THE CHEMISTRY OF CYCLIC SULPHIMIDES

A thesis presented by

RAYMOND S. GAIRNS

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Hofmann Laboratory,

Chemistry Department,

Imperial College,

South Kensington,

LONDON, SW7 2AY.

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For my parents

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ABBREVIATIONS

The following abbreviations have been used throughout the text.

i.r.	:	infrared
u.v.	:	ultra-violet
n.m.r.	:	nuclear magnetic resonance
n.O.e.	:	nuclear Overhauser effect
m.s.	:	mass spectrum
t.l.c.	:	thin layer chromatography
DMF	:	dimethylformamide
THF	:	tetrahydrofuran
Tosyl	:	p -toluenesulphonyl

ABSTRACT

The synthesis and chemistry of sulphimides are briefly reviewed. Examples of cyclic sulphimides are examined and the reactions of these systems compared with those of the thiabenzenes.

Several 1H-1,2-thiazines are synthesised by thermal decomposition of aryl azides which have an alkylthio or arylthio substituent 1,4 conjugated to the azide function. The thermal and photochemical rearrangements of these cyclic sulphimides are also investigated. Thermally, the thiazines rearrange by a [1,4] shift of the sulphur substituent. If the sulphur substituent is a methyl group then a ring expansion reaction also occurs to give a 1,3-thiazepine. Photochemically, sulphur-nitrogen bond cleavage occurs generating a nitrene intermediate which after cyclisation and rearrangement gives a pyrrole derivative. Photolysis of appropriately substituted azides also gives pyrrole derivatives.

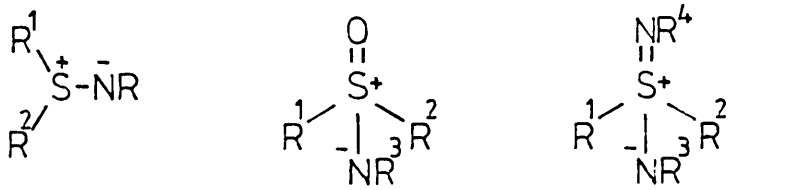
Utilising the photolysis reactions, observations are made on the relative rates of migratory aptitude of substituent groups. For the formyl, acetyl and ethoxycarbonyl groups the observations are in accord with those reported in the literature for other systems. It is found by comparison that sulphur groups are faster migrators and in all cases, except where the competing group was hydrogen, exclusive migration of the sulphur substituent is observed.

CONTENTS

1. INTRODUCTION

In recent years sulphur-nitrogen ylides have been a source of considerable interest.[1,2] The chemistry of sulphoxides and sulphur-carbon ylides is well known. However until recently the chemistry of sulphur-nitrogen ylides has been the subject of relatively little investigation.

Scheme 1 shows the classes of sulphur-nitrogen ylides. These are named according to I.U.P.A.C. conventions.[3]



Sulphimide Sulphoximide Sulphodi-imide

Scheme 1

This introduction concentrates on the synthesis and chemistry of sulphimides (sulphilimines and iminosulphuranes are names also in use in the current literature). By definition the groups R^1 and R^2 are organic with the sulphur bonded to carbon. Other closely related systems which are not sulphimides but possess structural features of interest have, however, been included.

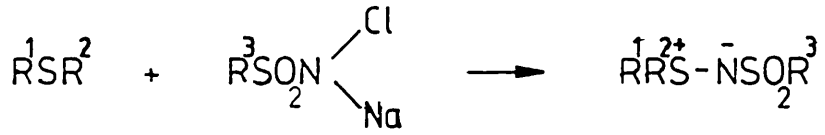
The subject has been comprehensively reviewed up to 1976.[2] Nevertheless, an account of the synthesis and reactions of sulphimides, with particular emphasis on the relatively little, more recent work, is included.

1.1 Synthesis of Sulphimides

1.1.1 Nucleophilic Attack at Nitrogen

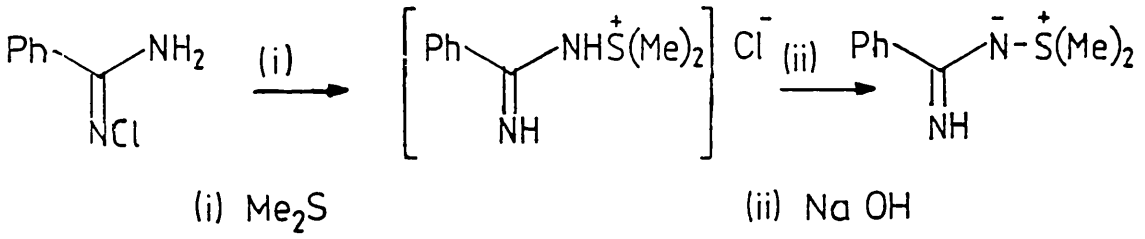
The first method discovered for preparing sulphimides is also the method generally used for preparing N-sulphonylsulphimides.

Raper[4] reported in 1917 that a crystalline product was obtained from the reaction of mustard gas and chloramine-T. Nicolet and Willard[5] proposed the sulphimide structure after similar experiments using chloramine-T and diethyl sulphide. Finally it was Mann and Pope[6] who developed the reaction and synthesised several sulphimides. The Mann and Pope reaction, as it is sometimes called, proceeds as outlined in Scheme 2.



Scheme 2

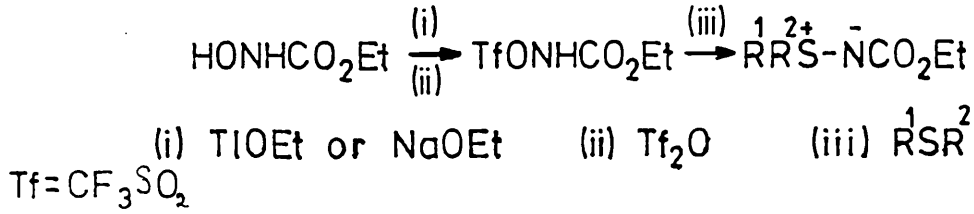
Other N-halo compounds also react with sulphides. When N-halo derivatives of amides, amidines, guanidines, ureas and urethanes were reacted with sulphides in the presence of a base, good yields of sulphimides were obtained.[2] An example of this is the reaction between N-chlorophenylamidine and dimethyl sulphide as shown in Scheme 3.[7]



Scheme 3

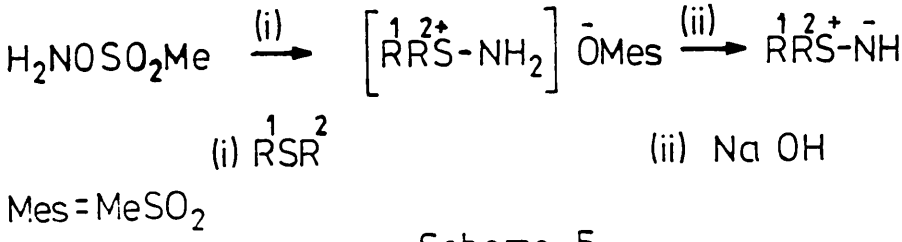
Recently Japanese workers have reported an efficient synthesis of N-acylsulphimides using N-[(trifluoromethanesulphonyl)] oxy carbamate (Scheme 4).[8] The reaction is similar to that of

chloramine-T with sulphides, but here trifluoromethanesulphonic acid is eliminated.



Scheme 4

Similarly, mesitylenesulphonylhydroxylamine is used to produce N-unsubstituted sulphimides (Scheme 5).[9] The reagent reacts with sulphides to give an azasulphonium salt which on treatment with base yields the sulphimide.

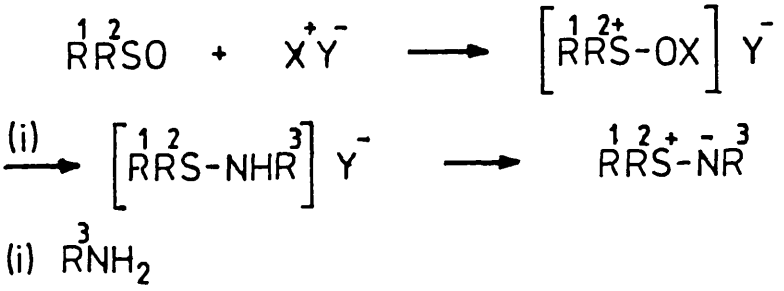


Scheme 5

1.1.2 Nucleophilic Attack at Sulphur

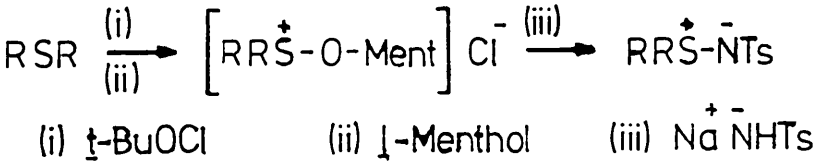
1.1.2.1 Oxosulphonium Salts

Oxosulphonium salts are reactive species and can be generated by the reaction of sulphoxides with electrophilic reagents. Subsequent treatment with an aminating agent produces an azasulphonium salt, which is readily converted into the sulphimide on treatment with base (Scheme 6). Acetic anhydride, trifluoroacetic anhydride, phosphorus pentoxide, phosphorus oxychloride, oxalyl chloride and trifluoromethanesulphonic anhydride are some of the reagents which have been used to prepare sulphimides by this route.[2,10,11,12]



Scheme 6

Oxosulphonium salts have been used in the synthesis of chiral sulphimides *via* asymmetric induction.[13] The sulphide is initially reacted with t-butyl hypochlorite in the presence of l-menthol. Subsequent reaction of the intermediate salt with sodium p-tolylsulphonamide yields the chiral sulphimide in 15-30% optical purity (Scheme 7). The sulphimide can then be made 100% optically pure by one recrystallisation.



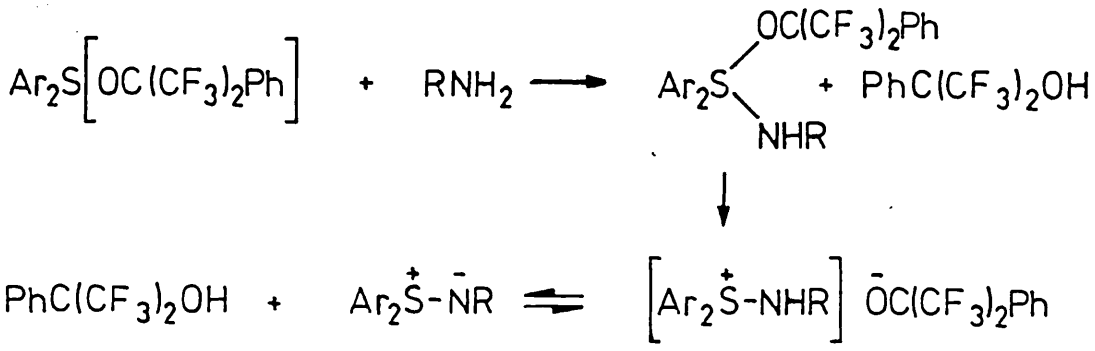
Scheme 7

If an aminating agent is used in place of l-menthol then the corresponding azasulphonium salt is generated directly which provides a good route to sulphimides.[14]

1.1.2.2 Sulphuranes

When diaryl sulphides are treated with bromine and potassium hexafluoro-2-phenyl-2-propoxide an insoluble sulphurane is produced.

Subsequent reaction with ammonia, primary amines, primary amides and sulphonamides gives good yields of sulphimides (Scheme 8).[15]



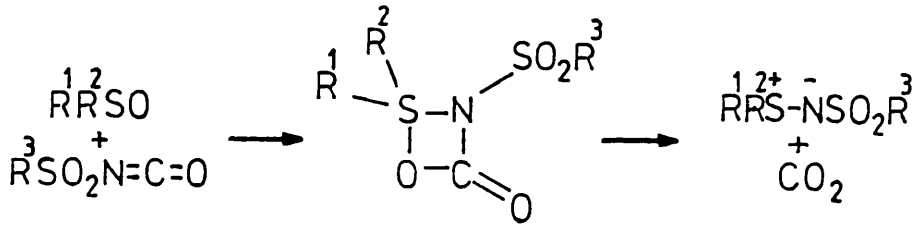
Scheme 8

The preparation of N-unsubstituted sulphimides by the reaction of ammonia with S,S-disubstituted sulphur dihalides is analogous (Scheme 9).[16,17]

Scheme 9

1.1.2.3 Sulphoxides with Isocyanates

The single step treatment of a sulphoxide with an arenesulphonyl isocyanate has been used to afford various sulphimides in high yield (Scheme 10).[18] Sulphur diimides and sulphinylamines react in a similar manner.[2]

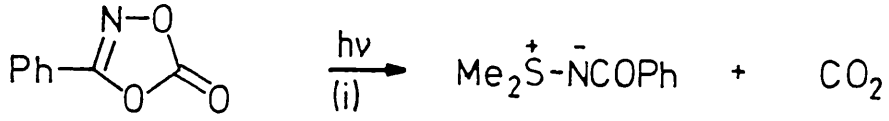


Scheme 10

1.1.3 Sulphimides from Azides and Nitrene Precursors

When organic azides are photolysed in the presence of sulphides, sulphimides may be isolated. This is often the case with sulphonyl and acyl azides.[2] Thermal decomposition of organic azides in the presence of sulphides provides an alternative method of preparing sulphimides. However, as the sulphimides produced often tend to be unstable at the temperatures required for decomposition of the azide, this route is generally less successful. Recent work has shown that copper catalysis may reduce the temperature required for decomposition and so possibly reduce this problem.[19]

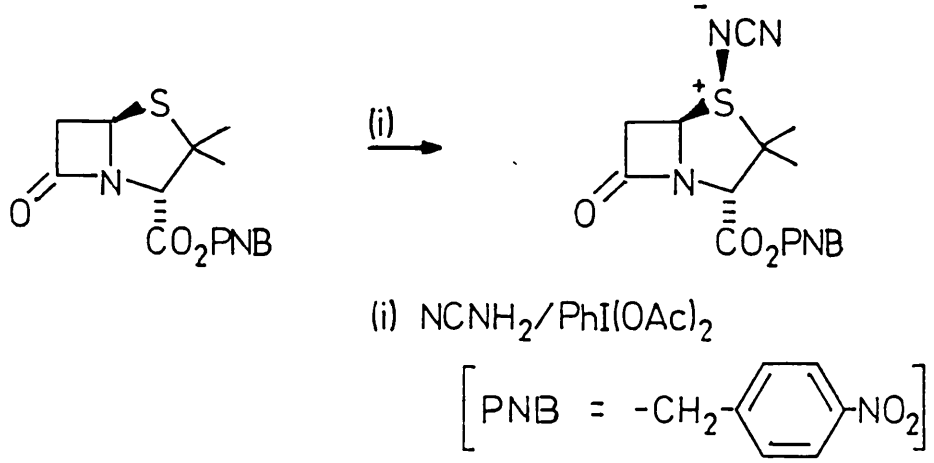
Other reactions between sulphides and nitrene precursors are known. When 5-phenyl-1,3,4-dioxazol-2-one (1) is photolysed in dimethyl sulphide solution, N-benzoyl-S,S-dimethylsulphimide (2) is isolated in 34% yield.[20]



(1) (i) Me_2S (2)

Oxidation of N-aminophthalimide by lead tetraacetate in the presence of dimethyl sulphide or diethyl sulphide leads to formation of the corresponding sulphimides.[21] Similarily, cyanamide/

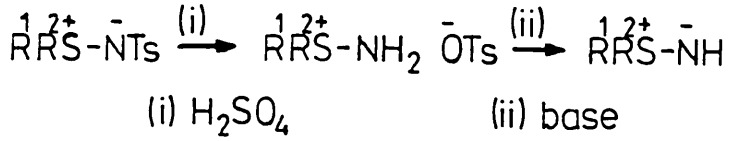
iodobenzene diacetate has been shown to be a convenient reagent which reacts with sulphides to give N-cyanosulphimides (Scheme 11).[22]



Scheme 11

1.1.4 Preparation of N-Substituted Sulphimides from N-Unsubstituted Sulphimides

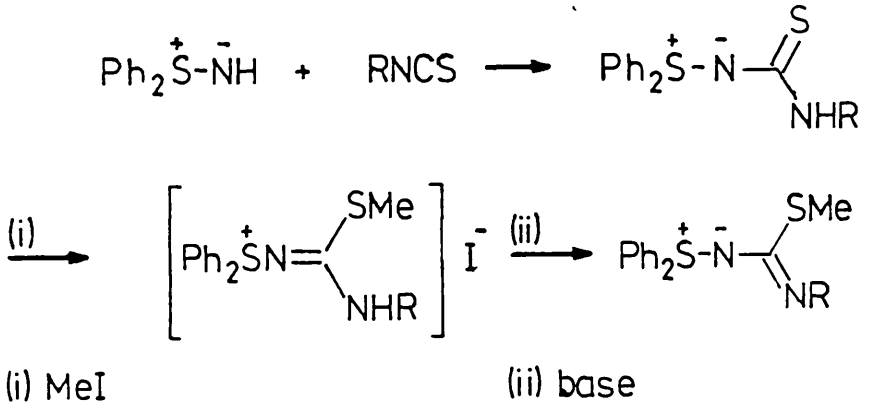
Several methods exist for the synthesis of N-unsubstituted sulphimides. Two of these have already been discussed in sections 1.1.1 and 1.1.2.2. A third important method utilises the readily obtainable N-tosylsulphimides. Cleavage of the tosyl group with concentrated sulphuric acid followed by neutralisation and extraction of the cold solution provides a convenient preparation of N-unsubstituted sulphimides (Scheme 12).[23]



Scheme 12

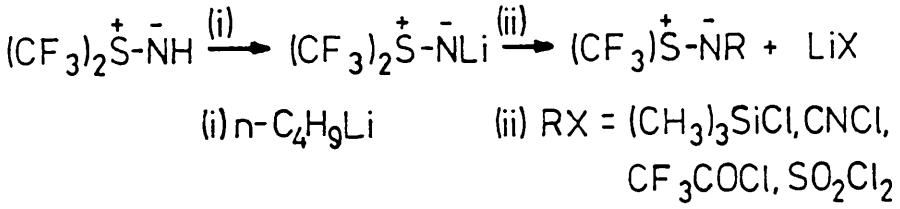
The treatment of N-unsubtituted S,S-diaryl sulphimides with a

variety of electrophilic reagents has been utilised as a method of synthesising a wide range of N-substituted sulphimides.[2] An example of this is the reaction of S,S-diphenylsulphimide with isothiocyanates shown in Scheme 13.[24]



Scheme 13

An investigation of the lithiation of S,S-bis(trifluoromethyl)-sulphimides and subsequent reaction with electrophiles has also been reported (Scheme 14).[17]



Scheme 14

1.2 CHEMISTRY OF SULPHIMIDES

1.2.1 Thermal Reactions of S-Alkylsulphimides

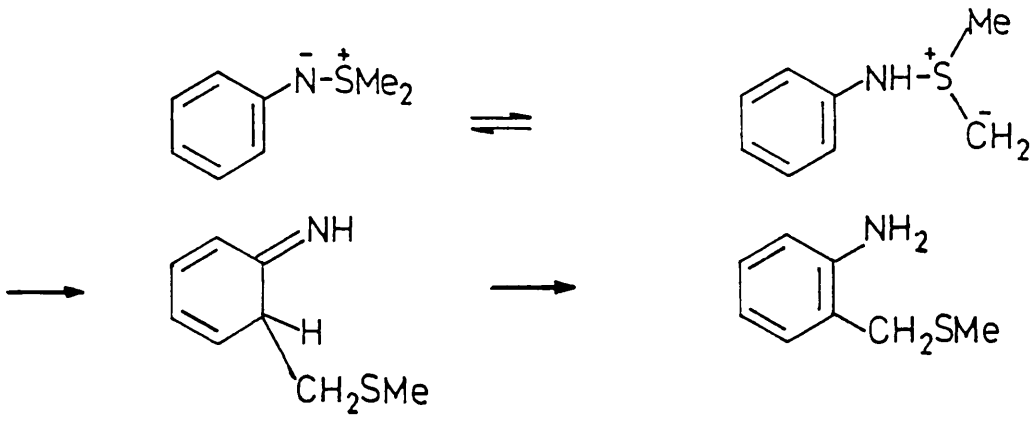
1.2.1.1 α-Hydrogen atoms - [1,2] Shifts and Sommelet-Hauser Reactions

In the case of S-alkylsulphimides possessing a hydrogen atom α to sulphur, a rearrangement can occur involving a [1,2] shift of nitrogen. The reaction is thought to involve isomerisation of the sulphimide to the sulphonium ylide followed by 1,2-migration of the nitrogen group from sulphur to carbon (Scheme 15).

$$R^1CH_2\overset{+}{S}(R^2)\text{-}\overset{-}{N}R^3 \rightleftharpoons R^1\overset{-}{C}H\overset{+}{S}(R^2)NHR^3 \longrightarrow R^1CH(NHR^3)SR^2$$

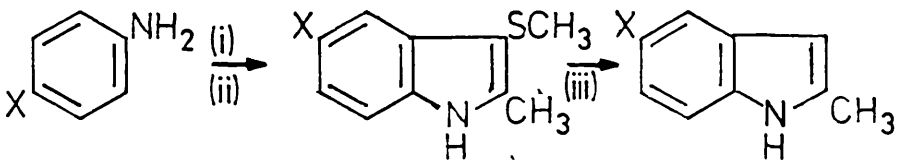
Scheme 15

N-Aryl-S-alkylsulphimides react differently when thermolysed in aprotic solvents in the presence of base or in protic solvents without base. The initial stage of the reaction is thought to be isomerisation to the sulphonium ylide as above. However, instead of rearranging by a [1,2] shift of nitrogen, a Sommelet-Hauser rearrangement, involving a [2,3] shift, occurs as shown in Scheme 16.[25]

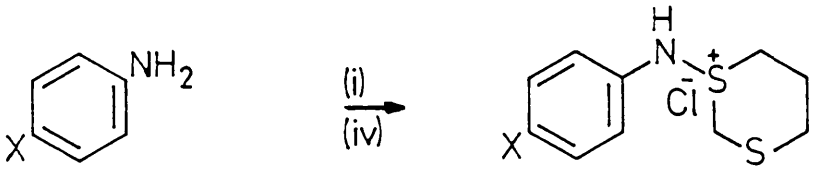


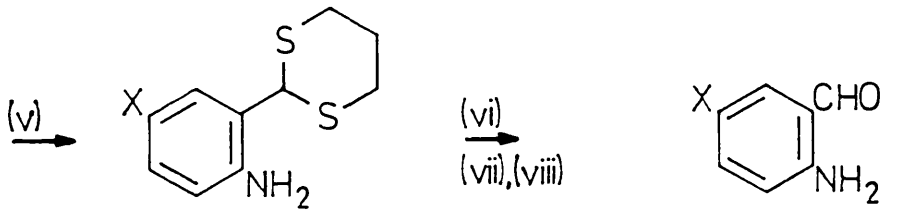
Scheme 16

As sulphimides are readily available from anilines this reaction provides a useful route to ortho-substituted anilines (Scheme 17).[26,27]



X = CH_3, H, Cl, CO_2CH_3



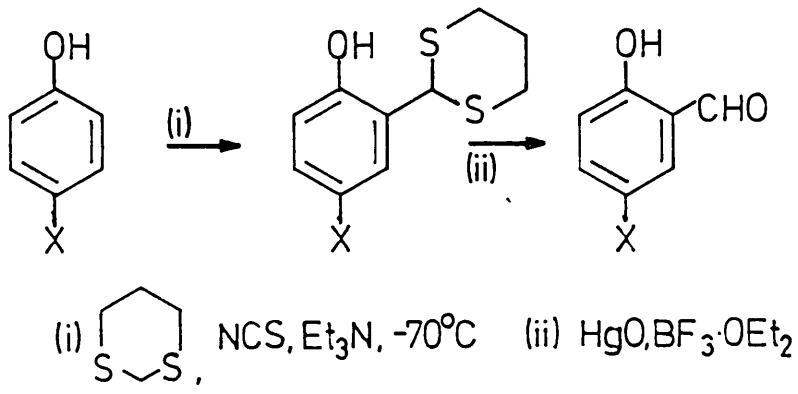


(i) t-BuOCl (ii) $CH_3SCH_2COCH_3$, Et_3N (iii) Ra Ni (iv) 

(v) $NaOCH_3$ (vi) $(CH_3CO)_2O$, pyr (vii) HgO, $BF_3.OEt_2$ (viii) Na_2CO_3

Scheme 17

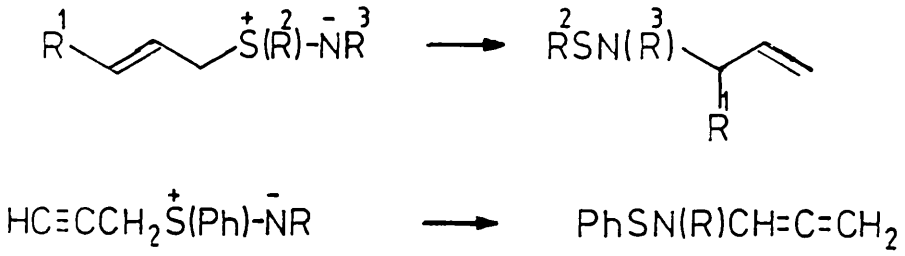
An intermolecular extension of this type of reaction has been demonstrated in the reaction between sulphimides and phenols (Scheme 18).[28]



Scheme 18

1.2.1.2 S-Allylsulphimides - [2,3] Shifts

With S-allysulphimides the course of reaction is different from other S-alkylsulphimides. When heated, a [2,3] sigmatropic shift occurs. Similarily, with S-propargylsulphimides the same process predominates (Scheme 19).[2]

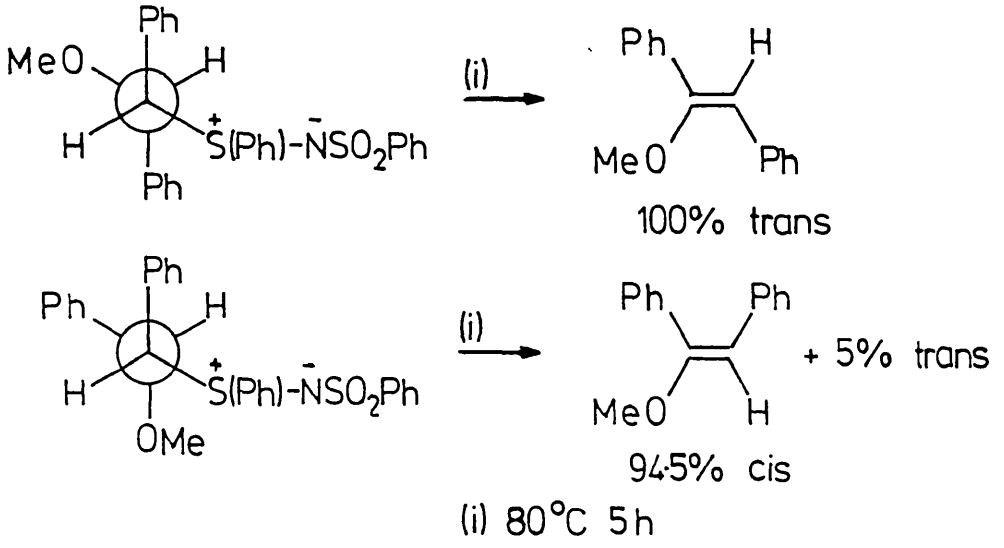


Scheme 19

1.2.1.3 β-Hydrogen atoms - Olefin Formation

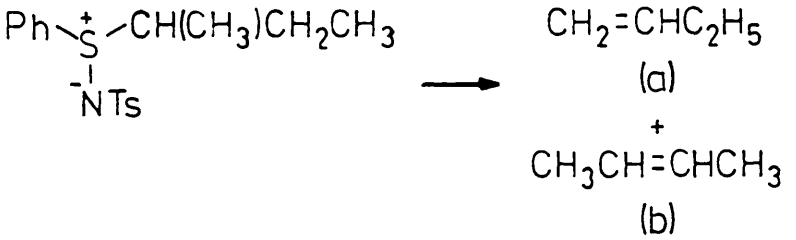
S-Alkylsulphimides possessing β-hydrogen atoms undergo cycloelimination reactions to give high yields of olefins. Often the reaction is carried out using N-tosylsulphimides as these are

simple to prepare and relatively stable. The reaction generally proceeds with high stereoselectivity as shown in the following example (Scheme 20).[29]



Scheme 20

It has been observed that the orientation of elimination shows some solvent dependence as outlined in Scheme 21.[30]

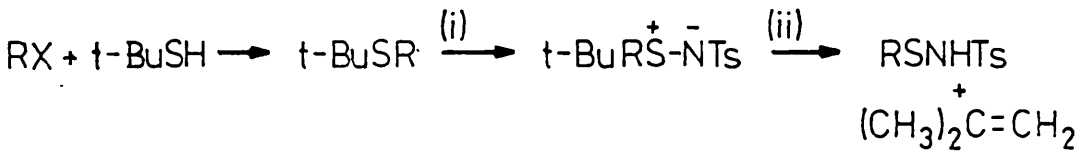


Solvent	Temperature	Ratio (a)/(b)
neat	115-120°C	2/1
neat	160-170°C	1·7/1
Me_2SO	115-120°C	1·5/1
C_6H_6	115-120°C	0·67/1

Scheme 21

Other studies have shown that the rate of elimination can be accelerated by the presence of an electron withdrawing group at either the α or β positions.[1,31]

As the other product from this reaction is a sulphenamide, inclusion of a suitable R group (e.g. t-Bu) to force elimination in one direction can give high yields of specific sulphenamides (Scheme 22).[32]

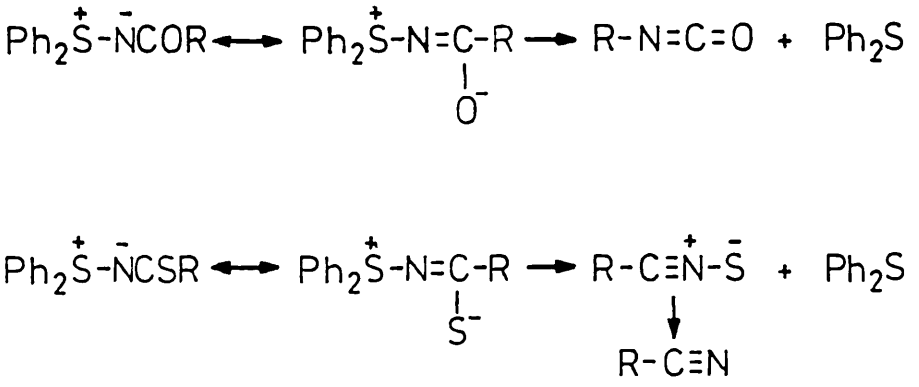


Scheme 22

1.2.1.4 N-Acylsulphimides and Related Compounds - Isocyanate Formation

Thermolysis of N-acylsulphimides gives isocyanates.[33] The reaction is thought to proceed via a Curtius-type rearrangement. N-Acyl-S,S-diphenylsulphimides are often used in this type of reaction as they are simply generated from the N-unsubstituted sulphimide by treatment with acylating agents.

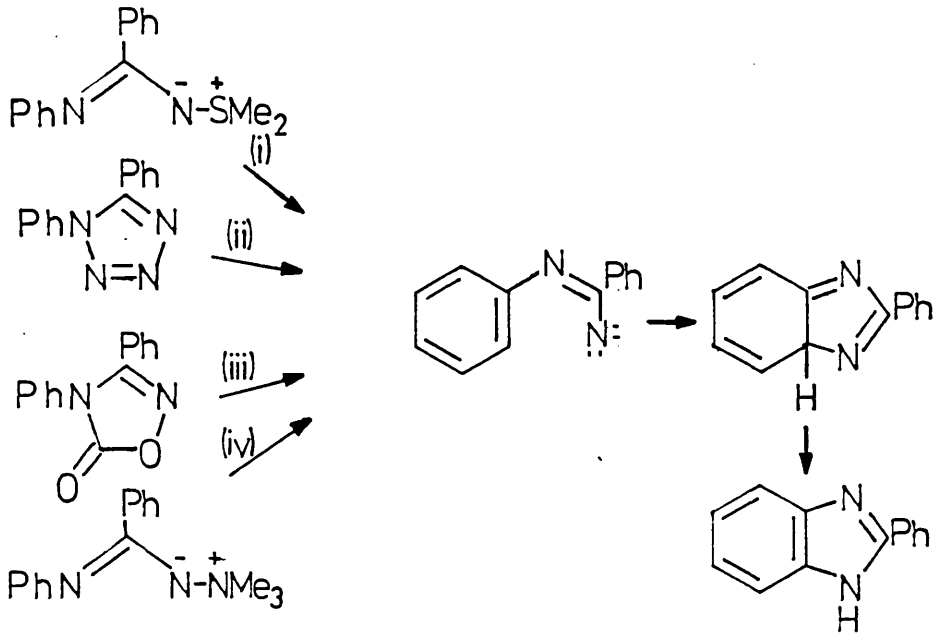
In contrast, thermolysis of N-thioacylsulphimides does not give the corresponding isothiocyanate. Nitriles and elemental sulphur are produced in the reaction which is thought to proceed by a similar pathway (Scheme 23).[34,35]



Scheme 23

1.2.2. Photochemistry

In general the photochemical reactions of sulphimides involve cleavage of the nitrogen-sulphur bond. Consequently, products obtained from these reactions are often similar to those obtained from the corresponding azides or similar nitrene sources (Scheme 24).[36]



(i) hν, $-SMe_2$ (ii) hν, $-N_2$

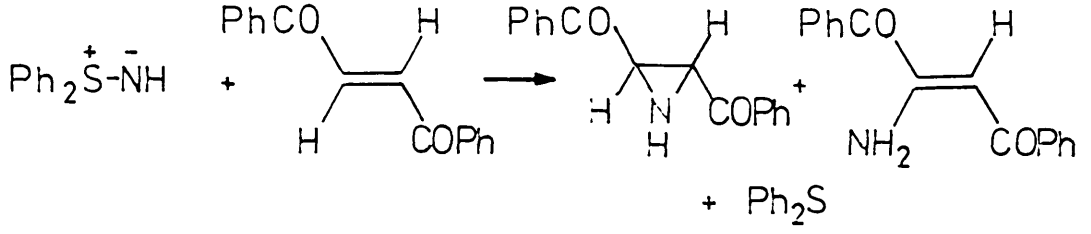
(iii) Δ, $-CO_2$ (iv) Δ, $-NMe_3$

Scheme 24

1.2.3 Reactions as Nucleophiles

1.2.3.1 With Alkenes

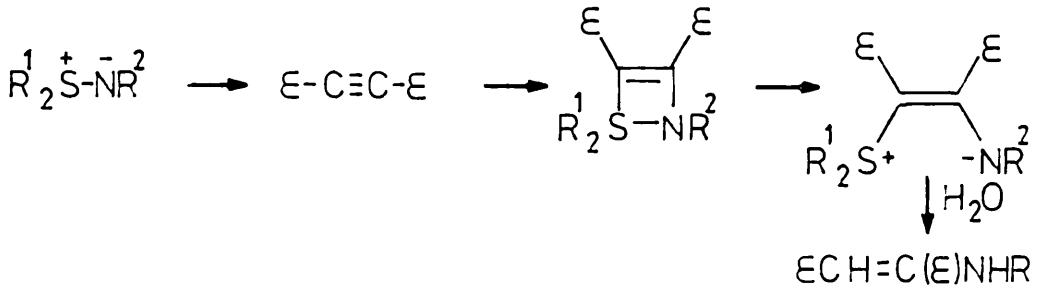
N-Unsubstituted sulphimides are good nucleophiles and as such undergo Michael addition to enones. With certain olefins reasonable yields of aziridines are isolated, along with enaminoketones (Scheme 25).[37]



Scheme 25

1.2.3.2 With Acetylenes

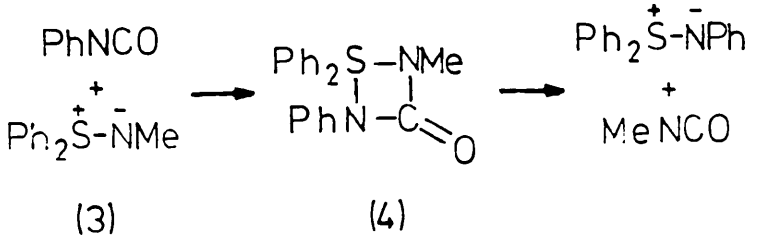
Dimethyl acetylenedicarboxylate and other electrophilic acetylenes have been shown to react with sulphimides.[2] The main products are those derived from nucleophilic addition of the sulphimide to the acetylene and this is thought to proceed via a four centred intermediate (Scheme 26).



Scheme 26

1.2.3.3 With Phenylisocyanate

As in the reaction of sulphimides with dimethyl acetylene-dicarboxylate, the reaction between S,S-diphenyl-N-methylsulphimide (3) and phenyl isocyanate has been proposed to proceed by a four centre intermediate (4) which accounts for the production of methyl isocyanate.[15]



(3) (4)

1.2.3.4 With Aldehydes

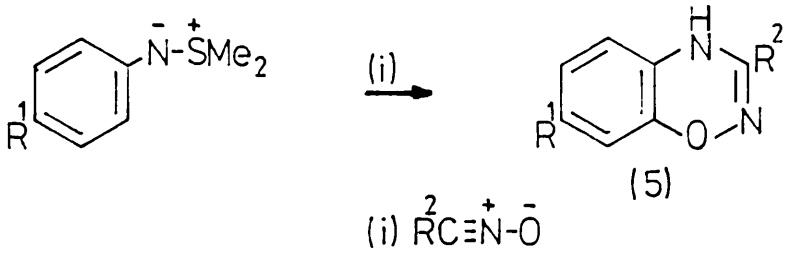
The reaction of an N-unsubstituted sulphimide with an aldehyde in refluxing benzene produces a nitrile in good yield. Aldehydes of various types can easily be converted to nitriles by this method (Scheme 27).[38]

Scheme 27

1.2.3.5 With Nitrile-N-oxides

The reaction of N-arylsulphimides with nitrile-N-oxides is dependent on the nature of the aryl substituent.

