Generation and reactions of aryl and alkyl thionitroso compounds

Julie N. Heaton

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GENERATION AND REACTIONS OF ARYL AND ALKYL THIONITROSO COMPOUNDS

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A Thesis submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Durham.

November 1992

Statement of Copyright

Declaration

The work described in this thesis was carried out in the Department of Chemistry at the university of Durham between October 1989 and September 1992. All the work is my own, unless otherwise stated, and it has not been submitted previously for a degree at this or any other university.

Dedicated to Mum, Dad and Becky.

Acknowledgements

I would particularly like to thank my supervisor Dr. Martin Bryce for his support and ideas throughout the last three years.

I would like to thank Shell, Sittingbourne for funding the work through an SERC-CASE award. Thank you to my industrial supervisors, Dr. Martin Anderson and Dr. Ernie Haddock, for useful ideas and comments, and particularly to Martin for supervising my work while I was at Sittingbourne. Thank you to everyone in SCP 1 who helped me during the time I spent at Shell and for making me feel very welcome.

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Finally I would like to thank everyone else in the department, especially Steve, who have helped in so many ways, even if it was just long chats over coffee.

Abstract

Transient thionitrosoarenes (102) with *para* substituents have been generated from *N*-(arylaminothio)-phthalimide derivatives (101) and intercepted with chloroprene and piperylene to give regioisomeric Diels-Alder adducts. Reaction of thionitrosoarenes (102) with 1-methylcyclohexene, α-pinene and β-pinene gave sulphenamides. Sulphenamides (110) and(123) have been reacted with 2,6-difluorobenzoylisocyanate. Heteroaryl thionitroso compounds have been prepared.

Thionitrosoarenes with an *ortho* substituent have been generated *via* two different routes and trapped with 2,3-dimethyl-1,3-butadiene to give mixtures of Diels-Alder and ene adducts; the ene adduct was the major isomer for each system. Thionitrosoarene (159b) was generated from 3-aminobenzisothiazole (157b) using lead tetraacetate and was intercepted with 2,3-dimethyl-1,3-butadiene to give Diels-Alder (160) and ene (161) adducts.

Thionitrosoalkanes have been generated using two different routes and trapped with 2,3-dimethyl-1,3-butadiene to give Diels-Alder and ene adducts.

CONTENTS

CHAPTER 1 INTRODUCTION 1

1.1 Introduction 2

1.2 Thionitrosoamines and Dithionitrites 2

1.3 Thionitrosoarenes 9

1.3.1 Generation of Thionitrosoarenes from Sulphenamides 9

1.3.2 Thionitrosoarenes from Benzisothiazoles and Related Compounds 16

1.3.3 Other Synthetic Approaches to Thionitrosoarenes 21

1.4 Thionitrosoalkanes 23

1.5 Thionitrosoformates and Thionitrososulphonates 26

1.6 Summary 31

CHAPTER 2 GENERATION AND REACTIONS OF ARYL AND HETEROARYL THIONITROSO COMPOUNDS 32

2.1 Regiochemistry of Diels-Alder Additions to Thionitrosoarenes 33

2.1.1 Introduction 33

2.1.2 Reaction of Thionitrosoarenes with Chloroprene 35

2.1.3 Reaction of Thionitrosoarenes with Piperylene 41

2.1.4 Discussion 43

2.2 Ene Reactions of Thionitrosoarenes 44

2.2.1 Introduction 44

2.2.2 Reaction with 1-Methylcyclohexene 46

2.2.3 Reaction with α-Pinene 47

2.2.4 Reaction with β-Pinene 47

2.2.5 Discussion 48

2.3 Effect of Solvent on the Ratio of Diels-Alder : Ene Adducts of Thionitrosoarenes 51

2.3.1 Introduction 51

2.3.2 Results and Discussion 52

2.4 Catalysis of the Reactions of Thionitrosoarenes 54

2.4.1 Introduction 54

2.4.2 Results and Discussion 54

2.5 Derivatisation of Ene Adducts with Benzoylisocyanates 55

2.5.1 Introduction 55

2.5.2 Reaction of Ene Adducts with Benzoylisocyanates 56

2.5.3 Purification of Isomer Mixtures Using Benzoylisocyanate Derivatisation 57

2.6 Electron Deficient Thionitroso Compounds 59

2.6.1 Introduction 59

2.6.2 2-Thionitrosopyridine Derivatives 60

2.6.3 2-Thionitrosopyrazine Derivatives 64

2.6.4 2-Thionitrosothiazole Derivatives 64

2.6.5 Thionitrosopentafluorobenzene 66

2.7 Summary 66

CHAPTER 3 ORTHO-SUBSTITUTED THIONITROSOARENES 68

3.1 Ortho-Substituted Thionitrosoarenes from Phthalimide Precursors 69

3.1.1 Introduction 69

3.1.2 Preparation and Reactions of New Thionitrosoarenes 69

3.1.3 Effect of the Position of the Substituent on the Ratio of Diels-Alder to Ene Adducts Formed with Thionitrosoarenes 73

3.2 Generation of Thionitrosoarenes from 3-Azido-2,1-Benzisothiazoles 77

3.2.1 Introduction 77

3.2.2 Reactions of Thionitrosoarenes Generated From 3-Azido-2,1-Benzisothiazoles (158) 79

3.2.3 Other Reactions of Thionitroso Compounds Generated From 3-Azido-2,1-Benzisothiazoles 85

3.3 Mechanism of 3-Azido-2,1-Benzisothiazole Fragmentation 88

3.3.1 Introduction 88

3.3.2 Results and Discussion 89

CHAPTER 4 GENERATION AND REACTIONS OF THIONITROSOALKANES 94

4.1 Introduction 95

4.2 Oxaziridine Route to Thionitrosoalkanes 96

4.2.1 Generation and Reaction of Thionitrosoalkanes with 2,3-Dimethyl-1,3-Butadiene 96

4.2.2 Regioselectivity of Diels-Alder Reactions of Thionitrosoalkanes 99

4.3 Thionitrosoalkanes Generated from *N*-Chlorothio-*N*-Alkylamines 102

4.3.1 Introduction 102

4.3.2 Generation and Reactions of Thionitrosoalkanes 102

4.4 Summary 107

CHAPTER 5 EXPERIMENTAL 108

5.1 General Methods 109

5.2 Experimental Procedures for Chapter 2 110

5.2.1 Experimental for Section 2.1 110

5.2.2 Experimental for Section 2.2 116

5.2.3 Experimental for Section 2.3 119

5.2.5 Experimental for Section 2.5 123

5.2.6 Experimental for Section 2.6 126

5.3 Experimental Procedures for Chapter 3 130

5.3.1 Experimental for Section 3.1 130

5.3.2 Experimental for Section 3.2 138

5.3.3 Experimental for Section 3.3 143

5.4 Experimental Procedures for Chapter 4 144

5.4.2 Experimental for Section 4.2 144

5.4.3 Experimental for Section 4.3 150

REFERENCES 152

APPENDICES: COLLOQUIA, CONFERENCES, PUBLICATIONS. 161

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Thionitroso compounds (1) are the sulphur analogues of nitroso compounds (2). Although organic nitroso compounds (2) and the related sulphinylamines(3) and sulphur diimides (4) have been widely studied and their chemistry reviewed,[1-3] organic thionitroso compounds are relatively unknown. Compounds (1) are highly reactive, evidence for their formation coming from trapping reactions and isolation under special conditions. In this respect the reactivity of the thionitroso compounds (1) closely resembles that of chalcogeno aldehydes (5).[4]

$R-N=S$ (1)

$R-N=O$ (2)

$R-N=S=O$ (3)

$R-N=S=N-R$ (4)

$RCH=X$ (5)
X=S, Se, Te

This introduction will discuss the preparation and reactions of organic thionitroso compounds according to the nature of the substituent group, R.

1.2 THIONITROSOAMINES AND DITHIONITRITES

Thionitroso compounds were first reported in 1966 by Middleton.[5] He chose to prepare the *N*-thionitrosoamines (6) as these were expected to be amongst the most stable thionitroso compounds because of resonance stabilisation.

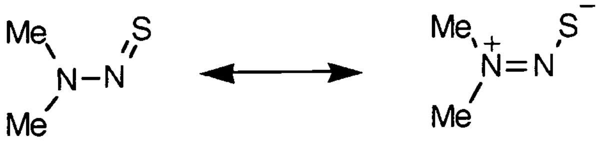
Compounds (6a-c) were prepared in low yields by stirring the corresponding 1,1-dialkylhydrazines with a suspension of elemental sulphur in ether for six days. Compounds (6a) and (6b) were also prepared by reduction of the *N*-sulphinylhydrazines (R_2N-N=S=O) with lithium aluminium hydride in ether. The products were obtained in low yields, mainly because the *N*-thionitrosoamines (6a-b) were reduced to the hydrazine by lithium aluminium hydride in a competing reaction. This reaction provides evidence for the compounds (6) having the proposed structure and not the isomeric structure R_2N-S≡N. Compound (6a) was obtained as a deep purple crystalline solid. (M. pt. 20-21°C). Compounds (6b) and (6c) were not obtained pure due to their lack of crystallinity.

$R_2N-N=S$

(6)

(a) R=Me
(b) R_2=-$(CH_2)_5$-
(c) R_2=-$(CH_2)_6$-
(d) R=Ph

N-thionitroso dimethylamine (6a) was unstable and decomposed to give yellow products that appeared to contain sulphur, dimethyl sulphide and azides, only at low temperatures (*ca.* < -30°C) or in dilute solution in non-polar solvent was (6a) stable. The decomposition was accelerated in acidic conditions. Bases such as pyridine, triphenylphosphine and even sodium hydroxide did not greatly increase the rate of decomposition. The absence of reaction with bases was unexpected and provides evidence for a major contribution from the dipolar resonance form (6a').

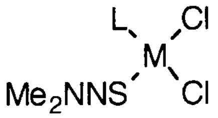


(6a) (6a')

Additional evidence for the importance of the dipolar resonance form (6a') comes from the ^{1}H NMR data. Two singlets were observed in the ^{1}H

NMR spectrum for the methyl groups. The chemical shift difference between the two peaks varied with solvent (*e.g.* 23 Hz in D_2O, 30 Hz in CCl_4) and also decreased at higher temperatures. These results indicate that the two methyl groups are non-equivalent with respect to sulphur, which can be explained by a large contribution from the planar canonical form (6a'). The ultraviolet-visible spectra of (6a) showed a large hypsochromic shift for the band assigned to the $n \rightarrow \pi^*$ transition on going from cyclohexane to ethanol. This is evidence for extensive hydrogen bonding in ethanol[6] and is a further indication that (6a') makes an important contribution to the structure of (6a).

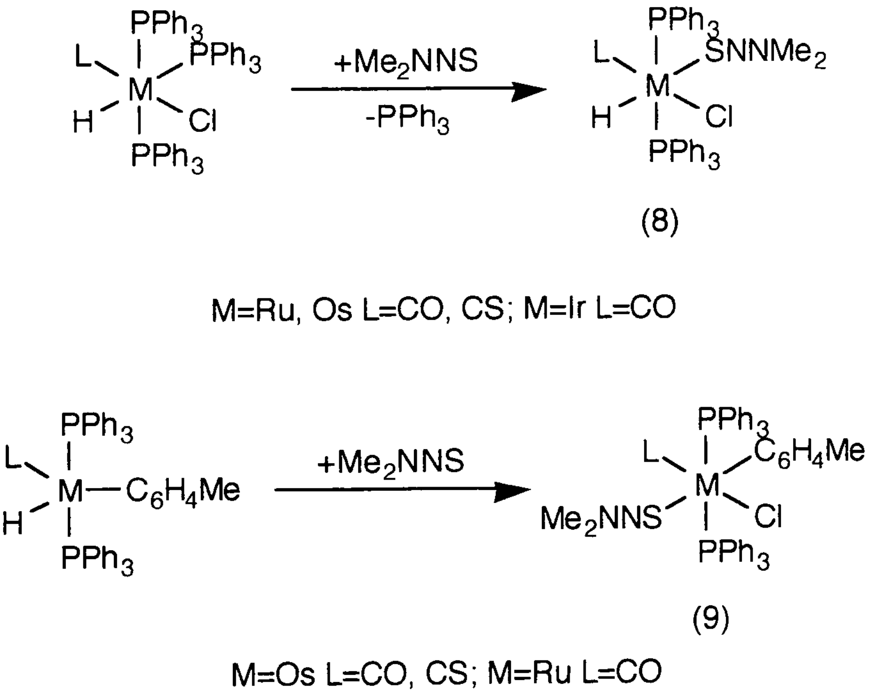
The thionitrosoamine (6d) was prepared by Roesky *et al* [7] by the action of sulphur monochloride on 1,1-diphenylhydrazine at -20°C in the presence of triethylamine. Triethylamine was necessary to remove the HCl produced in the reaction as the resulting thionitrosoamine is acid sensitive. Compounds (6a) and (6d) formed stable complexes with chromium pentacarbonyl of the type $R_2NNSCr(CO)_5$.[7,8] Crystal structures were obtained for both of these complexes.



(7)

M=Pd; L=Me_2NNS, PPh_3, *p*-tolyl, P(*o*-tolyl)$_3$, $AsPh_3$, $SbPh_3$
M=Pt; L=PPh_3, (*p*-tolyl)PPh_2

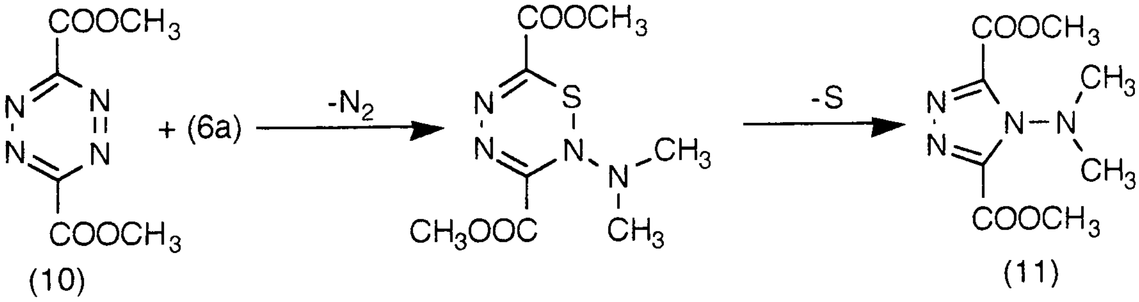
Complexes (7) with palladium and platinum have been prepared by the reaction of M(diene)Cl_2 (diene = 1,5-cyclooctadiene, norbornadiene, 1,3,5,7- cyclooctatetraene, dicyclopentadiene) with (6a) to give $M(MeNNS)_2Cl_2$.[9] One of the *N*-thionitrosoamine ligands was subsequently displaced to form the other complexes. Herberhold and Hill have made ruthenium, osmium and iridium complexes (8) and (9) containing thionitrosodimethylamine.[10] These reactions are summarised in Scheme 1.1.



Scheme 1.1

Studies of the above complexes (7-9) gave useful information about the structure of *N*-thionitrosoamine (6a) and provided further evidence for there being a large contribution from the resonance structure (6a'). X-ray crystallography and IR evidence showed that the *N*-thionitrosoamine ligand was bonded to the metal through sulphur in each case indicating a large electron density on sulphur . The N-N bond is shortened as a result of double bond character. In the ^1H NMR spectra obtained for $M(Me_2NNS)($*p* -tolyl $PPh_2)Cl_2$ where M=Pd or Pt the methyl groups of the *N*-thionitrosoamine ligand are inequivalent as a result of restricted rotation about the N-N bond.

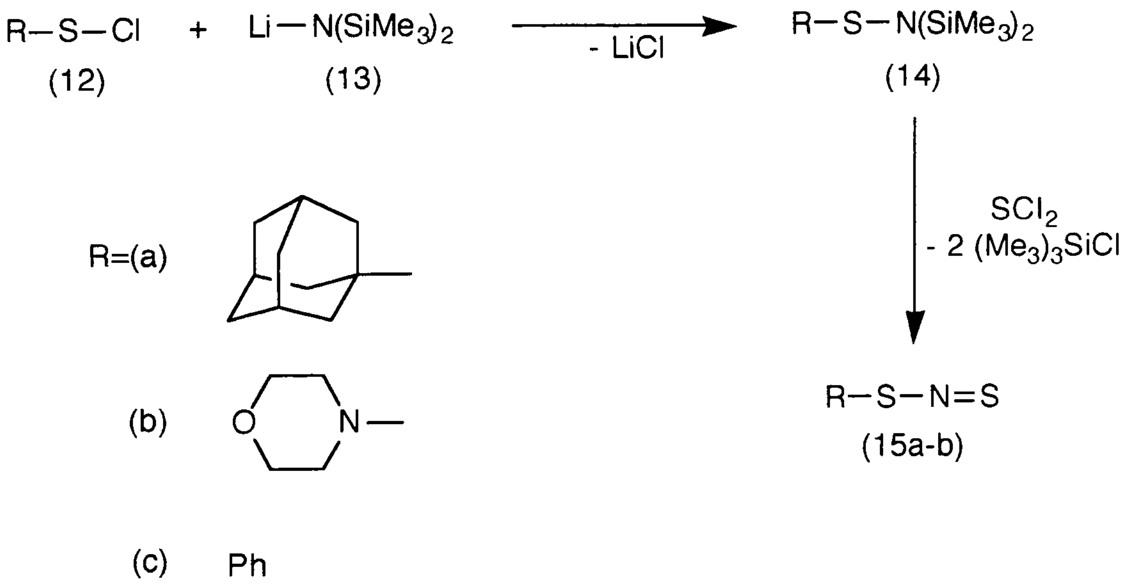
N-Thionitrosoamines are, therefore not true thionitroso compounds. Despite this, compound (6a) will still react as a 2π component in an inverse electron demand Diels-Alder reaction with tetrazine derivative (10) with loss of nitrogen and sulphur to yield triazole (11) (Scheme 1.2).[11] This is the only example of an *N*-thionitrosoamine reacting in a Diels-Alder reaction.



Scheme 1.2

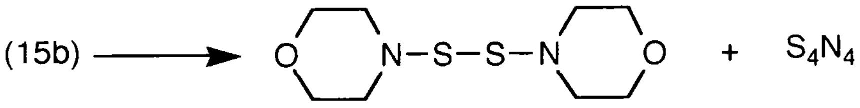
Quantum mechanical calculations[12-14] show that as the substituent group on nitrogen becomes more electron donating the multiplicity of the N=S bond decreases with respect to H-N=S and there is an increase in the negative charge on sulphur. This is probably because of the delocalisation of electron density over three centres. An electron donating group on nitrogen also stabilises the molecule with respect to radical anion formation and lowers reactivity towards nucleophiles. Therefore an electron donating group will stabilise the thionitroso group.

The *N*-thionitrosodimethylamine (6a) prepared by Middleton[5] clearly shows that this is the case. The same conclusions led Russian workers to prepare thionitroso compounds (15) with an RS- group on nitrogen in the hope that such compounds would be stable.[14] (Scheme 1.3).



Scheme 1.3

The dithionitrites (15a) and (15b) were prepared by the action of sulphur dichloride on the corresponding *N,N*- bis(trimethylsilyl)-sulphenamides (14). These in turn were prepared from the sulphenyl chlorides (12) using [bis(trimethylsilyl)amino]lithium (13). The adamantane derivative (15a) was prepared in ether at -70°C and isolated as a brownish red solid in 30% yield. It was stable at 20°C under an argon atmosphere for several hours. After longer periods of time or heating at 100°C a mixture of unidentified products was formed. The morpholino dithionitrite (15b) was stable at room temperature for several hours. Heating at 110°C gave dimorpholino disulphide (16) and tetrasulphide tetranitride (S_4N_4).



(16)

Decomposition of (15b) in ether at 20°C followed other pathways. Evidence for this comes from ^{15}N NMR spectroscopy. Labelled (14b) (δ_N 35.1 ppm) was reacted with sulphur dichloride to make ^{15}N labelled (15b). This reaction was followed by low temperature ^{15}N NMR. After 20 minutes the ^{15}N NMR spectrum showed one signal (δ_N 56.5 ppm) which was assigned to the dithionitrite (15b). After 10 hours at 20°C the peak for (15b) had disappeared and there were seven new signals. The most intense peak was assigned to S_4N_4 after comparison with an authentic sample. The phenyl dithionitrite (15c) could not be isolated. This was probably due to the rapid decomposition of the product.

It was concluded that an RS- group is able to stabilise the thionitroso group more effectively than an aryl or alkyl group. The nature of the substituent R also influences the stability of the dithionitrites and the path of their decomposition. Thionitroso compounds usually dimerise with loss of sulphur to form sulphur diimides. The formation of (16) and S_4N_4 in the decomposition of (15b) may be explained by quantum chemical calculations on $H_2N\text{-}S\text{-}N{=}S$. The results show that there is a large contribution from the resonance structure $H_2NS^{+}\text{-}{}^{-}N{=}S$, which would favour fragmentation to form the ion pair $H_2N\text{-}S^{+}$ and ^{-}NS. These ion pairs could be converted into radical pairs and recombine to form disulphides and S_4N_4.

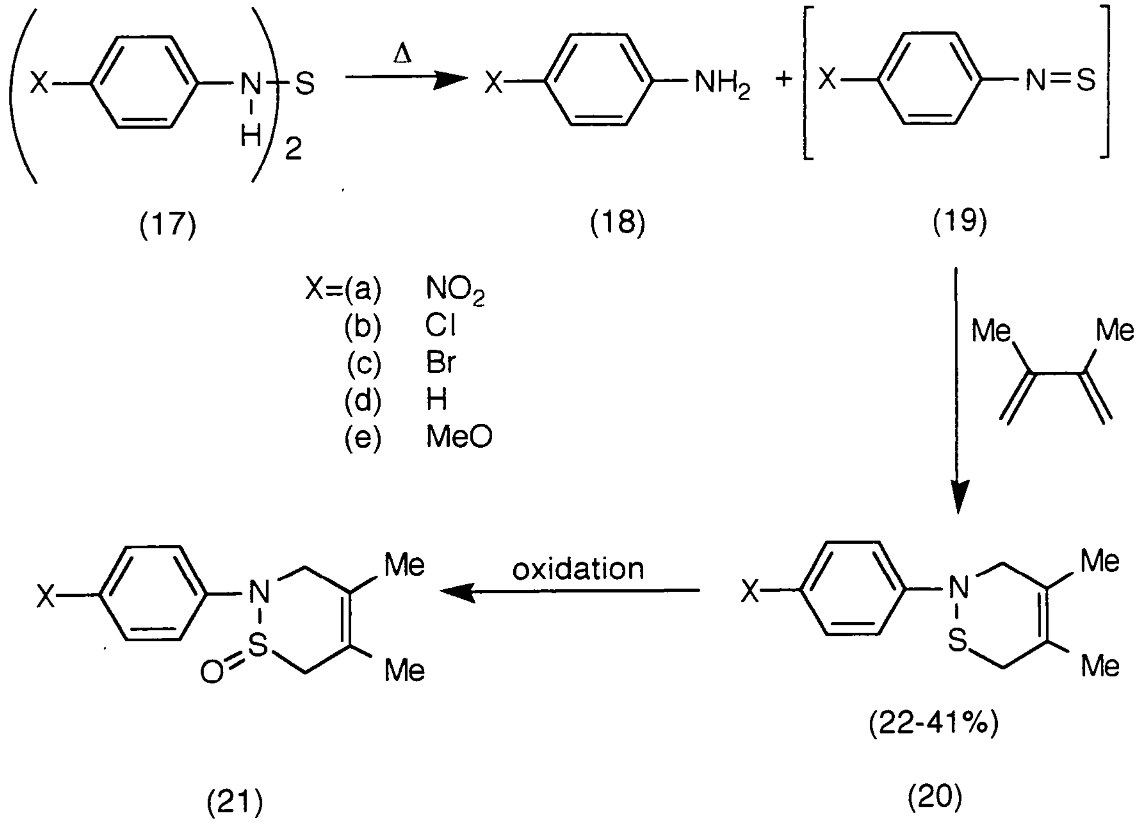
Several studies, therefore, demonstrate that the stability of thionitroso compounds is enhanced by electron donating substituent groups such as R_2N- or RS-. This stability can be accounted for by the existence of a resonance form, which makes them, in some respects, not true thionitroso compounds.

1.3 THIONITROSOARENES

Thionitrosoarenes have been suggested as reaction intermediates, without firm evidence, on several occasions but these earlier studies did not provide a synthetically useful method for their preparation.[15,16] Two general methods for the preparation of thionitrosoarenes will be discussed in this section. These are: (i) from sulphenamides and (ii) from benzisothiazoles and related compounds. Other methods will be briefly described.

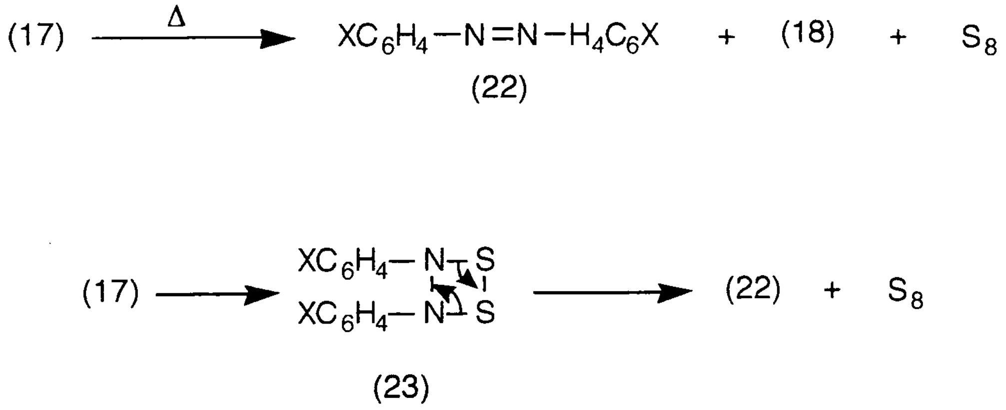
1.3.1 Generation of Thionitrosoarenes from Sulphenamides

In the same year that Middleton published work on the preparation of isolable *N*-thionitrosoamines (6a-c),[5] Tavs reported evidence of the first thionitrosoarenes as intermediates in the decomposition of the *N,N*-thiodiamines (17).[17] The *N,N*-thiodiamines (17a-d) were prepared from piperidine-1-sulphenyl chloride and the corresponding amine. Compounds (17a-d) were stable for several months at -15°C but, with the exception of (17a) decomposed at room temperature within 2-6 weeks. When compounds (17b-d) were refluxed in excess 2,3-dimethyl-1,3-butadiene for six hours the thiazines (20b-d) were isolated in 22-41% yield providing good evidence that thionitrosoarenes (19b-d) were intermediates in this reaction. (Scheme 1.4). Evidence for the structure of the thiazines (20b-d) came from the oxidation to the corresponding thiazine oxides (21) using perphthalic acid. These products were the same as those obtained from the corresponding sulphinylamines (ArN=S=O) and dimethylbutadiene.



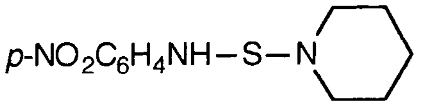
Scheme 1.4

Davis and Skibo[18] also investigated the thermal decomposition of the *N,N'*-thiodiamines (17). Heating compounds (17b-d) in benzene at 50°C for 72 hours in the absence of trap gave azobenzene (22), arylamine (18) and sulphur. Compound (17a) required heating at 120°C in bromobenzene for 96 hours in order for the reaction to occur. The mechanism put forward to explain the formation of (18) and (22) was the head to head dimerisation of two thionitroso groups to give (23) which could disproportionate to azobenzene and sulphur (Scheme 1.5). Intermediates similar to (23) have been suggested in other cases.[18] However, head to tail dimerisation has been suggested for other thionitroso derivatives [*cf.* structure (60) Section 1.3.2]. When 2,3-dimethyl-1,3-butadiene was used as a trap under Davis and Skibo's reaction conditions, compound (20d) was obtained in 66% yield.



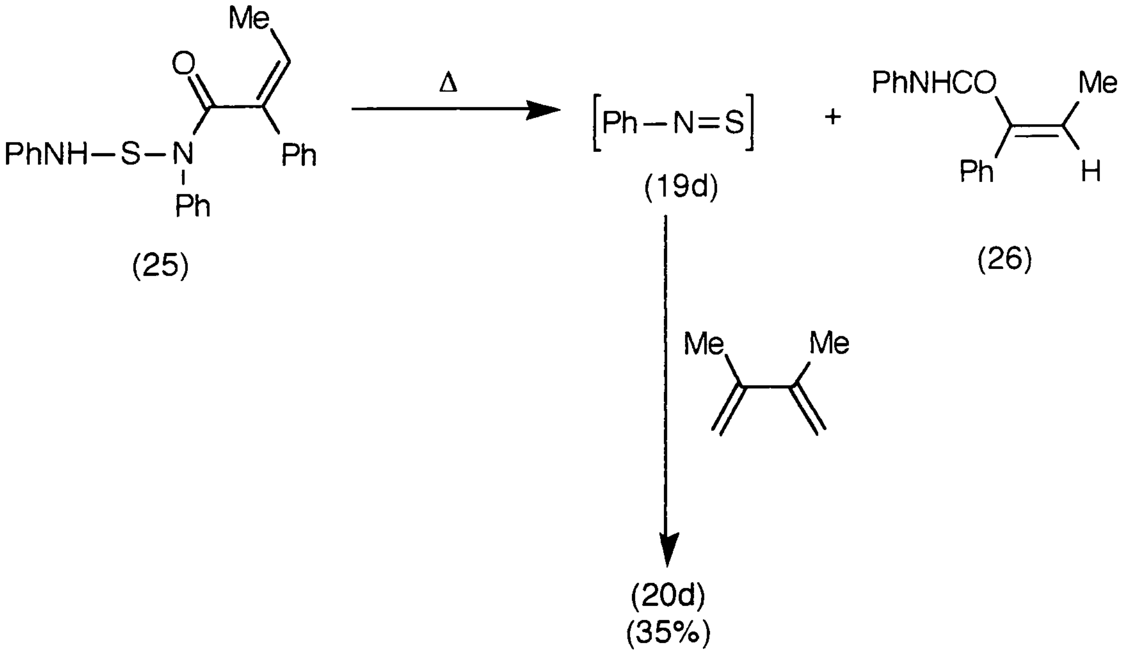
Scheme 1.5

When the addition of piperidine-1-sulphenyl chloride to arylamines was carried out at -78°C instead of 20°C thioareneaminopiperidines, *e.g.* compound (24), were obtained in good yield. When (24) was heated in the presence of 2,3-dimethyl-1,3-butadiene compound (20a) was obtained in 10% yield.[18]



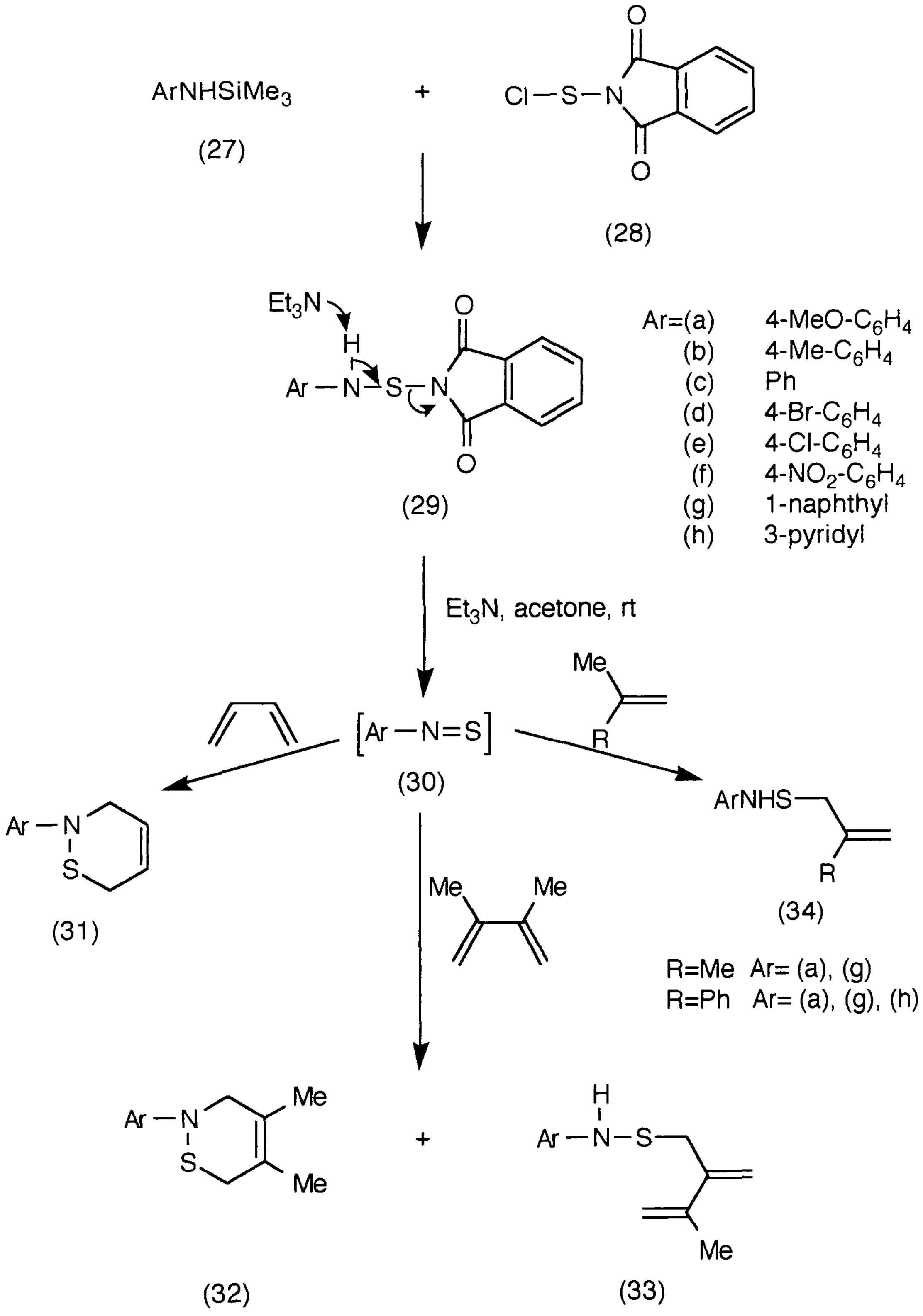
(24)

During work on the reactions of sulphur diimides with ketenes it was noted that thermal decomposition of the unsymmetrical thiodiamine (25) gave the thionitrosoarene (19d) with loss of the alkene (26). Evidence for the formation of thionitrosoarene (19d) was obtained by trapping with with dimethylbutadiene at 140°C to give thiazine (20d) in 35% yield (Scheme 1.6).[19] When tetraphenylcyclopentadienone was used as a trap for (19d), instead of dimethylbutadiene, no 1,2-thiazine was observed. Instead azobenzene (14a) was obtained in 65% yield indicating that (19d) is not reacting with the diene but is dimerising *via* intermediate (23d).



Scheme 1.6

Earlier work on the generation of thionitrosoarenes from the *N*-sulphenylaniline derivatives (17)[17], (24)[18] and (25)[19] provided the basis for a new route developed in our group which made the aryl thionitroso compounds much more accessible.[20] The phthalimide derivatives (29) were prepared in high yields by reacting the corresponding trimethylsilylamine (27) with *N*-chlorosulphenyl phthalimide (28). The precursors (29) were air- and moisture-stable and could be kept for years at room temperature. The thionitrosoarenes (30) were generated from (29) by reaction with base, in a 1,2-elimination reaction at room temperature , and trapped in situ with dienes or alkenes. (Scheme 1.7). The precursors (29) dissolved slowly in acetone at room temperature and therefore the thionitroso intermediates (30) were formed in a very low steady state concentration. This promoted efficient trapping of (30) as dimerisation reactions were suppressed. This method of generating thionitrosoarenes had two major advantages over Tavs' route[17]; the precursors (29) were stable and the reaction could be carried out at room

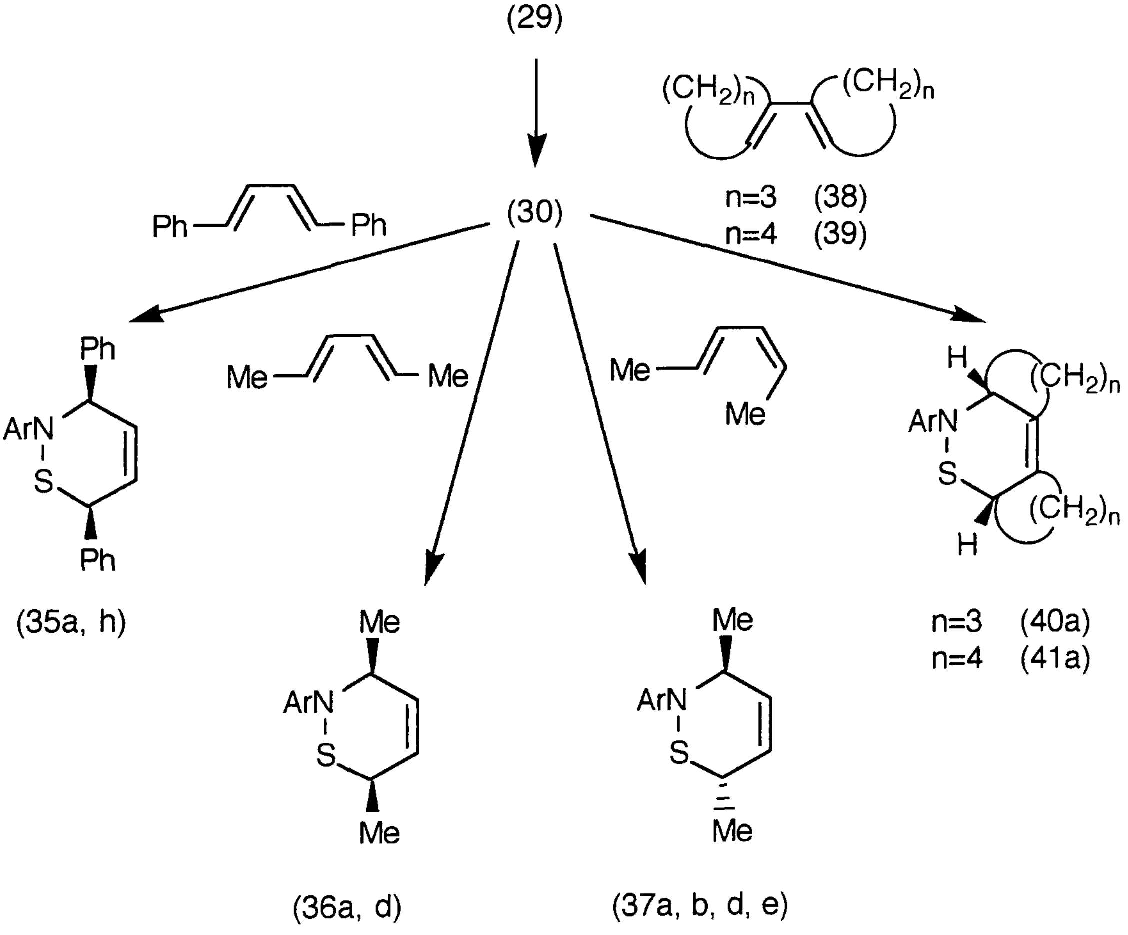

ArNHSiMe3
+
Cl—S—N
(27)
(28)
Et3N
H
Ar—N—S—N
(29)
Ar=(a) 4-MeO-C6H4
(b) 4-Me-C6H4
(c) Ph
(d) 4-Br-C6H4
(e) 4-Cl-C6H4
(f) 4-NO2-C6H4
(g) 1-naphthyl
(h) 3-pyridyl
Et3N, acetone, rt
[Ar—N=S]
(30)
Me
R
ArNHS
(34)
R=Me Ar= (a), (g)
R=Ph Ar= (a), (g), (h)
Ar—N
S
(31)
Me Me
Ar—N
S
Me
Me
(32)
+
H
Ar—N—S
Me
(33)

Scheme 1.7

temperature. The first example of a heterocyclic thionitroso compound (30h) was also generated using this route.

Trapping of (30) with butadiene gave Diels-Alder adduct (31). When dimethylbutadiene was used as a trap, both Diels-Alder (32) and ene (33) adducts were observed. The ratio of Diels-Alder to ene adducts was determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures. The ratio of adducts was dependent upon the electronic properties of the substituent on the aryl ring attached to the thionitroso group. An electron withdrawing substituent, *e.g.* (30d-f), favoured the ene adduct (33) while an electron donating substituent, *e.g.* (30a), gave Diels-Alder adducts (32) as the major product. Reaction of (30g) and (30h) with isobutene and α-methylstyrene gave ene adducts (34). It was deduced from IR and ^{1}H NMR that the ene reaction proceeds regiospecifically with C-S bond formation and not C-N bond formation.

The stereochemical outcome of the Diels-Alder reaction of thionitrosoarenes was investigated (Scheme 1.8).[20a,c] Reaction of 1,4-diphenyl-1,3-butadiene with (30a) and (30h) gave only the *cis*-adduct (35). Thionitrosoarenes (30a) and (30d) reacted with (*E*, *E*) hexa-2,4-diene to give the *cis*-diasteriomers (36a) and (36d) in greater than 90% diasteriomeric excess. Reaction of (30a), (30b), (30d) and (30e) with the (*E*, *Z*) diene gave the *trans*-isomer (37) accompanied by the *cis*-isomer (36). The ratios of *cis*- and *trans*-isomers, determined from ^{1}H NMR spectra and NOE experiments, were dependent upon the electronic nature of the substituent on the aryl ring. In the case of the electron withdrawing substituents (30d) and (30e) the formation of the *trans*-products was favoured (> 90% d.e.) while the electron rich methoxy derivative (30a) gave a 1:1 mixture of *cis*- (36) and *trans*- (37) products. It was deduced that the formation of the *cis*-isomer was due to an impurity of (*E*, *E*) hexa-2,4-diene in the diene. A large excess of diene is required in these reactions therefore it was possible for a 1:1 mixture of *cis* and *trans* products to be formed even though the relative amount of impurity was quite small. Reaction of the methoxy derivative (30a) with a 1:1 mixture of the (*E*, *E*) and (*E*, *Z*) diene gave only the *cis*-isomer (36a). It was concluded that the (*E*, *E*) hexadiene and the (*E*, *Z*) hexadiene both react with thionitrosoarenes (30) with retention of stereochemistry. Reaction of the tetra-substituted dienes (38) and (39) with (30a) gave adducts (40a) and (41a) with a single stereochemistry (> 95% d.e.). The above results show that thionitrosoarenes react stereospecifically with dienes.



