VINYL AZIDES IN HETEROCYCLIC SYNTHESIS

A thesis presented by

SIU CHUNG TSOI

in partial fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

Hofmann Laboratory,

Chemistry Department,

Imperial College,

South Kensington,

London, SW7 2AY.

For Daisy and my parents

ACKNOWLEDGEMENTS

I am indebted to Professor C.W. Rees and Dr. C.J. Moody for their helpful guidance and constant encouragement throughout the course of this work. I also thank Mr. D. Neuhaus for the n.m.r. spectroscopy and helpful discussions, Mrs. C. Clifford and Mrs. L. Briggs for their diligent typing of the introduction and the experimental section of this thesis respectively and Dr. W.W.L. Chen for the generous use of his typing equipment.

I am most grateful to my parents for their constant support and encouragement and my wife, Daisy, for her love, care and understanding.

I take pleasure in expressing my thanks to Dr. A.M. Roe and Smith, Kline and French Research Limited (Welwyn Garden City) for the award of a Research Studentship, 1978-1981, and Kodak Limited (Research Division, Harrow) for the generous and magnificent reproduction of this thesis.

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
t.l.c.	:	thin layer chromatography
p.l.c.	:	preparative layer chromatography
DMF	:	dimethylformamide
THF	:	tetrahydrofuran
DMSO	:	dimethylsulphoxide
DEAZD	:	diethyl azodicarboxylate
PTAD	:	4-phenyl-1,2,4-triazole-3,5-dione
LTA	:	lead tetraacetate
Ts	:	p-toluenesulphonyl

ABSTRACT

The synthesis and the decomposition of vinyl azides are briefly reviewed.

Intramolecular interactions of substituents which are 1,4 conjugated to the azide function are investigated. The synthesis and the decomposition of a number of such vinyl azides are described.

A chlorine substituent has shown very little interaction, its main function being that of a blocking group. It raises the energy barrier for the cyclization of the nitrene to give five-membered ring heterocycles. Thus, thermolysis of ethyl 2-azido-5-chloro-4-methylhexa-2,4-dieneonate gave ethyl 5-chloro-4-methylpyridine-2-carboxylate by the formal nitrene insertion reaction, as well as other 5-membered heterocyclic products.

When the substituent is an azido group, as in the case of ethyl 2-azido-3-(3-azidothien-2-yl)propenoate, thermolysis gave the expected ethyl thieno[3,2-c]pyridazine-3-carboxylate (26%), the unexpected ethyl 5-cyanoisothiazole-3-carboxylate (27%) with the unprecedented extrusion of acetylene (21%). The mechanisms of their formation are discussed.

From the mechanism of the above acetylene extrusion reaction, it is suggested that there is a strong sulphur-nitrene interaction which forms a $\overset{+}{S}\text{-}\bar{N}$ ylidic linkage. This sulphur-nitrene interaction has been confirmed by the decomposition of a vinyl azide and two aryl azides which have an alkyl or aryl thio substituent 1,4 conjugated to

the azide function. In each case, a derivative of azathiabenzene, a rare heterocyclic system which is a cyclic sulphimide, was obtained in excellent yield. This provides a novel synthesis of azathiabenzene derivatives.

The thermal and photochemical rearrangements of the cyclic sulphimides are also investigated. Thermally, the substituent on the 4-valent sulphur undergoes a [1,4] sigmatropic shift; in addition, when the substituent is a methyl group, a ring expansion reaction leading to a 1,3(3H)-thiazepin or its derived product may also occur. Photochemically, the sulphur-nitrogen bond of the cyclic sulphimides cleaves to generate the corresponding nitrene which then cyclizes to give a pyrrole derivative.

CONTENTS

1. INTRODUCTION

Vinyl azide itself $CH_2=CHN_3$ was first described in 1910.[1] However, most of the chemistry concerning the synthesis and reactions of this class of compounds has been discovered during the past fifteen years.

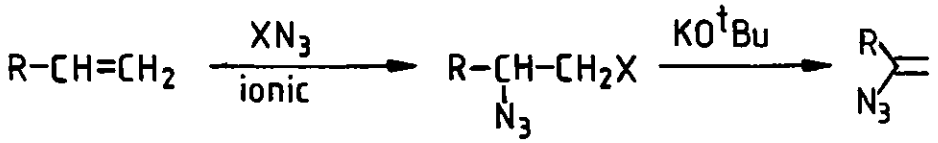
The azide function of this system is susceptible to photolysis, pyrolysis, cycloadditions and attack by nucleophiles as well as by electrophiles. The presence of a neighbouring double bond accentuates the reactivity of the azide group and provides additional intramolecular pathways for reactions. All these factors contribute to the interest generated in these compounds as important intermediates in organic synthesis, and in particular heterocyclic synthesis.

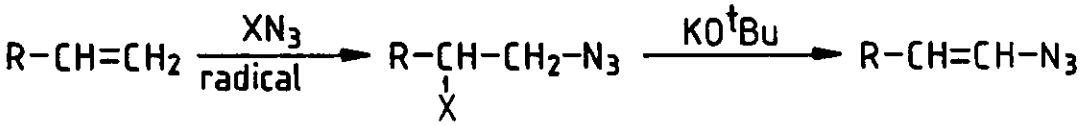
I PREPARATION OF VINYL AZIDES

1.1 Addition-Elimination from Olefins

A general synthetic method for vinyl azides was discovered by Hassner, and has since been widely used.[2] It involves the addition of halogen azides to olefins, followed by dehydrohalogenation of the resulting β-haloalkyl azides with a base such as potassium t-butoxide, sodium methoxide, or 1,4-diazabicyclo[2.2.2]octane.

The addition of halogen azides can occur by either an ionic or a free radical pathway and leads to regioisomeric vinyl azides (SCHEME 1).



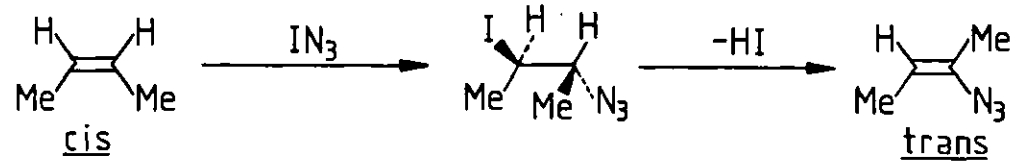


Scheme 1

The preference of halogen azides for heterolytic cleavage increases in the order: $ClN_3 < BrN_3 < IN_3$. Hence iodine azide reacts preferentially by an ionic pathway and stereospecifically anti[2,3] via a cyclic iodonium ion (1),[4] and the dehydroiodination of the β-haloalkyl azide by potassium t-butoxide proceeds in an anti fashion to give the corresponding cis or trans vinyl azides (SCHEME 2). In most cases the transition

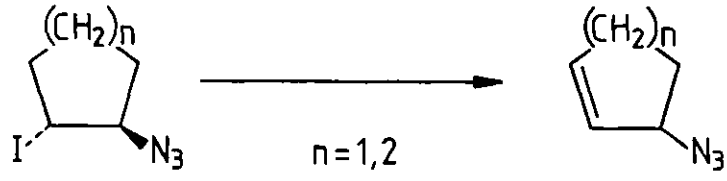
state for anti-dehydrohalogenation to the vinyl azide is of lower energy than that leading to the allyl

(1)



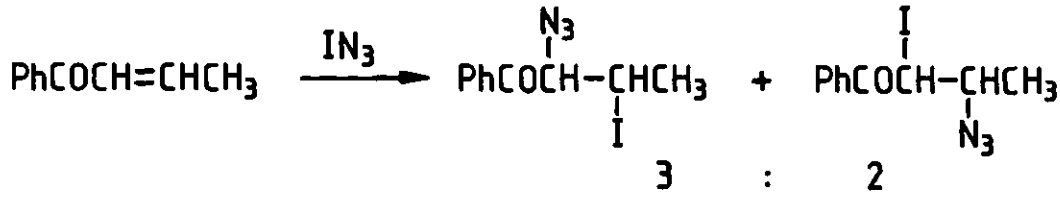
Scheme 2

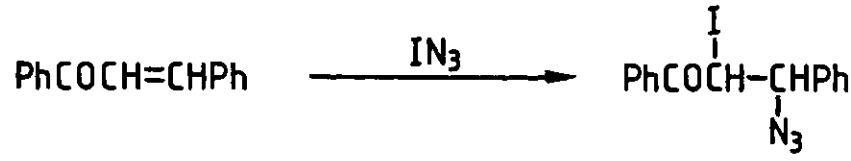
azide; hence regiospecific elimination of hydrogen halide to the vinyl azide is usually observed. An exception is provided by trans-halocycloalkyl azides (ring size smaller than eight) which lead to allyl azides rather than vinyl azides (SCHEME 3).[4]

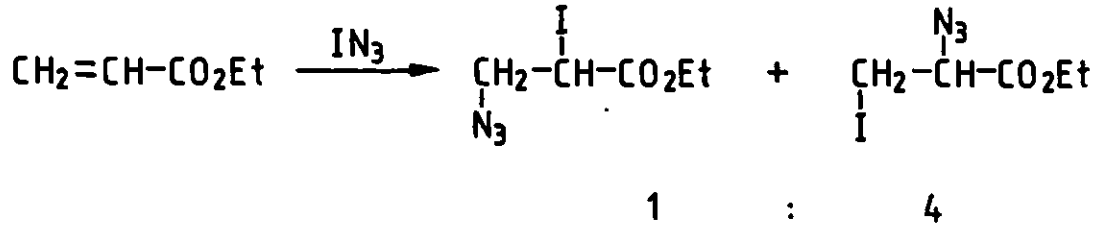


Scheme 3

As expected, the electronic factors of the substituents on the olefins have considerable influence on the mode of halogen azide addition, and can often lead to non-regiospecific reactions (SCHEME 4).[5,6]





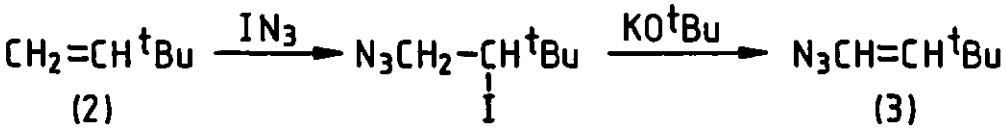


Scheme 4

Steric hindrance can also affect the general mode of addition of IN_3 (electronic control) to olefins,[4,7] as for example with 3,3-dimethyl-1-butene (2), where a steric effect accounts for the exclusive formation of the terminal vinyl azide (3) (SCHEME 5).[4]

With bromine azide, predominantly ionic or predominantly free radical reaction can be obtained, as desired, by changing the solvent and/or addition

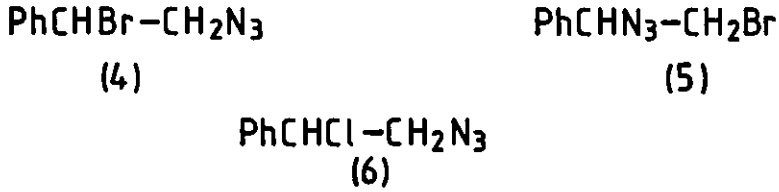
of a free radical inhibitor or initiator.[5,8-10] For example, addition of bromine azide to styrene under



(2) (3)

Scheme 5

radical conditions (in pentane and absence of air) gave a quantitative yield of the precursor (4), while reaction in a more polar solvent (under ionic conditions) gave a very high yield of the regioisomer (5).



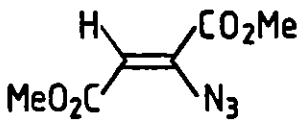
Chlorine azide adds to olefins primarily as a free-radical reagent, a source of azide radical. Thus in pentane or dichloromethane, even in the presence of air, styrene furnished (6) as the sole product. However, under forcing conditions in the presence of fuming sulphuric acid, an ionic reaction was observed.[5]

Thus the above procedure provides a good and general method for preparing vinyl azides regio-specifically from terminal and symmetrical olefins. With unsymmetrical internal olefins, regiospecificity cannot generally be expected. One must also take into account the ability of the substituents on the olefin to stabilize an α carbonium ion or a free

radical, which can change the regioselectivity of the reaction.

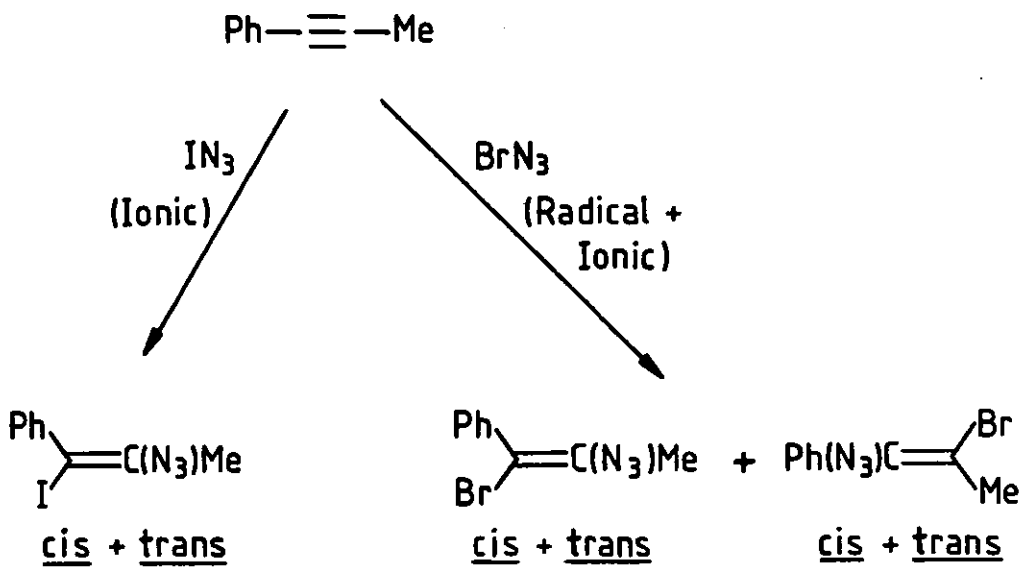
1.2 Addition of XN_3 to Alkynes and Allenes

Addition of hydrazoic acid or sodium azide to acetylenes as a method of preparation of vinyl azides is very limited, and only in a few cases have vinyl azides been obtained. For example, addition of hydrazoic acid to dimethyl acetylenedicarboxylate gave the corresponding vinyl azide (7).[2] A more



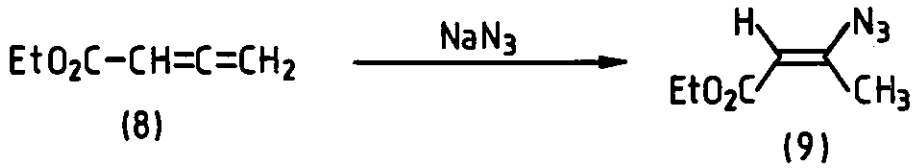
(7)

successful approach is found in the addition of halogen azides to alkynes (SCHEME 6).[11,12]



Scheme 6

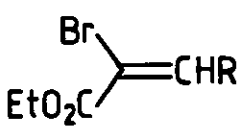
Treatment of allenic esters and amides with an excess of sodium azide has also been found to produce vinyl azides, e.g. (8)→(9).[13]