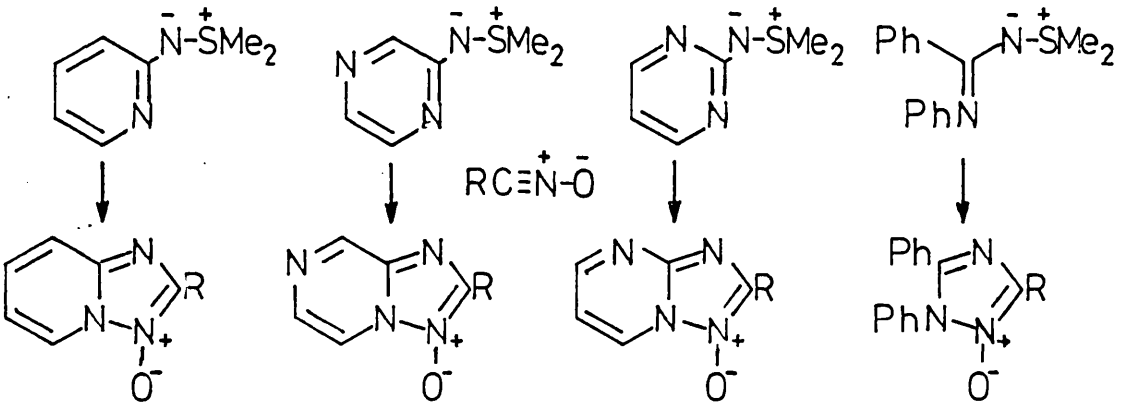
For simple N-aryl compounds in which there are no ortho-substituents the product is mainly the 1,2,4-benzoxadiazine (5).[39,40]



(5)

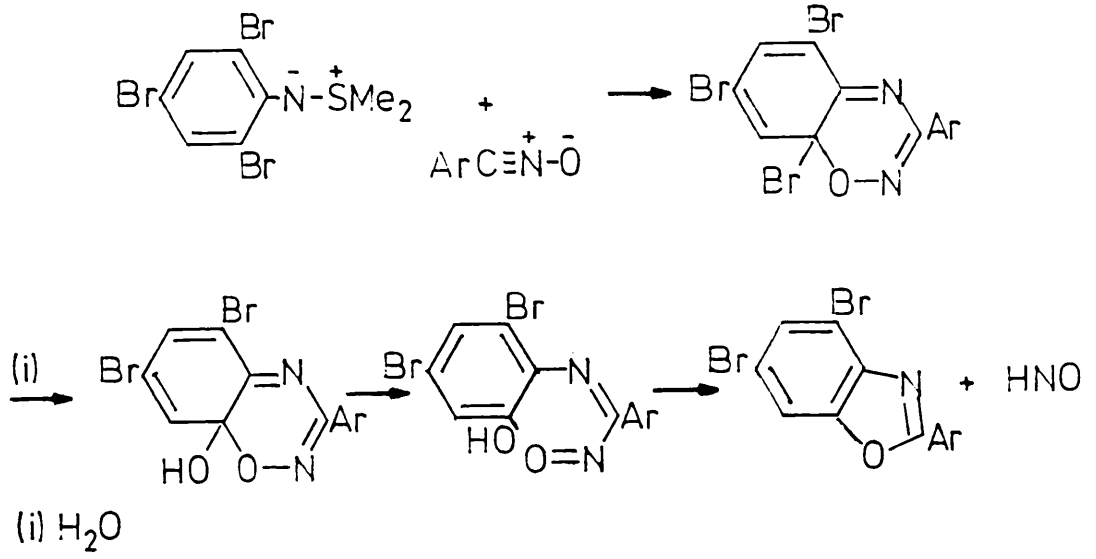
(i) $R^2C{\equiv}\overset{+}{N}\text{-}\overset{-}{O}$

However with the nitrogen containing heteroaryl-substituted sulphimides shown in Scheme 28, the predominant products are the triazole-N-oxides.[41]



Scheme 28

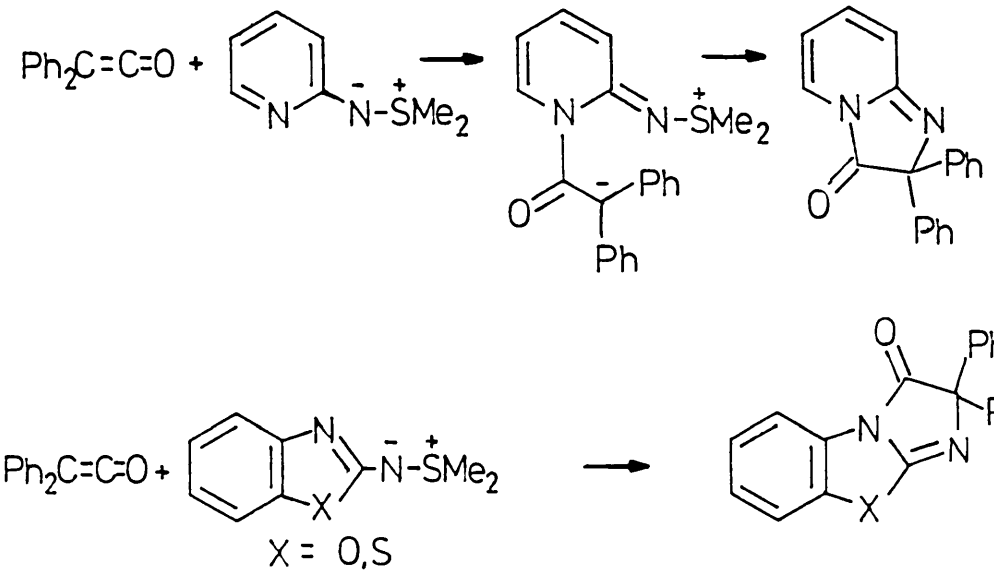
When the ortho-positions of the N-aryl substituent are blocked by halogen atoms, the reaction pathway is blocked. The product isolated from this reaction is a benzoxazole derivative. As yet the mechanism of this reaction is unknown. However, it has been suggested that the initial step is a cyclisation step similar to the one observed in benzoxadiazine formation. Then, after hydrolysis and ring opening, cyclisation with loss of a nitroso group occurs (Scheme 29).[42,43]



Scheme 29

1.2.3.6 With Diphenylketene

In contrast with the reaction of nitrile-N-oxides, the product from the reaction of N-(2-pyridyl)-S,S-dimethylsulphimide with diphenylketene is one derived from attack by the pyridyl nitrogen (Scheme 30).[44]

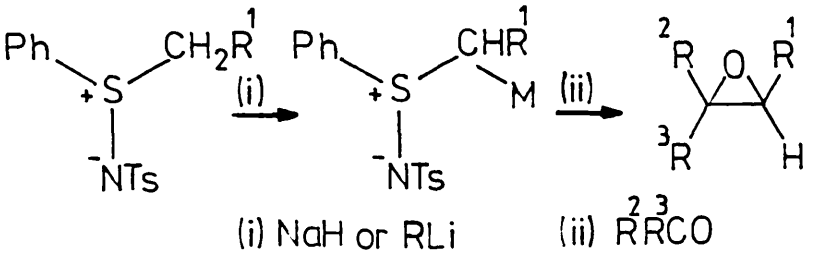


Scheme 30

1.2.4. Reaction of Sulphimides with Organometallics

1.2.4.1 Metalation of S-Alkyl Sulphimides

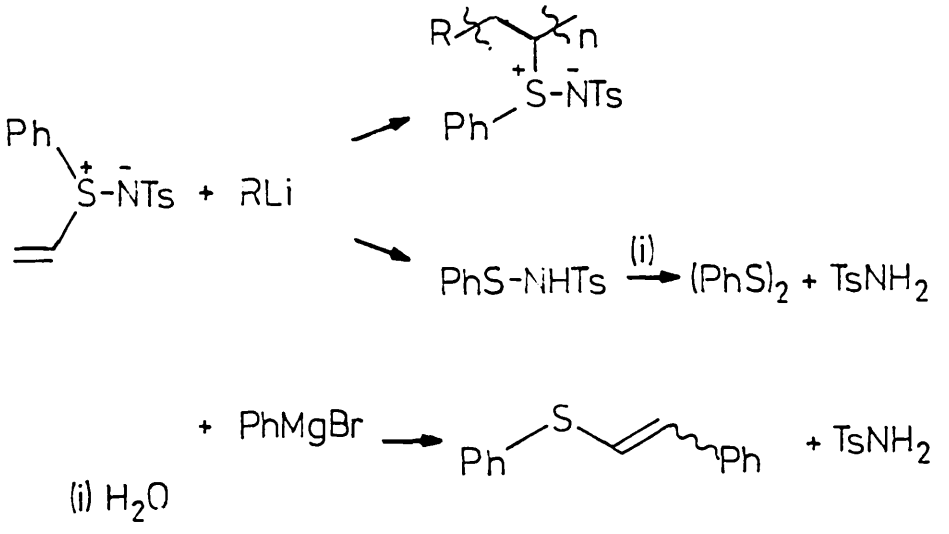
When N-p-tosyl-S-alkyl-S-phenylsulphimides are treated with an alkyllithium or sodium hydride the reactive α-carbanion is generated. This anion can be quenched with various electrophiles: in particular, reaction with carbonyl compounds leads to high yields of epoxides (Scheme 31).[45,46]



Scheme 31

1.2.4.2 Reaction with S-Vinyl Sulphimides

When S-vinyl sulphimides are treated with an alkyllithium, the products are mainly those of a polymeric nature. However, when a Grignard reagent is used, substituted vinyl sulphides are obtained in high yield (Scheme 32).[47]



Scheme 32

1.2.5 Oxidation and Reduction of Sulphimides

1.2.5.1 Oxidation

The oxidation of sulphimides gives the corresponding sulphoximides. Reagents most commonly used are m-chloroperbenzoic acid or potassium permanganate.[2] The use of a two phase system with sodium hypochlorite as oxidant has also been reported.[48]

1.2.5.2 Reduction

Several methods exist for the reduction of sulphimides to the corresponding sulphides.[2] A few of the more recently reported methods are presented in Table 1.

Table 1 Reduction of Sulphimides to Sulphides

Reagent	% Yield	Ref.
$TiCl_4/Zn/ether/CH_2Cl_2$	65-100	49
$(F_3CCO)_2O/NaI/(CH_3)_2CO$	80-98	49
P_4S_{10}/CH_2Cl_2	77-98	50
p-$TolSO_2NO$	54-90	51
t-$BuSNO_2$	80	51
RSH/Me_3SiCl	72-91	52

1.3 Cyclic Sulphimides and Related Compounds

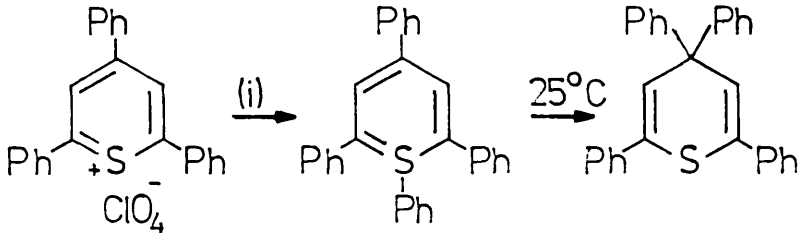
Sulphimides in which the sulphur and nitrogen atoms form part of a ring system are of interest as the properties associated with molecules of this type often show substantial differences from those of their acyclic counterparts. Those sulphimides in which the sulphur and nitrogen atoms form part of a fully unsaturated ring system are of particular interest; if the sulphur-nitrogen linkage is regarded as having some double bond character then, in a planar arrangement of the

ring atoms, overlap of the π-orbital system can occur leading to the possibility of aromatic or antiaromatic properties.

In this chapter cyclic systems possessing some of these features are discussed. As an introduction, the synthesis and chemistry of thiabenzenes is outlined.

1.3.1 Thiabenzenes

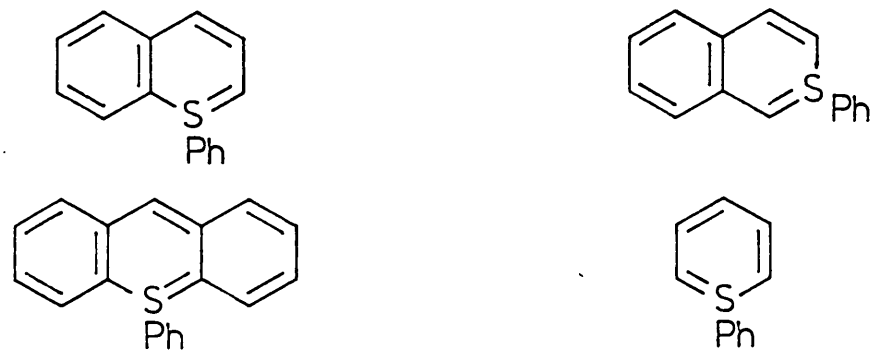
In 1961, Price et al reported the first synthesis of a thiabenzene derivative.[53] When the thiopyrylium perchlorate (6) was treated with phenyllithium a deep red solution of thiabenzene (7) was obtained. On standing for several hours the solution decolourised and the rearrangement product (8) was obtained.



(6) (7) (8)

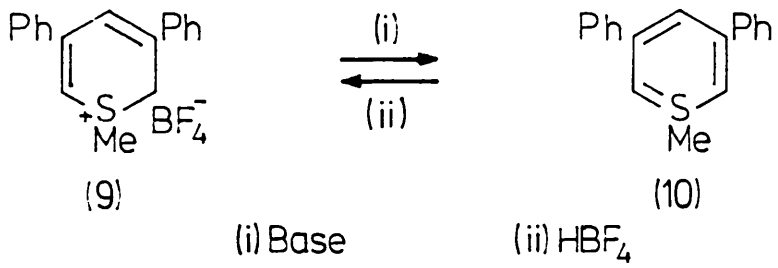
(i) PhLi

Soon after this, Price and coworkers reported the synthesis of several thiabenzene derivatives. Unlike compound (7), these new derivatives, shown in Scheme 33, were reported as being stable, isolable compounds.[54,55]



Scheme 33

It was Hortmann and Harris who first expressed doubts concerning these reportedly stable thiabenzenes.[56,57] Their results showed that when the sulphonium tetrafluoroborate (9) was treated with base at low temperature an orange solution was obtained. The product was only stable at low temperatures and could be readily reconverted into (9) using tetrafluoroboric acid. N.m.r. data obtained for this intermediate were not in agreement with previous reports but did, however, suggest that the product was the thiabenzene (10) and, furthermore, indicated that the bonding in this system was ylidic in nature, where charge localisation occurs on the sulphur and the 2-, 4- and 6- carbon atoms.



(9) (10)

(i) Base (ii) HBF_4

These inconsistencies prompted Mislow et al to reinvestigate the synthesis and properties of thiabenzenes.[58] They confirmed that

thiabenzenes could be generated by the published methods. However, in contrast to the results described by Price et al,[54,55] these molecules were not stable. Often the techniques used to purify the thiabenzenes had resulted in their decomposition and the reported products were not thiabenzenes but were actually oligomers. Furthermore, Mislow agreed with the findings of Hortmann and Harris and supported their theory of ylidic type bonding.

After the publication of this work, it was shown that, by incorporation of electron withdrawing substituents in either the 2- or 4- position of the thiabenzene ring, it was possible to isolate the stable thiabenzenes shown in Scheme 34.[59]

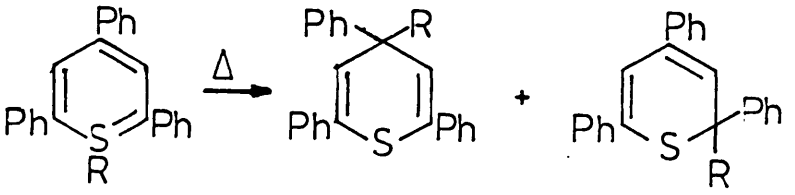
(11a-c)

(a) R = CN (b) R = COPh (c) R = C_6F_5

Scheme 34

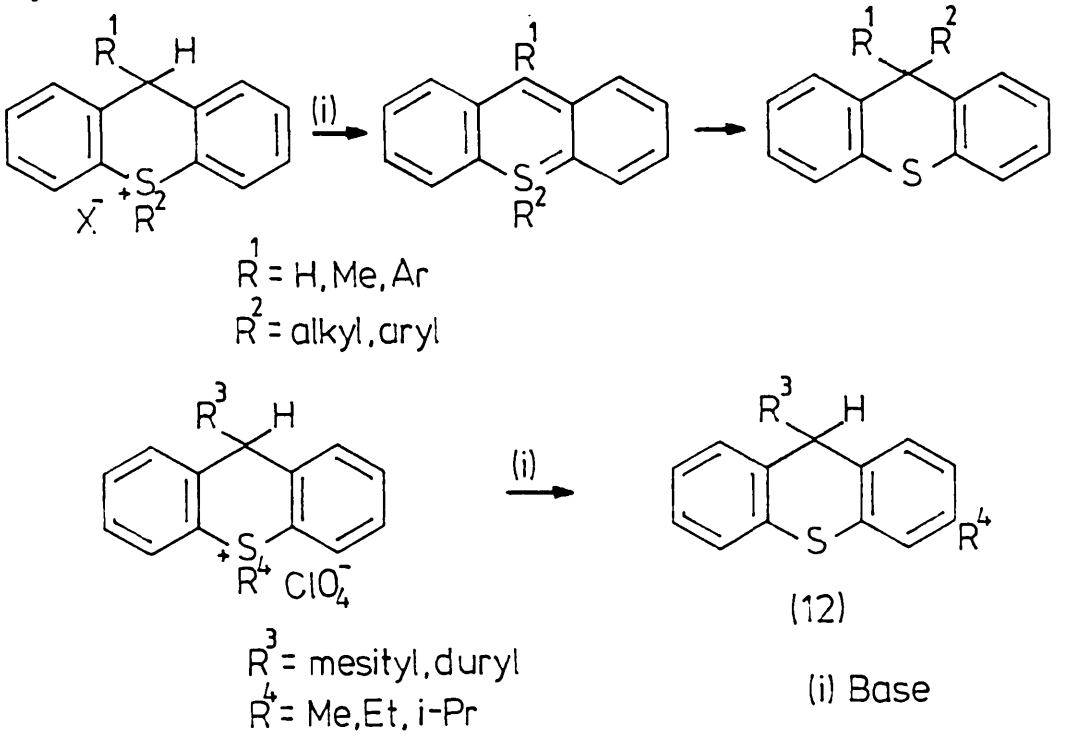
This stabilisation of the ring system by electron withdrawing substituents, along with X-ray data for (11b), confirm the ylidic bonding in these thiabenzenes. The chemical properties of these systems also reflects their ylidic nature.

It is well documented that upon thermolysis, thiabenzenes undergo rearrangement to give products derived from either [1,2] or [1,4] migration of the R group (Scheme 35). Crossover experiments have shown these rearrangements to be intramolecular.[60,61]



Scheme 35

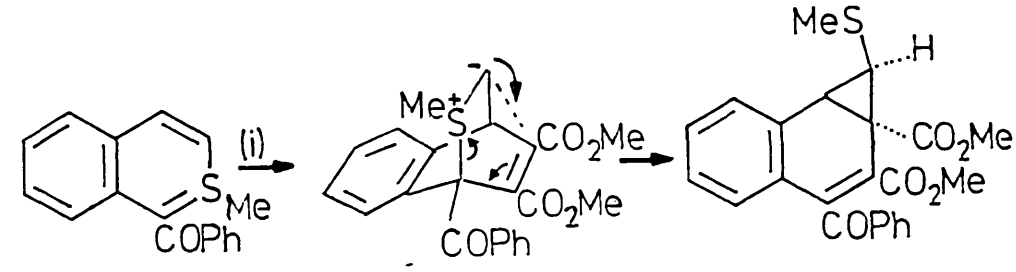
Recently, the thermal rearrangement of thiaanthracenes was reported by Hori et al.[62,63] These also exhibit thermal [1,4] rearrangements. However, S-alkylthiaanthracenes with a bulky substituent at the 9- position rearrange to give 3-alkyl-9-arythioxanthenes (12) instead (Scheme 36).

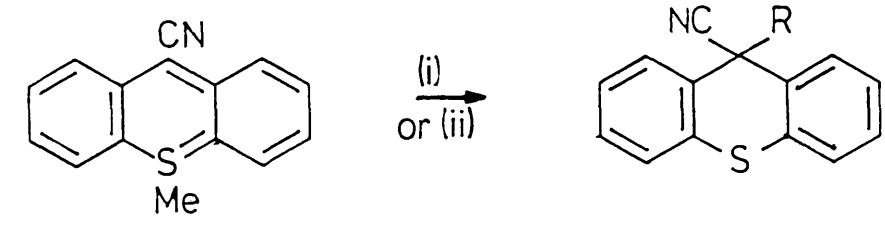


Scheme 36

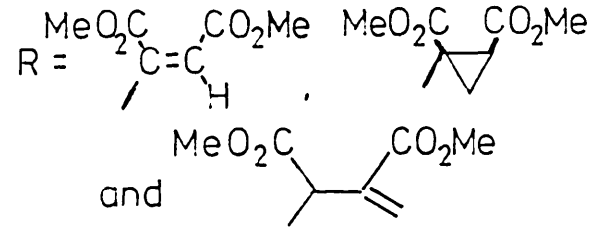
The reactions of thiabenzenes with electrophilic reagents such as dimethyl acetylenedicarboxylate and tetracyanoethylene have also

been reported.[64] As shown in Scheme 37, these reactions demonstrate the ylidic nature of these systems.





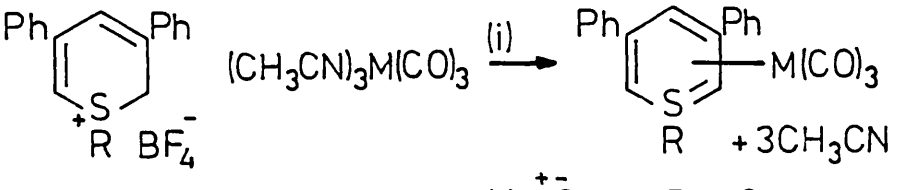
(i) $MeO_2CC{\equiv}CCO_2Me$

R = 

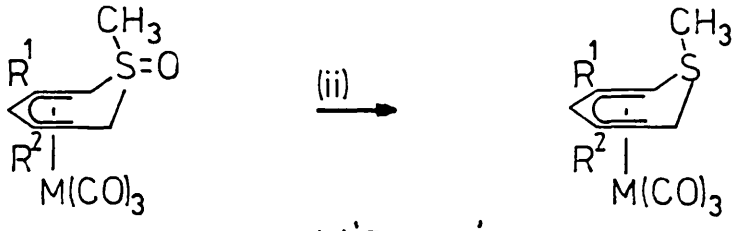
(ii) $(NC)_2C{=}C(CN)_2$ R = $-CH(CN)_2$

Scheme 37

More recently, a series of papers by Weber and coworkers have detailed how some of the earlier unstable thiabenzenes may be isolated as their stable chromium-, molybdenum- and tungsten- tricarbonyl complexes.[65,66,67] The methods of preparation of these complexes and some of their properties are shown in Scheme 38.



M = Cr, Mo, W R = Me, Et (i) $K^{+}\,^{-}Ot\text{-}Bu$, DMSO



(ii) 'Red-al', C_6H_6

M = Cr R^1 = Ph | Ph | Ph | t-Bu; R^2 = Ph | Me | t-Bu | t-Bu

M = Mo, W $R^1 = R^2$ = t-Bu

(iii) t-BuLi (iv) R^3X

M = Cr, Mo, W R^3X = MeI

M = Cr RX = C_3H_5Br, $PhCH_2Br$, Me_3SiCl, Me_3GeCl

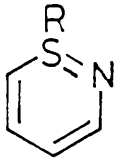
Scheme 38

Finally, thiabenzenes have been shown to be unstable molecules, ylidic in structure, which are stabilised by electron withdrawing groups. They may, therefore, be considered as cyclic sulphonium ylides. Since sulphimides are in general more stable than the corresponding sulphonium ylides, cyclic sulphimides with the same structural features would be expected to be isolable molecules.

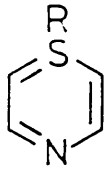
1.3.2 Thiazines (azathiabenzenes)

Six membered rings containing sulphur-nitrogen ylides where conjugation exists between sulphur and nitrogen have attracted special interest. Chemical and physical studies have been undertaken to investigate whether these systems possess aromatic properties similar to the benzenoid molecules of which they are azathia-analogues.

Within the C_4NS ring class there are two systems of main interest. These are the 1H-1,2-thiazines (13) and the 1H-1,4-thiazines (14). Although the latter are not sulphimides they possess important structural features and will be considered here.

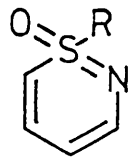


(13)



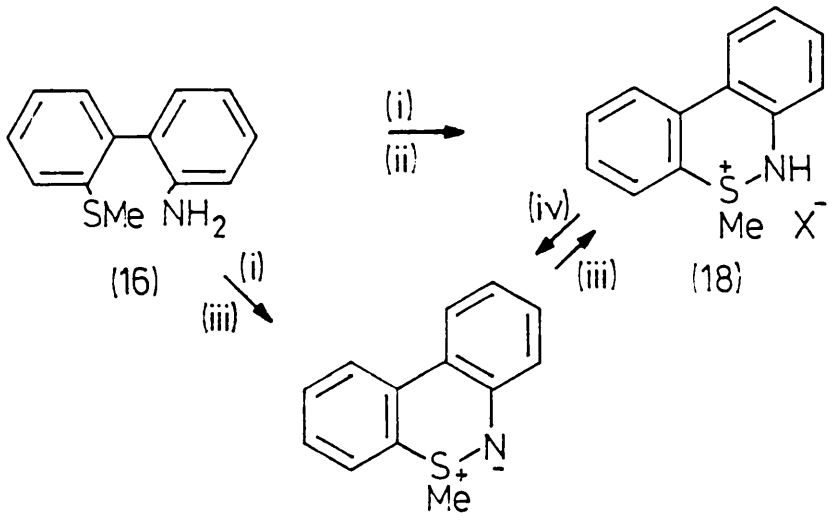
(14)

Unlike the corresponding sulphoximides (15), the unoxidised 1H-1,2-thiazine system is rare with only ring fused derivatives being known.



(15)

The first synthesis of these novel heterocycles was reported by Hori et al in 1979.[68] The stable 9-methyl-10-aza-9-thiaphenanthrene (17) was obtained from 2-amino-2'-methylthiobiphenyl (16) by reaction with N-chlorosuccinimide followed by treatment with base. Azasulphonium salts (18) were also isolated, and these were readily converted into the sulphimide (17) on treatment with base.

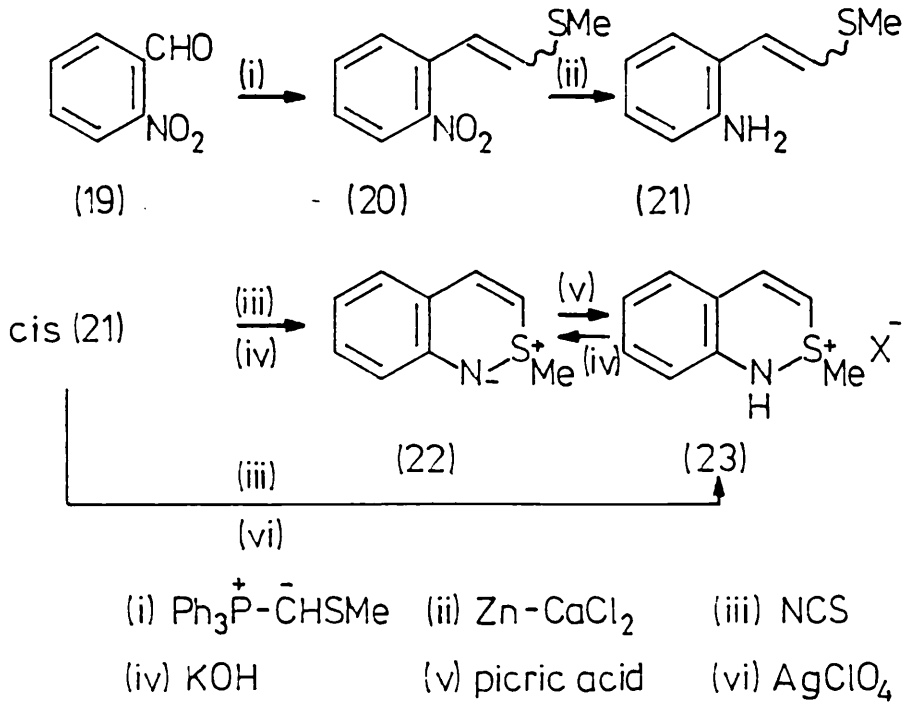


(i) NCS (ii) $AgClO_4$ (iii) KOH (iv) picric acid

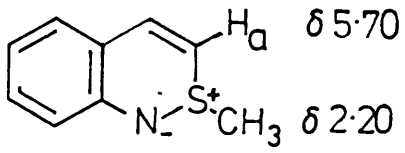
Using the same procedure, cis-o-aminostyryl methyl sulphide (21) was converted into the 2-methyl-1-aza-2-thianaphthalene (22). The trans-olefin could not be converted into the sulphimide (22).

o- Aminostyryl methyl sulphide was synthesised from o-nitrobenzal-

dehyde (19) in two steps. Reaction with triphenylphosphonium methylthiomethylide yielded the o-nitrostyryl methyl sulphide (20) which was reduced to the corresponding amine (21) with zinc/calcium chloride. Column chromatography afforded both cis and trans isomers.

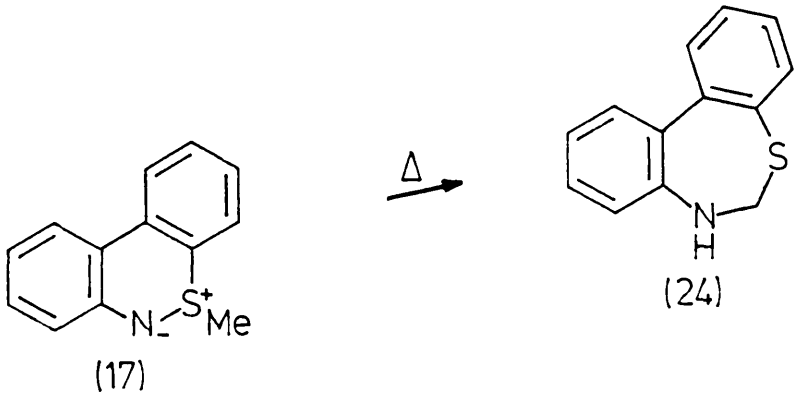


In comparison with the azathiaphenanthrene (17), the azathianaphthalene (22) is only moderately stable and decomposes slowly on standing at room temperature. The sulphur-nitrogen bonding in these molecules is considered to be ylidic. Evidence for this can be seen in the proton n.m.r. spectrum of the azathianaphthalene (22) which shows a doublet in the olefinic regions for H^a (see overleaf).

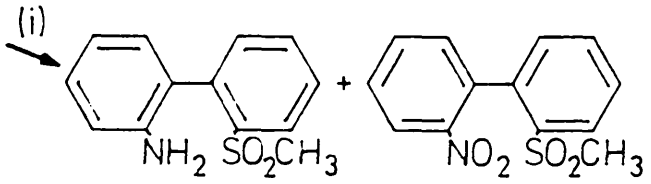


(22)

At 140°C, 9-methylazathiaphenanthrene (17) underwent ring expansion to give the 1,3-thiazepine (24).



(17) (24)



(i) mcpba

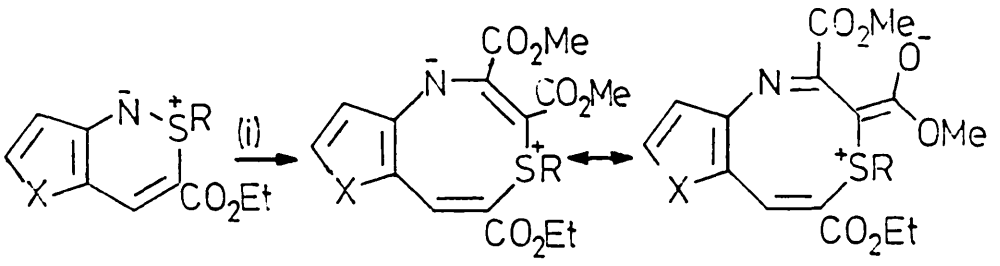
Scheme 39

Attempts to prepare the corresponding sulphoximide from sulphimide (17) failed, the only products isolated arising from cleavage of the sulphur-nitrogen bond (Scheme 39).

An alternative route to 1H-1,2-thiazines has been developed in these Laboratories.[69,70] This will be discussed in a later section.

Studies of some of the properties of these new heterocycles have also been undertaken by this group.

The X-ray structure of an azathiabenzene derivative was obtained and from this it was apparent that the 1H 1,2-thiazine ring is not planar.[69] This confirms that these compounds are ylidic in nature. Furthermore, the reactions of these thiazines with dimethyl acetylene-dicarboxylate were reported and it was concluded that these heterocycles react as sulphimides.[71] In aprotic solvents the thiazines (25 - 27) reacted to give the 1 λ^4,4-thiazocines (28).



(25-27) (28)

(25) X = CH_2=CH_2 R = Ph

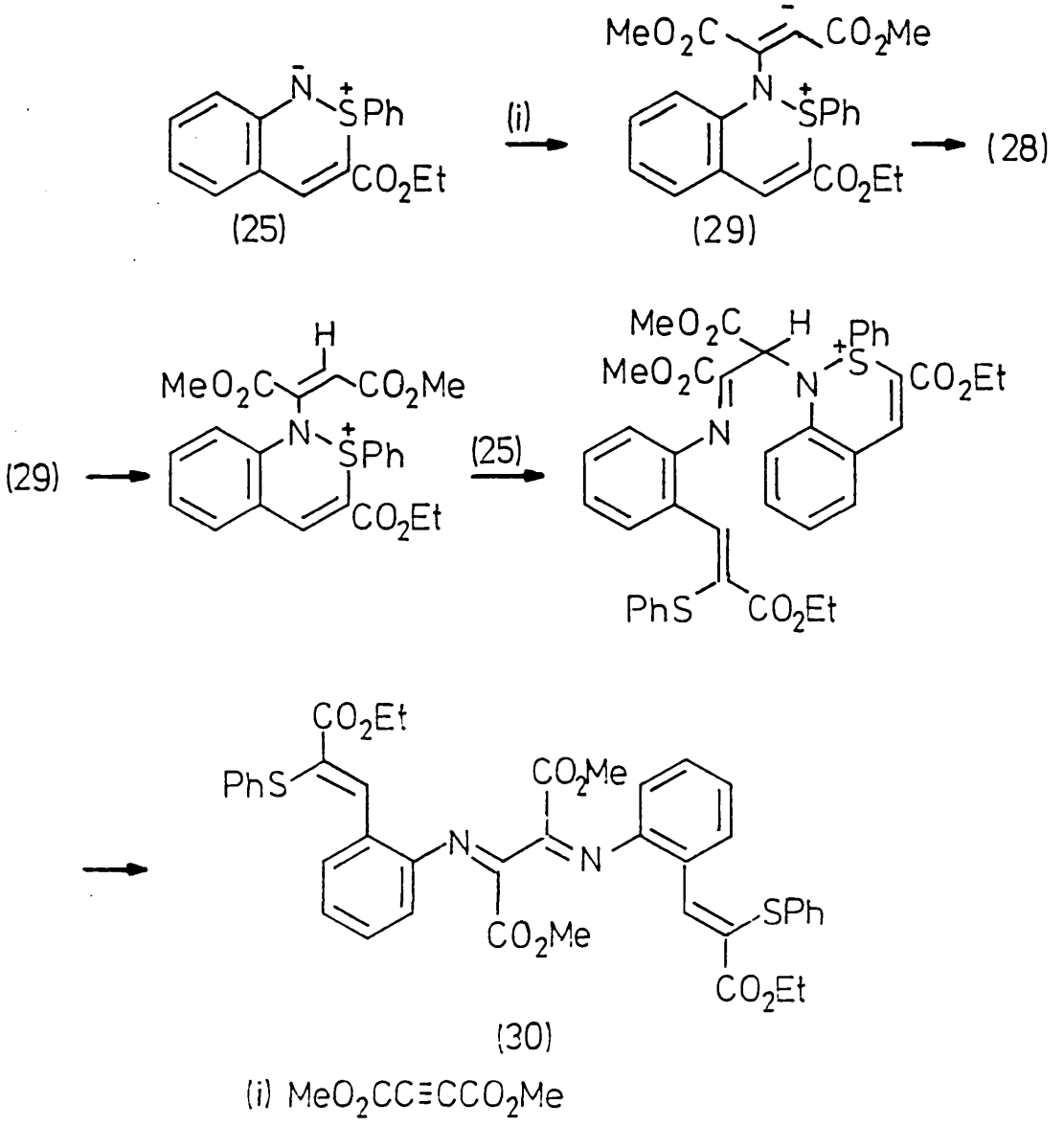
(26a) X = S R = Ph

(27a) X = O R = Ph

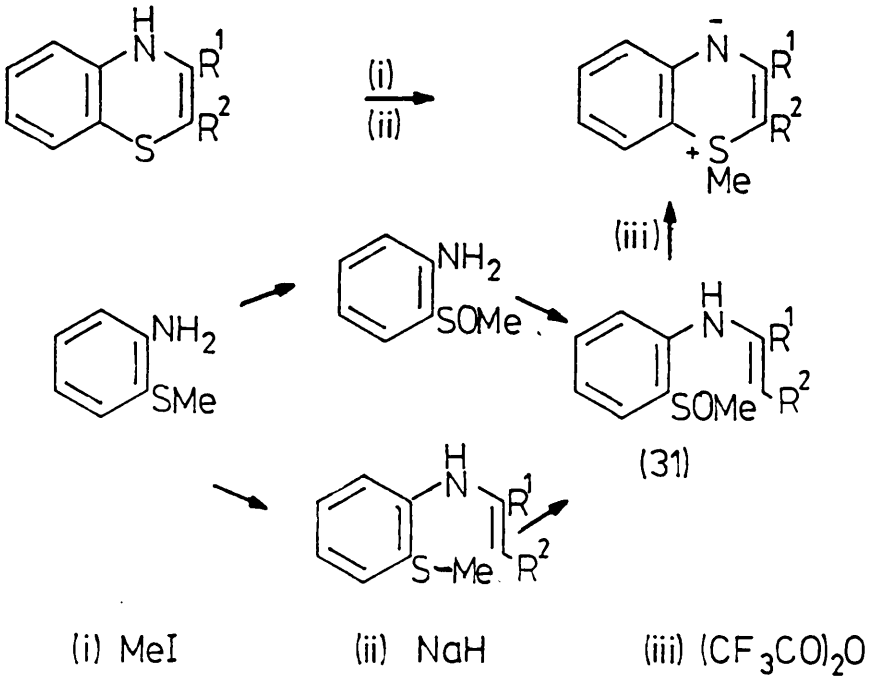
(27b) X = O R = Me

(i) $MeO_2CC{\equiv}CCO_2Me$

Under protic conditions a 2:1 adduct (30) was obtained. This is thought to be derived from protonation of the initial intermediate (29) followed by attack of a second molecule of (25).

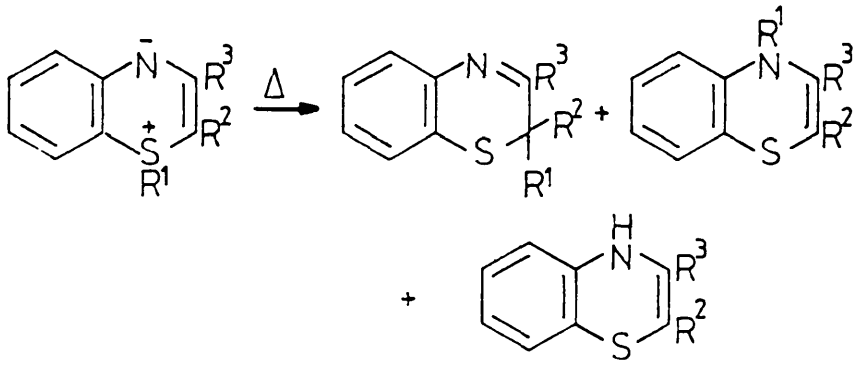


In the study of azathia-analogues of benzene, 1H-1,4-thiazines are also of interest. Fused 1H-1,4-thiazines have been synthesised from the corresponding 4H-1,4-thiazines by treatment with alkyl halides and sodium hydride.[72,73] Gilchrist et al have demonstrated that sulphoxides (31) can be cyclised with trifluoroacetic anhydride to give moderate yields of 1H-1,4-thiazines (Scheme 40).[74]



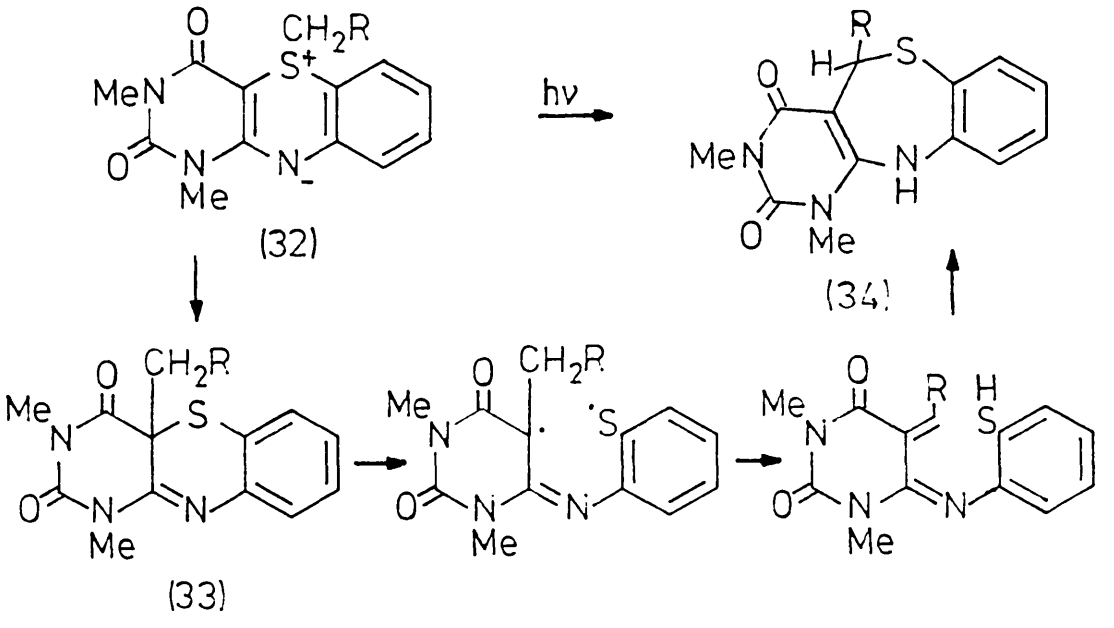
Scheme 40

Thermolysis of 1H-1,4-thiazines has been shown to cause [1,2] and [1,4] rearrangements or β-elimination, depending on the nature of the substituent present at sulphur (Scheme 41).[75]



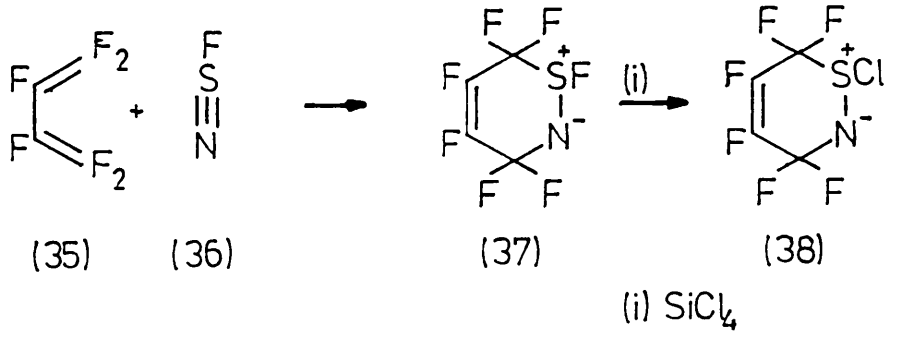
Scheme 41

Photolysis of 1H-1,4-thiazines has also been studied. The results show that when the derivatives (32) were irradiated, 1,4-thiazepines (34) were isolated in 90% yield. Shortening the reaction time led to the isolation of the [1,2] rearrangement products (33). Irradiation of these under the same conditions gave the 1,4-thiazepines. It was therefore concluded that the initial reaction of (32) was a photo-Stevens rearrangement to give (33) which then rearranges via a free-radical pathway to give the product (34).[73]



As yet, the parent thiabenzene system has not been reported. There has, however, been a report of an azathiahexa-1,4-diene. Bludssus and Mews described the reaction of thiazyl fluoride (36) with perfluorobutadiene (35). The resulting perfluoro-1λ^4,2-thiazacyclohexa-1,4-diene (37) was formed in almost quantitative yield and was shown to

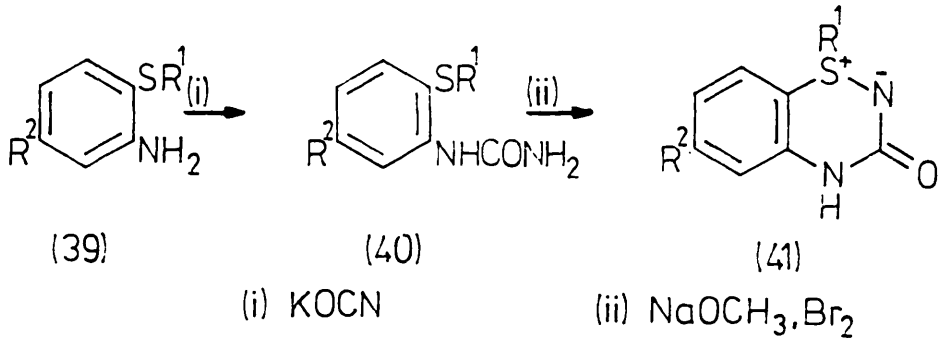
react with silicon tetrachloride to give the corresponding S-chloro compound (38).[76]



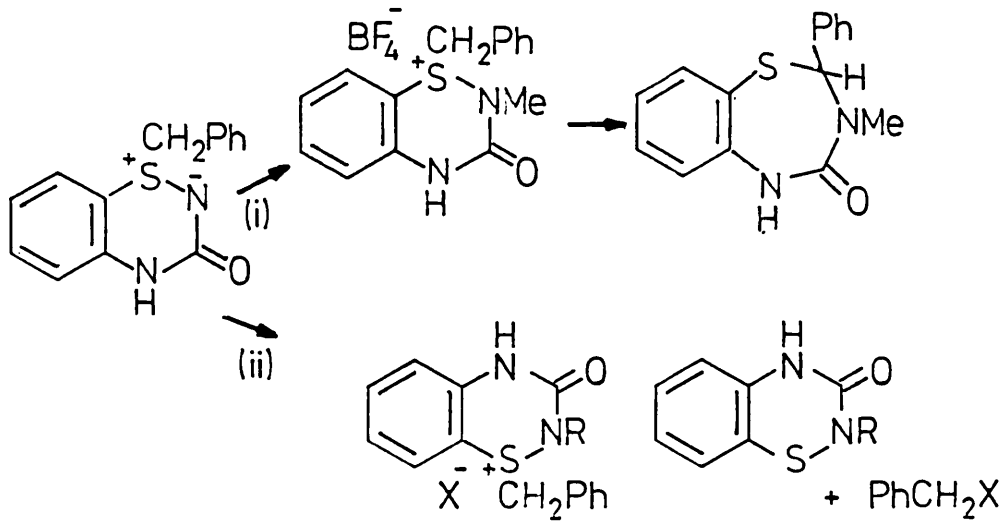
Thiazyl fluoride reacts explosively with alkylbutadienes and consequently alkyl derivatives could not be prepared by this route.