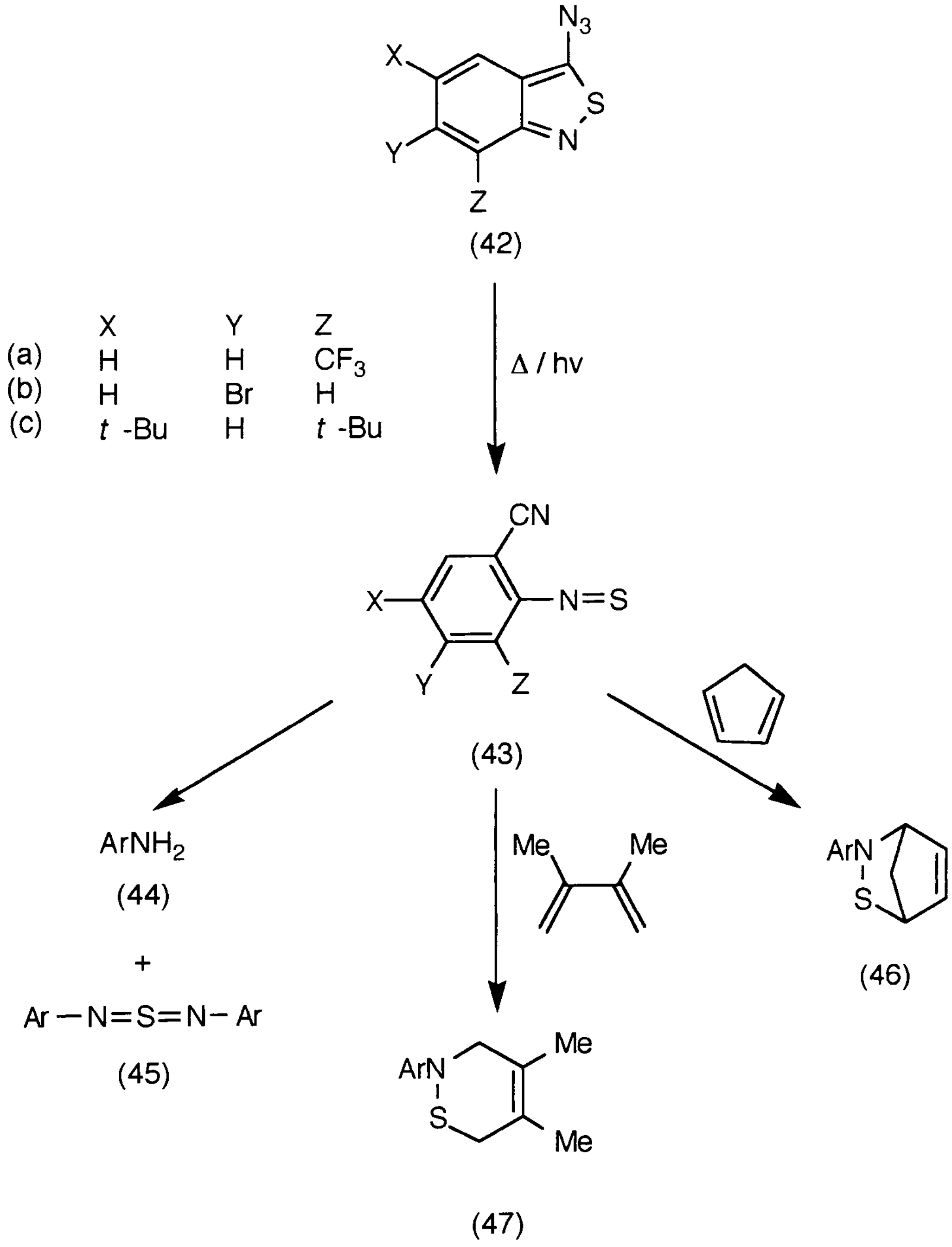
Scheme 1.8

1.3.2 Thionitrosoarenes from Benzisothiazoles and Related Compounds

The known ring opening reactions of five-membered heterocyclic rings with carbene or nitrene precursors in the α-position form the basis of a route to thionitroso compounds first described by Joucla and Rees (Scheme 1.9).[21]

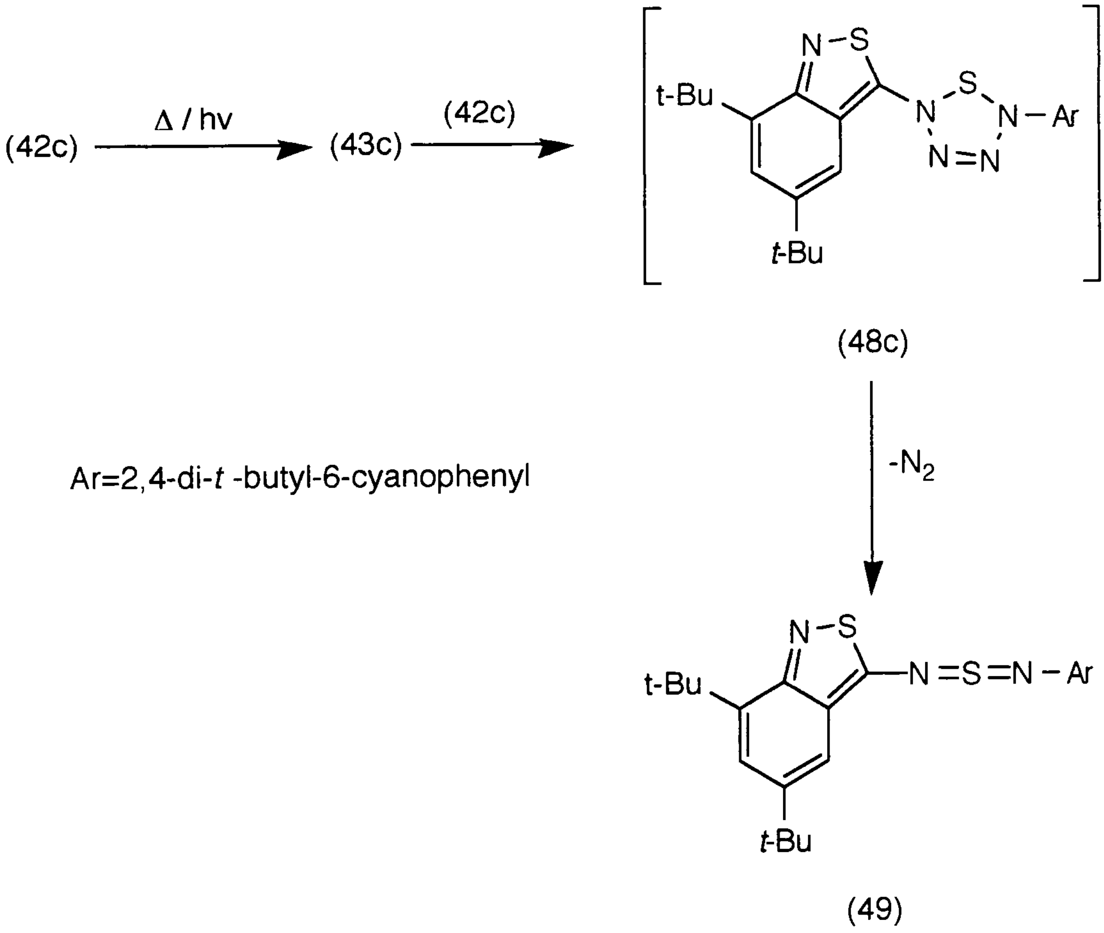
The thermally unstable azide (42a) prepared from the corresponding 3-amino-2,1-benzisothiazole was photolysed at room temperature in ether to give the thionitroso compound (43a) (mass spectroscopic evidence) in less than two hours. Compound (43a) could not be isolated and decomposed to give the amine (44a). When photolysis was carried out in the presence of cyclopentadiene, the Diels-Alder adduct (46a) was formed as the major product with a small amount of amine. Thermal decomposition of the azide (42a) in the absence of a trap gave the sulphur diimide (45a) formed by dimerisation of the thionitroso compound (43a) with loss of sulphur. Heating the benzisothiazole (42b) in neat dimethylbutadiene gave the Diels-Alder adduct (47b) providing firm evidence for the intermediacy of thionitroso compounds in the thermal decomposition of 3-azido-2,1-benzisothiazoles.

Further work on the generation of thionitroso compounds from 2,1-benzisothiazoles was carried out by Okazaki *et al.*[22-24] who studied the bis (*t*-butyl) derivative (42c). Thermal generation of (43c) and trapping with dimethylbutadiene gave the expected Diels-Alder adduct (43c) along with (44c) and (45c). These workers were unable to trap (43c) with a cyclic diene, *e.g.* cyclopentadiene in a [4+2] cycloaddition reaction, which could be due to steric factors.



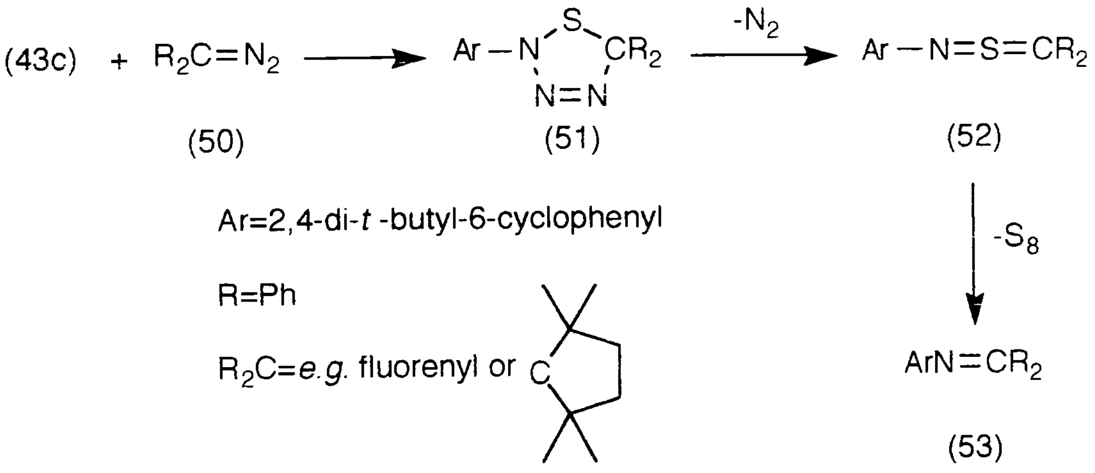
Scheme 1.9

Heating or photolysis of (42c) in the absence of trap (Scheme 1.10) gave (44c), (45c) and a small amount (*ca.* 2%) of the unsymmetrical sulphur diimide (49). The intermediate (48) proposed in this reaction could be formed *via* a



Scheme 1.10

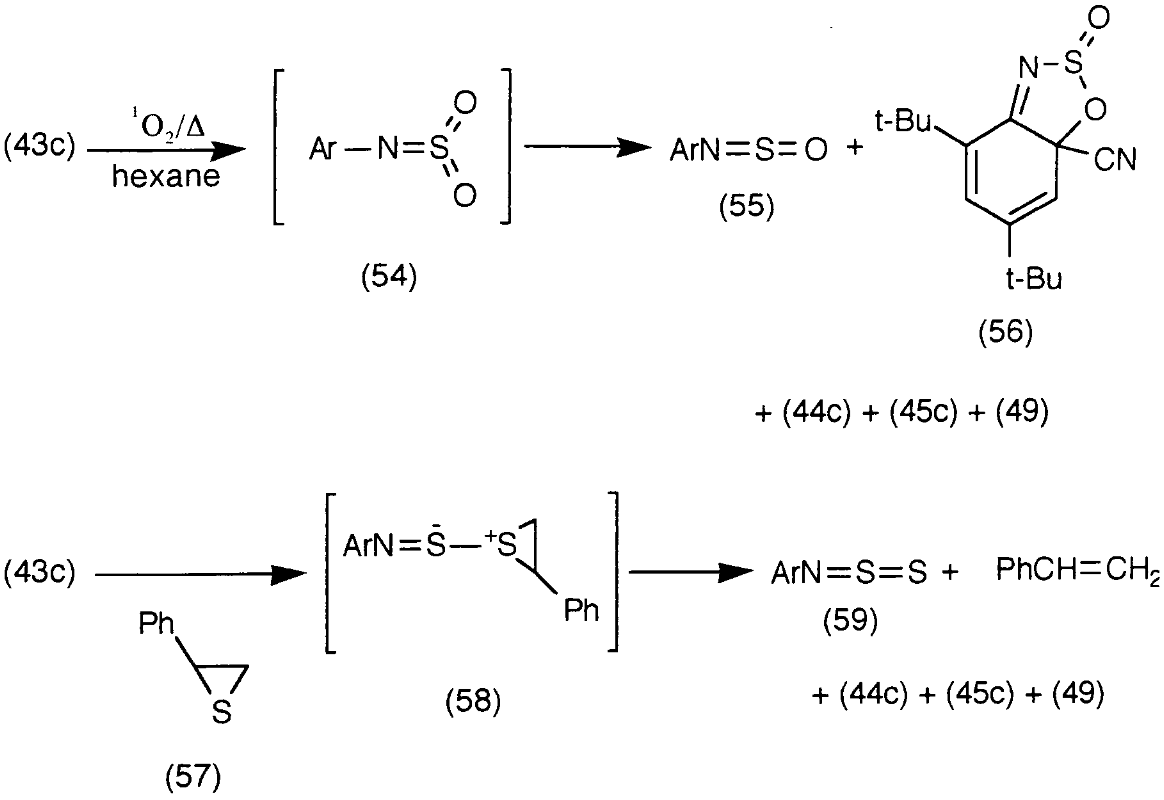
[2+3] cycloaddition reaction between the thionitrosoarene (45c) and the starting azide (42c). Although these results indicated that thionitrosoarenes could take part in [2+3] cycloaddition reactions, attempted cycloadditions of (43c) with aryl azides proved unsuccessful. Reaction of (43c) with diazo compounds (50) gave either thiatriazole (51), thiocarbonylimine (52) or imine (53) depending on the bulkiness of the substituent group R. Large substituents were capable of stabilising the novel thiatriazole (51). (Scheme 1.11) These reactions are, to date, the only examples of the [2+3] cycloaddition of a thionitroso compound. Reaction of (43c) with other 1,3-dipoles, *e.g.* mesitonitrile oxide, did not give cycloaddition products.



Scheme 1.11

Reactions of the thionitrosoarene (43c) with molecular oxygen and phenylthiirane (57) were also investigated (Scheme 1.12). The formation of (55) and (56) from the reaction of thionitrosoarene (43c) with singlet oxygen was accounted for by the postulated intermediate (54). The heterocycle (56) was formed thermally but not photochemically, possibly due to the photochemical instability of (56). The reaction with phenylthiirane (57) is thought to proceed through the intermediate (58) which could be formed from the nucleophilic attack of thiirane (57) on the sulphur atom of thionitrosoarene (43c).

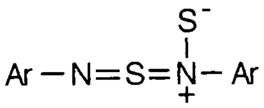
Thionitrosoarenes are reactive intermediates and cannot be isolated under normal conditions. However, they can be detected by UV-visible and IR spectroscopy in matrices at cryogenic temperatures.[22, 23] 3-Azido-2,1-benzisothiazole derivative (42c) was chosen for these investigations since the bulky *t*-butyl groups should stabilise the reactive thionitrosoarene species (43c). Irradiation of (42c) was carried out in argon matrices at 12K. Peaks in the electronic spectrum at 460 and 484 nm, and in IR spectrum at 1120 and 1200cm^{-1}, were assigned to the N=S group. Experiments carried out in



Ar=2,4-di-t-butyl-6-cyanophenyl

Scheme 1.12

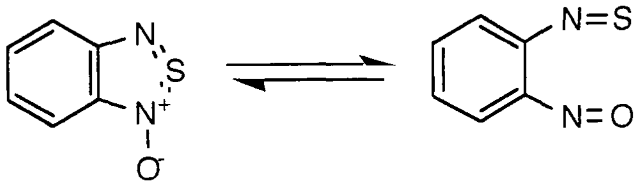
organic glasses to determine the stability of the thionitrosoarene (43c) gave information about the dimerisation of (43c) to give the sulphur diimide (45c). From the spectroscopic data it was possible to assign structure (60) to an intermediate in the dimerisation process.



$$\mathrm{Ar-N=S=\overset{S^-}{\underset{+}{N}}-Ar}$$

(60)

Spectroscopic evidence for the existence of thionitrosoarenes also comes from the photolysis of benzo[*c*]-1,2,5-thiadiazole-2-oxide (61) in ethanol at 20K (Scheme 1.13).[25] 1-Nitroso-2-thionitrosobenzene (62) was formed in a reversible reaction based on UV and IR spectroscopic data. Results obtained in both of these spectroscopic investigations are in agreement. Photolysis and UV spectroscopy of the 1,2,5-selenadiazole analogue of (61) at 100K gave evidence for the formation of a selenonitroso intermediate (R-N=Se). This is the only report of the formation of the selenium analogue of a thionitroso compound.[26]



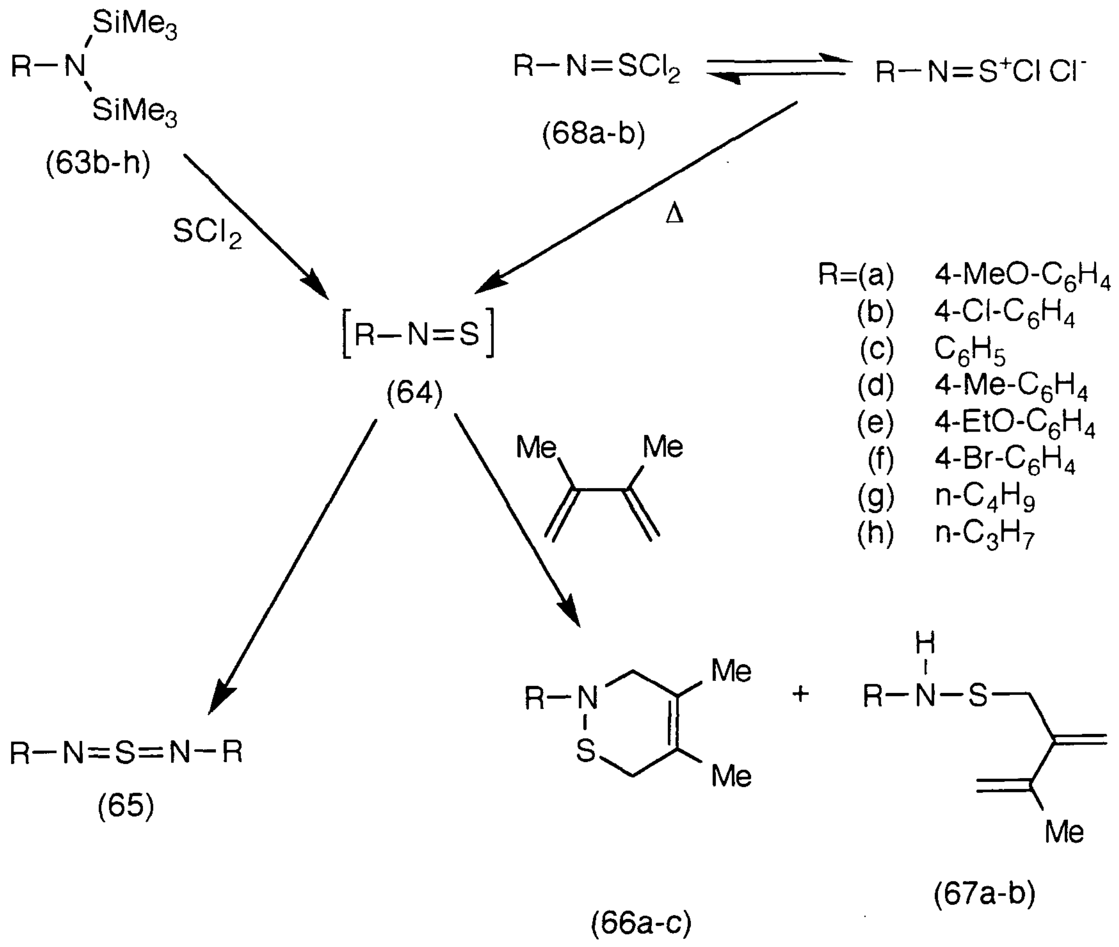
(61) (62)

Scheme 1.13

1.3.3 Other Synthetic Approaches to Thionitrosoarenes

Other routes to thionitrosoarenes have also been investigated with varying degrees of success.

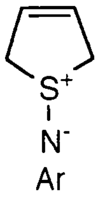
Thionitrosoarenes were postulated as intermediates in the reaction of *N*,*N*-bis-trimethylsilylamines (63) with sulphur dichloride at low temperatures which gave the sulphur diimides (65) (Scheme 1.14).[27] Further evidence for the intermediacy of thionitrosoarenes (64) in this reaction came from trapping with dimethylbutadiene to give the thiazine (66b).[28] The alkyl sulphur diimides (65g) and (65h) were also prepared *via* this route but the postulated thionitroso intermediates (64) were not trapped with dimethylbutadiene.



Scheme 1.14

In our laboratory thionitrosoarenes have also been generated from *N*-aryliminosulphur dichlorides (68)[20a] in a 1,1-elimination reaction. The unstable iminosulphur compounds (68) were prepared by chlorination of a mixture of the of the corresponding amine and sulphur dichloride. When compounds (68) were treated with 2,3-dimethyl-1,3-butadiene, Diels-Alder (66 a-b) and ene adducts (67 a-b) of thionitrosoarene (64) were isolated. However it is possible that addition initially occurs to species (68), followed by dechlorination. The instability of the precursors (68) means that this route has limited use in the preparation of thionitrosoarenes.

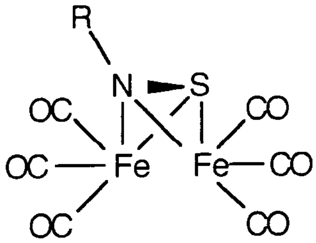
Attempts have been made to prepare ArN=S species from the *S,N*-ylide (69)[29] and by treating a nitrosobenzene derivative with phosphorous pentasulphide.[30] Both of these methods proved unsuccessful, the product in the latter case being the *N*-thiosulphinylaniline (ArN=S=S).



(69)

1.4 THIONITROSOALKANES

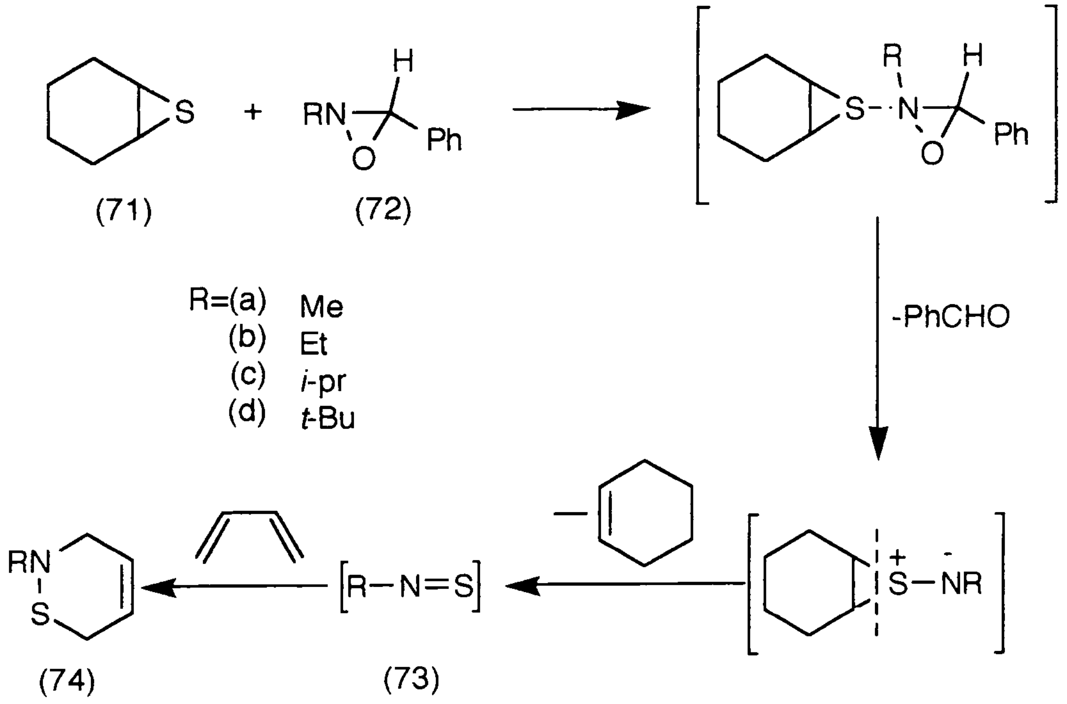
The first report of an alkyl thionitroso compound was as a bridging ligand in a binuclear iron complex (70).[31] Compounds (70 a-c) were prepared by decomposition of the appropriate sulphinylamine, or sulphur diimide, in the presence of iron carbonyl complexes.[31,32] Compound (70c) is readily hydrolysed to give (70d) which can be methylated with diazomethane to give (70e). The IR and mass spectra of compounds (70) show similarities, including the parent compound (70d), indicating that they all have the same basic structure. The IR spectra show that the N-S bond is single in complexes (70). It is possible that the complexes are formed directly from the sulphinylamine or sulphur diimide and that the thionitrosoalkanes do not exist as free species.



(70)

R=(a) Ph
(b) t-Bu
(c) $SiMe_3$
(d) H
(e) Me

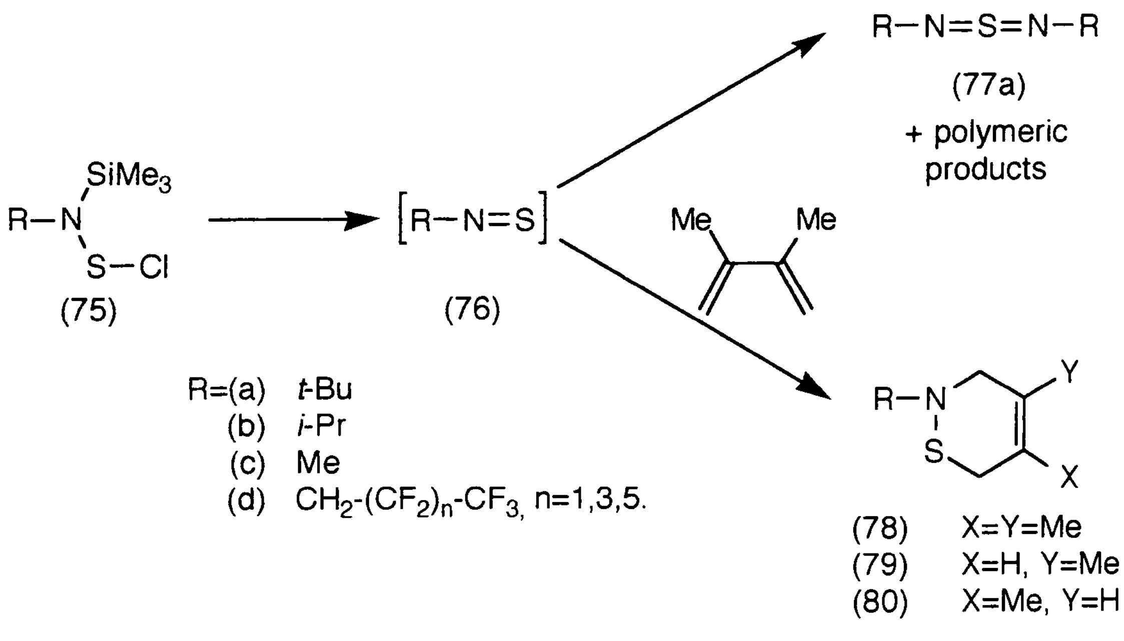
The generation and trapping of true alkyl thionitroso compounds was first described by Hata and Watanabe (Scheme 1.15).[33] The reaction of cyclohexene sulphide (71) and the oxaziridines (72) proceeded chelotropically to give cyclohexene and the thionitroso compound (73). When (72a) was reacted in this way, evidence for the intermediacy of the thionitroso compound (73) came from the formation of the corresponding sulphur diimide (83%) and a small amount of azomethane. When the reaction was carried out in the presence of 1,3-butadiene the alkyl thionitroso compounds (73) were trapped in a Diels-Alder reaction to give the thiazines (74). The oxaziridine (72d) was less reactive and therefore attempts to generate and trap *t*-butyl thionitrosoalkane (73d) were unsuccessful.



Scheme 1.15

The alkyl thionitroso compounds (76) have recently been prepared by Russian workers by the thermal decomposition of *N*-trimethylsilyl-*N*-chlorothioalkylamines (76) (Scheme 1.16).[34] The stability of compounds (75) appears to be dependent upon the size of the alkyl substituent (R). Thermal decomposition of (75a) gave the sulphur diimide (77a) and polymeric products, while the less bulky isopropyl derivative (75b) gave only polymeric products. Compound (75c) could not be isolated, attempted preparation resulted in the formation of polymeric products. This was explained by the chlorothioalkylamine (75c) decomposing to thionitrosomethane and polymerising under the conditions of synthesis. The thionitrosoalkanes (76a) and (76b) were trapped with dimethylbutadiene to give thiazines (78) in good yield

Fluorinated alkyl derivatives were also prepared via this route[35]. The thionitrosoarenes (76d) were generated in the same way and trapped with dimethylbutadiene to give thiazine (78d). Trapping with isoprene gave the adducts (79) and (80) in a 1:4 ratio.



Scheme 1.16

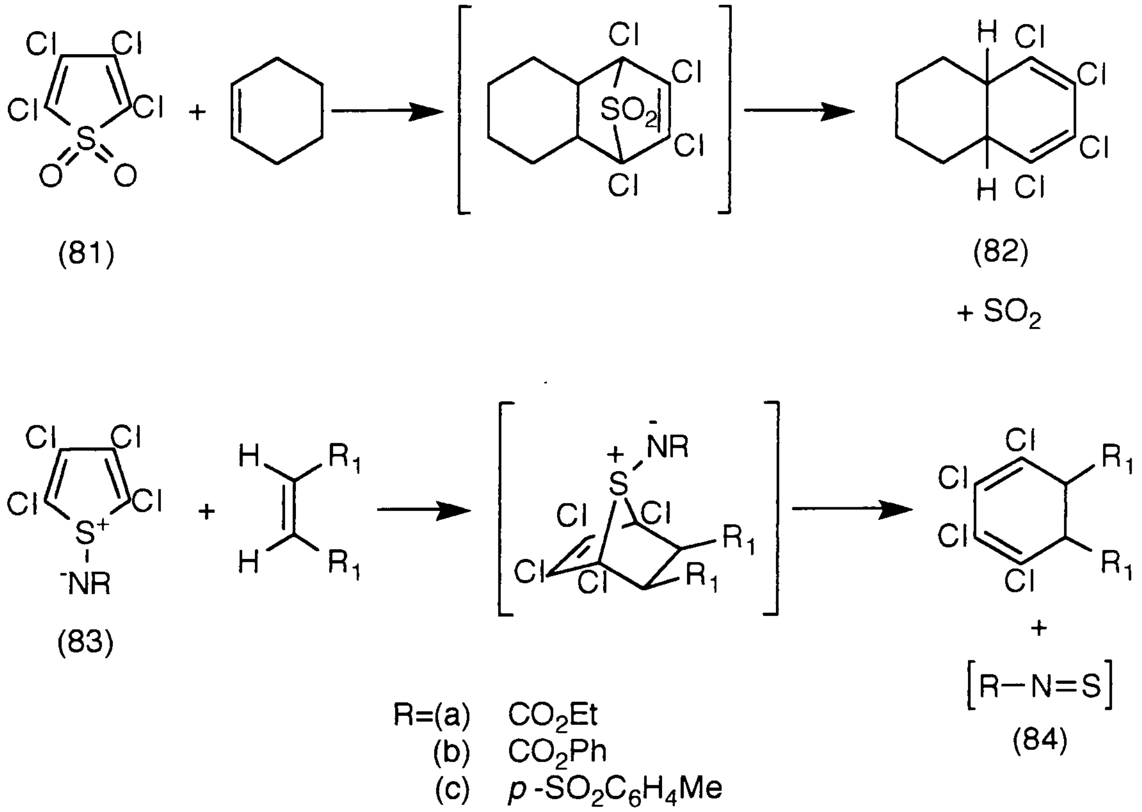
It should be noted that the generation of thionitrosoalkanes from precursors (75) is related to the route described by Mayer[27] (Scheme 1.14).

Mayer's reactions can be considered as proceeding by addition of sulphur dichloride to form an intermediate *N*-trimethylsilyl-*N*-chlorothioalkylamine with subsequent elimination of trimethylsilylchloride. Two alkyl derivatives were investigated in this study. Dimerisation occurred to form the sulphur diimides but the thionitrosoalkanes (64g-h) were not trapped in a Diels-Alder reaction.

1.5 THIONITROSOFORMATES AND THIONITROSOSULPHONATES

The thionitrosoformates and thionitrososulphonates have highly electron withdrawing substituents on the nitrogen of the thionitroso group. Molecular orbital calculations have suggested that electron deficient thionitroso compounds of this type will be very unstable and highly reactive.[12]

Most of the work on electron deficient thionitroso compounds has been carried out by Meth-Cohn and co-workers.[36, 37] They noted that when tetrachlorothiophene-1,1-oxide (81) underwent [4+2] cycloaddition reactions there was a simultaneous extrusion of sulphur dioxide to give adducts of the type (82) (Scheme 1.17). By analogy, it might be expected that thiophene *S,N*-ylides (83) could extrude RN=S, so compounds (83) were prepared by decomposing azidoformates or tosyl azide in tetrachlorothiophene solution. The thionitroso compounds (84) were generated by reacting the S,N-ylides (83) with alkenes in a cycloaddition reaction: the most efficient alkene for this purpose was acenaphthylene (86) which reacted rapidly with (83) at room temperature in high yields. When the generation of thionitroso compounds (84) from (83) was carried out in the absence of trap in dichloromethane, a complex mixture of products was obtained. In benzene , toluene, or cumene solution, compound (84a) decomposed to give the bisurethanosulphide (85)

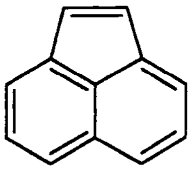


Scheme 1.17

in 18% yield. This reactivity is different from that observed for the aryl and alkyl thionitroso compounds which give sulphur diimides.

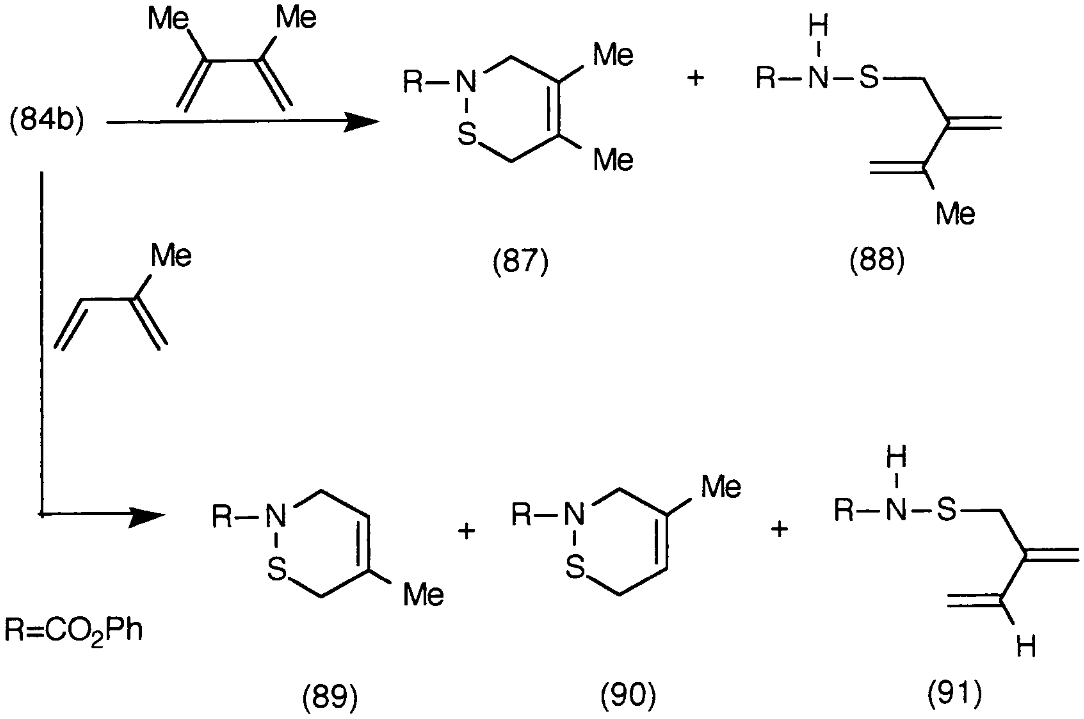
$(EtO_2CNH)_2S$

(85)



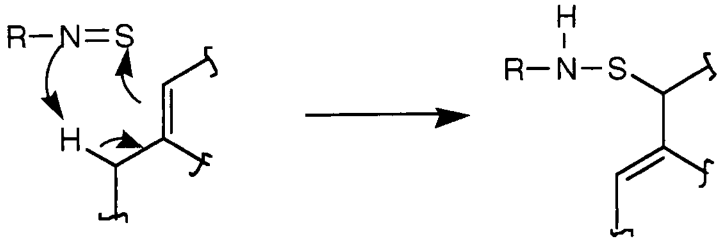
(86)

The highly reactive electron deficient thionitroso compounds (84) were intercepted with a range of alkenes and dienes[38] *e.g.* thionitroso compound (84a) reacted with butadiene or cyclohexa-1,3-diene to give the expected Diels-Alder adducts. Trapping (84b) with 2,3-dimethyl-1,3-butadiene gave Diels-Alder (87) and ene adducts (88) in a 1:1 ratio. The ene reaction proceeded stereospecifically with C-S bond formation as observed for ArN=S ene adducts (Section 1.3.1). Reaction of (84b) with isoprene gave the two Diels-Alder regioisomers (89) and (90) and the ene adduct (91) in a 1:1:2 ratio. (Scheme 1.18).



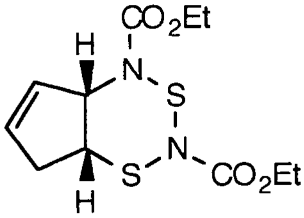
Scheme 1.18

Thionitroso compounds (84) reacted readily in ene reactions with a selection of alkenes *e.g.* cyclohexene, α-methyl styrene and dicyclopentadiene. (Scheme 1.19). The alkene could be used as both the dienophile for the cycloaddition reaction with the *S*,*N*-ylide (84) and as the ene trap for the



Scheme 1.19

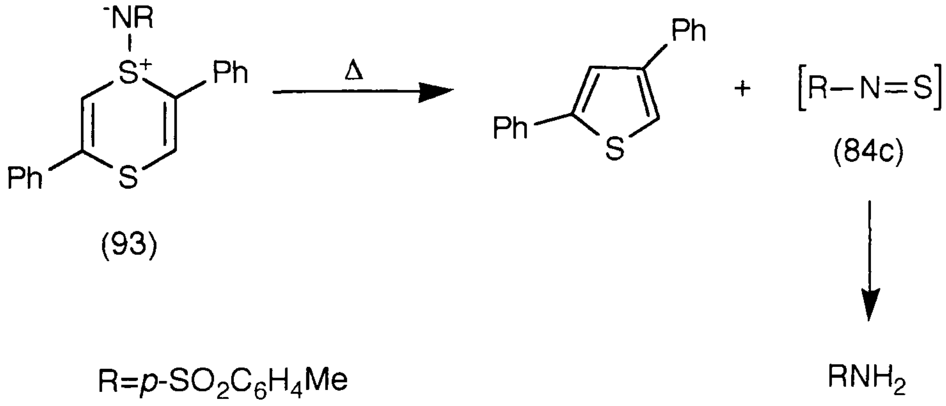
thionitroso compound. The preference for ene reactivity over diene reactivity was surprising. These observations may be explained by the possible involvement of a triplet state species. An interesting reaction occurred between (84a) and cyclopentadiene: the 2:1 adduct (92) of ethylthionitrosoformate and cyclopentadiene being formed in a [2+2+2] addition reaction in 14% yield. This was the first example of a 1,3,2,4-dithiadiazine derivative.



(92)

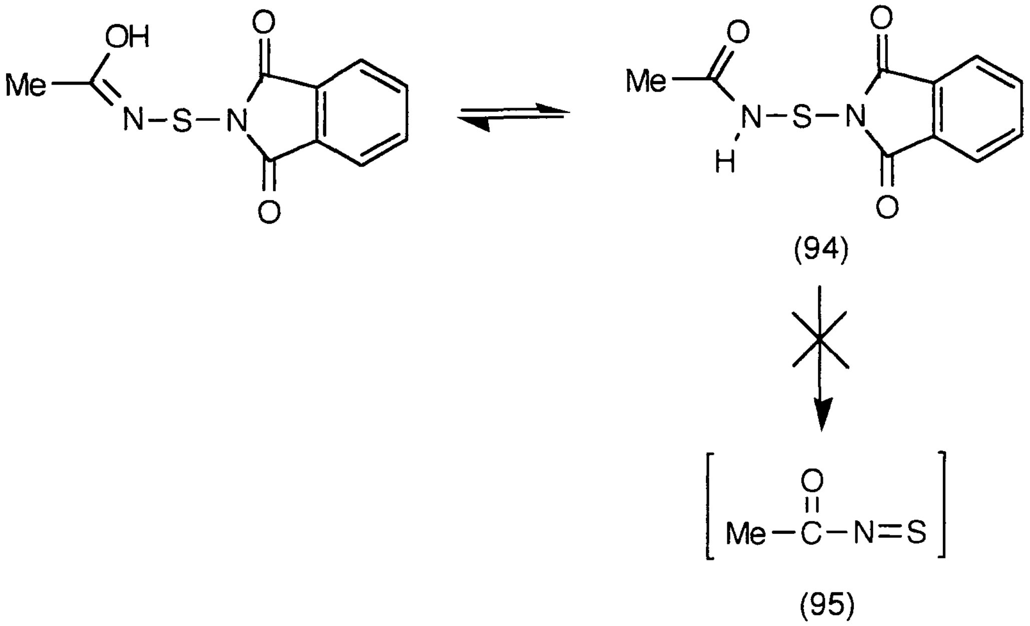
Chiral derivatives of the of the ylide (83) have been prepared by Meth-Cohn and co-workers[39] where R=-CO_2-(-)-menthyl and -CO_2-(+)-fenchyl. It was hoped that these ylides would act as asymmetric inductors in Diels-Alder reactions with alkenes, but this did not occur. Presumably, the chiral substituent is too far removed from the cycloaddition site to influence the stereochemistry of the addition reaction. When these chiral thionitroso compounds were generated and reacted with 1,4-diphenylbutadiene, an inseparable mixture of diastereomers was obtained.

The thionitroso compound (84c) has also been postulated as a transient intermediate in the thermal decomposition of the dithiin (93) but has not been trapped (Scheme 1.20).[40]



Scheme 1.20

Attempts to generate the electron deficient acyl thionitroso compound (95) in our laboratory from phthalimide precursor (94) have been unsuccessful. (Scheme 1.21).[20a]



Scheme 1.21

1.6 SUMMARY

Thionitroso compounds can prepared in a variety of ways. The methods of their generation can be divided into three broad groups: from sulphenamide and related compounds in a 1,2-elimination reaction; via a 1,1-elimination reaction *e.g.* from *S*,*N*-ylides[33, 37] or *N*-aryliminodichlorides,[20] and by ring opening reactions *e.g.* from 2,1-benzisothiazoles.[21]

We have seen that, in general, thionitroso compounds are very reactive intermediates. Their reactivity is dependent upon the electronic and steric nature of the substituent group. This is supported by molecular orbital calculations[12] that suggest that thionitroso compounds with electron donating substituents (*e.g.* thionitrosoamines) are relatively stable, while those with electron withdrawing substituent groups (*e.g.* thionitrosoformates) are highly reactive.