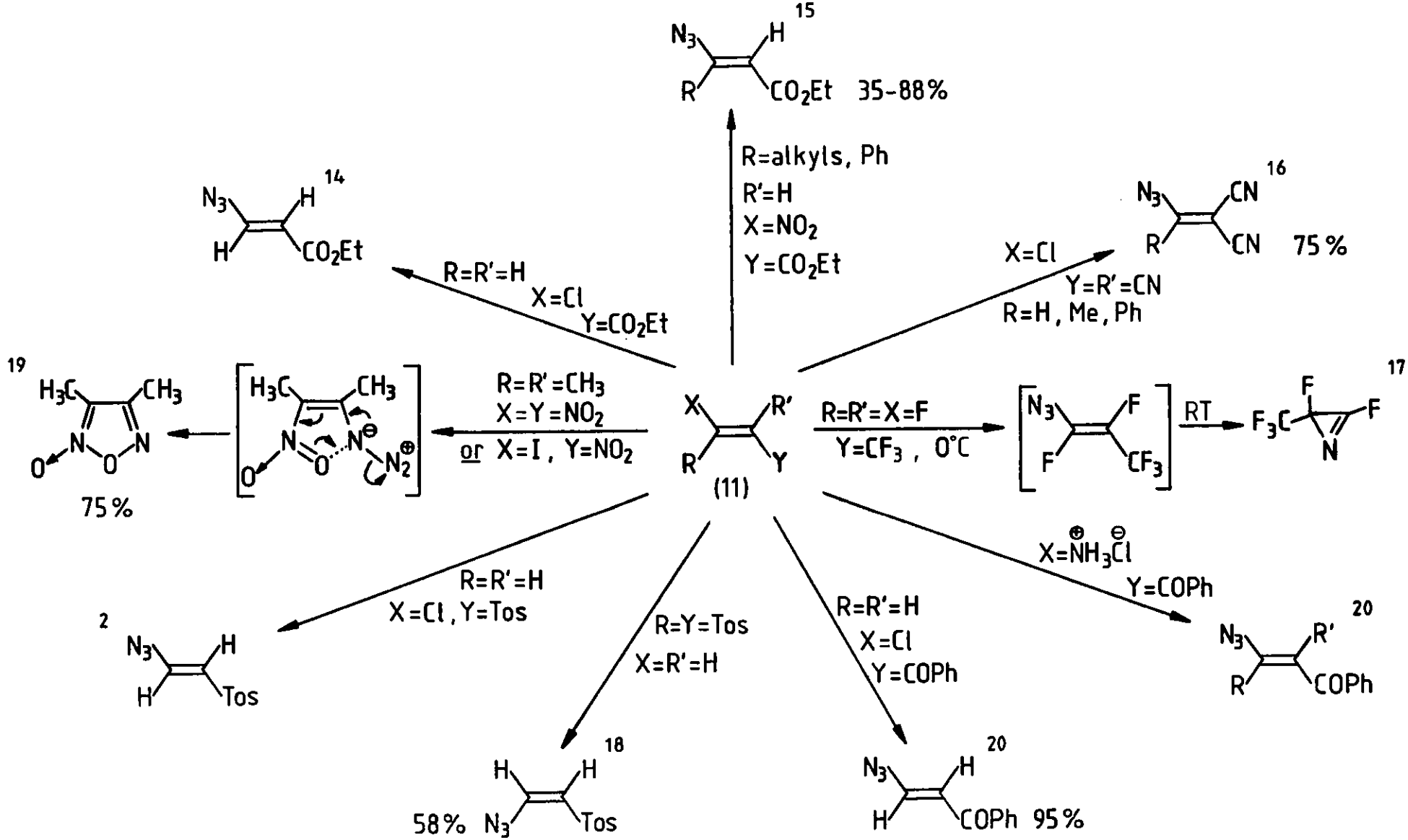
(8) (9)

1.3 Displacement of Activated Olefinic Leaving Groups

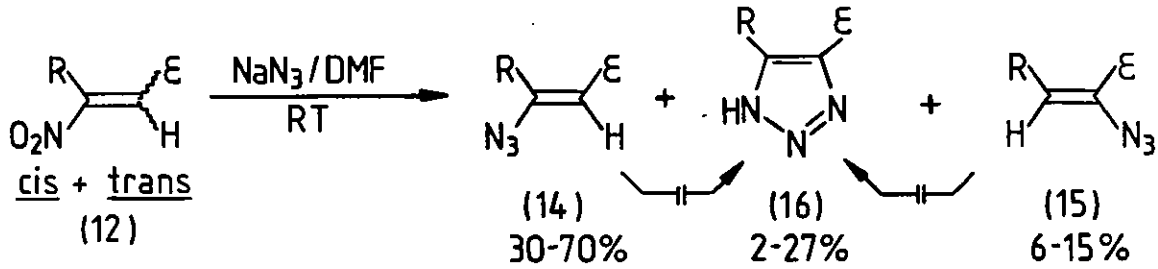
When vinyl halides or other potential leaving group-X, with an electron withdrawing substituent-Y in the β-position, are treated with sodium azide in dipolar aprotic solvents, conjugate addition of the azide ion to the X-carrying carbon of (11) followed by a fast elimination of X^-, will produce the vinyl azide predominantly with retention of configuration about the carbon-carbon double bond.[2] However, if the ester is α to the leaving group X, as in (10), the reaction does not take place.[14] Some of these reactions are summarized in SCHEME 7.

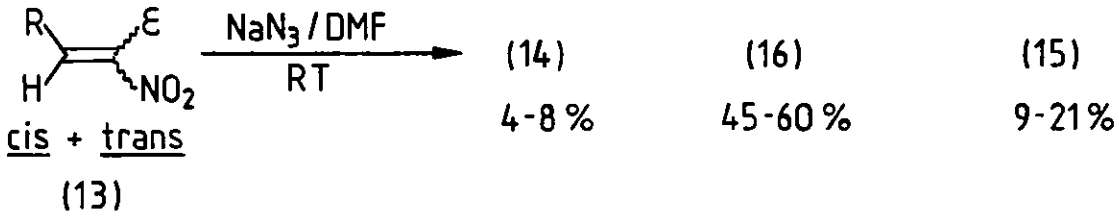


(10)


15
R=alkyls, Ph
R'=H
X=NO2
Y=CO2Et
35-88%
14
R=R'=H
X=Cl
Y=CO2Et
16
X=Cl
Y=R'=CN
R=H, Me, Ph
75%
19
R=R'=CH3
X=Y=NO2
or X=I, Y=NO2
75%
(11)
R=R'=X=F
Y=CF3, 0°C
RT
17
2
R=R'=H
X=Cl, Y=Tos
R=Y=Tos
X=R'=H
18
58%
R=R'=H
X=Cl
Y=COPh
20
95%
X=NH3Cl
Y=COPh
20

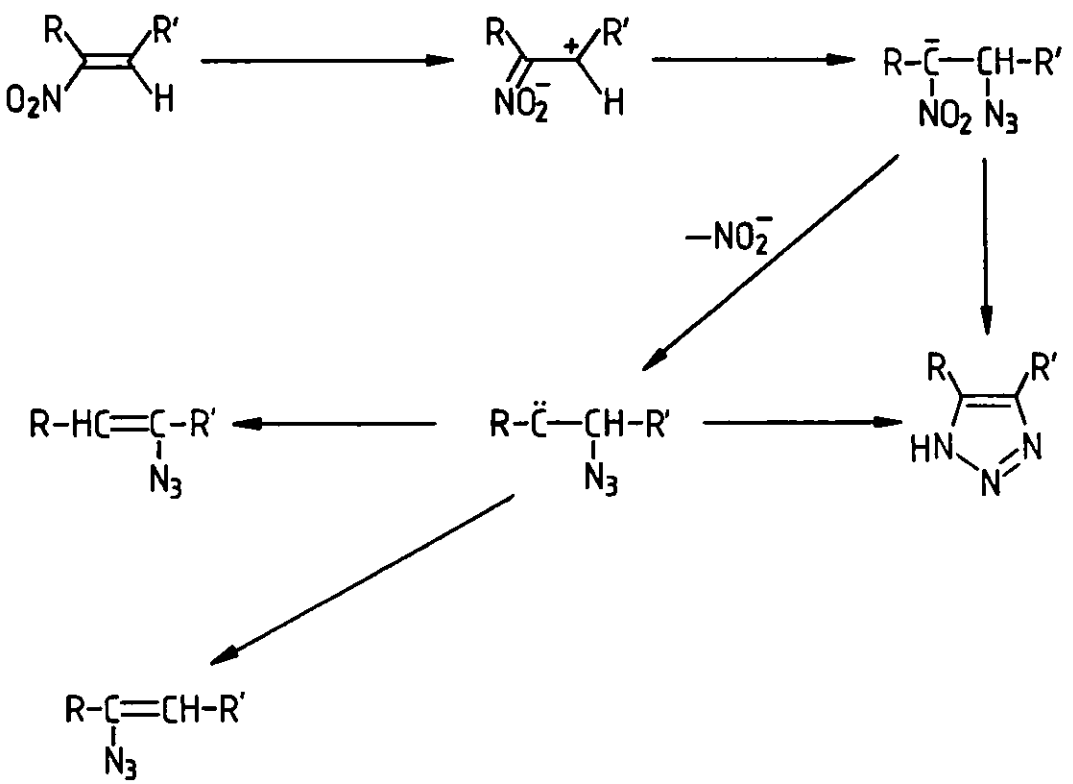
Scheme 7





R=CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, Ph
E=CO_2Et

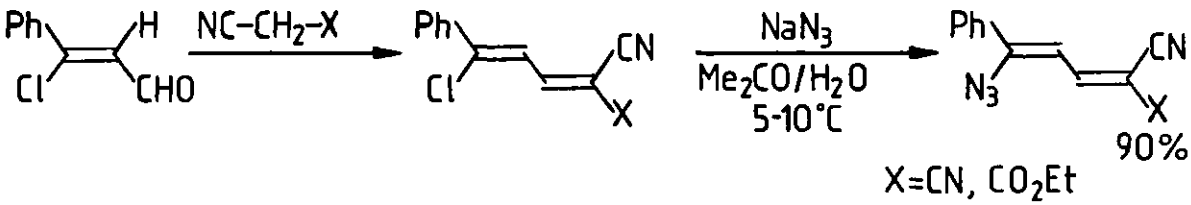
Scheme 8



Scheme 9

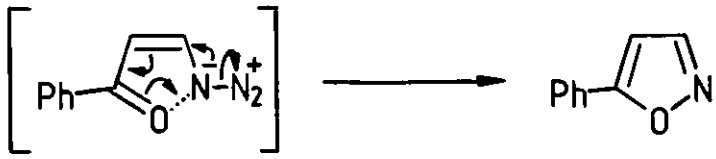
An interesting reaction of this type was reported,[14] where mixtures of cis and trans derivatives of ethyl 3-nitro-2-propenoate (12) and ethyl 2-nitro-2-propenoate (13) were treated with sodium azide in anhydrous DMF at room temperature. Three products were isolated and identified as ethyl 3-azido-2-propenoate (14), ethyl 2-azido-2-propenoate (15) and the 1,2,3-triazole (16). The results of the two reactions and the proposed mechanism are shown in SCHEME 8 and 9. However, when the reaction was carried out in a mixture of DMF and THF, regiospecific displacement of the nitro group was observed.[15]

Recently, this method of preparing vinyl azides has been successfully applied to 1,3-butadienes system as shown in SCHEME 10.[21]



Scheme 10

It is noteworthy that the cis-β-azidovinyl ketone (17) cannot be isolated in the free form, as it decomposes spontaneously to the isoxazole (18) under the reaction conditions.[2]



(17) (18)

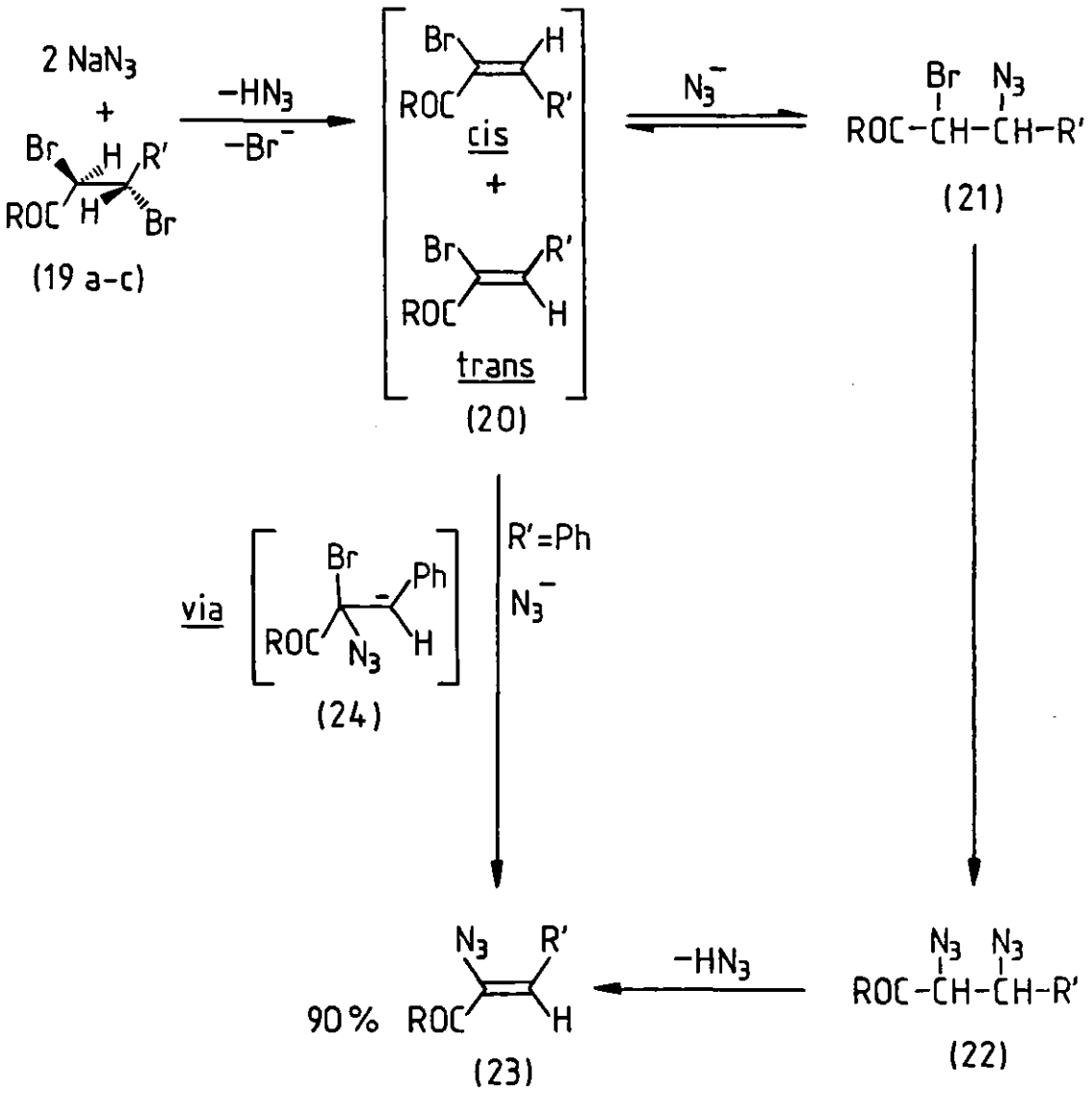
In general, any cis or cyclic vinyl halide with a β-carbonyl function as an activating group will give rise to a relatively unstable vinyl azide, and in many cases, cyclized product will be isolated. A number of azidoquinones and azidomaleimides have been prepared by this method from the corresponding halo-compounds.[2]

1.4 Synthesis of α-Azidovinyl Ketones and Esters

There are two main types of synthetic approach towards the synthesis of α-azidovinyl ketones and esters. Minor variations within the two main procedures have also been reported.

The first method involves the reaction of α,β-dibromoketones (19) with two equivalents of sodium azide in DMF at room temperature.[22,23] A detailed mechanistic study of this reaction carried out by Hassner and co-workers,[22] revealed that the reaction proceeds through a sequence of elimination-addition-substitution-elimination reactions (SCHEME 11). The cis-bromovinyl ketones (20) resulted from the elimination of hydrogen bromide from (19), and isomerized readily to the trans form under the reaction conditions. Conjugate addition of azide

ion to (20) gives the bromoazide (21). The compound (21) then undergoes further nucleophilic substitution (S_N2) by azide ion to give the unstable bis-azide (22), which eliminates HN_3 regiospecifically to yield the thermodynamically more stable <u>trans</u>-α-azidovinyl ketone (23). It was further observed that when R^1=Ph,



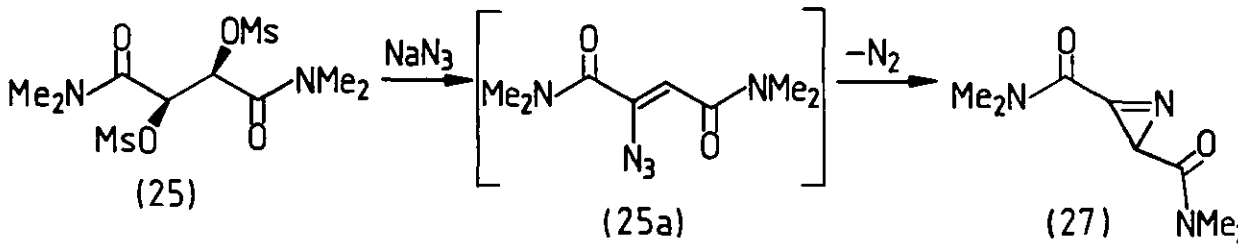
a: R=Ph; R'=Me b: R=Ph; R'=Ph c: R=Me; R=Ph

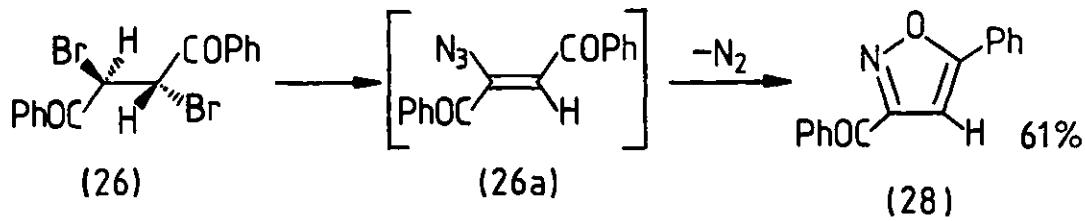
Scheme 11

the direct conversion of (20) into (23) *via* intermediate (24) competes with the reaction sequence described.