1.3.3 Thiadiazines

3,4-Dihydro-1H-1,2,4-benzothiadiazin-3-one (41) was the first system belonging to this class of compounds to be described. In 1964 Wagner et al reported that treatment of 2-alkylthio- or 2-arylthio-anilines (39) with potassium cyanate gave the corresponding ureas (40). These were then cyclised via the N-bromo compound to give (41).[77]



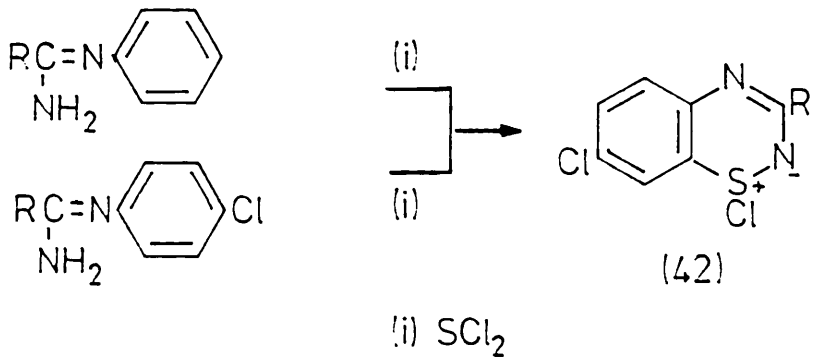
Attempts to O-alkylate this system to give the fully unsaturated benzothiadiazine system failed. Alkylation occurred at nitrogen and the products derived were dependent on the reagent used (Scheme 42).[78]



(i) $Me_3\overset{+}{O}\,\overset{-}{BF_4}$ (ii) RX = $PhCH_2Br$, MeI, EtI

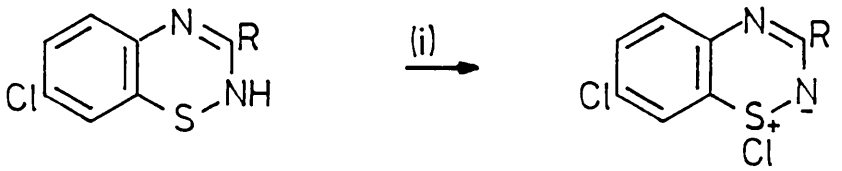
Scheme 42

The first fully unsaturated benzothiadiazines were reported by Markovski and coworkers in 1973. The S-chloro derivatives (42) were synthesised from N-arylamidines by treatment with sulphur dichloride.[79]



(i) SCl_2

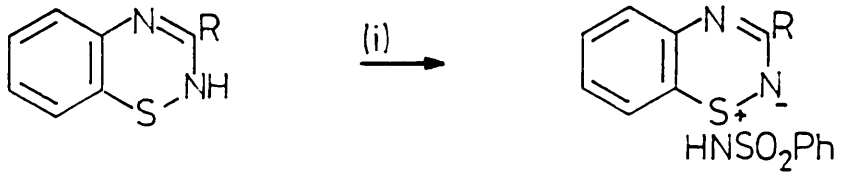
These S-chloro compounds could also be prepared from the 2H-benzothiadiazine (43) by treatment with chlorine gas.[79]



(43) (42)

(i) Cl_2

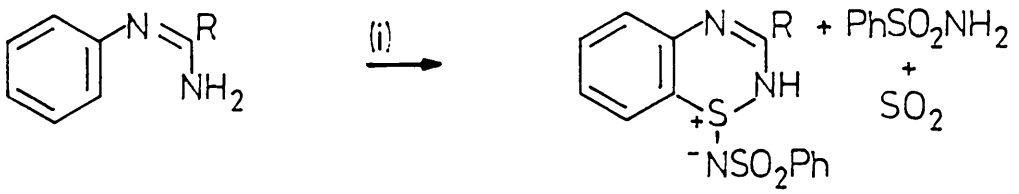
Reaction of (43) with N,N-dichlorobenzenesulphonamide did not give the S-chloro derivative as expected but gave the N-phenylsulphonamido-1,2,4-benzothiadiazine (44).[79]



(43) (44a)

(i) $PhSO_2NCl_2$

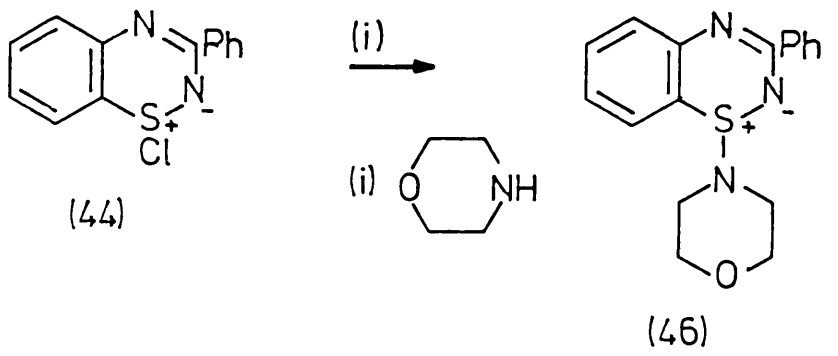
Compound (44a), which presumably exists largely in the tautomeric form (44b), had previously been synthesised from the reaction of N-arylbenzamidine (45) with N-sulphonylsulphonamides.[80]



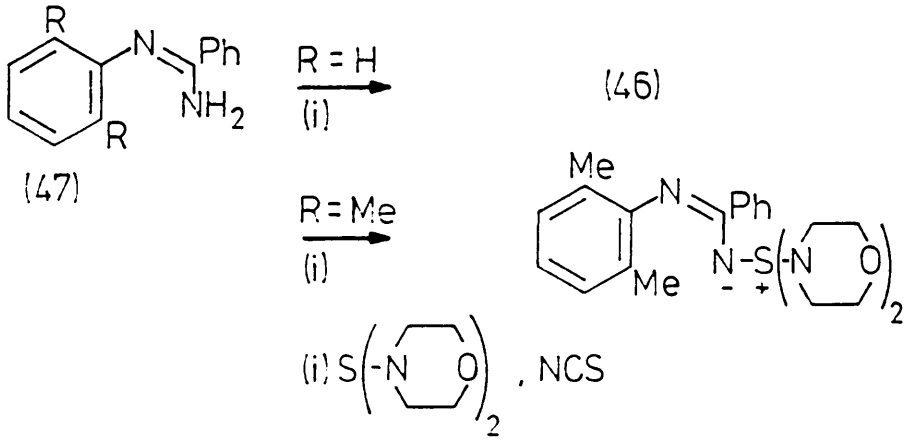
(45) (44b)

(i) $PhSO_2-N=SO$

Treatment of the chloro derivative (44) with morpholine gave good yields of the S-morpholino-1,2,4-benzothiadiazine (46).[79]

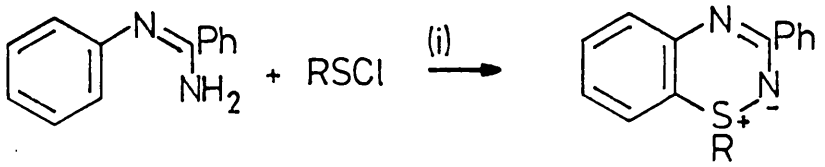


Gilchrist et al reported the synthesis of (46) from the reaction of N-arylbenzamidines (47) with 4,4'-thiobismorpholine and N-chloro-succinimide.[81] Introducing substituents into the ortho-positions of the aryl group successfully blocked the formation of the cyclic ylide (Scheme 43).



Scheme 43

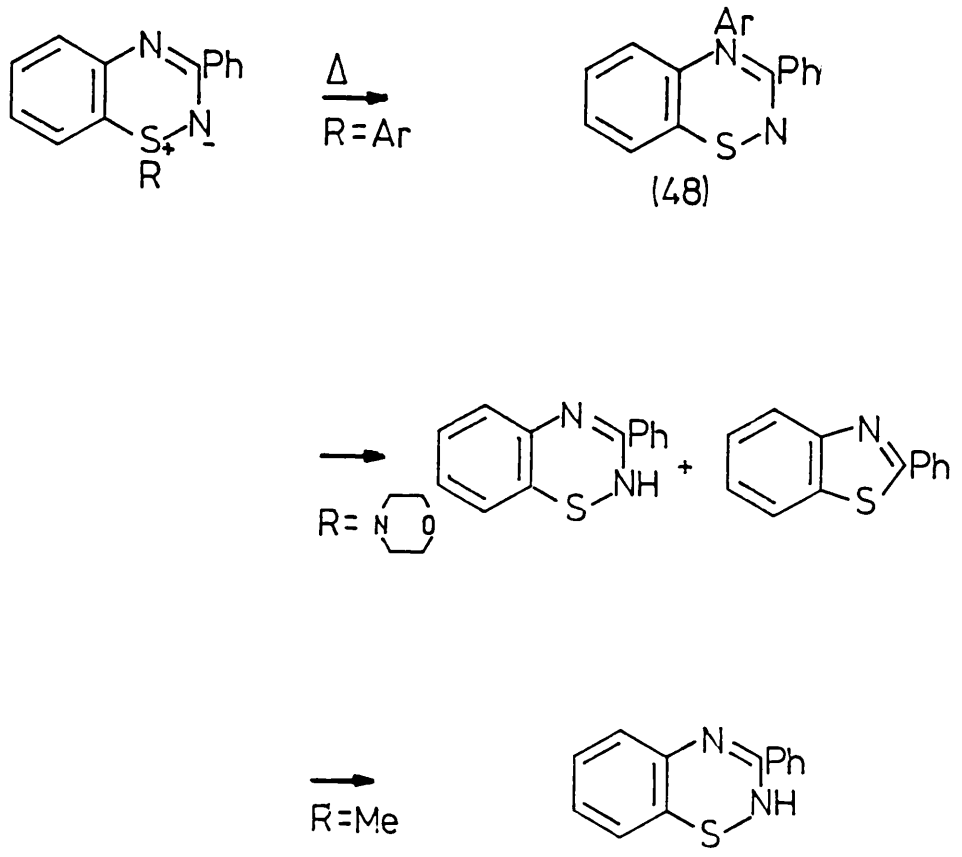
Furthermore they demonstrated that sulphenyl chlorides react with benzamidines under similar conditions to give higher yields of 1,2,4-benzothiadiazines. This method has been used to synthesis S-alkyl- and S-aryl- 1,2,4-benzothiadiazines (Scheme 44).



(i) NCS

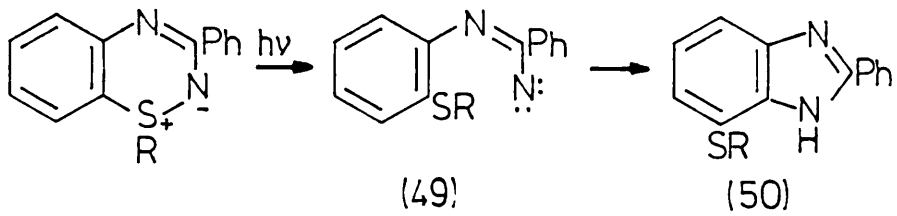
Scheme 44

Studies of the photochemical and thermal reactions of these benzothiadiazines have been reported.[82] The thermal stability of the benzothiadiazine was found to be dependent on the substituent at sulphur; S-aryl-1,2,4-benzothiadiazines decomposed around 180°C yielding rearranged product (48) whereas the S-morpholino derivatives (46) are somewhat less stable and decompose at 130°C. The products isolated from (46) were 2H-1,2,4-benzothiadiazines, probably produced by β elimination, together with, in some cases, benzothiazoles, which were thought to be derived from the 2H-1,2,4-benzothiadiazines. Least stable of the benzothiadiazines are the S-methyl derivatives. These decompose at 80°C to give the corresponding 2H-1,2,4-benzothiadiazines (Scheme 45).



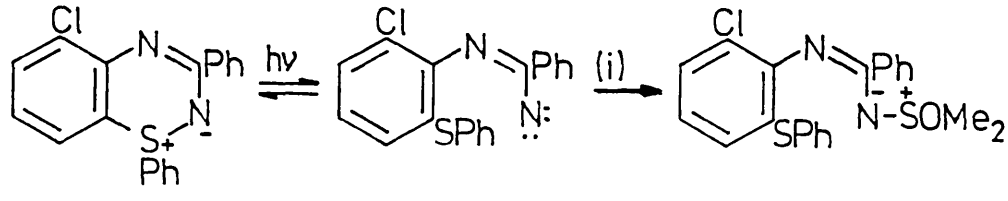
Scheme 45

Photolysis of benzothiadiazines effects the cleavage of the sulphur-nitrogen bond presumably generating the nitrene (49) as an intermediate which then cyclises onto the free ortho-position of the benzene ring leading to the benzimidazole (50).[82]



Should the ortho-position be blocked this cyclisation is suppressed and the benzothiadiazine is reformed. As an example, photolysis of 5-chloro-1,3-diphenyl-1,2,4-benzothiadiazine (51)

is very slow and implies that (51) is stable to u.v. radiation. However, introduction of dimethyl sulphoxide, a good nitrene trap, results in good yields of sulphoximide (52) thus, demonstrating that sulphur-nitrogen bond cleavage is occurring.[82]



(51) (52)

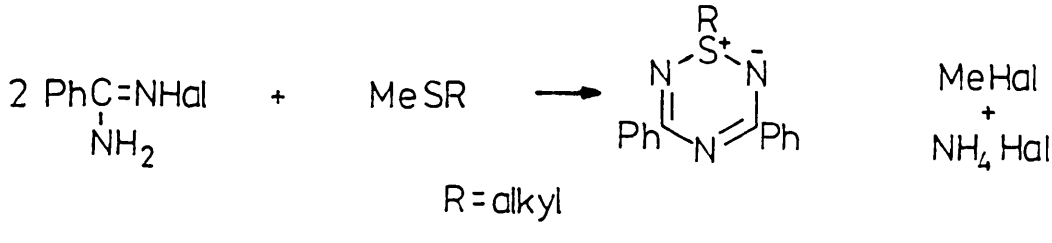
(i) DMSO

From the reactions of the benzothiadiazines described above, some similarity can be noted between these and the reactions of the thiazines and thiabenzenes. This would suggest that they may also be ylidic in nature and, as such, not aromatic systems.

1.3.4. Thiatriazines

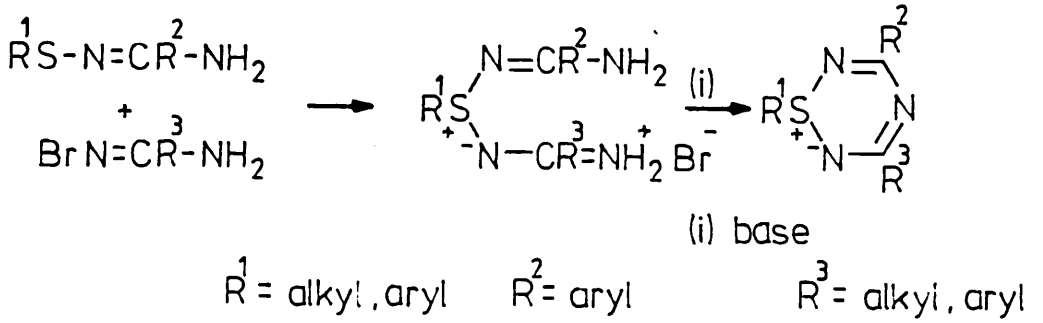
The 1H-1,2,4,6-thiatriazine ring system has been known for some time. Although not a cyclic sulphimide, the ring system does contain a sulphur-nitrogen bond at the appropriate oxidation level giving rise to the possibility of this system exhibiting aromatic properties.

One of the earliest syntheses describes the formation of this hetrocyclic ring system from N-halo amidines by reaction with sulphides (Scheme 46).[83]



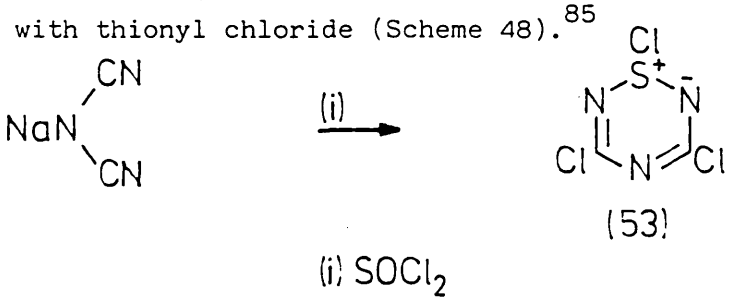
Scheme 46

Later, an improved synthesis was reported which was used to prepare several trisubstituted 1H-1,2,4,6-thiatriazines. This was based on the reaction of N-bromoamidines with N-sulphenyl-amidine derivatives (Scheme 47).[84]



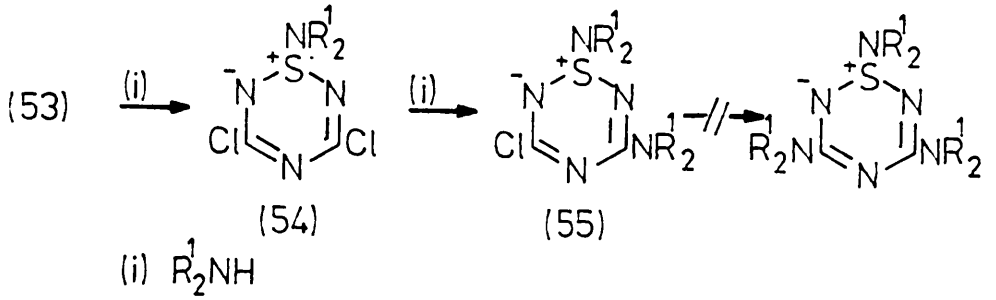
Scheme 47

Thiatriazines have also been prepared by treating sodium dicyanamide with thionyl chloride (Scheme 48).[85]

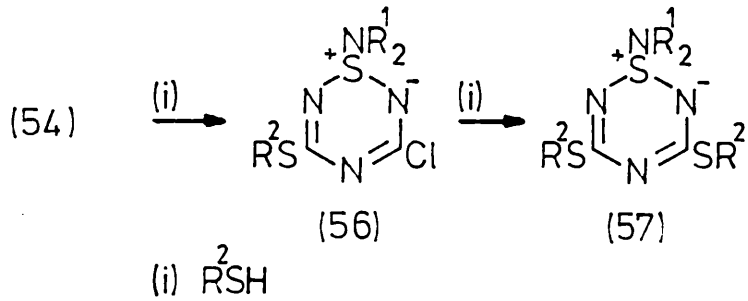


Scheme 48

Treatment of (53) with amines gave the 1-amino derivatives (54).

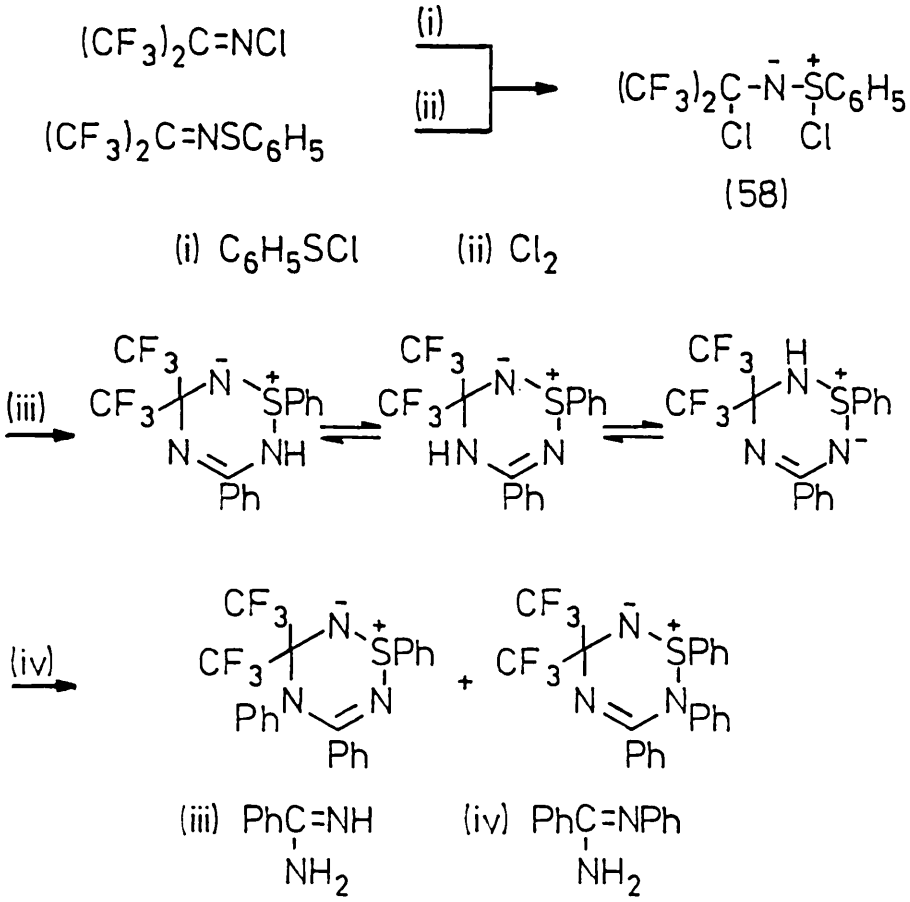


Subsequent treatment with an excess of amine was shown to produce the diamino compounds (55); further reaction was not observed.[86] In contrast, thiols reacted with the 1-amino-3,5-dichlorothiatriazines (54) to give either (56) by displacement of one chlorine atom or (57) by displacement of both chlorine atoms.[87]



In general these thiatriazines are air sensitive, crystalline compounds with a tendency to undergo spontaneous decomposition. X-ray structures of derivatives have shown that the ring system is not planar.[88,89] As yet, it is not known whether these compounds show any aromatic character or not.

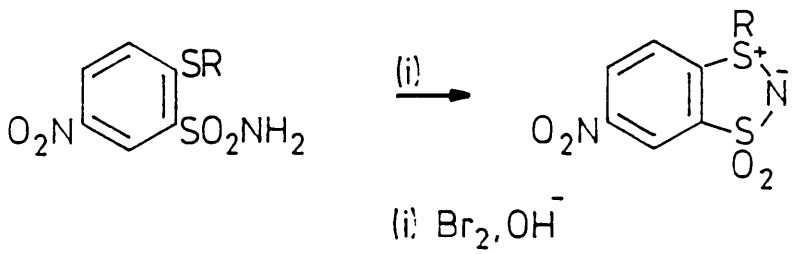
A synthesis of dihydro 1,2,4,6-thiatriazines has also been reported. Shermolovich et al have shown that arenesulphinimidoyl chlorides (58) react with benzamidines to give the cyclic products shown in Scheme 49.[90]



Scheme 49

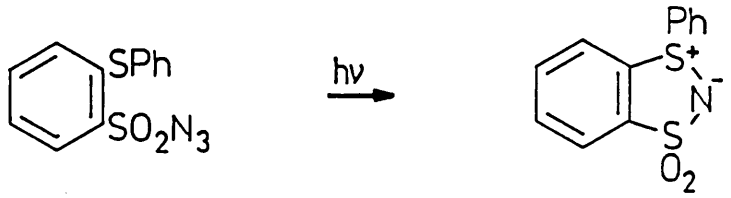
1.3.5. Five Membered Rings

The first five membered ring sulphimides reported were prepared from substituted arylsulphonamides by treatment with bromine under basic conditions (Scheme 50).[91]



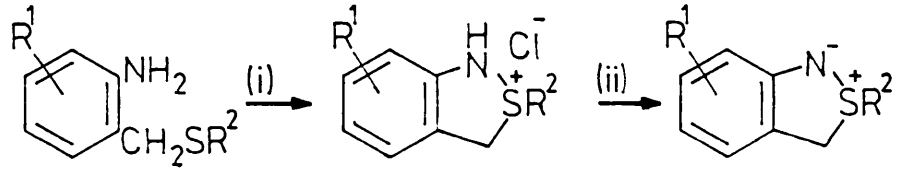
Scheme 50

These sulphimides have also been isolated as photolysis products of 2-(phenylthio)phenylsulphonyl azides (Scheme 51).[92]



Scheme 51

Unfortunately, the properties of these cyclic sulphimides have not been described. The related cyclic sulphimides (61) were synthesised by Claus et al.[93] Treatment of the anilines (59), produced by the Sommelet-Hauser rearrangement of N-aryl-S-alkylsulphimides, with N-chlorosuccinimide led to the generation of the cyclic sulphonium chlorides (60). These were then converted into the corresponding cyclic sulphimides (61) by treatment with base.

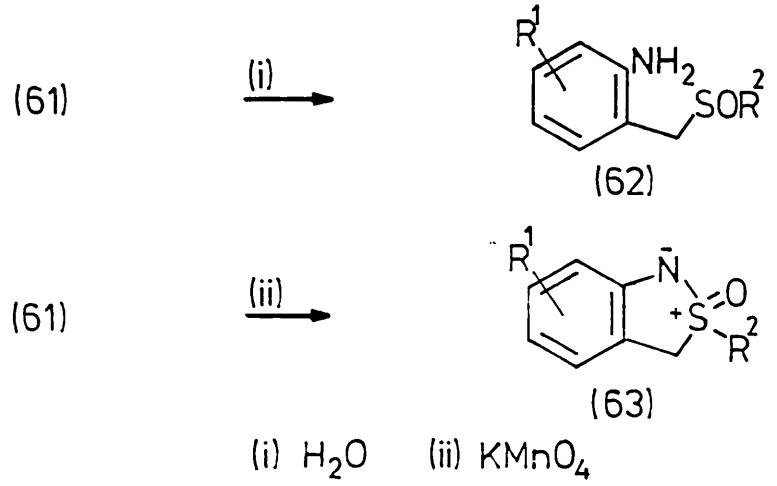


(59) (60) (61)

(i) NCS (ii) base

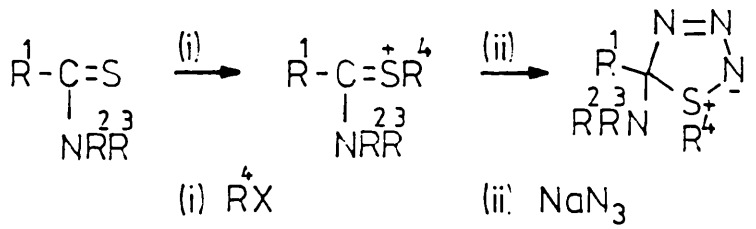
The stability of these sulphimides is highly dependent on the nature of both R^1 and R^2. In cases where R^1 is an electron withdrawing substituent, then the system is stabilised. Derivatives in which R^1 is an electron donating group are only stable at low temperatures.

Hydrolysis of the sulphimides (61) to sulphoxides (62) occurred in the presence of water. The corresponding sulphoximides (63) were obtained when the sulphimide (61) was oxidised using potassium permanganate in aqueous dioxan.



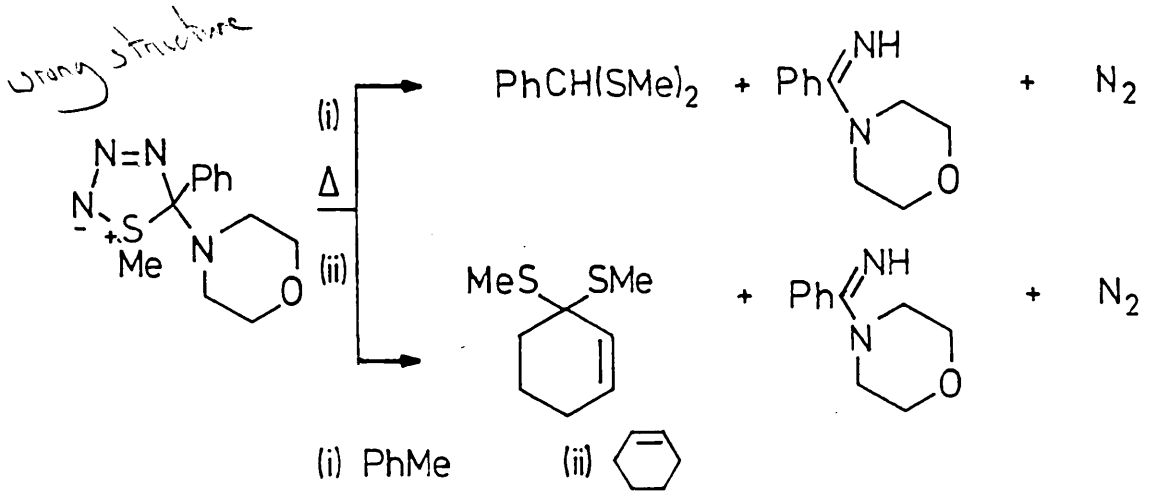
The only other reported synthesis of a five membered cyclic sulphimide concerns the synthesis of 1,5-dihydro-1,2,3,4-thiatriazoles from quaternary salts of N,N-disubstituted thioamides by treatment with sodium azide (Scheme 52).[94]

wrong structure



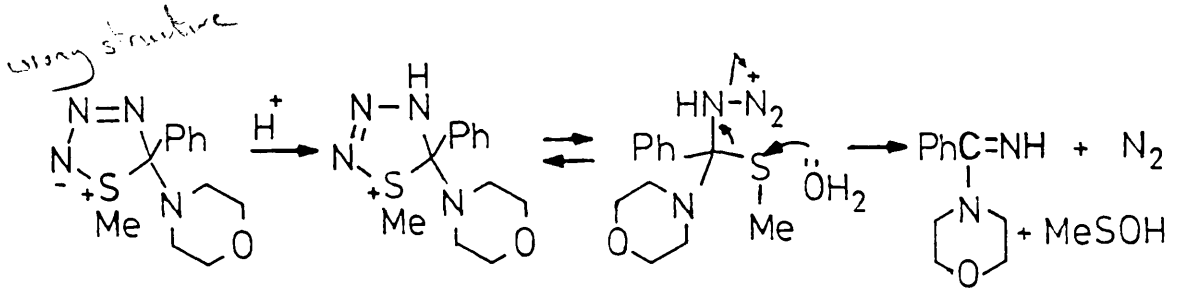
Scheme 52 See R.S. Beddoes – O.S. Mills J. Chem Res (S) 1981, 132

These 1,5-dihydro-1,2,3,4-thiatriazoles are colourless, crystalline solids which can be stored at room temperature for several days or for longer periods at 0°C. They decompose at 80-105°C with evolution of nitrogen. Thermolysis of these compounds in toluene or cyclohexene proceeds smoothly resulting in the formation of high yields of amidines, together with a product derived from reaction with the solvent (Scheme 53).



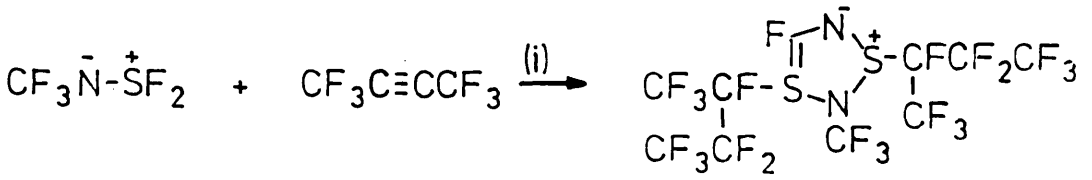
Scheme 53

Treatment of these 1,2,3,4-thiatriazoles with 2M hydrochloric acid at room temperature also produces amidines. The proposed mechanism for this reaction is shown in Scheme 54.



Scheme 54

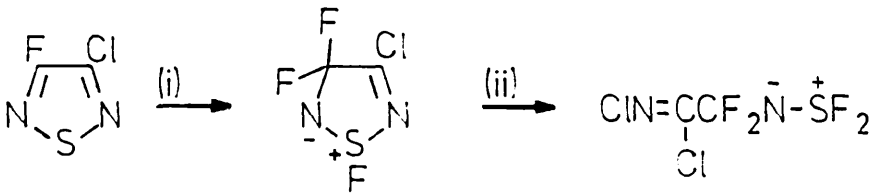
Two other heterocycles have been reported which although not sulphimides, possess similar structural features. The first was isolated from the reaction between N-trifluoromethylimidosulphurous difluoride and hexafluorobut-2-yne over caesium fluoride (Scheme 55).[95]



(i) CsF

Scheme 55

The other heterocycle, a 3H-1,2,5-thiadiazole, has been observed as a product from the reaction between chlorofluorothiadiazole and xenon difluoride (Scheme 56).[96]



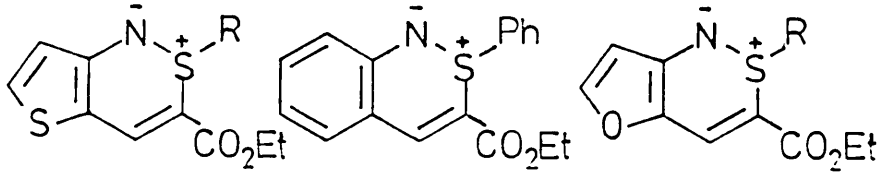
(i) XeF_2 (ii) ClF

Scheme 56

2. RESULTS AND DISCUSSION

2.1 Synthesis of Cyclic Sulphimides

In 1981 a method for the synthesis of cyclic sulphimides was published from these Laboratories.[69] Work by Grant[97] and Tsoi[98] had established a viable synthesis of the cyclic sulphimides shown in Scheme 57.

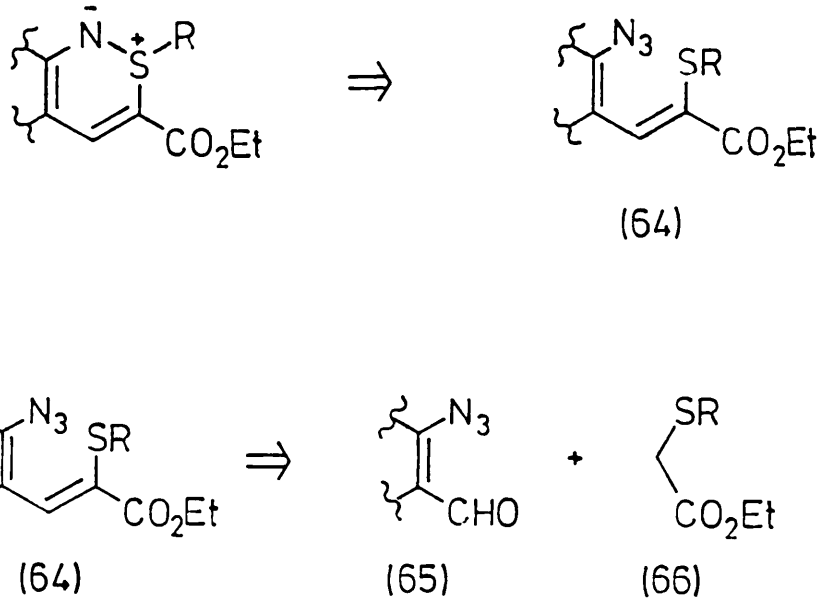


(26a,b) (25) (27a,b)

(a) R=Ph (b) R=Me

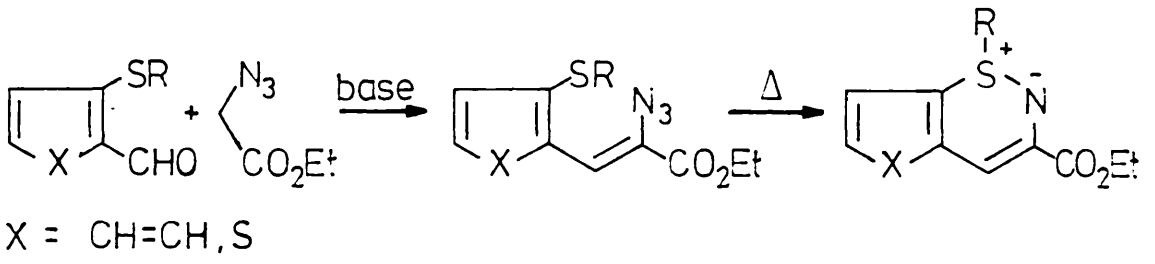
Scheme 57

In the synthesis of each of these, the nitrogen-sulphur bond was formed as the last step. The method developed involved the use of azides. As described earlier, decomposition of azides in the presence of sulphides may produce good yields of sulphimides. Thus, for any of the sulphimides shown in Scheme 57, the first retrosynthetic step would give the azide (64) shown in Scheme 58. Disconnection of the azide (64) leads to the aldehyde (65) and active methylene compound (66). The aldehydes (3-azidothiophen-2-carbaldehyde,[99] 3-azidofuran-2-carbaldehyde[100] and o-azidobenzaldehyde[101]) required for the syntheses had all been described in the literature.



Scheme 58

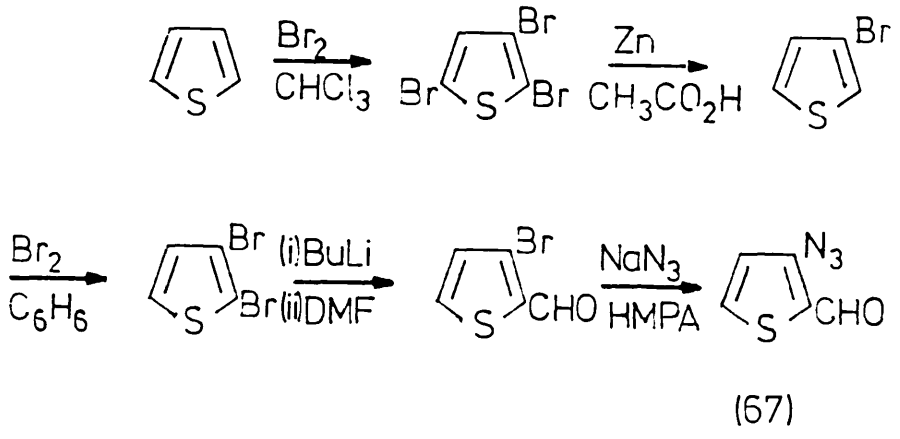
Similarily the isomeric cyclic sulphimides shown in Scheme 59 were synthesised from the appropriate aldehydes and ethyl azidoacetate.[102]



Scheme 59

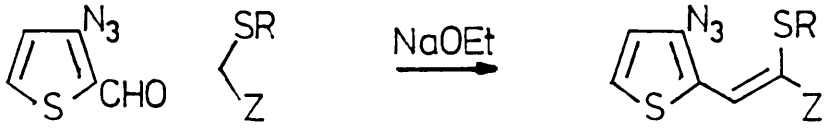
2.1.1 Thieno[3,2c][1λ^4,2]thiazines

3-Azidothiophen-2-carbaldehyde (67) was prepared by the method of Gronowitz from 2,3-dibromothiophen.[99] Lithiation of 2,3-dibromothiophen at low temperature occurs exclusively at the 2-position. Subsequent reaction with dimethylformamide gave 3-bromothiophen-2-carbaldehyde which reacted with sodium azide in hexamethylphosphoramide solution to give (67) by nucleophilic displacement of bromine. 2,3-Dibromothiophen is available from thiophen by a series of bromination, partial debromination and bromination reactions.[103] The synthesis is shown in Scheme 60.

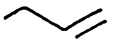


Scheme 60

The azide (67) is relatively stable and can be stored for prolonged periods in the dark at 0°C. In sodium ethoxide/ethanol solution the azido-aldehyde (67) underwent condensation reactions with a variety of active methylene compounds, details of which are given in Scheme 61.