The competition observed between Diels-Alder and ene reactivity is of interest. Work on the phthalimide route (Scheme 1.7)[20] has shown that the ratio of isomers is highly dependent upon the electronic character of the substituent. Meth-Cohn[37] noted that competition between Diels-Alder and ene reaction with the same diene has been observed for very few dienophiles. The other dienophiles are benzyne,[41] $PhS{=}O^{+}$,[42] $EtO_2CN{=}NCO_2Et$,[43] $R_2NC(O)NO$[44] and $^1O_2$.[45]

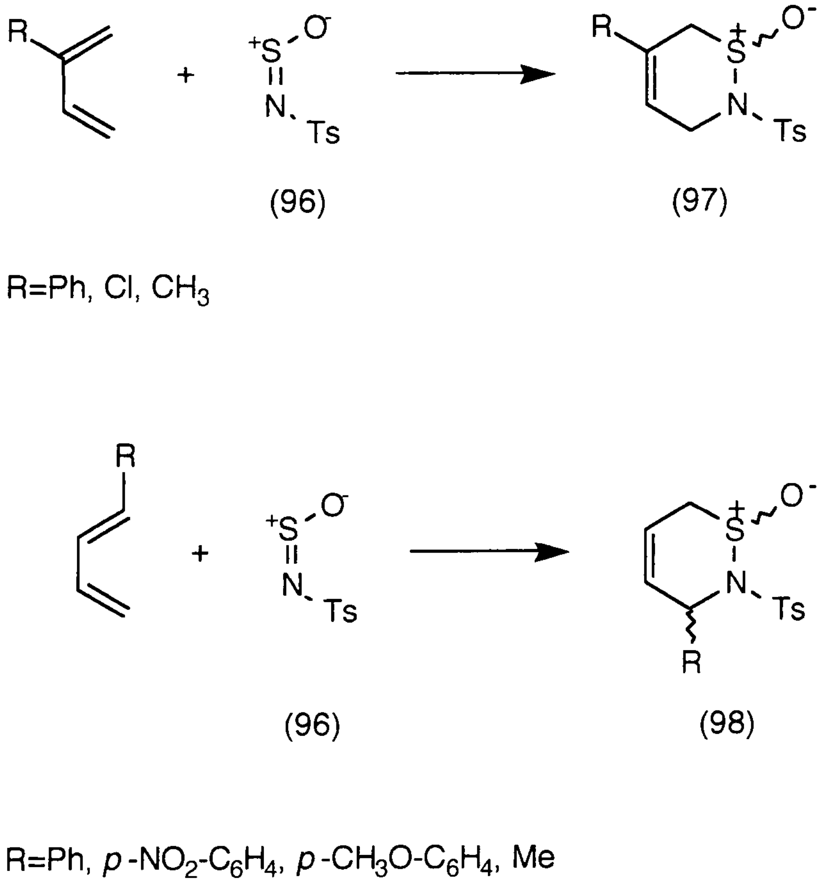
CHAPTER 2

GENERATION AND REACTIONS OF ARYL AND HETEROARYL THIONITROSO COMPOUNDS

2.1 REGIOCHEMISTRY OF DIELS-ALDER ADDITIONS TO THIONITROSOARENES

2.1.1 Introduction

A Diels-Alder reaction between an unsymmetrical dienophile (*e.g*. a thionitroso compound) and an unsymmetrical diene (*e.g*. isoprene) can give rise to two regioisomeric adducts. The regioselectivity of dienophiles related to thionitroso compounds has been investigated. Sulphinylamines and sulphur diimides usually react in Diels-Alder reactions only when there is an electron withdrawing substituent on nitrogen. Kresze and Wagner[46] showed



(96) (97)

R=Ph, Cl, CH_3

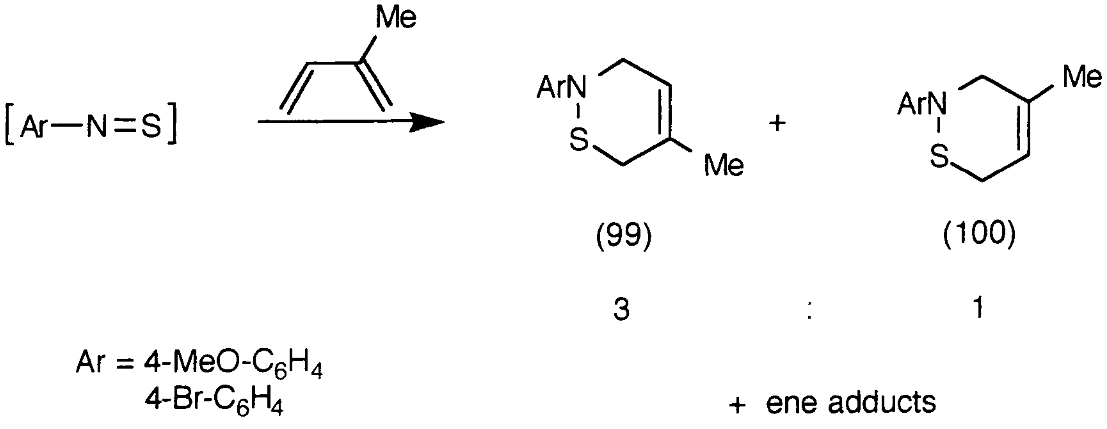
(96) (98)

R=Ph, *p*-NO_2-C_6H_4, *p*-CH_3O-C_6H_4, Me

Scheme 2.1

that the cycloaddition reactions of *N*-sulphinyl-*p*-toluenesulphonamide (96) were regioselective (Scheme 2.1). Addition of 2-substituted dienes yielded only 5-substituted dihydrothiazine oxides (97) while addition of 1-substituted dienes gave 3-substituted products (98). Sulphur diimides were found to react regiospecifically in a similar fashion.[47] Likewise, electron deficient thioaldehydes react with 2-substituted dienes to give 5-substituted adducts, but electron rich thioaldehydes give 4-substituted products.[48] The regiochemistry of addition to nitroso compounds is not clearly defined but it is known to be dependent upon the electronic and steric nature of both the dienophile and the diene.[3]

Addition of isoprene to acyl and sulphonyl thionitroso compounds gave a 1:1 mixture of 5- and 4-substituted adducts along with the ene adduct.[38] Trapping of fluorinated alkyl thionitroso compounds with isoprene gave a 4:1 ratio of the 5-substituted product over the 4-substituted product.[35] When thionitrosoarenes were trapped with isoprene the 5- and 4- substituted thiazines (99) and (100) were obtained in a 3:1 isomer ratio.[20b] (Scheme 2.2).

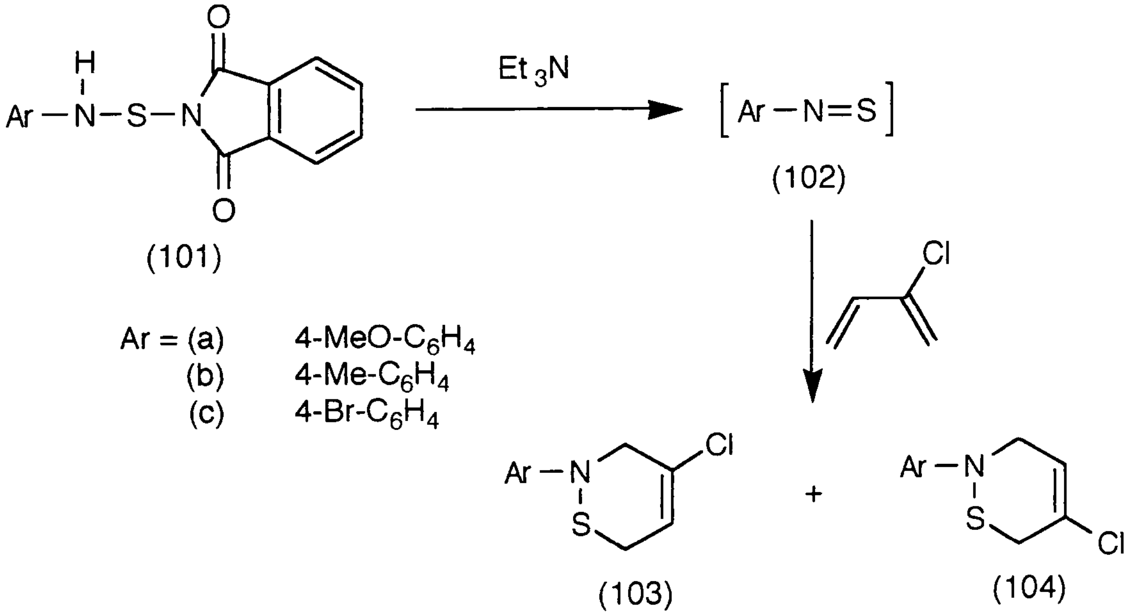


Scheme 2.2

2.1.2 Reaction of Thionitrosoarenes with Chloroprene

The observation that the 5-substituted thiazine was the major isomer when thionitrosoarenes were reacted with isoprene can be explained by steric factors, *i.e.* the methyl group is further away from the substituted nitrogen in the transition state leading to the major isomer. Therefore, we chose to a carry out trapping reactions of thionitrosoarenes with 2-chloro-1,3-butadiene (chloroprene) which is sterically similar to isoprene but has different electronic properties.

Thionitrosoarenes (102) were generated from phthalimide precursors (101) by adding triethylamine to a stirring suspension of precursor and excess chloroprene in acetone at room temperature. After stirring overnight a clear solution was obtained. This solution was evaporated and the residue was extracted with cyclohexane to remove the phthalimide salts which were produced in the reaction. (Scheme 2.3).



Scheme 2.3

Crude mixtures containing the adducts (103) and (104) in high yields were analysed by 250MHz ^{1}H NMR spectroscopy to determine accurately the isomer ratios. Two multiplets (δ_H ~ 6.0ppm) were assigned to the vinylic protons. By analogy with previous work[20] the peaks at δ_H 4.2 and δ_H 3.2 ppm were assigned to CH_2N and CH_2S protons respectively. These signals were in the same position for each of the two isomers (Fig 2.1). It was not possible to assign the vinylic multiplets to each isomer. To overcome this problem the adducts obtained from the bromo derivative (102c) were separated by column chromatography and ^{1}H NMR decoupling experiments were carried out on the individual isomers.

The ^{1}H NMR spectrum of the major isomer showed a multiplet at δ_H 6.16 ppm. When the spectrum was decoupled at δ_H 4.2 ppm, *i.e.* when the CH_2N protons were decoupled, the multiplet collapsed to a triplet with a coupling constant of 4.4 Hz. When the spectrum was decoupled at δ_H 3.2, *i.e.* when the CH_2S protons were decoupled, the multiplet at δ_H 6.16 ppm again collapsed to a triplet, this time with a coupling constant of 1.6 Hz. Larger coupling constants are observed for adjacent protons, while long distance couplings are smaller.[49] Therefore, the multiplet at δ_H 6.16 ppm was assigned to the vinylic proton adjacent to CH_2S because a smaller coupling constant was observed when these protons were decoupled. Thus the major isomer is (103c) with chlorine in the 4-position. (Fig 2.2)

Conversely, when the septet at δ_H 6.05 ppm for the minor isomer was decoupled at δ_H 3.2 ppm it collapsed to a triplet with a coupling constant of 3.47 Hz. When the septet was decoupled at δ_H 4.2 ppm it collapsed to a triplet with a coupling constant of 1.5 Hz. Therefore, structure (104c) was assigned to this isomer. (Fig 2.3).

Figure 2.1 - ^{1}H NMR Spectrum of Adduct (103c)

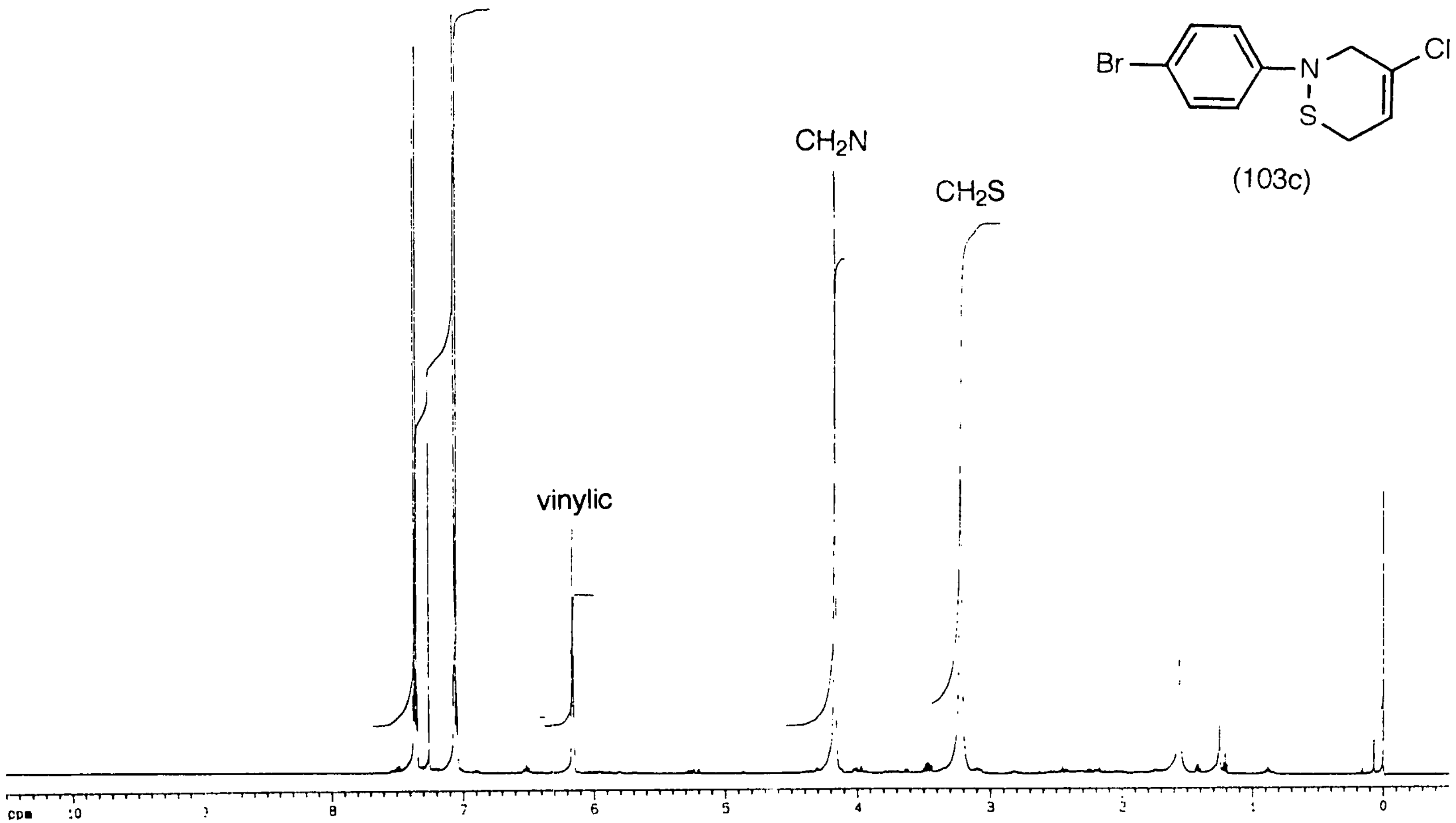
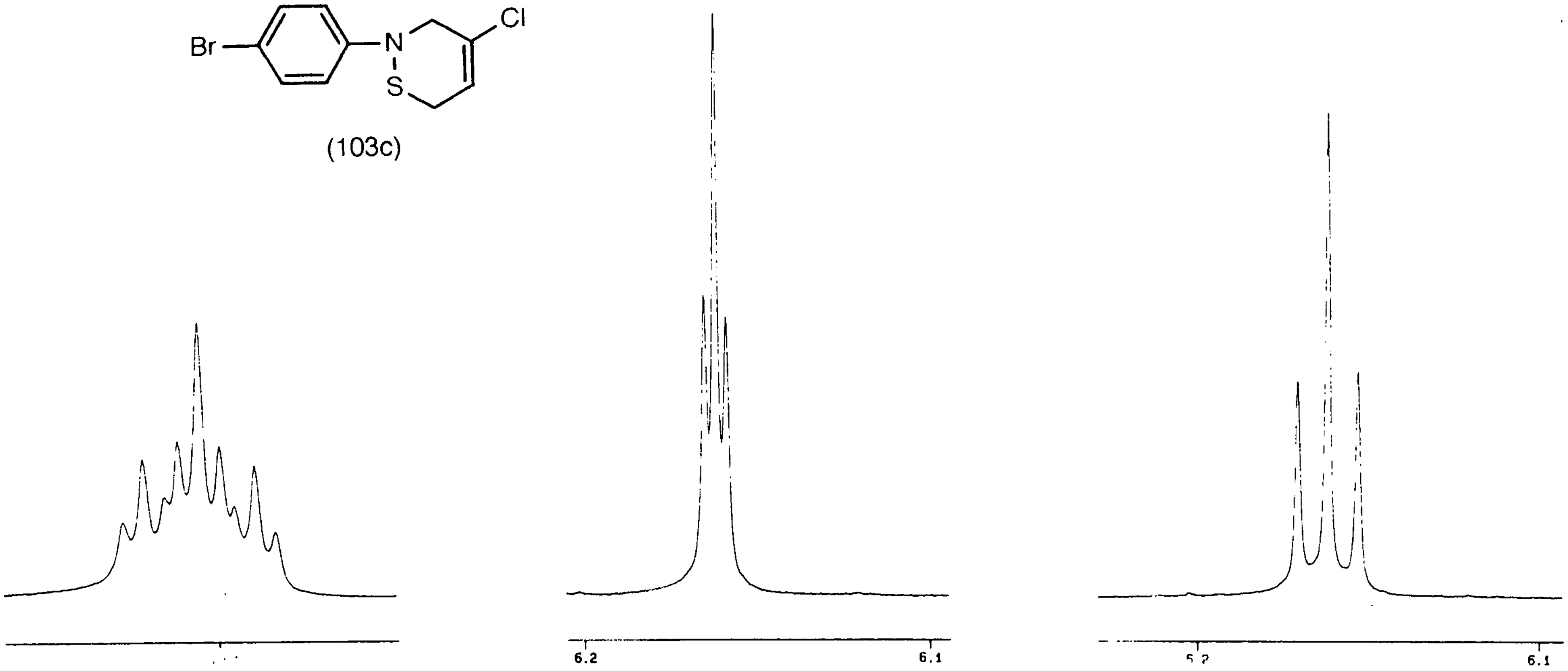


Figure 2.2 - Decoupling of ^{1}H NMR Spectrum of Adduct (103c)



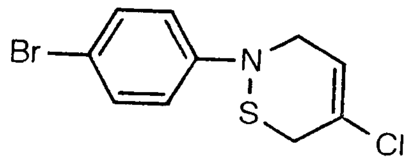
(103c)

Original Spectrum

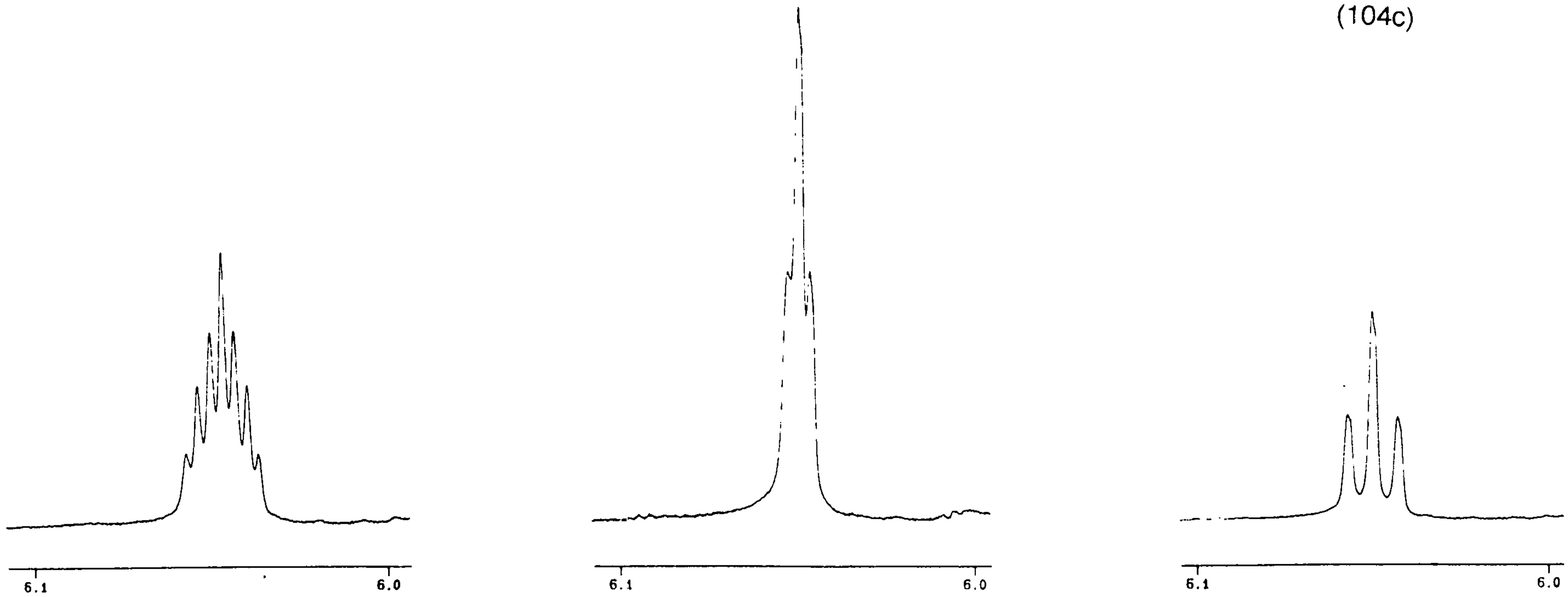
Decoupled at 3.2 ppm
J=1.6 Hz

Decoupled at 4.2 ppm
J=4.4 Hz

Figure 2.3 - Decoupling of ^{1}H NMR Spectrum of Adduct (104c)



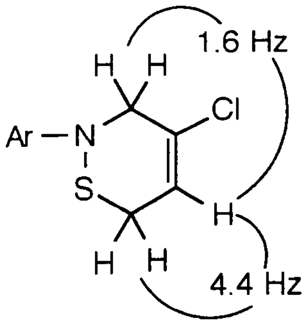
(104c)



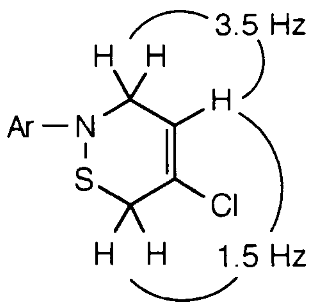
Original Spectrum

Decoupled at 4.2 ppm
J=1.5 Hz

Decoupled at 3.2 ppm
J=3.5 Hz



Major
(103c)

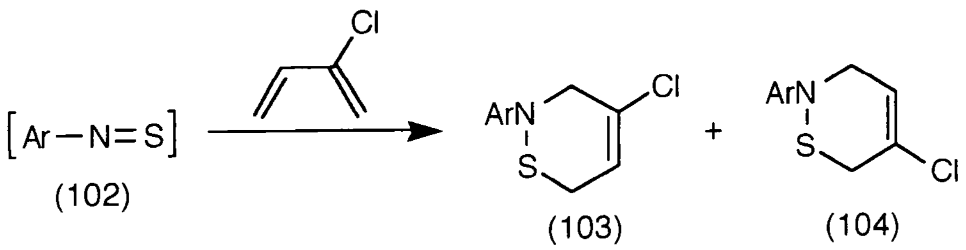


Minor
(104c)

The ratios of isomers were determined by integration of the peaks for the vinylic protons in the ^{1}H NMR spectra and are summarised in Table 2.1. For the MeO and Me derivatives a 1:1 ratio of 4 and 5-substituted adducts was observed while in the case of the Br derivative the 4-substituted thiazine (103c) was the major isomer. This was in contrast to the products obtained with isoprene, where the 5-substituted adduct (99) was the major isomer. Therefore electronic factors are influencing this addition reaction.

Table 2.1

Adducts of Thionitrosoarenes (101) with Chloroprene



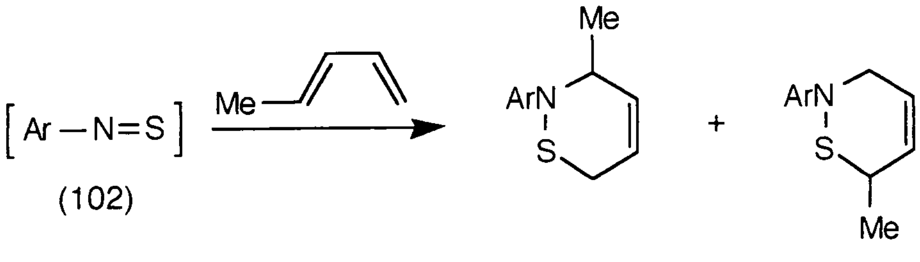
	Ar	Adduct Ratios, (103), (104)
(a)	4-MeO-C_6H_4	1:1
(b)	4-Me-C_6H_4	1:1
(c)	4-Br-C_6H_4	2:1

2.1.3 Reaction of Thionitrosoarenes with Piperylene

1,3-Pentadiene (piperylene) has a terminal methyl group which introduces steric factors into the regioselectivity of cycloaddition reactions. Reactions with piperylene were carried out under conditions similar to those used for the reactions with chloroprene. The crude reaction mixtures containing Diels-Alder adducts (105) and (106) were analysed by 250MHz ^{1}H NMR. Two doublets at δ_H 1.5 and 1.0 ppm were assigned to the methyl group on the thiazine ring in each of the isomers. The signals of higher chemical shift (δ_H 1.5-1.4 ppm) were assigned to the methyl group adjacent to nitrogen while those at lower chemical shift (δ_H 1.1-1.0 ppm) were assigned to the methyl group adjacent to sulphur. Therefore, it was possible to obtain the product isomer ratios from the relative integrals of these doublets. These results are summarised in Table 2.2.

Table 2.2

Adducts of Thionitrosoarenes (102) with Piperylene



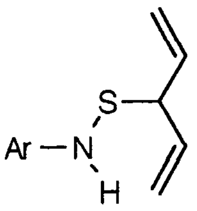
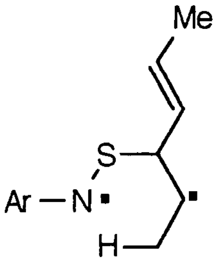
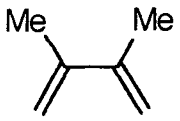
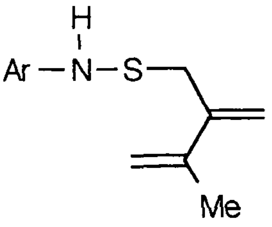
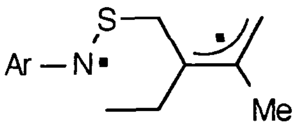
	Ar	Adduct Ratios, (105), (106)
(a)	4-MeO-C_6H_4	3:1
(b)	4-Me-C_6H_4	3:1
(c)	4-Br-C_6H_4	2:1

In each case the major isomer was the 3-substituted product. This is the sterically more hindered product and again indicates the importance of electronic factors in the regiochemical outcome of these reactions.

Piperylene has a methyl group adjacent to the double bond and could therefore react with thionitrosoarenes (102) in an ene reaction but no ene adducts are observed. This behaviour is similar to that observed for the 2,4-hexadienes.[20] The lack of ene reactivity can be accounted for by comparing the transition states for the ene addition of 2,3-dimethyl-1,3-butadiene and

Figure 2.4

Transition States for Ene Addition to 1,3-Pentadiene and 2,3-Dimethylbutadiene

Diene	Concerted	Stepwise Biradical
		
1,3-Pentadiene	Non-conjugated product	Non-stabilised intermediate
		
2,3-Dimethylbutadiene	Conjugated Product	Allylically stabilised intermediate

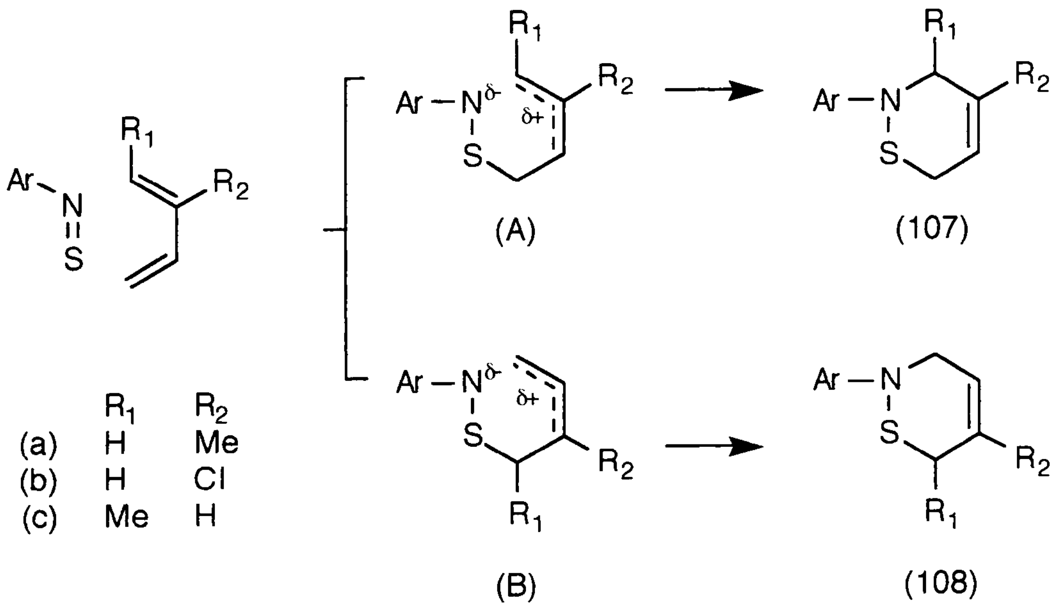
piperylene. For any likely mechanism , concerted or stepwise, the transition states for piperylene are much less stabilised than those for 2,3-dimethylbutadiene. In a concerted process the forming double bond is conjugated for 2,3-dimethylbutadiene but not for piperylene while in a biradical mechanism the intermediate is allylically stabilised for 2,3-dimethylbutadiene but not for piperylene. (Figure 2.4).

2.1.4 Discussion

We have therefore established for the first time that electronic factors are important in determining the regiochemical outcome of Diels-Alder reactions of thionitroso compounds. The regioselectivity is similar to that observed for Ar-N=S=O. Kresze and Wagner put forward a mechanistic model to explain the products that were formed in these reactions.[46b] They proposed that the reaction proceeded through a dipolar transition state. The adduct ratios obtained in the reactions of chloroprene, piperylene and isoprene with thionitrosoarenes can be explained by the substituent (R) on the diene stabilising or destabilising the proposed transition states. (Scheme 2.4). Reaction of thionitrosoarenes with isoprene (R_2=Me) will yield predominantly the 5-substituted thiazine (108a) because transition state B is stabilised relative to transition state A. With chloroprene (R_2=Cl) transition state B is destabilised, and therefore, the 4-substituted thiazine (107b) is favoured. In the case of piperylene (R_1=Me) transition state A is stabilised while there is no stabilisation of transition state B. Therefore the 6-substituted thiazine (107c) is the major adduct.

The substituent on the aryl ring of the thionitrosoarene also has a subtle influence on the regiochemical outcome of the Diels-Alder reaction. This is shown by the fact that different isomer ratios are observed for the electron deficient bromo derivative (102c), when compared with the methyl

(102b) and methoxy (102a) derivatives, in the reactions with both chloroprene and piperylene. This provides further evidence for the importance of electronic effects in the regiochemical outcome of these reactions. A similar substituent effect was observed for the addition reactions of the nitrosobenzenes.[50]



Scheme 2.4

2.2 ENE REACTIONS OF THIONITROSOARENES

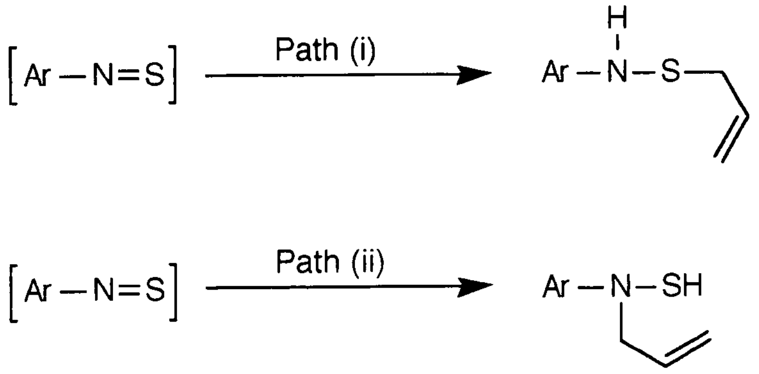
2.2.1 Introduction

The ene reaction has been defined as the " indirect substituting addition of a compound with a double bond (enophile) to an olefin possessing an allylic hydrogen."[51]

We have already seen in Chapter 1 that thionitroso compounds will react as enophiles in ene reactions.[20,38] They can react with C-S [Path (i)] or

C-N [Path (ii)] bond formation. (Scheme 2.5). The first reported ene reactions of thionitroso compounds were the competitive ene *versus* Diels-Alder reactions of 2,3-dimethyl-1,3-butadiene with acyl and sulphonyl thionitroso compounds.[38] These thionitroso compounds also reacted with a range of alkenes including cyclohexene, cyclopentene and dicyclopentadiene, regiospecifically with C-S bond formation [Path (i)]. Thionitrosoarenes reacted with dimethylbutadiene, isobutene and α-methylstyrene, also with C-S bond formation [Path (i)].(20)

The ene reactions of species related to thionitroso compounds have been investigated. Sulphur diimides and sulphinylamines react regiospecifically with C-S bond formation.[52,53] Nitroso compounds react regiospecifically, but with C-N bond formation.[54] Thioaldehydes give both regioisomers in ene reactions *i.e.* there is C-C and C-S bond formation,[55,56] although thioaldehydes with an electron deficient substituent group favour C-S bond formation.[56]



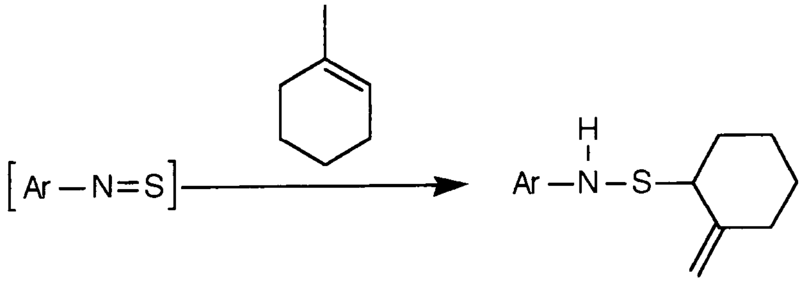
Scheme 2.5

New ene reactions of thionitrosoarenes (102) with various alkenes have now been investigated.

2.2.2 Reaction with 1-Methylcyclohexene

Thionitrosoarenes (102) were generated by adding an excess of triethylamine to a stirring suspension of precursor (101) and excess 1-methylcyclohexene at room temperature. The resulting mixture was stirred until a clear brown solution was obtained. The crude reaction mixtures were analysed by 250 MHz ^{1}H NMR . Peaks for the ene adducts (NH and $=CH_2$) occurred in the δ_H 4.5-5.5 ppm region and were assigned by analogy with the products formed in reactions with α-methylstyrene and isobutene.[20]

Ene adducts were formed with thionitrosoarenes (102a-c) in *ca.* 50% yield. The presence of an NH peak in the ^{1}H NMR spectra of the adducts formed with thionitrosoarenes (102a-c) and an NH, but no SH, absorption in the IR spectrum of the adduct of (102b), clearly supports the regiochemistry of addition as shown in structure (109) (Scheme 2.6). Therefore the reaction of 1-methylcyclohexene with thionitrosoarenes proceeds regiospecifically with C-S bond formation [Path (i), Scheme 2.5]



(102 a-c)

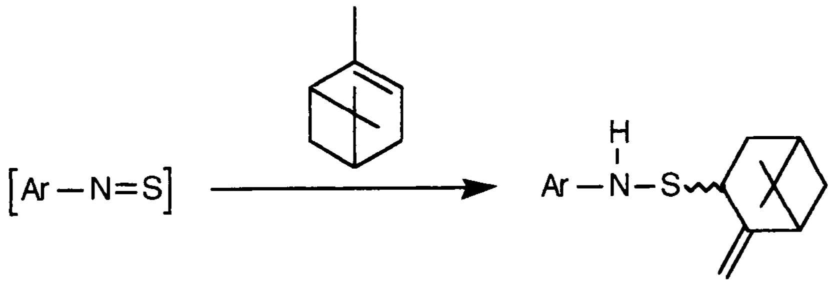
(109 a-c)

Ar = (a) 4-MeO-C_6H_4
(b) 4-Me-C_6H_4
(c) 4-Br-C_6H_4

Scheme 2.6

2.2.3 Reaction with α-Pinene

The reactions of α-pinene with thionitrosoarenes (102a-c) were carried out in the same way as those of 1-methylcyclohexene and spectroscopic analysis of the crude reaction mixtures showed that the reaction proceeds regiospecifically with C-S bond formation. (Scheme 2.7). Adducts (110) were purified on a silica gel column and isolated to give the products as yellow oils (25-65% Yield).



(102 a-c)

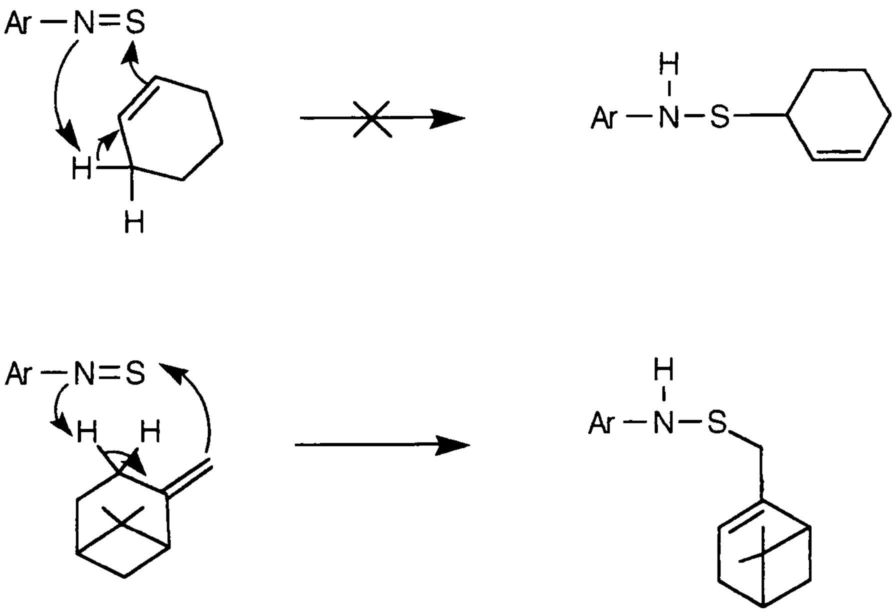
(110 a-c)

Scheme 2.7

2.2.4 Reaction with β-Pinene

Earlier attempts in our laboratory to trap thionitrosoarenes with cyclohexene were unsuccessful.[20a] This lead us to postulate that there was a requirement for a methyl group adjacent to the double bond in the alkene for an ene reaction to occur. To investigate this further, reactions were performed with β-pinene, which has an exocyclic methylene group, *i.e.* there is a CH_2 group adjacent to the double bond, as there is in cyclohexene.

The reaction of β-pinene with thionitrosoarene (102c) was carried out in the same way as those of 1-methylcyclohexene. The ^1H NMR spectrum of the product mixture established that ene adduct (111) was present. This is the first example of an alkene with exocyclic methylene group participating in an ene reaction with a thionitrosoarene. (Scheme 2.8).



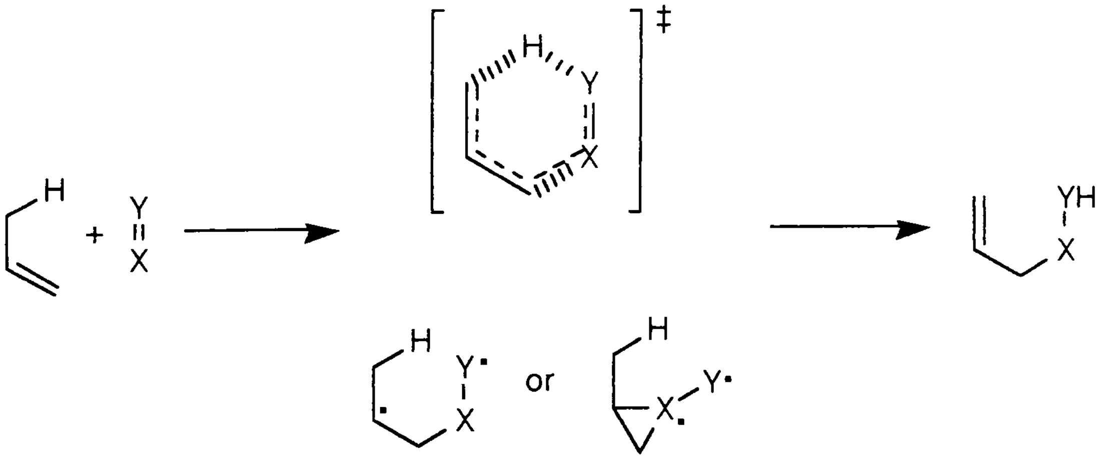
Ar=Br-C_6H_4-

(111c)

Scheme 2.8

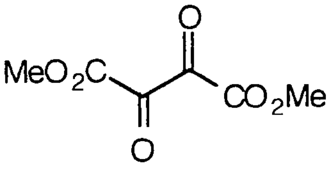
2.2.5 Discussion

Hoffmann[51] concluded in his review of the ene reaction that it could proceed *via* a concerted or stepwise biradical mechanism (Scheme 2.9). Experiments using deuterium isotope effects have provided evidence for the existence of both of these mechanisms. Reactions of the carbonyl compounds

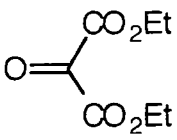


Scheme 2.9

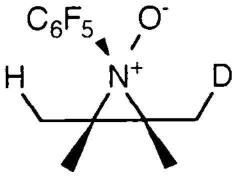
(112) and (113) with methylenecyclohexane have been shown to proceed *via* a concerted mechanism when the reaction is carried out thermally.[57] The ene reaction of the more closely related pentafluoronitrosobenzene was shown to proceed in a stepwise biradical manner through the intermediate (114).[58]



(112)

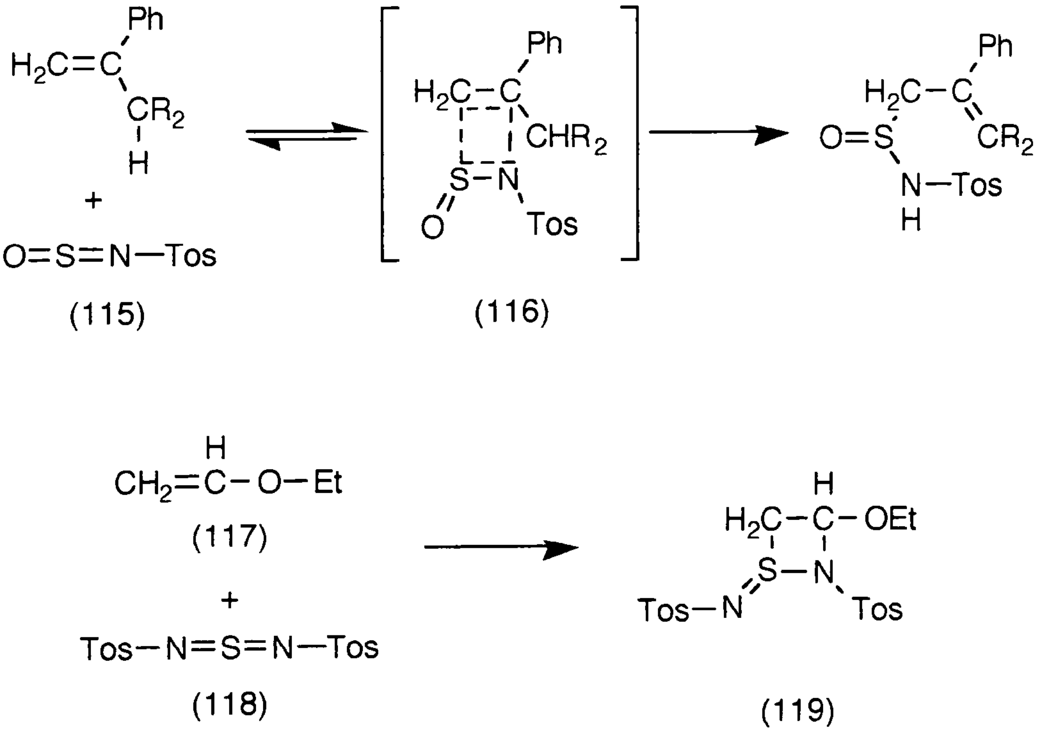


(113)



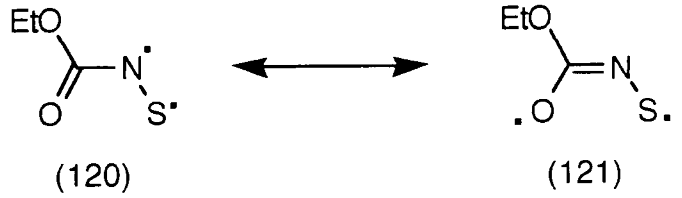
(114)

Münsterer *et al* have studied the reaction of the tosylsulphinylamine (115) with various alkenes.[59] This system undergoes ene reactions to the N=S bond with the same regioselectivity as thionitroso compounds (*i.e.* with C-S bond formation). Compound (115) was described as a super enophile as it reacted readily at ambient temperature in the same way as thionitrosoarenes (102) without the need for higher temperatures which are usually necessary for an ene reaction to occur. It was proposed that the reaction of (115) proceeded through a four membered cyclic transition state (116) followed by non-linear hydrogen transfer (Scheme 2.10). Further evidence for a four membered ring transition state is provided by work on sulphur diimide (118). When (118) was reacted with vinyl ether (117), thiazete (119) was isolated in 75% yield.