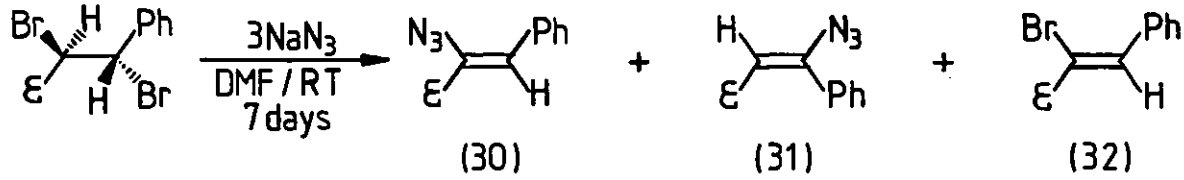
It can be seen from the mechanism outlined in SCHEME 11 that α-bromovinyl ketones (20) and the BrN_3 or IN_3 adducts of α,β-unsaturated ketones (21) can also be used as starting materials for α-azidovinyl ketones.[6,23]

An analogous reaction has also been reported; when the α,β-dimesylate (25)[24] and α,β-dibromide (26)[23] were treated with NaN_3, the corresponding azirine (27) and isoxazole (28) were isolated. The reaction presumably proceeded *via* the vinyl azide intermediate (25a) and (26a).

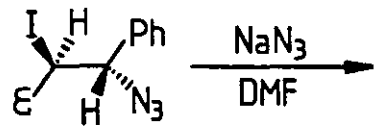




Unlike the case of the ketone (19), treatment of the erythro-cinnamate dibromide (29) with sodium azide gives a 1:1:1 mixture of α- and β-azidovinyl esters (30) and (31) and α-bromovinyl ester (32).[25] Similar results are obtained with the corresponding iodine azide adduct (33).



(30) (31) (32)



(33) (30) + (31)

E=CO2Et

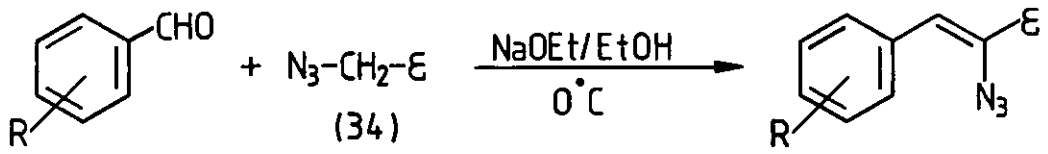
The methods described so far in this section are more suited for the synthesis of α-azidovinyl ketones than of the corresponding esters. However, the second type of synthetic approach, which will be discussed here, provides a more convenient method of preparing α-azidovinyl esters.

A general synthetic method developed by Hemetsberger[26] involves the condensation of ethyl azidoacetate with aromatic aldehydes in ethanolic sodium ethoxide, to give the α-azidovinyl esters in moderate yields. In order to minimize the base induced decomposition of the azidoacetate,[27] a low reaction temperature (0°C) and a four-fold excess

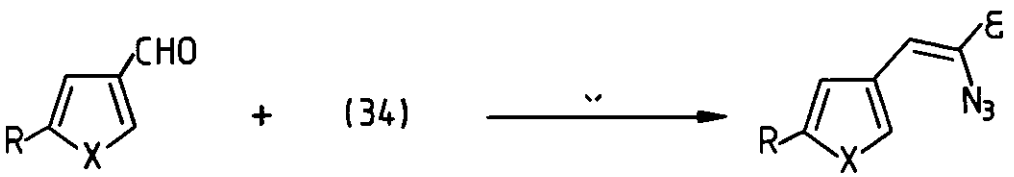
of the azidoacetate and sodium ethoxide are required. This method has also been successfully applied to various heteroaromatic aldehydes[28-32] and non-aromatic α,β-unsaturated aldehydes.[33,34] The reaction is somewhat limited to aryl and α,β-unsaturated aldehydes. There is no report of this procedure being successfully applied to normal saturated aldehydes,this is not too surprising, as one would expect the saturated aldehyde to undergo self-condensation and polymerize under the reaction conditions. Steric hindrance around the aldehyde function can also lower the yield of the vinyl azide. Some examples of this condensation are illustrated in SCHEME 12.

If azidoacetophenone (35) is used instead of ethyl azidoacetate, the corresponding α-azidovinyl ketones are obtained. The reaction normally proceeds smoothly at room temperature in the presence of piperidine acetate or triethylammonium acetate. Thus the α-azidovinyl ketones (36) and (37) can be prepared from the corresponding saturated aldehydes[35] and aromatic aldehydes[36] respectively in moderate to excellent yields (SCHEME 13), in contrast with ethyl azidoacetate which only gives vinyl azides with aromatic and α,β-unsaturated aldehydes.

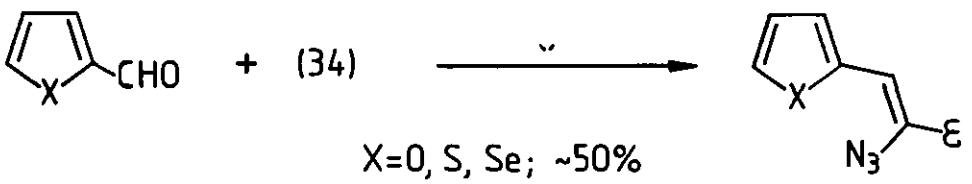
The two main synthetic approaches described in this section have still not provided a useful synthesis for the α-azidovinyl esters of the type (40). However, Shin[15,37] has recently developed a more versatile route to (40), and the methods are outlined



R=H, 43%; R=4-Me, 61%; R=2,6-OMe, 19%

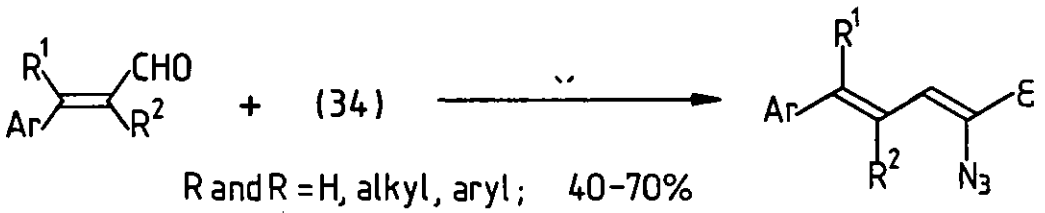


R=H, X=O, S, Se; ~65%
R=E, X=NH; 20%



X=O, S, Se; ~50%
X=NMe; 12%

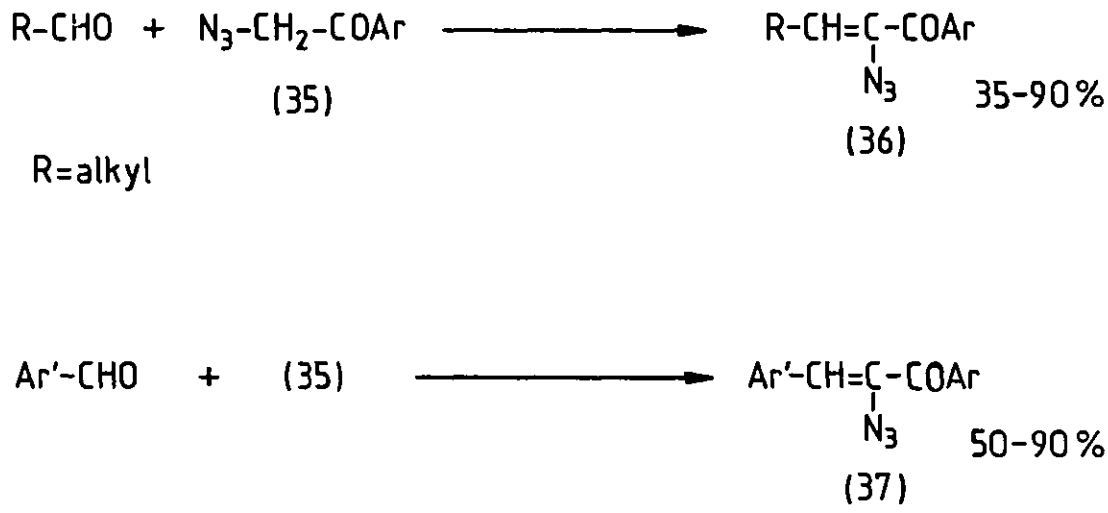
X=S, Se; 50-65%



R and R = H, alkyl, aryl; 40-70%

E = CO_2Et

Scheme 12



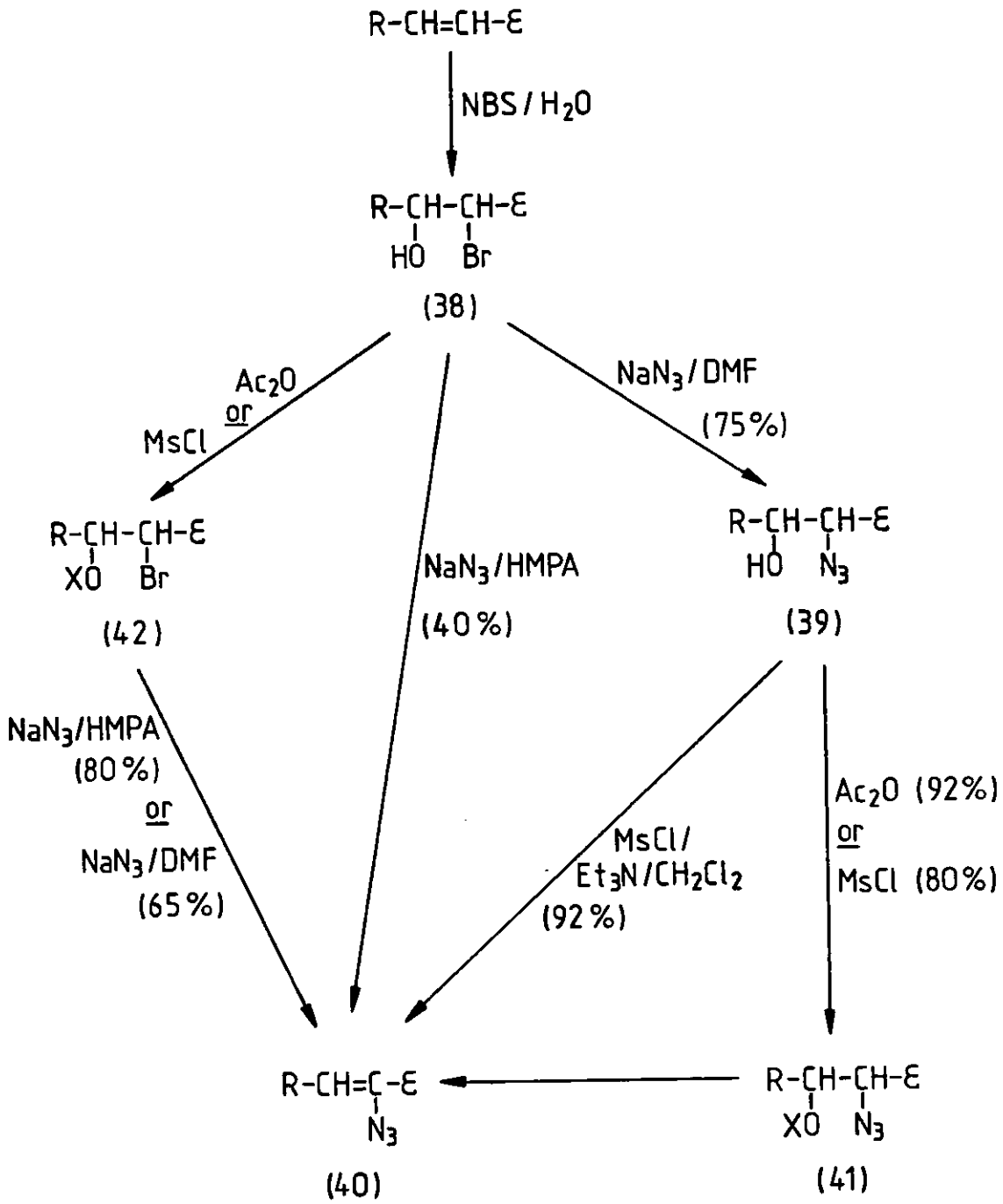
Scheme 13

in SCHEME 14. The most satisfactory method for the preparation of (41) from (38) is through the sequence (38)→(39)→(40), and this is generally applicable for the conversion of α-hydroxy azides into the corresponding azido olefins.

1.5 Miscellaneous Reactions

a Conversion of Trifluoromethyl Sulphones to Vinyl Azides[38,39]

Trifluoromethyl sulphones (43) were found to react with toluenesulphonyl azide in the presence of two equivalents of base (NaH/glyme) to give the vinyl azides (44) in good yield. The proposed mechanism is shown in SCHEME 15. This preparative method is complementary to the IN_3 method, and the azide function is always produced at the position originally occupied by SO_2CF_3 group.

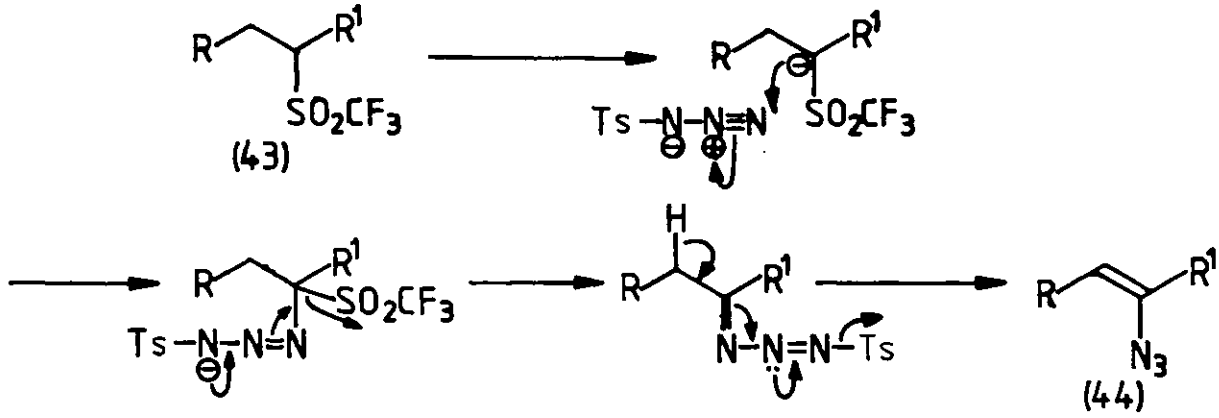


X=$COCH_3$, SO_2CH_3

R=CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, Ph

E=CO_2Et

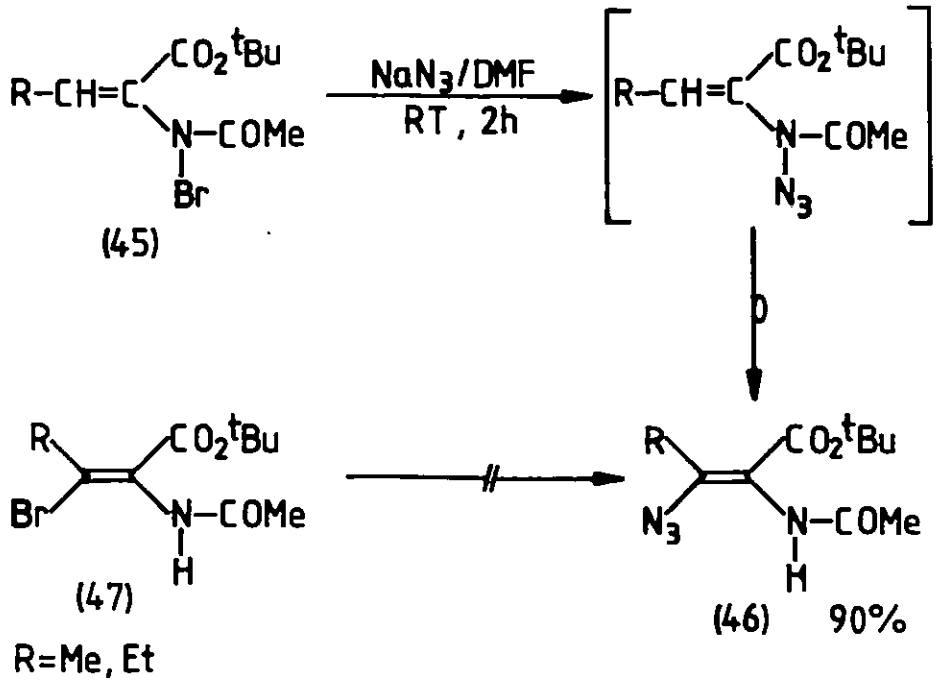
Scheme 14



Scheme 15

b Substitution-Migration[40]

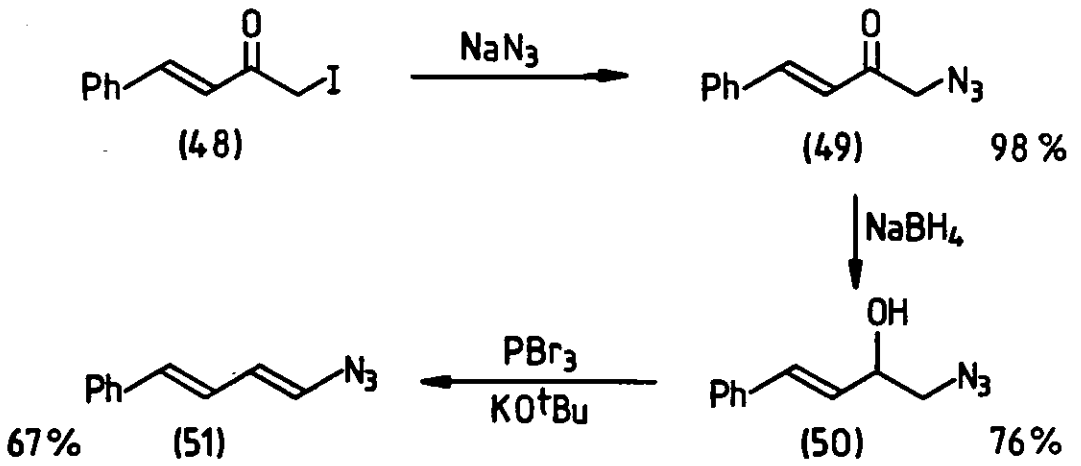
Substitution of the bromine of t-butyl 2-(N-bromoacetamido)-2-alkenoates (45) with azide ion gave the corresponding vinyl azides (46) as the migration products. It was further shown that under the same conditions, the vinyl bromide (47) did not produce the same product (46), therefore implying that the reaction did not proceed through (47) (SCHEME 16).