(67) (66) (68)

(a)	R=Ph	$Z=CO_2Et$	Yield=90%
(b)	=Me	$=CO_2Et$	=50%
(c)	=Ph	$=COCH_3$	=75%
(d)	=Ph	=CHO	=50%
(e)	=Ph	=CN	=80%
(f)	=Et	$=CO_2Et$	=50%
(g)	= 	$=CO_2Et$	=57%

Scheme 61

With the exception of 2-phenylthioacetaldehyde and ethyl 2-allylthioacetate, the methylene compounds were obtained by reaction of the sodium salt of the appropriate thiol with either ethyl 2-chloroacetate,[104] 2-chloroacetonitrile[105] or chloroacetone.[104] 2-Phenylthioacetaldehyde was prepared in a similar manner from 2-bromoacetaldehyde diethylacetal.[106] Phenylthioacetaldehyde was then stored in the protected form. Immediately before use, the aldehyde (66d) was obtained by treatment of its diethylacetal with 2M hydrochloric acid. Ethyl 2-allylthioacetate[107] was obtained from the reaction of the sodium salt of ethyl 2-mercaptoacetate with allylchloride (Scheme 62).

$$RSH \xrightarrow[(i)]{NaOEt} RSCH_2Z \quad (66)$$

(a) R=Ph (i) $ClCH_2CO_2Et$

(b) =Me (i) $ClCH_2CO_2Et$

(c) =Ph (i) $ClCH_2COCH_3$

(d) =Ph (i) $BrCH_2CH(OEt)_2$ (ii) 2M HCl

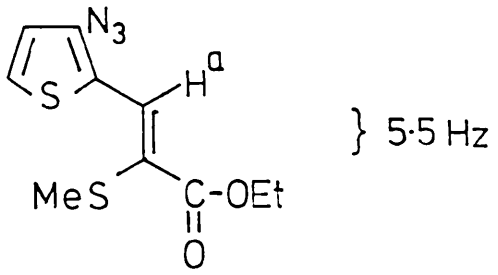
(e) =Ph (i) $ClCH_2CN$

(f) =Et (i) $ClCH_2CO_2Et$

(g) $=CH_2CO_2Et$ (i) $ClCH_2CH=CH_2$

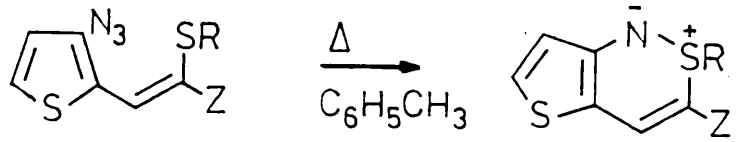
Scheme 62

In all of the above condensation reactions, only one double bond isomer was obtained. The ^1H n.m.r. spectrum of the crude reaction mixture showed only one resonance for the vinylic proton H^a, indicating that only one of the possible isomeric products was formed. From the undecoupled ^{13}C n.m.r. spectrum of (68b), a coupling constant of 5.5 Hz was measured for the coupling between H^a and the carbon atom of the ester carbonyl group. This indicates a <u>syn</u> arrangement as shown.[108]



(68b)

When the azides (68a-e) were heated in refluxing toluene, decomposition took place. As the reaction proceeds, the solution changed from being pale yellow to deep red. Following the reaction by t.l.c. showed that as the starting material was consumed, a polar, deep red product, the cyclic sulphimide, was formed. After all of the starting material had been consumed, the solvent was removed and the resulting dark red gum was chromatographed to give the pure sulphimide in good yield. Cyclic sulphimides bearing a phenyl substituent on sulphur were highly crystalline solids. The sulphimides prepared by this route are shown in Scheme 63.



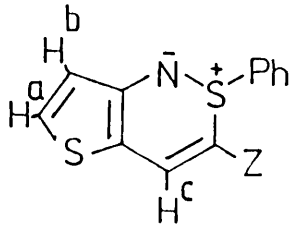
(68) (26)

(a)	R = Ph	Z = CO_2Et	Yield = 90%
(b)	= Me	= CO_2Et	= 75%
(c)	= Ph	= $COCH_3$	= 90%
(d)	= Ph	= CHO	= 75%
(e)	= Ph	= CN	= 90%

Scheme 63

Assignment of the structures (26c-e) was based on comparison of the spectral data (^1H and ^{13}C n.m.r., i.r., u.v., m.s.) with that of the known sulphimide (26a). The structure of (26a) had previously been confirmed by X-ray diffraction analysis.[69] The u.v. spectra (26c-e) showed the same characteristic absorbtions at around 460 nm, 330 nm and 220 nm. Comparison of the ^1H and ^{13}C n.m.r. spectra also confirmed the structural similarities of (26c-e). The chemical shift data from the ^1H n.m.r. spectra are shown in Table 2.

TABLE 2. ^{1}H n.m.r. Data of Thieno [3,2c][1λ^4,2] thiazines

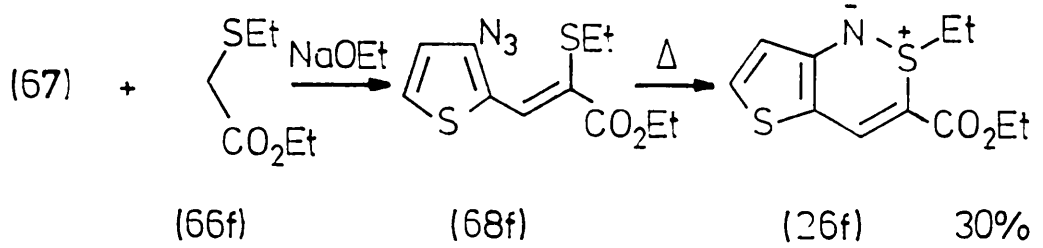


(26a) Z= CO_2Et
(26c) = $COCH_3$
(26d) = COH
(26e) = CN

	H^a	H^b	H^c
(26a)	7.59 (1H,d,J5.5Hz)	6.89 (1H,dd,J5.5Hz and J0.8Hz)	8.12 (1H,d,J0.8Hz)
(26c)	7.64 (1H,d,J5.6Hz)	6.87 (1H,d,J5.6Hz)	7.93 (1H,s)
(26d)	7.71 (1H,d,J5.6Hz)	6.88 (1H,d,J5.6Hz)	7.78 (1H,s)
(26e)	7.63 (1H,d,J5.5Hz)	6.9 (1H,dd,J5.5Hz and J0.6Hz)	7.7 (1H,d,J0.6Hz)

It is known from the X-ray structure of (26a) that the thiazine ring is not planar, the sulphur adopting tetrahedral geometry. This is reflected in the ^1H n.m.r. spectrum of (26a) and (26b) which show the prochiral methylene group of the ethyl ester to be split into two doublets of quartets. This effect is only observed because inversion at sulphur is slow compared with the n.m.r. time scale. It was hoped that this observation could be used to measure the inversion barrier at sulphur, by obtaining the coalescence temperature from variable temperature n.m.r.. However, as the methylene group is far removed from the "chiral" centre in structures (26 a and b) the splitting observed in the ^1H n.m.r. spectrum is small and as such not suited to this type of experiment.

Using the same route as described for the preparation of S-methylthieno[3,2c][1λ^4,2]thiazine (26b) the corresponding S-ethyl derivative (26f) was prepared in low yield (Scheme 64).



Scheme 64

The pro-chiral methylene of the S-ethyl group, being closer to the chiral centre, showed a larger splitting in the ^1H n.m.r. spectrum (Figure 1). However, as reflected in the low yield obtained from the thermolysis of azide (68f), it appeared that sulphimide (26f) was unstable at elevated temperatures. This would therefore mean that (26f) was unsuitable for variable temperature n.m.r. studies. Thermolysis of (26f) at 110°C showed that it did decompose. Although no products could be isolated from the reaction, it seems probable that

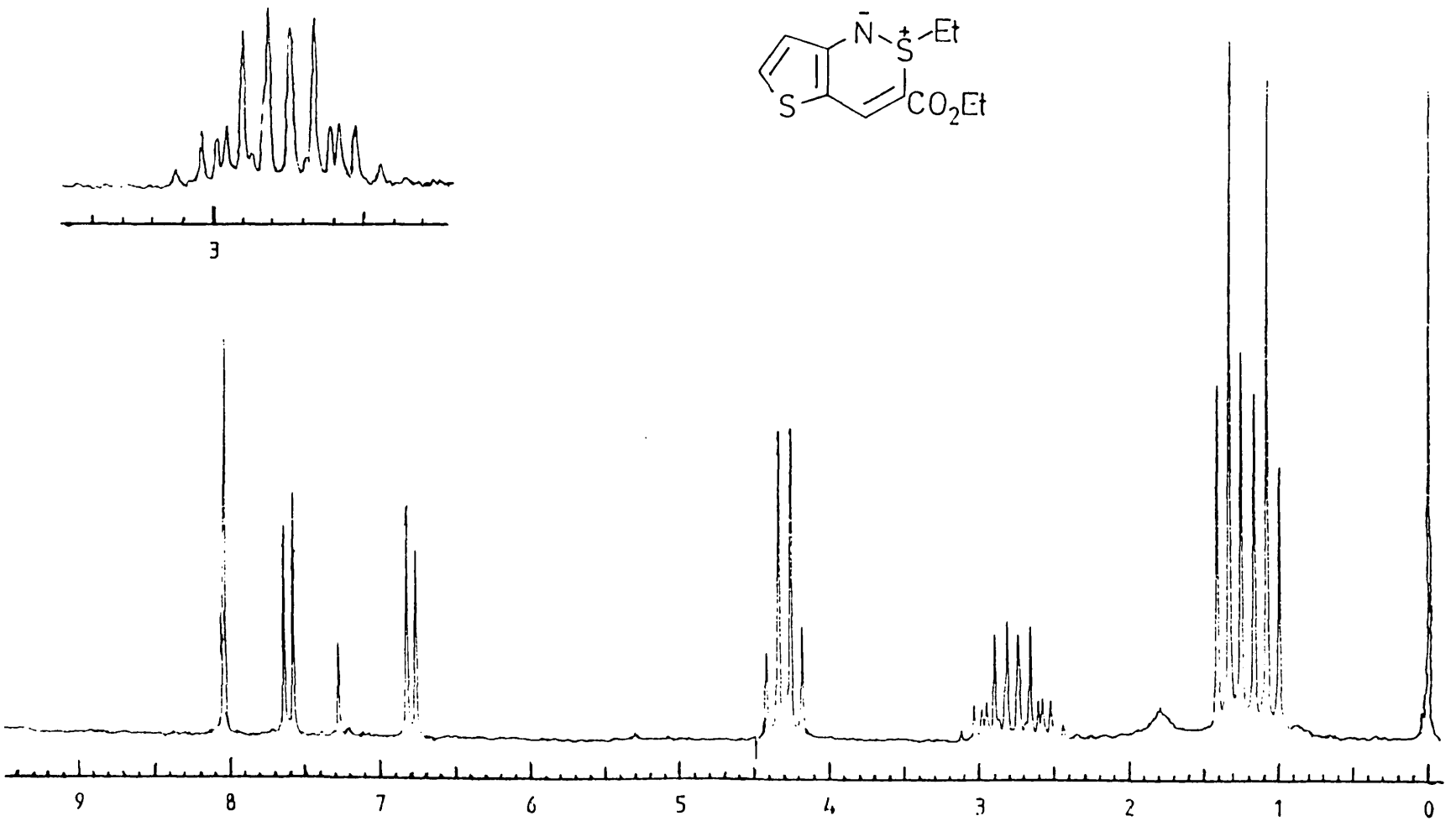
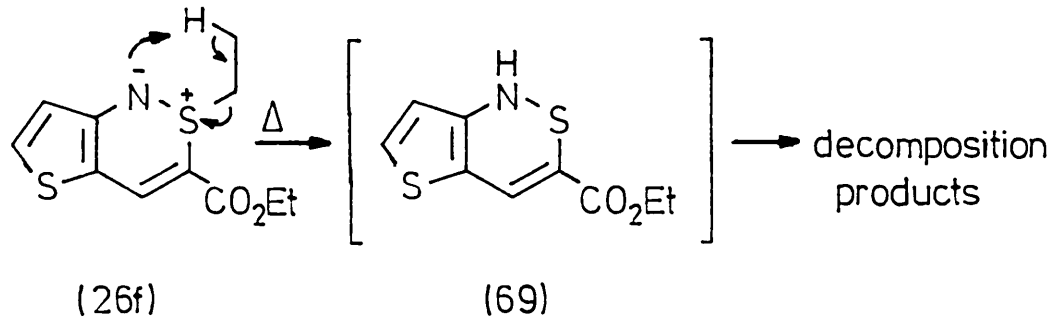


FIGURE 1.

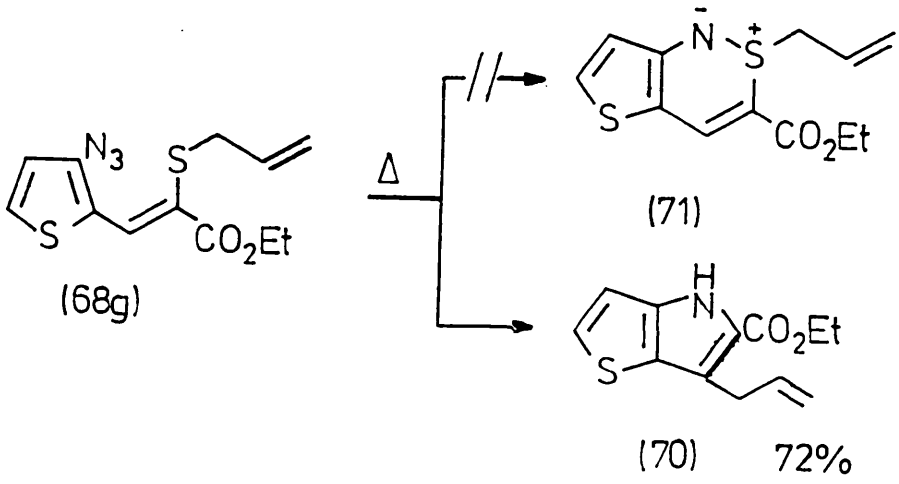
(26f) would undergo a cycloelimination reaction to give the 2H-thiazine (69), as shown in Scheme 65.



(26f) (69)

Scheme 65

Finally, attempts were made to prepare an S-allythienothiazine. When the azide (68g) was thermolysed in refluxing toluene, the single product obtained proved not to be the corresponding sulphimide (26g). The spectral data obtained for this product showed none of the characteristics associated with a cyclic sulphimide. The ^{1}H n.m.r. data indicated that the allyl group and ester functionality were intact. Resonances for the thiophen ring protons were as expected. However the singlet expected for the thiazine ring proton was not present. Moreover, a broad exchangeable signal was present at δ9.2. From the i.r. spectrum it was apparent that this resonance was due to the presence of a N-H function. Initially it was thought that the product was a thienopyrrole which resulted from a competing reaction in which the nitrene intermediate cyclised onto the adjacent double bond (see later). However, mass spectral and microanalytical data indicated that sulphur had been lost (Scheme 66).



Scheme 66

Using n.O.e. data obtained for the product, it was assigned the 6-allylthienopyrrole structure (70). Presaturation of the N-H resonance resulted in an enhancement of H-3 and of the methylene protons of the ethyl ester. No enhancement of the allyl protons was observed. Similarily, presaturation of the ethyl ester methylene protons produced an enhancement of the N-H and H-3 (Figure 2).

Two possible mechanisms for the formation of (70) are presented in Scheme 67. Both involve the initial formation of the cyclic sulphimide (71), which undergoes subsequent rearrangement by two possible pathways, leading to the isolated product. The first pathway follows the conventional thermal rearrangement of the cyclic sulphimide by invoking a [1,4] shift (see later). Alternatively a [3,3] rearrangement may occur as depicted in the second pathway.

While the second pathway is likely to proceed with only one inversion of the allyl group, the first could involve two. It was hoped to gain more information about the course of this reaction by preparing the methyl substituted precursors (72) and (73). Unfortunately the active methylene compounds required to prepare (72) and (73) could not be obtained. Attempts to displace the halogen atoms of either

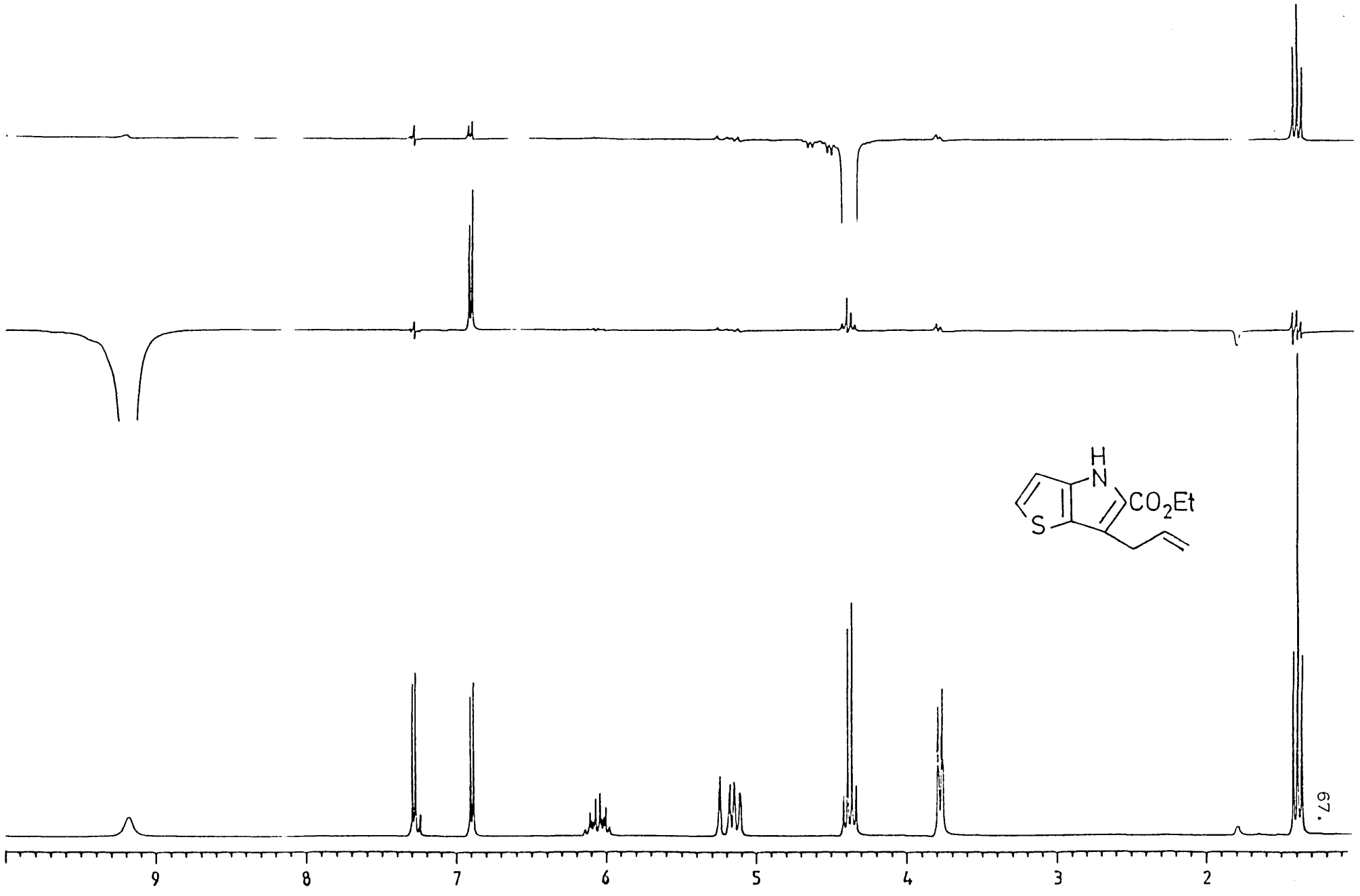
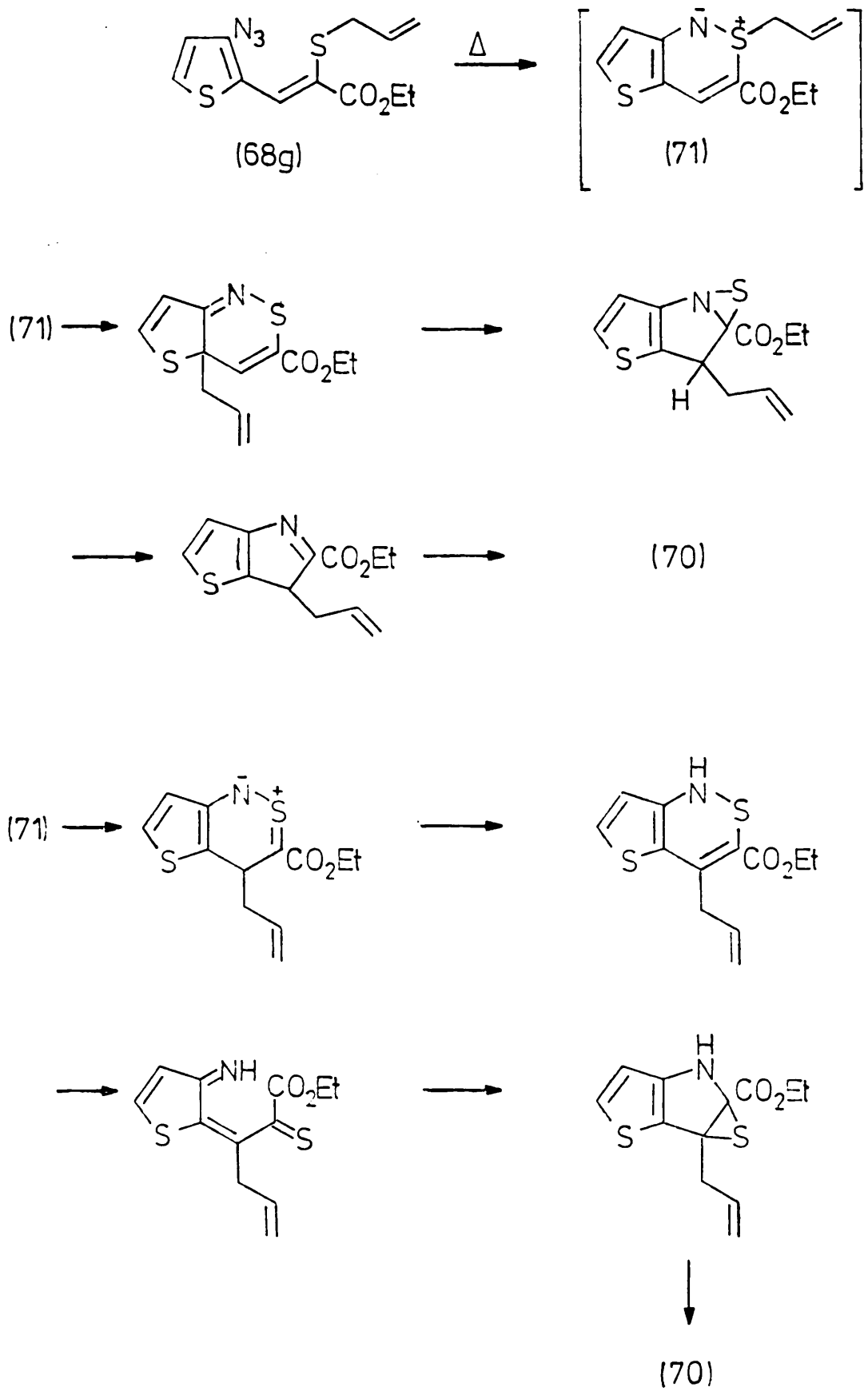
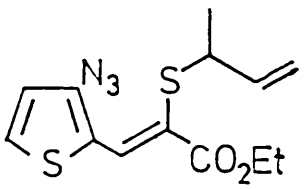


FIGURE 2.

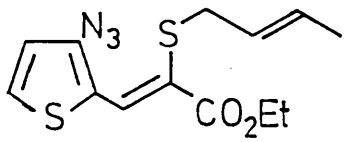


Scheme 67

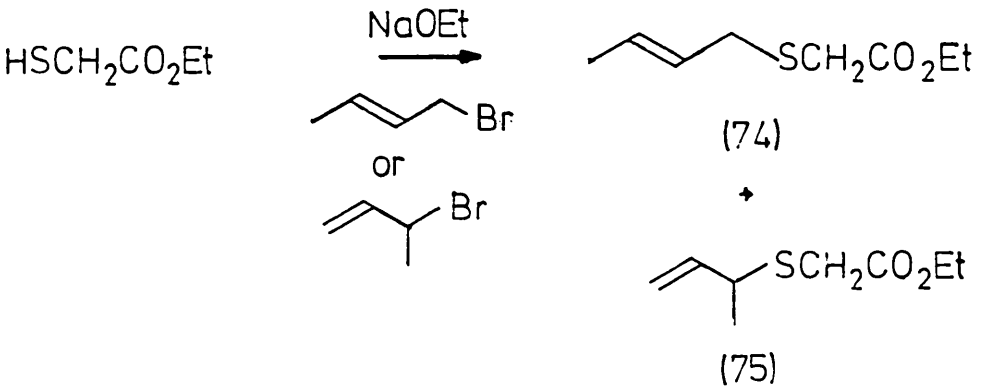
1-bromobut-2-ene or 3-bromobut-1-ene gave inseparable mixtures of isomeric sulphides. Since the ^1H n.m.r. spectra of the crude products obtained from both reactions were identical, the products were assumed to be a mixture of sulphides (74) and (75).



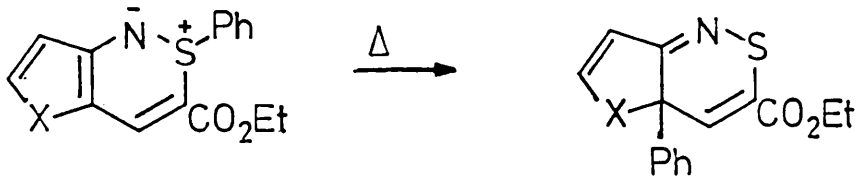
(72)



(73)



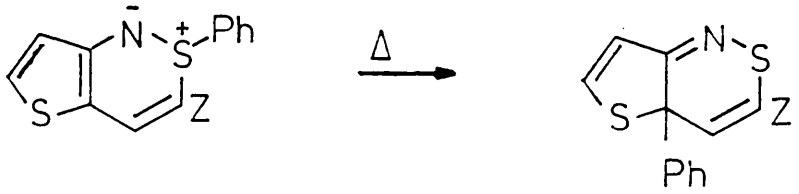
In general, the thermolysis of a suitable azide in refluxing toluene solution has been shown to give good yields of cyclic sulphimides. However if the thermolysis temperature is increased, further reaction of the sulphimide may occur. As previously reported from these laboratories, thermolysis of thiazines of the type (26) or (27) resulted in formation of unusual rearrangement products (76) and (77) in which the sulphur substituent had migrated to a bridgehead position.[70] This rearrangement had been observed for all the thiazines previously reported except for the benzo-fused derivatives. Presumably, disruption of the highly aromatic benzene ring inhibits this process. Examples of similar rearrangements in related systems have also been reported and are described in section 1.3.



X=S (26a) (76a)

X=O (27a) (77a)

Thermolysis of the thienothiazines (26c-e) possessing differing electron withdrawing substituents also gave the corresponding rearrangement products (76c-e) in good yield.

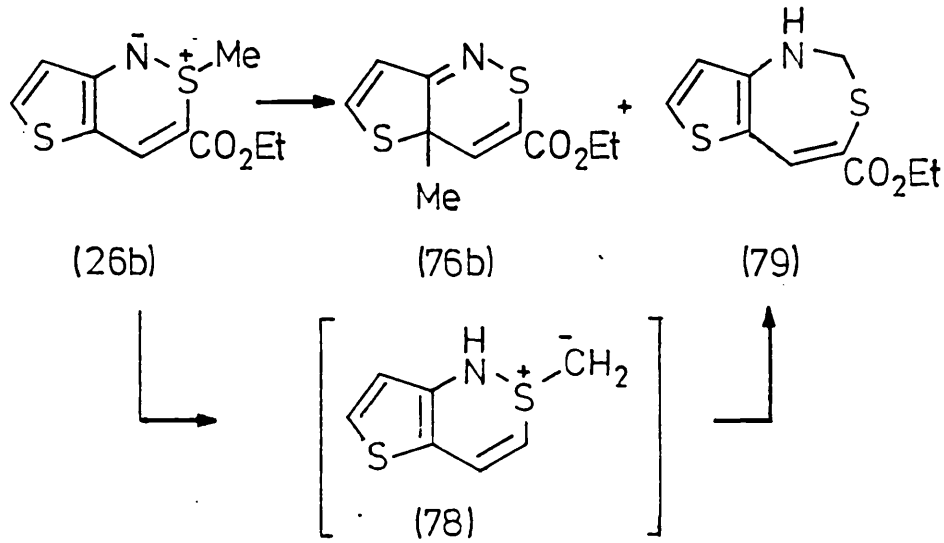


(26c-e) Z = $COCH_3$ 80% (76c-e)

= CHO 75%

= CN 88%

In the case of the S-methylthienothiazine (26b) another product was isolated from the reaction. The spectral data for this product showed it to have the same molecular weight and composition as the starting material. From the ^1H n.m.r. and i.r. spectra the presence of an NH adjacent to a methylene unit was noted. On this basis structure (79) was assigned to the new product, which although not detected earlier[70] is not unexpected. Presumably (79) is formed by isomerisation of (26a) to the corresponding sulphonium ylide (78) followed by a [1,2] nitrogen shift.

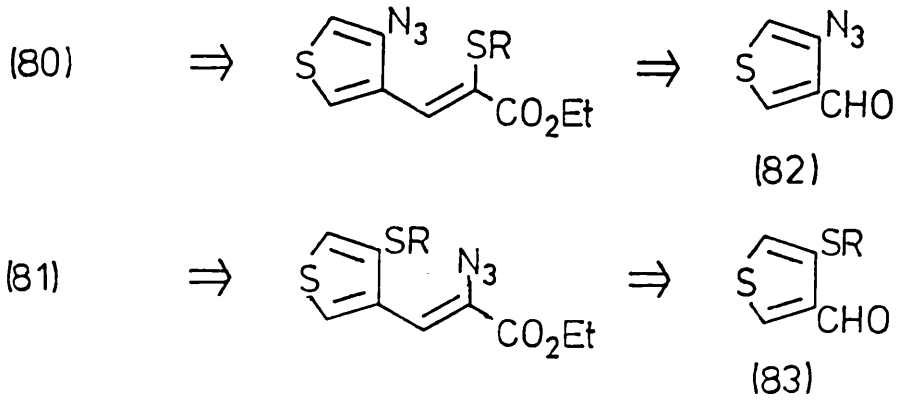


2.1.2 Thieno [3,4c] [$1\lambda^4$,2] thiazines

Using a route similar to the one described for the preparation of the thieno [3,2c] [$1\lambda^4$,2] thiazines it was envisaged that the isomeric thieno [3,4c] [$1\lambda^4$,2] thiazines (80) and (81) could be synthesised.

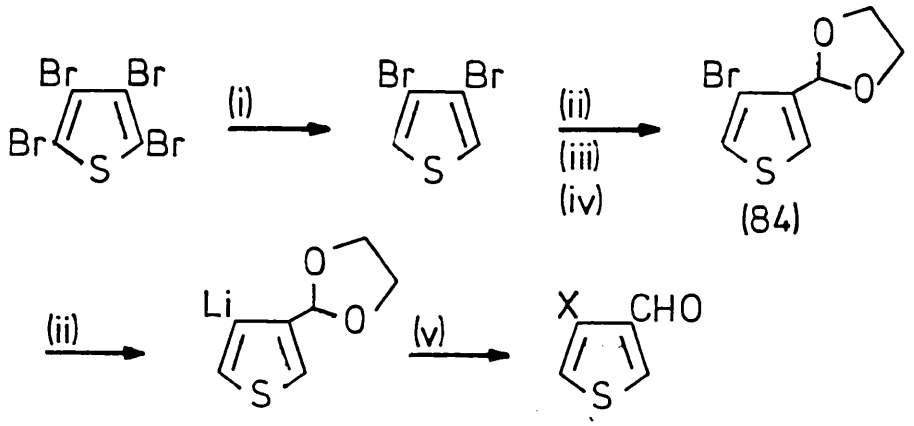
(80) (81)

Disconnection as before leads to the corresponding azides, which should be readily available from the known aldehydes depicted in Scheme 68.[109,110]



Scheme 68

The aldehydes (82) and (83) were synthesised from a common intermediate, 4-bromothiophen-3-carbaldehyde ethylene acetal (84). Following a literature procedure, (84) was prepared from 3,4-dibromothiophen.[109] Halogen-metal exchange, using n-butyllithium at -78°C, then generated 4-lithiothiophen-3-carbaldehyde ethylene acetal which reacted with either tosyl azide or diphenyl disulphide to give the protected form of the required aldehydes. Deprotection using 2M hydrochloric acid on the crude reaction product afforded good yields of the aldehydes (82) and (83) after chromatography (Scheme 69).

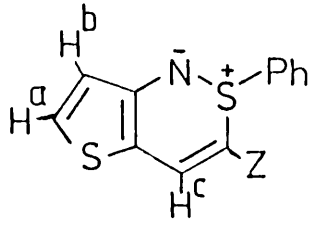


Scheme 69

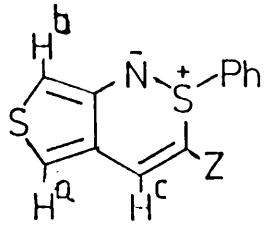
4-Azidothiophen-3-carbaldehyde was found to condense with ethyl 2-phenylthioacetate (66a) and ethyl 2-methylthioacetate (66b). Thermolysis of the resulting azides (85) in toluene solution did not proceed cleanly to the corresponding cyclic sulphimides: t.l.c. showed mainly baseline material together with some polar, highly coloured components. These polar products were unstable to chromatography on either silica gel or alumina. However, it was possible to isolate the product (80a) from the thermolysis of (85a) by flash chromatography on alumina. Unfortunately the product from thermolysis of (85b) was not sufficiently stable to be isolated (Scheme 70).

The thermolysis product (80a) was isolated as an unstable red gum. Its structure was assigned mainly by comparison of its spectral data with those of the previously described sulphimides (Table 3).

TABLE 3. ^{1}H n.m.r. Data of Thiazines (26a) and (80a)

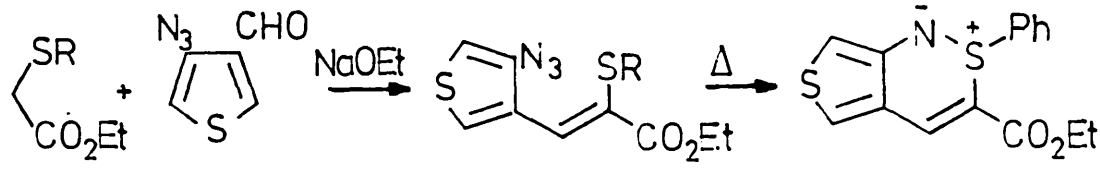


(26a)



(80a)

	H^a	H^b	H^c
(26a)	7.59 (1H,d,J5.5Hz)	6.89 (1H,dd,J5.5Hz and J0.8Hz)	8.12 (1H,d,J0.8Hz)
(80a)	7.49 (1H,d,J3.3Hz)	6.53 (1H,dd,J3.3Hz and J0.7Hz)	8.16 (1H,d,J0.7Hz)



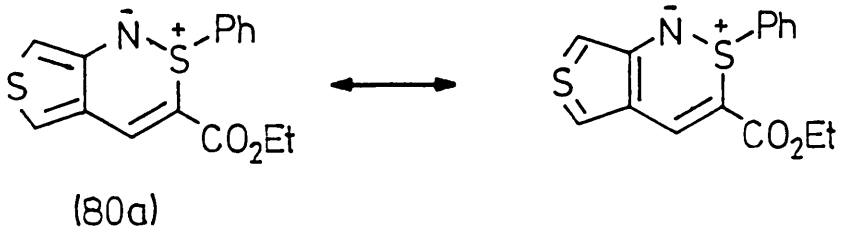
(85a) R=Ph 57%

(85b) R=Me 51%

(80a) 58%

Scheme 70

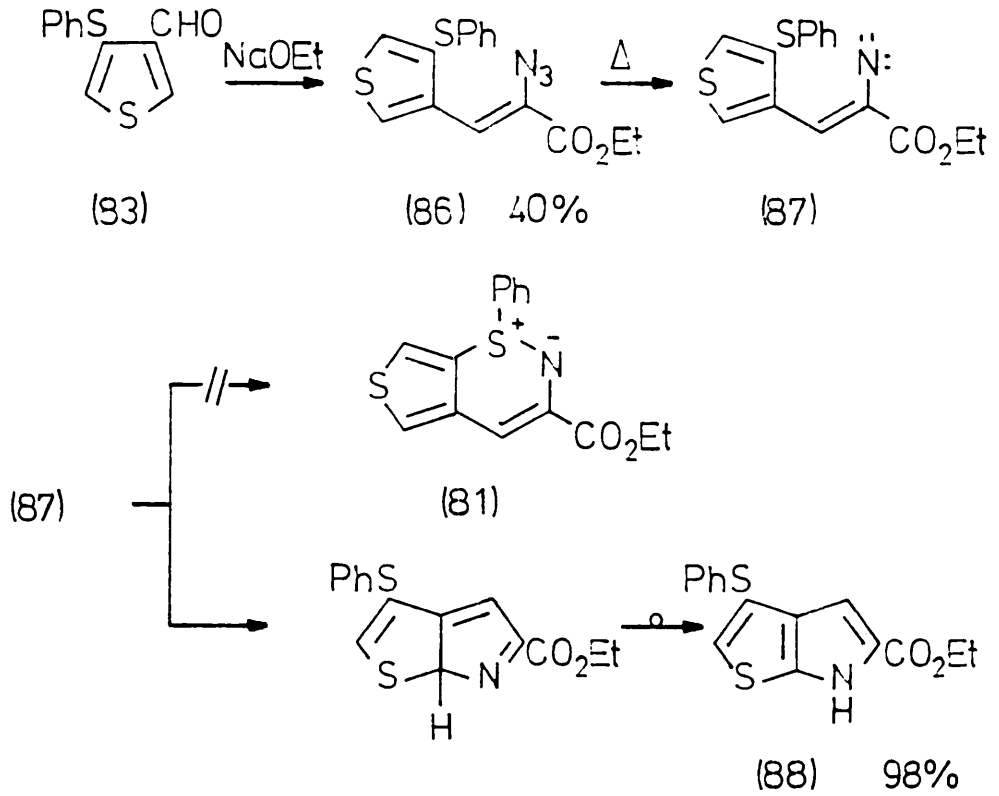
Indeed, the similarity between the data obtained for sulphimides (80a) and (26a) would confirm both to have cyclic ylidic structures rather than thiabenzene structures, - that is, a structure in which localised changes exist rather than a fully delocalised arrangement. This conclusion is based on the differences in bonding expected between the two systems. Due to "bond fixation" in the thiophen ring it is unlikely that (80a) would show much contribution from the resonance form shown in Scheme 71. If there was a major contribution from this form, then one would expect this to be reflected in the spectral properties of (80a). Since there is little difference between the data obtained for (80a) and the other thienothiazines one would conclude that there is no unusual bonding in the thiophen ring of (80a). For the same reason one would conclude that the bonding in the thiazine rings is similar which argues against a thiabenzene structure.



(80a)

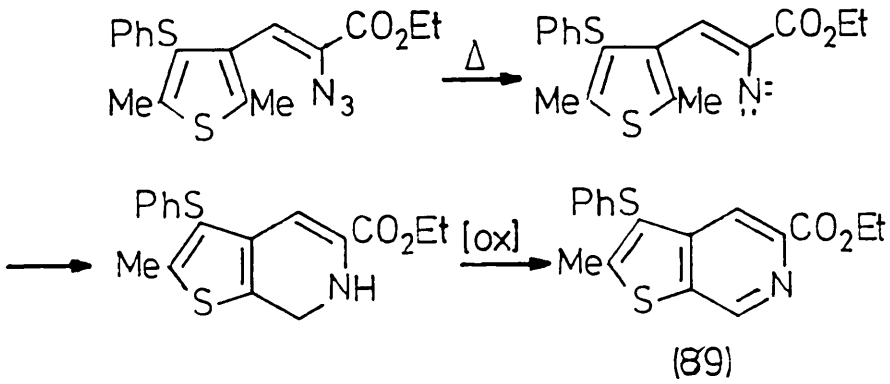
Scheme 71

Attempts to prepare the isomeric thiazine (81) were unsuccessful. The aldehyde (83) was treated with ethyl azidoacetate in basic ethanolic solution to give the desired azide (86) in 40% yield. However, thermolysis failed to produce the corresponding cyclic sulphimide. Instead, the thienopyrrole (88) was isolated in 98% yield; presumably this was formed by cyclisation of the nitrene intermediate (87) onto the 2- position of the thiophen ring (Scheme 72).



Scheme 72

Introduction of methyl groups into the 2- and 5- positions did not induce cyclisation onto sulphur to give the corresponding sulphimide. The product isolated was the thienopyridine (89), presumably arising from oxidation of the dihydro-intermediate formed by a nitrene insertion reaction (Scheme 73).

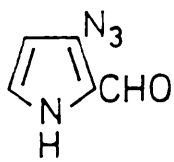


(89)

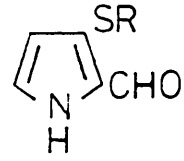
Scheme 73

2.1.3 Pyrrolothiazines

During an investigation into the generality of this method for the preparation of cyclic sulphimides, attention was turned to nitrogen heterocycles which could act as a stable aromatic ring onto which the thiazine system could be constructed. The pyrrole ring was the first to be considered, being a logical progression from thiophen. A search of the literature revealed that the necessary aldehydes (90) and (91) were not readily available.



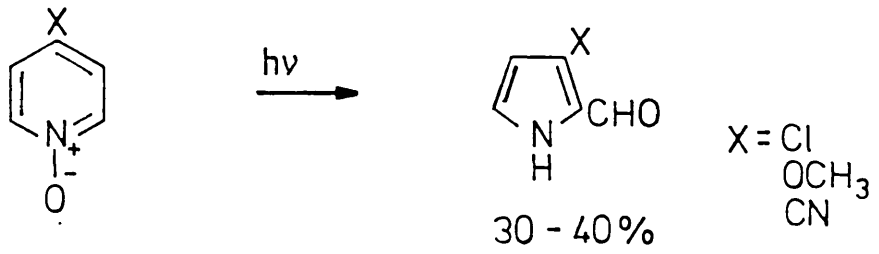
(90)



(91)

However, a report concerning the photochemical rearrangement of 4-substituted pyridine-N-oxides to give 3-substituted pyrrole-2-carbaldehydes was considered as a possible route to (90) and (91).[111]

4-Substituted pyridine-N-oxides are readily prepared in large quantities. Therefore, although the photolysis step proceeds in moderate yield, the overall process could be synthetically viable (Scheme 74).