Scheme 2.10

The fact that thionitrosoarene (102b) will react with β-pinene, but not with cyclohexene, can be accounted for by a concerted mechanism. Scheme 2.8 shows that it is not possible for cyclohexene to achieve a six membered transition state whereas this is possible for β-pinene. The lack of reactivity with cyclohexene can also be accounted for if the reaction proceeded *via* a [2+2] transition state analogous to (116). The ene reactivity of thionitrosoarene (102c) towards β-pinene and cyclohexene is in contrast to that observed by Meth-Cohn for acyl and sulphonyl thionitroso compounds (84).[38] These electron deficient thionitroso compounds unexpectedly did not form ene adducts with β-pinene, but did form adducts with cycloalkenes, including cyclohexene. It has been suggested that acyl and sulphonyl thionitroso compounds may react *via* a radical mechanism. in which the triplet state could be stabilised by the adjacent electron deficient group [Structures (120) and (121)].



2.3 EFFECT OF SOLVENT ON THE RATIO OF DIELS-ALDER : ENE ADDUCTS OF THIONITROSOARENES

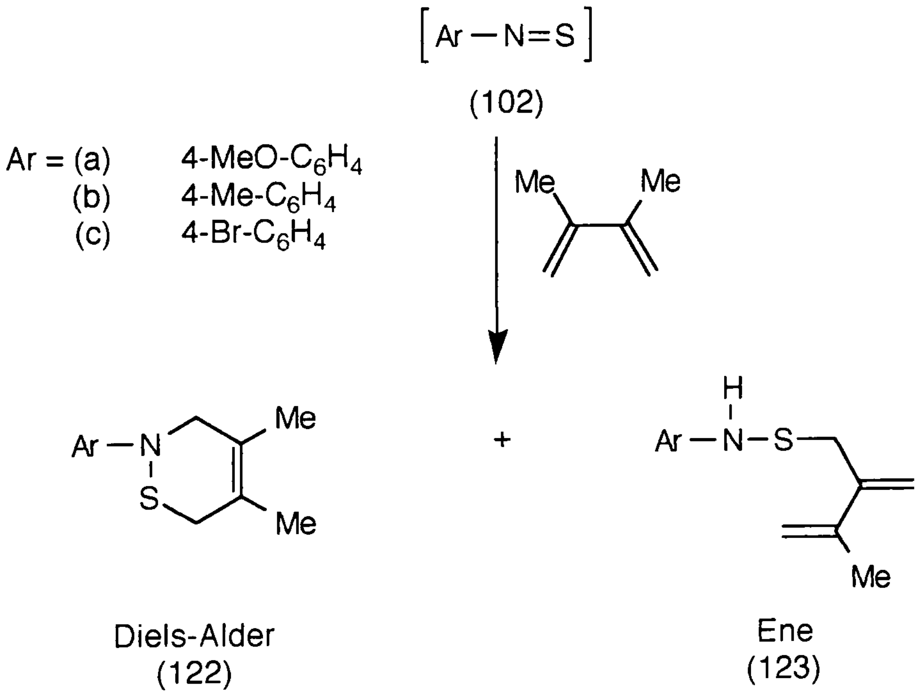
2.3.1 Introduction

Competition between Diels-Alder and ene reactions with the same diene has been observed only for a small number of dienophiles.[41-45] The effect of varying the solvent in these reactions has not been reported. We considered this aspect of ArN=S reactivity to be worthy of investigation.

Okazaki *et al.* have generated thionitrosoarenes by irradiation of 3-azido-2,1-benzisothiazoles (42) in various solvents in the absence of trap.[22] The major products were sulphur diimide (44) and amine (45), the ratios of which were found to vary with solvent. Sulphur diimide (44) was the major product in non-polar hexane, while in more polar solvents, *e.g*. ethanol, amine (45) was the major product.

2.3.2 Results and Discussion

Thionitrosoarenes (102 a-c) were generated from phthalimide precursors (101) and trapped *in situ* with 2,3-dimethyl-1,3-butadiene in various solvents. (Scheme 2.11 and Table 2.4). In previous studies we had performed this reaction in acetone as phthalimide precursors (101) are sparingly soluble in acetone at room temperature. This enables thionitrosoarenes (102) to be formed in very low steady state concentration which suppresses dimerisation reactions.[20] Thus, varying amounts of the solvents were used so that the phthalimide precursors would dissolve slowly



Scheme 2.11

In each case a mixture of Diels-Alder (122) and ene adducts (123) was obtained. Isomer ratios were determined from the integration of the 250MHz ^1H NMR spectra of the product mixtures. The results are summarised in Table 2.4. In each solvent a higher proportion of ene adducts (123) is formed in the case of the electron withdrawing bromo derivative (102c). The Diels-Alder adduct (122) is the major isomer in each solvent for the electron rich methoxy derivative. These results were as expected from previous work using acetone as solvent.[20] Table 2.4 clearly shows that the solvent has a significant effect upon the ratio of adducts obtained. In the more polar solvents at the top of the table, *e.g.* DMF, a higher proportion of ene adducts (123) is formed, while in the less polar solvents lower down the table a higher proportion of Diels-Alder adducts (122) are formed.

Table 2.4

Ratios of Diels-Alder (122) : Ene Adducts (123) in Various Solvents

para - substituent	MeO	Me	Br
Adducts	Ene : D-A	Ene : D-A	Ene : D-A
DMF	20 : 80	45 : 55	77 : 23
Acetonitrile	17 : 83	41 : 59	75 : 25
Acetone[20]	15 : 85	40 : 60	75 : 25
Chloroform	15 : 85	30 : 70	65 : 35
Toluene	12 : 88	24 : 76	50 : 50

Polar solvents clearly enhance the ene reaction. This can be explained by postulating a dipolar transition state for the ene adduct which would have a greater degree of stabilisation in polar solvents. Kinetic investigations show that the Diels-Alder reaction of the related species $EtO_2C-N=S=O$ proceeds *via* a pericyclic mechanism.[60] A concerted mechanism has also been proposed for the Diels-Alder reaction of thionitrosoarenes.[29] The Diels-Alder reaction appears to be unaffected by solvent in these reactions which also supports a concerted mechanism. These explanations are tentative because, as described in Section 2.2, the mechanism of the ene reactions of thionitrosoarenes (102) is still uncertain.

2.4 CATALYSIS OF THE REACTIONS OF THIONITROSOARENES

2.4.1 Introduction

Catalysis of Diels-Alder reactions was first reported in 1942[61] but at that time the effects observed were small. In 1960 the remarkable acceleration of Diels-Alder reactions by aluminium trichloride was reported.[62] Various catalysts, including stannic chloride and aluminium chloride, have also been used to enhance ene reactions.[51] Of particular interest is the reaction of isoprene with trichloroacetaldehyde (chloral) in dichloromethane. Without catalyst a temperature of 150°C was required for this reaction and Diels-Alder and ene adducts were obtained in a 90:10 ratio. When stannic chloride was used as a catalyst the reaction proceeded at room temperature and the ratio of adducts was reversed to 5:95.

If there is a catalytic effect on the Diels-Alder and ene reactions of thionitrosoarenes we would therefore expect to see a change in the isomer ratio.

2.4.2 Results and Discussion

Thionitrosoarenes (102) were generated from phthalimide precursors (101) using triethylamine in the presence of the catalyst and excess dimethylbutadiene in chloroform. Acetone, which is the solvent usually used for trapping reactions was not suitable because of possible complexation between acetone and the catalyst. The catalysts used were BF_3 etherate and aluminium chloride. The isomer ratios were determined from the integration of the 250 MHz ^1H NMR spectra of the crude reaction mixtures and found to be unchanged by the presence of catalyst.

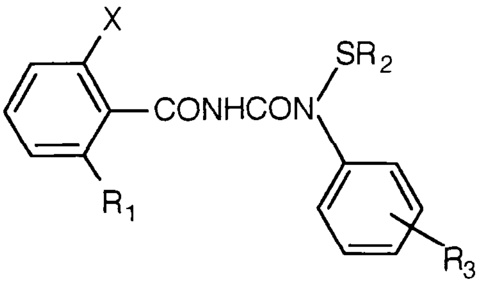
Lewis acids are thought to catalyse Diels-Alder reactions by forming a complex with a basic centre on the electron withdrawing group of the dienophile. This lowers the energy of the lowest unoccupied molecular orbital (LUMO) of the dienophile and the separation between the molecular orbitals of the reactants will decrease allowing the reaction to proceed more readily.[63] There is no evidence from the above results that a similar complexation occurs with thionitrosoarenes, possibly due to their short lifetime.

2.5 DERIVATISATION OF ENE ADDUCTS WITH BENZOYL ISOCYANATES

2.5.1 Introduction

To date it has not been possible to separate mixtures of ene (123) and Diels-Alder adducts (122) of thionitrosoarenes (102).[20] The products are oils that decompose on standing for a few days at room temperature. It was hoped that derivatisation of the ene adducts (123) (which are the more unstable products) would enable the mixtures to be separated and also give stable solid derivatives of the ene adducts (123).

Compounds of general structure (124) are characteristically stable crystalline solids and have insecticidal activity.[64] They are prepared by the action of benzoyl isocyanates[65] on the corresponding amines which have a structure similar to that of the ene adducts of thionitrosoarenes. Therefore, we chose to react our ene adducts with benzoyl isocyanates.

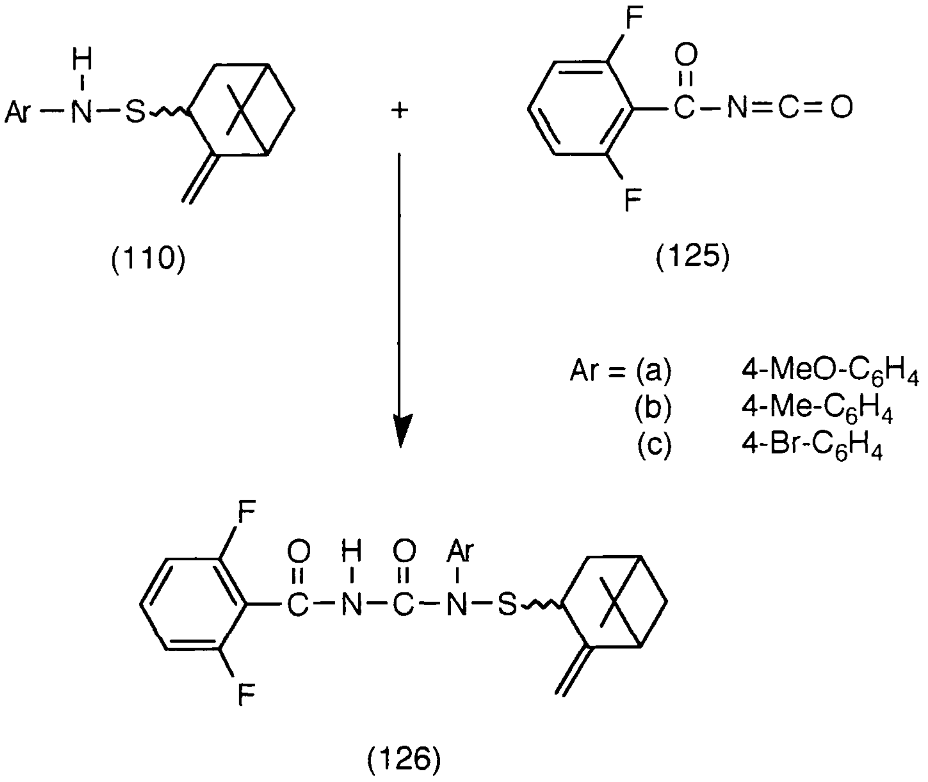


(124)

X=halo; R_1=H, halo; R_2=CN, haloalkyl, haloalkoxy, aryloxy;
R_3=aryl, haloalkyl

2.5.2 Reaction of Ene Adducts with Benzoyl Isocyanates

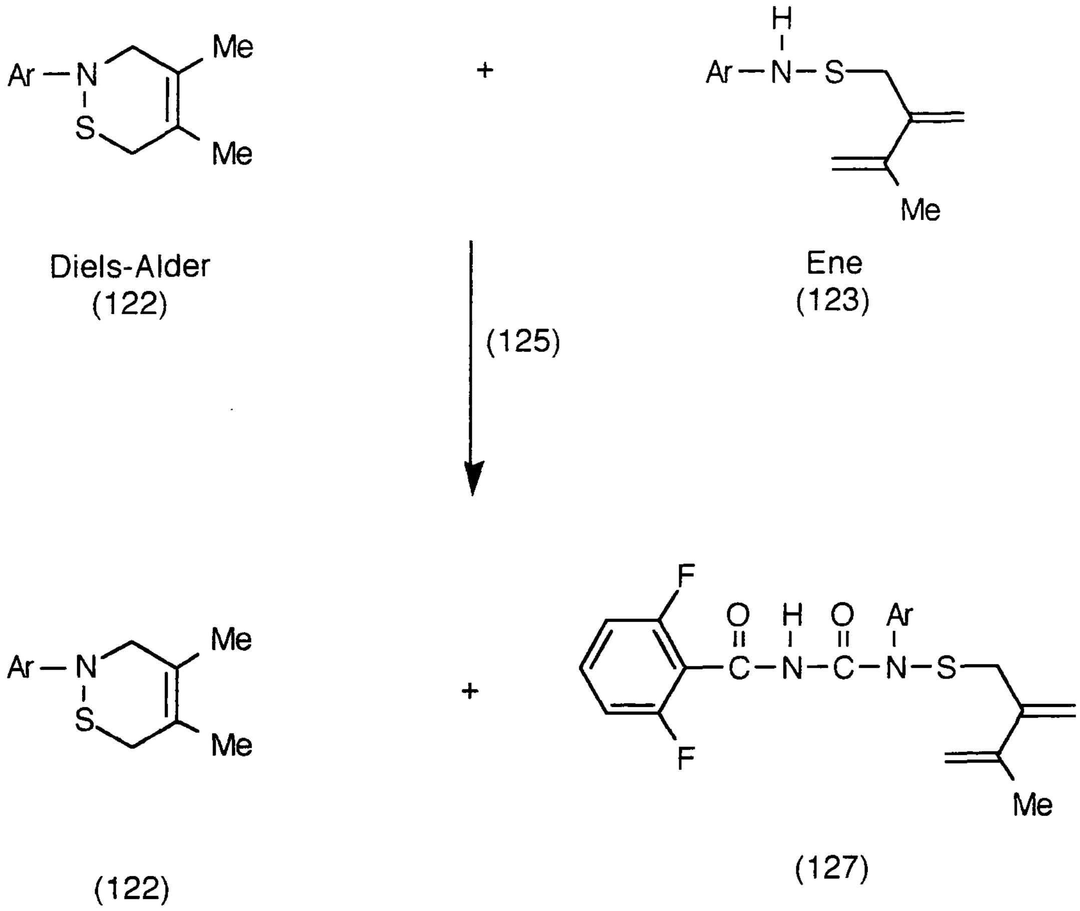
The ene adducts (110) of thionitrosoarenes (102) with α-pinene were chosen for preliminary reactions. As described in Section 2.2.3 only ene adducts are formed in these reactions and the product can be purified. Therefore, there is little possibility of the benzoyl isocyanates reacting with impurities. 2,6-Difluorobenzoyl isocyanate (125) was added to a solution of the ene adducts (110) in toluene and stirred for 2 hours. The derivatised products (126) were isolated after chromatography as white solids in low yield (Scheme 2.12).



Scheme 2.12

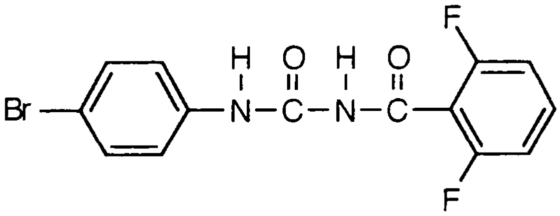
2.5.3 Purification of Isomer Mixtures Using Benzoyl Isocyanate Derivatisation

In view of the formation of compounds (126), we aimed to similarly derivatise the ene adducts (123) of thionitrosoarenes (102) and dimethylbutadiene. We would expect the Diels-Alder adducts (122) to be unreactive towards benzoyl isocyanate (125). The derivatives should also have different Rf values from the Diels-Alder adducts allowing separation by column chromatography. Thus, 2,6-difluorobenzoyl isocyanate (125) was reacted with crude mixtures of Diels-Alder (122 a-c) and ene adducts (123 a-c) in the same way as described for reaction of the α-pinene adducts. (Scheme 2.13). This enabled the Diels-Alder adducts (122 a-c) to be isolated pure after



Scheme 2.13

column chromatography. The product of reaction between the ene adducts (123 a-c) and benzoyl isocyanate (125) was isolated only for the 4-bromophenyl derivative (127c). The 250 MHz ^{1}H NMR spectrum of compound (127c) showed that (128) was present as an impurity. The formation of this compound can be explained by cleavage of the N-S bond in compound (127c) resulting in loss of a thiol fragment. Compounds (127a) and (127b) were not isolated. This is probably because only very small amounts of the derivative were formed because the corresponding ene adducts (123a) and (123b) were the minor isomers in the crude reaction mixture, and because of cleavage of the N-S bond of (127).



(128)

Derivatisation of the ene adducts (110 a-c) was also attempted with methyl isocyanate and acetyl chloride. No observable reaction occurred with methyl isocyanate. On reaction with acetyl chloride a large number of unidentified products were formed.

In conclusion derivatisation of the ene adducts (110) and (123) with benzoyl isocyanate (125) provides a method for purifying Diels-Alder adducts (122) and for making isolable solid derivatives of the ene adducts, where these form a large percentage of the isomer mixture.

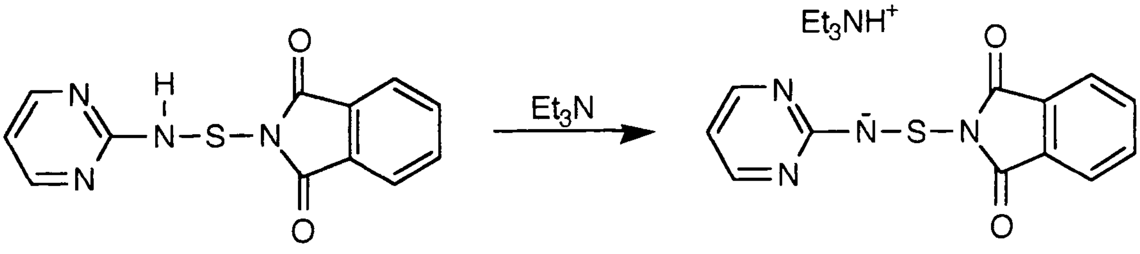
2.6 ELECTRON DEFICIENT THIONITROSO COMPOUNDS

2.6.1 Introduction

The only example of a heterocyclic thionitroso compound to have been reported is the 3-thionitrosopyridine (30g) which was generated from phthalimide precursor (29g) and successfully trapped in Diels-Alder and ene reactions.[20a] Several heterocyclic sulphinylamines have been prepared.[66-68] It has been shown that the pyridine derivatives react as 4π heterodienes in Diels-Alder reactions.[66, 67] This contrasts with the usual reactivity of more activated sulphinylamines (*e.g*. Ts-N=S=O) which behave as dienophiles in Diels-Alder reactions. We have now prepared new heterocyclic thionitroso compounds to investigate the versatility of the phthalimide precursor route to these systems, and to study their adduct chemistry.

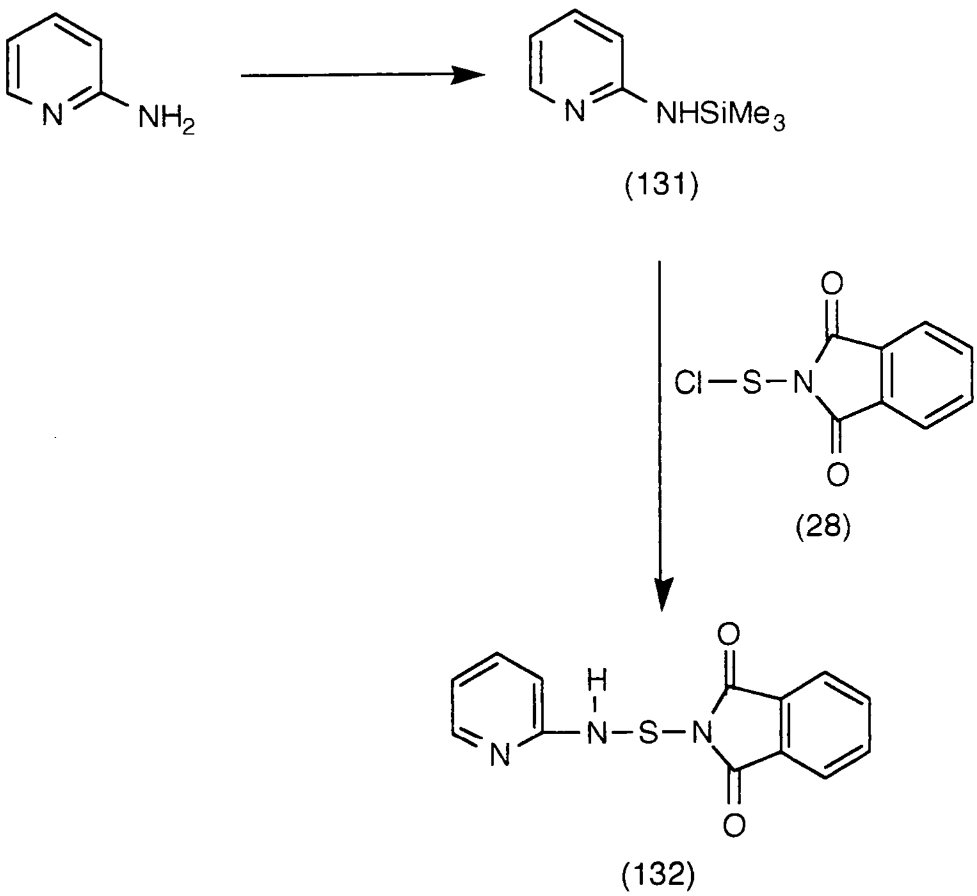
2.6.2 2-Thionitrosopyridine Derivatives

The phthalimide precursor (129) had previously been prepared in our laboratory but fragmentation to give 2-thionitrosopyrimidine did not occur.[29] It was thought that this was because the initially formed anion (130) was stabilised by the electron demanding substituent and would be unlikely to eliminate phthalimide anion to give a thionitroso compound. However, we considered that 2-thionitrosopyridine, with only one nitrogen in the hetero-aryl ring could possibly be prepared *via* this route.



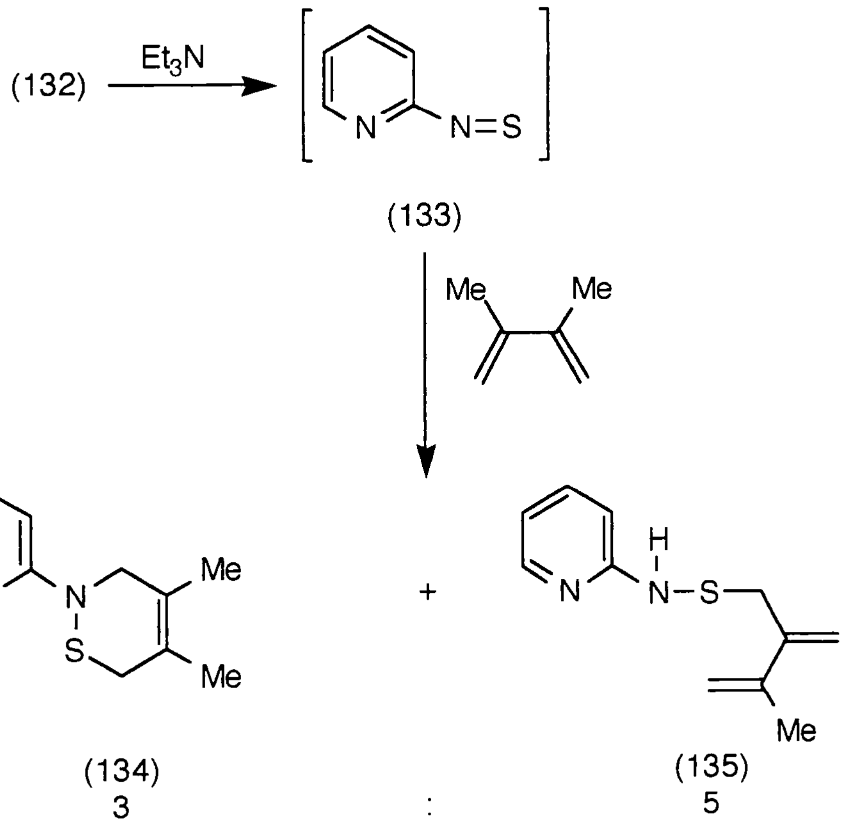
(129) (130)

Attempts to prepare precursor (132) from silylamine (131) and *N*-chlorosulphenyl phthalimide (28) as described in Scheme 1.7 immediately met with problems. The silylation procedure previously used for aryl amine derivatives, using triethylamine and chlorotrimethylsilane, proved unsuccessful in this case. Therefore, trimethylsilylamine (131) was prepared using *n*-butyllithium and chlorotrimethylsilane, adapting a literature procedure.[69] Reaction of silylamine (131) with reagent (28) proceeded as expected to give precursor (132) as a white solid (15% yield) (Scheme 2.14). It was also possible to prepare precursor (132) directly from the amine without silylation (<15% yield).



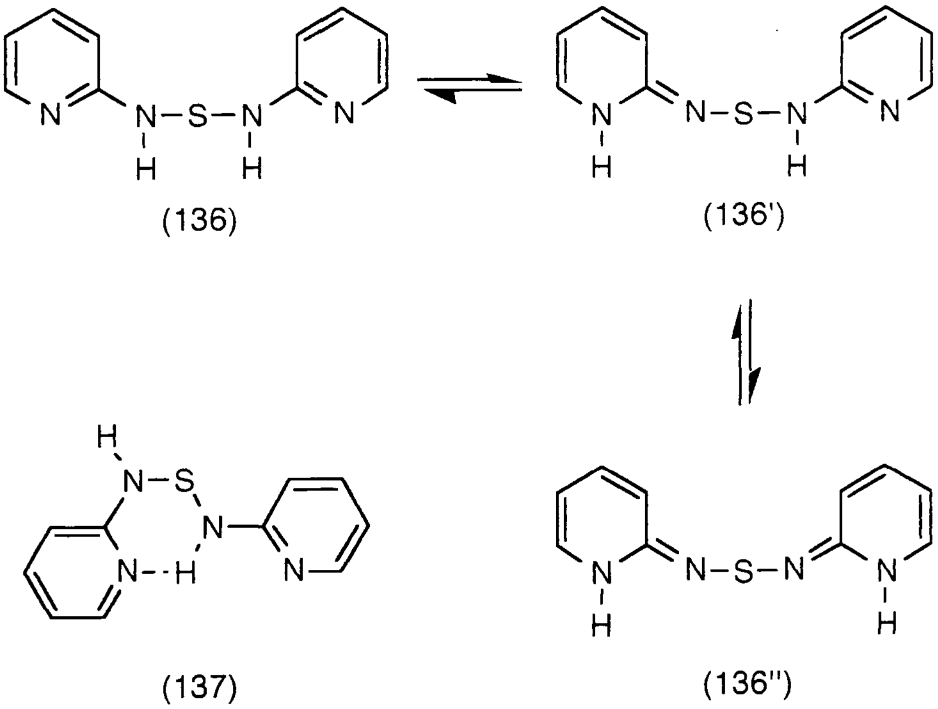
Scheme 2.14

2-Thionitrosopyridine (133) was generated and trapped by adding excess triethylamine to a stirring suspension of precursor (132) and excess 2,3-dimethyl-1,3-butadiene in acetone (Scheme 2.15). The isomer ratio of the products was determined from the 250 MHz ^{1}H NMR spectrum of the crude reaction mixture. Diels-Alder (134) and ene adducts (135) were formed in a 3:5 ratio (total yield 65%). This isomer ratio is consistent with previous work which has shown that for electron deficient thionitroso compounds the ene adduct predominates.[20] Ene reactions can occur when the diene is in the transoid or cisoid conformation, whereas Diels-Alder reactions can only occur in the latter situation. Electron deficient thionitroso compounds , *e.g.* (133), are more reactive and hence more likely to react with a diene in the transoid configuration to give ene adducts than the less reactive electron rich thionitroso compounds.



Scheme 2.15

On one occasion attempted synthesis of precursor (132), by stirring a solution of 2-aminopyridine and *N*-chlorosulphenyl phthalimide (28), precipitated a white solid. The ^{1}H NMR, IR and mass spectra, along with elemental analysis showed this compound to be *N,N'*-thiobis-(2-aminopyridine) (28% yield) (136). Compound (136) is air- and moisture-stable which contrasts with the thiodianilines (17) prepared by Tavs[17] which were unstable. The stability of (136) can be explained by resonance forms in which the amine hydrogens shift to the nitrogen of the pyridine ring (136') and (136'') (Scheme 2.16) or by hydrogen bonding between the amine hydrogen

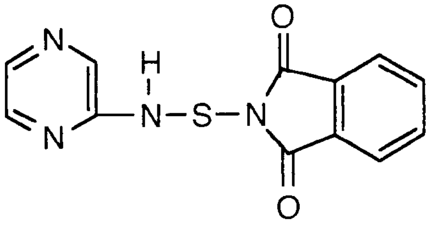


Scheme 2.16

and the nitrogen of the pyridine ring (137). Attempts to generate thionitroso compound (133) from compound (136) either by heating or by treatment with base were unsuccessful, possibly due to a large contribution from structures (136') and (136"). The mass spectrum of compound (136) did , however, show a peak at *m*/*z* (EI) 124 which can be assigned to thionitroso compound (133). This shows that compound (136) will fragment to give 2-thionitrosopyridine (133) in the mass spectrometer providing further evidence in favour of structure (136). We thought that the anomalous formation of compound (136) may be the result of an impurity of *N*,*N*'-dithiobisphthalimide in the *N*-chlorosulphenyl phthalimide (28) acting as a sulphur transfer reagent. However, this is not the case as no appreciable reaction occurred between 2-aminopyridine and pure *N*,*N*'-dithiobisphthalimide.

2.6.3 2-Thionitrosopyrazine Derivatives

Precursor (138) was prepared in 85% yield from 2-(trimethylsilylamino)pyrazine and *N*-chlorosulphenyl phthalimide (28) analogously to compound (132). Unlike the pyridine analogue, it was not possible to prepare precursor (138) using the amine without silylation. 2-Thionitrosopyrazine was generated from phthalimide precursor (138) using triethylamine, and successfully trapped with 2,3-dimethyl-1,3-butadiene to give a mixture of Diels-Alder and ene adducts in *ca.* 10% yield (^{1}H NMR evidence). Because of the low yield and the presence of side products it was not possible to determine the isomer ratios from the ^{1}H NMR spectra. Attempted purification of the adducts was unsuccessful.

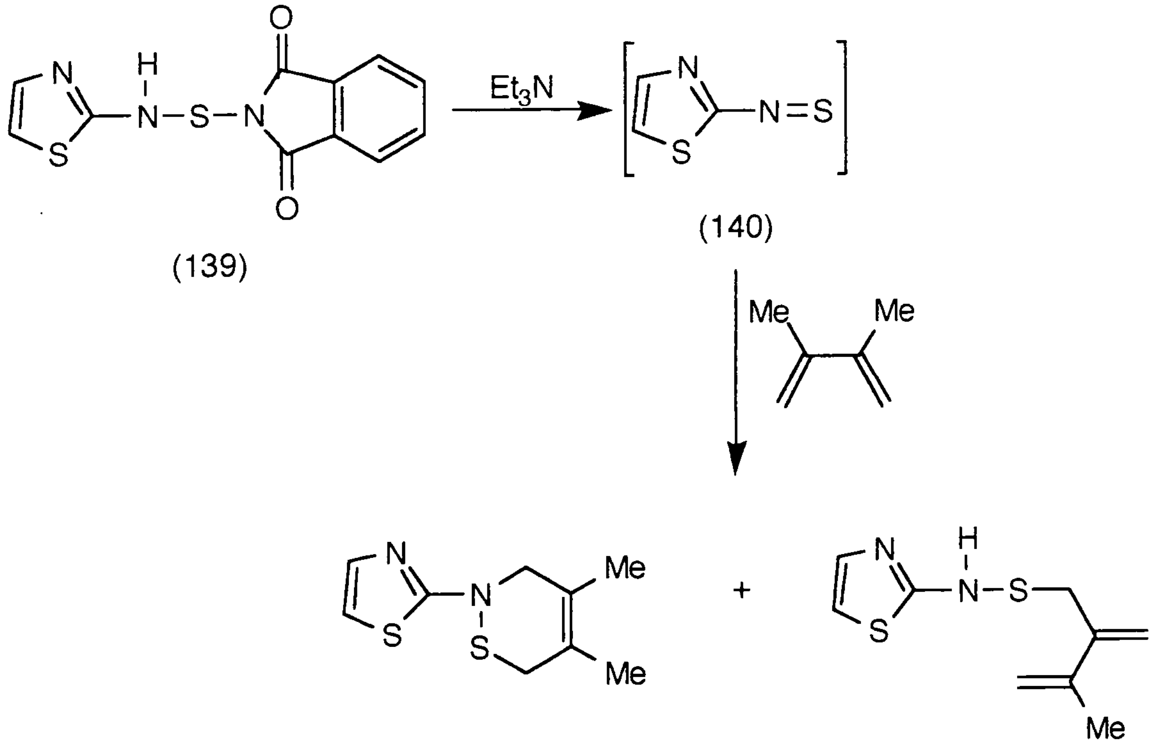


(138)

2.6.4 2-Thionitrosothiazole Derivatives

The successfully trapped heterocyclic thionitroso compounds, 2-thionitrosopyridine (133) and 3-thionitrosopyridine (30g), are both electron deficient giving ene adducts as the major product upon reaction with 2,3-dimethyl-1,3-butadiene. Therefore, it was of interest to prepare 2-thionitrosothiazole (139) which might behave as a potentially electron rich thionitroso compound. The 2-sulphinylamine derivative of thiazole has been prepared.[67]

Phthalimide precursor (139) was prepared analogously to precursor (132) and 2-thionitrosothiazole was generated from precursor (139) using triethylamine and trapped *in situ* with dimethylbutadiene. (Scheme 2.16). The ratio of Diels-Alder (141) and ene (142) adducts, determined from the 250 MHz ^{1}H NMR spectrum, was found to be 1:4. The fact that ene adduct (142) predominates implies that the thiazole ring of thionitroso compound (140) was behaving as an electron withdrawing substituent. This can be explained by interaction of the ring nitrogen with the adjacent thionitroso group.



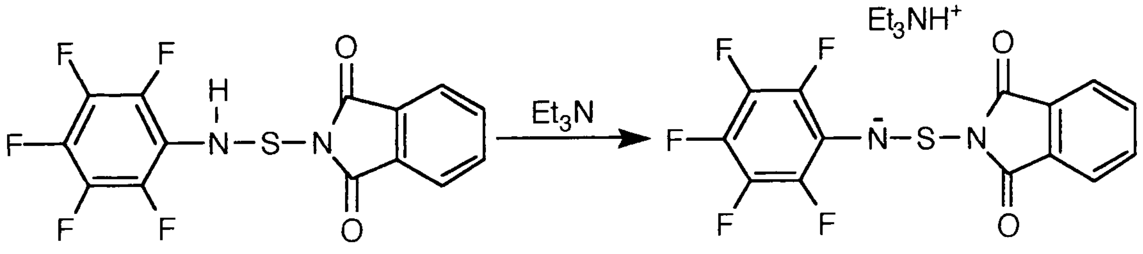
(139) (140) (141) (142)

Scheme 2.16

2.6.5 Thionitrosopentafluorobenzene

Thionitrosopentafluorobenzene would, clearly, be a highly electron deficient derivative and might, therefore, be expected give only ene adducts with the total exclusion of the Diels-Alder adduct when trapped with dimethylbutadiene.

Phthalimide precursor (143) was prepared in the standard way in 40% yield. Attempts to generate thionitrosopentafluorobenzene from precursor (143) using triethylamine as base and trap it *in situ* with dimethylbutadiene were unsuccessful. It seems that the anion (144) initially formed is highly stabilised by the electron withdrawing substituents to the extent that it will not fragment. The thionitroso compound, if formed, would be expected to be highly reactive due to the electron demanding substituents.



(143) (144)

It appears, therefore, that one of the limitations of the phthalimide route is the difficulty in preparing highly electron deficient thionitroso compounds by this method.

2.7 SUMMARY

We have shown that the reactions of thionitrosoarenes (102) are influenced by many subtle effects. The regiochemistry of the Diels-Alder addition of unsymmetrical dienes is dependent upon electronic factors while the ratio of Diels-Alder to ene adducts formed with dimethylbutadiene appears to be influenced by solvent polarity. New ene reactions of thionitrosoarenes (102) with alkenes have been investigated, providing an insight into the mechanism. The ene adducts have been reacted with benzoyl isocyanates to form stable derivatives, allowing pure Diels-Alder adducts to be isolated. New heterocyclic thionitroso compounds have been prepared and trapped.

CHAPTER 3

ORTHO-SUBSTITUTED THIONITROSOARENES

3.1 ORTHO-SUBSTITUTED THIONITROSOARENES FROM PHTHALIMIDE PRECURSORS

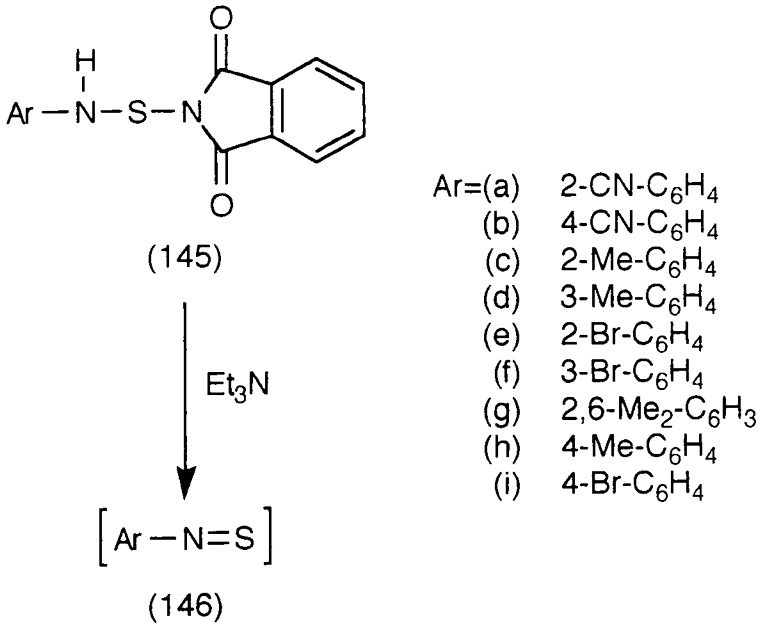
3.1.1 Introduction

When 1-thionitrosonaphthalene (30g) was trapped with dimethylbutadiene, Diels-Alder and ene adducts were obtained in a 45:55 ratio.[20] It was thought that steric factors could be influencing the product isomer ratio as a higher percentage of ene adduct was formed than would have been expected solely from electronic considerations. A substituent in the *ortho* position would be expected to hinder the approach of the diene and thereby increase the proportion of ene adduct formed in the trapping reaction. Therefore, it was of interest to synthesise other precursors with substituents in the *ortho* position to investigate the importance of steric factors in the reactions of thionitrosoarenes, an aspect of their reactivity which had not been previously explored.

3.1.2 Preparation and Reactions of New Thionitrosoarenes

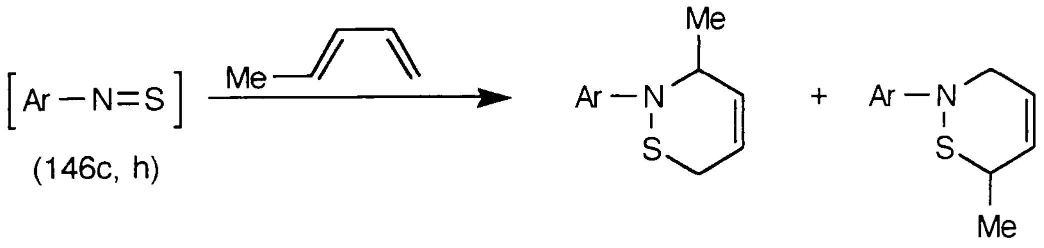
New *ortho-*, *meta-* and *para*-substituted thioarylphthalimides (145 a-g) were prepared from *N*-chlorosulphenyl phthalimide (28) and the corresponding silylamines. Thionitrosoarenes generated from 3-azido-2,1-benzisothiazoles[21-24] have an *ortho*-cyano substituent (Section 1.3.2). Thus, the *para*-and *ortho*-cyano substituted precursors were prepared so that the two routes could be directly compared.

The amines were silylated in a procedure using *n*-butyllithium and trimethylsilylchloride. The thionitrosoarenes (146 a-g) were generated from the precursors (145) using triethylamine (Scheme 3.1) and were trapped *in situ* with various alkenes and dienes.



Scheme 3.1

The *ortho*-methyl derivative (146c) was reacted with piperylene to investigate the effect of an *ortho* substituent on the regioselectivity of the Diels-Alder reaction (Scheme 3.2). The adducts (147c) and (148c) were formed in high yield. The crude reaction mixture was analysed by 250 MHz ^1H NMR spectroscopy and the ratio of isomers (147c) : (148c) was found to be 3 : 2, *i.e.* the more sterically hindered 3-methyl adduct was the major isomer. When the *para*-methyl derivative (146h) was trapped with piperylene, there was an increased preference for the formation of the 3-methyl adduct with (147h) and (148h) being formed in a 3 : 1 ratio (see Section 2.1.3). Therefore, there is a steric effect which results in a smaller percentage of the more sterically hindered 3-methyl adduct (147c) being formed when the aromatic ring has an *ortho* substituent.



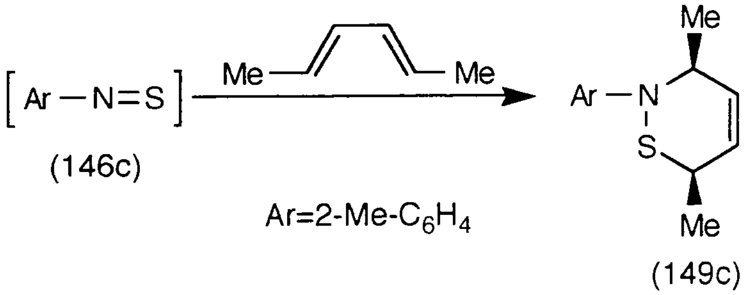
(146c, h)

Ratio of Isomers: (147c) 60% (148c) 40%
(147h) 75% (148h) 25%

Scheme 3.2

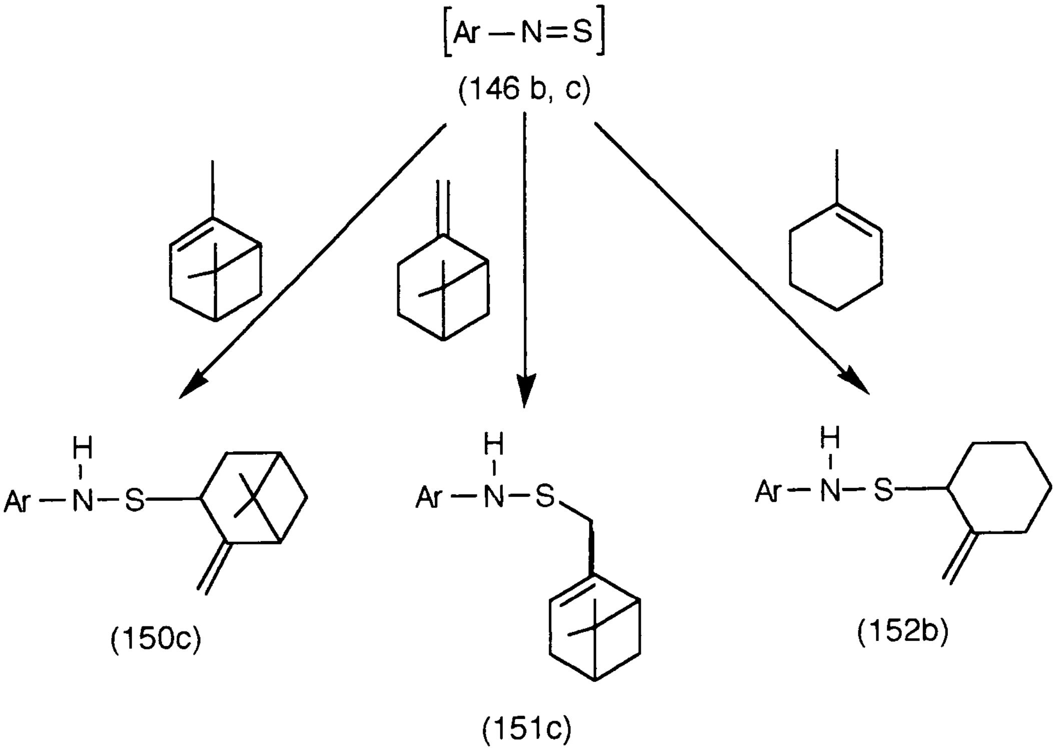
Previous work in our laboratory had shown that (*E, E*) and (*E, Z*) hexa-2,4-dienes undergo Diels-Alder reactions with thionitrosoarenes with retention of stereochemistry, the (*E, E*) hexadiene reacting in preference to the (*E, Z*) isomer (Section 1.3.1).[20] A thionitrosoformate derivative has been reported by Meth-Cohn *et al* to react with 1,4-diphenylbutadiene to give an inseparable mixture of diasteriomers.[39] *N*-Sulphinylamines and sulphur diimides have been shown to react with 1,4-substituted dienes with retention of stereochemistry.[3, 60, 70]

The effect of an *ortho* substituent on the stereoselectivity of the Diels-Alder reaction of thionitrosoarenes was investigated by reacting (*E, E*) hexa-2,4-diene with thionitrosoarene (146c). The 250 M Hz ^{1}H NMR spectrum showed that the reaction proceeded stereospecifically to give the *cis* adduct (149c) (60% yield) in high diasteriomeric excess (>90%). Therefore, it appears that an *ortho* methyl group has little effect on the stereochemical outcome of the reaction (Scheme 3.3).