Scheme 16

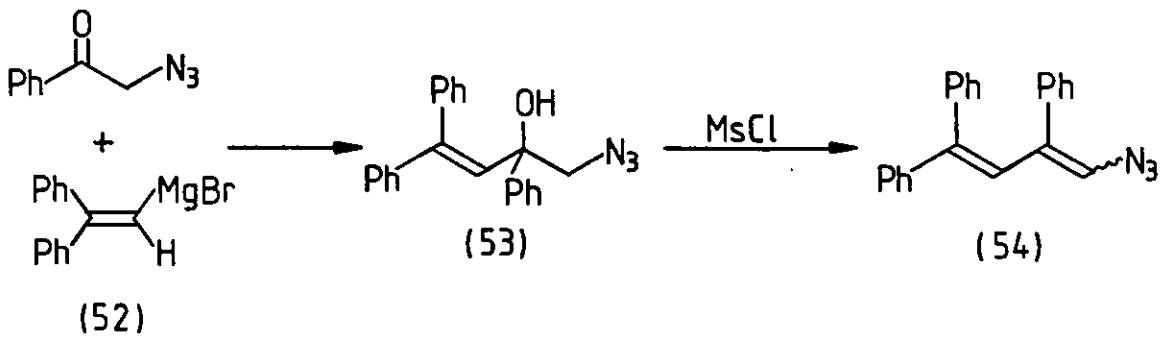
c Synthesis of 1-Azido-1,3-Butadienes[41]

Isomura has developed two synthetic routes to this class of vinyl azide (51). The first involves a nucleophilic substitution of the iodine in compound (48) with an azide ion, followed by reduction of the vinyl ketone (49). Treatment of the hydroxy azide (50) with PBr_3 and potassium t-butoxide gives the vinyl azide (51) (SCHEME 17).



Scheme 17

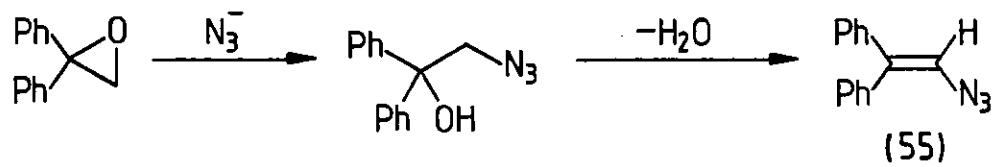
The second route involves reaction of azido-acetophenone with a vinyl Grignard (52) to give the hydroxy azide (53), followed by dehydration to give vinyl azide (54) (SCHEME 18).



Scheme 18

d Epoxide ring opening[42,43]

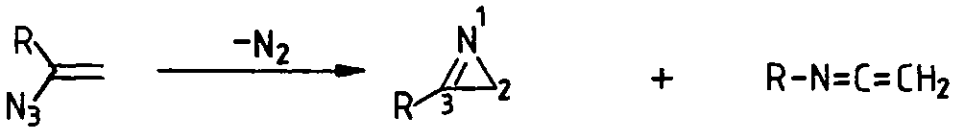
This involves the opening of an epoxide ring by sodium azide, followed by dehydration, as exemplified for 2-azido-1,1-diphenylethylene (55).



II REACTIONS OF VINYL AZIDES

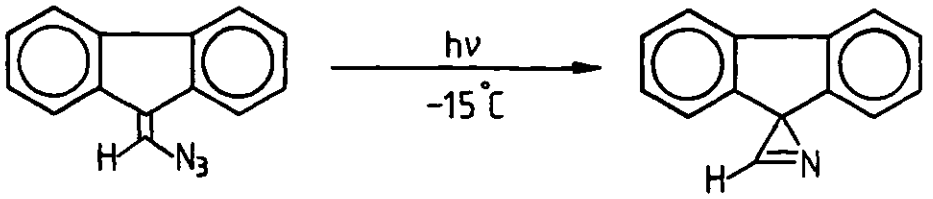
1.6 2H-Azirine Formation

Smolinsky investigated the pyrolysis of α-substituted vinyl azides (56) and found that 2H-azirines (57) are formed in addition to small amounts of ketenimines.[44,45]



(56) (57) (58)

Further investigations have established the generality of the azirine synthesis by thermolysis and photolysis of vinyl azides, and furthermore it is now the preferred route to 2H-azirines.[46,47] In many instances, photolysis appears to be the method of choice, especially in the formation of the more unstable 3-unsubstituted 2H-azirines, as the reaction can be carried out at low temperature. For example, the synthesis of 2H-azirine (60), which was achieved by irradiation of the vinyl azide (59) at -15°C, could not be achieved by the thermolysis approach.[48]



(59) (60)

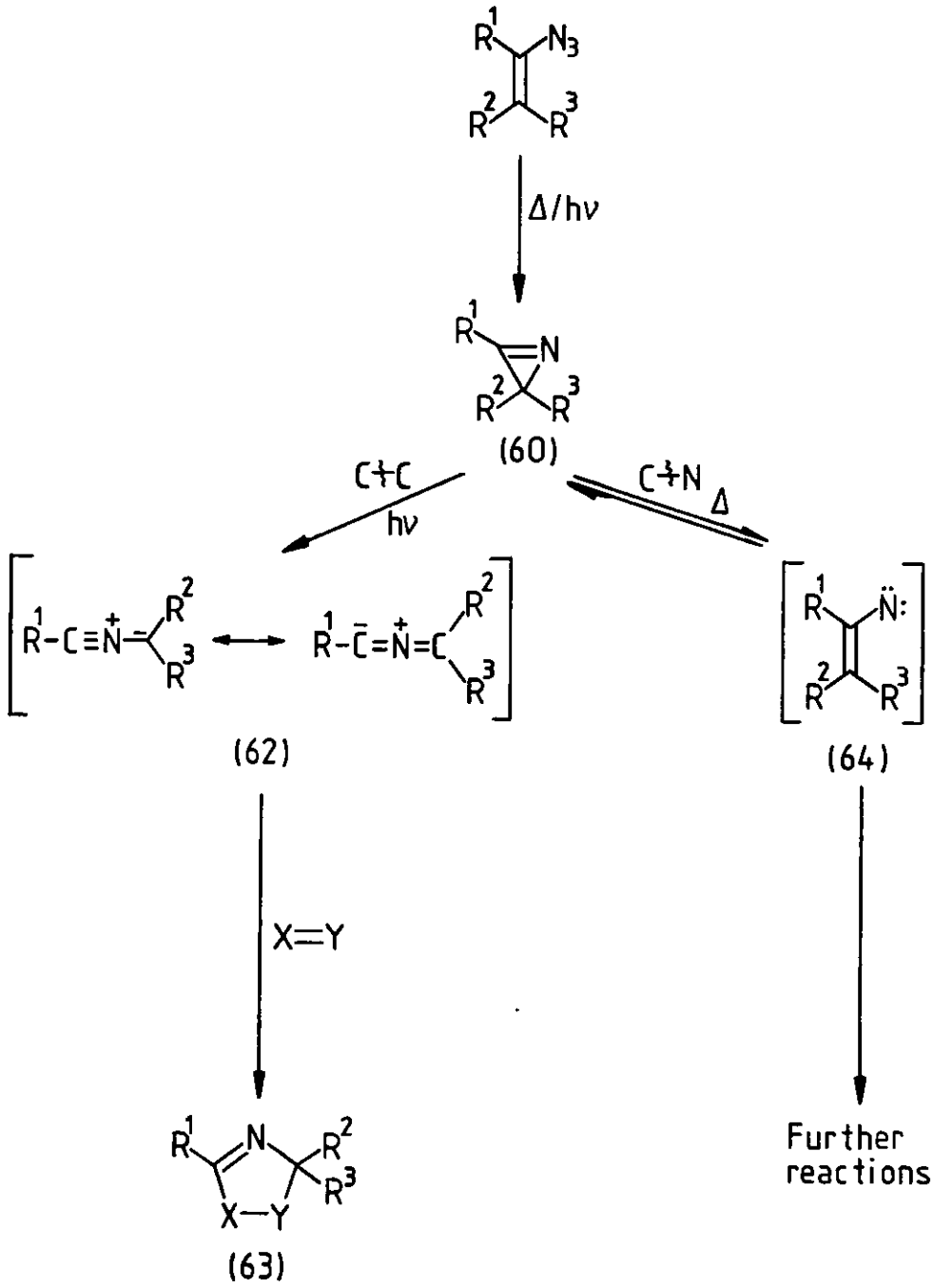
The formation of identical products from the decomposition reaction of vinyl azides and the corresponding 2H-azirines, suggested that, 2H-azirines are formed as the primary products in the decomposition of vinyl azides. The subsequent reactions are those of the azirine. In some situations where the azirines are too unstable to be isolated, their intermediacy has been confirmed by low temperature n.m.r. and i.r. spectroscopy, and by chemical means such as reduction to aziridines[49,50] and interception in Diels-Alder reactions.[35,51,52]

Owing to the close relationship between vinyl azides and 2H-azirines, the reactions of those 2H-azirines derived from vinyl azides will also be reviewed. However, intermolecular cycloadditions and those reactions which involve external reagents will only be mentioned briefly.

1.7 Decomposition of Vinyl Azides

As already mentioned, the decomposition of vinyl azides will initially give rise to the corresponding 2H-azirines. Therefore it is appropriate to examine the photochemical and thermal reaction pathways of 2H-azirines in general terms.

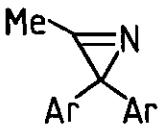
It has been established that 2H-azirines (60) will undergo irreversible ring opening by cleavage of C-C bond on photolysis to give nitrile ylides (62) as reactive intermediates.[53,54] These species can be intercepted with a variety of dipolarophiles to form five-membered heterocyclic rings (63).[53,54] On the



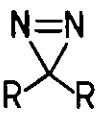
Scheme 19

other hand, because of the large number of products resulting from the thermolysis of various vinyl azides and 2H-azirines which can be explained by intramolecular reaction of a transient vinyl nitrene, it is a generally accepted view that the 2H-azirine (61) may be in thermal equilibrium with the vinyl nitrene (64) resulting from the reversible C-N bond cleavage of the 2H-azirine. The two general pathways are summarized in SCHEME 19.

Recently, an X-ray crystallographic study of a single crystal of 2,2-bis(4-methoxyphenyl)-3-methyl-2H-azirine (65) revealed the azirine as a lopsided triangular structure with an unusually long C-N bond.[55] The bond length measurements are listed in TABLE 1 together with appropriate comparisons. The long C-N bond supports the idea of its preferential cleavage in thermal reactions.



(65)

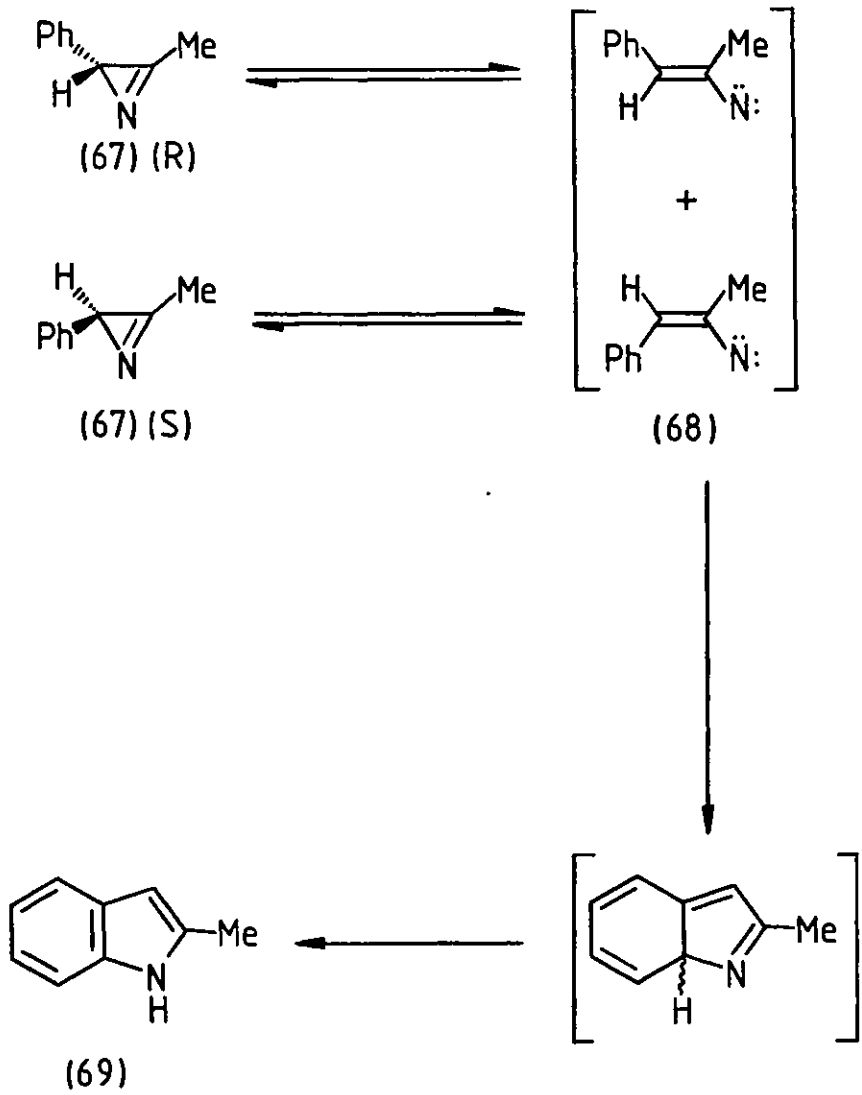


(66)

	C-N/Å	C=N/Å	C-C/Å
Azirine (65)	1.598	1.256	1.463
Diazirine (66)	1.48	-	-
Non-conj. C=N	-	1.29-1.31	-
Cyclopropene	-	-	1.52

TABLE 1

Furthermore, recent kinetic studies on the thermal racemization versus indole formation, of an optically active 3-methyl-2-phenyl-2H-azirine (67) provides the evidence for the intermediacy of a vinyl nitrene (68).[56] It was found that the racemization proceeded 2039 times faster than rearrangement to 2-methylindole (69). This observation is rationalized as indicated in SCHEME 20.