Scheme 74

It is unlikely that 3-azidopyrrole-2-carbaldehyde could be synthesised directly by this route since azides are photolabile. However, 3-chloropyrrole-2-carbaldehyde was prepared in the hope that the chlorine atom could be displaced by azide ion.

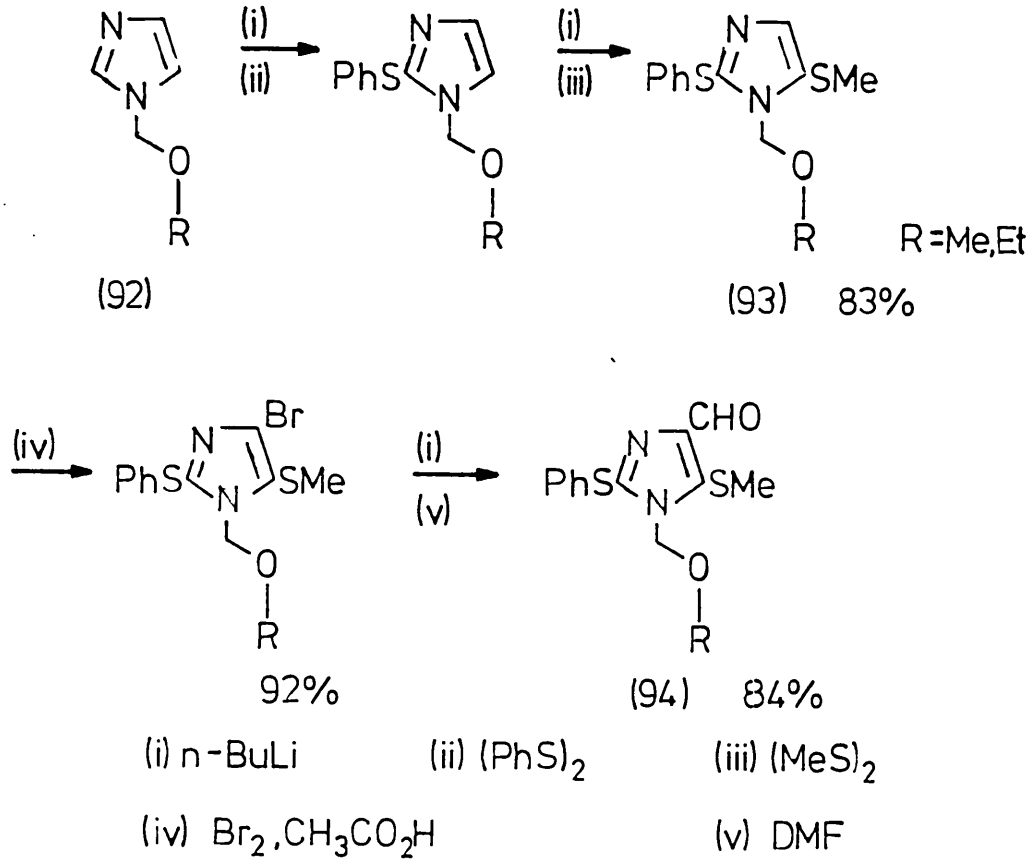
In contrast with the formation of 3-azidothiophen-2-carbaldehyde, however, it was not possible to displace the halogen atom using sodium azide in hexamethylphosphoramide solution.

Attempts to synthesise the aldehydes (91) were more successful. 4-Phenylthio- and 4-methylthio- pyridine-N-oxides[112] were prepared and although the 4-phenylthiopyridine-N-oxide failed to react on irradiation, 4-methylthiopyridine-N-oxide gave the corresponding 3-methylthiopyrrole-2-carbaldehyde. Unfortunately, the condensation of this aldehyde with ethyl azidoacetate proved unsuccessful. As ethyl azidoacetate does not form a particularly stabilised enolate anion, this

may contribute to the failure of the reaction. Also, limitations on the temperature and concentrations under which these reactions could be carried out without causing extensive decomposition of the ethyl azidoacetate, contributed to the failure of this reaction.

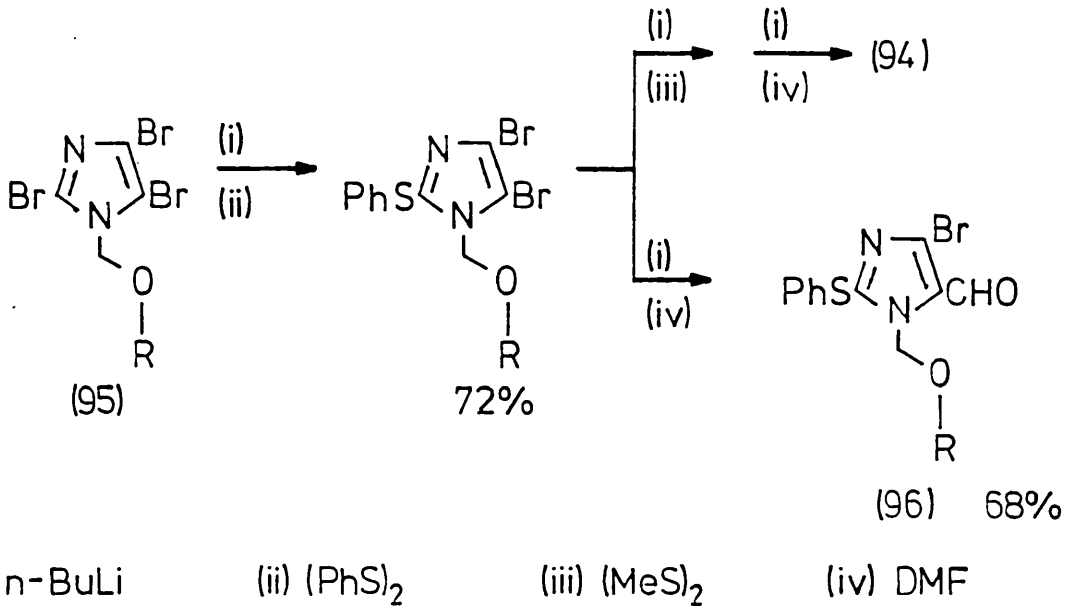
2.1.4 Imidazothiazines

In 1982 a synthesis of substituted imidazoles was published by Iddon et al[113,114] where the ethoxymethyl group was used to protect nitrogen. They had developed an idea of Breslow's[115] that either an N-ethoxymethyl or a N-methoxymethyl protecting group could be used to direct lithiation to the 2- and 5- positions. We repeated this work using the N-methoxymethyl protecting group for convenience; using this method, the N-protected imidazole (92) was lithiated in the 2- position. Quenching of the anion with diphenyl disulphide introduced a phenylthio group thus blocking this position. Further treatment with n-butyllithium generated the anion in the 5- position which was quenched with dimethyl disulphide to give the N-protected 2-phenylthio-5-methythioimidazole (93). Bromination of (93) occurs at the 4- position. Subsequent halogen-metal exchange and treatment with dimethylformamide gave the aldehyde (94) shown in Scheme 75. This aldehyde is a potential precursor for an imidazothiazine synthesis.



Scheme 75

An alternative route was also reported. Instead of lithiating the N-protected imidazole (92), the tribromo derivative (95) was used. This is readily available from imidazole by bromination followed by N-protection with either chloromethyl methyl ether or chloromethyl ethyl ether. Then by a similar process of repeated halogen metal exchanges and quenches with suitable electrophiles the aldehyde (94) was obtained. The aldehyde (96) was also obtained by this route (Scheme 76).[116]



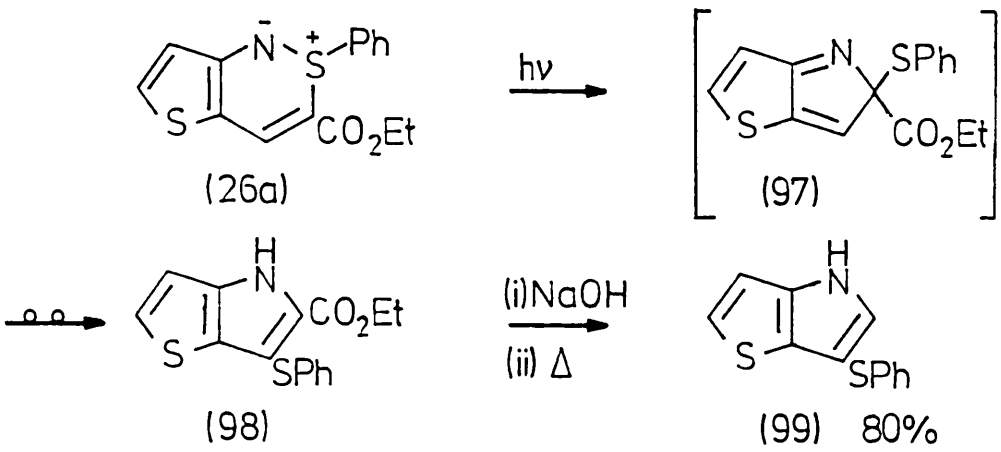
Scheme 76

It was hoped that treatment of (96) with sodium azide in hexamethylphosphoramide solution would afford the corresponding azide by displacement of the bromine atom. This was indeed the case. However, the reaction did not proceed to completion and, although this in itself was not a problem, separation from unreacted starting material proved difficult. Consequently, it was decided to continue the synthesis without further separation. Unfortunately, all attempts to condense the mixture of aldehydes with active methylene compounds in sodium ethoxide/ethanol solution failed, recovery of the aldehyde being low. Similarly attempts to react aldehyde (94) with ethyl azidoacetate were also unsuccessful. A possible explanation of this failure is that the nucleophilic base could be deprotecting the imidazoles. This would account for the low recovery of starting material. Due to these difficulties this investigation was subsequently abandoned.

2.2.1 Photochemistry of the Thieno [3,2c] [$1\lambda^4$,2] thiazines

Initial photochemical experiments, reported previously, had shown these new cyclic sulphimides to be photolabile.[69] When a solution of the thiazine (26a) in acetonitrile was irradiated at 350 nm, cleavage of the nitrogen-sulphur linkage occurred, presumably generating a

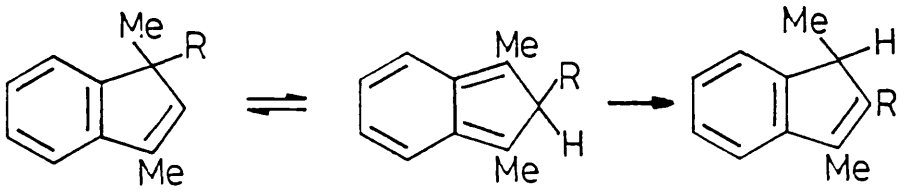
nitrene intermediate, followed by cyclisation to give the intermediate (97), which underwent further rearrangement to give the product (98). Confirmation of the structure of this product was obtained by hydrolysis of the ester and decarboxylation to give the thienopyrrole (99) which was identified by n.m.r.[69]



If this reaction pathway is correct, then it is interesting to note the exclusive migration of the phenylthio group in preference to the ester group. Further evidence to support the proposed reaction mechanism was gained from photolysis of the azide (68a) which is the sulphimide precursor, the product obtained again being the thienopyrrole (98).

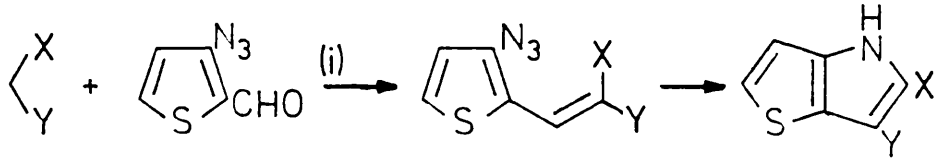
We were curious about the nature of this rearrangement reaction and had noted with interest the work of Jones et al,[117-122] describing detailed studies of the migratory aptitudes of various substituent groups in related carbocyclic systems. The 1H-indene (100), when heated, may isomerise to the 2H-indene (101) by migration of the R group. If the R group migrates faster than hydrogen then the 1H-indene is reformed. However, if hydrogen is the faster migrator, then the 1H-indene (102) is obtained. If (100) is prepared in an optically active form, then the migration of the R group to the symmetrical 2H-indene will destroy this

optical activity. By studying the rate of racemisation of the starting material and observing the products formed, an order of migratory aptitude for a series of substituents was obtained.[118] The order of increasing migratory aptitude was found to be: alkyl $<$ -C≡CH $<$ -CN $<$ $-CO_2Me$ $<$ $-CO_2Ph$ $<$ -CO-NHMe $<$ vinyl $<$ H $<$ $-COCH_3$ $<$ -COPh $<$ -CHO. Thus, if as has been suggested, the photolysis of cyclic sulphimides produces thienopyrroles via the proposed intermediate (97), then a similar order of migratory aptitude could be derived.



(100) (101) (102)

In order to establish whether the general trend of migratory aptitude observed for the indene derivatives also applied to the photolysis of the sulphimides and their precursor azides, the azides shown in Scheme 77 were prepared and photolysed.



X= CO_2Et , Y= $COCH_3$ (i) NaOEt (103)

= $COCH_3$, = H (i) NaOH (104)

Scheme 77

From the n.O.e. difference experiments, shown in Figures 3 and 4, the structures of the products could be assigned. Presaturation of the NH produced an enhancement of the nearest group thus establishing the substitution pattern of the thienopyrroles.

Our results show that migration of an acetyl group is faster than an ethoxycarbonyl group. However, migration of a hydrogen atom appears to be faster than an acetyl group. The latter observation is not consistent with the findings of Jones.[118] This difference in the order of migratory aptitudes can be rationalised if one considers the process by which the thienopyrrole is formed.

When the azide (105) is photolysed the intermediate (106) is formed. Then if neither R^1 nor R^2 are hydrogen a [1,5] shift of one of the substituents may occur. Work on 2H-pyrroles has shown that migration is from carbon to carbon, the substituent only moving to nitrogen if all other positions are blocked.[123] The rearrangement product (107) can then undergo further rearrangement. Thermally this can be either by a [1,5] shift of R^1 or by a [1,5] shift of hydrogen. The former process would only regenerate (106).

However, the latter process would generate the intermediate (108) which could rearrange by a rapid irreversible [1,5] hydrogen shift from carbon to nitrogen. Alternatively, the rearrangement product (107) could isomerise by a photochemically allowed [1,3] hydrogen shift. This process may be more favourable as this does not involve disruption of the aromatic thiophen ring (Scheme 78).

In the case of acetyl versus hydrogen, the initial intermediate which is formed can undergo the same process. However, a [1,5] hydrogen shift from carbon to nitrogen would lead directly to the thienopyrrole. Therefore it seems likely that the observed product is derived from this latter process.

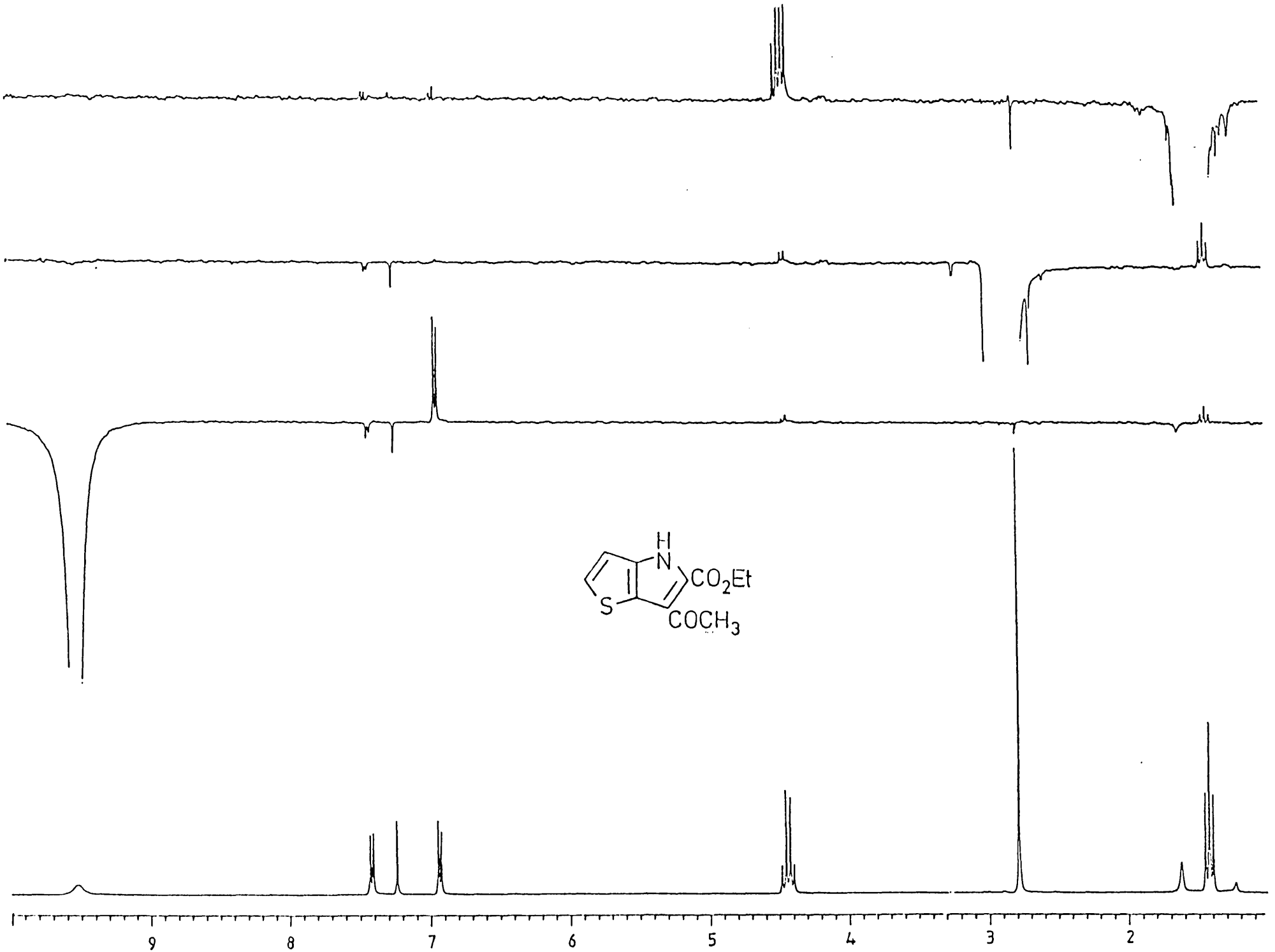


FIGURE 3.

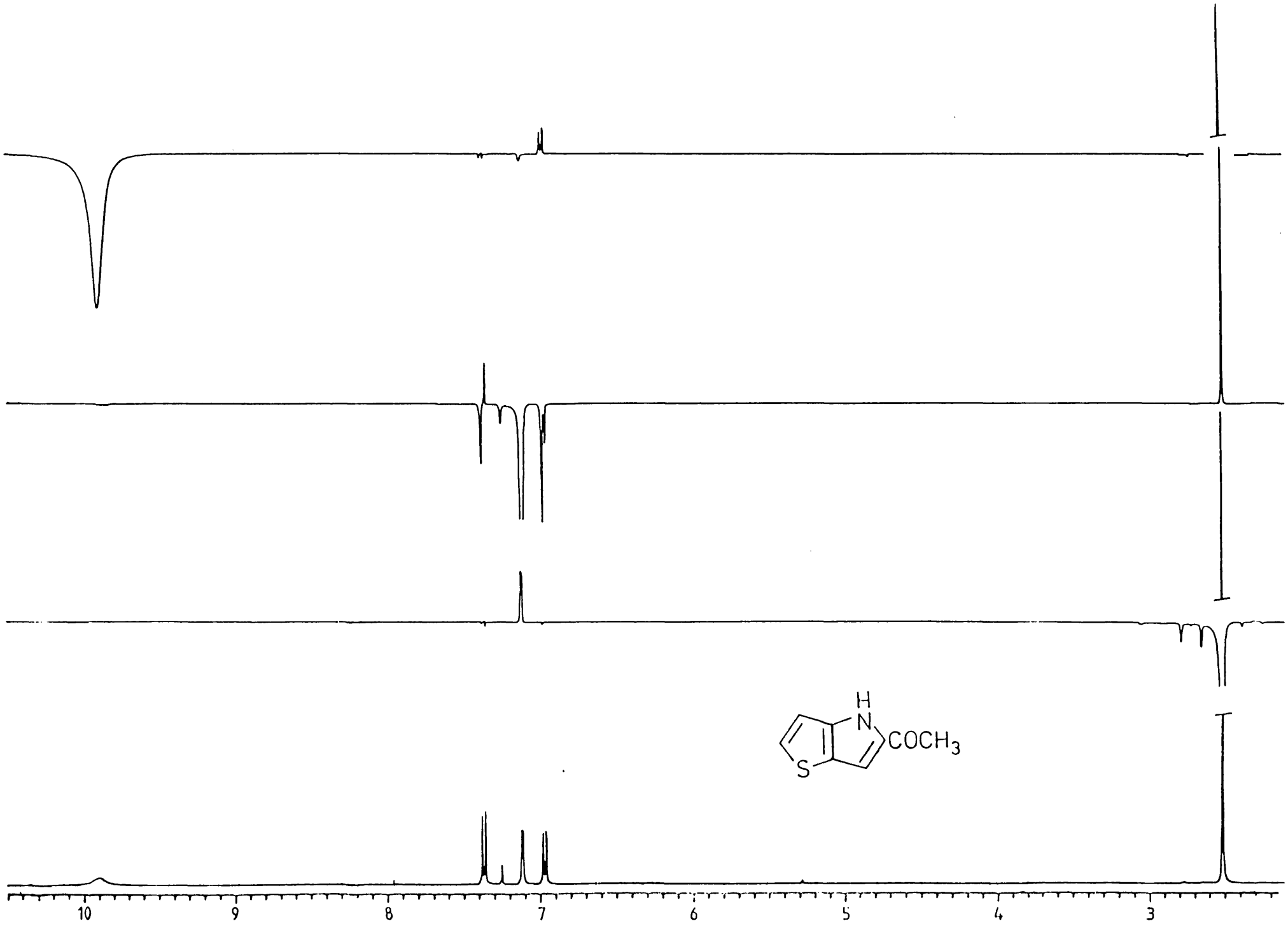
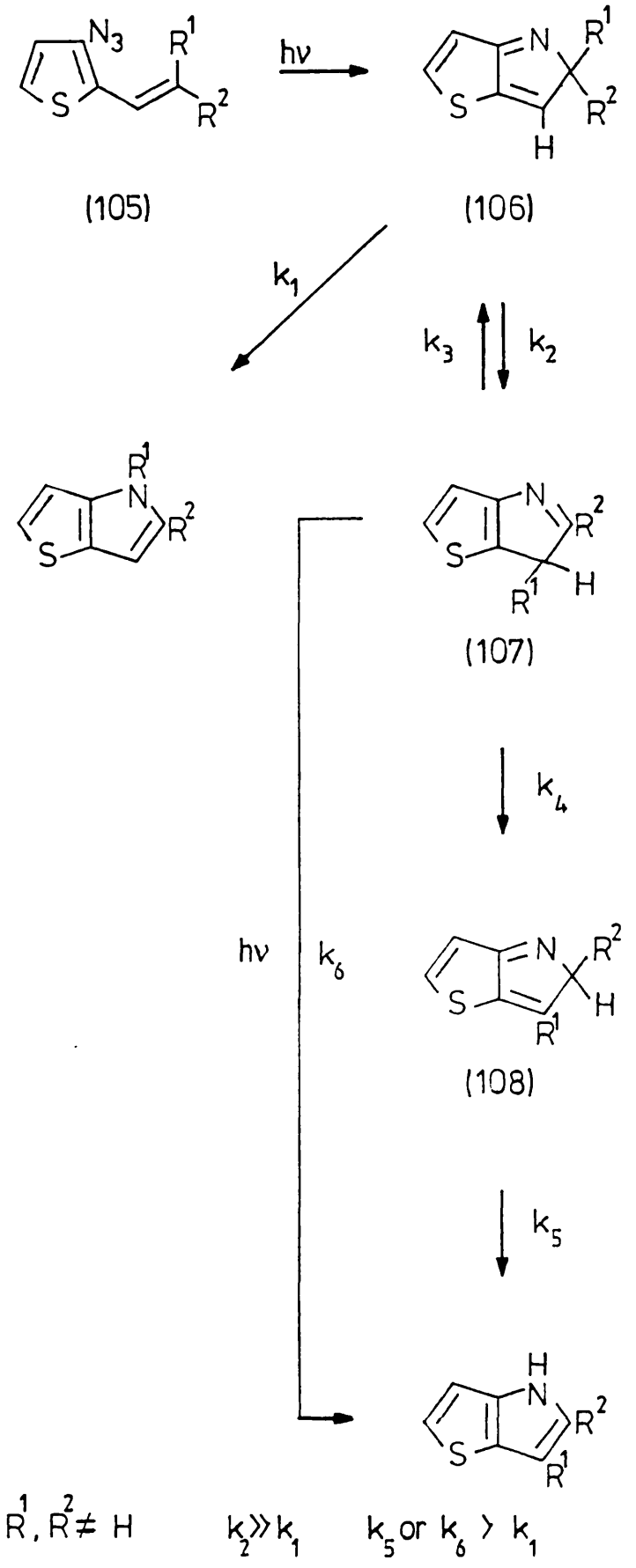
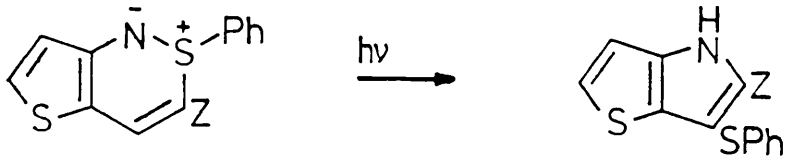


FIGURE 4.



Scheme 78

With the exception of hydrogen, the relative rates of migration are similar to those found by Jones in his studies of 1H-indenes. From our observations, the rate of migration of sulphur substituents was faster than an ester group. The ester group is not a fast migrator by comparison with acetyl or formyl groups,[124] and therefore the thiazines (26c) and (26d) were photolysed and the products isolated.



(26c) Z= $COCH_3$ 77% (109)

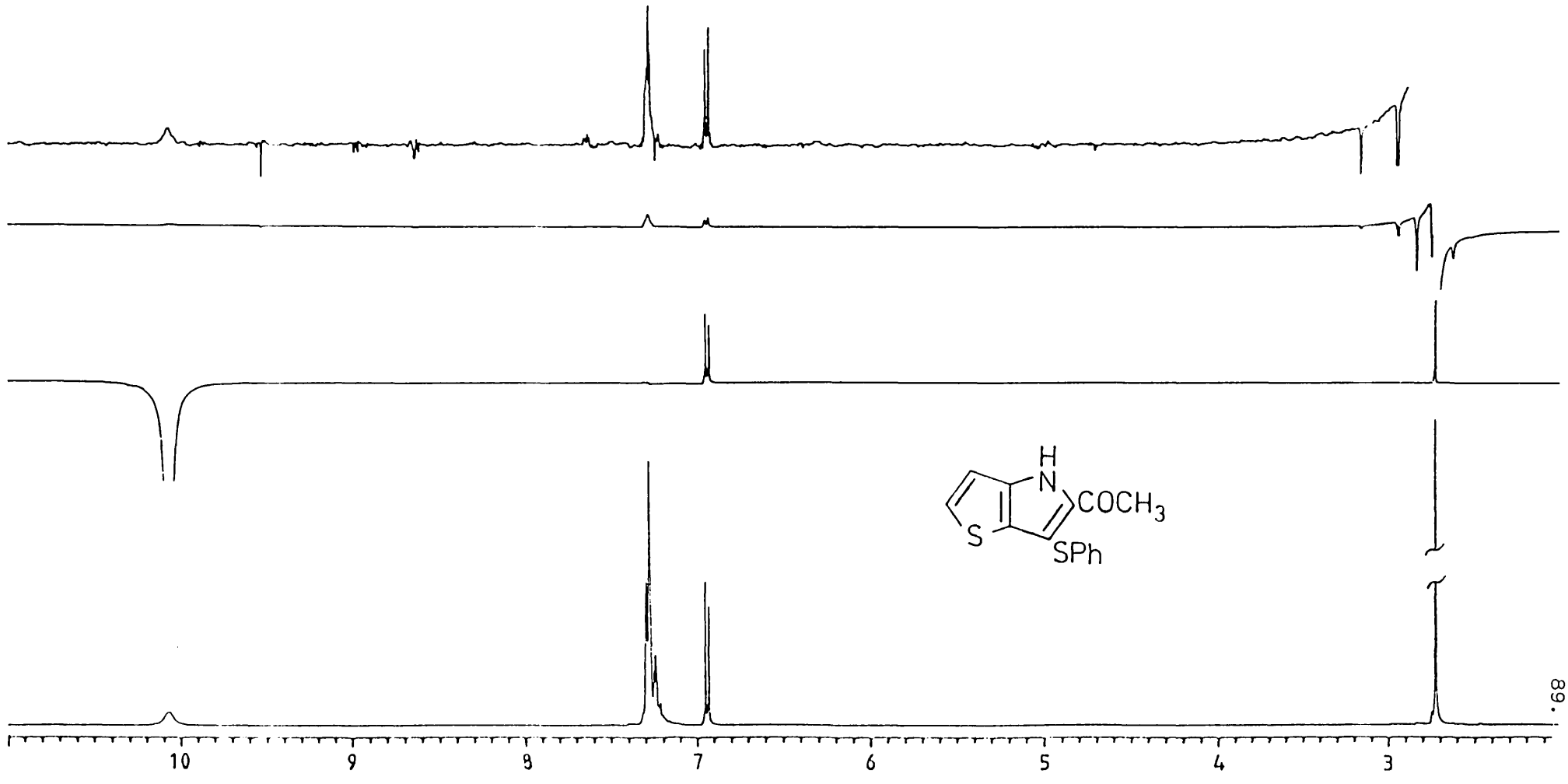
(26d) = CHO 75% (110)

As before only one thienopyrrole was obtained from each reaction. The structures (109) and (110) were confirmed as before by n.O.e. difference experiments. In the case of (110), it was necessary to N-methylate the product since the NH and formyl proton signals were coincident. The results are shown in Figures 5 and 6.

Again exclusive migration of the sulphur group was observed, even in the case of the sulphur group versus the formyl group. It had been expected that in this last example the other regioisomer might have been isolated since, in the indene series, the formyl group is such an extremely fast migrator.[118,122]

One explanation of this apparently very fast migration of the sulphur group is that this is not a true sigmatropic process. The mechanism shown in Scheme 79 makes use of the lone pair on sulphur to effect the migration via the three membered ring intermediate (111).

FIGURE 5.



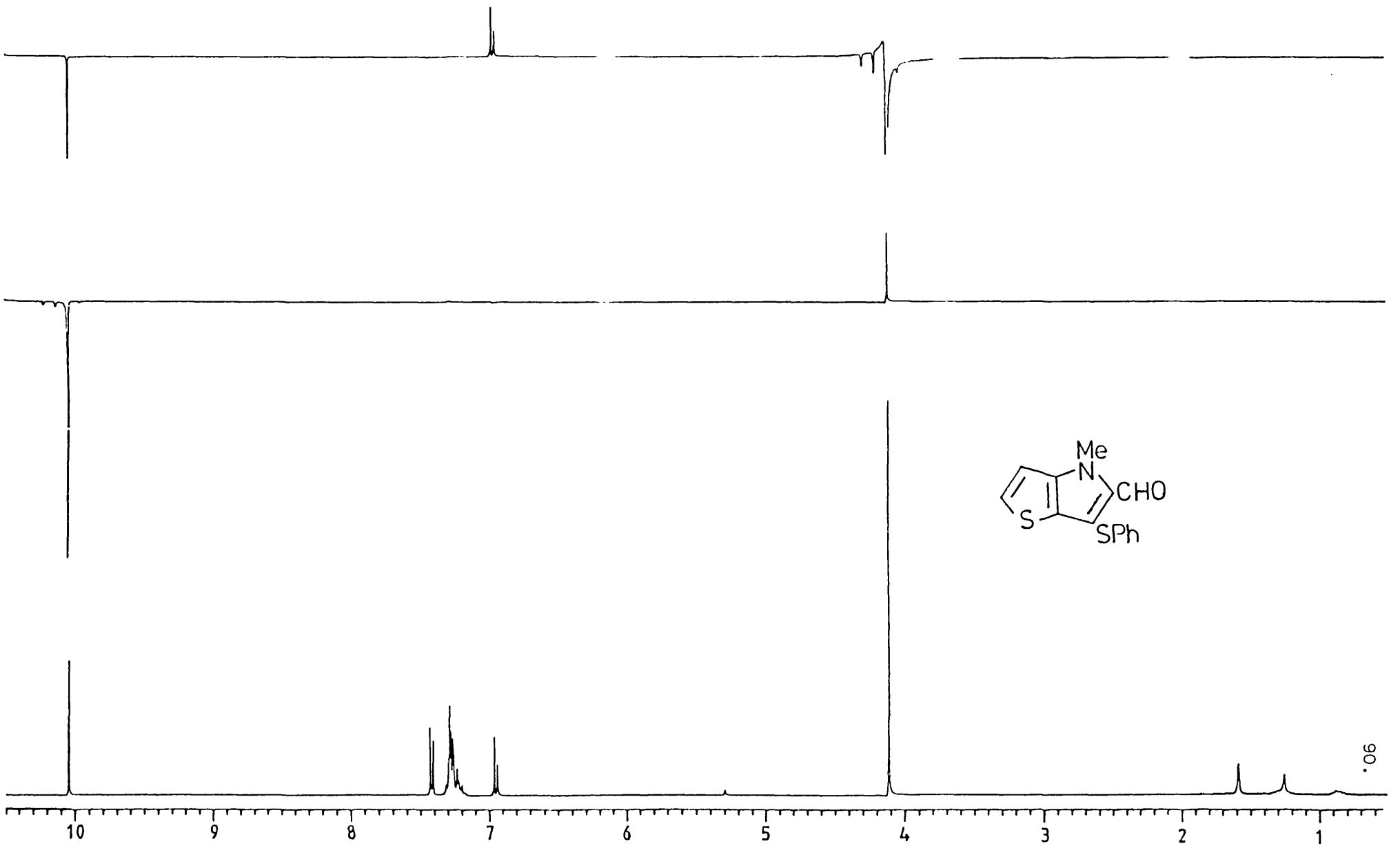
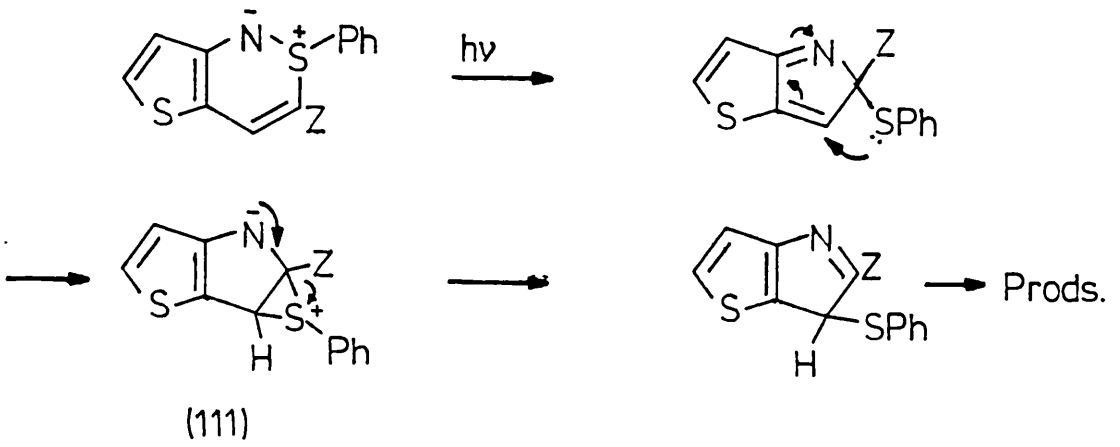


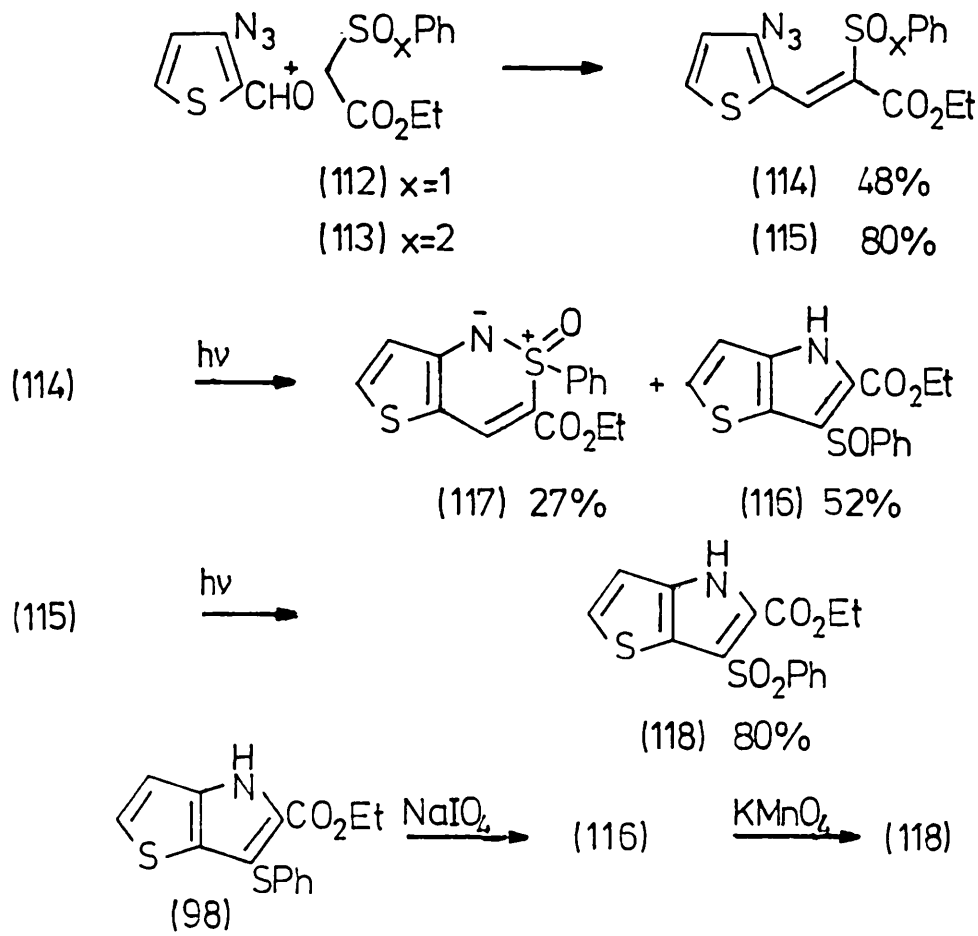
FIGURE 6.



(111)

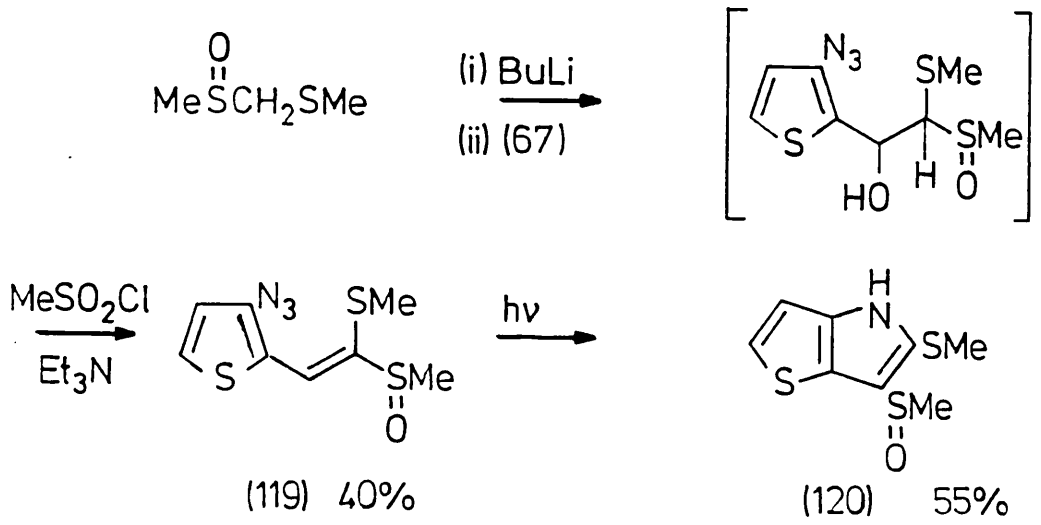
Scheme 79

To verify this mechanism it was necessary to demonstrate the effect of participation of the lone pair on sulphur, for example, by inhibiting this participation. Therefore the sulphoxide (114) and the sulphone (115) were synthesised from 3-azidothiophen-2-carbaldehyde and the enolates derived from ethyl phenylsulphinylacetate (112)[125] and ethyl phenylsulphonylacetate (113).[126] Increasing the oxidation level of the sulphur atom reduces the nucleophilicity. From the photolysis of these azides, thienopyrroles were isolated, along with a smaller amount of sulphoximide (117) obtained from the photolysis of (114). Confirmation of the structures of (116) and (118) was obtained by oxidation of the known thienopyrrole (98). Mono-oxidation was achieved by treatment of (98) with sodium metaperiodate. Then the resultant sulphoxide was treated with acidified potassium permanganate to obtain complete oxidation to the sulphone (Scheme 80). The sulphoxide and sulphone prepared by this route were identical with those isolated from the photolysis experiments.



Scheme 80

From these results it would seem that oxidation of the sulphur had little effect on the rate of migration. As a final test of the effect of oxidation levels on sulphur, an example was required in which two sulphur substituents of differing oxidation levels were competing. It was found that when the anion generated from methyl methylsulphinylmethyl sulphide and n-butyllithium was reacted with 3-azidothiophen-2-carbaldehyde (67), the corresponding alcohol was obtained. If this was then treated in situ with methanesulphonyl chloride and triethylamine the azide (119) resulted (Scheme 81).