Scheme 3.3

Thionitrosoarene (146c) reacted with α– and β-pinene to give adducts (150c) and (151c) (50-68% yield), thereby establishing that *ortho*-substituted thionitrosoarenes will readily react with alkenes in ene reactions. The previously unreported *para*-cyanothionitrosoarene (146b) gave the ene adduct (152b) (16% yield) with 1-methylcyclohexene. These ene reactions proceed regiospecifically with C-S bond formation (Scheme 3.4).



Scheme 3.4

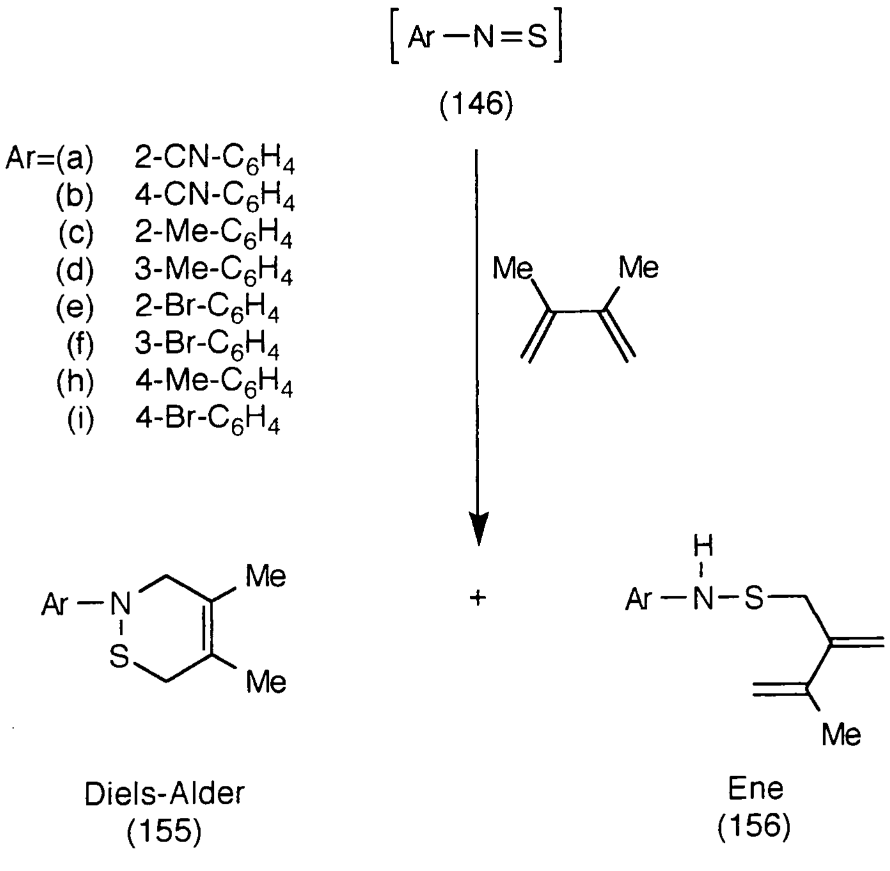
Attempted generation and interception of 2,6-dimethyl thionitrosoarene (146g) proved unsuccessful. This is probably due to steric factors, as the approach of triethylamine in the 1,2-elimination reaction from precursor (145g) would be hindered by the *ortho* methyl groups. The precursor to *ortho*-propyl thionitrosoarene could not be prepared either, possibly for similar reasons. Therefore, it seems that the phthalimide route cannot be used to prepare thionitrosoarenes with bulky substituents in the *ortho* position.

3.1.3 Effect of the Position of the Substituent on the Ratio of Diels-Alder to Ene Adducts Formed with Thionitrosoarenes

We have already seen that the ratio of Diels-Alder and ene adducts formed when thionitrosoarenes react with 2,3-dimethyl-1,3-butadiene is dependent upon both the electronic nature of the substituent group (Section 1.3.1)[20] and the reaction solvent (Section 2.3). The possible steric effect in the reaction of the 1-naphthylthionitrosoarene with dimethylbutadiene was discussed at the beginning of this chapter. The regioselectivity of the reaction of piperylene with *ortho*-methylthionitrosobenzene (146c) appears to be influenced by steric factors. Therefore, it was of interest to investigate in some detail the effect of the position of the substituent on the ratio of Diels-Alder to ene adducts formed between thionitrosoarenes (146a-f) and 2,3-dimethyl-1,3-butadiene.

Thionitrosoarenes (146 a-f) were generated from phthalimide precursors (145 a-f) in the standard way using acetone as the solvent and trapped *in situ* with dimethylbutadiene (Scheme 3.5). The Diels-Alder (155) and ene (156) adducts were obtained in high yield and the crude reaction mixtures were analysed by 250 MHz ^1H NMR spectroscopy. Peaks were assigned by analogy to previous work.[20] The isomer ratios obtained are shown in Table 3.1.

The new *para*-substituted thionitrosobenzene, *i.e.* 4-cyanothionitrosobenzene (146b) gave Diels-Alder (155b) and ene (156b) adducts in a 1:4 ratio when trapped with 2,3-dimethyl-1,3-butadiene. The ene adduct is the major isomer, as we would expect from previous work[20] for a derivative bearing an electron withdrawing substituent on the aryl ring. Indeed, the product ratio is the same as that reported for the *para*-nitro derivative.[20]



Scheme 3.5

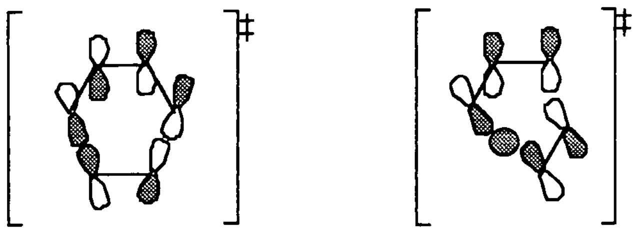
Table 3.1

Effect of the Position of Substituent on Ratio of Diels-Alder (155) : Ene Adducts (156) of (146) and 2,3-Dimethyl-1,3-butadiene (in acetone)

	ortho	*meta*	*para*
Substituent	D-A : Ene	D-A : Ene	D-A : Ene
CN	9 : 91	a	20 : 80
Me	33 : 67	40 : 60	60 : 40 [20]
Br	12 : 88	30 : 70	25 : 75 [20]

[a] Compound not prepared

Thionitrosobenzene derivatives with a substituent in the *ortho*-position gave a considerably larger ratio of ene adducts than derivatives with the same substituent in the *para* position. Therefore an *ortho*-substituent does exert a significant steric effect. This is most clearly shown by the methyl derivatives. When the substituent is *para* to the reactive N=S bond the Diels-Alder adduct (155h) predominates, but when the methyl substituent is in the *ortho*-position the ene adduct (156c) is the major isomer. The same trend is observed for the electron withdrawing bromo and cyano derivatives, where for the ortho substituted isomers the ene adducts (156a) and (156e) comprise *ca.* 90% of the reaction mixtures. Thus, a substituent in the *ortho* position favours the formation of ene adducts. This is consistent with the accepted transition state geometries for Diels-Alder and ene reactions,[71] for which the former would be more hindered than the latter by a substituent in the *ortho* position (Fig 3.1). As discussed in sections 1.6 and 2.4, competition between Diels-Alder and ene reactions has only been observed in a few cases.[41-45] It has previously been noted that dienes with bulky substituent groups favour ene reactions[72] but our results are the first to show clearly how the competition between Diels-Alder and ene reactions is affected by the steric effect of the enophile.


Diels-Alder Transition State

Ene Transition State

Figure 3.1

Trapping of *meta*-substituted thionitrosoarenes also provided interesting results. Methyl and bromo groups are both *ortho* and *para* directing, therefore we would expect to see a smaller electronic effect for the *meta*-substituted examples. The bromo substituent is electron withdrawing and would be expected to favour ene adducts. When 3-bromothionitrosoarene (146f) was trapped with 2,3-dimethyl-1,3-butadiene the ene adduct (156f) was the major isomer, but more Diels-Alder adduct (155f) was formed compared with the *ortho* and *para* bromo derivatives showing that, as expected, there is a smaller electronic effect. The effect is more dramatic for the methyl substituted thionitrosoarenes (146c) and (146h). The methyl substituent favours Diels-Alder adducts; this is clearly seen for the *para* substituted derivative (146h), but the steric effect dominates for the *ortho* derivative (146c). When the methyl group is in the *meta* position, the ene adducts (156d) predominate, presumably because the electronic effect is less significant.

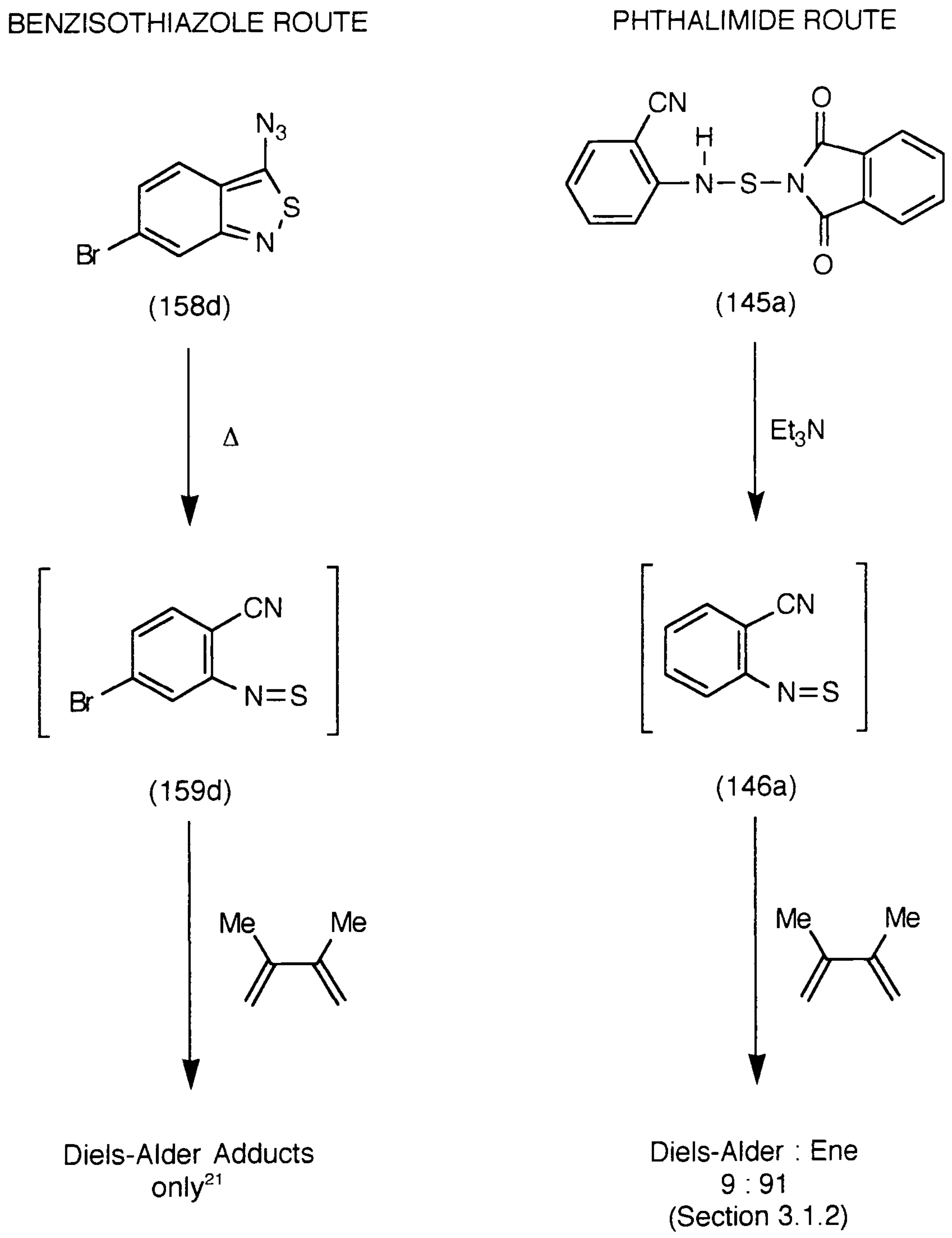
When *ortho*-cyanothionitrosobenzene (146a) was trapped with 2,3-dimethylbutadiene in chloroform, the isomer ratio was the same as that obtained in acetone. Thus, it appears that steric factors are more significant than the type of solvent used.

3.2 GENERATION OF THIONITROSOARENES FROM 3-AZIDO-2,1-BENZISOTHIAZOLES

3.2.1 Introduction

The generation of thionitrosoarenes from 3-azido-2,1-benzisothiazoles, first reported by Joucla and Rees[21], has been discussed in section 1.3.2. Thionitrosoarenes generated in this way have an *ortho*-cyano substituent (originating from the 3-azido group). From our work we know that the presence of a cyano group in the aryl ring, favours ene adducts.[20] In the last section we also saw that the formation of ene adducts is favoured by substituents *ortho* to the thionitroso group. Indeed, the 2-cyanothionitrobenzene (146a) gave ene (156a) and Diels-Alder (155a) adducts in a 10:1 ratio. Therefore, we would expect thionitrosoarenes generated from 3-azido-2,1-benzisothiazoles to give predominantly ene adducts when trapped with 2,3-dimethyl-1,3-butadiene. Surprisingly, Joucla and Rees observed only Diels-Alder adducts in this reaction.[21] A thionitroso intermediate is postulated for both the phthalimide and benzisothiazole routes (Scheme 3.6). If, indeed the two routes do give different adduct ratios it would indicate that the reactions proceed *via* different intermediates.

Therefore, we reinvestigated the work of Joucla and Rees because we believed that the ene adduct should be the major isomer from precursor (158d) if both routes proceed *via* thionitroso intermediates.


BENZISOTHIAZOLE ROUTE
PHTHALIMIDE ROUTE
N_3
S
N
Br
(158d)
CN
H
N
S
N
O
O
(145a)
Δ
Et_3N
CN
Br
N=S
(159d)
CN
N=S
(146a)
Me
Me
Me
Me
Diels-Alder Adducts only[21]
Diels-Alder : Ene
9 : 91
(Section 3.1.2)

Scheme 3.6

3.2.2 Reactions of Thionitrosoarenes Generated From 3-Azido-2,1-Benzisothiazoles (158)

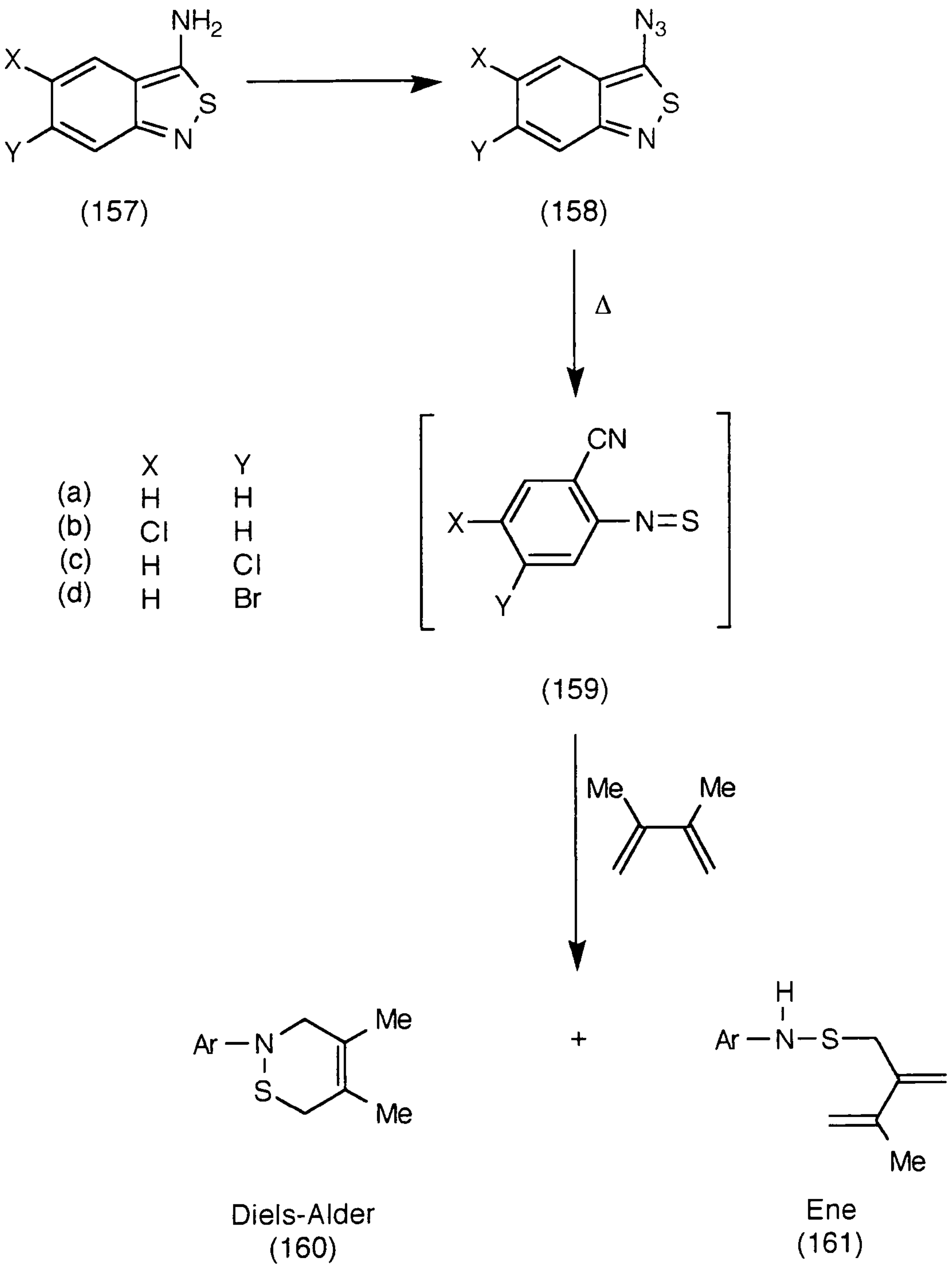
A series of 3-azido-2,1-benzisothiazoles (158) was prepared from the corresponding amines (157) under standard conditions.[73] Azides (158) were then heated in neat 2,3-dimethyl-1,3-butadiene (69°C) under nitrogen as described by Joucla and Rees (Scheme 3.7).[21] Trapping was efficient and product isomer ratios, determined from the 250MHz ^1H NMR spectra of the crude reaction mixtures, are listed in Table 3.2. A typical ^1H NMR spectrum is shown in Figure 3.2.

Table 3.2

Ratios of Diels-Alder (160) and Ene (161) Adducts Formed with Thionitrosoarenes (159a-d) at 69°C

Precursor	Diels-Alder (160) (%)	Ene (161) (%)
(158a)	23	77
(158b)	20	80
(158c)	22	78
(158d)	23	77

It is very significant that in each case the ene adduct is by far the major product; a fact which had been overlooked in the previous work when (158d) was heated in neat 2,3-dimethyl-1,3-butadiene.[21] However, we immediately noted that the ratio found for the trapping of (159a) is not the same as that observed for (146a) generated *via* the phthalimide route (Table 3.1) although the same structure had been postulated for intermediates (159a) and (146a). Fragmentation of (158a)was carried out in neat 2,3-dimethyl-1,3-butadiene whereas the phthalimide route reactions were carried out in solvents;



	X	Y
(a)	H	H
(b)	Cl	H
(c)	H	Cl
(d)	H	Br

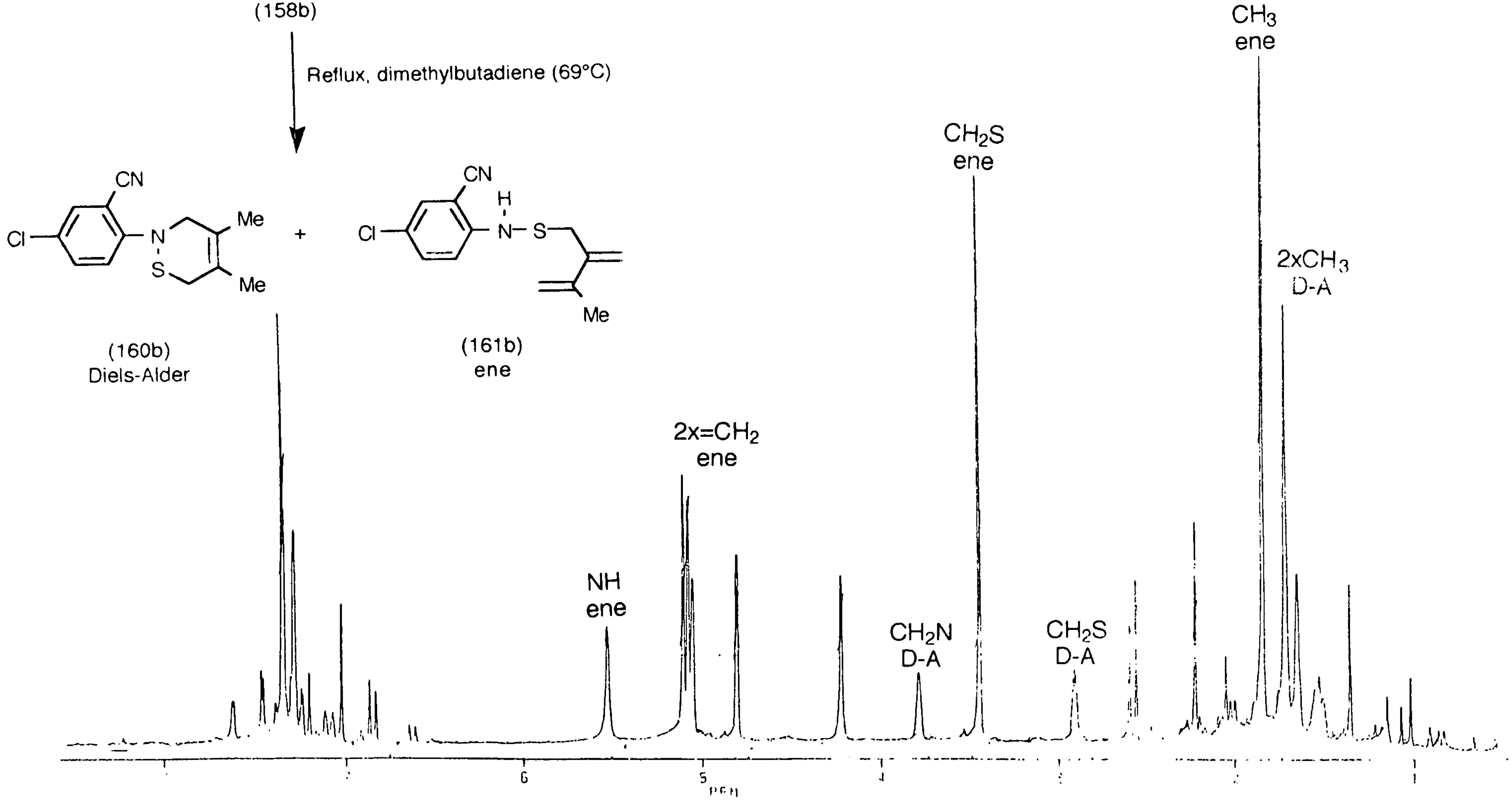
Scheme 3.7

however, we have shown that the steric effect of the substituent appears to be more important than the solvent effect (Section 3.1.2), so this could not explain the large discrepancies in the adduct ratios. We thought that the

Figure 3.2

^{1}H NMR Spectrum of Crude Product Mixture from the Thermal Decomposition of Benzisothiazole (158 b) in the Presence of

2,3-Dimethyl-1,3-butadiene



differing isomer ratios may be due to the fact that these reactions were carried out at different temperatures. Thus, the benzisothiazole ring opening reactions were repeated at room temperature. Azides (158a-b) were dissolved in excess 2,3-dimethyl-1,3-butadiene and were stirred at room temperature for 96 hours. The resulting isomer ratios, determined from the 250MHz ^{1}H NMR spectra, are shown in Table 3.3.

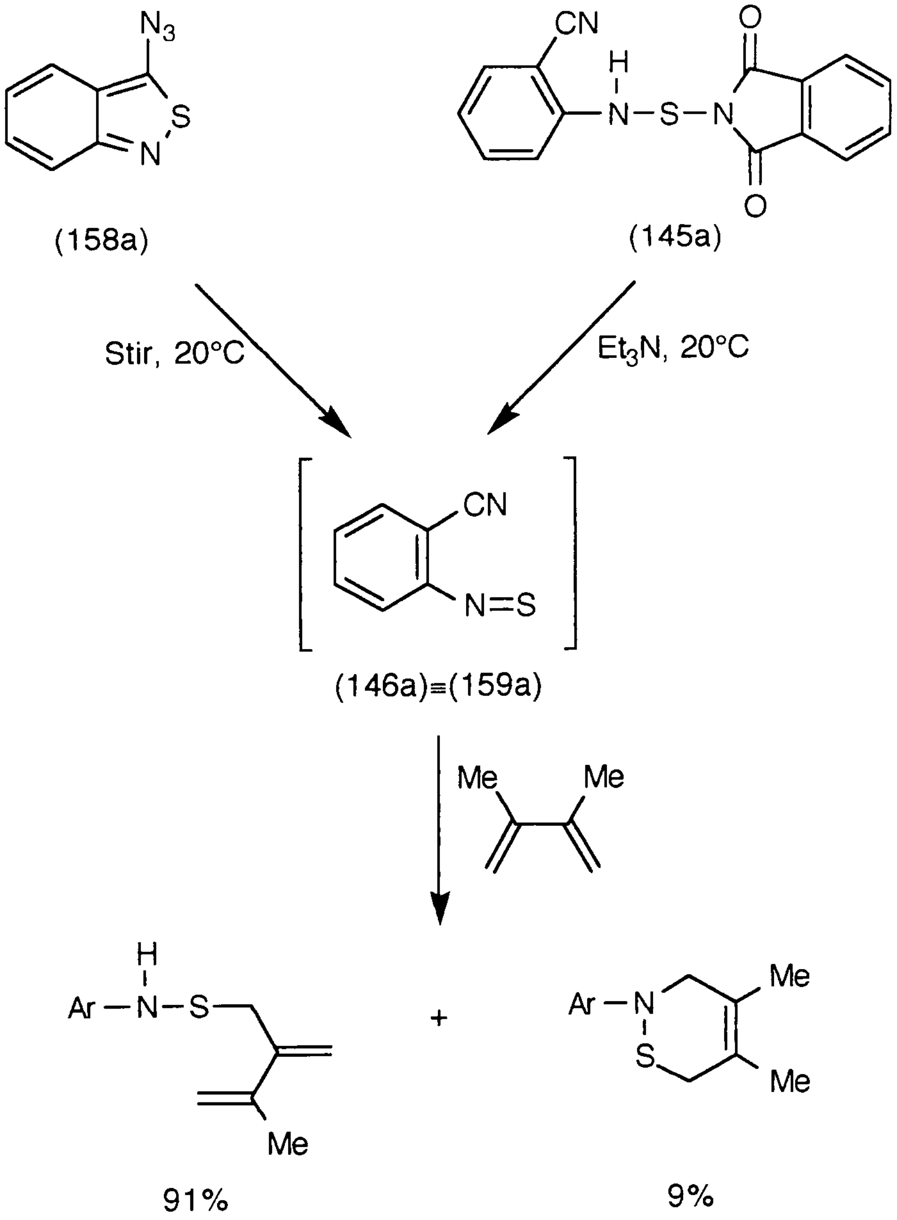
Table 3.3

Ratios of Diels-Alder (160) and ene (161) Adducts Formed With Thionitrosoarenes (159a-b) at 20°C

Precursor	Diels-Alder (160) (%)	Ene (161) (%)
(158a)	9	91
(158b)	8	92

The results in Table 3.3 show that a larger percentage of ene adducts is formed at room temperature than at 69°C (*cf.* Table 3.2). The isomer ratios observed for the trapping of (159a) generated from (158a) at room temperature are precisely the same as those for trapping of (146a) *via* the phthalimide route. This confirms that the two routes do proceed through the same thionitroso intermediate, *i.e.* (146a) and (159a) have the same structure (Scheme 3.8).

The ratio of Diels-Alder and ene adducts formed is temperature dependent. It was thought that the smaller percentage of ene adducts being formed at higher temperatures could be due to decomposition, as the ene adducts are thought to be thermally unstable. Thus, a mixture of adducts (160a) and (161a), obtained at 20°C, was heated in dimethylbutadiene at 69°C for 16 hours, *i.e.* under the same conditions that are used for the thermal decomposition of the benzisothiazoles. The isomer ratio was unchanged



Scheme 3.8

which showed that the significant effect of the reaction temperature on the adduct ratio was not due to interconversion of Diels-Alder and ene adducts at higher temperatures, or thermal decomposition of the ene adducts. In some ways this result is surprising as ene reactions are enhanced at higher temperatures.[51] A theory originally put forward by Taylor[29] to account for ene adducts being favoured by electron deficient thionitroso compounds, can be extended to account for the formation of a smaller percentage of ene adducts at higher temperatures.

Dienes, such as 2,3-dimethyl-1,3-butadiene, can exist in either *cis* or *trans* configurations, but the *trans* form predominates as it is of lower energy.[74] Ene reactions can take place when the diene is in either the *cis* or *trans* configuration but Diels-Alder reaction can occur only when the diene is in the *cis* configuration. Molecular orbital calculations predict that electron deficient thionitroso compounds will be more reactive than electron rich thionitroso compounds[11]. Therefore, electron deficient thionitroso compounds will be less selective and hence will more readily react with a diene in the *trans* configuration. At higher temperatures there will be a larger proportion of dimethylbutadiene in the *cis* form and therefore Diels-Alder reactions can occur more readily and the percentage of ene adduct will decrease, as observed in these experiments.

Thionitrosoarenes have previously been generated photochemically from 3-azido-2,1-benzisothiazoles and trapped with cyclopentadiene in a Diels-Alder reaction.[21] Therefore, we generated thionitrosoarenes (159a-b) from azides (158a-b) photochemically using a high pressure mercury lamp (1kW) in the presence of 2,3-dimethyl-1,3-butadiene. In each case a mixture of Diels-Alder (160a-b) and ene (161a-b) adducts was obtained. The isomer ratios were determined in the usual way and are recorded in Table 3.4. It is significant that the isomer ratio obtained for the trapping of (159a) in the photochemical reaction is the same as that obtained for both (i) benzisothiazole ring opening and *in situ* trapping at room temperature (Table 3.3) and (ii) the phthalimide route to the *ortho*-cyano derivative (146a) (Table 3.1). This indicates that the three reactions proceed through the same intermediate regardless of the route used, and provides further compelling evidence for the existence of the thionitroso intermediate. It is interesting to note that when thionitrosoarene (42c) (Section 1.3.2) was trapped with dimethylbutadiene the major product was amine (44c) and no ene adducts were observed.[22] This was surprising because thionitrosoarene (42c) has a *tert*-butyl group in the ortho position which should favour ene adducts. It has been suggested that amine (44c) could be formed from the ene adduct by hydrolysis of the N-S bond upon column chromatography.

Table 3.4

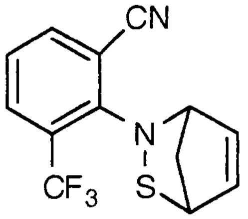
Ratios of Diels-Alder (160) and Ene (161) Adducts Formed with Thionitrosoarenes (159a-b) Generated Photochemically at 20°C

Precursor	Diels-Alder (160) (%)	Ene (161) (%)
(158a)	9	91
(158b)	8	92

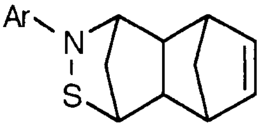
In conclusion, a reinvestigation of benzisothiazole reactions has corrected earlier work and has shown that the phthalimide and the benzisothiazole precursors fragment to yield the same thionitroso intermediates. The ratio of ene and Diels-Alder adducts formed is dependent upon the temperature at which the reaction is carried out.

3.2.3 Other Reactions of Thionitroso Compounds Generated From 3-Azido-2,1-Benzisothiazoles

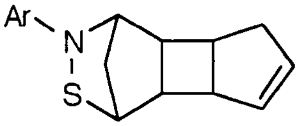
One example of the trapping of a thionitrosoarene, generated from a 3-azido-2,1-benzisothiazole, with cyclopentadiene to give thiazine (162) has been reported.[21] There was also mass spectroscopic evidence for the formation of a 1:2 adduct of the thionitrosoarene and cyclopentadiene,[75] which could have one of two structures, either (163) or (164). When Meth-Cohn and van Vuuren reacted the electron deficient acyl thionitroso compound (EtO_2C-N=S) with cyclopentadiene the 2:1 adduct (92) was obtained (Section 1.5).[38] Okazaki *et al* were unable to trap thionitrosoarene (42c) (Section 1.3.2) with cyclopentadiene, possibly due to steric hindrance.[22] In the light of these results, the reactions of thionitrosoarenes (159) with cyclopentadiene were examined.



(162)

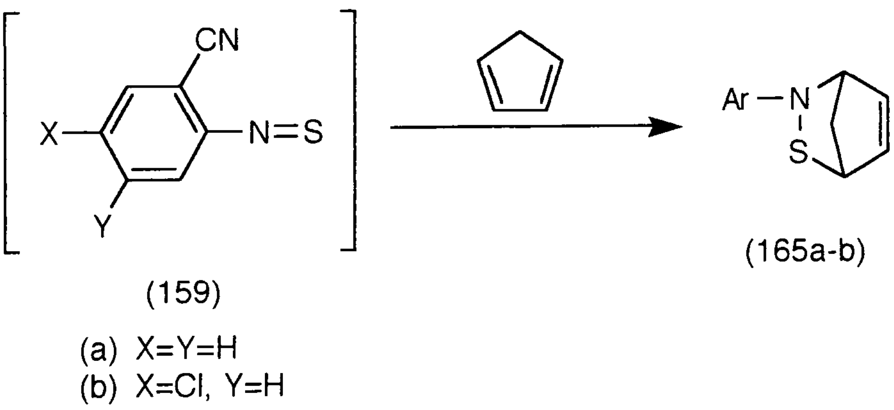


(163)



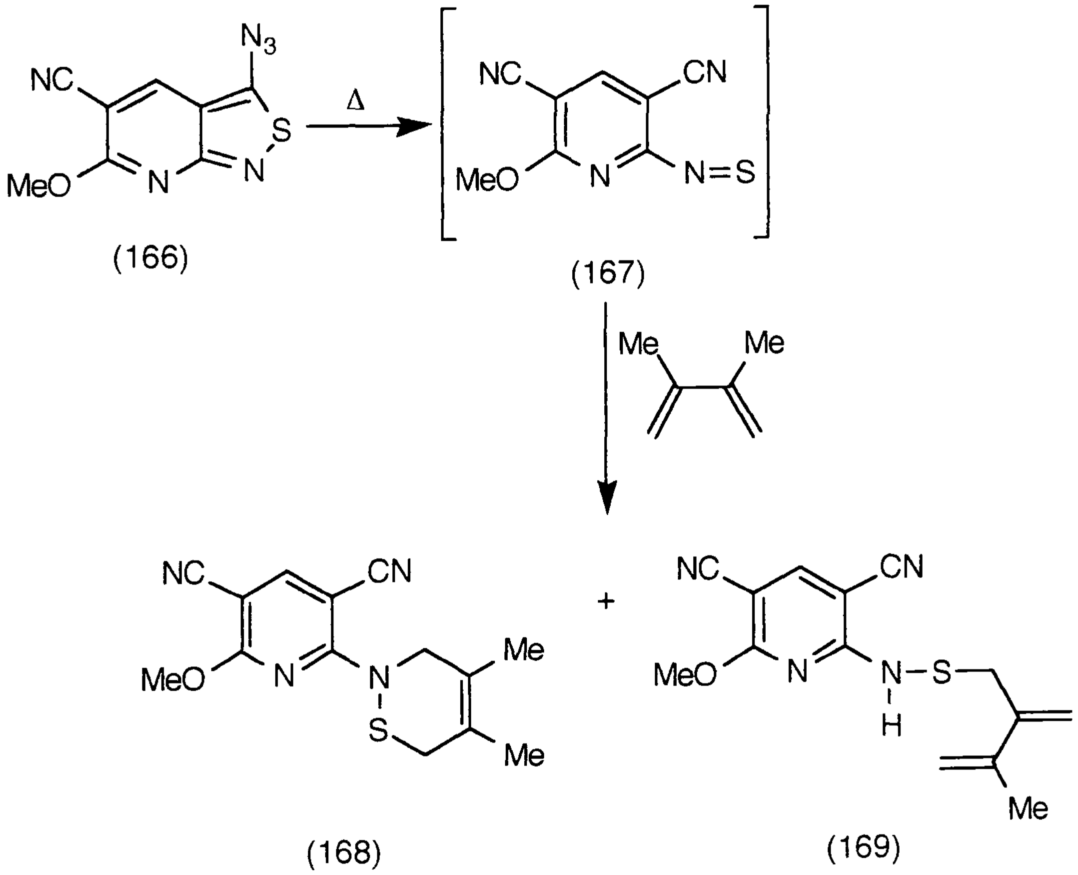
(164)

When thionitrosoarenes (159a-b) were generated photochemically from the corresponding azide (158a-b) in neat cyclopentadiene, adducts (165) were formed in low yield (Scheme 3.9). There was also mass spectroscopic evidence for the presence of the 1:2 adduct with a structure similar to (163) or (164). Unfortunately the ^1H NMR spectra were very complex and it was not possible to assign peaks to this product, therefore evidence for its formation is very tentative. However, there was no evidence for a product with a structure similar to that of (92).



Scheme 3.9

The highly substituted thionitroso compound (167) generated by thermal decomposition of the azide (166) provides the first example of a heterocyclic thionitroso species to be prepared using this route. Intermediate (167) was trapped with 2,3-dimethyl-1,3-diene to give Diels-Alder (168) and ene (169) adducts in a 1:1 ratio with a combined yield of 40% (Scheme 3.10). A larger proportion of ene adduct was expected due to the combined effects of the *ortho*-cyano substituent and the pyridyl ring [2-thionitrosopyridine gave the ene adduct as the major product (Section 2.6.2)]. However, the electron donating methoxy group favours Diels-Alder addition which could account for the observed isomer ratio (Scheme 3.10). It is also important to note that



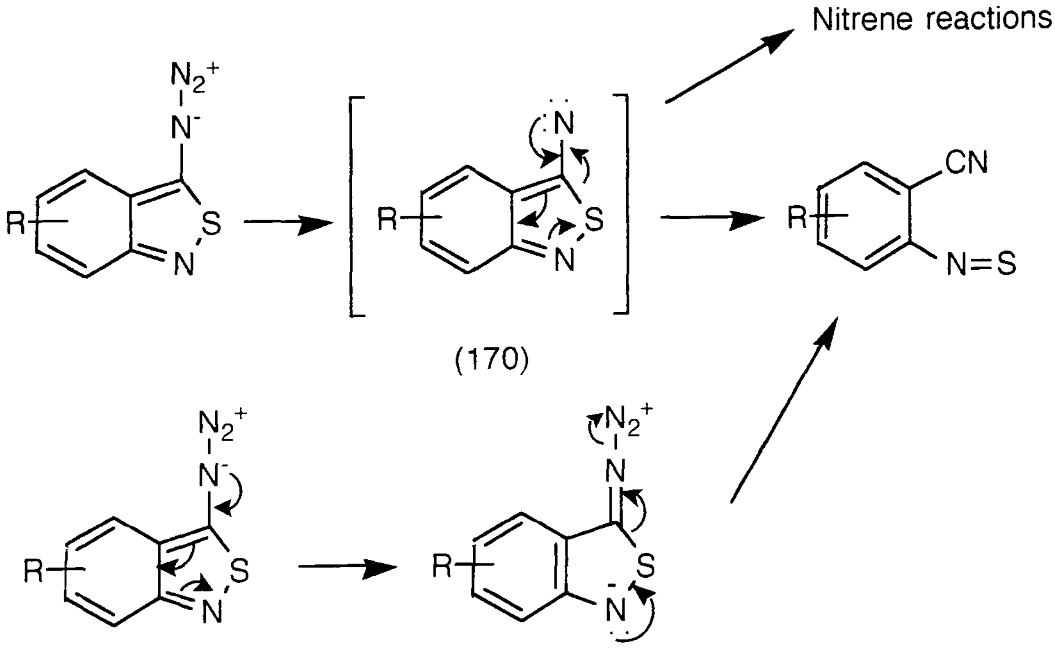
Scheme 3.10

this reaction was carried out at 69°C and that higher temperatures favour the Diels-Alder reaction (168). Thus we have shown that the benzisothiazole route to thionitroso compounds can be used to prepare heterocyclic derivatives. The major disadvantage of this route is that the derivatives prepared always have an *ortho*-cyano group, and the precursors require lengthy syntheses.

3.3 MECHANISM OF 3-AZIDO-2,1-BENZISOTHIAZOLE FRAGMENTATION

3.3.1 Introduction

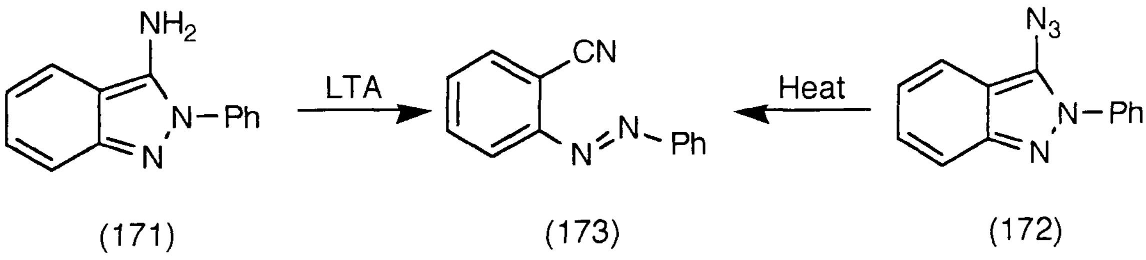
There are two possible mechanisms for the formation of thionitrosoarenes from 3-azido-2,1-benzisothiazole precursors; either by way of a nitrene or *via* a concerted process (Scheme 3.11). If species (170) was generated we would expect to observe reactions typical of a nitrene,



Scheme 3.11

such as the formation of azo-compounds or proton abstraction to give 3-amino-2,1-benzisothiazoles.