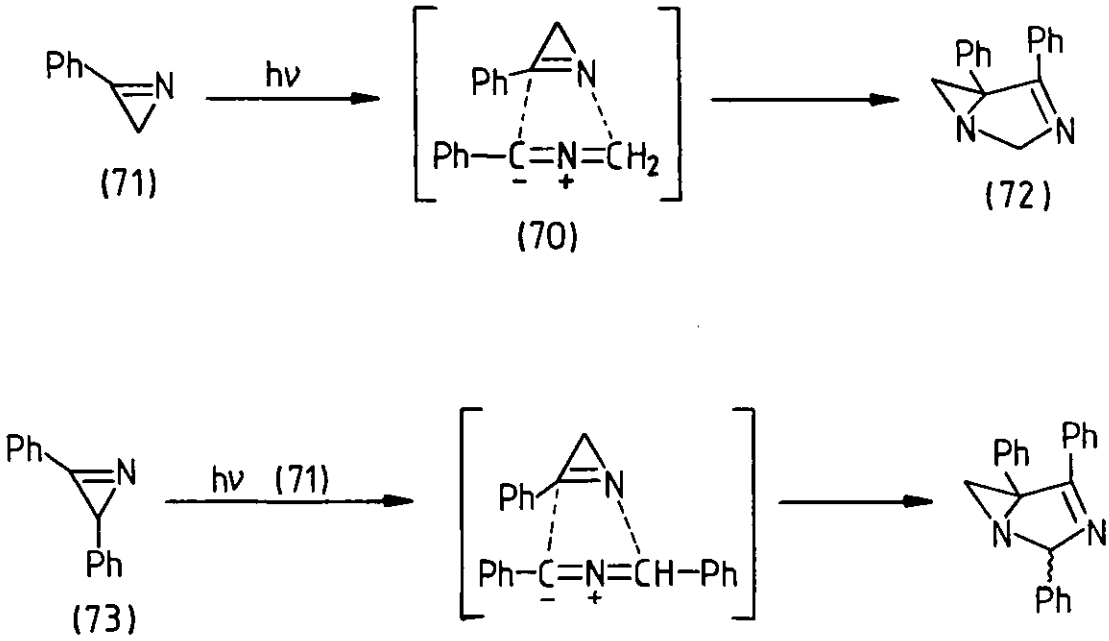


Scheme 20

a <u>α-Substituted Vinyl Azides</u>

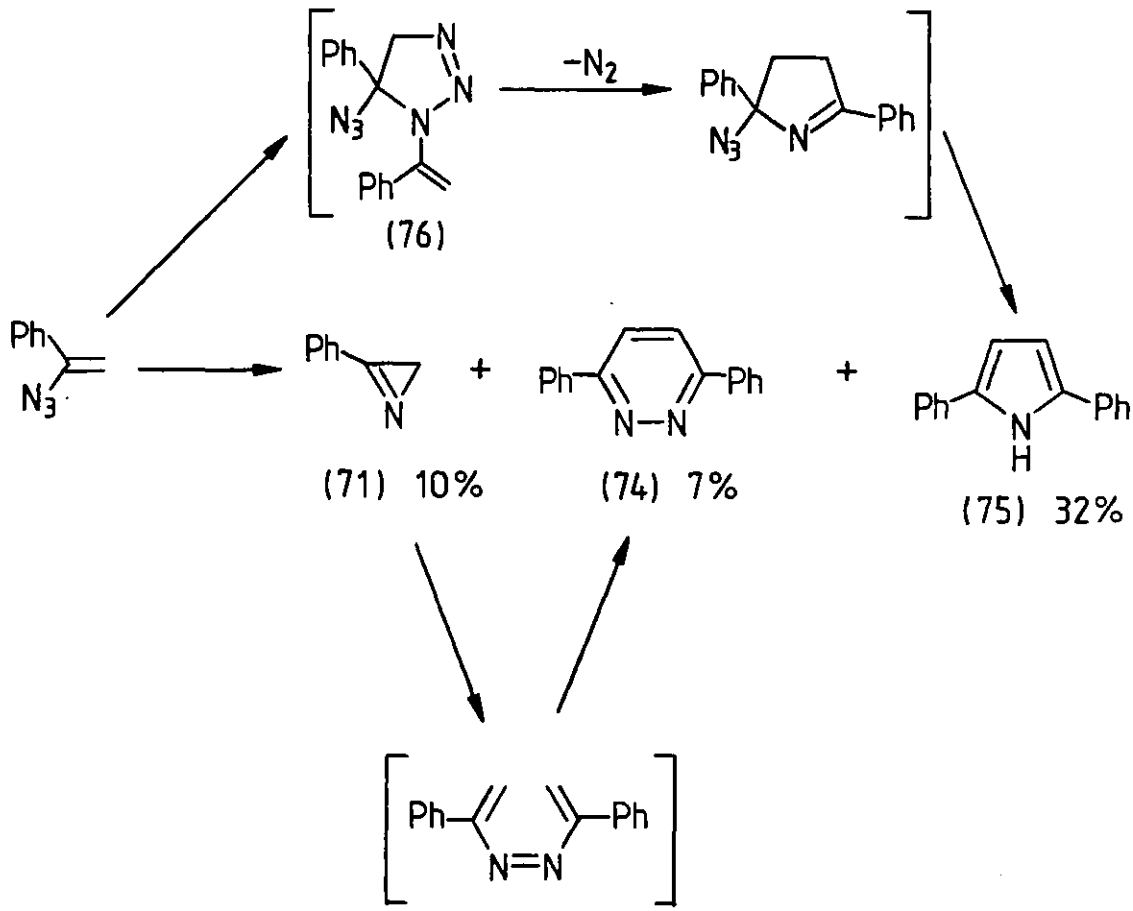
Thermal or photochemical decomposition of α-substituted vinyl azides usually gives rise to isolable 3-substituted 2<u>H</u>-azirines and ketenimines as minor product.[46] In thermolysis, ketenimine formation can be inhibited by addition of tertiary amines.[57]

On irradiation of 3-aryl-2<u>H</u>-azirines, dimerization occurs. The reaction proceeds <u>via</u> 1,3-dipolar addition of a nitrile ylide intermediate, such as (70), to a ground state azirine molecule.[58] For example, 3-phenyl-2<u>H</u>-azirine (71) gives the 1,3-diazabicyclohexene (72).[58] A crossed dimerization of (73) to the ground state of (71) has also been realized (SCHEME 21).[59] This photodimerization is a general reaction of 3-aryl-2<u>H</u>-azirines.[53]



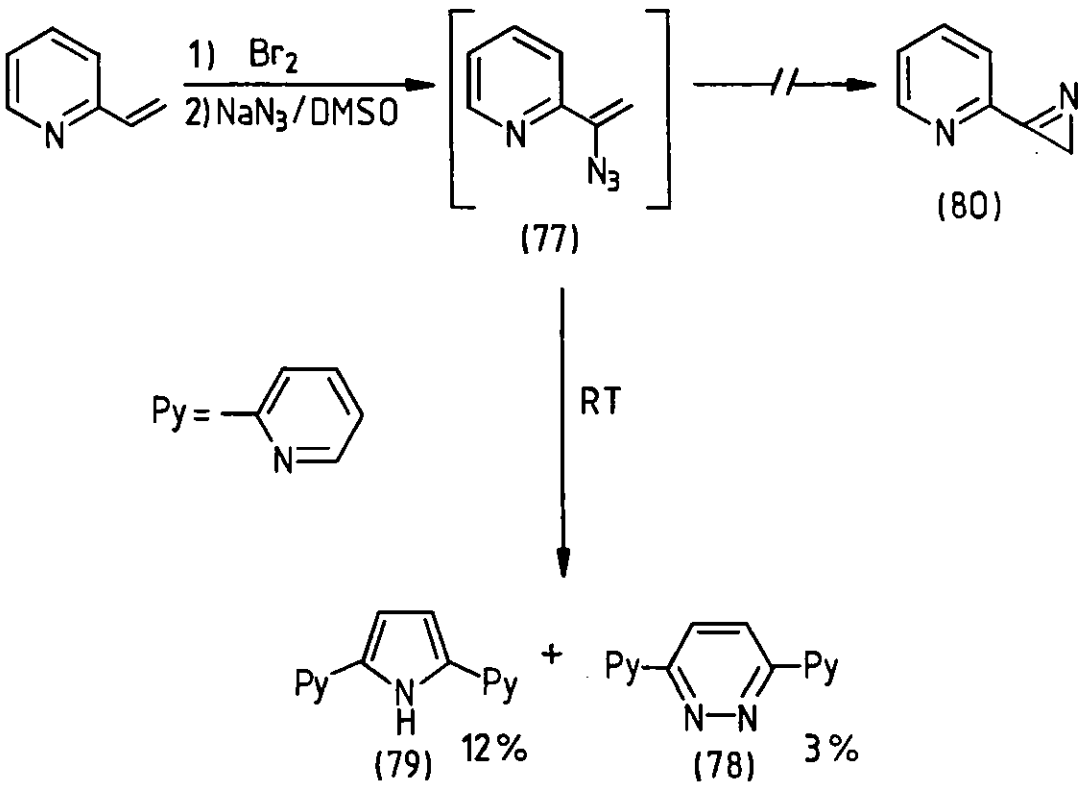
Scheme 21

However, α-azidostyrene, the precursor of (71), decomposes slowly at room temperature to give a mixture of 3-phenyl-2H-azirine (71), 3,6-diphenyl-pyridazine (74) and 2,5-diphenylpyrrole (75).[60] The pyridazine (74) is presumably formed by dimerization of α-styrylnitrene, followed by electrocyclic ring closure and oxidation. The formation of the pyrrole (75) can be interpreted as intermolecular 1,3-dipolar cycloaddition of the azide to the olefinic double bond of a second molecule to give a triazoline (76), which decomposes by loss of N_2 and elimination of HN_3 (SCHEME 22).



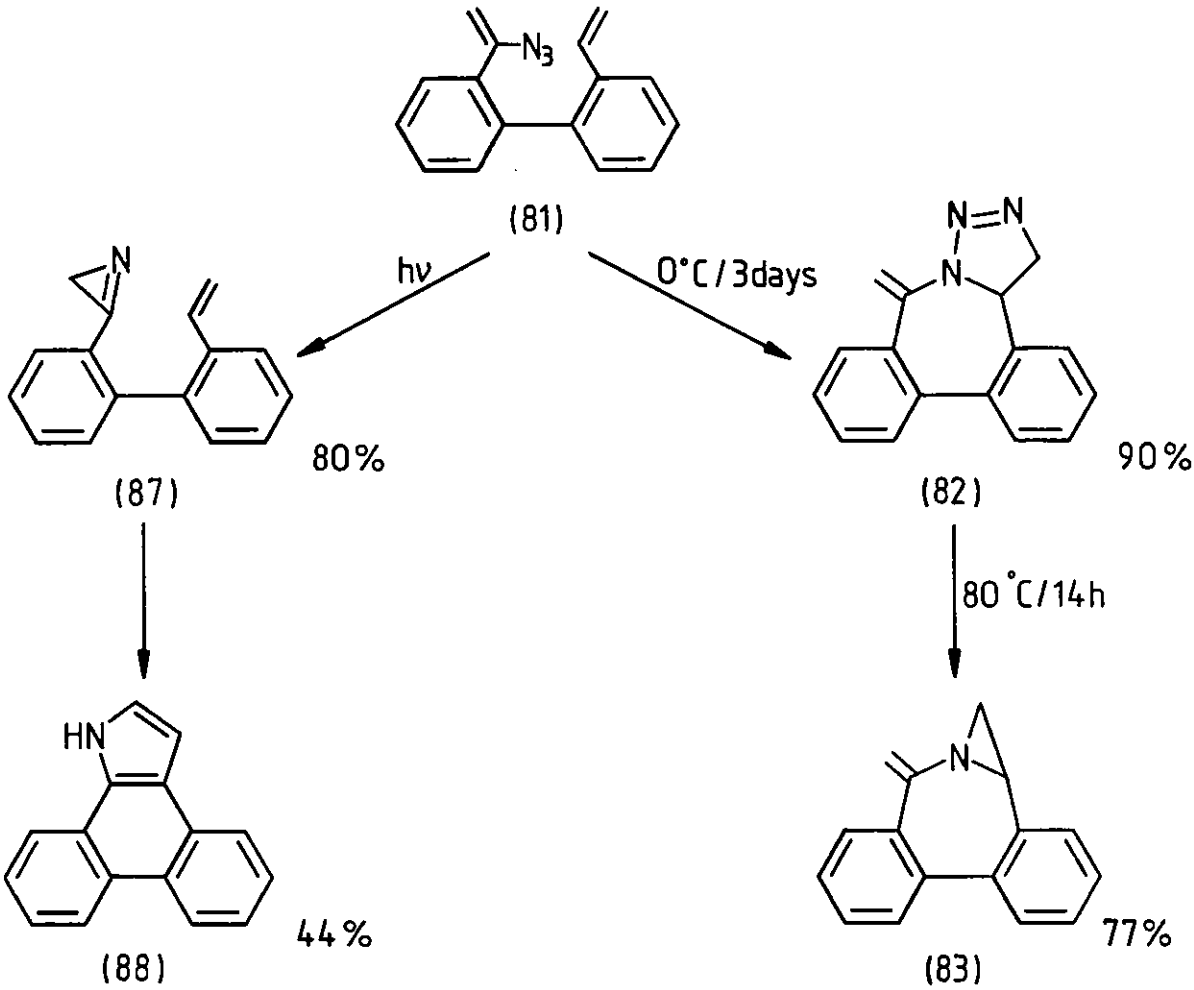
Scheme 22

Analogous to this reaction is that of the corresponding 2-pyridine compound (77). Attempts to prepare this vinyl azide resulted in the formation of the pyridazine (78) and the pyrrole (79). The azirine (80) was not isolated (SCHEME 23).[61]

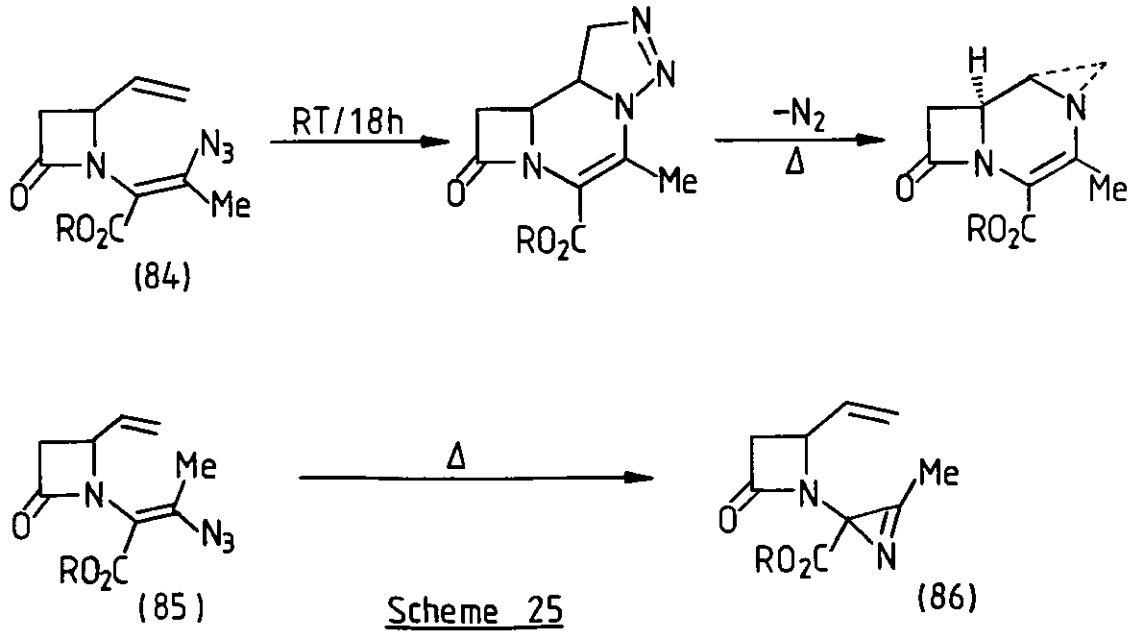


Scheme 23

In general, the α-substituent of vinyl azide does not take part in the decomposition reactions. However, when the α-substituent contains a group which is capable of interaction with the azide function, products of intramolecular reaction are observed. For example, the biphenyl vinyl azide (81) decomposes to the triazoline (82) at 0°C. On further heating, (82) loses N_2 to give the aziridine



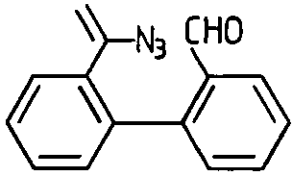
Scheme 24



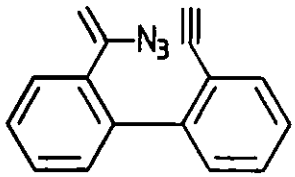
Scheme 25

(83) (SCHEME 24).[62] Similar reactions are observed from vinyl azide (84). However, the E isomer (85) is stable at room temperature and gives the azirine (86) on thermolysis (SCHEME 25).[63]

Photolysis of (81) gives the fused pyrrole (88) as the final product. The reaction involves intramolecular cycloaddition of the nitrile ylide generated from the initially formed azirine (87) (SCHEME 24).[64] The corresponding o-aldehyde (89) and acetylene (90) give similar results.