Scheme 81

Photolysis of (119) again resulted in the formation of only one thienopyrrole (120). The structure, as assigned, shows exclusive migration of the methylsulphinyl group. As before, this assignment was made from n.O.e. difference experiments, shown in Figure 7. Presaturation of the N-H resonance resulted in an enhancement of the methyl signal of the methylthio group. No enhancement of the methylsulphinyl group was observed. Presaturation of the methyl signals in turn, confirmed these to be adjacent with only the methylthio group causing an enhancement of the N-H. From these observations it was apparent that, in our system, the methylsulphinyl group is a faster migrator than the methylthio group.

The fast migration of hydrogen in comparison with an acetyl group has already been discussed. Therefore, since sulphur groups appear to undergo fast carbon to carbon migration then the results of experiments involving competing hydrogen and sulphur substituent migrations are of some importance.

The synthesis of a suitable azide of the type (123) proved difficult. Initially, the reaction of the anion of thioanisole,

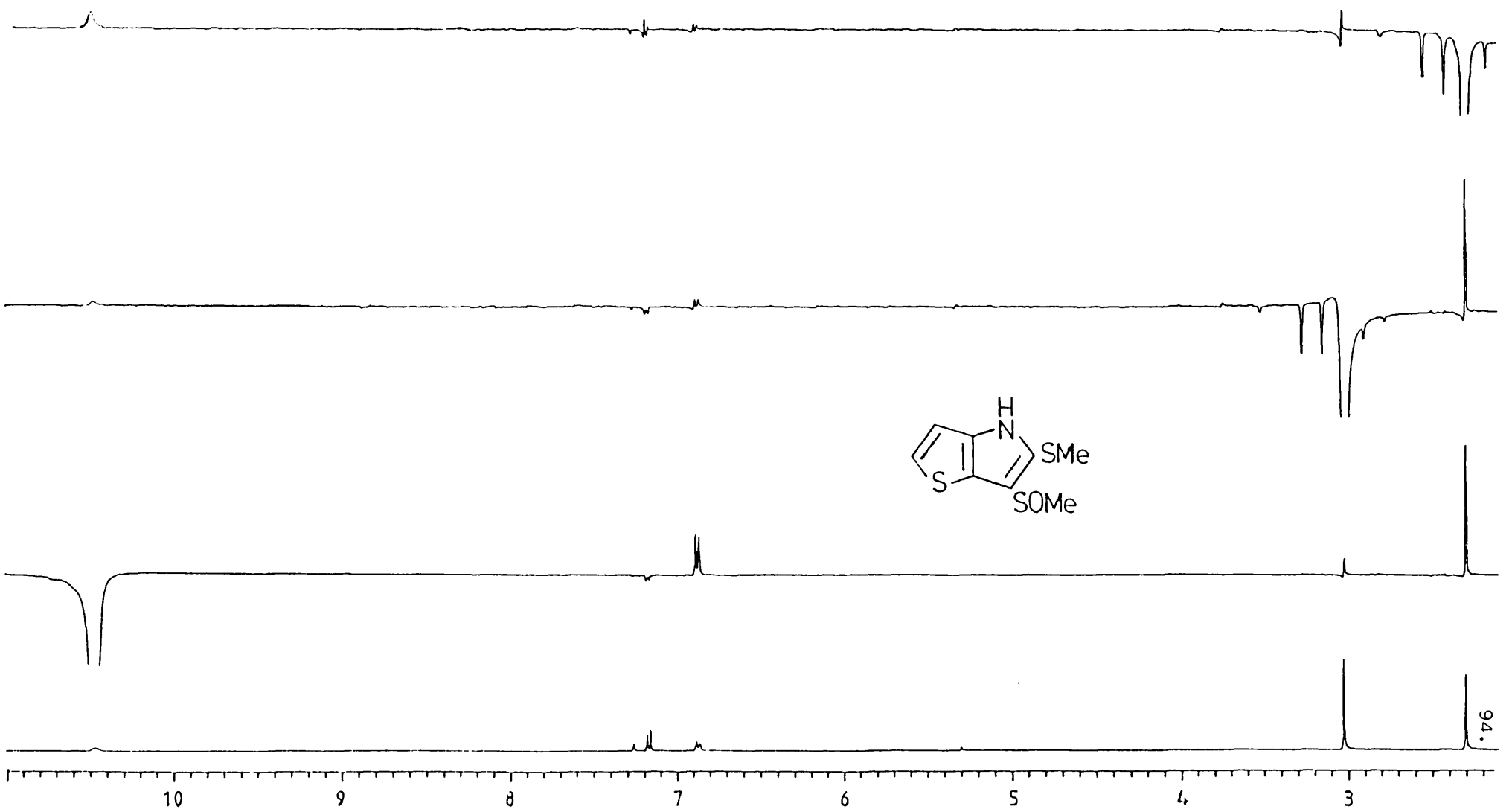
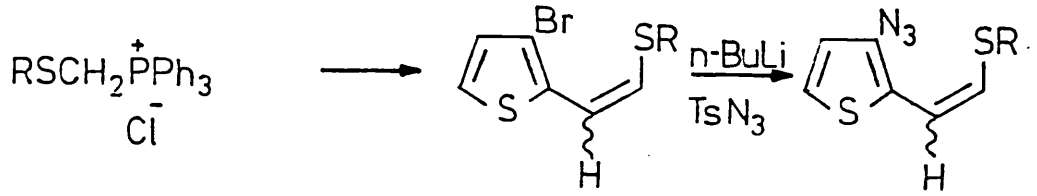


FIGURE 7.

generated by treatment of thioanisole with n-butyllithium, with 3-azidothiophen-2-carbaldehyde (67) was attempted. This failed to give the desired product, probably due to reaction of the anion with the azido function of (67). Then the use of a Wittig reaction was considered. The reaction was repeated using phenylthiomethyl-thiphenylphosphonium chloride[127] in place of thioanisole. Again this reaction failed. This failure of (67) to undergo Wittig reactions has also been noted by Gronowitz et al.[128] However, it was found that the Wittig reagent (121a) would react with 3-bromothiophen-2-carbaldehyde to give the corresponding vinyl compound (122a). Subsequently, this product could be converted into the azide (123a) by treatment with n-butyllithium at -78°C and reaction of the resulting anion with tosyl azide (Scheme 82).

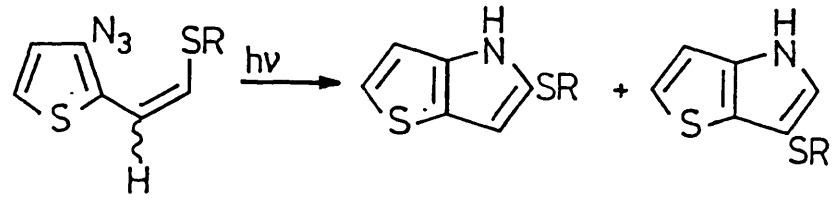


R=Ph (121a) (122a) (123a)
R=Me (121b) (122b) (123b)

Scheme 82

Although (123a) could be prepared, difficulties were encountered in purifying the product; because of this it was not possible to achieve its complete characterisation. However, photolysis of the impure material was attempted. For the first time two thienopyrroles were isolated from this reaction, these having the structures (124) and (99). Although these were isolated in approximately a 1:1 ratio, this

result is viewed with caution since the starting materials were impure.



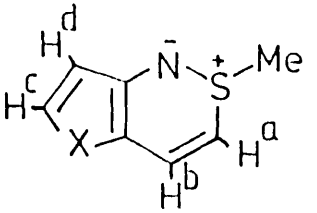
R=Ph	(123a)	(124)	(99)
R=Me	(123b)	(125)	(126)

The series was repeated with R=Me in the hope of improving separation of the products. This proved successful, (122b) and (123b) being obtained in a pure state together with some separation of the cis and trans isomers.

Photolysis of either cis or trans azide (123b) gave the same result. The thienopyrroles (125) and (126) were isolated in a 1:1 ratio. The material recovered accounted for only 40% of the reaction mixture. T.l.c. showed only the two products and dark baseline material.

This result was indeed significant, since if the assumed mechanism for the reaction is correct, then the rate of migration of the sulphur substituent must be faster than the rate of migration of a hydrogen atom from carbon to nitrogen. Photolysis of the corresponding thienothiazine (127) would be expected to give the same results. However, thermolysis of (123b) failed to give appreciable yields of the cyclic sulphimide. Since there is no electron withdrawing group present to stabilise the sulphimide it can only be assumed that the thienothiazine was not sufficiently stable to the harsh reaction conditions. The thienopyrroles (125) and (126) were isolated as the main products along with traces of a polar component. This was assigned as the thiazine (127). As can be seen from the data in Table 4, the ^{1}H n.m.r. of (127), shows

TABLE 4. ^{1}H n.mr. Data of Thiazines (127) and (22)

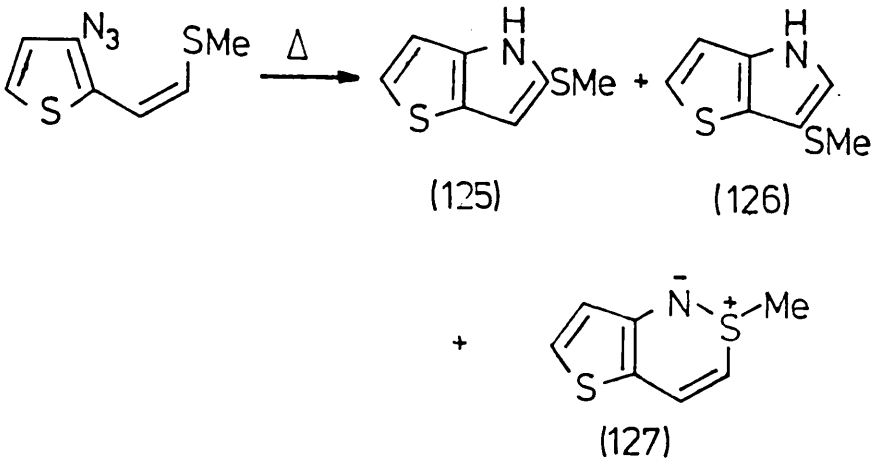


(22) X = CH=CH

(127) = S

	^{1}H n.m.r. (127)	^{1}H n.m.r. (22)
Me	2.20 (3H,s)	2.20 (3H,s)
H^a	4.99 (1H,d,J8.5Hz)	5.70 (1H,d)
H^d	6.82 (1H,dd,J5.5Hz and J0.7Hz)	)
H^b	7.2 (1H,dd,J8.5Hz and J0.7Hz)	) 6.75 - 7.45 (5H,m)
H^c	7.37 (1H,d,J5.5Hz)	)

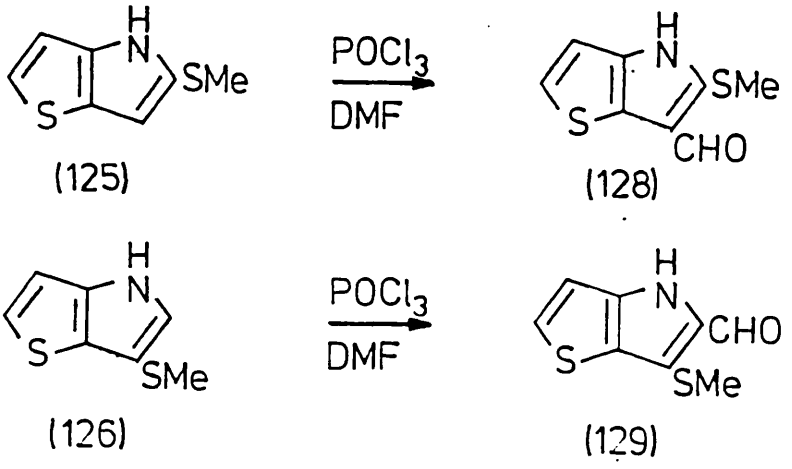
similarity with the data reported for the azathianaphthalene (22).[68]



(125) (126)

(127)

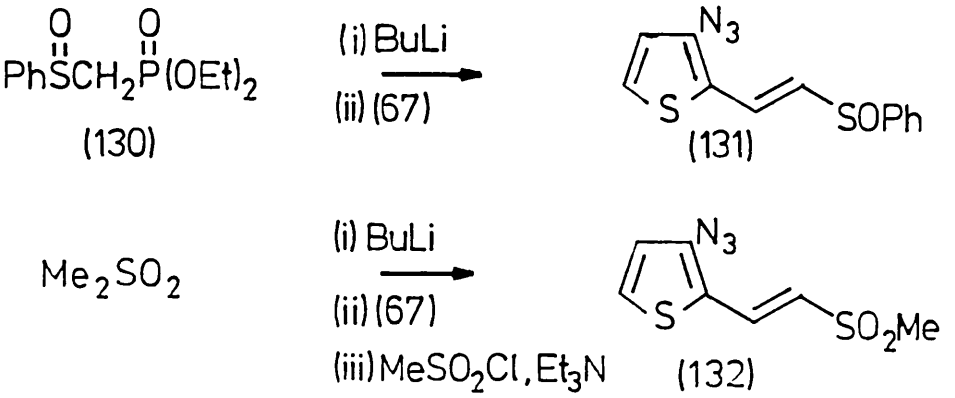
Our failure to isolate both possible thienopyrrole isomers from the earlier photolysis reactions, had been of some concern until two thienopyrroles were obtained from the photolysis of azides (122 a,b). There had always been a possibility that the unobserved isomer had indeed been formed but that it had been unstable to the reaction conditions or the work up procedure. With this in mind it was decided to attempt the formylation of the thienopyrroles (125) and (126) so that, in this case, we would have specimens of both possible rearrangement products available. This was achieved by treating a solution of either thienopyrrole in dry dimethylformamide with a slight excess of phosphoryl chloride (Scheme 83). The formylated products (128) and (129) were then shown to be stable to the photolysis conditions and the work up procedure used for these reactions.



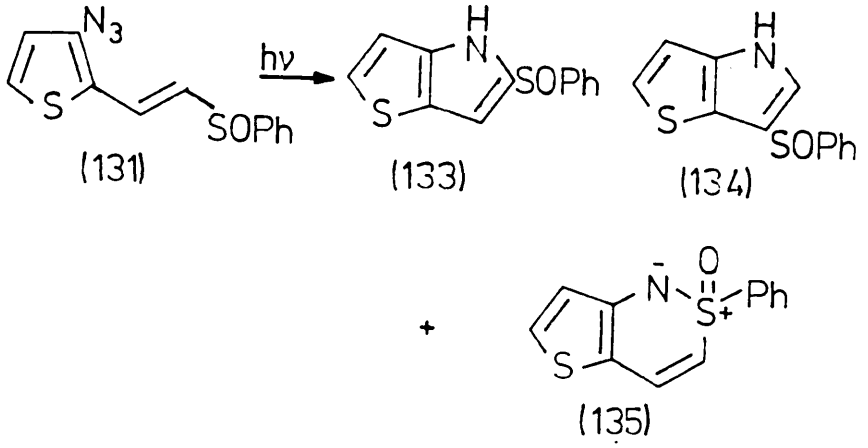
Scheme 83

From earlier experiments, it had been shown that the effect of oxidation level on sulphur group migrations was not as expected. The methylsulphinyl group was shown to migrate faster than the methylthio group. Therefore, the azides (131) and (132) were prepared in order to compare any effects the oxidation level may have on the outcome of the subsequent rearrangements of the initial photolysis products.

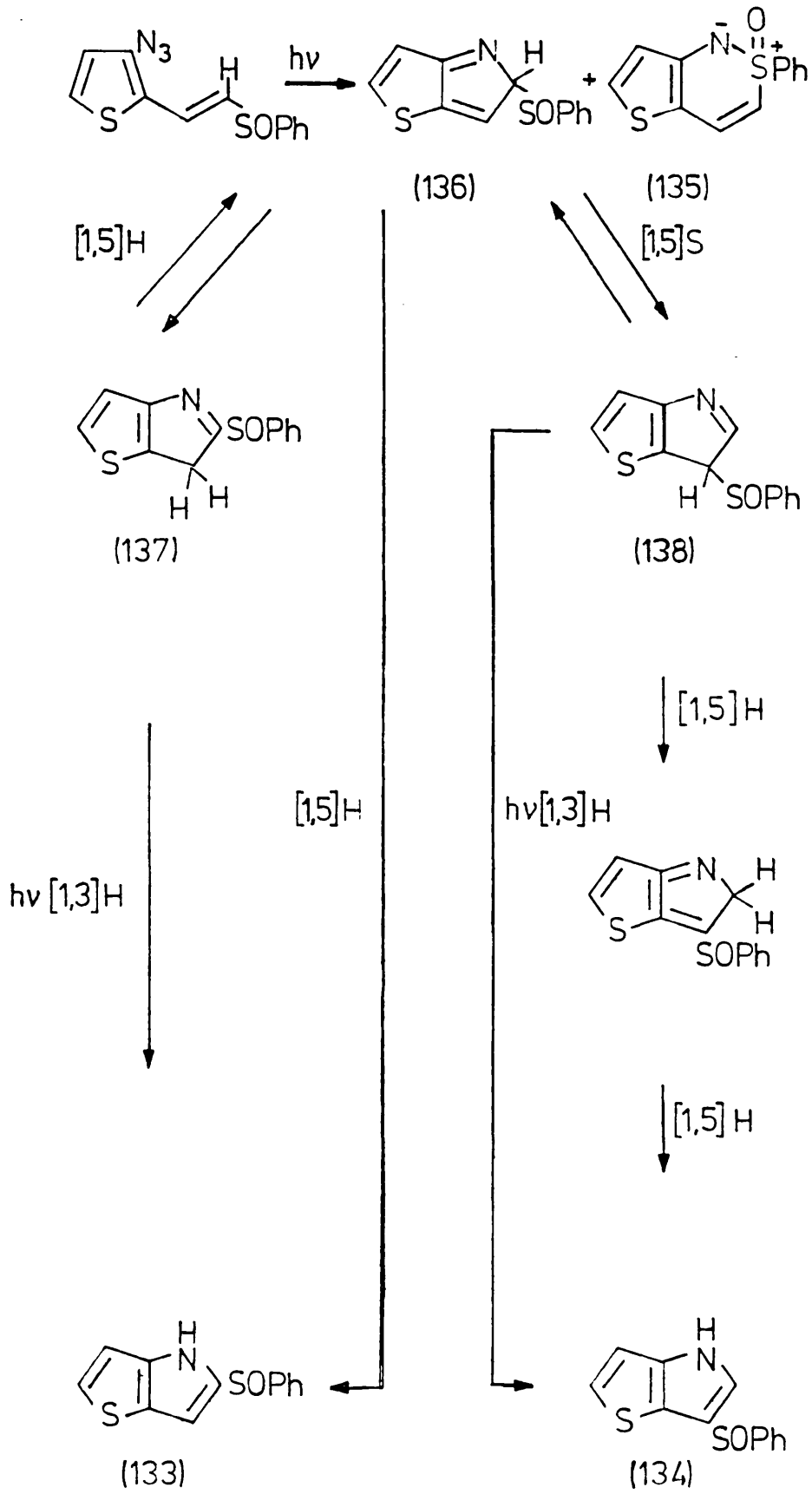
The azide (131) was obtained directly from 3-azidothiophen-2-carbaldehyde (67) by reaction with the anion generated by deprotonation of diethyl phenylsulphinylmethylphosphonate (130).[129] Reaction of (67) with the anion formed from dimethyl sulfone and n-butyllithium followed by treatment of the resulting alcohol with methanesulphonyl-chloride and triethylamine gave the vinyl sulphone (132).



Photolysis of the azide (131) gave two thienopyrroles (133) and (134), plus a small amount of the sulphoximide (135). The ratio of the yields of the thienopyrroles was approximately 2:1 for the products (134):(133).



This supports the previous observation that sulphinyl groups migrate faster than sulphenyl groups. Furthermore this observation may provide evidence concerning the proposed mechanism. Of the possible pathways shown in Scheme 84, it is likely that (133) was formed from (136) by a [1,5] hydrogen shift from carbon to nitrogen.



Scheme 84

The pathway by which (134) is formed, however, is less clear. Presumably the initial step must be a [1,5] shift of the sulphur group from carbon to carbon resulting in the aromatisation of the thiophen ring and generation of the intermediate (138). This intermediate may then undergo further rearrangement. If, as assumed from previous experiments, the sulphinyl group is a faster migrator than the sulphenyl group then it is probable that the product is derived from a photochemical [1,3] hydrogen shift. The reason the series of [1,5] hydrogen shifts can be discounted is as follows. For the case of the sulphenyl group, a 1:1 product ratio was observed. If the products are derived only from a series of [1,5] shifts, it must be assumed that the substituents are moving rapidly from carbon to carbon, and therefore that the product ratio is a result of the pathways by which a hydrogen atom migrates to nitrogen. Since the sulphinyl group migrates faster than the sulphenyl group this means that it must be moving faster from carbon to carbon. This should not affect the product ratio. However, if when either of the intermediates (137) or (138) is formed, the reverse reaction was disfavoured due to the aromaticity now present in the thiophen ring and that the products (133) and (134) were then derived by photochemical [1,3] shifts then an effect on the product ratio would be observed.

In contrast, photolysis of (132) gave a single product. From the n.O.e. difference experiments shown in Figure 8, the structure was assigned as the thienopyrrole (139). Presaturation of the N-H signal resulted in an enhancement of the methylsulphonyl group. Similarily presaturation of the methylsulphonyl group signal resulted in an enhancement of the N-H signal and the C-H signal. Exclusive migration of hydrogen was observed. Therefore, further increasing the oxidation level of the sulphur had decreased the migratory aptitude. Since the

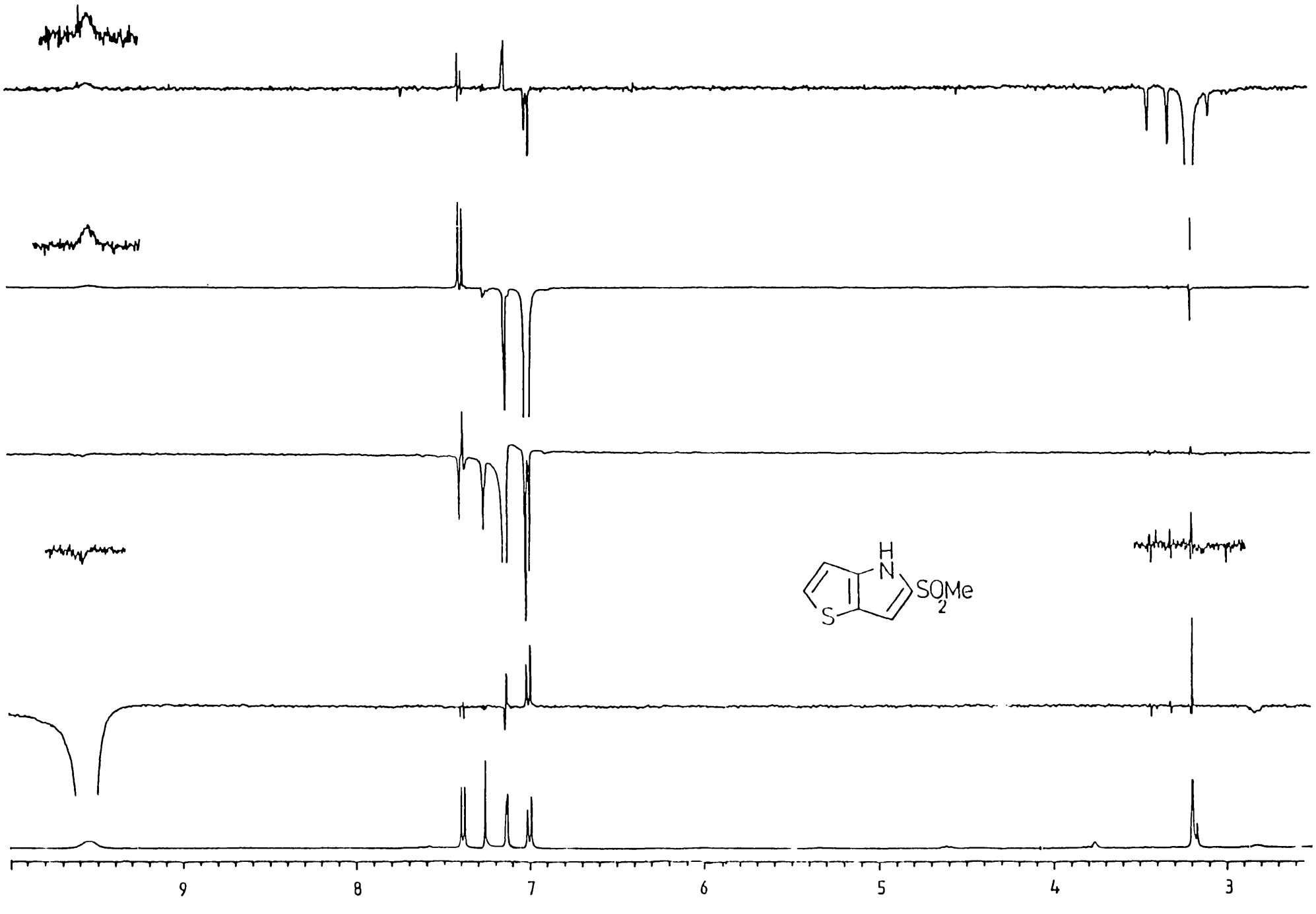
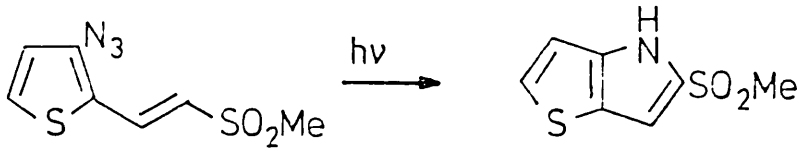


FIGURE 8.

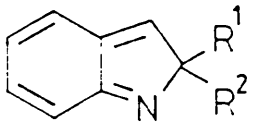
sulphonyl group is tetrahedral, this may lead to greater steric restrictions on the migration process. As the [1,5] hydrogen shift from carbon to nitrogen to aromatise the system must be a very rapid process, any slight change in the rate of migration of the sulphur group for steric or other reasons could be enough to cause exclusive hydrogen migration.



(132) (139)

2.2.2 Photochemistry of the Benzothiazines

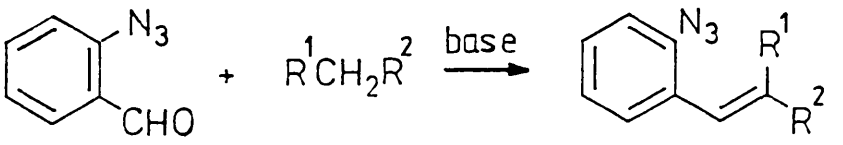
The photochemical reactions of the thienothiazines and azidothiophens to give thienopyrroles had revealed an interesting trend in migratory aptitudes of substituent groups, which showed some analogies to those discovered in the indene series.[118] Since there are significant differences between the systems being compared, a brief study of the related 2H-indole system (140) was undertaken.



(140)

o-Azidobenzaldehyde (141) is readily available by a literature procedure from o-nitrobenzaldehyde.[101]

Using the appropriate conditions, outlined in Scheme 85, (141) underwent condensation with the enolates derived from ethyl acetoacetate, acetaldehyde and ethyl phenythioacetate to give the azides (142-144).

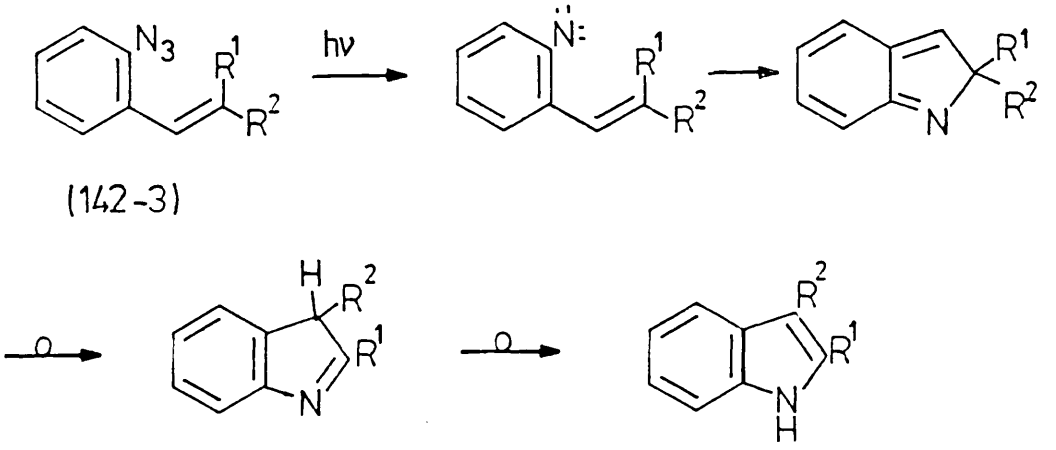


(141) (142-4)

R^1	R^2	base		%
$CO_2C_2H_5$	$COCH_3$	$NaOC_2H_5$	142	80
H	CHO	KOH	143	78
SPh	$CO_2C_2H_5$	$NaOC_2H_5$	144	86

Scheme 85

Irradiation of the azide (142) afforded the indole (145)[130] as the sole product. Similarly, the indole (146)[131] was formed exclusively on irradiation of the azide (143). Presumably the mechanism of the reaction is as shown in Scheme 86 and involves cyclisation of the initially formed nitrene to give a 2H-indole which then undergoes further rearrangement to the observed products.

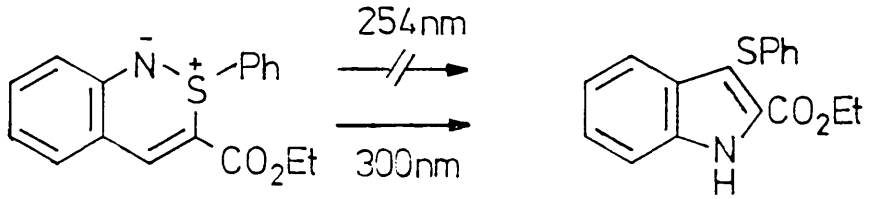


(142-3) (145-6)

	R^1	R^2	%	
(142)	CO_2Et	$COCH_3$	88	(145)
(143)	CHO	H	90	(146)

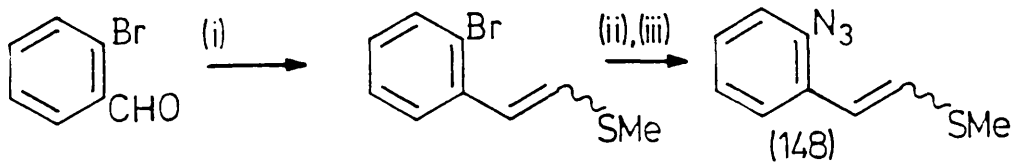
Scheme 86

Previously, work with the benzothiazine (25) had shown it to be stable to irradiation at 254 nm.[97] From the u.v. spectrum of (25) a strong absorbtion was noted in this region and although irradiation at the wavelength of strongest absorbtion normally results in the breaking of the sulphur-nitrogen bond, this did not happen. However, when thiazine (25) was irradiated at 300 nm rearrangement was induced and the indole (147) was obtained in 75% yield as the sole product. From n.O.e. experiments, it was not possible to make a definite assignment of the structure. It was thought that the phenylthio group could be removed to give a known indole and so prove the structure. However, treatment of indole (147) with Raney nickel failed to effect any change. Similarly, treatment of (147) with nickel boride[132] also failed to produce any change. Finally an X-ray diffraction analysis was performed and the structure (147) was confirmed (Figure 9.)



(25) (147)

As a final experiment in the benzenoid series the azide (148) a 1:1 mixture of cis and trans isomers was prepared via a Wittig reaction between o-bromobenzaldehyde and triphenylphosphonium methylthiomethylide followed by halogen-metal exchange and quenching of the resultant anion with tosyl azide (Scheme 87.)



(i) $Ph_3P{=}CHSMe$ (ii) n-BuLi (iii) TsN_3

Scheme 87

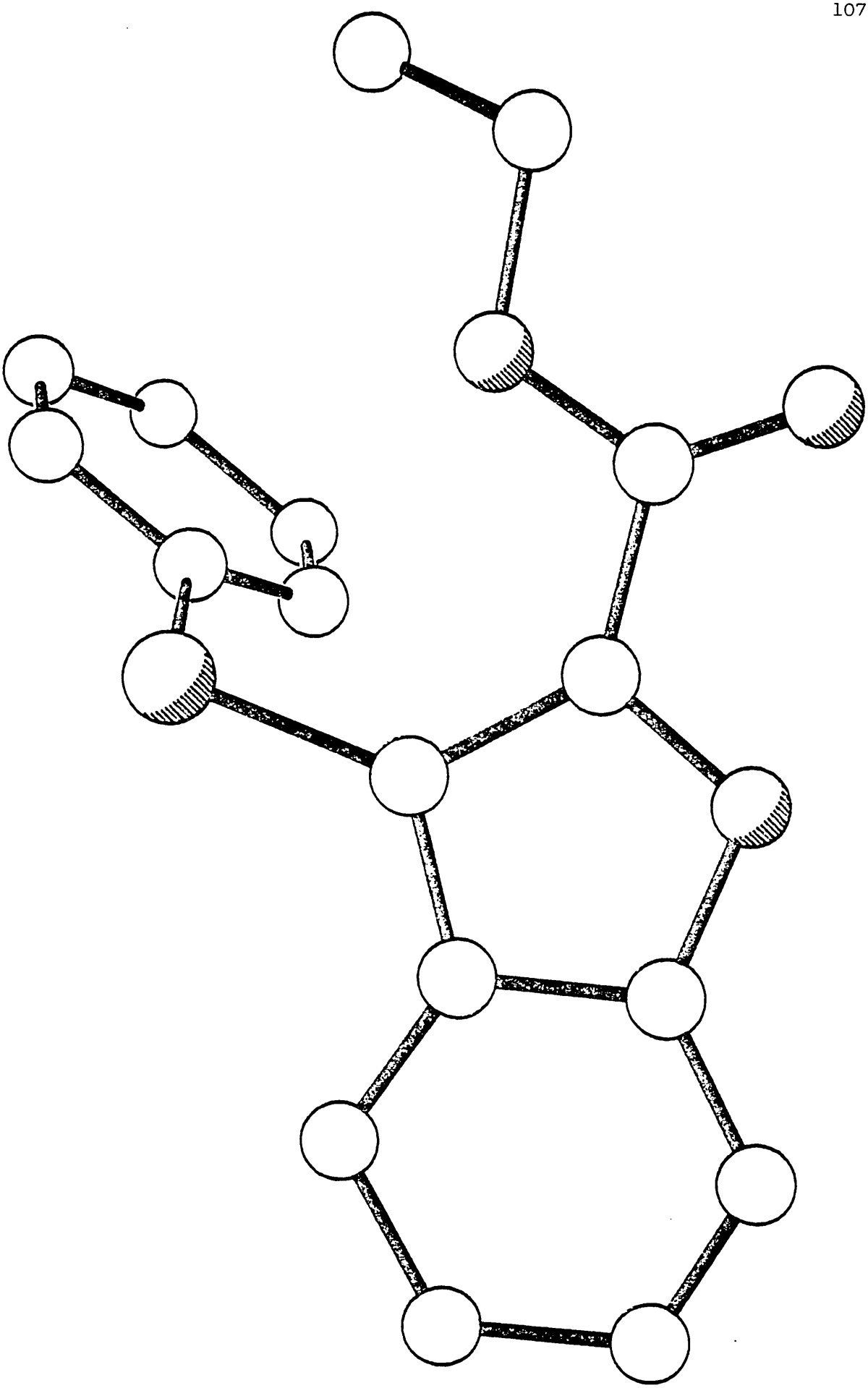


FIGURE 9.

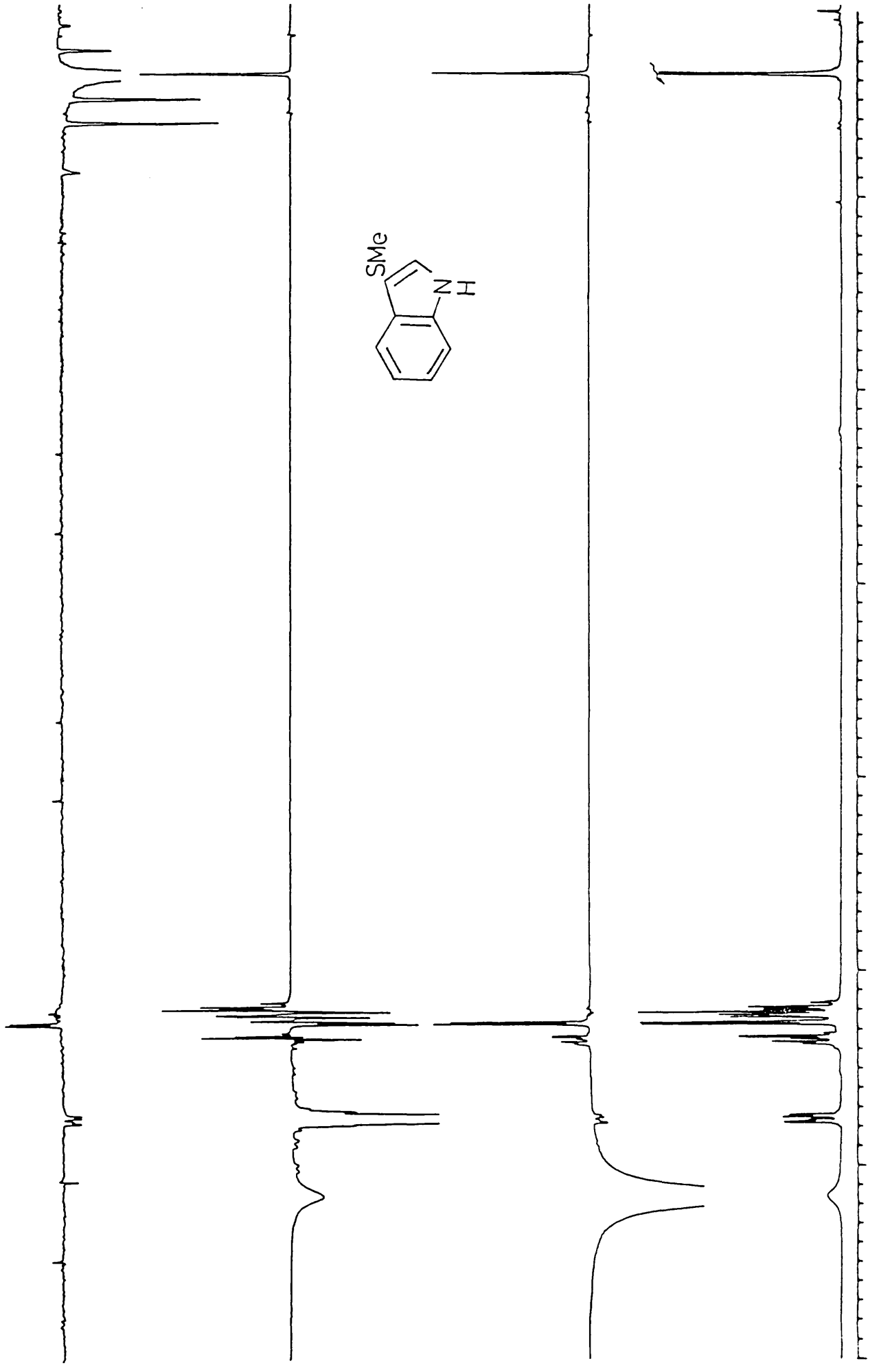
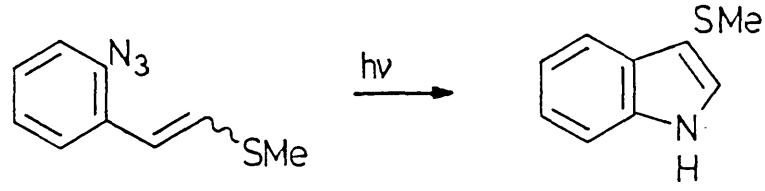


FIGURE 10.

Photolysis of (148) gave a single product. From the ^{1}H n.m.r. and i.r. spectra it was apparent that the product was an indole. The 2-methylthio-[133] and 3-methylthio-[134] indoles are known compounds, however the ^{1}H n.m.r. spectrum of the product did not agree with either of the reported spectra. For this reason the ^{13}C n.m.r. spectrum was obtained and this agreed with the spectrum reported for the 3-methylthioindole. In order to strengthen the structural assignment, n.O.e. experiments were undertaken on the product. The results are shown in Figure 10. Presaturation of the N-H produces an enhancement of H-2 and a smaller enhancement of the S-methyl group which is probably due to power spillage into the neighbouring signal since presaturation of the S-methyl signal shows no enhancement of the NH signal but shows enhancements of H-2 and H-4. From these results the structure was assigned as indole (149).

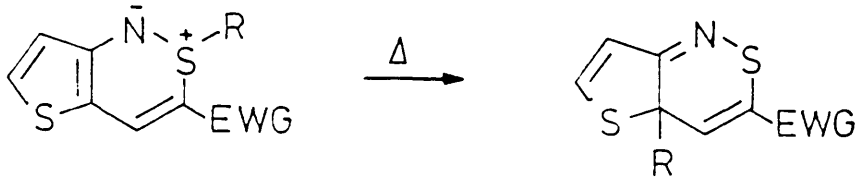


(148) (149)

In contrast to the photolysis of azide (123b) the isomeric product, 2-methylthioindole, was not isolated. This result shows a significant difference between the thiophen and benzenoid series and must reflect the differences in the two systems, i.e. the difference in strain and geometry between a 5,5 fused system and a 6,5 fused system combined with the differences in aromatic stability of the benzene and thiophen rings. However, the results underline the high migratory aptitude of the sulphur group and support the trends in migratory aptitudes observed for substituent groups.

