2757

4 Woodward, R B , Hoffmann, R *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, **1970**

5 Leuenberger, C , Hoesch, L , Dreiding, A S *J Chem Soc Chem Commun* **1980**, 1197

6 Kaupp, G , Dohle, J A *Angew Chem Int Ed Engl* **1985**, *24*, 341

7 Wang, S Y , Apicella, M , Stone, B S *J Am Chem Soc* **1956**, *78*, 4180

8 Moore, J A , Anet, F A L *Comprehensive Heterocyclic Chemistry*, Vol 7 653-707

9 a) Hamada, T , Nishida, A , Yonemitsu, O *J Am Chem Soc* **1986**, *108*, 140
b) Li, C , Fuchs, P L *Tetrahedron Lett* **1993**, *34*, 1855
c)Art, J F , Kestemont, J P , Soumillion, J P *Tetrahedron Lett* **1991**, *32*, 1425

10 a) Nishida, A , Hamada, T , Yonemitsu, O J *Org Chem* **1988**, *53*, 3387
b) Binkley, R W , Koholic, D J *J Org Chem* **1989**, *54*, 3577

11 a) Spassov, A , Demirov, G *Chem Ber* **1969**, *102*, 2530
b) Reimlinger, H , Lingier, W R F , Vandewalle, J J M *Chem Ber* **1971**, *104*, 639

12 a) Katritzky, A R , Nie, P-L , Dondoni, A , Tassi, D *J Chem Soc Perkin Trans 1* **1979**, 1961
b) Davidson, J S *Synthesis*, **1979**, 359

13 Hodosan, F , Serban, N *Bull Soc Chim Fr* **1959**, 507

14 a) Huisgen, R , Grashey, R , Seidel, M , Wallbillich, G , Knupfer, H , Schmidt, R *Justus, Liebigs Ann Chem* **1962**, 105
b) Sauer, J , Mayer, K K *Tetrahedron Lett* **1968**, *3*, 325
c) Shchipanov, V P , Klyuev, N A *Chem Heterocycl Compd (Engl Transl)* **1981**, *17*, 516
d) Tomilenko, E I , Ogoiko, P I , Staninets, V I *Chem Heterocycl Compd (Engl Transl)* **1987**, *23*, 1226

15 Healy, C Ph D Thesis, DCU, pending