(89)



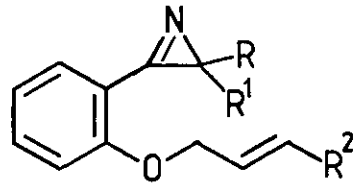
(90)

Photolysis of a number of o-allyloxy, o-butenyl, o-allyl and o-vinylphenyl substituted 2H-azirines have been examined in mechanistic details.[65,66] Upon irradiation, with the exception of o-vinylphenyl-2H-azirine, these systems undergo intramolecular 1,1- and/or 1,3-cycloaddition of the nitrile ylide. The mode of cycloaddition depends on the substituents attached to the 2 position of the azirine ring and also on the substituents of the olefinic double bond. Thus, for example, the 2,2-dimethyl azirine (91a) produces exclusively the 1,1-cycloadduct (92a) while the 2-unsubstituted azirine (91b) gives only the 1,3-cycloadduct (93b). However, a mixture of equal amounts of 1,1- and 1,3-cycloadducts (92c) and (93c) is obtained from the photolysis of the 2-methyl

azirine (91c). Photolysis of the azirine (91d) gives a 3:4 mixture of (92d) and (93d) whereas the azirine (94) produces exclusively the 1,3-dipolar cycloadduct (95) (SCHEME 26).

The two types of intramolecular processes mentioned above, require that the methylene chain is of sufficient length to allow the nitrile ylide and the double bond to approach each other in parallel planes. In the case of o-allylphenyl substituted 2H-azirines (96a-c), this parallel plane approach cannot be easily attained, and a nonconcerted mechanism for the formation of the 1,1-dipolar cycloadducts (97a-c) is proposed (SCHEME 27). All these results have been rationalized by the substituent's electronic effect and the relative geometry of the nitrile ylide, and also in terms of the Molecular Orbital Theory.

Irradiation of the o-vinylphenyl substituted 2H-azirines (98a-b) give the N-alkylideneindene-3-amines (99a-b). The proposed reaction pathway is outlined in SCHEME 28.



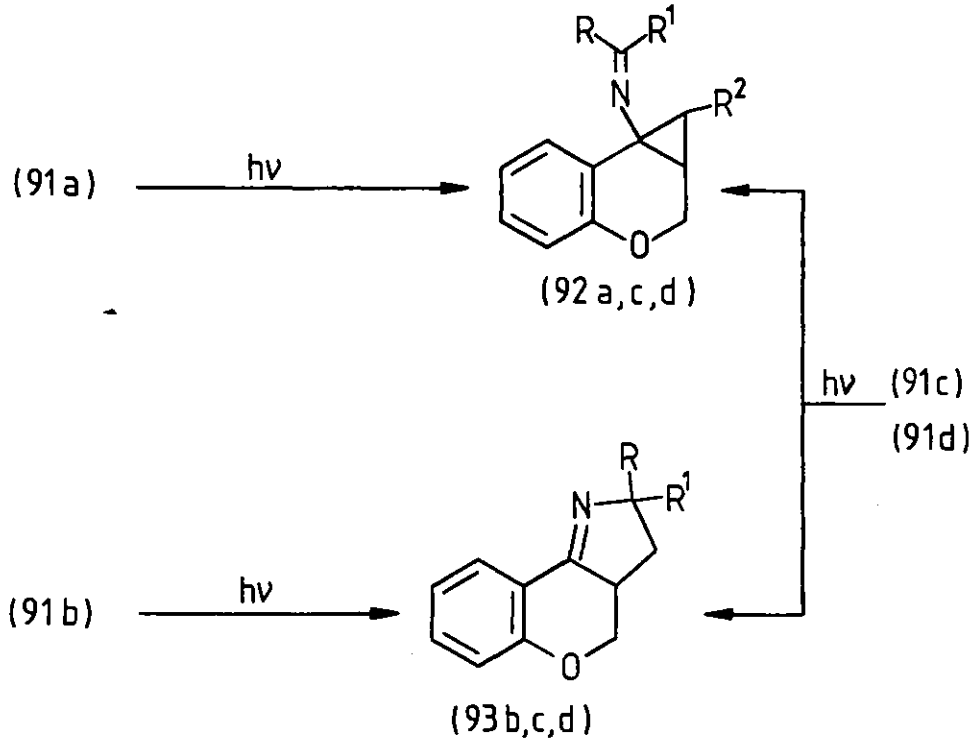
(91)

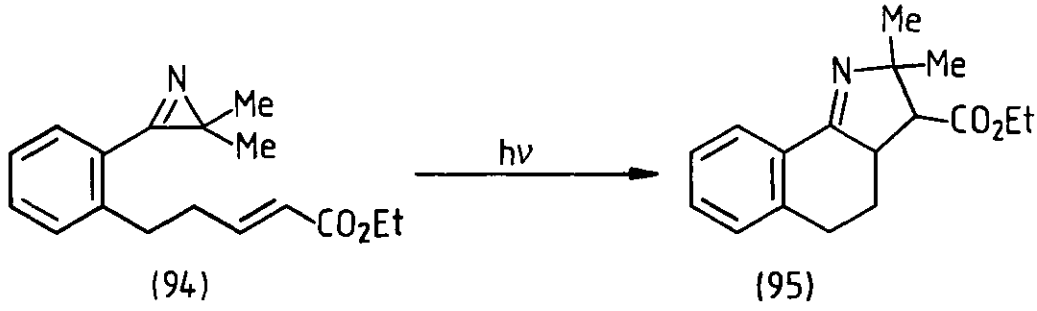
a: $R=R^1=Me$, $R^2=H$

b: $R=R^1=R^2=H$

c: $R=R^2=H$, $R^1=Me$

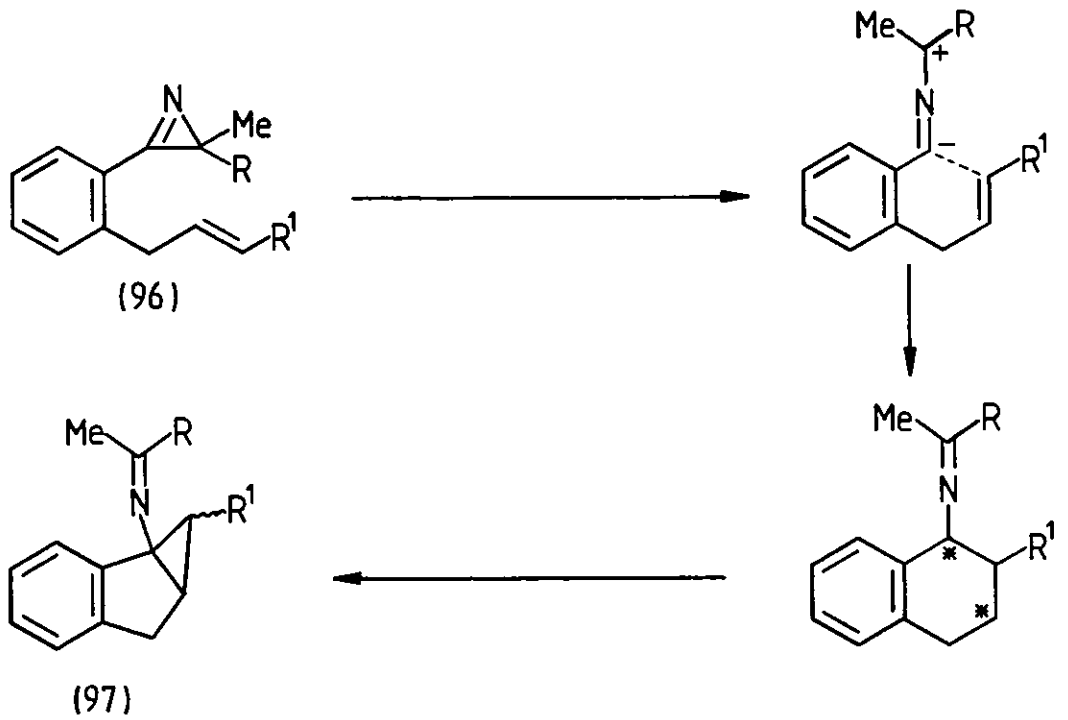
d: $R=R^1=H$, $R^2=Me$





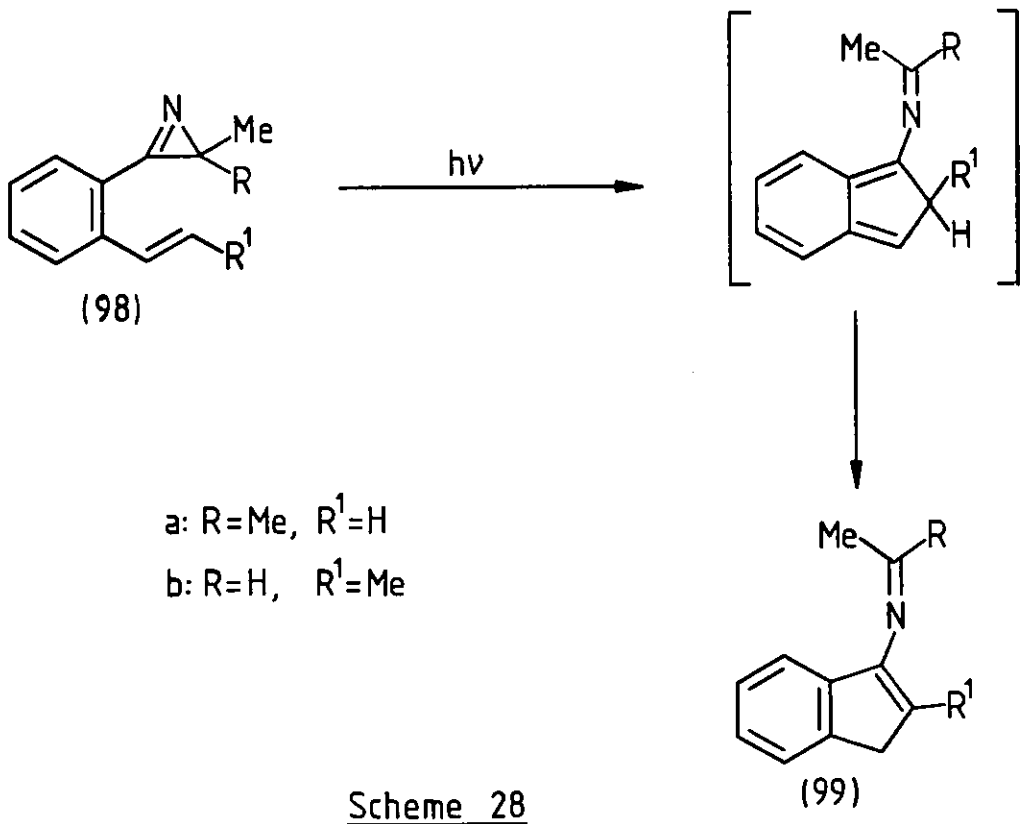
(94) (95)

Scheme 26



a: R = Me, R^1 = H b: R = R^1 = Me c: R = R^1 = H

Scheme 27



a: R = Me, R^1 = H

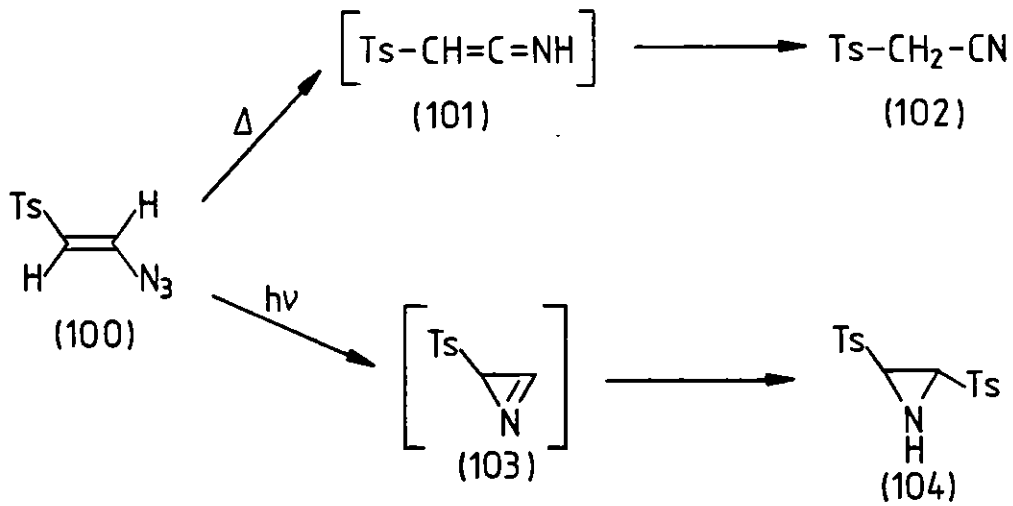
b: R = H, R^1 = Me

Scheme 28

b α-Unsubstituted Vinyl Azides

Decomposition of α-unsubstituted vinyl azides initially gives rise to the 3-unsubstituted 2H-azirines. 3-Unsubstituted 2H-azirines are less stable than the corresponding substituted ones and they decompose to different products depending on the substituent. In many cases nitriles or polymeric materials are obtained.[42]

Thermolysis of β-azidovinyl p-tolyl sulphone (100) gives the nitrile (102) presumably via the ketenimine (101), whereas irradiation produces the aziridine (104).[67] The latter was shown to arise from the azirine (103) by addition of p-tolouenesulphinic acid generated during photolysis.



More useful reactions have been found in the decomposition of β-azidostyrene[49] and a number of 1-azido-1,3-butadienes.[68] The former case gives rise to a mixture of indole and phenylacetonitrile, whereas the latter compounds produce pyrroles. The

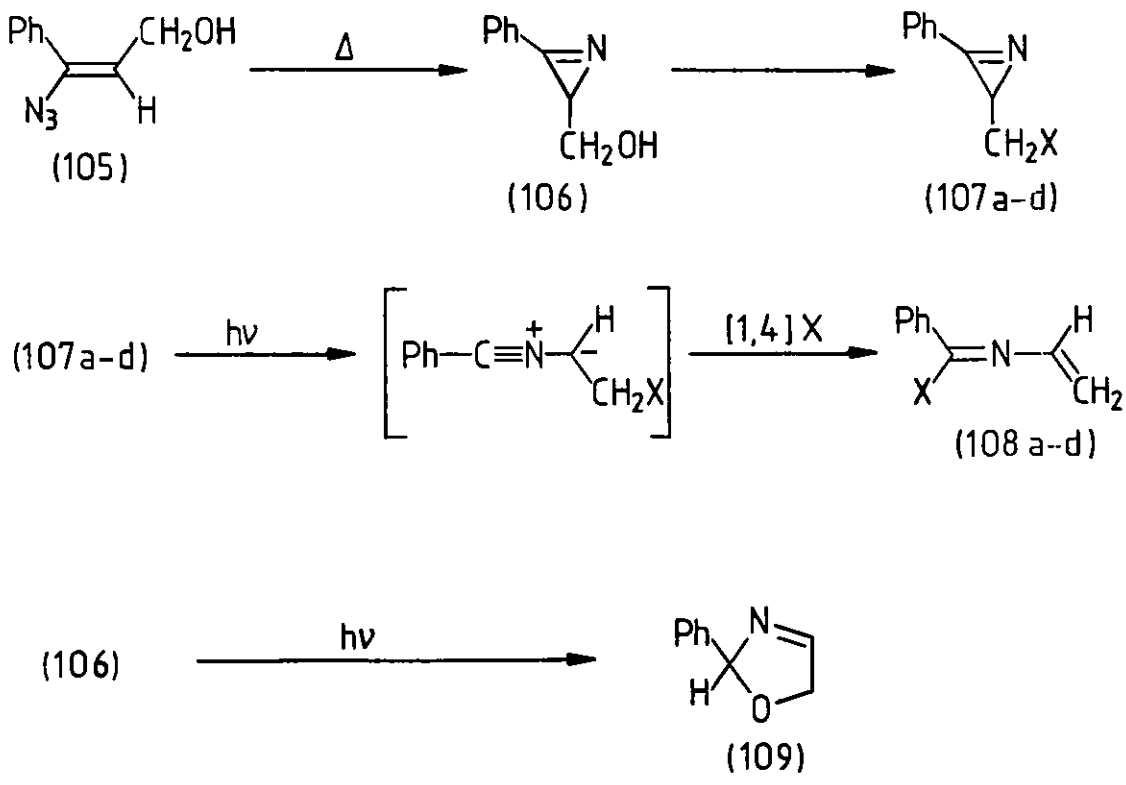
formation of these compounds will be discussed in later sections.

c α,β-Disubstituted Vinyl Azides

i 2-(Substituted methyl)-3-phenyl-2H-azirines

These 2H-azirines (107a-d) are derivatives of 3-phenyl-2H-azirine-2-methanol (106), which is in turn prepared from the thermolysis of 3-azido-3-phenyl-2-propen-1-ol (105).[69-71]

Photolysis of these azirines (107a-d) has been found to afford the N-vinylimines (108a-d) in quantitative yield.[70,71] The reaction involves a nitrile ylide intermediate from which a novel 1,4-shift to the final product is observed. In contrast, irradiation of (106) gives 2-phenyl-3-oxazoline (109) (SCHEME 29).[69]