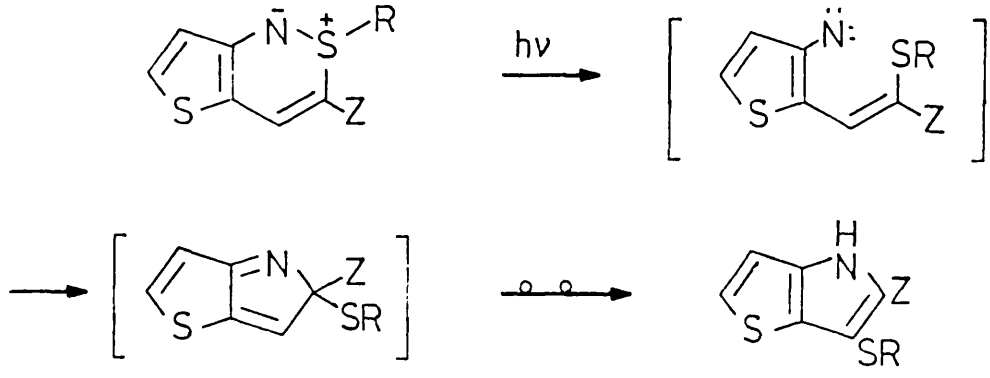
3. CONCLUSION

We have synthesised and studied fused derivatives of the 1H-1,2-thiazine ring system. Although these could be considered as "azathiabenzenes", the properties exhibited by these compounds indicate that the bonding is ylidic rather than the covalent aromatic type bonding that may have been expected. Similarly, it has been observed in the literature that related systems, 1H-1,4-thiazines[73] and 1H-1,2,4-thiadiazines[82] also exhibit ylidic properties. In comparison with the thiabenzenes which have been the subject of major studies and have been shown to be unstable and ylidic in nature, the 1H-1,2-thiazines are more stable. However, when subjected to thermolysis, these have been shown to undergo rearrangements similar to the thiabenzenes (Scheme 88).



Scheme 88

The view that these compounds may be more rightly regarded as cyclic sulphimides is reinforced by their photochemistry. When these thiazines are subjected to u.v. irradiation sulphur-nitrogen bond cleavage occurs. Sulphimides are known to exhibit this type of reaction under photochemical conditions and the products obtained are often the result of a pathway involving nitrenes. Our studies have shown that thienopyrroles are the main products from the photolysis of 1H-1,2-thiazines.



Scheme 89

As shown in Scheme 89, the 4H-thieno [3,2b] pyrroles derived from 1H-1,2-thiazines are thought to be the result of the cyclisation of the initially formed nitrene intermediate to give the 5H-thieno [3,2b] pyrrole which subsequently rearranges. We noted with interest the exclusive migration of the sulphur group. The work of Jones et al on 1H-indenes had established an order of migratory aptitudes for substituent groups,[113] this is as follows: $-CO_2Et < H < -COCH_3 < -CHO$. In 5H-thieno [3,2b] pyrrole system the order of migratory aptitude was found to be as follows: $CO_2Et < -COCH_3 < -CHO < -SR \sim H$.

4. EXPERIMENTAL

Spectra

Ultra violet and visible (u.v.) spectra were measured using a Pye Unicam SP800 spectrophotometer and calibrated against a holmium glass reference. Unless otherwise stated spectra were run in ethanol solution.

Infra-red (i.r.) spectra were recorded in the range 4000 - 600 cm^{-1} using a Perkin-Elmer 298 spectrometer. Unless otherwise stated, spectra of solids were run as Nujol mulls, and spectra of liquids and oils as thin films between sodium chloride plates.

Proton nuclear magnetic resonance (n.m.r.) spectra were recorded using Varian EM360A (60 MHz), Perkin-Elmer R32 (90 MHz), Jeol FX90Q (90 MHz) or Bruker WM250 (250 MHz) instruments, with an internal tetramethylsilane reference. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br). Carbon-13 nuclear magnetic resonance (^{13}C n.m.r.) spectra were recorded on either the Jeol FX90Q (operating at 22.51 MHz) or the Bruker WM250 (operating at 62.9 MHz).

Mass spectra were recorded on an A.E.I. MS12 and VG Micromass 7070E instruments, and unless otherwise stated electron impact ionisation was used.

Melting Points

Melting points were measured on a Kofler hot stage apparatus and are uncorrected.

Solvents

Petrol refers to petroleum ether, b.p. 40-60°C, and was distilled before use. Acetonitrile was dried by refluxing over phosphorus pentoxide, followed by distillation and storage over molecular sieves 4A.

Dimethylformamide and hexamethylphosphoramide were dried by distillation from calcium hydride at reduced pressure. Tetrahydrofuran was dried using the potassium-benzophenone method and distilled directly into the reaction vessel. Hydrocarbon solvents were dried by storage over sodium wire. Other solvents were used as supplied commercially unless otherwise stated.

Chromatography

Column chromatography was carried out using Merck Kieselgel H (Type 60), under pump pressure. Thin layer chromatography (t.l.c.) used as a qualitative analytical technique for following the progress of reactions; aluminium sheets pre-coated with Merck Kieselgel $60F_{254}$ or Merck alumina GF_{254} were used. Preparative layer chromatography (p.l.c.) was carried out using Merck $60PF_{254}$ silica, on 20 cm x 20 cm glass plates.

Photolysis

Photochemical reactions were carried out using a Rayonet photochemical reactor with lamps of 253.7, 300 or 350 nm wavelength. No external cooling was applied, so reactions proceeded at slightly above ambient temperature.

4.1 Preparation of Active Methylene Compounds

The following general method was used in the preparation of active methylene compounds. To a solution of sodium ethoxide (50 mmol) in ethanol (75 ml per 1 g sodium) at room temperature the thiol (50 mmol) was added. After 30 min the halo-compound (50 mmol) was added dropwise. The reaction mixture was stirred for 12 h. It was then poured into water and extracted with ether (2 x 150 ml). The ether layer was washed successively with water, dilute sodium hydroxide and brine. It was then dried ($MgSO_4$) and the solvent removed.

Ethyl Phenylthioacetate (66a)

Prepared by the general method from thiophenol and ethyl chloroacetate. Vacuum distillation of the crude oil gave ethyl phenylthioacetate (7.8 g, 80%), b.p. 156-158°C/14 mmHg (lit.,[104] b.p. 130-135°C/10 mmHg).

Ethyl methylthioacetate (66b)

Prepared by the general method from methanethiol and ethyl chloroacetate. Vacuum distillation of the crude oil gave ethyl methylthioacetate (4 g, 60%) b.p. 69°C/22 mmHg (lit.,[104] b.p. 174-176°C).

Phenylthioacetone (66c)

Prepared by the general method from thiophenol and chloroacetone. Vacuum distillation of the crude oil gave phenylthioacetone (6.1 g, 73%), b.p. 85°C/0.4 mmHg (lit.,[104] b.p. 265-267°C).

Phenylthioacetaldehyde (66d)

From the reaction of thiophenol and bromoacetaldehyde diethylacetal under the general reaction conditions the titled compound was isolated (100%) as the diethylacetal derivative. Further purification was not necessary, the sample being pure by n.m.r.. The named compound was

stored in protected form. Before use the acetal was hydrolysed by treatment with 2M hydrochloric acid. The acid solution was poured into water and extracted with ether (2 x 100 ml). The ether layer was washed successively with sodium bicarbonate solution and brine. After drying the organic layer over magnesium sulphate, the solvent was removed. This gave crude phenylthioacetaldehyde[106] (90%) which was used without further purification.

Phenylthioacetonitrile (66e)

Prepared by the general method from thiophenol and chloroacetonitrile. Vacuum distillation of the crude oil gave phenylthioacetonitrile (5.96, 80%), b.p. 150-152°C/16 mmHg (lit.,[105] b.p. 146-147°C/14 mmHg).

Ethyl ethylthioacetate (66f)

Prepared by the general method from ethanethiol and ethyl chloroacetate. Vacuum distillation of the crude oil gave ethyl ethylthioacetate (4.8 g, 65%) b.p. 86°C/20 mmHg (lit.,[135] b.p. 98-103°C/35 mmHg).

Ethyl 2-(3-propenylthio)acetate (66g)

Following the general method ethyl thioacetate and allyl chloride gave ethyl 2-(3-propenylthio)acetate[107] (5.9 g, 74%), δ^{H}(90 MHz, $CDCl_3$) 6.0 - 5.0 (3H, m), 4.13 (2H, q, $\underline{J}$ 7 Hz), 3.22 (2H, d, $\underline{J}$ 6.8 Hz), 3.1 (2H, s), 1.26 (3H, t, $\underline{J}$ 7 Hz).

Ethyl azidoacetate

Prepared according to the literature procedure[102] from ethyl chloroacetate and sodium azide, b.p. 66-68°C/12 mmHg (lit.,[102] b.p. 75°C/21 mmHg).

Ethyl phenylsulphinylacetate (112)

To a solution of sodium metaperiodate (11.5 g, 54 mmol) in water (75 ml) was added ethyl phenylmercaptoacetate (66a) (10 g, 51 mmol) dissolved in ethanol (50 ml). The reaction mixture was stirred for 18 h after which time the insoluble sodium iodate was filtered off. The aqueous solution was extracted with dichloromethane (2 x 100 ml). After washing the organic phase with water and brine, it was dried over

magnesium sulphate. Removal of the solvent gave ethyl phenylsulphinylacetate in quantitative yield. δ_H (90 MHz, $CDCl_3$) 7.8-7.4 (5H, m), 4.10 (2H, q, J 7 Hz), 3.8 (2H, s), 1.17 (3H, t); m/z 212, 184, 167, 125, (100%).[125]

Ethyl phenylsulphonylacetate (113)

Following a literature method for the oxidation of sulphides,[136] ethyl phenylsulphinylacetate was oxidised using potassium permanganate in acetic acid to give ethyl phenylsulphonylacetate in quantitative yield, m.p. 41-42°C (lit.,[126] m.p. 42-43°C).

4.2 Preparation of Substituted Thiophen Intermediates

Tetrabromothiophen

Prepared by the literature method[137] from thiophen by treatment with bromine in chloroform, m.p. 115°C (lit.,[137] 115.5-116°C).

2,3,5-Tribromothiophen

Following the literature procedure[138] the titled compound was prepared from thiophen by treatment with bromine in chloroform, b.p. 134-135°C/14 mmHg (lit.,[138] b.p. 123-124°C/9 mmHg).

3-Bromothiophen

Treatment of 2,3,5-tribromothiophen with zinc dust in acetic acid according to literature procedure[103] afforded 3-bromothiophen, b.p. 44-46°C/11 mmHg (lit.,[103] b.p. 159-160°C).

3,4-Dibromothiophen

Prepared by the literature method[139] from tetrabromothiophen on treatment with zinc dust in acetic acid, b.p. 96-97°C/12 mmHg (lit.,[139] 93-95°C/10 mmHg).

2,3-Dibromothiophen

According to literature procedure[103] the title compound was prepared from 3-bromothiophen and bromine in benzene solution, b.p. 85-86°C/12 mmHg (lit.,[103] b.p. 89-91°C/13 mmHg).

3-Bromothiophen-2-carbaldehyde

Prepared from 2,3-dibromothiophen by treatment with n-butyllithium at -78°C followed by N,N-dimethylformamide, according to literature procedure,[99] (65%) b.p. 119-120°C/14 mmHg (lit.,[99] 113-115°C/10 mmHg).

4-Bromothiophen-3-carbaldehyde

Prepared by the literature procedure[110] from 3,4-dibromothiophen by treatment with n-butyllithium at -78°C followed by N,N-dimethylformamide, (68%), b.p. 115°C/15 mmHg (lit.,[110] b.p. 111-111.5°C/11 mmHg).

4-Bromothiophen-3-carbaldehyde ethylene acetal

Prepared from 4-bromothiophen-3-carbaldehyde and ethylene glycol in refluxing benzene solution using a catalytic amount of p-toluenesulphonic acid in quantitative yield.

3-Azidothiophen-2-carbaldehyde (67)

A mixture of 3-bromothiophen-2-carbaldehyde (7.17 g, 37.5 mmol) and sodium azide (9.75 g, 150 mmol) in dry hexamethylphosphoramide (80 cm^3) was stirred at 30°C, under nitrogen, for three days. The mixture was poured into water. The solution was extracted with ether (2 x 150 ml). The organic layer was then washed successively with water (3 x 150 ml) and brine (150 ml), dried over magnesium sulphate and the solvent removed. The crude product was then purified by column chromatography (silica H, gradient elution from petrol to 50% dichloromethane in petrol) to give 3-azidothiophen-2-carbaldehyde (67) (3.45 g, 60%), m.p. 57°C (lit.,[99] 56-57°C).

4-Azidothiophen-3-carbaldehyde (78)

Prepared according to the literature procedure[109] from 4-bromothiophen-3-carbaldehyde ethylene acetal by treatment with n-butyllithium at -78°C followed by p-toluenesulphonylazide. This afforded crude 4-azidothiophen-3-carbaldehyde ethylene acetal which was hydrolysed in 2M hydrochloric acid to give 4-azidothiophen-3-carbaldehyde (78) (72%), m.p. 51°C (lit.,[109] 50-52°C).

4-Phenylthiothiophen-3-carbaldehyde (79)

To a solution of 4-bromothiophen-3-carbaldehyde ethylene acetal (1 g, 4.25 mmol) in dry ether (5 ml) at -78°C was added n-butyllithium (4.25 mmol) and the solution was stirred for 35 min. This solution was then added to a solution of diphenyl disulphide (0.93 g, 4.3 mmol) in dry ether (5 ml), under nitrogen. On stirring for 3 h the mixture was poured into water and the aqueous solution extracted with ether (2 x 150 ml). The ethereal solutions were washed successively with dilute sodium hydroxide solution and brine. Removal of the solvent gave crude 4-phenylthiothiophen-3-carbaldehyde ethylene acetal which was treated with 2M hydrochloric acid. The acid solution was extracted with ether (2 x 100 ml). The ethereal solution was then washed with sodium bicarbonate solution and brine before being dried over magnesium sulphate and the solvent removed. Column chromatography (silica H; gradient elution from petrol to dichloromethane) of the resulting residue gave 4-phenylthiothiophen-3-carbaldehyde (79) as an oil (750 mg, 80%), (Found: C, 59.7; H, 3.95. $C_{11}H_8OS_2$ requires C, 60.0; H, 3.7%); ν max 1695 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.9 (1H, s), 8.1 (1H, d, 3.2 Hz), 7.3-7.15 (5H, m), 7.0 (1H, d, 3.2 Hz); m/z 220 (M^+, 100%).

4.3 Preparation of Substituted Pyrroles

4-Nitropyridine-N-oxide

Using the literature procedure[140] pyridine-N-oxide was prepared from pyridine and hydrogen peroxide in glacial acetic acid, b.p. 139°C/15 mmHg (lit.,[140] b.p. 138-140°C/15 mmHg). Nitration of pyridine-N-oxide with concentrated nitric and sulphuric acid solution gave 4-nitropyridine-N-oxide m.p. 158°C (lit.,[140] m.p. 159°C).

4-Chloropyridine-N-oxide

Prepared by the literature procedure from 4-nitropyridine-N-oxide and acetylchloride (92%), m.p. 169°C). (lit.,[140] m.p. 169.5°C).

4-Phenylthiopyridine-N-oxide

To a sodium ethoxide in ethanol solution made from sodium metal (0.5 g, 21.7 mmol) and ethanol (10 ml) was added thiophenol (2.4 g, 21.8 mmol). The solution was heated to reflux and then 4-nitropyridine-N-oxide (2 g, 14.3 mmol) was added. After 3 h, the solution was poured into water and extracted with dichloromethane (5 x 100 ml). The organic phase was dried over magnesium sulphate before removing the solvent. The residue was then recrystallised to give 4-phenylthiopyridine-N-oxide (2.74 g, 95%), m.p. 137°C (petrol/CH_2Cl_2) (lit.,[112] m.p. 137°C).

4-Methylthiopyridine-N-oxide

To methanol (50 ml), sodium metal (0.33 g, 14.3 mmol) was added. Then methanethiol was bubbled through the solution for several minutes. Then 4-nitropyridine-N-oxide (1 g, 7 mmol) was added and the solution was heated to reflux. After 2 h the solution was poured into water and extracted with dichloromethane (3 x 100 ml). The organic layer was then dried over magnesium sulphate before removing the solvent. The pale yellow solid was recrystallised to give 4-methylthiopyridine-N-oxide (0.85 g, 85%), m.p. 142°C (Found: C, 51.2; H, 5.1; N, 10.2. C_6H_7NOS requires C, 51.0; H, 5.0; N, 9.9%); λ max (EtOH) 207 (logε 3.64), 307 nm (3.84); δ_H (90 MHz, $CDCl_3$) 8.06 (2H, d, J 7 Hz), 7.06 (2H, d, J 7 Hz), 2.55 (3H, s); m/z 141 (M^+, 100%).

3-Chloropyrrole-2-carbaldehyde

Prepared by the literature method[111] from 4-chloropyridine-N-oxide in copper sulphate solution by irradiation using a high pressure mercury lamp, (35%), m.p. 100°C (lit.,[111] m.p. 100°C).

3-Methylthiopyrrole-2-carbaldehyde

4-Methylthiopyridine-N-oxide (0.59 g, 4.2 mmol) and copper (II) sulphate (10 g) was dissolved in distilled water (150 ml) in a quartz photolysis tube. Nitrogen was bubbled through the solution while it was irradiated at 300 nm. After 17 h the solution was extracted with methylene chloride (2 x 100 ml), the organic layer dried over magnesium sulphate and the solvent removed. Purification of the resultant residue by column chromatography (silica H, gradient elution from 50% dichloromethane in petrol) gave 3-methylthiopyrrole-2-carbaldehyde (0.14 g, 27%), m.p. 74°C (Found: C, 51.2; H, 5.1; N, 10.2. C_6H_7NOS requires C, 51.0; H, 5.0; N, 9.9%); λ max (EtOH) 245 (log ε 3.07), 292 (3.85) and 331 nm (3.50); ν max 3440 m and 1630 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 10.3 (1H, br), 9.72 (1H, s), 7.15 (1H, d, J 3 Hz), 6.38 (1H, d, J 3 Hz), 2.5 (3H, s); m/z 141 (M^+, 100%).

4.4 Preparation of Substituted Imidazoles

1-Methoxymethyl-2,4,5-tribromoimidazole (91)

Following the literature procedure[141] imidazole was brominated using bromine in sodium acetate, acetic acid solution to give 2,4,5-tribromoimidazole, m.p. 225°C (lit.,[141] m.p. 225-226°C). Treatment of 2,4,5-tribromoimidazole with chloromethyl methyl ether and triethylamine in benzene gave 1-methoxymethyl-2,4,5-tribromoimidazole (91), (60%), m.p. 93°C (lit.,[142] 92-94°C).

4,5-Dibromo-1-methoxymethyl-2-phenylthioimidazole

Prepared by the literature method[116] from 1-methoxymethyl-2,4,5-tribromoimidazole by treatment with n-butyllithium followed by diphenyl disulphide. Column chromatography gave 4,5-Dibromo-1-methoxymethyl-2-phenylthioimidazole as a yellow oil (Found: C, 35.2; H 2.5; N, 7.4. $C_{11}H_{10}Br_2N_2OS$ requires C, 34.9; H, 2.7; N, 7.4%); δ_H (90 MHz, $CDCl_3$) 7.4-7.15 (5H, m), 5.5 (2H, s), 3.3 (3H, s), 2.5 (3H, s); m/z 378 (M^+, 100%).

1-Methoxymethyl-5-methylthio-2-phenylthioimidazole-4-carbaldehyde (90)

4-Bromo-1-methoxymethyl-5-methylthio-2-phenylthioimidazole was prepared (60%) according to the literature procedure for the preparation of the 1-ethoxymethyl derivative[116] from 4,5-dibromo-1-methoxymethyl-2-phenylthioimidazole. 4-Bromo-1-methoxymethyl-5-methylthio-2-phenylthioimidazole (0.5 g, 1.45 mmol) was immediately dissolved in dry THF (20 ml) and treated with n-butyllithium (1.45 mmol) at -78°C. After 2 h the solution was pushed, under nitrogen, into a stirred solution of N,N-dimethylformamide (150 mg, 2.05 mmol) in dry THF (30 ml). The mixture was allowed to warm to ambient temperature and after 1 h was poured into water. The aqueous solution was extracted with ether (2 x 100 ml), the organic phase washed with water, dried over magnesium sulphate and the solvent removed. Column chromatography (alumina, gradient from petrol to chloroform) gave 1-methoxymethyl-5-methylthio-2-phenylthioimidazole-4-carbaldehyde as a yellow oil (0.36 g, 84%) (Found: C, 53.1; H, 5.0; N, 9.6. $C_{13}H_{14}N_2O_2S_2$ requires C, 53.0; H, 4.8; N, 9.5%); ν max (film) 1690 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.95 (1H, s), 7.4-7.15 (5H, m), 5.48 (2H, s), 3.27 (3H, s), 2.5 (3H, s); m/z 294 (M^+, 100%).

4-Bromo-1-methoxymethyl-2-phenylthioimidazole-5-carbaldehyde (96)

Prepared according to the literature procedure for the preparation of the 1-ethoxymethyl derivative[114] from 4,5-dibromo-1-methoxymethyl-2-phenylthioimidazole (1 g, 2.65 mmol) by treatment with n-butyllithium (2.65 mmol) followed by N,N-dimethylformamide (200 mg, 2.74 mmol) to give 4-bromo-1-methoxymethyl-2-phenylthioimidazole-5-carbaldehyde (560 mg, 68%) as a pale yellow oil, (Found: M^+ 325.9719. $C_{12}H_{11}BrN_2O_2S$ requires M^+ 325.9725); δ_H (90 MHz, $CDCl_3$) 9.95 (1H, s), 7.35-7.15 (5H, m), 5.5 (2H, s), 3.3 (3H, s); m/z 327 (M^+), 298 (100%).

4.5 Condensation of Aldehydes with Active Methylene Compounds

The following general methods were used to condense aldehydes with active methylene compounds.

(A) The aldehyde (1 equiv.) was dissolved in the appropriate active methylene compound (1.1 equiv.). If necessary, ethanol was added to dissolve the aldehyde completely. This solution was added dropwise with stirring to a solution of sodium ethoxide (1.1 equiv.) in ethanol (100 ml per 1 g sodium) at -15°C. This temperature was maintained for 2 h and then the reaction mixture was allowed to warm to ambient temperature overnight. At all times light was excluded from the reaction. The reaction mixture was then poured into aqueous ammonium chloride and extracted with ether (2 x 150 ml). The organic layer was then washed with saturated sodium metabisulphite solution and after washing with brine was dried over magnesium sulphate. The solvent was removed and the resulting residue chromatographed (silica H, gradient elution from petrol to 70% dichloromethane in petrol).

(B) The aldehyde (1 equiv.) was dissolved in ethyl azidoacetate (4 equiv.). If necessary, ethanol was added to dissolve the aldehyde completely. This solution was added dropwise with stirring to a solution of sodium ethoxide (4 equiv.) in ethanol (100 ml per 1 g sodium) at -15°C. This temperature was maintained for 2 h and then the reaction mixture was allowed to warm to 5°C. It was then worked up as described in method A.

(C) The aldehyde (1 equiv.) was dissolved in the appropriate active methylene compound (1.1 equiv.). If necessary, ethanol was added to dissolve the aldehyde completely. This solution was added dropwise with stirring to a solution of piperidinium acetate (1.1 equiv.) in ethanol (100 ml per 50 mmol piperidinium acetate). The reaction mixture was stirred overnight and then worked up as described in method A.

Ethyl 3-(3-azido-2-thienyl)-2-phenylthioprop-2-enoate (68a)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl phenylthioacetate (140 mg, 0.72 mmol) gave ethyl 3-(3-azido-2-thienyl)-2-phenylthioprop-2-enoate (195 mg, 90%), m.p. 105-107°C (decomp.) (lit.,[98] m.p. 106-108°C (decomp.)).

Ethyl 3-(3-azido-2-thienyl)-2-methylthioprop-2-enoate (68b)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl methylthioacetate (96 mg, 0.72 mmol) gave ethyl 3-(3-azido-2-thienyl)-2-methylthioprop-2-enoate (88 mg, 50%), m.p. 54-55°C (lit.,[98] m.p. 54-55°C).

4-(3-azido-2-thienyl)-3-phenylthiobutenone (68c)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and phenylthioacetone (119 mg, 0.72 mmol) gave 4-(3-azido-2-thienyl)-3-phenylthiobutenone (147 mg, 75%), m.p. 96°C (from petrol, dichloromethane) (Found: C, 55.8; H, 3.7; N, 13.9. $C_{14}H_{11}N_3OS_2$ requires

C, 55.8; H, 3.7; N, 13.9%); λmax (EtOH) 252 (logε 4.13), and 355 nm (4.24); ν max (CCl_4) 3000 w, 2100 vs, and 1675 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 2.38 (3H, s), 7.0 (1H, d, J 5.5 Hz), 7.21 (5H, m), 7.53 (1H, dd, J 5.5 and 0.9 Hz), 8.37 (1H, d, J 0.9 Hz); δ_c (22.5 MHz, $CDCl_3$) 197, 142.8, 135.5, 134.9, 133.1, 129.3, 127.2, 126.2, 118.8, 27.2; m/z 301 (M^+), 273, 257, 231, 196 (100%).

3-(3-Azido-2-thienyl)-2-phenylthiopropenal (68d)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and phenylthioacetaldehyde (109 mg, 0.72 mmol) gave 3-(3-azido-2-thienyl)-2-phenylthiopropenal (94 mg, 50%), m.p. 82-83°C (from dichloromethane, petrol) (Found: C, 54.4; H, 3.2; N, 14.5. $C_{13}H_9N_3OS_2$ requires C, 54.3; H, 3.2; N, 14.6%); λ max (EtOH) 248 (logε 3.80), and 353 nm (3.97); ν max (CCl_4) 2100 vs, and 1690 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.05 (1H, d, J 5.5 Hz), 7.2-7.4 (5H, m), 7.6 (1H, dd, J 5.5 and 0.9 Hz); 8.15 (1H, d, J 0.9 Hz) 9.6 (1H, s); m/z 287 (M^+), 259, 243 (100%) 182.

3-(3-Azido-2-thienyl)-2-phenylthiopropenenitrile (68e)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and phenylthioacetonitrile (107 mg, 0.72 mmol) gave 3-(3-azido-2-thienyl)-2-phenylthiopropenenitrile (148 mg, 80%), m.p. 98-99°C (Found: C, 55.1; H, 2.8; N, 19.7. $C_{13}H_8N_4S_2$ requires C, 54.9; H, 2.8; N, 19.7%); λmax (EtOH) 235 (logε 3.97) and 360 nm (4.35); ν max (CCl_4) 2210 m, and 2120 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.7 (1H, d, J 1 Hz), 7.56 (1H, dd, J 5.4 and 1 Hz), 7.5-7.32 (5H, m), 7.0 (1H, d, J 5.4 Hz); δ_c (22.5 MHz, $CDCl_3$) 101.7, 118, 118.9, 122.1, 128.6, 129.6, 131.0, 131.3, 132.6, 136.6, 141.7; m/z 284 (M^+), 256, 179 (100%).

Ethyl 3-(3-azido-2-thienyl)-2-ethylthioprop-2-enoate (68f)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl ethylthioacetate (106 mg, 0.72 mmol) gave ethyl 3-(3-azido-2-thienyl)-2-ethylthioprop-2-enoate (92.5 mg, 50%) as an unstable yellow

oil, ν max (film) 2120 s, 1710 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.2 (1H, s), 7.5 (1H, d, J 5 Hz), 6.95 (1H, d, J 5 Hz), 5.26 (2H, q, J 7.5 Hz), 2.83 (2H, q, J 7.5 Hz), 1.35 (3H, t, J 7.5 Hz), 1.22 (3H, t, J 7.5 Hz).

Ethyl 3-(3-azido-2-thienyl)-2-allylthioprop-2-enoate (68g)

Using method A, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl allylthioacetate (115 mg, 0.72 mmol) gave ethyl 3-(3-azido-2-thienyl)-2-allylthioprop-2-enoate (110 mg, 57%) as a pale yellow oil (Found: C, 48.7; H, 4.4; N, 14.0. $C_{12}H_{13}N_3O_2S_2$ requires C, 48.8; H, 4.4; N, 14.2%); λ max (EtOH) 245 (logε 3.84), 320 (4.07) and 354 nm (4.16); ν max (film) 2100 s and 1700 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.24 (1H, d, J 0.9 Hz), 7.53 (1H, dd, J 5.3 and 0.9 Hz), 6.99 (1H, d, J 5.3 Hz), 6.05-5.58 (1H, m), 5.25-4.9 (2H, m), 4.33 (2H, q, J 7.7 Hz) 3.5 (2H, d, J 6.4 Hz), 1.37 (3H, t, J 7.7 Hz).

Ethyl 3-(4-azido-3-thienyl)-2-phenylthioprop-2-enoate (85a)

Using method A, 4-azidothiophen-3-carbaldehyde (100 mg, 0.65 mmol) and ethyl phenylthioacetate (140 mg, 0.72 mmol) gave ethyl 3-(4-azido-3-thienyl)-2-phenylthioprop-2-enoate (123 mg, 57%) as a pale yellow oil, (Found: M^+ 331.0461. $C_{15}H_{13}N_3O_2S_2$ requires M^+ 331.0449); λ max (EtOH) 208 (logε 4.20), 253 (4.16), 280 (4.07), 340 nm (3.84); ν max (film) 2140 s, 1710 s cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.36 (1H, dd, J 4 and 0.85 Hz), 7.9 (1H, d, J 0.85 Hz), 7.35-7.15 (5H, m), 6.84 (1H, d, J 4 Hz), 4.11 (2H, q, J 7.5 Hz), 1.08 (3H, t, J 7.5 Hz); m/z 331 (M^+), 303, 226 (100%).

Ethyl 3-(4-azido-3-thienyl)-2-methylthioprop-2-enoate (85b)

Using method A, 4-azidothiophen-3-carbaldehyde (100 mg, 0.65 mmol) and ethyl methylthioacetate (96 mg, 0.72 mmol) gave ethyl 3-(4-azido-3-thienyl)-2-methylthioprop-2-enoate (90 mg, 51%) as an unstable yellow oil, ν max (film) 2120 s, 1710 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.3 (1H, d, J 3 Hz), 7.9 (1H, s), 6.8 (1H, d, J 3 Hz), 4.1 (2H, q, J 7 Hz),

2.4 (3H, s), 1.1 (3H, t, J 7 Hz); m/z 269 (M^+), 241 (100%).

Ethyl 2-azido-3-(4-phenylthio-3-thienyl)prop-2-enoate (86)

Using method B, 4-phenylthiothiophen-3-carbaldehyde (100 mg, 0.45 mmol) and ethyl azidoacetate (235 mg, 1.82 mmol) gave ethyl 2-azido-3-(4-phenylthio-3-thienyl)prop-2-enoate (60 mg, 40%) as an unstable pale yellow oil, ν max (CCl_4) 2120 s, 1690 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.3 (1H, d, J 3 Hz), 7.4 (1H, d, J 3 Hz), 7.2-7.1 (5H, m), 6.95 (1H, s), 4.25 (2H, q, J 7 Hz), 1.3 (3H, t, J 7 Hz); m/z 331 (M^+), 303 (100%).

Ethyl 2-azido-3-(2,5-dimethyl-4-phenylthio-3-thienyl)prop-2-enoate

Using method B, 2,5-dimethyl-4-phenylthiothiophen-3-carbaldehyde (100 mg, 0.4 mmol) and ethyl azidoacetate (208 mg, 1.61 mmol) gave ethyl 2-azido-3-(2,5-dimethyl-4-phenylthio-3-thienyl)prop-2-enoate (86.9 mg, 60%) as an unstable pale yellow oil, ν max (film) 2110 s, 1690 s; δ_H (90 MHz, $CDCl_3$) 7.2-7.0 (5H, m), 6.65 (1H, s), 4.23 (2H, q, J 7 Hz), 2.55 (3H, s), 2.45 (3H, s), 1.3 (3H, t, J 7 Hz); m/z 359 (M^+), 331, 254 (100%).

Ethyl 2-acetyl-3-(3-azido-2-thienyl)prop-2-enoate

Using method C, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl acetoacetate (93.5 mg, 0.72 mmol) gave ethyl 2-acetyl-3-(3-azido-2-thienyl)prop-2-enoate (147 mg, 85%) m.p. 63-64°C (Found: C, 49.8; H, 4.1; N, 15.7. $C_{11}H_{11}N_3O_3S$ requires C, 49.8; H, 4.2; N, 15.9%); λ max (EtOH) 238 (logε3.63) and 343 nm (3.99); ν max (CCl_4) 2100 vs, 1710 s, 1690 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.7 (1H, s), 7.5 (1H, d, J 6 Hz), 6.97 (1H, d, J 6 Hz), 4.4 (2H, q, J 7 Hz), 2.4 (3H, s), 1.36 (3H, t, J 7 Hz); m/z 265 (M^+), 237, 221 (100%).

3-(3-Azido-2-thienyl)butenone

Prepared according to the literature procedure[128] from 3-azido-thiophen-2-carbaldehyde and acetone to give 3-(3-azido-2-thienyl)-butenone m.p. 104°C (lit.,[128] m.p. 105°C).

Ethyl 3-(3-azido-2-thienyl)-2-phenylsulphinylprop-2-enoate (114)

Using method C, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl phenylsulphinylacetate (152 mg, 0.72 mmol) gave ethyl 3-(3-azido-2-thienyl)-2-phenylsulphinylprop-2-enoate (109 mg, 48%), m.p. 125-126°C (decomp.) (Found: C, 51.8; H, 3.7; N, 12.0. $C_{15}H_{13}N_3O_3S_2$ requires C, 51.9; H, 3.8; N, 12.1%); λ max (EtOH) 208 (logε 4.26), 235 (3.96) and 354 nm (4.38); ν max 2100 vs and 1710 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.28 (1H, s), 8.8-8.6 (3H, m), 8.55-8.4 (2H, m), 7.03 (2H, d, J 6.4 Hz), 4.2 (2H, q, J 7 Hz), 1.21 (3H, t, J 7 Hz); δ_c (22.5 MHz, $CDCl_3$) 14.0, 61.4, 118.8, 120.6, 126.1, 128.3, 128.8, 129, 131.4, 133.9, 143.8, 144.4, 162.5; m/z 347 (M^+) 319, 274, 242, 222, (100%).

Ethyl 3-(3-azido-2-thienyl)-2-phenylsulphonylprop-2-enoate (115)

Using method C, 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) and ethyl phenylsulphonylacetate (164 mg, 0.72 mmol) gave ethyl 3-(3-azido-2-thienyl)-2-phenylsulphonylprop-2-enoate (190 mg, 80%) as pale yellow crystals, m.p. 128-130°C (decomp.) (Found: C, 49.7; H, 3.5; N, 11.4. $C_{15}H_{13}N_3O_4S_2$ requires C, 49.6; H, 3.6; N, 11.6%); λ max (EtOH) 207 (logε 4.05), 240 (3.80) and 354 nm (4.21); ν max (CCl_4) 2100 s and 1705 m cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.56 (1H, d, J 0.9 Hz), 8.0-8.5 (2H, m), 7.75 (1H, dd, J 5 and 0.9 Hz), 7.63-7.45 (3H, m), 7.05 (1H, d, J 5 Hz), 4.2 (2H, q, J 7 Hz), 1.17 (3H, t, J 7 Hz); δ_c (22.5 MHz, $CDCl_3$) 13.7, 61.8, 119.1, 119.2, 126.0, 128.3, 128.6, 133.0, 136.0, 136.4, 140.7, 146.1, 162.1; m/z 363 (M^+), 335, 318, 77 (100%).

2-(3-Azido-2-thienyl)-1-methylthioethenyl methyl sulphoxide (119)

To a solution of methyl methylsulphinylmethyl sulphide (81 mg, 0.65 mmol) in dry THF (20 ml) at -78°C was added n-butyllithium (0.65 mmol). After 20 min, a solution of 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) was added. The reaction mixture was then allowed to warm to ambient temperature and after 2 h, methylsulphonyl chloride (115 mg, 1 mmol) and triethylamine (1 ml) was added. The reaction mixture was then stirred overnight and finally worked up as described in method A. This gave 2-(3-azido-2-thienyl)-1-methylthioethenyl methyl sulphoxide (67.7 mg, 40%) as an unstable oil which darkened rapidly on standing, (Found: M^+ 258.9897. $C_8H_9N_3OS_3$ requires M^+ 258.9908.); λ max (EtOH) 204 (logε 3.81), 250 (3.63), 333 nm (3.98); ν max (CCl_4) 2100 s, 1580 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.85 (1H, s), 7.45 (1H, d, J 5 Hz), 6.96 (1H, d, J 5 Hz), 2.71 (3H, s), 2.38 (3H, s); m/z 259 (M^+), 244, 231 (100%).

2-(3-Azido-2-thienyl)ethenyl phenyl sulphide (123a)

To a stirred solution of phenylthiomethyltriphenylphosphonium chloride[127] (1.08 g, 2.6 mmol) in dry THF (30 ml) was added dropwise n-butyllithium (2.6 mmol). After the addition was complete the solution was cooled to -78°C before adding a solution of 3-bromo-thiophen-2-carbaldehyde (493 mg, 2.6 mmol) in dry THF (10 ml). The temperature was maintained at -78°C for 1 h then the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was then worked up according to method A this gave an impure mixture of cis and trans isomers (1:1) of 2-(3-bromo-2-thienyl)ethenyl phenyl sulphide (618 mg, 80%). Subsequent treatment of this mixture in dry THF (20 ml) at -78°C with n-butyllithium (2.1 mmol) and tosylazide (410 mg, 2.1 mmol) gave 2-(3-azido-2-thienyl) phenyl sulphide (323 mg, 60%) as in impure, unstable oil. ν max (film) 2100 s cm^{-1}; m/z 231 (M^+ -28).

2-(3-Azido-2-thienyl)ethenyl methyl sulphide (123b)

To a stirred solution of methylthiomethyltriphenylphosphonium chloride[143] (376 mg, 1.05 mmol) in dry THF (30 ml) was added dropwise n-butyllithium (1.05 mmol). When the addition was complete, the solution was cooled to -78°C and then a solution of 3-bromothiophen-2-carbaldehyde (200 mg, 1.05 mmol) in dry THF (10 ml) was added. After 1 h the reaction was allowed to warm to ambient temperature overnight. The reaction mixture was worked up as described in method A to give a 1:1 mixture of cis and trans 2-(3-bromo-2-thienyl)ethenyl methyl sulphide (214 mg, 87%) as an oil (Found: C, 35.5; H, 2.9. $C_7H_7BrS_2$ required C, 35.75; H, 3.0%); λ max (EtOH) 204 (logε 3.82), 224 (3.77), 318 nm (4.23); ν max 1580 s cm^{-1}; trans δ_H (90 MHz, $CDCl_3$) 7.0 (1H, d, J 5 Hz), 6.88 (1H, d, J 5 Hz), 6.75 (1H, d, J 15.3 Hz), 6.52 (1H, d, J 15.3 Hz), 2.38 (3H, s); cis δ_H (90 MHz, $CDCl_3$) 7.3 (1H, d, J 5 Hz), 6.97 (1H, d, J 5 Hz), 6.75 (1H, d, J 11 Hz), 6.25 (1H, d, J 11 Hz), 2.43 (3H, s); cis δ_c (22.5 MHz, $CDCl_3$) 18.7, 110.7, 117.5, 125.2, 128.9, 129.5, 134.7; trans δ_c (22.5 MHz, $CDCl_3$) 14.8, 107.7, 116.3, 122.5, 128.2, 130.4, 136.6; m/z 235 (M^+), 155, 140 (100%).

A mixture of cis and trans 2-(3-bromo-2-thienyl)ethenyl methyl sulphide (100 mg, 0.43 mmol) in dry THF (20 ml) at -78°C was treated with n-butyllithium (0.43 mmol). After 20 min a solution of tosyl-azide (88.7 mg, 0.45 mmol) in THF (5 ml) was added. After 2 h the reaction was worked up according to method A to give a mixture of cis and trans 2-(3-azido-2-thienyl)ethenyl methyl sulphide (50.3 mg, 60%) as an unstable oil (Found: 197.0088. $C_7H_7N_3S_2$ requires 197.0081); λmax (EtOH) 203 (logε 3.79), 230 (3.88), 253 (3.89), 320 nm (4.26); νmax (film) 2100 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) cis 7.33 (1H, d, J 5.5 Hz), 6.94 (1H, d, J 5.5 Hz), 6.67 (1H, d, J 10 Hz), 6.11 (1H, d, J 10 Hz), 2.44 (3H, s); trans 7.02 (1H, d, J 5.5 Hz), 6.8 (1H, d, J 5.5 Hz),

6.6 (1H, d, J 17 Hz), 6.45 (1H, d, J 17 Hz), 2.36 (3H, s); m/z 197 (M^+), 169, 154 (100%).

2-(3-Azido-2-thienyl)ethenyl phenyl sulphoxide (131)

To a solution of diethyl phenylsulphinylmethylphosphonate[129] (179 mg, 0.65 mmol) in dry THF (20 ml) was added n-butyllithium (0.65 mmol) at -78°C with stirring. After 20 min a solution of 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) in dry THF (10 ml) was added. The temperature was maintained for 2 h and then the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was then worked up according to method A to give 2-(3-azido-2-thienyl)ethenyl phenyl sulphoxide (116 mg, 64.5%) as an unstable oil (Found: M^+ 275.0233. $C_{12}H_9N_3OS_2$ requires M^+ 275.0223); λmax (EtOH) 205 (logε 4.12), 225 (3.96), 247 (3.89), 319 nm (4.25); νmax (film) 2100 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.65-7.4 (5H, m), 7.35-7.23 (2H, m), 6.9 (1H, d, J 5 Hz), 6.65 (1H, d, J 15 Hz); m/z 275 (M^+), 247, 227, 199 (100%).