Nitrene (170) should also be available by direct reaction of the 3-amino-2,1-benzisothiazole with lead tetraacetate. Indeed, analogous ring opening reactions of 3-amino-2-phenylindazole (171) to give azo compound (173) have been carried out in this way.[21] The product (173) was the same as that obtained from the thermal decomposition of azide (172). (Scheme 3.12).



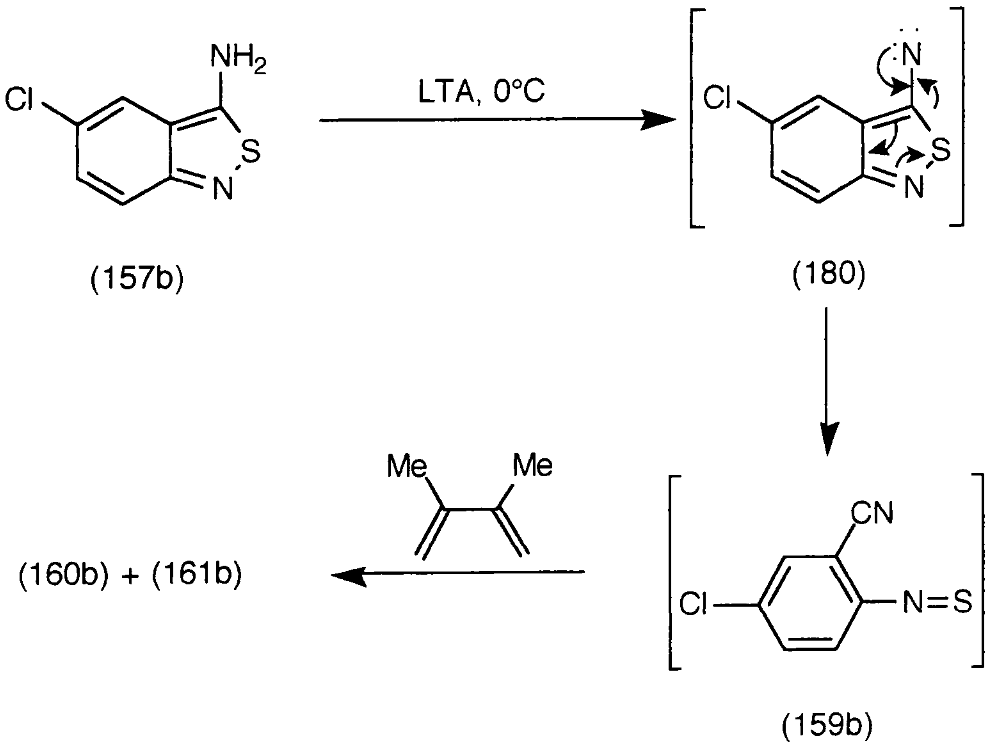
Scheme 3.12

Therefore, benzisothiazoles (157b) and (174) were treated with lead tetraacetate to investigate the mechanism of the ring opening of 2,1-benzisothiazoles.

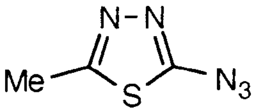
3.3.2 Results and Discussion

3-Amino-2,1-benzisothiazoles (157b) and (174) were reacted with lead tetraacetate in toluene at 0°C. Mass spectroscopy gave evidence for the formation of both amine (175) and di-azo compound (176) upon the decomposition of benzisothiazole (157b), and amine (177), sulphur diimide (178) and di-azo compound (179) from benzisothiazole (174) (Scheme 3.13). The mixtures could not be purified and the ^{1}H NMR spectra were difficult to interpret due to the insolubility of the products and the similarity of their structures.

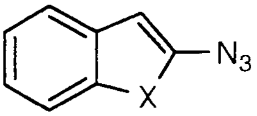
adducts. Thus, the reaction of 3-amino-2,1-benzisothiazole (157b) with lead tetraacetate was carried out at 0°C in the presence of dimethylbutadiene (Scheme 3.14). Diels-Alder (160b) and ene (161b) adducts were formed in a 1:2 ratio along with other unidentified products (^{1}H NMR evidence). Evidence for the formation of the Diels-Alder (160b) and ene (161b) adducts was obtained by the comparison of the ^{1}H NMR spectrum with that obtained for the thermal decomposition of the 3-azido-2,1-benzisothiazole (158b) in 2,3-dimethyl-1,3-butadiene where Diels-Alder (160b) and ene (161b) adducts were formed in a 1:4 ratio. The different product isomer ratio can possibly be explained by hydrolysis of the ene adduct during the aqueous work up to remove lead tetra acetate. The use of lead tetraacetate in this reaction provides a new method for the generation of thionitrosoarenes.



Scheme 3.14

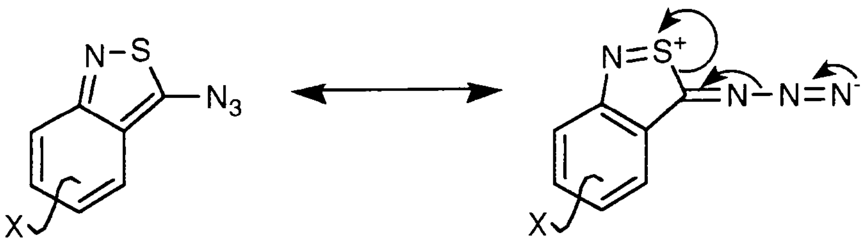


(181)



(182)
X=S, NMe, O

These results, however, give no conclusive information about the mechanism of the generation of thionitrosoarenes from 3-azido-2,1-benzisothiazoles (158). Recent work has shown that the ring opening reactions of azido compounds (181) and (182) proceed *via* nitrene intermediates,[76] a result supported by MNDO calculations in the case of (181).[76a] However, Okazaki *et al.* did not observe a nitrene when they irradiated a 3-azido-2,1-benzisothiazole in a matrix at 12K (Section 1.3.2).[22] It was suggested that this was due to the special structure of 3-azido-2,1-benzisothiazoles (183) in which the canonical form (183') is important and allows simultaneous loss of nitrogen and ring opening (Scheme 3.15). Another possibility is that the nitrene intermediate is formed from (183) but has a very short lifetime.



(183) (183')

Scheme 3.15

In conclusion, reaction of 3-amino-2,1-benzisothiazole (157b) with lead tetraacetate has provided a new route to thionitrosoarenes which appears to proceed through a nitrene intermediate (180). The mechanism of the generation of thionitrosoarenes from 3-azido-2,1-benzisothiazoles (183) is still uncertain, although a concerted mechanism seems most likely.

We have also shown for the first time that both steric and temperature effects profoundly influence the ratio of Diels-Alder and ene adducts formed between thionitrosoarenes and 2,3-dimethyl-1,3-butadiene. Thionitrosoarenes generated *via* two different routes gave the same isomer ratios providing compelling evidence that both routes proceed through the same thionitroso intermediate.

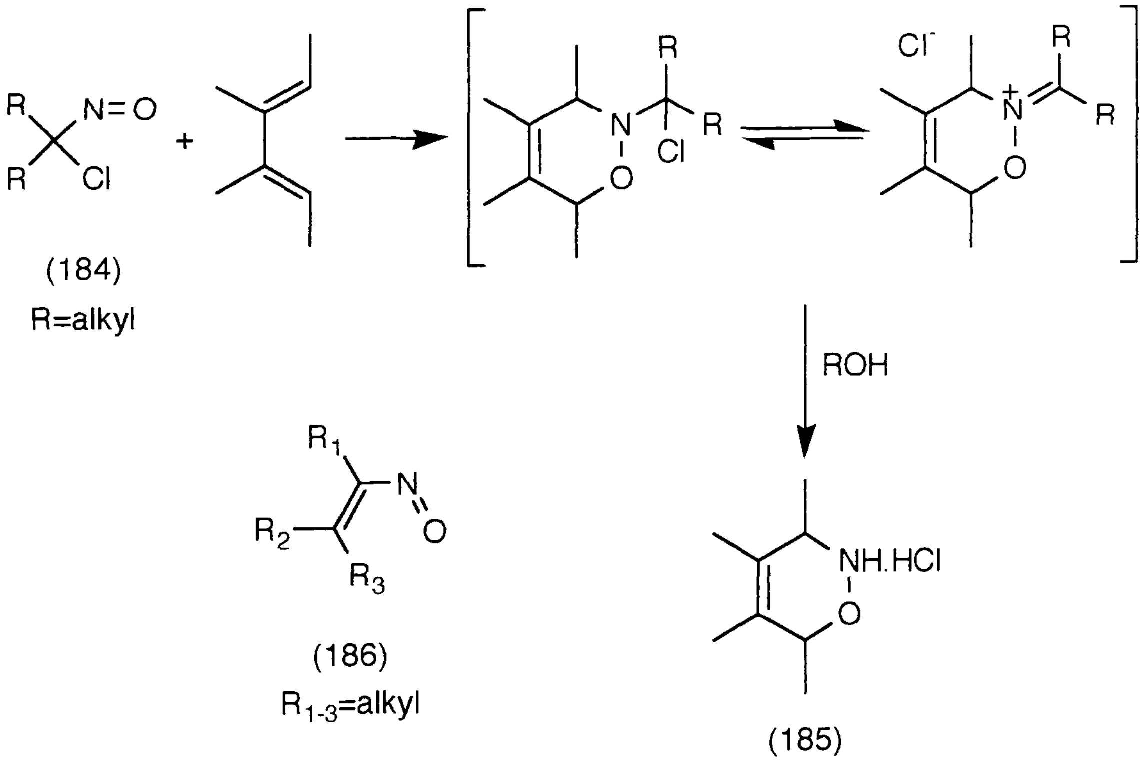
CHAPTER 4

GENERATION AND REACTIONS OF THIONITROSOALKANES

4.1 INTRODUCTION

The generation and reactions of thionitrosoalkanes was discussed in Section 1.4. The two most successful routes to thionitrosoalkanes are the reaction between cyclohexene sulphide and oxaziridines as described by Hata and Watanabe,[33] and the decomposition of *N*-trimethylsilyl-*N*-chlorothioalkylamines reported by Markovskii *et al.*[34] We have now investigated the thionitrosoalkanes with a view to studying chiral thionitroso compounds for the first time. Attempts to generate the *t*-BuN=S *via* the phthalimide route were unsuccessful. The phthalimide precursor was prepared but it would not fragment to give the thionitroso compound, possibly due to steric factors. Therefore, we turned our attention to the routes that had already been used to prepare thionitrosoalkanes.

Reactions of related alkyl heterodienophiles can be summarised as follows: alkyl derivatives of nitroso compounds, sulphinylamines and thioaldehydes are known. The α-chloro (184) and trifluoromethyl nitroso compounds are known to react as dienophiles in [4+2] cycloaddition reactions (Scheme 4.1).[1, 77] The product in the former case was unstable and in alcoholic solvent oxazine (185) was isolated. The trifluoromethyl analogue ($CF_3N=O$) underwent an ene reaction with isobutene with C-N bond formation.[77] A few nitrosoalkenes (186) have been isolated, although they are normally only observed in solution.[78] They have been shown to react as the 4π component in Diels-Alder reactions. Trifluoromethylsulphinylamine (CF_3-N=S=O) behaves as an electron deficient sulphinylamine and has been trapped with dimethylbutadiene in a Diels-Alder reaction.[79] Sulphinylamines with electron donating alkyl groups are usually unreactive; however, in the presence of a Lewis Acid catalyst or under high pressure, cycloaddition reactions will occur.[80] Various aliphatic thioaldehydes have been prepared and trapped with dienes.[81]



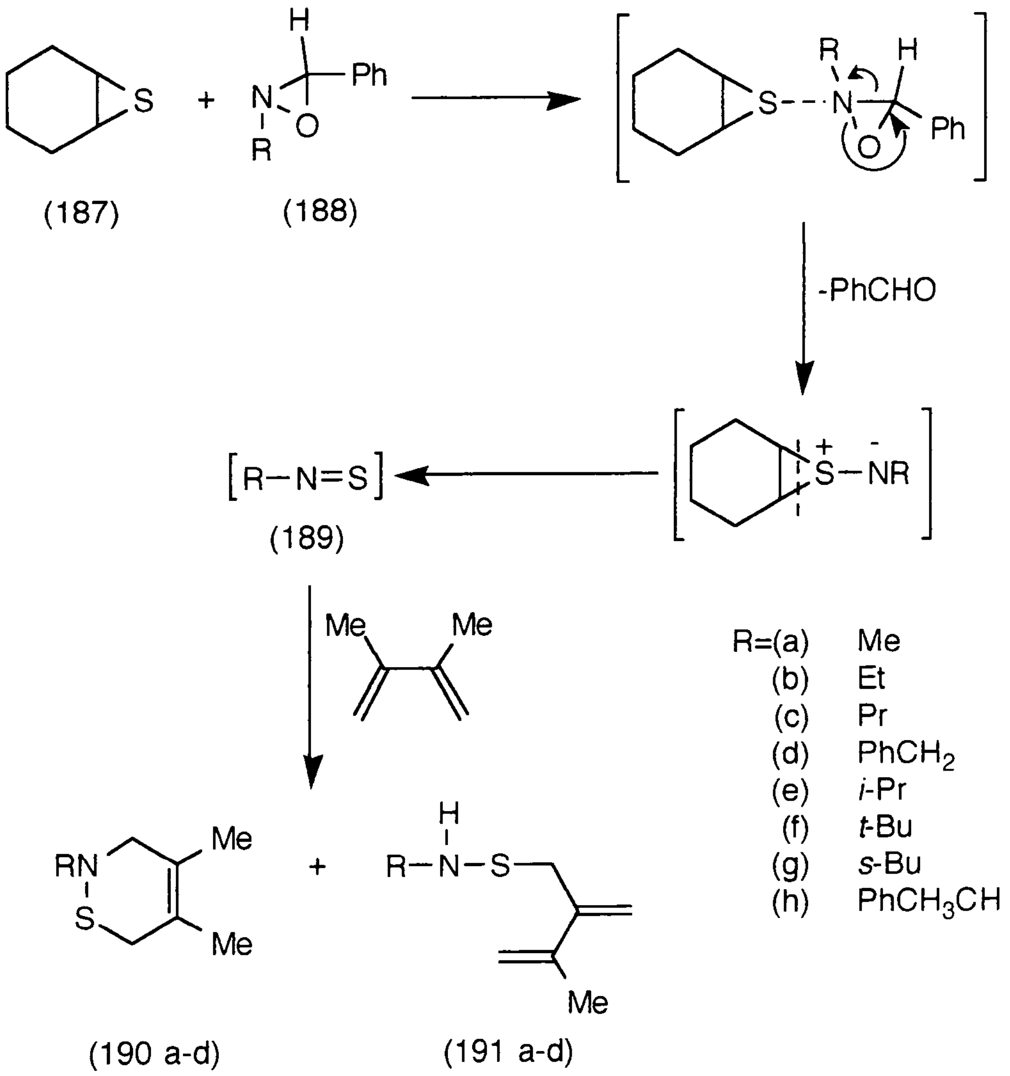
Scheme 4.1

4.2 OXAZIRIDINE ROUTE TO THIONITROSOALKANES

4.2.1 Generation and Reaction of Thionitrosoalkanes with 2,3-Dimethyl-1,3-Butadiene

Oxaziridines (188 a-h) were prepared by oxidation of the corresponding imine using MCPBA. The ^1H NMR spectra showed that mixtures of *cis* and *trans* oxaziridines were formed. Thionitrosoalkanes (189 a-d) were generated by reacting the corresponding oxaziridine (188) with cyclohexene sulphide (187), as described by Hata and Watanabe,[33] and trapped *in situ* with 2,3-dimethyl-1,3-butadiene (Scheme 4.2). Thionitrosoalkanes (189a) and (189b) were formed at 20°C, while higher temperatures (60°C) were required for the generation of thionitrosoalkanes

(189c) and (189d). Adduct isomer ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures and are shown in Table 4.1. The combined adduct yield was *ca.* 70-80%.



Scheme 4.2

The Diels-Alder adduct was the major product in each case as would be expected from earlier work for an electron rich thionitroso compound.[20] A significant percentage of ene adducts were also formed, providing the first examples of thionitrosoalkanes undergoing ene reactions. Attempts to trap thionitrosoalkanes (189 a-d) in an ene reaction with α-pinene were, however unsuccessful. Previous work has shown that thioaldehydes are unreactive in an ene reaction with β-pinene because of competing self-condensation reactions;[81c] this is possibly occurring here with thionitrosoalkanes. It is important to note that the ratios of Diels-Alder (190) and ene adducts (191) obtained in each reaction are not directly comparable because the reactions were carried out at different temperatures. The results discussed in Section 3.2.2 show that the ratio of Diels-Alder to ene adducts is temperature dependent with ene adducts being favoured at lower temperatures. Adducts (190 a-d) and (191 a-d) were usually thermally unstable, although the benzyl Diels-Alder adduct (190d) was isolated pure after column chromatography. This is a significant result because the Diels-Alder and ene adducts of thionitroso species are usually obtained as inseparable mixtures.

Table 4.1

Ratios of Diels-Alder (190) and Ene Adducts (191) Formed with Thionitrosoalkanes (189 a-d)

Oxaziridine	Temperature of Reaction/°C	Ratio of Adducts Diels-Alder (190) (%)	Ene (191) (%)
(188a)	20	80	20
(188b)	20	60	40
(188c)	69	60	40
(188d)	69	80	20

Thionitrosoalkanes (189 e-h) could not be generated from the reaction between the corresponding oxaziridine (188) and cyclohexene sulphide (187), even in refluxing toluene. This was probably due to the bulkier substituent group, R, stabilising the oxaziridine (188). Oxaziridines were prepared using isobutyraldehyde instead of benzaldehyde as it was hoped that the smaller group on carbon would increase the reactivity of the oxaziridines. The more volatile butyraldehyde would also be easier to remove once the trapping reaction had taken place making the ^{1}H NMR spectra of the crude reaction mixtures easier to interpret. However, the use of a different aldehyde had very little effect on the reaction. The reactions which proceeded with the benzaldehyde oxaziridines still took place with the butyraldehyde oxaziridines but the yields were not improved and no new thionitrosoalkanes were generated in this way. The imines and oxaziridines formed with isobutyraldehyde were much more volatile than those prepared with benzaldehyde and, consequently, were more difficult to work with.

In conclusion, thionitrosoalkanes (189 a-d) were generated and trapped but attempts to modify this route to prepare thionitrosoalkanes (189 e-h) with bulkier substituents failed. Therefore, the fragmentation of thiiranium ylides is not a widely applicable route to alkyl thionitroso compounds.

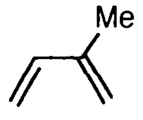
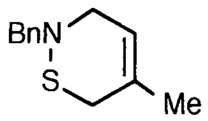
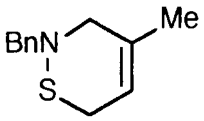
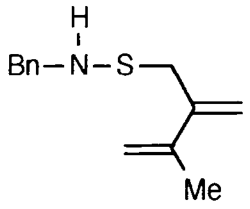
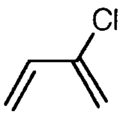
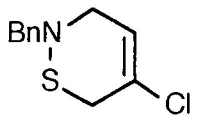
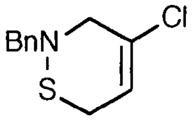
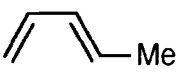
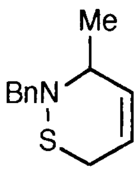
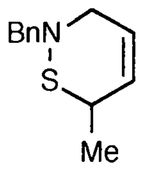
4.2.2 Regioselectivity of Diels-Alder Reactions of Thionitrosoalkanes

α-Chloroalkyl nitroso compounds and nitrosobenzenes react with the same regioselectivity with dienes. However, on reaction with piperylene nitrosobenzenes form the 4-methyl oxazine while the α-chloroalkyl derivatives give the 5-methyl oxazine as the major isomer.[81a] The regiochemistry of the Diels-Alder reactions of thioaldehydes is dependent upon the electronic character of the substituent group.[4b] The regioselectivity of the Diels-Alder reactions of thionitrosoarenes is also dependent upon electronic effects (Section 2.1) Therefore, it was of interest to compare the regioselectivity of the Diels-Alder reactions of electron rich thionitrosoalkanes with that observed for the thionitrosoarenes.

Benzylthionitroso compound (189d) was trapped with isoprene, chloroprene and piperylene in the same way as described for the reactions with 2,3-dimethyl-1,3-butadiene. Isomer ratios, determined from the 250 MHz ^{1}H NMR spectra of the crude reaction mixtures, are shown in Table 4.2. A typical ^{1}H NMR spectrum for the isoprene adducts is shown in Figure 4.1. The isomer ratios obtained for all three dienes are similar to those

Table 4.2

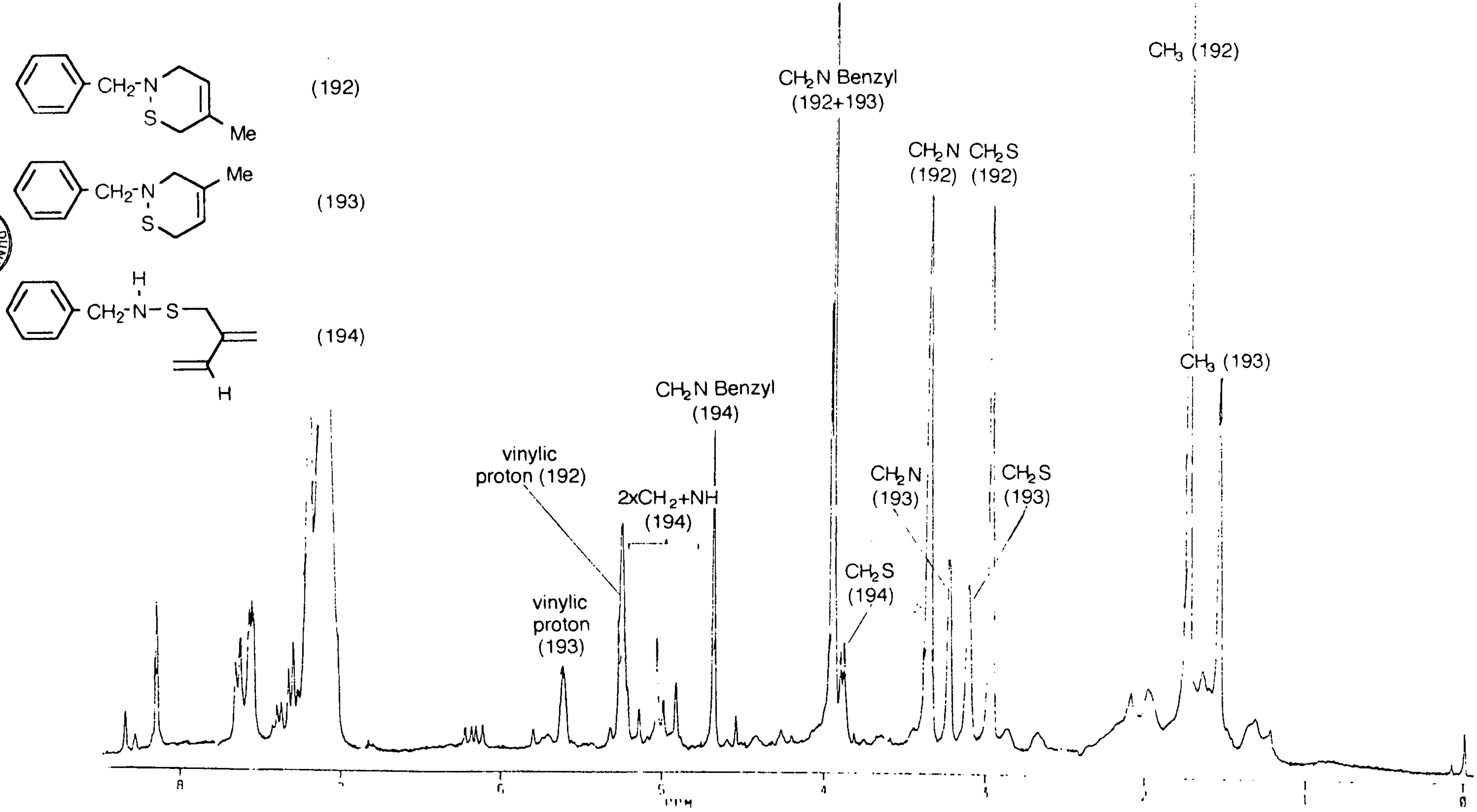
Ratios of Isomers Formed Between (189d) and Unsymmetrical Dienes

Diene	Products		
	 (192) 65%	 (193) 18%	 (194) 17%
	 (195) 50%	 (196) 50%	
	 (197) 70%	 (198) 30%	

Bn=Benzyl

Figure 4.1

^{1}H NMR Spectrum of the Crude Product Mixture from the Reaction of Thionitrosoalkane (189d) with Isoprene



observed for the methyl- and methoxy-thionitrosobenzenes. Therefore, it appears that the benzylthionitroso derivative (189d) reacts with unsymmetrical dienes with the same regioselectivity as the electron rich thionitrosoarenes. Electronic factors presumably influence the regiochemical outcome of the Diels-Alder reactions of thionitrosoalkanes, as they do with thionitrosobenzenes (Section 2.1).

4.3 THIONITROSOALKANES GENERATED FROM *N*-CHLOROTHIO-*N*-TRIMETHYLSILYLALKYLAMINES

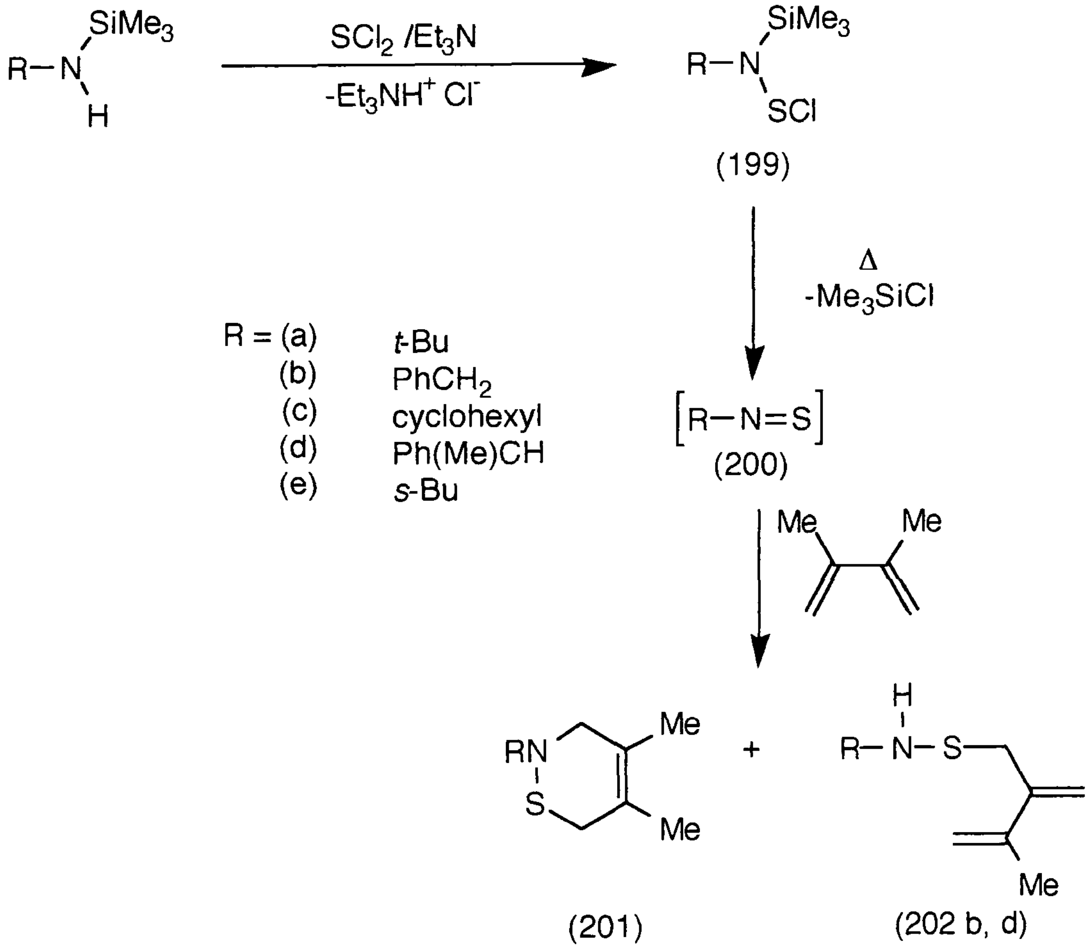
4.3.1 Introduction

The oxaziridine route to thionitrosoarenes is unsuitable for the preparation of thionitrosoalkanes with bulky substituent groups (Section 4.2.1). Therefore, we turned our attention towards generating thionitrosoalkanes from *N*-chlorothio-*N*-trimethylsilylalkylamines (Section 1.4). The *iso*-propyl and *tert*-butyl derivatives had been previously prepared and intercepted with 2,3-dimethyl-1,3-butadiene to give Diels-Alder adducts, but the methyl derivative could not be prepared *via* this route because the corresponding chlorothioalkylamine polymerised under the conditions of synthesis.[34]

4.3.2 Generation and Reactions of Thionitrosoalkanes

Thionitrosoalkanes (200 a-e) were generated and trapped *in situ* with 2,3-dimethyl-1,3-butadiene in toluene at 100°C (Scheme 4.3). The temperature at which the reaction is carried out is important. In refluxing chloroform (~60°C) the rate of decomposition of the *N*-chlorothio-*N*-trimethylsilylalkylamines (199) is slow, but at higher temperatures (>100°C) side reactions occur. The generation and trapping of (200a) was repeated, and this method was extended to provide a new route to (200b) which we had generated *via* the oxaziridine route. Thionitrosoalkanes (200 c-e) were previously unknown species.

When thionitrosoalkanes (200 a-e) were trapped with 2,3-dimethyl-1,3-butadiene the expected thiazines (201 a-e) were obtained. Additionally, ene adducts were observed for the benzyl (200b) and α-methyl benzyl (200d) derivatives. The isomer ratios are shown in Table 4.3. The complete lack of ene adducts (202 a, c, e) and the very small percentage observed for the benzyl derivative (202b) when compared to the oxaziridine route can be explained by temperature and solvent effects. These reactions are carried out



Scheme 4.3

at high temperatures in a non-polar solvent; conditions which favour the formation of Diels-Alder adducts (Sections 2.3 and 3.22). Ene adducts were observed for the α-methyl benzyl derivative (200d), most likely because it is more sterically hindered which would favour ene adduct (202d).

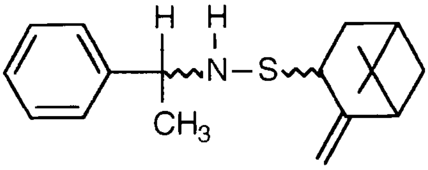
Table 4.3

Ratios of Diels-Alder (201) and Ene Adducts (202) Formed with 2,3-Dimethyl-1,3-Butadiene and Thionitrosoalkanes (200 a-d)

	Ratio of Adducts	
Precursor	Diels-Alder (201) (%)	Ene (202) (%)
(199a)	100	0
(199b)	91	9
(199c)	100	0
(199d)	92	8
(199e)	100	0

Thiazines (201) formed in these reactions are unstable, although the benzyl derivatives (201b) and (201d) could be purified by column chromatography, possibly because the phenyl group has a stabilising effect. The *N*-chlorothio-*N*-trimethylsilylalkylamines (199a) and (199e) and thiazines (201a) and (201e) were particularly unstable and difficult to work with. The instability of *N*-chlorothio-*N*-trimethylsilylalkylamines (199a) and (199e) shows that this route is not applicable to the preparation of thionitrosoalkanes with simple alkyl substituent groups.

The α-methyl benzyl thionitroso compound (200d) was trapped in an ene reaction with α-pinene to give sulphenamide (203) (15% yield). This is the first example of a thionitrosoalkane undergoing an ene reaction with an alkene. *tert*-Butylthioaldehyde (t-BuHC=S) failed to give ene adducts with β-pinene because of competing self-condensation reactions.[81c] Self-condensation reactions could also be occurring with thionitrosoalkanes (200 a-c, e) but the bulky α-methyl benzyl substituent decreases the chance of this and stabilises intermediates in the ene reaction.



(203)

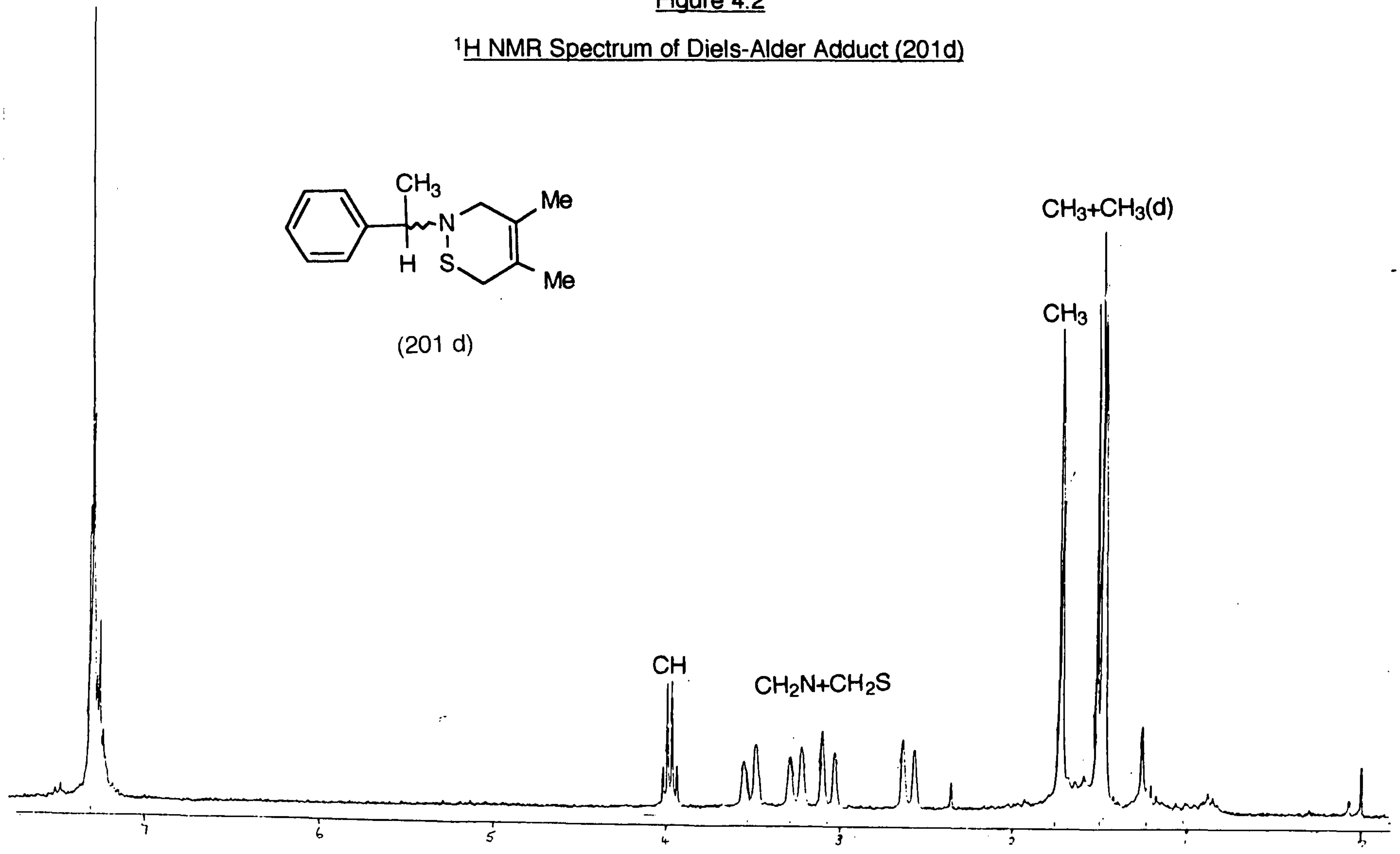
Thionitrosoalkanes (200d) and (200e) have a chiral substituent group. The only previously reported chiral thionitroso compounds were the (-)-menthyl and (+)-fenchyl esters prepared by Meth-Cohn and co-workers.[39] When these thionitroso compounds were trapped with 1,4-diphenylbutadiene an inseparable mixture of diasteriomers was obtained.

The ^1H NMR spectrum of the purified (±) α-methyl benzyl adduct (201d) is shown in Figure 4.2. It is of interest because there is splitting of the peaks for the CH_2 protons in the thiazine ring. Usually two singlets are observed, one for the CH_2 protons adjacent to nitrogen and one for the CH_2 protons adjacent to sulphur. For the (±) α-methyl benzyl derivative (201d) two quartets are observed, one for each set of CH_2 protons. This splitting is possibly due to the chiral substituent on nitrogen. The (+) and (-) α-methyl benzyl compounds were also generated and trapped with 2,3-dimethyl-1,3-butadiene. The ^1H NMR spectra of the purified adducts (201d) were the same as those obtained for the mixture of isomers.

In conclusion, the decomposition of *N*-chlorothio-*N*-trimethylsilylalkylamines provides a method of generating thionitrosoalkanes with bulky substituent groups and enables chiral derivatives to be prepared.

Figure 4.2

^{1}H NMR Spectrum of Diels-Alder Adduct (201d)



This work has paved the way for asymmetric synthesis using chiral thionitroso compounds.

4.4 SUMMARY

An investigation of the preparation of thionitrosoalkanes has resulted in the generation of several new examples, including chiral derivatives. The oxaziridine route is applicable to the synthesis of thionitrosoalkanes with small substituent groups (*e.g*. Me, Et), while the *N*-chlorothio-*N*-trimethylsilylalkylamine route is more suitable for examples with bulky substituent groups (*e.g*. *t*-Bu and α-methyl benzyl). Preparation of the butyl derivatives (200a) and (200e) using the latter route proved difficult because of the instability of the *N*-chlorothio-*N*-trimethylsilylalkylamines. The only thionitrosoalkane which was successfully generated *via* both routes was the benzyl derivative.

The reactions of the thionitrosoalkanes are similar to those of the electron rich thionitrosoarenes *i.e.* Diels-Alder adducts are favoured. Other factors, *e.g*. temperature and solvent, which effect the ratio of Diels-Alder and ene adducts formed with thionitrosoarenes, also appear to be important for the thionitrosoalkanes.

CHAPTER 5

EXPERIMENTAL

5.1 GENERAL METHODS

Proton and carbon NMR spectra were recorded on a Bruker AC 250 (250.13 MHz) spectrometer (Durham) or a GE 300 spectrometer (Shell, Sittingbourne). Chemical shifts are quoted in ppm relative to tetramethylsilane as the internal standard.

Mass spectra were obtained on a VG 7070E spectrometer and were recorded in either electron impact (EI) or chemical ionisation (CI) mode. In the CI mode ammonia was used as the impingent gas. High resolution masses were measured in the EI mode unless stated otherwise.

Infrared spectra were recorded as KBr discs or thin films on a Perkin Elmer 577 spectrophotometer .

Carbon, hydrogen and nitrogen analyses were obtained using a Carbo Erba 1106 analyser.

Melting points were obtained on a Kofler hot stage microscope and are uncorrected.

Nitrogen was dried by passing through phosphorus pentoxide. Solvents were distilled from the following drying agents: diethyl ether (sodium, benzophenone); THF (potassium or sodium/benzophenone); chloroform (phosphorus pentoxide); acetone (anhydrous potassium carbonate); acetonitrile (calcium hydride); toluene (lithium aluminium hydride); triethylamine (3Å molecular sieves); dichloromethane (phosphorous pentoxide).

Kugelrohr distillations were carried out on a Buchi GKR-51 apparatus.

Column chromatography refers to gravity chromatography on Merck silica gel (70-230) mesh.

5.2 EXPERIMENTAL PROCEDURES FOR CHAPTER 2

5.2.1 Experimental for Section 2.1

***N, N'*-Dithiobis(phthalimide).** This was prepared by a literature procedure[82] as a white crystalline solid in 55% yield.

***N*-Chlorosulphenyl phthalimide (28).** This was prepared by the literature procedure[83] for the chlorinolysis of *N*-dithiobis(phthalimide) in quantitative yield and stored in a glove box under dry nitrogen.

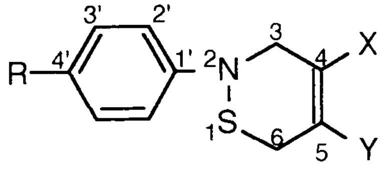
***N*-Trimethylsilylarylamines.** These were prepared according to a literature procedure[20] and used without further purification.

Thioarylaminophthalimides (101 a-c). These were prepared according to the literature procedure[20] from the corresponding silylamine and *N*-chlorosulphenyl phthalimide. The following known thioarylphthalimides were prepared:
(101a) *N*-(4-methoxyphenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide[20]
(101b) *N*-(4-methylphenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide[20]
(101c) *N*-(4-bromophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide[20]

Adducts of Thionitrosoarenes (102 a-c) with Chloroprene. To a stirring suspension of thioarylaminophthalimide (101) (0.5mmol) dissolved in freshly distilled acetone (50ml) under dry nitrogen, was added sequentially, chloroprene (50% in xylene, 2ml, 11mmol) and triethylamine (2ml, 14mmol). Stirring was continued at room temperature until a clear solution was obtained (*ca.* 12 hours). After evaporation the residue was stirred vigorously with cyclohexane (100ml) for 30 minutes. The precipitated triethylammonium phthalimide was removed by filtration and the filtrate was evaporated to afford crude (103 a-c) and (104 a-c) as brown oils. Isomer ratios were determined from the 250 MHz ^{1}H NMR spectra of the crude reaction mixtures. Isomers (103a, c) and (104a, c) were separated by column chromatography on a silica gel column eluted with cyclohexane to give colourless oils, and in the case of (104c) a white solid (mp. 59-62 °C). Data are recorded in Table 5.1 for the following compounds:

(103a)	2-(4-methoxyphenyl)-4-chloro-3,6-dihydro-2*H*-1,2-thiazine.
(104a)	2-(4-methoxyphenyl)-5-chloro-3,6-dihydro-2*H*-1,2-thiazine.
(103b)	2-(4-methylphenyl)-4-chloro-3,6-dihydro-2*H*-1,2-thiazine.
(104b)	2-(4-methylphenyl)-5-chloro-3,6-dihydro-2*H*-1,2-thiazine.
(103c)	2-(4-bromophenyl)-4-chloro-3,6-dihydro-2*H*-1,2-thiazine.
(104c)	2-(4-bromophenyl)-5-chloro-3,6-dihydro-2*H*-1,2-thiazine.

^{13}C NMR data for compounds (103b), (103c) and (104c) are given below.



(103b) R=Me, X=Cl, Y=H
(103c) R=Cl, X=Cl, Y=H
(104c) R=Cl, X=H, Y=Cl

(103b): ^{13}C NMR $\delta_C(CDCl_3)$: 147.8 (C-1'), 131.3 (C-4), 129.3 (C-3'), 127 (C-5), 122.2 (C-4'), 118.8 (C-2'), 55.6 (C-3), 30.3 (Me), 28.1 (C-6).

(103c): ^{13}C NMR $\delta_C(CDCl_3)$: 150.0 (C-1'), 132.1 (C-3'), 131.3 (C-4), 122.6 (C-5); 120.8 (C-2'), 114.6 (C-4'), 55.8 (C-3), 28.9 (C-6).

(104c): ^{13}C NMR $\delta_C(CDCl_3)$: 149.5 (C-1'), 131.7 (C-3'), 128.3 (C-5), 123.1 (C-4), 120.4 (C-2'), 114.2 (C-4'), 52.2 (C-3), 32.1 (C-6).