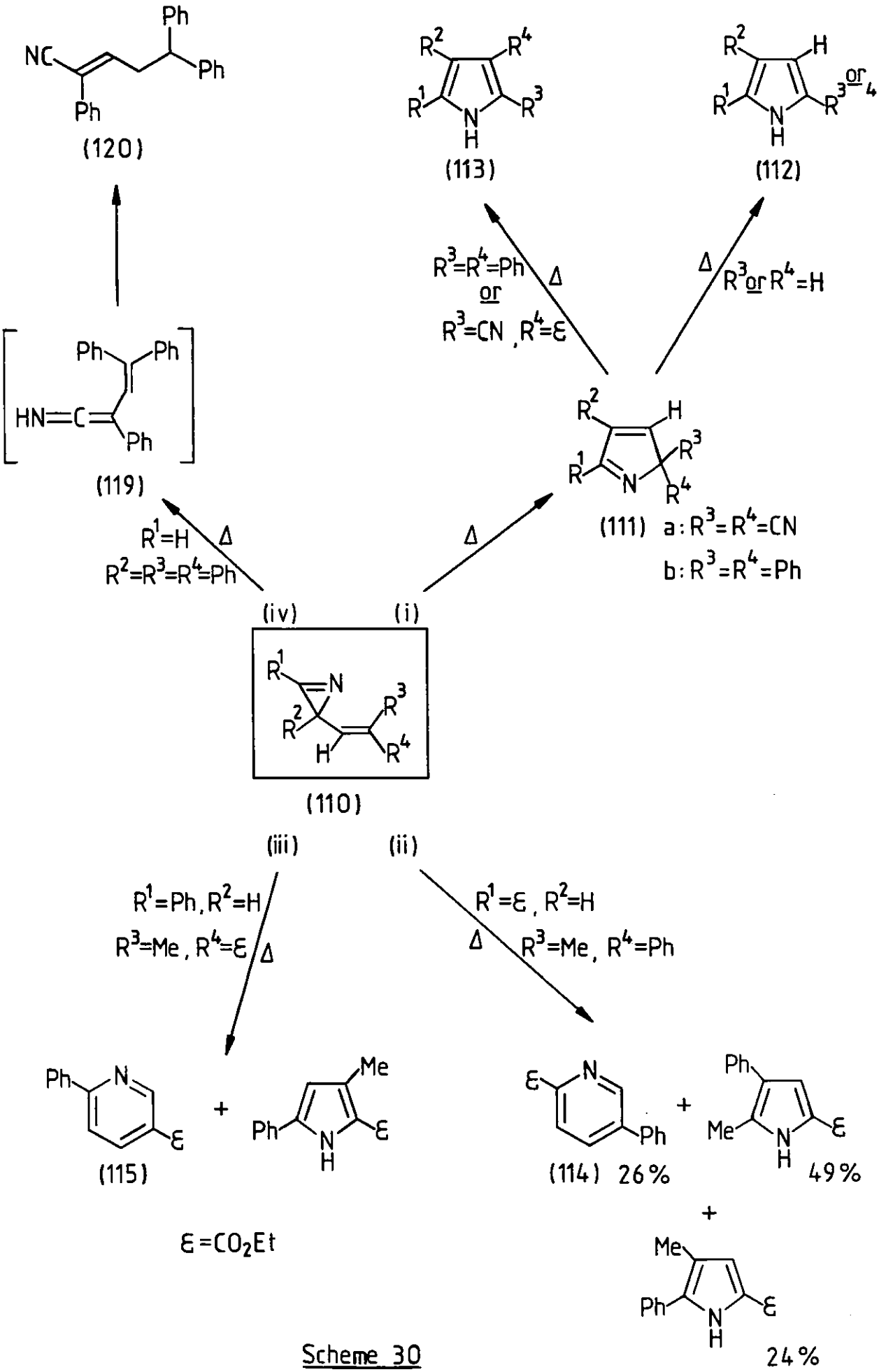
a: X=Cl, b: X=Br, c: X=OCOMe, d: X=OCOAc

Scheme 29

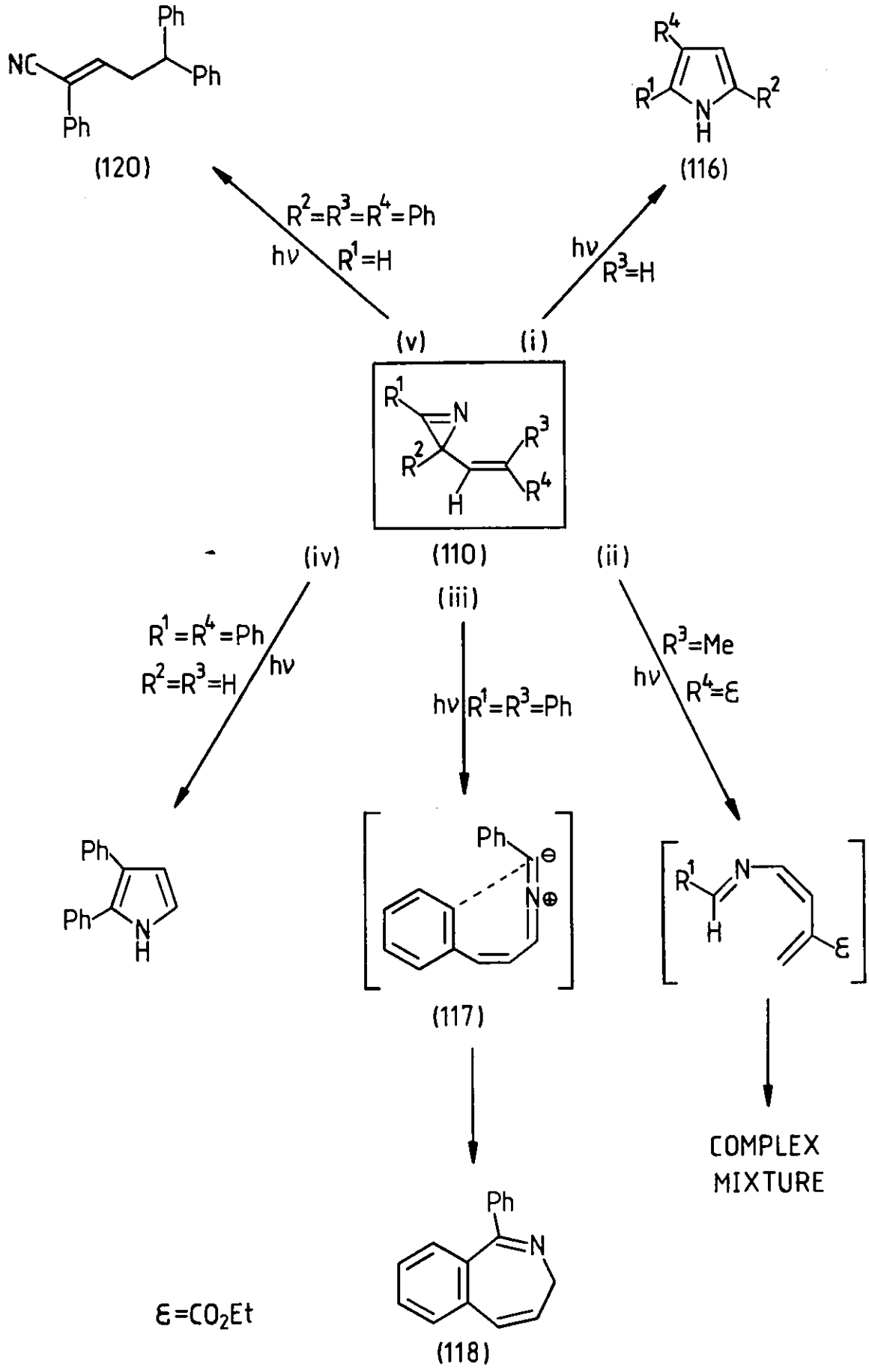
ii 1-Azido-1,3-butadienes

There are two general pathways in which the transient vinyl nitrene generated from the thermolysis of these systems can react. Firstly, it can undergo an electrocyclic ring closure onto C-4 of the butadiene, to give a 5-membered ring intermediate (path (i) of SCHEME 30) which can aromatise to the 1H-pyrrole (112) or (113) depending on the substituents.[21,33,34,72,73] The intermediacy of (111) has been confirmed by the isolation of (111a-b).[21,33,68] Secondly, if C-4 of the butadiene is disubstituted, and at least one of the substituents is a methyl group then a formal C-H insertion into the methyl group by the vinyl nitrene is observed (path (ii) and (iii) of SCHEME 30).[33,74] Subsequent aerial oxidation of the intermediate will result in the formation of the pyridines (114) and (115).

In photolysis, the nitrile ylide generated can cyclize to form a 5-membered ring intermediate, which is then followed by a 1,3-hydrogen shift to give a 1H-pyrrole (116) (path (i) of SCHEME 31).[68,72,73] It is interesting to note that when C-4 of the butadiene is disubstituted (path (ii) of SCHEME 31), a complex mixture is obtained.[74] When the 1 and 4 position of the butadiene is substituted with a phenyl group, cyclization of the nitrile ylide (117) to give a benzazepine (118) is observed (path (iii) of SCHEME 31).[73,75] This seven-membered ring formation requires the C-4 phenyl group to be cis to the azirine and furthermore, the C-1 phenyl is also


(120)
(113)
(112)
$R^3=R^4=Ph$ or $R^3=CN$, $R^4=E$
Δ
Δ
R^3 or $R^4=H$
(119)
(111) a: $R^3=R^4=CN$
b: $R^3=R^4=Ph$
$R^1=H$
$R^2=R^3=R^4=Ph$
Δ
Δ
(iv)
(i)
(110)
(iii)
(ii)
$R^1=Ph$, $R^2=H$
$R^3=Me$, $R^4=E$
Δ
$R^1=E$, $R^2=H$
Δ
$R^3=Me$, $R^4=Ph$
(115)
(114) 26%
49%
24%
$E=CO_2Et$

Scheme 30

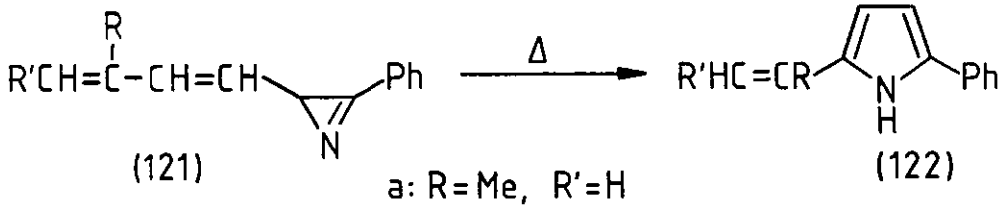

Ph
NC
Ph
Ph
(120)
R4
R1
N
H
R2
(116)
R2=R3=R4=Ph
hν
R1=H
hν
R3=H
(v)
(i)
R1
N
R2
R3
R4
H
(110)
(iv)
(iii)
(ii)
R1=R4=Ph
R2=R3=H
hν
hν
R1=R3=Ph
R3=Me
hν
R4=ε
Ph
Ph
N
H
Ph
⊖
N⊕
R1
N
H
ε
(117)
COMPLEX
MIXTURE
Ph
N
ε=CO2Et
(118)

Scheme 31

a necessity (i.e. R^1=R^3=Ph in (110)). If either one of these requirements is not met, the normal ring closure to 1H-pyrrole is observed (path (i) and (iv) of SCHEME 31).[68,72,73]

Finally, butenonitrile (120) is obtained from the decomposition of (110, R^1=H, R^2=R^3=R^4=Ph), presumably via the keteneimine (119) (path (iv) of SCHEME 30 and path (v) of SCHEME 31).[68] Some of the reactions in SCHEMES 30 and 31 have also been carried out from the corresponding vinyl azide without the isolation of the 2H-azirine (110). However, for convenience, only the 2H-azirine is illustrated.

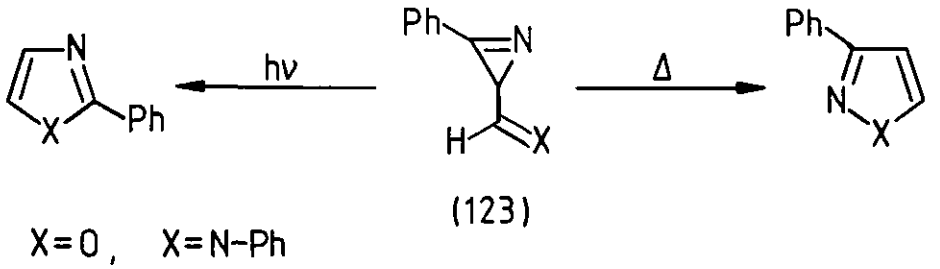
Similarly, thermolysis of closely related systems, 2-(buta-1,3-dienyl)-2H-azirines (121a-c) affords the 2-vinylpyrroles (122a-c); no azepine formation was reported.[76]



(121) a: R=Me, R'=H (122)

b: R=H, R'=Me c: R=H, R'=CO_2Et

In another related system where the vinyl group is replaced by a C=X function (123), similar results are obtained (SCHEME 32).[73]

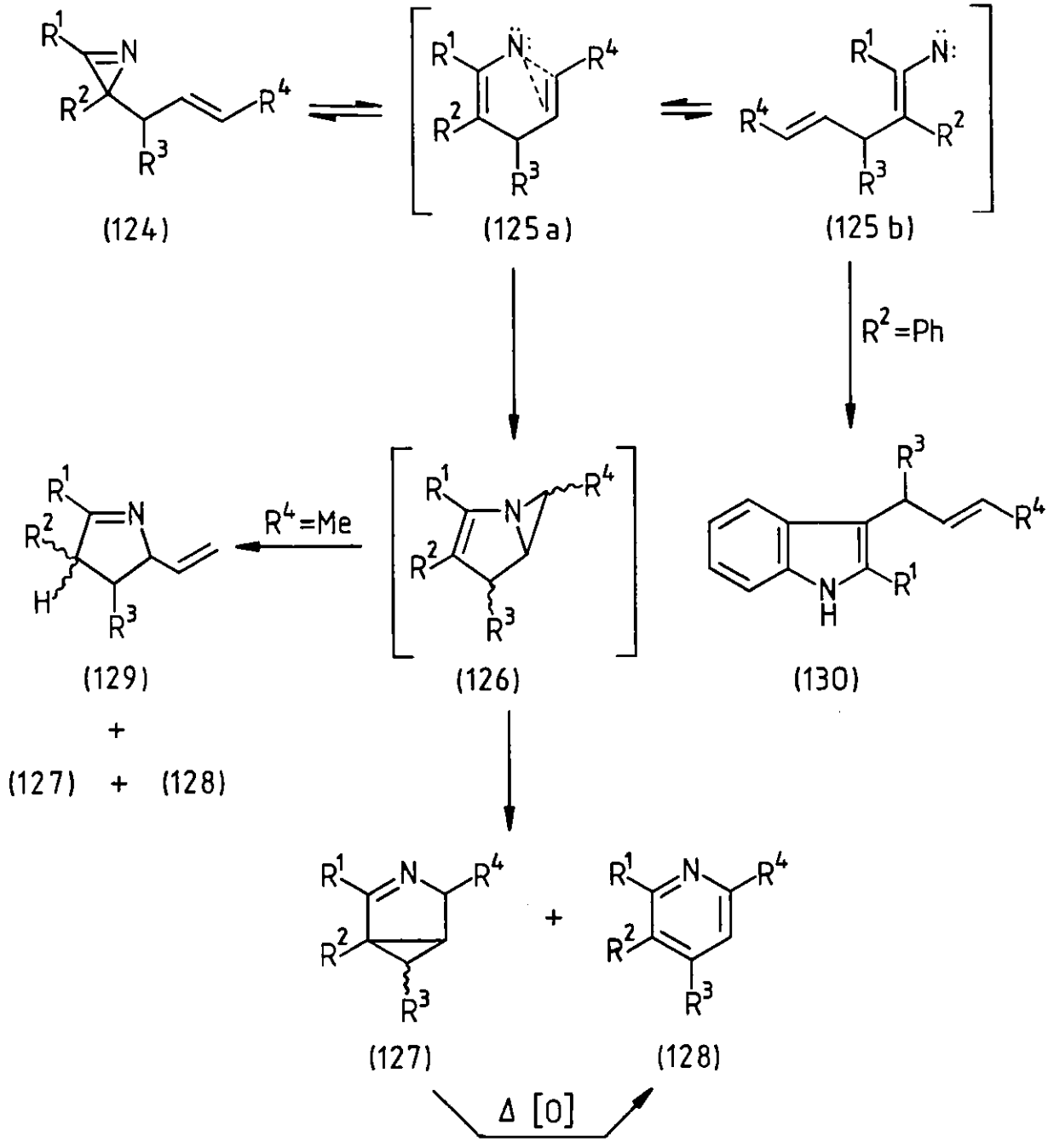


Scheme 32

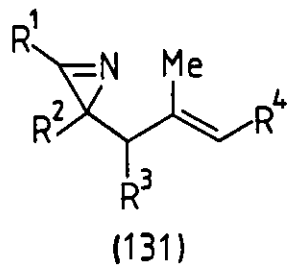
iii 2-Allyl-substituted 2H-azirines

The 2H-azirines described in this section are not prepared from the corresponding vinyl azides, but a modified Neber reaction.[77]

Two general thermolytic reaction pathways are observed in 2-allyl-substituted 2H-azirines.[77,78] Firstly, the vinyl nitrene (125a) which is in thermal equilibrium with the 2H-azirine (124) can undergo direct addition onto the olefinic double bond to give a bicycloaziridine (126) as a transient intermediate. This species can subsequently rearrange to the observed product (127) either by a 1,3-sigma-tropic shift or via a radical process. Further support for this mechanism is provided by the isolation of the Δ^1-pyrroline system (129) (SCHEME 33). However, the above reactions will be inhibited if a blocking methyl group is attached to the internal position of the olefinic double bond e.g. (131). The second pathway requires R^2=Ph, for example (125b). In this case, in addition to products (127) and (128), the indole (130) is also observed.