2-(3-Azido-2-thienyl)ethenyl methyl sulphone (132)

To a solution of dimethyl sulphone (61 mg, 0.65 mmol) in dry THF (20 ml) was added n-butyllithium (0.65 mmol) at -78°C with stirring. After 20 min a solution of 3-azidothiophen-2-carbaldehyde (100 mg, 0.65 mmol) in dry THF (10 ml) was added and the reaction mixture stirred for 1 h at -78°C. After allowing the reaction to warm to ambient temperature, methylsulphonyl chloride (115 mg, 1 mmol) and triethylamine (1 ml) was added. The reaction mixture was stirred overnight and then worked up as described in method A to give 2-(3-azido-2-thienyl)ethenyl methyl sulphone (97 mg, 65%) as an oil (Found: M^+ 228.9972. $C_7H_7N_3O_2S_2$ requires M^+ 228.9979); λmax (EtOH) 204 (logε 3.89), 247 (3.82), 317 nm (4.23); νmax (CCl_4) 2100 s, 1600 m cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.55 (1H, d, J 15 Hz), 7.45 (1H,

d, J 5 Hz), 6.95 (1H, d, J 5 Hz), 6.7 (1H, d, J 15 Hz), 2.97 (3H, s); m/z 229 (M^+), 201, 122, (100%).

Ethyl 2-acetyl-3-(2-azidophenyl)propenoate (142)

Using method C, o-azidobenzaldehyde (100 mg, 0.68 mmol) and ethyl acetoacetate (97 mg, 0.75 mmol) gave a mixture of cis and trans ethyl 2-acetyl-3-(2-azidophenyl)propenoate (141 mg, 80%), as an oil, (Found: C, 60.4; H, 5.0; N, 16.1. $C_{13}H_{13}N_3O_3$ requires C, 60.2; H, 5.05; N, 16.2%); λ max (EtOH) 207 (logϵ 4.07), 253 (4.20), 283 (4.12), 327 nm (3.69); ν max (CCl_4) 2120 s, 1720 s, 1695 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.76 (1H, s), 7.68 (1H, s), 7.45-7.0 (8H, m), 4.3 (2H, q, J 7 Hz), 4.23 (2H, q, J 7 Hz), 2.38 (3H, s), 2.22 (3H, s), 1.3 (3H, t, J 7 Hz), 1.16 (3H, t, J 7 HZ); m/z 259 (M^+), 231, 217, 202, 189, 170, 143 (100%).

3-(2-Azidophenyl)propenal (143)

To a 3% wv solution of potassium hydroxide was added a mixture of o-azidobenzaldehyde (100 mg, 0.68 mmol) and acetaldehyde (33 mg, 0.75 mmol) with stirring. After 3 h the solution was worked up according to method A to give 3-(2-azidophenyl)propenal (92 mg, 78%), δ_H (90 MHz, $CDCl_3$) 9.6 (1H, d, J 7 Hz), 7.68 (1H, d, J 16 Hz), 7.59-7.05 (4H, m), 6.69 (1H, dd, J 16 and 7 Hz); m/z 173 (M^+), 145, 144, 117, 90 (100%).

Ethyl 3-(2-azidophenyl)-2-phenylthiopropenoate (144)

Using method A, o-azidobenzaldehyde (100 mg, 0.68 mmol) and ethyl phenylthioacetate (147 mg, 0.75 mmol) gave ethyl 3-(2-azidophenyl)-2-phenylthiopropenoate[97] (190 mg, 86%), δ_H (90 MHz, $CDCl_3$) 8.1 (1H, s), 7.9-6.9 (9H, m), 4.1 (2H, q, J 7 Hz), 1.0 (3H, t, J 7 Hz).

o-Azidostyryl methyl sulphide (148)

To a stirred solution of methylthiomethyltriphenylphosphonium chloride[143] (194 mg, 0.54 mmol) in dry THF (25 ml) was added dropwise

n-butyllithium (0.54 mmol). When the addition was complete, the solution was cooled to -78°C and then a solution of o-bromobenzaldehyde (100 mg, 0.54 mmol) in dry THF (10 ml) was added. After 1 h the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was worked up as described in method A to give a 1:1 mixture of cis and trans o-bromostyryl methyl sulphide (89 mg, 72%) as an oil, ν max (film) 1590 s; δ_H (90 MHz, $CDCl_3$) 7.6-7.0 (8H, m), 6.7-6.3 (4H, m), 2.35 (3H, s), 2.3 (3H, s); m/z 230, 228 (M^+), 149 (100%).

To a mixture of cis and trans o-bromostyryl methyl sulphide (85 mg, 0.37 mmol) in dry THF (10 ml) at -78°C was added n-butyllithium (0.37 mmol). After 20 min a solution of tosyl azide (78.8 mg, 0.4 mmol) in THF (5 ml) was added. The reaction mixture was stirred for 2 h then worked up according to method A to give o-azidostyryl methyl sulphide (40.4 mg, 57%) as an unstable oil, λ max (EtOH) 206 (logε 3.88), 225 (3.84), 264 (3.92), 291 nm (4.12); ν max (film) 2120 vs, 1590 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.35-6.8 (6H, m), 2.35 (3H, s); m/z 191 (M^+), 163, 148 (100%) and methyl styryl sulphide[144] as a contaminent.

4.6 Thermolysis of Azides

General Method

The appropriate azide was dissolved in dry toluene (50 ml per 100 mg azide) in a r.b. flask fitted with reflux condenser. The apparatus was flushed with nitrogen before heating the solution to reflux in a hot oil bath. The reaction was followed by t.l.c. and when the starting material was consumed thermolysis was stopped. After removal of the solvent the residue was chromatographed. Unless otherwise stated column chromatography was used (silica H, gradient elution from 50% dichloromethane in petrol to dichloromethane, the product being obtained by further elution with 5% ether in dichloromethane).

Ethyl 2-phenylthieno[3,2c][1λ^4,2]thiazine-3-carboxylate (26a)

Following the general method, ethyl 3-(3-azido-2-thienyl)-2-phenylthioprop-2-enoate (100 mg, 0.3 mmol) gave ethyl 2-phenylthieno-[3,2c][1λ^4,2]thiazine-3-carboxylate (82 mg, 90%) as red crystals, m.p. 128-129°C (lit.,[98] 128-129°C).

Ethyl 2-methylthieno[3,2c][1λ^4,2]thiazine-3-carboxylate (26b)

Following the general method, ethyl 3-(3-azido-2-thienyl)-2-methylthioprop-2-enoate (100 mg, 0.37 mmol) gave ethyl 2-methylthieno-[3,2c][1λ^4,2]thiazine-3-carboxylate (67 mg, 75%) as red crystals, m.p. 71-72°C (lit.,[98] 72-73°C).

3-Acetyl-2-phenylthieno[3,2c][1λ^4,2]thiazine (26c)

Following the general method, 4-(3-azido-2-thienyl)-3-phenylthiobutenone (100 mg, 0.33 mmol) gave 3-acetyl-2-phenylthieno[3,2c]-[1λ^4,2]thiazine (81.6 mg, 90%) as red crystals, m.p. 135-136°C, (Found: C, 61.5; H, 4.0; N, 5.1. $C_{14}H_{11}NOS_2$ requires C, 61.5; H, 4.1; N, 5.1%); λmax (EtOH) 221 (logε 4.20), 332 (3.96) and 478 nm (3.66); νmax (CCl_4) 1635 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.93 (1H, s), 7.63 (1H, d, J 5.5 Hz), 7.5-7.25 (5H, m), 6.87 (1H, d, J 5.5 Hz), 2.47 (3H, s); δ_c (22.5 MHz, $CDCl_3$) 25.1, 96.5, 115.1, 123.7, 125.3, 128.9, 130.7, 135.5, 138.3, 138.9, 164.6, 191.5; m/z 273 (M^+), 257, 230, 196 (100%).

2-Phenylthieno[3,2c][1λ^4,2]thiazine-3-carbaldehyde (26d)

Following the general method, 3-(3-azido-2-thienyl)-2-phenylthiopropenal (100 mg, 0.35 mmol) gave 2-phenylthieno[3,2c][1λ^4,2]-thiazine-3-carbaldehyde (67.7 mg, 75%) as red crystals, m.p. 138-140°C, (Found: C, 60.0; H, 3.5; N, 5.4. $C_{13}H_9NOS_2$ requires C, 60.2; H, 3.5; N, 5.4%); λmax (EtOH) 219 (logε 4.03), 334 (3.78) and 476 nm (3.48); νmax (CCl_4) 1650 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.53 (1H, s), 7.78 (1H, s), 7.71 (1H, d, J 5.6 Hz), 7.41-7.36 (5H, m), 6.88 (1H, d, J 5.6 Hz); δ_c (22.5 MHz, $CDCl_3$) 96.5,

115.9, 124.0, 125.2, 129.2, 131.1, 138.7, 139.4, 140.0, 166.2, 184,8; m/z 259 (M^+), 243, 182 (100%).

2-Phenylthieno[3,2c][1λ^4,2]thiazine-3-carbonitrile (26e)

Following the general method 3-(3-azido-2-thienyl)-2-phenylthiopropenenitrile (100 mg, 0.35 mmol) gave 2-phenylthieno[3,2c]-[1λ^4,2]thiazine-3-carbonitrile (81 mg, 90%) as red crystals, m.p. 161-162°C, (Found: C, 60.9; H, 3.15; N, 10.9. $C_{13}H_8N_2S_2$ requires C, 60.9; H, 3.1; N, 10.9%); λ max (EtOH) 220 (logϵ 4.18), 286 (3.86), 330 (3.88) and 457 nm (3.43); ν max (CCl_4) 2195 m cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.71 (1H, d, J 0.6 Hz), 7.63 (1H, d, J 5.5 Hz), 7.55-7.25 (5H, m), 6.9 (1H, dd, J 5.5 and 0.6 Hz); δ_c (62.9 MHz, $CDCl_3$) 64.5, 116.4, 116.8, 123.9, 125.3, 129.2, 131.5, 137.4, 138.4, 138.7, 161.8; m/z 256 (M^+), 179 (100%).

Ethyl 2-ethylthieno[3,2c][1λ^4,2]thiazine-3-carboxylate (26f)

According to the general method, ethyl 3-(3-azido-2-thienyl)-2-ethylthioprop-2-enoate (100 mg, 0.35 mmol) gave ethyl 2-ethylthieno-[3,2c][1λ^4,2]thiazine-3-carboxylate (27 mg, 30%) as a dark red gum (Found: M^+ 255.0376. $C_{11}H_{13}NO_2S_2$ requires M^+ 255.0388); λ max (EtOH) 220 (logϵ 4.05), 270 (3.96), 323 (3.96) and 468 nm (3.72); ν max (CCl_4) 1690 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.04 (1H, s), 7.6 (1H, d, J 5 Hz), 6.8 (1H, d, J 5 Hz), 4.3 (2H, q, J 6.5 Hz), 2.68 (2H, qm, J 7 Hz), 1.33 (3H, t, J 6.5 Hz), 1.1 (3H, t, J 7 Hz); δ_c (22.5 MHz, $CDCl_3$) 6.3, 14.4, 36.4, 61.1, 83.8, 114.5, 124, 136.1, 136.7, 162.5, 163.2; m/z 255 (M^+), 226 (100%), 198.

Ethyl 6-(3-propenyl)thieno[3,2b]pyrrole-5-carboxylate (70)

According to the general method, ethyl 3-(3-azido-2-thienyl)-2-(3-propenylthio)prop-2-enoate (100 mg, 0.34 mmol) gave ethyl 6-(3-propenyl)thieno[3,2b]pyrrole-5-carboxylate (65 mg, 72%),

m.p. 96-98°C (Found: C, 61.2; H, 5.6; N, 5.9. $C_{12}H_{13}NO_2S$ requires C, 61.25; H, 5.6; N, 5.95%); λmax (EtOH) 210 (logε 3.73), 291 (4.24), 302 nm (4.20); νmax (CCl_4) 3460 m, 1690 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.0 (1H, s), 7.28 (1H, d, J 5 Hz), 6.9 (1H, d, J 5 Hz), 6.3-5.8 (1H, m), 5.35-5.0 (2H, m), 4.37 (2H, q, J 7.5 Hz), 3.77 (2H, m), 1.4 (3H, t, J 7.5 Hz); δ_c (22.5 MHz, $CDCl_3$) 14.5, 31.0, 60.5, 111.1, 116.4, 122.3, 122.5, 125.6, 129.7, 135.5, 139.9, 162.1; m/z 235 (M^+), 100%), 206, 189.

Ethyl 2-phenylthieno [3,4c][1λ^4,2] thiazine-3-carboxylate (80a)

According to the general method, ethyl 3-(4-azido-3-thienyl)-2-phenylthioprop-2-enoate (100 mg, 0.3 mmol) gave ethyl 2-phenylthieno-[3,4c][1λ^4,2] thiazine-3-carboxylate (52 mg, 58%) as an unstable dark red gum, (Found: M^+ 303.0387. $C_{15}H_{13}NO_2S_2$ requires M^+ 303.0388); λmax (EtOH) 228 (logε 4.06), 266 (3.99), 320 nm (3.89); νmax (CCl_4) 1690 s cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.16 (1H, d, J 0.7 Hz), 7.56-7.51 (2H, m), 7.49 (1H, d, J 3.3 Hz), 7.3-7.2 (3H, m), 6.53 (1H, dd, J 3.3 and 0.7 Hz), 4.35 (2H, qm, J 7 Hz), 1.35 (3H, t, J 7 Hz); δ_c(62.9 MHz, $CDCl_3$) 14.2, 61.9, 100.3, 113.8, 125.4, 125.7, 128.7, 129.2, 130.9, 137.5, 143.4, 148.7, 162.8; m/z 303 (M^+), 258, 226 (100%).

Ethyl 3-phenylthiothieno [2,3b] pyrrole-5-carboxylate (88)

According to the general method, ethyl 2-azido-3-(4-phenylthio-3-thienyl)prop-2-enoate (100 mg, 0.3 mmol) gave ethyl 3-phenylthio-thieno [2,3b] pyrrole-5-carboxylate (80.6 mg, 88%), m.p. 163°C, (Found: C, 59.4; H, 4.3; N, 4.5. $C_{15}H_{13}NO_2S_2$ requires C, 59.3; H, 4.3; N, 4.6%); λmax (EtOH) 242 (logε 4.39) and 290 nm (4.38); νmax (CCl_4) 3470 m, 1685 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 10.7 (1H, s), 7.15 (5H, m), 6.9 (1H, s), 6.72 (1H, s), 4.32 (2H, q, J 7 Hz), 1.36 (1H, t, J 7 Hz); m/z 303 (M^+), 257 (100%), 227.

Ethyl 2-methyl-3-phenylthiothieno [2,3c] pyridine-5-carboxylate (89)

According to the general method, 2-azido-3-(2,5-dimethyl-4-phenylthio-3-thienyl)prop-2-enoate (60 mg, 0.16 mmol) gave ethyl 2-methyl-3-phenylthiothieno [2,3c] pyridine-5-carboxylate (45 mg, 82%) as an oil (Found: C, 61.9; H, 4.7; N, 4.2. $C_{17}H_{15}NO_2S_2$ requires C, 62.0; H, 4.6; N, 4.25%); λ max (EtOH) 208 (logϵ 3.83), 237 (4.00), 302 (3.18), 313 nm (3.21); ν max (CCl_4) 1710 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.16 (1H, s), 8.5 (1H, s), 7.2-6.95 (5H, m), 4.48 (2H, q, J 6.5 Hz), 2.76 (3H, s), 1.43 (3H, t, J 6.5 Hz); m/z 329 (M^+), 257 (100%).

Thermolysis of 2-(3-Azido-2-thienyl)ethenyl methyl sulphide (123b)

Following the general method, 2-(3-Azido-2-thienyl)ethenyl methyl sulphide (77 mg, 0.39 mmol) was thermolysed in benzene solution to give 5-methylthiothieno [3,2b] pyrrole (11.9 mg, 18%), 6-methylthiothieno [3,2b] pyrrole (12 mg, 18%) which were identical to the thienopyrroles isolated from the photolysis of sulphide (123b) and 2-methylthieno [3,2c][1λ^4,2]thiazine (3 mg, 4.5%) as an oil (Found: M^+ 169.0012. $C_7H_7NS_2$ requires M^+ 169.0020); λ max (EtOH) 211 (log 3.35), 232 (3.36), 282 (3.29), 392 nm (2.73); δ_H (250 MHz, $CDCl_3$) 7.37 (1H, d, J 5.5 Hz), 7.2 (1H, dd, J 8.5 and 0.7 Hz), 6.82 (1H, dd, J 5.5 and 0.7 Hz), 4.99 (1H, d, J 8.5 Hz), 2.2 (3H, s); m/z 169 (M^+), 154 (100%).

4.7 Thermolysis of Thieno [3,2c][1λ^4,2] thiazines

General Method

The appropriate thiazine was dissolved in dry xylene (50 ml per 100 mg) in a r.b. flask fitted with reflux condenser. The apparatus was then flushed with nitrogen and then heated on an oil bath to attain gentle refluxing of the solution. The reaction was then

monitored by t.l.c. and when the starting material had been consumed heating was stopped. After removal of the solvent the residue was chromotographed on a column of silica (gradient elution from petrol to dichloromethane) to obtain the product.

Ethyl 4a-phenyl-4aH-thieno[3,2c][1,2]thiazine (76a)

Following the literature method,[98] ethyl 2-phenylthieno[3,2c]-[1λ⁴,2]thiazine (100 mg, 0.33 mmol) gave ethyl 4a-phenyl-4aH-thieno-[3,2c][1,2] thiazine (96 mg, 96%).

Ethyl 4a-methyl-4aH-thieno[3,2c][1,2] thiazine (76b)

Following the general method, ethyl 2-methylthieno[3,2c][1λ⁴,2]-thiazine (100 mg, 0.37 mmol) gave ethyl 4a-methyl-4aH-thieno[3,2c]-[1,2]thiazine[98] (40 mg, 40%) and ethyl thieno[3,2d][1,3]thiazepine-4-carboxylate (26 mg, 26%) m.p. 117-118°C, (Found: C, 49.8; H, 4.5; N, 5.6. $C_{10}H_{11}NO_2S_2$ requires C, 49.8; H, 4.6; N, 5.8%); λ max (EtOH) 263 (logε 3.92), 302 (3.91), 313 (3.83), 388 nm (3.88); ν max (CCl_4) 3440 m, 1700 s cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.1 (1H, s), 7.36 (1H, d, J 5 Hz), 6.63 (1H, d, J 5 Hz), 5.48 (1H, t, J 4 Hz), 4.37 (2H, d J 4 Hz), 4.29 (2H, q, J 7 Hz), 1.34 (3H, t, J 7 Hz); δ_c (62.9 MHz, $CDCl_3$) 14.4, 53.3, 61.5, 114.7, 122.4, 124.3, 129.5, 134.3, 148.1, 169.9; m/z 241 (M^+, 100%), 212, 209, 196.

3-Acetyl-4a-phenyl-4aH-thieno[3,2c][1,2] thiazine (76c)

Following the general method, 3-acetyl-2-phenylthieno[3,2c][1,2]-thiazine (100 mg, 0.37 mmol) gave 3-acetyl-4a-phenyl-4aH-thieno-[3,2c][1,2] thiazine (80 mg, 80%) as an oil (Found: C, 61.5; H, 42; N, 5.0. $C_{14}H_{11}NO_2S_2$ requires C, 61.5; H, 4.1; N, 5.1%); λ max (EtOH) 215 (log 4.08), 279 (3.75), 336 nm (3.60); ν max 1680 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.36 (1H, d, J 6.5 Hz), 7.3-7.06 (6H, m), 2.48 (3H, s); δ_c (22.5 MHz, $CDCl_3$) 26.5, 59.4, 120.1, 125.5, 128.6, 137.5, 139.1, 142.1, 166.2, 193.0; m/z 273 (M^+), 257, 230 (100%).

4a-Phenyl-4aH-thieno[3,2c][1,2]thiazine-3-carbaldehyde (76d)

Following the general method, 2-phenylthieno[3,2c][1λ^4,2]-thiazine-3-carbaldehyde (100 mg, 0.39 mmol) gave 4a-phenyl-4aH-thieno-[3,2c][1,2]thiazine-3-carbaldehyde (54 mg, 54%), m.p. 90°C (Found: C, 60.2; H, 3.4; N, 5.4. $C_{13}H_9NOS_2$ requires C, 60.2; H, 3.5; N, 5.4%); λmax (EtOH) 215 (logε 4.23), 279 (3.51), 335 nm (3.35); νmax (CCl_4) 1690 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.67 (1H, s),7.39 (1H, d, J 6.4 Hz), 7.25-7.2 (6H, m), 6.53 (1H, d, J 6.4 Hz); δ_c (22.5 MHz, $CDCl_3$) 29.7, 59.2, 120.3, 125.6, 127.5, 128.8, 137.2, 139.4, 142.1, 166.5, 186.4; m/z 259 (M^+), 230 (100%).

4a-Phenyl-4aH-thieno[3,2c][1,2]thiazine-3-carbonitrile (76e)

Following the general method, 2-phenylthieno[3,2c][1λ^4,2]-thiazine-3-carbonitrile (100 mg, 0.39 mmol) gave 4a-phenyl-4aH-thieno[3,2c][1,2]thiazine-3-carbonitrile (88 mg, 88%), m.p. 161-162°C (Found: C, 61.2; H, 3.1; N, 10.9. $C_{13}H_8N_2S_2$ requires C, 60.9; H, 3.15; N, 10.9%); λmax (EtOH) 210 (logε 4.08), 270 (3.53), 333 (3.48); νmax (CCl_4) 2220 m cm^{-1}; δ_H (90 MHz, $CDCl_3$) 7.46 (1H, d, J 6.4 Hz), 7.36-7.02 (6H, m), 6.53 (1H, d, J 6.4 Hz); δ_c (22.5 MHz, $CDCl_3$) 59.1, 112.8, 113.5, 119.8, 125.5, 125.8, 128.8, 128.9, 136.2, 144.4, 166.1; m/z 256 (M^+, 100%), 223, 179.

4.8 Photolysis of Azides and Thiazines

General Method

The appropriate starting material was dissolved in acetonitrile (150 ml per 100 mg of material). Then nitrogen was bubbled through the solution for 0.5 h. The solution was then irradiated at the appropriate wavelength while maintaining the nitrogen flow. The reaction was monitored by t.l.c. and when the starting material had been consumed the irradiation was stopped. Removal of the solvent gave a residue which was chromatographed using a column of silica

(gradient elution from petrol to dichloromethane then to 10% ether in dichloromethane).

Ethyl 6-acetylthieno [3,2b] pyrrole-5-carboxylate (103)

Following the general method, ethyl 2-acetyl-3-(3-azido-2-thienyl)propenoate (100 mg, 0.38 mmol) was irradiated at 350 nm and gave ethyl 6-acetylthieno [3,2b] pyrrole-5-carboxylate (89 mg, 90%), m.p. 110°C (Found: C, 55.7; H, 4.6; N, 5.85. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.7; N, 5.9%); λ max (EtOH) 247 (logϵ 3.75), 255 (3.76), 325 nm (3.61); ν max (CCl_4) 3420 m, 1720 s, 1680 s, 1640 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.75 (1H, s), 7.42 (1H, d, J 5 Hz), 6.96 (1H, d, J 5 Hz), 4.45 (2H, q, J 7 Hz), 2.83 (3H, s), 1.43 (3H, t, J 7 Hz); δ_c (22.5 MHz, $CDCl_3$) 14.3, 30.8, 61.6, 110.4, 122.2, 125.0, 128.0, 132.2, 138.2, 160.1, 194.2; m/z 237 (M^+), 222, 191 (100%), 176.

5-Acetylthieno [3.2b] pyrrole (104)

Following the general method, 3-(3-azido-2-thienyl)butenone (100 mg, 0.52 mmol) was irradiated at 350 nm and gave 5-acetylthieno [3,2b] pyrrole (77 mg, 90%) m.p. 161-162°C (lit.,[128] m.p. 160.5-163°C).

Ethyl 6-phenylthiothieno [3,2b] pyrrole-5-carboxylate (98)

Following the general method, ethyl 2-phenylthieno [3,2c] - [1λ^4,2] thiazine-3-carboxylate (100 mg, 0.33 mmol) was irradiated at 350 nm and gave ethyl 6-phenylthiothieno [3,2b] pyrrole-5-carboxylate (80 mg, 80%), m.p. 136°C (lit.,[98] m.p. 136-137°C).

5-Acetyl-6-phenylthiothieno [3,2b] pyrrole (109)

Following the general method, 3-acetyl-2-phenylthieno [3,2c] - [1λ^4,2] thiazine (100 mg, 0.37 mmol) was irradiated at 350 nm and gave 5-acetyl-6-phenylthiothieno [3,2b] pyrrole (77 mg, 77%), m.p. 127-129°C (Found: C, 61.5; H, 4.3; N, 5.1. $C_{14}H_{12}NOS_2$ requires C, 61.5; H, 4.1; N, 5.1%); λ max (EtOH) 205 (logϵ 4.11), 247 (3.96),

320 nm (4.22); ν max (CCl_4) 3440 m, 1630 s; δ_H (90 MHz, $CDCl_3$) 10.09 (1H, s), 7.37-7.2 (6H, m), 6.93 (1H, d, J 5 Hz), 2.74 (3H, s); δ_c (62.9 MHz, $CDCl_3$) 28.0, 111.4, 112.2, 126.8, 129.1, 129.2, 129.7, 131.5, 134.6, 135.6, 140.8, 189.1; m/z 273 (M^+, 100%), 258, 231.

6-Phenylthiothieno [3,2b] pyrrole-5-carbaldehyde (110)

Following the general method 2-phenylthieno [3,2c][$1\lambda^4$,2] thiazine-3-carbaldehyde (100 mg, 0.39 mmol) was irradiated at 350 nm and gave 6-phenylthiothieno [3,2b] pyrrole-5-carbaldehyde (75 mg, 75%), m.p. 189-191°C (Found: C, 60.0; H, 3.5; N, 5.2. $C_{13}H_9NOS_2$ requires C, 60.0; H, 3.5; N, 5.4%); λmax (EtOH) 203 (logε 3.96), 221 (3.74), 246 (3.71), 325 nm (4.04); ν max (CCl_4) 3440 m, 1645 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.92 (1H, s), 9.55 (1H, s), 7.42 (1H, d, J 5.6 Hz), 7.31-7.26 (5H, m), 6.98 (1H, d, J 5.6 Hz); m/z 259 (M^+), 243 (100%).

4-Methyl-6-phenylthiothieno [3,2b] pyrrole-5-carbaldehyde

To a suspension of sodium hydride (2.3 mg, 0.1 mmol) in dry DMF (3 ml) at 0°C was added a solution of 6-phenylthiothieno [3,2b]-pyrrole-5-carbaldehyde (21.4 mg, 0.08 mmol) in dry DMF (0.5 ml). After 5 min, methyl iodide (34 mg, 0.24 mmol) was added and the reaction mixture was stirred for 30 min. The reaction mixture was then poured into water and extracted with ether (2 x 100 ml). The organic phase was collected, dried over magnesium sulphate and the solvent removed. The residue was chromatographed on silica gel to give 4-methyl-6-phenylthiothieno [3,2b] pyrrole-5-carbaldehyde (15.9 mg, 70%), m.p. 123-125°C, (Found: C, 61.3; H, 4.1; N, 5.2. $C_{14}H_{11}NOS_2$ requires C, 61.5; H, 4.05; N, 5.1%); ν max (CCl_4), 1655 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 10.3 (1H, s), 7.41 (1H, d, J 5.6Hz), 7.3-7.18 (5H, m), 6.95 (1H, d, J 5.6 Hz), 4.11 (3H, s); m/z 273 (M^+, 100%).

Ethyl 6-phenylsulphinylthieno [3,2b] pyrrole-5-carboxylate (116)

Following the general method ethyl 3-(3-azido-2-thienyl)-2-phenylsulphinylpropenoate (100 mg, 0.29 mmol) was irradiated at 350 nm and gave ethyl 6-phenylsulphinylthieno [3,2b] pyrrole-5-carboxylate (48 mg, 52%), m.p. 154°C (Found: C, 56.2; H, 4.0; N, 4.4. $C_{14}H_{13}NO_3S_2$ requires C, 56.4; H, 4.1; N, 4.4%); λ max (EtOH) 233 (logε 3.98) and 302 nm (4.21); ν max (CCl_4) 3440 m, 1695 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 10.68 (1H, s), 7.93-7.8 (2H, m), 7.5-7.3 (3H, m), 7.23 (1H, d, J 5 Hz), 6.84 (1H, d, J 5 Hz), 4.35 (2H, q, J 6.5 Hz), 1.3 (3H, t, J 6.5 Hz); δ_c (22.5 MHz, $CDCl_3$) 14.3, 61.4, 110.9, 122.1, 124.1, 129.0, 130.8, 141,0, 144.9, 160.0; m/z 319 (M^+), 303, 271, 257, 225 (100%) and ethyl 2-phenylthieno-[3,2c][1,2] thiazine-3-carboxylate-2-oxide (24.8 mg, 27%) m.p. 148-151°C (Found: C, 56.3; H, 4.1; N, 4.4. $C_{15}H_{13}NO_3S_2$ requires C, 56.4; H, 4.0; N, 4.4%); λ max (EtOH) 206 (logε 4.24), 318 (4.14), 388 nm (3.79); ν max (CCl_4) 1705 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.5 (1H, s), 8.0-7.82 (2H, m), 7.77 (1H, d, J 5.5 Hz), 7.65-7.5 (3H, m), 6.98 (1H, d, J 5.5 Hz), 4.1 (2H, qm, J 7 Hz), 1.02 (3H, t, J 7 Hz); δ_c (22.5 MHz, $CDCl_3$) 13.8, 61.4, 101.7, 112.9, 123.7, 128.4, 129.4, 133.1, 136.9, 137.6, 141.8, 154.7, 162.3; m/z 319 (M^+, 100%).

Ethyl 6-phenylsulphonylthieno [3,2b] pyrrole-5-carboxylate (118)

Following the general method ethyl 3-(3-azido-2-thienyl)-2-phenylsulphonylpropenoate (100 mg, 0.28 mmol) was irradiated at 350 nm and gave ethyl 6-phenylsulphonylthieno [3,2b] pyrrole-5-carboxylate (74 mg, 80%), m.p. 171-175°C (Found: C, 53.7; H, 3.8; N, 4.2. $C_{15}H_{13}NO_4S_2$ requires C, 53.7; H, 3.9; N, 4.2%); λ max (EtOH) 228 (logε 4.00), 242 (3.93), 255 (3.91), 306 nm (4.07); ν max (CCl_4) 3420 m, 1690 s, cm^{-1}; δ_H (90 MHz, $CDCl_3$) 10.02 (1H, s), 8.11-7.94 (2H, m), 7.6-7.46 (4H, m), 6.97 (1H, d, J 5.5 Hz),

4.3 (2H, q, J 6.5 Hz), 1.25 (3H, t, J 6.5 Hz); δ_c (62.9 MHz, $CDCl_3$) 14.1, 61.7, 110.9, 121.9, 124.7, 127.5, 127.8, 128.5, 132.0, 133.0, 138.2, 142.6, 158.7; m/z 335 (M^+, 100%), 289.

Independent Synthesis of Ethyl 6-phenylsulphinylthieno-3,2b pyrrole-5-carboxylate (116)

To a solution of ethyl 6-phenylthiothieno [3,2b] pyrrole-5-carboxylate (50 mg, 0.17 mmol) in ethanol (10 ml) was added a solution of sodium metaperiodate (53 mg, 0.25 mmol) in water : ethanol (5 ml : 5 ml). The reaction mixture was stirred until the starting material had been consumed. The solution was then poured into water and extracted with ether (2 x 200 ml). The organic layer was then dried over magnesium sulphate and the solvent removed. Column chromatography on silica gel gave ethyl 6-phenylsulphinylthieno-[3,2b] pyrrole-5-carboxylate (52 mg, 99%), m.p. 154°C.

Independent Synthesis of Ethyl 6-phenylsulphonylthieno-[3,2b] pyrrole-5-carboxylate (118)

Following the literature procedure for oxidation of sulphides,[136] ethyl 6-phenylthiothieno [3,2b] pyrrole-5-carboxylate (50 mg, 0.17 mmol) was treated with potassium permanganate in acetic acid, to give ethyl 6-phenylsulphonylthieno [3,2b] pyrrole-5-carboxylate (8.3 mg, 15%) m.p. 171-175°C.

6-Methylsulphonyl-5-methylthiothieno [3,2b] pyrrole (120)

Following the general method 2-(3-azido-2-thienyl)-1-methyl-thioethenyl methyl sulphoxide (100 mg, 0.39 mmol) was irradiated at 350 nm and gave 6-methylsulphonyl-5-methylthiothieno [3,2b] pyrrole (4.9 mg, 55%) as an unstable oil (Found: M^+ 230.9845. $C_8H_9NOS_3$ requires M^+ 230.9846); λmax (EtOH) 206 (logε 3.75), 230 (3.67), 253 (3.63), 275 (3.67); νmax (CCl_4) 3440 m cm^{-1}; δ_H (90 MHz,

$CDCl_3$) 10.22 (1H, s), 7.2 (1H, d, J 5 Hz), 6.86 (1H, d, J 5 Hz), 3.0 (3H, s), 2.4 (3H, s); m/z 231 (M^+), 215, 200, 184, 169, 154 (100%).

Photolysis of 2-(3-Azido-2-thienyl)ethenyl phenyl sulphide (123a)

Following the general method, impure 2-(3-azido-2-thienyl)ethenyl phenyl sulphide (250 mg) was irradiated at 300 nm and gave, after column chromatography a non polar fraction (100 mg) thought to be the impurities in the starting material and two polar components identified as 5-phenylthiothieno [3,2b] pyrrole (20 mg) as an oil (Found: C, 62.6; H, 3.9; N, 5.8. $C_{12}H_9NS_2$ requires C, 62.3; H, 3.9; N, 6.05%); ν max 3470 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 8.3 (1H, s), 7.3-7.05 (6H, m), 6.9 (1H, dd, J 5 and 0.7 Hz), 6.8 (1H, dd, J 2.5 and 0.7 Hz); m/z 231 (M^+, 100%) and 6-phenylthiothieno [3,2b] pyrrole (27 mg) m.p. 131-132°C (lit.,[98] m.p. 131-132°C).

Photolysis of 2-(3-Azido-2-thienyl)ethenyl methyl sulphide (123b)

Following the general method, 2-(3-azido-2-thienyl)ethenyl methyl sulphide (100 mg, 0.5 mmol) was irradiated at 300 nm and gave 5-methylthiothieno [3,2b] pyrrole (23 mg, 27%) as an oil (Found: M^+ 169.0015. $C_7H_7NS_2$ requires M^+ 169.0020); λ max (EtOH) 213 (logε 3.76), 232 (3.82), 274 nm (4.17); ν max (CCl_4) 3465 s; δ_H (90 MHz, $CDCl_3$) 8.2 (1H, s), 7.12 (1H, d, J 5 Hz), 6.88 (1H, d, J 5 Hz), 6.58 (1H, d, J 1.5 Hz), 2.43 (3H, s); δ_c (62.9 MHz, $CDCl_3$) 21.7, 107.7, 110.8, 119.0, 124.5, 127.5, 139.7; m/z 169 (M^+), 154 (100%) and 6-methylthiothieno [3,2b] pyrrole[98] (19 mg, 22%).

Formylation of the methylthiothienopyrroles

The thienopyrrole (1 equiv.) was dissolved in dry DMF (2 ml) and cooled to 0°C. Then phosphoryl chloride (1 equiv.) was added.

The reaction mixture was stirred for 1 h then poured into ice water. The aqueous phase was extracted with ether (2 x 250 ml). The organic phase was washed with water (100 ml) and brine (100 ml) before drying over magnesium sulphate and removing the solvent. Column chromatography on silica gel gave the product. 5-Methylthiothieno [3,2b] pyrrole (30 mg, 0.17 mmol) gave 5-methylthiothieno-[3,2b] pyrrole-6-carbaldehyde (30 mg, 86%) m.p. 181-183°C (Found: C, 48.2; H, 3.4; N, 7.1. $C_8H_7NOS_2$ requires C, 48.7; H, 3.6; N, 7.1%); λ max (EtOH) 215 (logε 3.32), 248 (3.55), 261 (3.55), 290 (3.27), 320 nm (3.03); ν max (CCl_4) 3440 m, 1645 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 10.05 (1H, s), 7.26 (1H, d, J 5 Hz), 6.9 (1H, d, J 5 Hz), 2.52 (3H, s); m/z 197 (M^+, 100%), 182, 164, 154. 6-Methylthiothieno [3,2b] pyrrole (30 mg, 0.17 mmol) gave 6-methylthiothieno [3,2b] pyrrole-5-carbaldehyde (29.7 mg, 85%) m.p. 177-178°C (Found: C, 48.6; H, 3.5; N, 7.0. $C_8H_7NOS_2$ requires C, 48.7; H, 3.6; N, 7.1%); λ max (EtOH) 232 (logε 3.11), 2.58 (3.03), 323 nm (3.37); ν max (CCl_4) 3450, 1645 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.76 (1H, s), 7.4 (1H, d, J 5 Hz), 6.93 (1H, d, J 5 Hz), 2.55 (3H, s); m/z 197 (M^+, 100%), 182, 164, 154.

Photolysis of 2-(3-azido-2-thienyl)ethenyl phenyl sulphoxide (131)

Following the general method, 2-(3-azido-2-thienyl)ethenyl phenyl sulphoxide (100 mg, 0.36 mmol) was irradiated at 300 nm and gave 5-phenylsulphinylthieno 3,2b pyrrole (23 mg, 26%), (Found: M^+ 247.0131. $C_{12}H_9NOS_2$ requires M^+ 247.0126); λ max (EtOH) 203 (logε 3.58), 230 (3.15), 273 nm (3.26); ν max (CCl_4) 3440 m cm^{-1}; δ_H (90 MHz, $CDCl_3$) 10.9 (1H, s), 7.8-7.4 (5H, s), 7.32 (1H, d, J 6 Hz), 7 (1H, s), 6.94 (1H, d, J 6 Hz); m/z 247 (M^+), 231, 199 (100%), and 6-phenylsulphinylthieno [3,2b] pyrrole (43 mg, 48%) (Found: M^+ 247.0131. $C_{13}H_9NOS_2$ requires M^+ 247.0125); λ max (EtOH)

205 (logε 3.70), 236 nm (3.76); δ_H (90 MHz, d_6 DMSO) 12.91 (1H, s), 7.83 (1H, s), 7.7-7.4 (5H, m), 7.17 (1H, d, J 4.6 Hz), 7.0 (1H, d, J 4.6 Hz); m/z (M^+), 231, 199 (100%) and 2-phenylthieno[3,2c][1,2]-thiazine-2-oxide (20 mg, 22%) as an oil (Found: M^+ 247.0132. $C_{12}H_9NOS_2$ requires M^+ 247.0126); λ max (EtOH) 206 (logε 4.02), 284 (3.78), 243 nm (3.23); δ_H (90 MHz, $CDCl_3$) 8.0-7.88 (2H, m), 7.79 (1H, d, J 9 Hz), 7.68-7.58 (3H, m), 7.5 (1H, d, J 5.5 Hz), 7.0 (1H, d, J 5.5 Hz), 6.0 (1H, d, J 9 Hz); m/z 247 (M^+, 100%).

5-Methylsulphonylthieno[3,2b]pyrrole (139)

Following the general method, 2-(3-azido-2-thienyl)ethenyl methyl sulphone (100 mg, 0.43 mmol) was irradiated at 300 nm and gave 5-methylsulphonylthieno[3,2b]pyrrole (75 mg, 86%), m.p. 175-176°C (Found: C, 41.7; H, 3.3; N, 6.9. $C_7H_6NO_2S_2$ requires C, 42.0; H, 3.0; N, 7.0%); λmax (EtOH) 213 (logε 3.33), 265 (3.86), 276 nm (3.74); νmax (CCl_4) 3440 m cm^{-1}; δ_H (250 MHz, $CDCl_3$) 9.6 (1H, s), 7.39 (1H, d, J 5.5 Hz), 7.13 (1H, dd, J 2.2 and 0.6 Hz), 7.0 (1H, dd, J 5.5 and 0.6 Hz); m/z 201 (M^+), 108 (100%).

Ethyl 3-acetylindole-2-carboxylate (145)

Following the general method, ethyl 2-acetyl-3-(2-azidophenyl)-propenoate (100 mg, 0.39 mmol) was irradiated at 350 nm and gave ethyl 3-acetylindole-2-carboxylate (78.5 mg, 88%), m.p. 96-97°C (lit.,[130] 96-97°C).

Indole-2-carbaldehyde (146)

Following the general method, 3-(2-azidophenyl)propenal (100 mg, 0.58 mmol) was irradiated at 300 nm and gave indole-2-carbaldehyde (75 mg, 90%), m.p. 141°C (lit.,[131] 140-142°C).

Ethyl 3-phenylthioindole-2-carboxylate (147)

Following the general method, ethyl 3-(2-azidophenyl)-2-phenylthiopropenoate (100 mg, 0.3 mmol) was irradiated at 300 nm and gave ethyl 3-phenylthioindole-2-carboxylate (68.5 mg, 75%), m.p. 135°C

(Found: C, 68.8; H, 5.1; N, 4.7. $C_{17}H_{15}NO_2S$ requires C, 68.7; H, 5.1; N, 4.7%); λ max (EtOH) 209 (log ϵ 4.27), 237 (4.22), 300 nm (4.00); ν max (CCl_4) 3450 m, 1690 s cm^{-1}; δ_H (90 MHz, $CDCl_3$) 9.35 (1H, s), 7.6 (1H, d, J 7.7 Hz), 7.38 (1H, dd, J 6.4 and 1 Hz), 7.27-7.0 (7H, m), 7.38 (2H, q, J 7.7 Hz), 1.3 (3H, t, J 7.7 Hz); m/z 297 (M^+), 251 (100%).

3-Methylthioindole (149)

Following the general method, o-azidostyryl methyl sulphide (60 mg, 0.3 mmol) was irradiated at 300 nm and gave 3-methylthioindole[134] (2 8 mg, 55%) δ_H (250 MHz, $CDCl_3$) 8.16 (1H, s), 7.77 (1H, m), 7.36 (1H, m), 7.3-7.15 (3H, m), 2.46 (3H, s); δ_c (62.9 MHz, $CDCl_3$) 20.1, 108.7, 111.5, 119.3, 120.4, 122.8, 127.6, 128.9, 136.5; m/z 163 (M^+), 148 (100%).

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