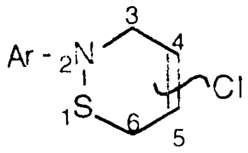


Table 5.1

Properties of Diels-Alder Adducts (103) and (104) From Chloroprene Additon to Thionitrosoarenes (102)

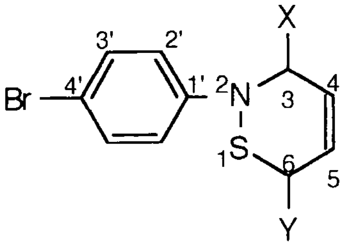
Phthalimide precursor	Overall Yield[a]	Isomer Ratio	^{1}H NMR δ_H ($CDCl_3$) (excluding aromatics)	M$^+$ Found (Required)	m/z M$^+$ (ArNS)
(101a)	60%	50% (103a) 50% (104a)	6.14 [1H, m, vinylics (C5)] 6.04 [1H, m, vinylics (C4)] 4.1 (2H, m, CH_2N) 3.78 (3H, s, OMe) 3.4 (1H, m, CH_2S)		
(101b)	50%	50% (103b)	6.15 [1H, m, vinylic (C5)] 4.16 (1H, m, CH_2N) 3.19 (1H, m, CH_2S) 2.29 (3H, s, Me)	225.03533 (225.03790)	225 (137)
		50% (104b)	6.05 [1H, m, vinylic (C4)] 4.21 (1H, m, CH_2N) 3.23 (1H, m, CH_2S) 2.29 (3H, s, Me)		
(101c)	30%	67% (103c)	6.16 [1H, m, vinylic (C5)] 4.2 (1H, m, CH_2N) 3.22 (1H, m, CH_2S)	288.93387 (288.93277)	314 (201)
		33% (104c)	6.05 [1H, m, vinylic (C4)] 4.1 (1H, m, CH_2N) 3.4 (1H, m, CH_2S)		

[a] Estimated from ^{1}H NMR spectra of the crude reaction mixture.

Adducts of Thionitrosoarenes (102 a-c) with Piperylene. These were prepared analogously to the adducts of thionitrosoarenes (102 a-c) with chloroprene using the same quantities of starting material (101 a-c), triethylamine and solvent, but with piperylene (2ml, 40mmol) in place of chloroprene. Isomer ratios were determined from 250MHz ^{1}H NMR spectra. Data for the following compounds are given in Table 5.2:

(105a) (3-*RS*)-2-(4-methoxyphenyl)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(106a) (6-*RS*)-2-(4-methoxyphenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(105b) (3-*RS*)-2-(4-methylphenyl)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(106b) (6-*RS*)-2-(4-methylphenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(105c) (3-*RS*)-2-(4-bromophenyl)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(106c) (6-*RS*)-2-(4-bromophenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiazine.

^{13}C NMR data for compounds (105c) and (106c) are given below:



(105c) X=Me, Y=H
(106c) X=H, Y=Me

(105c) ^{13}C NMR $\delta_C(CDCl_3)$: 151.0 (C-1'), 131.5 (C-3'),125.4, 124.2 (C4, C5) 120.5 (C-2'), 112.6 (C-4'), 52.5 (C-3), 26.9 (Me), 20.4 (C-6).

(106c) ^{13}C NMR $\delta_C(CDCl_3)$: 156.2 (C-1'), 131.5 (C-3'), 127.2, 126.5 (C-4, C-5), 119.6 (C-2'), 112.4 (C-4'), 49.0 (C-3), 26.2 (Me), 18.5 (C-6).

Table 5.2

Properties of Adducts From Isoprene Addition to Thionitrosoarenes (102 a-c)

Phthalimide precursor	Total Yield (105) and (106) (Est. from NMR)	Isomer Ratio	^{1}H NMR δ_H ($CDCl_3$) (excluding aromatics)	M^+ Found (Required)	*m/z* M^+ (ArNS)
(101a)	70%	75% (105a)	6.0-5.7 (2H, m, vinylics) 3.8 (2H, m, CHN) 3.7(3H, s, OMe) 3.5 (1H, m, CH_2S) 2.3 (1H, m, CH_2S) 1.4 (3H, d, J=6.7 Hz, CH_3)		221 (153)
		25% (106a)	6.0-5.7 (2H, m, vinylics) 3.8 (2H, m, CH_2N) 3.7(3H, s, OMe) 3.5 (1H, m, CHS) 1.0 (3H, d, J=7.2 Hz, CH_3)		
(101b)	70%	75% (105b)	5.9-5.7 (2H, m, vinylics) 3.9 (2H, m, CHN) 3.4 (1H, m, CH_2S) 2.3 (1H, m, CH_2S) 2.18 (3H, s, CH_3) 1.4 (3H, d, J=8.6 Hz, CH_3)	205.03479 (205.092521)	205 (137)

Table 5.2 (continued)

		25% (106b)	5.9-5.7 (2H, m, vinylics) 3.9 (2H, m, CH_2N) 3.4 (1H, m, CHS) 2.3 (3H, s, CH_3) 1.1 (3H, d, J=7.1 Hz, CH_3)
(101c)	70%	67% (105c)	6.0-5.8 (2H, m, vinylics) 4.0 (2H, m, CHN) 3.4 (1H, m, CH_2S) 2.5 (1H, m, CH_2S) 1.5 (3H, d, J=6.6 Hz, CH_3)
		33% (106c)	6.0-5.8 (2H, m, vinylics) 4.0 (2H, m, CH_2N) 3.4 (1H, m, CHS) 1.2 (3H, d, J=7.2 Hz, CH_3)

5.2.2 Experimental for Section 2.2

Adducts of Thionitrosoarenes (102 a-c) with 1-Methylcyclohexene. These were prepared analogously to the adducts of thionitrosoarenes (102) with chloroprene using the same quantities of starting material (101), triethylamine and solvent, but with 1-methylcyclohexene (2ml, 26 mmol) in place of chloroprene. The crude product was placed under high vacuum to remove excess 1-methylcyclohexene and was then analysed by 250MHz ^{1}H NMR spectroscopy. (109c), IRυ_{max} (neat):3350 cm^{-1} (NH). Data for the following compounds are given in Table 5.3:

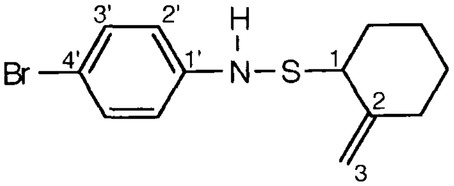
(109a) *N*-(4-methoxyphenyl)-1-(methylidenecyclohexane)-1-sulphenamide.
(109b) *N*-(4-methylphenyl)-1-(methylidenecyclohexane)-1-sulphenamide.
(109c) *N*-(4-bromophenyl)-1-(methylidenecyclohexane)-1-sulphenamide.

Table 5.3

Properties of Adducts (109a-c) From 1-Methylcyclohexane Addition to Thionitrosoarenes (102)

Adduct	Crude Yield	^{1}H NMR δ_H(CDCl$_3$) Excluding Aromatics	*m/z* M$^+$	Mass Found (Mass Calc.)
(109a) $C_{14}H_{19}NOS$	80%	4.7 (1H, s, =CH$_2$) 4.6 (1H, s, NH) 4.5 (1H, s, =CH$_2$) 3.7 (3H, s, MeO) 2.2 (1H, m, SCH) 2.0-1.5 (8H, m, cyclohexane)		
(109b) $C_{14}H_{19}NS$	95%	5.0-4.5 (3H, m, =CH$_2$ + NH 2.3 (3H, s, CH$_3$) 2.0-0.8 (9H, m, cyclohexane)	233	233.12384 (233.12864)
(109c) $C_{13}H_{16}BrNS$	85%	5.2-4.9 (3H, m, =CH$_2$+ NH 2.5-1.5 (9H, m, cyclohexane)	279, 299	297.60099 (297.61409) for ^{79}Br

^{13}C NMR data for compound (109c) are given below:



(109c) ^{13}C NMR δ_C(CDCl$_3$): 145.7 (C-1'), 132.3 (C-3'), 113.5 (C-3), 117.7 (C-2'), 118.4 (C-2), 111.4 (C-4'), 51.9 (C-1), 31.6, 29.3, 27.3, 26. 9 (ring carbons).

Adducts of Thionitrosoarenes (102 a-c) with α-Pinene. These were prepared analogously to the adducts of thionitrosoarene (102) with chloroprene using the same quantities of starting material (101), triethylamine and solvent, but with α-pinene (2ml, 17mmol) in place of chloroprene. The crude reaction mixtures were purified on a silica gel column eluted with dichloromethane to give the adducts (110 a-c) as yellow oils. The following compounds were prepared in this way:

(110a) *N*-(4-methoxyphenyl)-2-methylidene-6,6-dimethylbicyclo [3.1.1] heptan-3-yl-sulphenamide. Yield: 25% (Est. from ^{1}H NMR); δ_H(250 MHz, CDCl$_3$): 6.75-7.05 (4H, m, aromatics), 5.25 (1H, s, NH), 4.75 (1H, s, =CH$_2$), 4.45 (1H, s, =CH$_2$), 3.70 (1H, d, S-CH), 3.65 (3H, s, MeO), 2.6-1.5 (6H, m, ring protons), 1.25 (3H, s, gem CH$_3$), 0.70 (3H, s, gem CH$_3$).

(110b) *N*-(4-methylphenyl)-2-methylidene-6,6-dimethylbicyclo [3.1.1] heptan-3-yl-sulphenamide. Yield 60% (Est. from ^{1}H NMR). HRMS found: 273.1552. Calc for $C_{17}H_{23}NS$: 273.15255. δ_H(250MHz, CDCl$_3$): 7.1-6.9 (4H, m, aromatics), 5.3 (1H, s, NH), 4.75 (1H, s, =CH$_2$), 4.45 (1H, s, =CH$_2$), 3.8 (1H, d, S-CH), 2.4-1.4 (6H, m, ring protons), 2.3 (3H, s, Me), 1.25 (3H, s, gem CH$_3$), 0.70 (3H, s, gem CH$_3$); δ_C(CDCl$_3$): 129.81, 115.17, 117 (aromatics), 110.59 (=CH$_2$), 51.43

(CHS), 40.34, 40.02, 29.0, 27.47, 26.76, 25.84, 21.54 (ring carbons); *m/z* 273 (M^+) EI.

(110c) *N*-(4-bromophenyl)-2-methylidene-6,6-dimethylbicyclo [3.1.1] heptan-3-yl-sulphenamide. Yield 45% (Est. from ^{1}H NMR). δ_H(250 MHz, $CDCl_3$): 7.4-7.1 (4H, m, aromatics), 5.4 (1H, s, NH), 4.75 (1H, s, $=CH_2$), 4.45 (1H, s, $=CH_2$), 3.8 (1H, d, J=9Hz, S-CH), 2.4-1.4 (6H, m, ring protons), 1.25 (3H, s, gem CH_3), 0.70 (3H, s, gem CH_3); *m/z* 337, 339 (M^+) EI.

Adduct of Thionitrosoarene (102c) with β-Pinene. This was prepared analogously to the adducts of thionitrosoarenes (102) with chloroprene using the same quantity of precursor (101c), triethylamine and solvent, but with β-pinene (2ml, 17mmol) in place of chloroprene. The crude reaction mixture was pumped under high vacuum at room temperature to remove excess β-pinene. 250MHz ^{1}H NMR showed the product to be *N*-(4-bromophenyl)-6,6-dimethylbicyclo-[3.1.1]-2-hepten-3-yl-methylsulphenamide (111c) (60% est. from ^{1}H NMR). HRMS found:337.0527. Calc for $C_{14}H_{15}BrNS$ (^{79}Br): 337.0397; IRυ_{max} (neat): 3430 cm^{-1} (NH). δ_H(250 MHz, $CDCl_3$): 7.3-6.8 (4H, m, aromatics), 5.2 (1H, s, NH), 4.7 (1H, s, =CH),2.3 (1H, s, =CH), 3.14 (2H, s, CH_2S), 2.5-1.5 (6H, m, ring protons), 1.3 (3H, s, gem CH_3), 0.9 (3H, s, gem CH_3); *m/z* 339 (M^+) EI.

5.2.3 Experimental for Section 2.3

Adducts of Thionitrosoarenes (102 a-c) with 2,3-Dimethyl-1,3-Butadiene in Dimethylformamide (DMF). To a stirring suspension of thioarylaminophthalimide (101) (0.5 mmol) dissolved in DMF (8ml) under dry nitrogen was added sequentially, 2,3-dimethyl-1,3-butadiene (2ml, 30mmol) and triethylamine (2ml, 14mmol). Stirring was continued at room temperature until a clear solution was obtained (*ca.* 12 hours). The solution was extracted into cyclohexane and washed with water (4x 100ml) to remove DMF. The cyclohexane solution was dried over magnesium sulphate, filtered and evaporated to afford crude mixtures (122 a-c) and (123 a-c). Isomer ratios were determined from the 250MHz ^{1}H NMR spectra of the crude reaction mixtures (Table 5.5). 250MHz ^{1}H NMR data for the following known compounds are shown in Table 5.4:

(122a) 2-(4-methoxyphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(122b) 4,5-dimethyl-2-(4-methylphenyl)-3,6-dihydro-2*H*-1,2-thiazine.

(122c) 2-(4-bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(123a) *N*-(4-methoxyphenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

(123b) 3-methyl-2-methylidene-*N*-(4-methylphenyl)-3-butene-1-sulphenamide.

(123c) *N*-(4-bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

Table 5.4

Adducts of Thionitrosoarenes (102a-c) with 2,3-Dimethyl-1,3-butadiene

Phthalimide Precursor	Adducts	δ_H ($CDCl_3$) (excluding aromatics)
(101a)	(122a)	3.8 (2H, m, CH_2N) 3.7 (3H, s, CH_3O) 2.9 (2H, m, CH_2S) 1.7 (6H, s, 2x CH_3).
	(123a)	5.2-4.5 (5H, m, 2x=CH_2+NH) 3.7 (3H, s, CH_3O) 3.4 (2H, m, CH_2S) 1.9 (3H, s, CH_3).
(101b)	(122b)	3.8 (2H, m, CH_2N) 2.9 (2H, m, CH_2S) 2.4 (3H, s, CH_3Ar) 1.9 (6H, s, 2x CH_3).
	(123b)	5.2-4.5 (5H, m, 2x=CH_2+NH) 3.4 (2H, m, CH_2S) 2.4 (3H, s, CH_3Ar) 1.9 (3H, s, CH_3).
(101c)	(122c)	3.9 (2H, m, CH_2N) 2.9 (2H, m, CH_2S) 1.7 (6H, s, 2x CH_3).
	(123c)	5.2-4.6 (5H, m, 2x=CH_2+NH) 3.4 (2H, m, CH_2S) 1.9 (3H, s, CH_3).

Table 5.5

Yields and Ratios of Diels-Alder (122) and Ene (123) Adducts Formed in DMF

Precursor	Total Yield of Adducts (122) and (123) (%)	Ratio of Adducts (122) : (123)
(101a)	85	80 : 20
(101b)	85	55 : 45
(101c)	80	23 : 77

Adducts of Thionitrosoarenes (102 a-c) with 2,3-Dimethyl-1,3-Butadiene in Acetonitrile. To a stirring suspension of thioarylaminophthalimide (101) (0.5mmol) in acetonitrile (dry, 50ml) under dry nitrogen was added sequentially 2,3-dimethyl-1,3-butadiene (2ml, 30mmol) and triethylamine (2ml, 14mmol). Stirring was continued at room temperature until a clear solution was obtained (*ca.* 12 hours). After evaporation the residue was stirred vigorously with cyclohexane (100 ml) for 30 minutes. The precipitated triethylammonium phthalimide was removed by filtration and the filtrate was evaporated to afford crude (122a-c) and (123a-c) as brown oils. Isomer ratios were determined from the 250 MHz ^{1}H NMR spectra of the crude mixtures (Table 5.6). Compounds (122 a-c) and (123 a-c) were obtained with ^{1}H NMR data as in Table 5.4.

Table 5.6

Yields and Ratios of Diels-Alder (122) and Ene (123) Adducts Formed in Acetonitrile

Precursor	Total Yield of Adducts (122) and (123) (%)	Ratio of Adducts (122) : (123)
(101a)	85	83 : 17
(101b)	85	59 : 41
(101c)	80	25 : 75

Adducts of Thionitrosoarene (102 a-c) with 2,3-Dimethyl-1,3-Butadiene in Chloroform. These were prepared analogously to the adducts of thionitrosoarenes (102 a-c) with 2,3-dimethyl-1,3-butadiene in acetonitrile but using dry chloroform (10ml) instead of acetonitrile. Compounds (122 a-c) and (123 a-c) were obtained with ^{1}H NMR data as in Table 5.4. Isomer ratios were determined from the 300 MHz ^{1}H NMR spectra of the crude product mixtures (Table 5.7).

Table 5.7

Yields and Ratios of Diels-Alder (122) and Ene (123) Adducts Formed in Chloroform

Precursor	Total Yield of Adducts (122) and (123) (%)	Ratio of Adducts (122) : (123)
(101a)	70	95 : 5
(101b)	80	70 : 30
(101c)	57	35 : 65

Adducts of Thionitrosoarene (102 a-c) with 2,3-Dimethyl-1,3-Butadiene in Toluene. These were prepared analogously to the adducts of thionitrosoarenes (102 a-c) with 2,3-dimethyl-1,3-butadiene in acetonitrile but using toluene (dry, 30ml) instead of acetonitrile. Compounds (122 a-c) and (123 a-c) were obtained with ^{1}H NMR data as in Table 5.4. Isomer ratios were determined from the 250 MHz ^{1}H NMR spectra of the crude product mixtures (Table 5.8).

Table 5.8

Yields and Ratios of Diels-Alder (122) and Ene (123) Adducts Formed in Toluene

Precursor	Total Yield of Adducts (122) and (123) (%)	Ratio of Adducts (122) : (123)
(101a)	70	88 : 12
(101b)	50	76 : 24
(101c)	55	50 : 50

5.2.5 Experimental for Section 2.5

Reaction of Ene Adducts (110 a-c) with 2,6-Difluorobenzoyl Isocyanate. To a stirring solution of purified ene adducts (110 a-c) (0.36mmol) in toluene (20ml) was added 2,6-difluorobenzoyl isocyanate (80mg, 0.44 mmol). The resulting mixture was stirred for 2 hours at room temperature under dry nitrogen. Purification on a silica gel column eluted with dichloromethane gave adducts (126 a-c) as white solids.

(126a) [[[2-methylene-6,6-dimethylbicyclo-[3.1.1]-heptan-3-thio](4-methoxyphenyl)amino]carbonyl]-2,6-difluorobenzamide. Yield: 10mg (6%); Mpt: 96-98°C; δ_H(300 MHz, $CDCl_3$): 9.4 (1H, s, NHC=O), 7.5-6.9 (7H, m, aromatics), 5.4 (2H, s, $=CH_2$), 4.05 (1H, d, S-CH), 3.8 (3H, s, CH_3O), 2.4-1.5 (6H, m, ring protons), 1.3 (3H, s, gem CH_3), 0.7 (3H, s, gem CH_3); *m/z* 473 (M^+ + 1) CI.

(110b) [[[2-methylene-6,6-dimethylbicyclo-[3.1.1]-heptan-3-thio](4-methylphenyl)amino]carbonyl]-2,6-difluorobenzamide. Yield: 25mg (15%); Mpt: 96-98°C; Analysis found: C, 63.6; H, 4.8; N, 5.6. Calc for $C_{25}H_{26}F_2N_2O_2S$: C, 65.8; H, 5.7; N, 6.1%; δ_H(300MHz, $CDCl_3$): 9.4 (1H, s, NHC=O), 7.5-6.8 (7H, m, aromatics), 5.4 (2H, s, $2x=CH_2$), 4.05 (1H, d, S-CH)l, 2.4-1.5 (7H, m, CH_3Ar + 6 ring protons), 1.3 (3H, s, gem CH_3), 0.7 (3H, s, gem CH_3); *m/z* 457 (M^+ + 1) CI.

(110c) [[[2-methylene-6,6-dimethylbicyclo-[3.1.1]-heptan-3-thio](4-bromophenyl)amino]carbonyl]-2,6-difluorobenzamide. Yield: 10mg (5%); Mpt: 109-111°C; Analysis found: C, 54.4; H, 4.6; N, 5.4. Calc for $C_{24}H_{23}BrF_2N_2OS$: C, 55.4; H, 4.4; N, 5.4%; δ_H(300 MHz, $CDCl_3$): 9.5 (1H, s, NHC=O), 7.5-6.8 (7H, m, aromatics), 4.95 (1H, s, $=CH_2$), 4.9(1H, s, $=CH_2$), 4.0 (1H, d, S-CH), 2.3-1.5 (6H, m, ring protons), 1.3 (3H, s, gem CH_3), 0.7 (3H, s, gem CH_3); *m/z* 521 (M^+ + 1) CI.

Reaction of Crude Isomer Mixtures with 2,6-Difluorobenzoyl Isocyanate. To a stirring solution of the crude product mixture from the reaction of 2,3-dimethyl-1,3-butadiene with thionitrosoarenes (102 a-c) (180mg) in toluene (20ml) was added 2,6-difluorobenzoyl isocyanate (100mg, 0.55mmol). Stirring was continued for 16 hours at room temperature under dry nitrogen. Products were separated on a silica gel column eluted with dichloromethane.

Reaction of a mixture of (122a) and (123a) gave after column chromatography pure 2-(4-methoxyphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine (122a); δ_H(300MHz, $CDCl_3$): 7.1-6.7 (4H, m, aromatics); 3.35 (2H, m, CH_2N); 3.25 (3H, s, CH_3O); 2.9 (2H, m, CH_2S); 1.7 (6H, s, $2xCH_3$); *m/z* 236 (M^+ + 1) CI.

Reaction of a mixture of (122b) and (123b) gave after column chromatography pure 2-(4-methylphenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine (122b); δ_H(300 MHz, $CDCl_3$): 7.05 (4H, m, aromatics), 3.9 (2H, m, CH_2N), 2.9 (2H, m, CH_2S), 2.3 (3H, s, CH_3), 1.7 (6H, s, $2xCH_3$); *m/z* 220 (M^+ + 1) CI.

Reaction of a mixture of (122c) and (123c) gave after column chromatography: 2-(4-bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine (122c); δ_H(300MHz, $CDCl_3$): 7.1-6.95 (4H, m, aromatics), 3.9 (2H, m, CH_2N), 2.95 (2H, m, CH_2S), 1.7 (6H, s, $2xCH_3$); MS: *m/z* 283 (M^+ + 1) CI.

N-[[[3-methyl-2-methylidene-but-3-ene-1-thio](4-bromophenyl) amino]carbonyl]-2,6-difluorobenzamide (127c); δ_H(300MHz, $CDCl_3$): 9.55 (1H, s, NH), 7.4-6.8 (6H, m, aromatics), 5.5-5.1 (4H, m, $2x{=}CH_2$), 3.6 (2H, s, CH_2S), 1.9 (3H, s, CH_3); *m/z* 496 (M^+ + 1) CI.

2,6-difluoro-*N*-[[(4-bromophenyl)amino]carbonyl]-benzamide (128); Mpt. 135-136°C. Identified by comparison with an authentic sample (see below).

Preparation of an Authentic Sample of (128). 2, 6-Difluorobenzoyl isocyanate (600mg, 3.3mmol) was added to a stirring solution of bromoaniline (500mg, 2.9 mmol) in toluene (20ml). Stirring was continued for 10 minutes at room temperature under nitrogen. The reaction mixture was cooled, filtered and recrystallised from chloroform to give 2,6-difluoro-*N*-[[(4-bromophenyl)amino]carbonyl]-benzamide (128) as a white solid. Yield 700mg

(68%). Mpt. 135.7-135.9°C. Analysis found: C, 47.2; H, 2.7; N, 7.9. Calc for $C_{14}H_9BrF_2N_2O_2$: C,47.2; H, 2.5; N, 7.9%. δ_H(300MHz, $CDCl_3$): 10.4 (1H, s, NH), 8.6 (1H, s, NH), 7.5-6.9 (7H, m, aromatics); *m/z* 355 (M^+ + 1) CI.

5.2.6 Experimental for Section 2.6

***N*-Trimethylsilyl-2-aminopyridine (131).** This was prepared using a modified literature procedure.[69] Thus to a stirring solution of 2-aminopyridine (2.0g, 21mmol) in freshly distilled ether at (50ml) at 0°C under nitrogen was added dropwise *n*-butyllithium (2.5M in hexanes) (8.4ml, 21mmol). Stirring was continued at 0°C for 1.5 hours. Chlorotrimethylsilane (4ml, 30mmol) was added dropwise at 0°C. The resulting mixture was stirred for 16 hours at room temperature and filtered under nitrogen to remove the precipitate. Solvent was removed under vacuum to yield (131) (2.17g, 62%) as a yellow oil which could be used without further purification.

***N*-(2-pyridyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (132).** To a stirring solution of *N*-trimethylsilyl-2-aminopyridine (2g, 12mmol) dissolved in freshly distilled chloroform (25ml) under dry nitrogen, was added *N*-chlorosulphenyl phthalimide (28) (2.56g, 12mmol), dissolved in freshly distilled chloroform (25ml), dropwise over 5 minutes. A precipitate quickly formed and stirring was continued for 1 hour. The precipitate was collected by filtration and dried to give (132) as a white solid (480mg, 15%). Mpt. 147-148°C. Analysis found: C, 52.6; H, 3.3; N, 14.2. Calc for $C_{13}H_9N_3O_2S$: C, 57.6; H, 3.3; N, 15.5. HRMS found 271.03678. Calc for $C_{13}H_9N_3O_2S$: 271.04155. δ_H(250MHz, $CDCl_3$): 8.4 (8H, m, aromatics), 7.0 (1H, s, NH); *m/z* 271 (M^+) EI.

Adducts of 2-Thionitrosopyridine (133) with 2,3-Dimethyl-1,3-Butadiene. To a stirring suspension of precursor (132) (200mg, 0.74mmol) in dry acetone (50ml) under dry nitrogen was added sequentially, 2,3-dimethyl-1,3-butadiene (2ml, 30mmol) and triethylamine (2ml, 14mmol). Stirring was continued at room temperature until a clear solution was obtained (*ca.* 12 hours). After evaporation the residue was stirred vigorously with cyclohexane (100ml) for 30 minutes. The precipitated triethylammonium phthalimide was removed by filtration and the filtrate was evaporated to afford crude (134) and (135) as brown oils in a 3:2 ratio, as determined from the 250 MHz ^{1}H NMR spectrum of the crude product mixture. The combined yields of (134) and (135) was estimated from the ^{1}H NMR spectrum of this product mixture to be 65%. HRMS found 206.08777. Calc for $C_{11}H_{14}N_2S$: 206.07626. *m/z* 206 (M^+) EI.

^{1}H NMR data for the following compounds are given below:

(134) 2-(2-pyridyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(135) 3-methyl-2-methylidene-*N*-(2-pyridyl)-3-butene-1-sulphenamide.

δ_H(250MHz, $CDCl_3$): 8.4-6.7 (4H, m, heteroaromatic) (both isomers)

(134) 4.4 (2H, m, CH_2N), 3.0 (2H, m, CH_2S), 1.7 (6H, s, 2xCH_3).

(135) 6.5 (1H, s, NH), 5.2-4.8 (4H, m, 2x=CH_2), 3.5 (2H, s, CH_2S), 1.87 (3H, s, CH_3).

Bis (2-aminopyridyl)sulphide (136). To a stirring solution of 2-aminopyridine (0.44g, 4.7mmol) in freshly distilled dichloromethane (10ml) under dry nitrogen was added dropwise *N*-chlorosulphenyl phthalimide (28) dissolved in freshly distilled dichloromethane (10ml). Stirring was continued for 16 hours at room temperature under nitrogen. The precipitate which formed was collected by filtration and dried to yield (136) as a white powder (140mg, 28%), mp. 131-133°C. Analysis found: C, 55.6; H, 4.1; N, 23.6. Calc for $C_{10}H_{10}N_4S$: C, 55.0; H, 4.6; N, 23.6%; IR$_{\upsilon\ max}$ (KBr disc)/cm^{-1} 3130 (NH);

δ_H(250MHz, $CDCl_3$): 7.5-7.6 and 7.4-7.1 (8H, m, heteroaromatic); 6.8 (2H, s, 2xNH); *m/z* 218 (M^+), 124 (HetN=S) EI.

***N*-Trimethylsilylaminopyrazine.** This was prepared analogously to (131) and isolated as a white solid (1.5g, 85%)

***N*-(2-pyrazyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (138).** This was prepared analogously to (132) using *N*-trimethylsilylaminopyrazine (1.5g, 9mmol) and *N*-chlorosulphenyl phthalimide (1.9g, 9mmol) to give (138) as a white solid (1.27g, 50%), mp. 173-174°C. IR$_{\upsilon\ max}$ (KBr disc)/cm^{-1} 3400 (NH); δ_H(250MHz, $CDCl_3$): 9.25 (1H, s, heteroaromatic), 8.6-8.2 (2H, m, heteroaromatic), 7.6-7.8 (4H, m, phthalimide), 7.4 (1H, s, NH).

***N*-Trimethylsilyl-2-aminothiazole.** To a stirring solution of 2-aminothiazole (1.0g, 10mmol) in dry ether (50ml) under nitrogen at 0°C was added sequentially triethylamine (dry, 2ml, 14mmol) and chlorotrimethylsilane (1.4ml, 11mmol). Stirring was continued for 16 hours at room temperature. The precipitate was removed by filtration under nitrogen and the filtrate was evaporated under vacuum to give *N*-trimethylsilyl-2-aminothiazole as a white solid (0.98g, 57%).

***N*-(2-thiazolyl)-1,3-dihydro-1,3-dioxoisoindole (139).** This was prepared analogously to (132) using *N*-trimethylsilyl-2-aminothiazole (0.98g, 5.7mmol) and *N*-chlorosulphenyl phthalimide (28) (1g, 4.7mmol) to give (139) as a white solid (1.15g, 89%), mp. >230°C. Analysis found: C, 46.9; H, 2.5; N, 15.2. Calc for $C_{11}H_7N_3O_2S_2$: C, 47.7; H, 2.5; N, 15.2. δ_H(250MHz, d_6 DMSO): 8.5 (4H, m, phthalimide), 1.7 (1H, m, heteroaromatic), 7.5 (1H, m, heteroaromatic).

Adducts of 2-Thionitrosothiazole (140) with 2,3-Dimethyl-1,3-butadiene. These were prepared analogously to the adducts of 2-thionitrosopyridine with 2,3-dimethyl-1,3-butadiene using the same quantities of diene and solvent but with precursor (139) (150mg, 0.55mmol) instead of (132). The crude product mixture contained (141) and (142) in a 1:4 ratio. Crude yield (estimated from the ^{1}H NMR spectrum of the crude reaction mixture): 60%. HRMS found: 212.0362. Calc for $C_9H_{12}N_2S_2$: 212.0442; *m/z* 213 ($M^+ + 1$) CI.

^{1}H NMR data for the following isomers are given below:

(141) 2-(2-thiazole)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(142) 3-methyl-2-methylidene-*N*-(2-thiazole)-3-butene-1-sulphenamide.

δ_H(250MHz, $CDCl_3$): 7.1-6.4 (2H, m, heteroaromatic for both isomers)

(141) 4.2 (2H, m, CH_2N); 3.1 (2H, m, CH_2S); 1.65 (3H, s, CH_3); 1.5 (3H, s, CH_3)

(142) 5.1-4.9 (5H, m, 2x=CH_2+NH); 3.6 (2H, m, CH_2S); 1.8 (3H, s, CH_3).

1,1,1-Trimethyl-2-(pentafluorophenyl)-silazane. To a stirring solution of pentafluoroaniline (2g, 11mmol) in freshly distilled THF (50ml) at 0°C under dry nitrogen was added dropwise *n*-butyllithium (2.5M in hexanes) (4.2ml, 11mmol). Stirring was continued at 0°C for 1.5 hours. Chlorotrimethylsilane was added dropwise at 0°C. The resulting mixture was stirred for 16 hours at room temperature. Solvent was removed under vacuum. The product was distilled from precipitated lithium chloride to yield 1,1,1-trimethyl-2-(pentafluorophenyl)-silazane as a yellow oil (750mg, 27%).

***N*-Pentafluoro-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide (143).** This was prepared analogously to (132) using 1,1,1-trimethyl-2-(pentafluorophenyl)-silazane (750mg, 2.95mmol) and *N*-chlorosulphenyl phthalimide (28) (630mg, 2.95mmol). The precipitate was collected by filtration and dried to give precursor (143) as a white powder (40%), mp. 192-

194°C. IRυ_{max} (KBr disc)/cm^{-1} 3310 (NH), 1750, 1795 (CO). δ_H(250MHz, $CDCl_3$): 7.7-7.9 (4H, m, phthalimide), 5.96 (1H, s, NH).

5.3 EXPERIMENTAL PROCEDURES FOR CHAPTER 3

5.3.1 Experimental for Section 3.1

***N*-(Trimethylsilyl)-arylamines.** These were prepared by one of the following two methods:

(a) To a stirring solution of arylamine (10mmol) in dry ether (50ml) under dry nitrogen at 0°C, was added dropwise *n*-butyllithium (1.6M in hexanes) (6.25ml, 10mmol). Stirring was continued for 1 hour at 0°C to give a precipitate. Chlorotrimethylsilane (2ml, 15mmol) was added dropwise at 0°C and stirring was continued for 16 hours at room temperature. The mixture was filtered under nitrogen to remove precipitate and then solvent was removed under vacuum to give the products as oils. The crude products were used without further purification. The following trimethylsilylarylamines were prepared using this method:

2-(4-cyanophenyl)-1,1,1-trimethylsilazane.
2-(2-cyanophenyl)-1,1,1-trimethylsilazane.
1,1,1-trimethyl-2-(3-methylphenyl)-silazane.
2-(3-bromophenyl)-1,1,1-trimethylsilazane.
2-(2-bromophenyl)-1,1,1-trimethylsilazane.

(b) Reaction was carried out as described in (a) except freshly distilled THF (50ml) was used as a solvent instead of ether. After stirring overnight at room temperature, solvent was removed under vacuum and the products were distilled from lithium chloride under vacuum and isolated as oils. The following arylamines were prepared using this method:

1,1,1-trimethyl-2-(2-methylphenyl)-silazane.
1,1,1-trimethyl-2-(2,6-dimethylphenyl)-silazane.

Typical ^{1}H NMR data for *N*-trimethylsilylarylamines are:
δ_H(250MHz, $CDCl_3$): *ca.* 3.4 (1H, s, NH), 0.2 (9H, s, Me_3Si).

Thioarylaminophthalimides (145 a-g) *e.g.* *N*-3-(methylphenyl)-1,3-dihydro-1,3-dioxoisoindole (145d). To a stirring solution of silylamine (1.0g, 5.6mmol) dissolved in freshly distilled chloroform (10ml) was added *N*-chlorosulphenyl phthalimide (28) (1.2g, 5.6mmol) dissolved in freshly distilled chloroform (10ml) dropwise over 5 minutes. A precipitate quickly formed and stirring was continued for 1 hour. The precipitate was collected by filtration and dried to give (145d) as a white solid (620mg, 40%), mp. 158-160°C. Analysis found: C, 62.7; H, 4.16; N, 9.62. Calc for $C_{15}H_{12}N_2O_2S$: C, 63.4; H, 4.22; N, 9.86; *m/z* 284 (M^+), 137 (ArN=S) EI.

Compounds (145a-g) were prepared by this method [(145 c, d, e) were stirred for 16 hours and (145g) was stirred for 72 hours]. Yields, melting points, IR and ^{1}H NMR spectroscopic data for the following compounds are given in Table 5.9:

(145a) *N*-(2-cyanophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.
(145b) *N*-(4-cyanophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.
(145c) *N*-(2-methylphenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.
(145e) *N*-(2-bromophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.
(145f) *N*-(3-bromophenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.
(145g) *N*-(2,6-dimethylphenyl)-1,3-dihydro-1,3-dioxoisoindole-2-sulphenamide.

Table 5.9

Thioarylaminophthalimides (145 a-g)

Compound Formula	Yield (%) mp. (°C)	IR$\bar{v}_{max}$ (cm^{-1})	^{1}H NMR δ_H(CDCl$_3$)$^{a, b}$
(145a) $C_{15}H_9N_3O_2S$	64 221-223	3360 (NH) 1790 (CO) 1730 (CO)	8.3 (1H, m, Ar) 7.9-7.8 (4H, m, phth) 7.6 (1H, m, Ar) 7.4 (1H, m, Ar) 7.0 (2H, m, NH+Ar)
(145b) $C_{15}H_9N_3O_2S$	23 177-178	3320 (NH) 1780 (CO) 1730 (CO)	7.9-7.7 (4H, m, phth) 7.3-7.4 (4H, m, Ar) 6.5 (1H, s, NH)
(145c) $C_{15}H_{12}N_2O_2S$	74[c] 192-195	3330 (NH) 1785 (CO) 1730 (CO)	8.1-8.0 (4H, m, phth) 7.5-7.1 (4H, m, Ar) 6.6 (1H, s, NH) 2.3 (3H, s, CH_3)
(145d) $C_{15}H_{12}N_2O_2S$	40 158-160	3350 (NH) 1775 (CO) 1715 (CO)	7.9-7.7 (4H, m, phth) 7.5-7.2 (4H, m, Ar) 2.2 (2H, s, CH_3) NH not observed
(145e) $C_{14}H_9BrN_2O_2S$	26 150-153	3290 (NH) 1785 (CO) 1730 (CO)	8.1 (1H, m, Ar) 7.9-7.7 (4H, m, phth) 7.4-7.3 (2H, m, Ar) 6.9-6.8 (2H, m, Ar+NH)
(145f) $C_{14}H_9BrN_2O_2S$	54 192-195	3320 (NH) 1780 (CO) 1730 (CO)	7.9-7.8 (4H, m, phth) 7.3-7.1 (4H, m, Ar) 6.4 (1H, m, NH)
(145g) $C_{16}H_{14}N_2O_2S$	70 152-155	1740 (CO) 1710 (CO)	8.1-8.0 (4H, m, phth) 7.4-7.2 (3H, m, Ar) 2.4 (6H, s, 2xCH_3) NH not observed

[a] Phth=Phthalimide ring protons
[b] Ar=Aromatic protons
[c] Silylamine used neat to obtain this yield

Adducts of Thionitrosoarene (146c) with Piperylene. To a stirring suspension of precursor (145c) (150mg, 0.52 mmol) dissolved in dry acetone (50ml) under dry nitrogen was added sequentially, piperylene (2ml, 40 mmol) and triethylamine (2ml, 14mmol). Stirring was continued at room temperature until a clear solution was obtained (*ca.* 12 hours). After evaporation the residue was stirred vigorously in cyclohexane (100ml) for 30 minutes. The precipitated triethylammonium phthalimide was removed by filtration and the filtrate was evaporated under vacuum to give a mixture of (147c) and (148c) in a 3:2 ratio. Yield (estimated from the ^{1}H NMR spectrum of the crude reaction mixture): 65%. *m/z* 205 (M^+), 137 (ArN=S) EI. ^{1}H NMR data for the following compounds are given below:

(147c) (3*RS*)-2-(2-methylphenyl)-3-methyl-3,6-dihydro-2*H*-1,2-thiazine.

(148c) (6*RS*)-2-(2-methylphenyl)-6-methyl-3,6-dihydro-2*H*-1,2-thiazine.

δ_H(250MHz, $CDCl_3$): 7.3-6.6 (4H, m, aromatic) (for both isomers).

(147c) 6.1 (1H, m, vinylic), 5.9 (1H, m, vinylic), 4.5-3.2 (3H, m, CHN+CH_2S), 2.27 (3H, s, $ArCH_3$), 1.3 [3H, d, J=6.7 Hz, CH_3(C3)].

(148c) 6.0 (1H, m, vinylic), 5.9 (1H, m, vinylic), 4.5-3.2 (3H, m, CH_2N+CHS), 2.23 (3H, s, $ArCH_3$), 1.0 [3H, d, J=7.2 Hz, CH_3(C3)].

Adduct of Thionitrosoarene (146c) with (*E*, *E*)-1,4-Hexadiene. This was prepared analogously to the adducts of (146c) with piperylene using (*E*, *E*)-1,4-hexadiene (1ml, 17mmol) in place of piperylene. The filtrate was evaporated to give (3RS; 6RS)-2-(2-methylphenyl)-3,6-dimethyl-3,6-dihydro-2*H*-1,2-thiazine (149) (80%). Purification on a silica gel column eluted with 1:1 cyclohexane : dichloromethane gave the product as a yellow oil, (60% yield) >90% d.e. (from ^{1}H NMR). δ_H(250MHz, $CDCl_3$): 7.2-7.0 (4H, m, aromatics), 6.0-5.85 (2H, m, vinylics), 3.70 (1H, m, CHN), 3.4 (1H, m, CHS), 2.32 (3H, s, CH_3Ar), 1.4 [3H, d, J=6.6 Hz, CH_3(C3)], 1.1 [3H, d, J=7.2 Hz, CH_3(C6)]; *m/z* 219 (M^+), 137 (ArN=S) EI

Adduct of Thionitrosoarene (146c) with α-Pinene. This was prepared analogously to the adducts of (146c) with piperylene using α-pinene (2ml, 17mmol) in place of piperylene. The crude product was pumped under high vacuum at room temperature to remove excess α-pinene to give *N*-(2-methylphenyl-2-methylidene-6,6-dimethylbicyclo-[3.1.1]-heptan-3-yl-sulphenamide (150c) (68%) (estimated from ^{1}H NMR spectrum of the crude reaction mixture). HRMS found: 273.1551. Calc for $C_{17}H_{23}NS$: 273.1551. δ_H(250MHz, $CDCl_3$): 7.6-6.8 (4H, m, aromatics), 5.4 (1H, s, NH), 4.8 (1H, s, $=CH_2$), 4.3 (1H, s, $=CH_2$), 3.9 (1H, d, SCH), 2.6-1.1 (6H, m, ring protons), 2.3 (3H, s, $ArCH_3$), 1.3 (3H, s, gem CH_3), 0.9 (3H, s, gem CH_3); *m/z* 273 (M^+) EI.

Adduct of Thionitrosoarene (146c) with β-pinene. This was prepared analogously to the adducts of (146c) with piperylene using β-pinene (2ml, 17mmol) in place of piperylene. The crude product was pumped under high vacuum at room temperature to remove excess β-pinene yielding *N*-(2-methylphenyl)-6,6-dimethylbicyclo-[3.1.1]-hept-2-en-yl-methylsulphenamide (151c) (50%) (estimated from ^{1}H NMR spectrum of the crude reaction mixture). δ_H(250MHz, $CDCl_3$): 7.3-6.7 (4H, m, aromatics), 5.0 (1H, s, NH), 4.5 (1H, s, =CH), 3.0 (2H, m, CH_2S), 3.9 (1H, d, SCH), 2.2-1.5 (6H, m, ring protons), 2.0 (3H, s, $ArCH_3$), 1.2 (3H, s, gem CH_3), 0.8 (3H, s, gem,CH_3); *m/z* 273 (M^+) EI.

Adduct of Thionitrosoarene (146b) with 1-Methylcyclohexene. This was prepared analogously to the adducts of (146c) with piperylene using (145b) (150mg, 0.5mmol) and 1-methylcyclohexene (2ml, 26mmol) in place of piperylene, to give *N*-(4-cyanophenyl)-1-(2-methylidenecyclohexane)-1-sulphenamide (152b) (16%) (estimated from ^{1}H NMR spectrum of the crude reaction mixture). HRMS found:244.09529. Calc for $C_{14}H_{16}N_2S$: 244.10339.

δ_H(250MHz, $CDCl_3$): 7.5-6.6 (4H, m, aromatics), 5.18 (1H, s, NH), 4.7 (1H, s, $=CH_2$), 4.5 (1H, s, $=CH_2$), 2.5-1.0 (9H, m, ring protons), *m/z* 244 (M^+) EI.

Adducts of Thionitrosoarenes (146a-f) with 2,3-Dimethyl-1,3-butadiene. These were prepared analogously to the adducts of (146c) with piperylene using precursors (145a-f) (0.5mmol) and 2,3-dimethyl-1,3-butadiene (2ml, 30mmol). The filtrate was evaporated to give mixtures of (155 a-f) and (156 a-f) as oils. The isomer ratios were determined from the ^1H NMR spectra of the crude reaction mixtures. Separation of the mixtures of adducts from all other products was achieved on a silica gel column eluted with 1:1 cyclohexane : dichloromethane. Data for the following compounds are given in Table 5.10:

(155a) 2-(2-cyanophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(155b) 2-(4-cyanophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(155c) 4,5-dimethyl-2-(2-methylphenyl)-3,6-dihydro-2*H*-1,2-thiazine.
(155d) 4,5-dimethyl-2-(3-methylphenyl)-3,6-dihydro-2*H*-1,2-thiazine.
(155e) 2-(2-bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(155f) 2-(3-bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(156a) *N*-(2-cyanophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.
(156b) *N*-(4-cyanophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.
(156c) 3-methyl-2-methylidene-*N*-(2-methylphenyl)-3-butene-1-sulphenamide.
(156d) 3-methyl-2-methylidene-*N*-(3-methylphenyl)-3-butene-1-sulphenamide.
(156e) *N*-(2-bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.
(156f) *N*-(3-bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

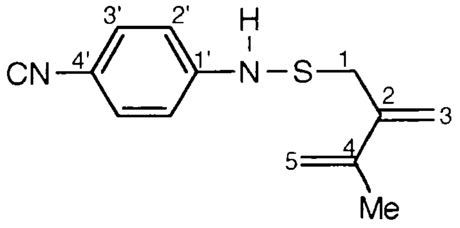
Table 5.10

Properties of Diels-Alder (155) and Ene (156) Adducts From 2,3-Dimethyl-1,3-Butadiene Additon to Thionitrosoarenes (146)

Phthalimide precursor	Overall Yield (Est. from NMR) %	Isomer Ratio	^1H NMR δ_H ($CDCl_3$) (excluding aromatics)	M^+ Found (Required)	*m/z* M^+ (ArNS)
(145a)	58%	9% (155a)	3.8 (2H, m, CH_2N) 2.9 (1H, m, CH_2S) 1.69 (3H, s, CH_3) 1.64 (3H, s, CH_3)	230.03703 (230.08777)	230 (148)
		91% (156a)	5.5 (1H, s, NH) 5.1-4.8 (4H, m, 2x=CH_2) 3.43 (2H, s, CH_2S) 1.83 (3H, s, CH_3)		
(145b)	65	20% (155b)	3.9 (2H, m, CH_2N) 2.9 (1H, m, CH_2S) 1.6 (6H, s, 2xCH_3)	230.08485 (230.0877)	230 (148)
		80% (156b)	5.2-4.7 (5H, m, 2x=CH_2+NH) 3.4 (2H, s, CH_2S) 1.8 (3H, s, CH_3)		
(145c)	50	45% (155c)	3.7 (2H, m, CH_2N) 2.8 (1H, m, CH_2S) 2.3 (3H, s, ArCH_3) 1.7 (3H, s, CH_3) 1.6 (3H, s, CH_3)	219.1052 (219.1082)	219
		55% (156c)	5.2-4.7 (5H, m, 2x=CH_2+NH) 3.4 (2H, s, CH_2S) 2.3 (3H, s, ArCH_3) 1.9 (3H, s, CH_3)		

Table 5.10 (continued)

(145d)	80	40% (155d)	3.9 (2H, m, CH_2N) 2.9 (1H, m, CH_2S) 2.3 (3H, s, $ArCH_3$) 1.7 (6H, s, 2xCH_3)	219.1208 (219.1082)	219
		60% (156d)	5.2-4.9 (5H, m, 2x=CH_2+NH) 3.45 (2H, s, CH_2S) 2.3 (3H, s, $ArCH_3$) 1.9 (3H, s, CH_3)		
(145e)	80	12% (155e)	3.7 (2H, m, CH_2N) 2.8 (1H, m, CH_2S) 1.7 (3H, s, CH_3) 1.6 (3H, s, CH_3)		
		98% (156e)	5.4 (1H, s, NH) 5.1-4.7 (4H, m, 2x=CH_2) 3.37 (2H, s, CH_2S) 1.85 (3H, s, CH_3)		
(145f)	80	30% (155f)	3.8 (2H, m, CH_2N) 2.9 (1H, m, CH_2S) 1.6 (6H, s, 2xCH_3)	283.01172 (283.00303) for ^{79}Br	283, 285 (201, 203)
		70% (156f)	5.1-4.8 (5H, m, 2x=CH_2+NH) 3.4 (2H, s, CH_2S) 1.85 (3H, s, CH_3)		



(156b)

(156b) ^{13}C NMR δ_C(CDCl$_3$): 151.3 (C-1'), 133.4 (C-3'), 123.4, 117.1 (C-2, C-4), 114.9 (C-3'), 115.63, 114.05 (C-3, C-5), 41.6 (C-1), 20.8 (Me).

5.3.2 Experimental for Section 3.2

Preparation of 3-Azido-2,1-Benzisothiazoles *e.g.* 3-Azido-5-chloro-2,1-Benzisothiazole (157b). A modified literature procedure was used.[73] Thus a mixture of 3-amino-5-chloro-2,1-benzisothiazole[84] (250mg, 1.35mmol) and conc. hydrochloric acid (0.5 ml) in water (10ml) was cooled to 0°C. A solution of sodium nitrite (0.1g, 1.4mmol) in water (10ml) was added dropwise and the mixture stirred for 1 hour at 0°C. The solution was quickly filtered to remove any solid, cooled to 0°C and ether (20ml) added. A solution of sodium azide (0.1g, 1.5mmol) in water (10ml) was added and the solution stirred until the evolution of nitrogen had ceased (*ca.* 30 minutes). The ether layer was separated and extracted with water. The organic fractions were combined and briefly dried over magnesium sulphate. After filtration and evaporation of solvent, (157b) was obtained (35% yield). IRv_{max} (Nujol)/cm^{-1} 2105 (N$_3$). The following compounds were prepared analogously:

(157a) 3-Azido-2,1-benzisothiazole.

(157c) 3-Azido-6-chloro-2,1-benzisothiazole.

(157d) 3-Azido-6-bromo-2,1-benzisothiazole.

Thermal Generation and Trapping of Thionitrosoarenes (159 a-d) from 3-Azido-2,1-benzisothiazoles (158 a-d). Azides (158 a-d) (0.5mmol) were refluxed for 16 hours in neat 2,3-dimethyl-1,3-butadiene (10ml) under dry nitrogen. Dimethylbutadiene was evaporated to give (160 a-d) and (161 a-d) as mixtures of isomers. The isomer ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures. HRMS found for isomers (160a) and (161a): 230.07115. Calc for $C_{13}H_{14}N_2S$: 230.08777; *m/z* 230 (M^+), 148 (ArNS). HRMS found for isomers (160b) and (161b): 264.04635. Calc for $C_{12}H_{13}ClNS$: 264.0880; *m/z* 264 (M^+), 182 (ArNS). Data for the following compounds are given in Table 5.11:

(160a) 2-(2-cyanophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(160b) 2-(2-cyano-4-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(160c) 2-(2-cyano-5-chlorophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(160d) 2-(2-cyano-5-bromophenyl)-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(161a) *N*-(2-cyanophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

(161b) *N*-(2-cyano-4-chlorophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

(161c) *N*-(2-cyano-5-chlorophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

(161d) *N*-(2-cyano-5-bromophenyl)-3-methyl-2-methylidene-3-butene-1-sulphenamide.

Table 5.11

Properties of Diels-Alder (160) and ene (161) Adducts From 2,3-Dimethyl-1,3-Butadiene Additon to Thionitrosoarenes (159) at 69°C

Benzisothiazole	Overall Yield (Est. from NMR) %	Isomer Ratio	^{1}H NMR δ_H (CDCl$_3$) (excluding aromatics)
(158a)	80	23% (160a)	3.8 (2H, m, CH$_2$N) 2.9 (2H, m, CH$_2$S) 1.7 (6H, s, 2xCH$_3$)
		77% (161a)	5.5-4.8 (5H, m, 2x=CH$_2$+NH) 3.4 (2H, s, CH$_2$S) 1.8 (3H, s, CH$_3$)
(158b)	60	22% (160b)	3.8 (2H, m, CH$_2$N) 2.9 (2H, m, CH$_2$S) 1.7 (6H, s, 2xCH$_3$)
		78% (161b)	5.5-4.8 (5H, m, 2x=CH$_2$+NH) 3.4 (2H, s, CH$_2$S) 1.8 (3H, s, CH$_3$)
(158c)	60	20% (160c)	3.9 (2H, m, CH$_2$N) 3.0 (2H, m, CH$_2$S) 1.8 (6H, s, 2xCH$_3$)
		80% (161c)	5.5-4.9 (5H, m, 2x=CH$_2$+NH) 3.5 (2H, s, CH$_2$S) 1.9 (3H, s, CH$_3$)
(158d)	35	23% (160d)	3.9 (2H, m, CH$_2$N) 3.0 (2H, m, CH$_2$S) 1.7 (6H, s, 2xCH$_3$)
		77% (161d)	5.6 (1H, s, NH) 5.2-4.9 (4H, m, 2x=CH$_2$) 3.5 (2H, s, CH$_2$S) 1.9 (3H, s, CH$_3$)

Generation and Trapping of Thionitrosoarenes (159a-b) from Benzisothiazoles (158 a-b) at 20°C. Azides (158 a-b) (0.5 mmol) were stirred in neat dimethylbutadiene (5ml) under dry nitrogen for 48 hours (158a) or 72 hours (158b). Dimethylbutadiene was evaporated to give (160 a-b) and (161 a-b) as isomer mixtures from which isomer ratios were by ^{1}H NMR spectroscopy. Total yield of (160a) and (161a): 40%; Isomer ratio (160a) : (161a): 9:91. Total yield of (160b) and (161b): 40%; Isomer ratio (160b) : (161b): 8:92.

Heating of Mixture of Adducts (160a) and (161a). A crude reaction mixture comprising (160a) (9%) and (161a) (91%) was refluxed in 2,3-dimethyl-1,3-butadiene under dry nitrogen for 12 hours. Dimethylbutadiene was evaporated. The ^{1}H NMR spectrum showed the adduct isomer ratio to be unchanged.

Photochemical Generation of Thionitrosoarenes (159 a-b) and Trapping with Dimethylbutadiene. A Carius tube was loaded with azide (158 a-b) and 2,3-dimethyl-1,3-butadiene (4ml, 60mmol) and sealed under vacuum. After irradiation of the mixture with a mercury lamp (1kW, 30cm) for two hours at room temperature, dimethylbutadiene was evaporated to give mixtures of (160 a-b) and (161 a-b) as yellow oils. Isomer ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures. Total yield of (160 a) and (161a): 80%; Isomer ratio (160 a) : (161a): 10:90. Total Yield of (160b) and (161b): 70%; Isomer ratio (160b) : (161b): 9:91.

Photochemical Generation of Thionitrosoarenes (159 a-b) and Trapping with Cyclopentadiene. These reactions were carried out analogously to the photochemical reaction of thonitrosoarenes (159 a-b) with dimethylbutadiene but using cyclopentadiene (4ml, 36mmol) as the diene. Baseline impurities were removed by preparative scale TLC on silica eluting with 1:1 cyclohexane : dichloromethane. The following compounds were prepared in this way:

(165a) 6-(2-cyanophenyl)-5-thia-6-azabicyclo-[2.2.1]-hept-2-ene. Yield: *ca.* 20%. HRMS found: 214.04718. Calc for $C_{12}H_{10}N_2S$: 214.0565; δ_H(250MHz, $CDCl_3$) : 7.5-6.8 (4H, m, aromatics),5.65 (2H, m, vinylics), 3.00 (1H, m, CHN), 2.6 (1H, m, CHS), 2.0 (1H, m, CH_2) 1.8 (1H, m, CH_2); *m/z* 214 (M^+), 280 (M^+ + cyclopentadiene) EI.

(165b) 6-(2-cyano-4-chlorophenyl)-5-thia-6-azabicyclo-[2.2.1]-hept-2-ene. Yield, 12%. HRMS found: 248.0009. Calc for $C_{12}H_9ClN_2S$: 248.0175; δ_H(250MHz, $CDCl_3$) : 7.5-6.8 (4H, m, aromatics),6.1 (1H, m, vinylic), 5.65 (1H, m, vinylic), 3.00 (1H, m, CHN), 2.6 (1H, m, CHS), 2.4-2.0 (2H, m, CH_2); *m/z* 248 (M^+), 314 (M^+ + cyclopentadiene) EI.

3-Azido-2,1-isothiazolo-[4,5-b]-6-methyl-5-cyanopyridine. This was prepared analogously to azides (158 a-d), from the corresponding amine.[85]

Generation and Trapping of Thionitrosopyridine Derivative (167). Thermal generation and trapping of thionitroso compound (167) with 2,3-dimethyl-1,3-butadiene was carried out analogously to the thermal generation of thionitrosoarenes (159 a-d). A mixture of (168) and (169) was obtained in a 1:4 ratio. Total yield of (168) and (169): 39%. *m/z* 286 (M^+) EI. HRMS found: 286.03894. Calc for $C_{13}H_{14}N_2OS$: 286.08884. ^1H NMR data for the following compounds are given below:

(168) 2-[2-(methoxy-4-cyano)-pyridyl]-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(169) 3-methyl-2-methylidene-N-[2-(3-methoxy-2-cyano)-pyridyl]-3-butene-1-sulphenamide.

(168) δ_H(250MHz, $CDCl_3$): 8.0 (1H, s, heteroaromatic), 4.3 (2H, m, CH_2N), 4.02 (3H, s, MeO), 3.3 (2H, m, CH_2S), 1.78 (3H, s, CH_3), 1.73 (3H, s, CH_3).

(169) δ_H(250MHz, $CDCl_3$): 7.9 (1H, s, heteroaromatic), 6.4 (1H, s, NH), 5.2-4.9 (4H, m, 2x=CH_2), 4.16 (3H, s, MeO), 3.73 (2H, m, CH_2S), 1.93(3H, s, CH_3).

5.3.3 Experimental for Section 3.3

Reaction of 3-Amino-2,1-Benzisothiazoles (157b and 174) with Lead Tetraacetate. To a stirring solution of lead tetraacetate (120mg, 0.27mmol) in freshly distilled toluene (5ml) at 0°C under nitrogen was added a suspension of amine (157b, 174) in toluene (10ml). Stirring was continued at 0°C for 1 hour. Washing with water (2x50ml) removed lead tetra acetate and the organic layer was then dried over magnesium sulphate.

From (157b) there was evidence for the formation of the following compounds:

(175) 2-cyano-4-chloroaniline. *m/z* 152 (M^+) EI.

(176) Diazo-(2-cyano-4-chlorobenzene). *m/z* 301 (M^+) EI.

From (174) there was evidence for the formation of the following compounds:

(177) 2-cyano-6-trifluoromethylaniline. *m/z* 186 (M^+) EI.

(178) *N, N*-Thiobis-2-cyano-6-trifluoromethylaniline. *m/z* 400 (M^+) 331 (M^+ - CF_3) EI.

(179) Diazo-(4-trifluoromethyl-2,1-benzisothiazole). *m/z* 433 (M^+) CI.

Generation of Thionitrosoarene (159b) from 3-Amino-2,1-Benzisothiazole (157b) and Trapping with 2,3-Dimethyl-1,3-butadiene. Reaction was carried out in the same way as the decomposition of 3-aminobenzisothiazole (157b) with lead tetraacetate except that 2,3-dimethyl-1,3-butadiene (2ml, 30mmol) was added to the suspension of amine in toluene. Products were purified on a silica gel column eluted with 1:1 cyclohexane : dichloromethane to give a pure mixture of (160b) and (161b) (30% yield). Isomer ratio (160b):(161b) determined from the 250 MHz ^1H NMR spectrum of the crude reaction mixture: 1:2. *m/z* (crude reaction mixture): 332 (M^+, sulphur diimide), 264 [M^+, (160b) and (161b)], 152 [M^+, amine (175)] EI.

5.4 EXPERIMENTAL PROCEDURES FOR CHAPTER 4

5.4.2 Experimental for Section 4.2

Preparation of Imines. These were prepared by stirring the corresponding amine (1mol) and benzaldehyde (10.6g, 1mol). An exothermic reaction occurred. The product was extracted with ether and dried over potassium carbonate. The ether was then evaporated and the resulting liquid distilled under reduced pressure. IRυ_{max} (neat)/cm^{-1} 1650 (C=N). The following imines were prepared by this method:

N-(benzylidene)-methylamine, (64%).
N-(benzylidene)-ethylamine, (73%).
N-(benzylidene)-propylamine, (90%).
N-(benzylidene)-*iso*-propylamine, (76%).
N-(benzylidene)-*tert*-butylamine, (74%).
N-(benzylidene)-*sec*-butylamine, (65%).
N-(benzylidene)-benzylamine, (66%).
N-(benzylidene)-α-methylbenzylamine, (62%).

Preparation of Oxaziridines (188 a-h). These were prepared *via* a literature procedure.[86] Thus to a stirring solution of imine (4.2 mmol) in dry chloroform (10ml) at 20°C was added *m*-chloroperoxybenzoic acid (900mg, 5.2 mmol, 60% active O_2) in chloroform (dry, 5ml). Stirring was continued for 30 minutes. The reaction mixture was then washed with 2M sodium sulphite and 2M sodium carbonate and the organic layer was separated and dried over magnesium sulphate. Oxaziridines (188 a-h) were obtained pure after vacuum distillation on a Kugelhor apparatus. The following oxaziridines were prepared by this method:

(188a) *cis*- and *trans*-2-methyl-3-phenyloxaziridine.
(188b) *cis*- and *trans*-2-ethyl-3-phenyloxaziridine.
(188c) *cis*- and *trans*-2-propyl-3-phenyloxaziridine.
(188d)*cis*- and *trans*-2-benzyl-3-phenyloxaziridine.
(188e) *cis*- and *trans*-2-*iso*-propyl-3-phenyloxaziridine.
(188f) *trans*-2-*tert*-butyl-3-phenyloxaziridine.
(188g) (±)*cis*- and(±) *trans*-2-*sec*-butyl-3-phenyloxaziridine.
(188h) (±)*cis*- and(±) *trans*-2-α-methylbenzyl-3-phenyloxaziridine.

Adducts of Thionitrosoarenes (189 a-d) with 2,3-Dimethyl-1,3-butadiene. A solution of oxaziridine (188) (1.32 mmol), cyclohexene sulphide (150mg, 1.32 mmol) and 2,3-dimethyl-1,3-butadiene in dry chloroform (5ml) under dry nitrogen was stirred (188 a-b) or refluxed (188 c-d) for 16 hours. Solvent was removed under vacuum, taking particular care with (188a) and (188b) because of the volatility of the products, to give mixtures of (190 a-d) and (191 a-d). Compound (190d) was purified by column chromatography on silica gel eluted with dichloromethane. Isomer ratios were determined from the 250 MHz ^{1}H NMR spectra of the crude reaction mixtures. Data for the following compounds are given in Table 5.12:

(190a) 2,4,5-trimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(190b) 2-ethyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(190c) 2-propyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(190d) 2-benzyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.
(191a) *N*-methyl-3-methyl-l,2-methylidene-3-butene-1-sulphenamide.

Table 5.12

Properties of Diels-Alder (190) and Ene (191) Adducts From 2,3-Dimethyl-1,3-Butadiene Additon to Thionitrosoalkanes (189)

Adduct Formula	Overall Yield (Est. from NMR) %	Isomer Ratio	^{1}H NMR δ_H ($CDCl_3$) (excluding aromatics)	M+ Found (Required)	*m/z* M+ (ArNS)
$C_7H_{13}NS$	70	80%(190a)	3.3 (2H, m, CH_2N) 3.0 (1H, m, CH_2S) 2.76 (3H, s, CH_3N) 1.74 (3H, s, CH_3) 1.58 (3H, s, CH_3)	143.05182 (143.07692)	143 (61)
		20% (191a)	5.3-4.9 (4H, m, 2x=CH_2+NH) 3.2 (2H, s, CH_2S) 2.67 (3H, s, CH_3N) 1.9 (3H, s, CH_3)		
$C_8H_{15}NS$	70	60% (190b)	3.4 (2H, m, CH_2N) 2.9 (1H, m, CH_2S) 2.8 (2H, q, J=5.1 Hz, CH_2) 1.7 (3H, s, CH_3) 1.6 (3H, s, CH_3) 1.1 (3H, t, J=6.8 Hz, CH_3)	157.08786 (157.09256)	157
		40% (191b)	5.7(1H, s, NH) 5.3-5.0 (4H, m, 2x=CH_2) 3.2 (2H, s, CH_2S) 2.8 (2H, q, J=5.1 Hz, CH_2) 1.9 (3H, s, CH_3) 1.3 (3H, t, J=7.2 Hz, CH_3)		

Table 5.12 (continued)

$C_9H_{17}NS$	75	60% (190c)	3.4 (2H, m, CH_2N) 2.95 (1H, m, CH_2S) 1.7 (3H, s, CH_3) 1.6 (3H, s, CH_3) 0.9 (3H, t, J=7.3 Hz, CH_3)	171.10272 (171.10822)	171
		40% (191c)	5.7(1H, s, NH) 5.1-4.9 (4H, m, 2x=CH_2) 3.2 (2H, s, CH_2S) 2.8 (2H, m, CH_2) 1.9 (3H, s, CH_3) 1.0 (3H, t, J=7.5 Hz, CH_3)		
$C_{13}H_{17}NS$	80	80% (190d)	7.2 (5H, m, aromatics) 4.05 (2H, 3, CH_2) 3.3 (2H, m, CH_2N) 3.1 (1H, m, CH_2S) 1.8 (3H, s, CH_3) 1.6 (3H, s, CH_3)		219
		20% (191d)	7.7-7.2 (5H, m, aromatics) 5.4-4.9 (4H, m, 2x=CH_2+NH+ CH_2) 3.1 (2H, s, CH_2S) 1.9 (3H, s, CH_3)		

(191b) *N*-ethyl-3-methyl-1,2-methylidene-3-butene-1-sulphenamide.
(191c) *N*-propyl-3-methyl-1,2-methylidene-3-butene-1-sulphenamide.
(191d) *N*-benzyl-3-methyl-1,2-methylidene-3-butene-1-sulphenamide.

Adducts of Thionitrosoalkane (189d) with Isoprene. These were prepared analogously to the adducts of (189d) with dimethylbutadiene except that isoprene (2ml, 20mmol) was used as the diene. Solvent was evaporated to give (192), (193) and (194) as a mixture of isomers, whose ratio was determined from the ^{1}H NMR spectrum of the crude reaction mixture. Crude yield of isomers estimated from the ^{1}H NMR spectrum: 70%. *m/z* 205 (M^+), 91 ($ArCH_2$) EI. Data for the following compounds is given in Table 5.13:
(192) 2-benzyl-5-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(193) 2-benzyl-4-methyl-3,6-dihydro-2*H*-1,2-thiazine.
(194) *N*-benzyl-2-methylidene-3-butene-1-sulphenamide.

Table 5.11

Adducts of Thionitrosoalkane (189d) with Isoprene

Adduct	Isomer Ratio	δ_H(250MHz, $CDCl_3$)
(192)	65%	5.4 (1H, m, vinylic, C4) 4.04 (2H, s, CH_2, benzyl) 3.43 (2H, m, CH_2N) 3.03 (2H, m, CH_2S) 1.78 (3H, s, CH_3, C5)
(193)	18%	5.7 (1H, m, vinylic, C5) 4.07 (2H, s, CH_2, benzyl) 3.31 (2H, m, CH_2N) 3.2 (2H, m, CH_2S) 1.6 (3H, s, CH_3, C4)
(194)	17%	5.3-5.0 (5H, m, 2x=CH_2+NH 4.8 (2H, s, CH_2 benzyl) 4.0 (2H, m, CH_2S)

Adducts of Thionitrosoalkane (189d) with Chloroprene. These were prepared analogously to the adducts of thionitrosoarene (189d) with dimethylbutadiene using chloroprene (50% solution in xylene, 2ml, 11mmol) as the diene. The solvent was evaporated to give a mixture of regioisomeric adducts (195) and (196) in a 1:1 ratio. Combined yield of adducts estimated from the 250 MHz ^{1}H NMR spectrum of the crude reaction mixture: 50%. *m/z* 225 (M^+) EI. There was obtained:

(195) 2-benzyl-5-chloro-3,6-dihydro-2*H*-1,2-thiazine.

(196) 2-benzyl-4-chloro-3,6-dihydro-2*H*-1,2-thiazine.

δ_H(250MHz, $CDCl_3$): 7.4-7.3 (5H, m, aromatics), 6.2 (1H, m, vinylic, C5), 5.8 (1H, m, vinylic, C4), 4.10 (2H, s, CH_2), 4.06 (2H, s, CH_2), 3.6 (2H, m, CH_2N), 3.4 (2H, m, CH_2S), 2.7 (3H, s, CH_3)

Adducts of Thionitrosoalkane (189d) with Piperylene. These were prepared analogously to the adducts of (189d) with dimethylbutadiene using piperylene (2ml, 40 mmol) as the diene. Solvent was evaporated to give adducts (197) and (198) in a 7:3 ratio. Crude yield of isomers estimated from the ^{1}H NMR spectrum of the crude reaction mixture: 50%. There was obtained:

(197) (3-*RS*)-2-Benzyl-3-methyl-3,6-dihydro-2*H*-1,2-thiazine. δ_H(250MHz, $CDCl_3$) (Excluding aromatics): 5.6 (2H, m, vinylics), 4.2 (2H, s, CH_2 benzyl), 3.9-2.5 (3H, m, CH_2S + CHN), 1.3 (3H, d, J=6.7 Hz, CH_3).

(198) (6-*RS*)-2-Benzyl-6-methyl-3,6-dihydro-2*H*-1,2-thiazine. δ_H(250MHz, $CDCl_3$) (Excluding aromatics): 6.0 (2H, m, vinylics), 4.2 (2H, s, CH_2 benzyl), 3.9-2.5 (3H, m, CH_2N+ CHS), 1.2 (3H, d, J=6.5 Hz, CH_3).

5.4.3 Experimental for Section 4.3

Preparation of *N*-Trimethylsilylamines. These were prepared analogously to trimethylsilylamines in section 5.3.1 using method (a). The *N*-trimethylsilylamines were distilled prior to further reaction. The following derivatives were prepared in this way:

N-(Trimethylsilyl)-*tert*-butylamine.
N-(Trimethylsilyl)-benzylamine.
N-(Trimethylsilyl)-cyclohexylamine.
N-(Trimethylsilyl)-α-methylbenzylamine.
N-(Trimethylsilyl)-*sec*-butylamine.

Preparation of *N*-Chlorothioalkylamines (199 a-e). These were prepared *via* the literature route described by Markovskii *et al.*[34] Thus, to a stirring solution of sulphur dichloride (300mg, 2.9 mmol) in ether (dry, 10ml) at -10°C under nitrogen was added dropwise a solution of *N*-(Trimethylsilyl)-amine (2.9 mmol) and triethylamine (0.4ml, 2.9 mmol) in ether (dry, 10ml). Stirring was continued at -10°C for 30 minutes and then at 20°C for 1 hour. Triethylamine hydrochloride was removed by filtration under nitrogen, and the filtrate was evaporated under vacuum at 20°C. The *N*-(Trimethylsilyl)-*N*-chlorothioalkylamines (199 a-e) were obtained as yellow oils. Further purification was not undertaken due to the instability of the products. The following compounds were prepared in this way:

(199a) *N*-(Trimethylsilyl)-*N*-chlorothio-*tert*-butylamine.
(199b) *N*-(Trimethylsilyl)-*N*-chlorothio-benzylamine.
(199c) *N*-(Trimethylsilyl)-*N*-chlorothio-cyclohexylamine.
(199d) *N*-(Trimethylsilyl)-*N*-chlorothio-α-methylbenzylamine.
(199e) *N*-(Trimethylsilyl)-*N*-chlorothio-*sec*-butylamine.

Adducts of Thionitrosoalkanes (200 a-e) with 2,3-Dimethyl-1,3-butadiene. A solution of *N*-chlorothioalkylamine (199 a-e) (0.6 mmol) and 2,3-dimethyl-1,3-butadiene (2ml, 30mmol) in dry toluene (30mmol) was heated at 100°C for 16 hours under dry nitrogen. The solvent was evaporated under vacuum to give (201 a-e) and (202b, d). Compounds (201b) and (201d) were successfully separated on a silica gel column eluted with 1:1 cyclohexane : dichloromethane. Data for the following compounds are given in Table 5.14:

(201a) 2-*tert*-butyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(201b) 2-cyclohexyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(201c) 2-benzyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(201d) 2-α-methylbenzyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(201e) 2-*sec*-butyl-4,5-dimethyl-3,6-dihydro-2*H*-1,2-thiazine.

(202b) *N*-(benzyl)-3-methyl-1,2-methylidene-3-butene-1-sulphenamide.

(202d) *N*-(α-methylbenzyl)-3-methyl-1,2-methylidene-3-butene-1-sulphenamide.

Adduct of Thionitrosoarene (200d) with α-Pinene. This was prepared in the same way as the adduct of thionitrosoalkane (200d) with 2,3-dimethyl-1,3-butadiene except that α-pinene (2ml, 17 mmol) was used in place of 2,3-dimethyl-1,3-butadiene. The crude reaction mixture was pumped under high vacuum to remove excess α-pinene to give *N*-(α-methylbenzyl)-2-methylene-6,6-dimethylbicyclo-[3.1.1]-heptan-3-yl-sulphenamide (203) in 15% yield (estimated from ^{1}H NMR spectrum of the crude reaction mixture). δ_H(250MHz, $CDCl_3$) (Excluding aromatics): 5.3 (1H, s, NH), 5.0 (1H, s, $=CH_2$), 4.8 (1H, s, $=CH_2$), 3.0-1.5 (7H, m, ring protons), 1.32 (3H, s, gem CH_3), 1.3 (3H, d, J=4.8 Hz, CH_3), 0.9 (3H, s, gem CH_3); *m*/*z* 287 ($M^+ + 1$), 152 (RNS + 1) CI.

Table 5.14

Adducts of Thionitrosoalkanes (200 a-e) with 2,3-Dimethyl-1,3-Butadiene

Adduct Formula	Total Yield (201)+(202) (Est. from ^{1}H NMR)/%	Isomer Ratio	^{1}H NMR δ_H ($CDCl_3$)	M$^+$ Found (Required)	m/z M$^+$ (ArNS)
$C_{10}H_{19}NS$	45	100% (201a)	3.55 (2H, m, CH_2N) 3.0 (2H, m, CH_2S) 1.7 (3H, s, CH_3) 1.6 (3H, s, CH_3) 1.2 (9H, s, 3xCH_3)		185
$C_{13}H_{17}NS$	40	91% (201b)	7.4 (5H, m, aromatics) 4.1 (2H, s, CH_2) 3.4 (2H, m, CH_2N) 3.1 (2H, m, CH_2S) 1.8 (3H, s, CH_3) 1.6 (3H, s, CH_3)	219.11838 (219.10818)	219 91 (ArCH_2)
		9% (202b)	7.7-7.2 (5H, m, aromatics) 5.4-4.9 (7H, m, 2x=CH_2+NH+CH_2) 3.1 (2H, s, CH_2S) 1.9 (3H, s, CH_3)		

Table 5.14 (continued)

$C_{12}H_{21}NS$	40	100% (201c)	3.5 (2H, m, CH_2N) 2.9 (2H, m, CH_2S) 2.1-1.0 (17H, m, 2xCH_3+cyclohexyl)	211.022960 (211.13946)	211 (129)
$C_{14}H_{19}NS$	20	92% (201d)	7.6-7.3 (5H, m, aromatics) 4.0 (1H, q, J=6.6 Hz, CH) 3.3 (2H, q, J=17, 91 Hz, CH_2N) 2.9 (2H, q, J=17, 146 Hz, CH_2S) 1.71 (3H, s, CH_3) 1.5 (3H, d, J=6.7 Hz, CH_3) 1.47 (3H, s, CH_3)	233.08907 (233.12387)	233 (185)
		8% (202d)	7.6-7.3 (5H, m, aromatics) 5.6-4.9 (5H, m, 2x=CH_2+NH) 3.4 (2H, m, CH_2S) 1.9 (3H, s, CH_3)		
$C_{10}H_{19}NS$	20	100% (201e)	3.3 (2H, m, CH_2N) 3.1 (1H, m, CH) 2.9 (2H, m, CH_2S)		186 ($M^+ + 1$) CI

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82 N-Z. Huang, M. V. Lakshmikantham and M. P. Cava, *J. Org. Chem.*, 1987, 52, 169.

83 M. U. Bombala and S. V. Ley, *J. Chem. Soc. Perkin Trans. 1*, 1979, 3013.

84 The 3-aminobenzisothiazole derivatives were kindly supplied by Kodak Ltd.

85 Kindly supplied by Dr. P Wight, ICI.

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APPENDICES

1 COLLOQUIA, LECTURES AND SEMINARS

* Seminars attended.

† Invited specially for the postgraduate training program.

17.10.89 Dr. F. Palmer (Nottingham University)
Thunder and Lightning .

25.10.89 Prof. C. Floriani (University of Lausanne, Switzerland)
* Molecular Aggregates - A Bridge between Homogeneous and Heterogeneous Systems.

1.11.89 Dr. J. P. S. Badyal (Durham University)
Breakthroughs in Heterogeneous Catalysis.

9.11.89 Prof. N. N. Greenwood (Leeds University)
Novel Cluster Geometries in Metalloborane Chemistry.

10.11.89 Prof. J. E. Bercaw (California Institute of Technology)
* Synthetic and Mechanistic Approaches to Ziegler-Natta Polymerisation Of Olefins.

13.11.89 Dr. J. Becher (Odense University)
Synthesis of New Macrocyclic Systems using Heterocyclic Building Blocks.

16.11.89 Dr. D. Parker (Durham University)
* Macrocycles, Drugs and Rock 'n' Roll.

29.11.89	Prof. D. J. Cole-Hamilton (St. Andrews University)
	New Polymers from Homogeneous Catalysis.
30.11.89	Dr. M. N. Hughes (King's College London)
*	A Bug's Eye View of the Periodic Table.
4.12.89	Dr. D. Graham (British Petroleum)
	How Proteins Absorb to Interfaces.
6.12.89	Dr. R. L. Powell (I.C.I)
	The Development of C.F.C. Replacements.
7.12.89	Dr. A. Butler (St. Andrews University)
	The Discovery of Penicillin: Facts and Fancies.
13.12.89	Dr. J. Klinowski (Cambridge University)
	Solid State N.M.R. Studies of Zeolite Catalysts.
15.12.89	Prof. R. Huisgen (Universität München)
*	Recent Mechanistic Studies of [2+2] Additions.
24.1.90	Dr. R. N. Perutz (York University),
	Plotting the Course of C-H Activations with Organometallics.
31.1.90	Dr. U. Dyer (Glaxo)
*	Synthesis and Conformation of C-Glycosides.
1.2.90	Prof. J. H. Holloway (Leicester University),
	Noble Gas Chemistry.

7.2.90	Dr. D. P. Thompson (Newcastle University) The Role of Nitrogen in Extending Silicate Crystal Chemistry.
8.2.90	Rev. R. Lancaster (Kimbolton Fireworks) Fireworks - Principles and Practice.
12.2.90	Prof. L. Lunazzi (University of Bologna) Application of Dynamic N.M.R. to the Study of Conformational Enantiomerism.
14.2.90	Prof. D. Sutton (Simon Fraser University, Vancouver B.C.), Synthesis and Applications of Dinitrogen and Diazo Compounds of Rhenium and Iridium.
15.2.90 *	Prof. L. Crombie (Nottingham University) The Chemistry of Cannabis and Khat.
21.2.90	Dr. C. Bleasdale (Newcastle University) The Mode of Action of some Anti-tumour Agents.
22.2.90	Prof D. T. Clark (I.C.I. Wilton) Spatially Resolved Chemistry (using Nature's Paradigm in the Advanced Materials Area).
28.2.90	Dr. R. K. Thomas (Oxford University) Neutron Reflectometry from Surfaces.
1.3.90 *	Dr. J. F. Stoddart (Sheffield University) Molecular Lego.

8.3.90 *	Dr. A. K. Cheetham (Oxford University) Chemistry of Zeolite Cages .
21.3.90	Dr. I. Powis (Nottingham University) Spinning off in a huff: Photodissociation of Methyl Iodide.
23.3.90	Prof. J. M. Bowman (Emory University) Fitting Experiment with Theory In Ar-OH.
9.7.90	Prof. L. S. German (U.S.S.R. Academy of Sciences, Moscow) New Syntheses in Fluoroaliphatic Chemistry: Recent Advances in the Chemistry of Fluorinated Oxiranes.
9.7.90	Prof. V. E. Platonov (U.S.S.R. Academy of Sciences, Novosibirsk) Polyfluoroindanes: Synthesis and Transformation.
9.7.90	Prof. I. N. Rozhkov (U.S.S.R. Academy of Sciences, Moscow) Reactivity of Perfluoroalkyl Bromides.
11.10.90	Dr. W. A. Macdonald (I.C.I. Wilton) Materials for the Space Age.
24.10.90 *	†Dr. M. Bochmann (University of East Anglia) Synthesis, Reactions and Catalytic Activity of Cationic Titanium Alkyls.
26.10.90 *	†Prof. R. Soulen (South Western University, Texas) Preparation and Reactions of Bicycloalkenes.

31.10.90 †Dr. R. Jackson (Newcastle University)
* New Synthetic Methods: α-aminoacids and Small Rings.

1.11.90 Dr. N. Logan (Nottingham University)
* Rocket Propellants.

6.11.90 †Dr. P. Kocovsky (Uppsala)
* Stereo-controlled Reactions Mediated by Transition and Non-Transition Metals.

7.11.90 †Dr. D. Gerrard (British Petroleum)
Raman Spectroscopy for Industrial Analysis.

8.11.90 Dr. S. K. Scott (Leeds University)
* Clocks, Oscillations and Chaos.

14.11.90 †Prof. T. Bell (SUNY, Stoney Brook, U.S.A.)
Functional Molecular Architecture and Molecular Recognition.

21.11.90 Prof. J. Pritchard (Queen Mary & Westfield College, London)
Copper Surfaces and Catalysts.

28.11.90 †Dr. B. J. Whitaker (Leeds University)
Two-Dimentional Velocity Imaging of State-Selected Reaction Products.

29.11.90 Prof. D. Crout (Warwick University)
* Enzymes in Organic Synthesis.

5.12.90	†Dr. P. G. Pringle (Bristol University)
*	Metal Complexes with Functionalised Phosphines.
13.12.90	Prof. A. H. Cowley (University of Texas)
	New Organometallic Routes to Electronic Materials.
15.1.91	Dr. B. J. Alder (Lawrence Livermore Laboratories, California)
	Hydrogen in all its Glory.
17.1.91	Dr. P. Sarre (Nottingham University),
	Comet Chemistry.
24.1.91	Dr. P. J. Sadler (Birkbeck College, London)
*	Design of Inorganic Drugs: Precious Metals, Hypertension + H.I.V.
30.1.91	Prof. E. Sinn (Hull University)
*	Coupling of Little Electrons in Big Molecules. Implications for the Active Sites of (Metalloproteins and other) Macromolecules.
31.1.91	Dr. D. Lacey (Hull University)
	Liquid Crystals.
6.2.91	†Dr. R. Bushby (Leeds University)
*	Biradicals and Organic Magnets.
14.2.91	Dr. M. C. Petty (Durham University)
	Molecular Electronics.

20.2.91 †Prof B. L. Shaw (Leeds University),
* Syntheses with Coordinated, Unsaturated Phosphine Ligands.

28.2.91 Dr. J. Brown (Oxford University)
Can Chemistry Provide Catalysts Superior to Enzymes?

6.3.91 †Dr. C. M. Dobson (Oxford University)
N.M.R. Studies of Dynamics in Molecular Crystals.

7.2.91 Dr. J. Markham (I.C.I. Pharmaceuticals)
* D.N.A. Fingerprinting.

24.4.91 Prof. R. R. Schrock (Massachusetts Institute of Technology)
Metal-Ligand Multiple Bonds and Metathesis Initiators.

25.4.91 Prof. T. Hudlicky (Virginia Polytechnic Institute)
* Biocatalysis and Symmetry Based Approaches to the Efficient
Synthesis of Complex Natural Products.

20.6.91 Prof. M. S. Brookhart (University of North Carolina)
Olefin Polymerisations, Oligomerisations and Dimerisations
using Electrophilic Late Transition Metal Catalysts.

29.7.91 Dr. M. A. Brimble (Massey University, New Zealand)
Synthetic Studies Towards the Antibiotic Griseusin-A.

17.10.91 Dr. J. A. Salthouse (University of Manchester)
* Son et Lumiere - a demonstration lecture.

31.10.91 Dr. R. Keeley (Metropolitan Police Forensic Science)
* Modern Forensic Science.

6/11/91 †Prof B. F. G. Johnson (Edinburgh University)
Cluster-Surface Analogies.

7/11/91 Dr. A. R. Butler (St. Andrews University)
* Traditional Chinese Herbal Drugs-A Different way of Treating Disease.

13/11/91 †Prof. D. Gani (St. Andrews University)
* The Chemistry of PLP-Dependent Enzymes.

20/11/91 †Dr. R. More O' Ferrall (University College, Dublin)
Some Acid Catalysed Rearrangements in Organic Chemistry.

28/11/91 Prof. I. M. Ward (IRC in Polymer Science, University of Leeds)
* The SCI Lecture: The Science and Technology of Orientated Polymers.

4/12/91 †Prof. R. Grigg (Leeds University)
* Palladium-Catalysed Cyclisation and Ion-Capture Processes.

5/12/91 Prof. A. L. Smith (ex-Unilever)
* Soap, Detergents and Black Puddings.

11/12/91 †Dr. W. D. Cooper (Shell Research)
Colloid Science: Theory and Practice.

22/1/92 †Dr. K. D. M. Harris (St. Andrews University)
Understanding the Properties of Solid Inclusion Compounds.

29/1/92 †Dr. A. Holmes (Cambridge University)
* Cycloaddition Reactions in the Service of the Synthesis of Piperidine and Indolizine Natural Products.

30/1/92 Dr. M. Anderson (Sittingbourne Research Centre, Shell Research)
* Recent Advances in the Safe and Selective Control of Insect Pests.

12/2/92 †Prof. D. E. Fenton (Sheffield University)
* Polynuclear Complexes of Molecular Clefts as Models for Copper Biosites.

13/2/92 Dr. J. Saunders (Glaxo Group Research Limited)
* Molecular Modelling in Drug Discovery.

19/2/92 †Prof. E. J. Thomas (Manchester University)
* Applications of Organostannanes to Organic Synthesis.

20/2/92 †Prof. E. Vogel (University of Cologne)
* *The Musgrave Lecture* Porphyrins: Molecules of Interdisciplinary Interest.

25/2/92 Prof. J. F. Nixon (University of Sussex)
The Tilden Lecture Phosphaalkynes: New Building Blocks in Inorganic and Organometallic Chemistry.

26/2/92	†Prof. M. L. Hitchman (Strathclyde University)
	Chemical Vapour Deposition.
5/3/92	Dr. N. C. Billingham (University of Sussex)
*	Degradable Plastics-Myth or Magic.
11/3/92	†Dr. S. E. Thomas (Imperial College)
*	Recent Advances in Organoiron Chemistry.
12/3/92	Dr. R. A. Hann (ICI Imagedata)
*	Electronic Photography-An Image of the Future.
18/3/92	†Dr. H. Maskill (Newcastle University)
*	Concerted or Stepwise Fragmentation in a Deamination-Type Reaction.
7/4/92	Prof. D. M. Knight (Philosophy Department, University of Durham)
	Interpreting Experiments: the Beginning of Electrochemistry.
13/5/92	Dr. J-C. Gehret (Ciba Geigy, Basel)
*	Some Aspects of Industrial Agrochemical Research.

2 RESEARCH CONFERENCES ATTENDED

April 1989.
North East Graduate Symposium.
Durham University.

December 1989.
Royal Society of Chemistry Perkin Division,
One Day Meeting.
Durham University.

April 1991
Royal Society of Chemistry Perkin Division,
One Day Meeting.
Leeds University.

April 1991.
Royal Society of Chemistry.
100th Annual Congress.
Imperial College, London.

May 1991.
Royal Society of Chemistry Heterocyclic Group,
10th Lakeland Heterocyclic Symposium.
Grasmere.

May 1992.
North East Graduate Symposium.
Durham University.

3 PUBLICATION

M. R. Bryce and J. N. Heaton, *Tetrahedron Lett.*, 1991, 32, 7459.