Scheme 33

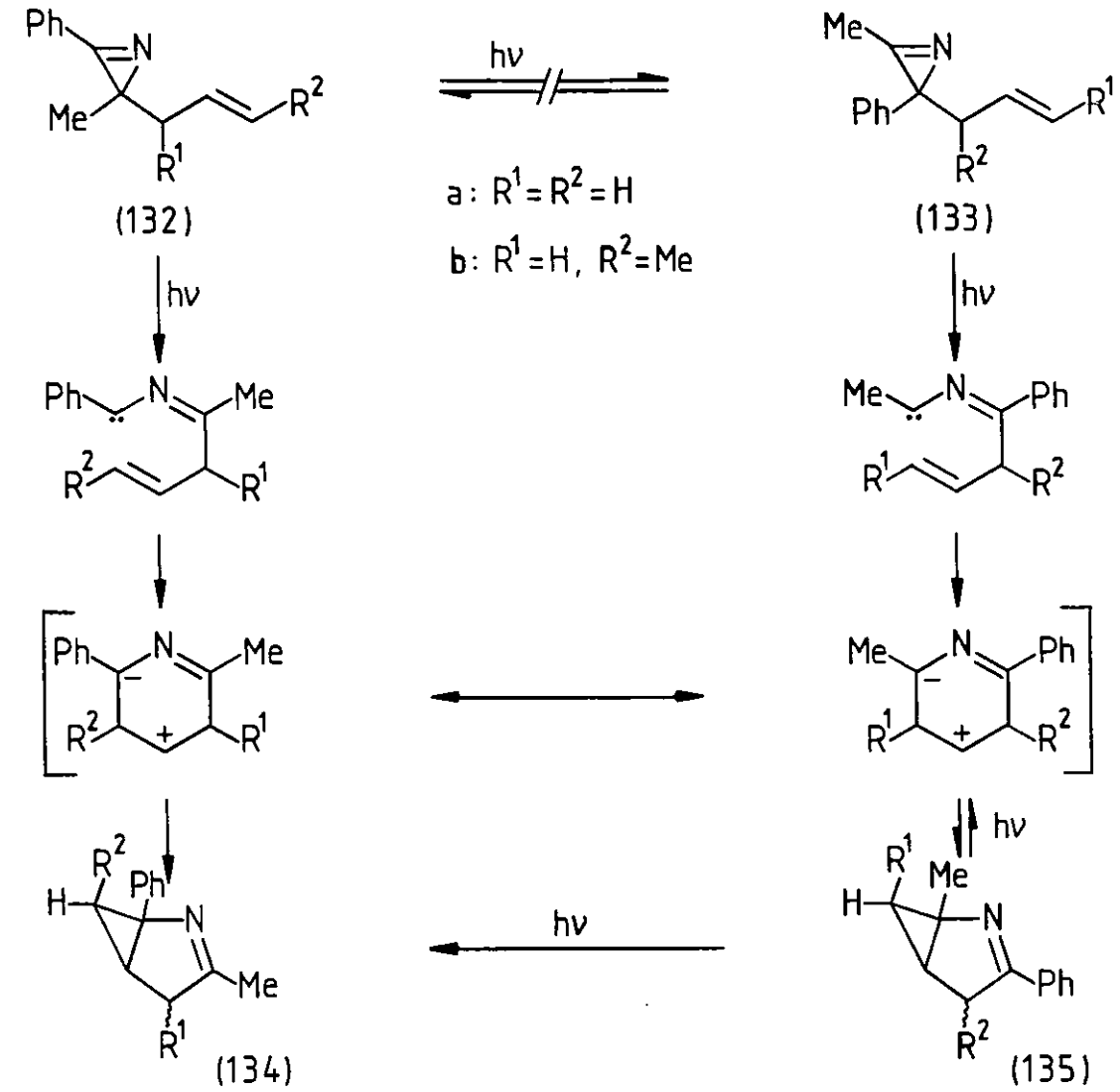


In photolysis of 2-allyl-substituted 2H-azirines, the nitrile ylide or its carbene resonance form adds intramolecularly to the double bond in a 1,1 fashion.[79-81] Thus, irradition of (132a) gives an equal mixture of azabicyclohexenes (134a) and (135a). On further irradiation, (135a) is isomerized to (134a). Photolysis of (132b) gives azabicyclohexene (134b) as the primary product. Similar photocycloadditions are observed for (133a-b). The reaction pathways are outlined in SCHEME 34. In this system, the "parallel plane approach" between the dipolarophile and the dipole is not possible, and consequently the normal mode of 1,3-dipolar addition does not occur.

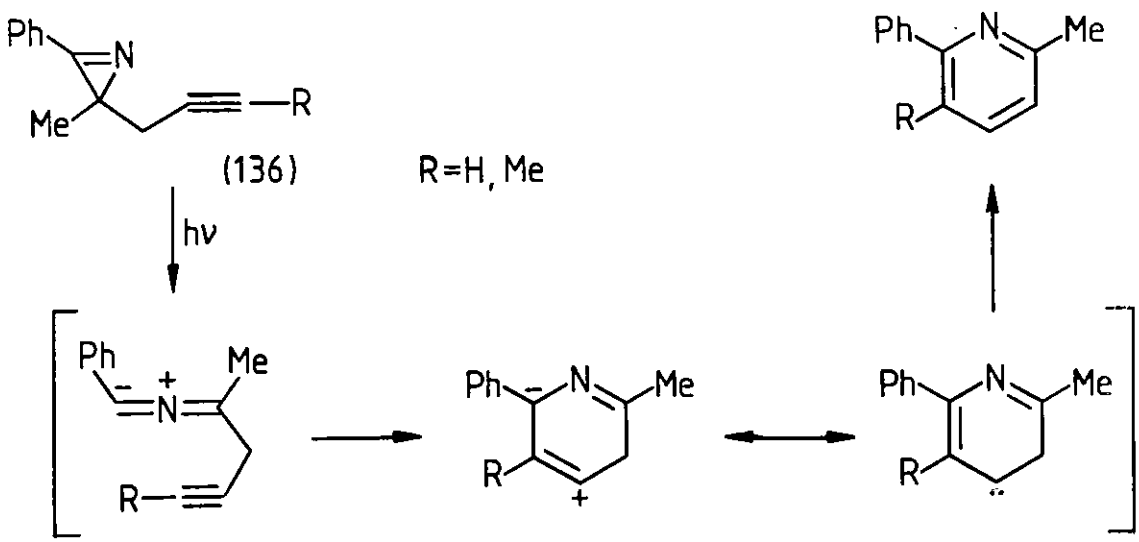
Similar photochemical behaviour of the closely related acetyleneic 2H-azirines (136) has also been realized (SCHEME 35).[82]

iv 2-(But-2-enyl)-2H-azirines

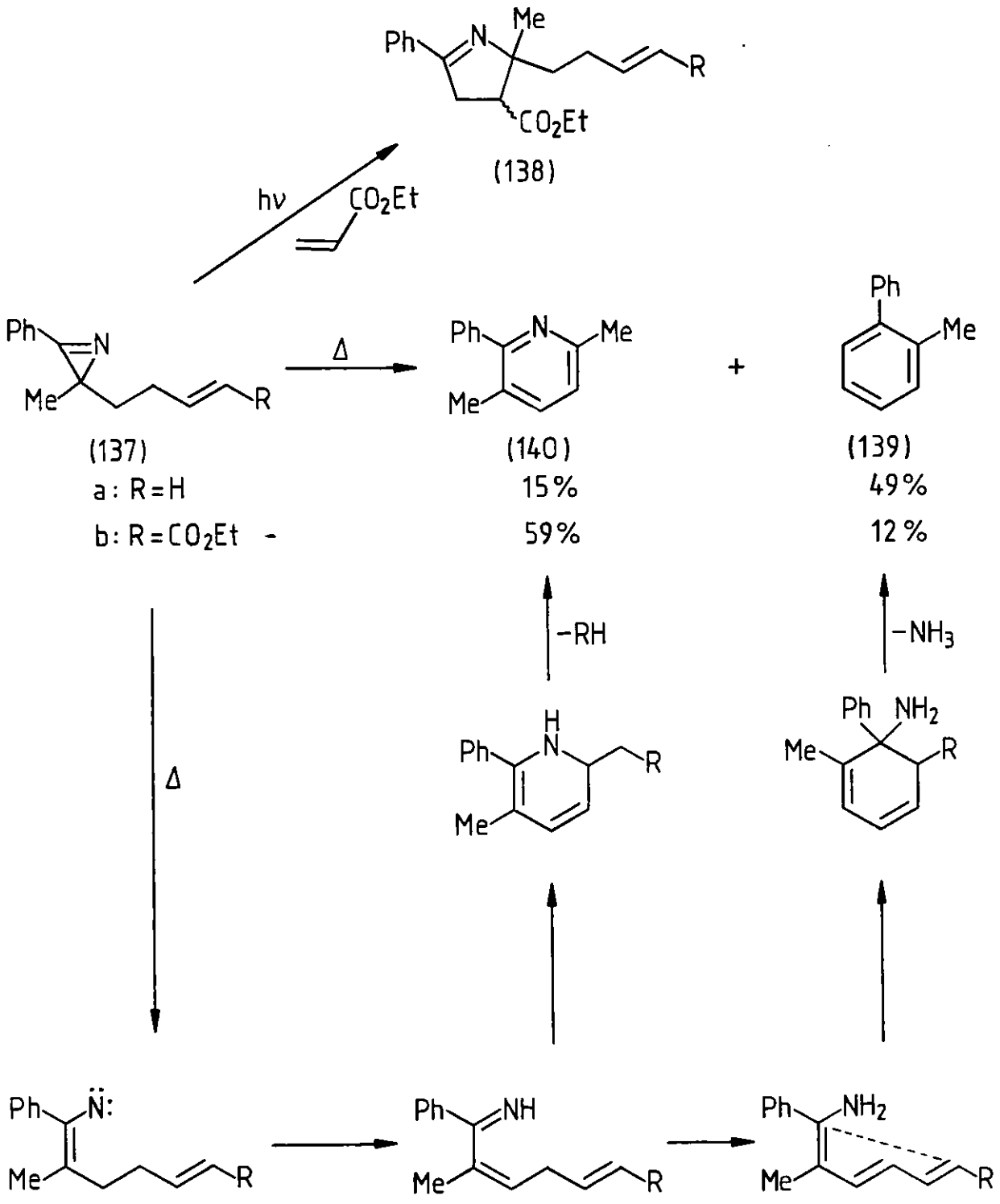
Irradiation of azirine (137a-b) resulted in formation of polymeric material. When the photolysis was carried out in the presence of methyl acrylate, the nitrile ylide intermediate is trapped as a mixture of adducts (138). However, the thermolysis took a different path and gave the corresponding biphenyls (139a-b) and the pyridines (140a-b). The isolation of pyridine (140b) as major product can readily be accounted for as internal Michael addition followed by loss of ethyl acetate (SCHEME 36).[83]



Scheme 34



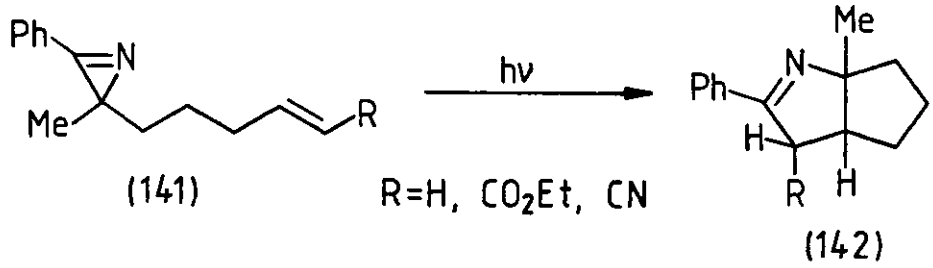
Scheme 35


Ph
N
Me
R
CO2Et
(138)
hν
CO2Et
Δ
(137)
a: R=H
b: R=CO2Et
(140)
15%
59%
(139)
49%
12%
+
-RH
-NH3
NH2
NH

Scheme 36

v 2-(4-Pentenyl)-2H-azirines

In contrast to (137), irradiation of the 2H-azirines (141) produces the intramolecular cycloadduct (142) in good yield.[83] In this system, the methylene chain is sufficiently long to allow the dipole and the olefinic portion to approach each other in parallel planes, hence the normal mode of 1,3-dipolar cycloaddition occurs (SCHEME 37).

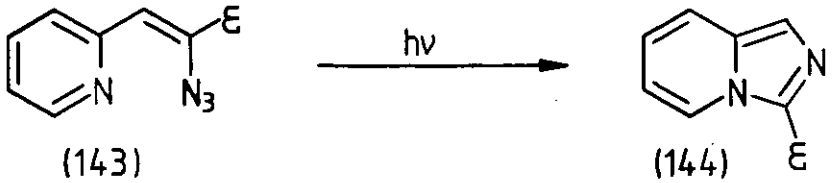


(141) R=H, CO_2Et, CN (142)

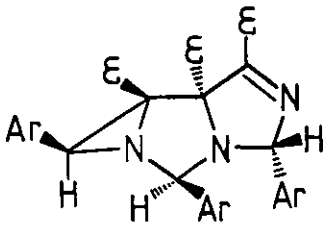
Scheme 37

d α-Azidoacrylates

The photochemistry of α-azidoacrylates is rather limited. As expected the general formation of 2H-azirines is observed.[15,47,84,85] In some cases iminoacrylates are also obtained.[15] Photolysis of (143) gives the expected product (144) via a nitrile ylide intermediate.[86] However, irradiation of a number of α-azidocinnamates gives unexpectantly the trimerization products (e.g. (145)) of the azirines.[86] Apart from these reactions, no other useful photo-induced intramolecular reaction has been reported.



(143) (144)



(145)

Ɛ = CO_2Et

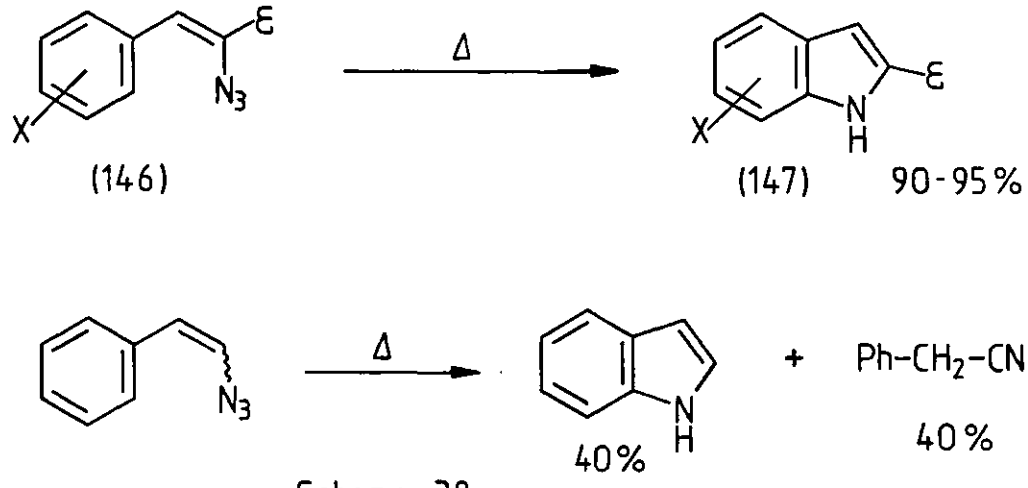
Ar = Ph, 2-Me-C_6H_4

In contrast, thermolysis of α-azidoacrylates has produced some interesting and useful intramolecular reactions. Formation of 2H-azirine as intermediate has also been described.[84,85,87]

In order to account for the product formation, it is necessary to invoke thermal equilibration between the 2H-azirines and the transient vinyl nitrenes. However, the reaction pathways taken by this type of vinyl nitrenes are very similar to those of the 1-azido-1,3-butadiene system described earlier in Section 1.7, *c ii*, namely, electrocyclic ring closure to give 5-membered ring products, and formal C-H insertion by the vinyl nitrene to form 6-membered ring products. In addition, there are two examples of 7-membered ring formation.

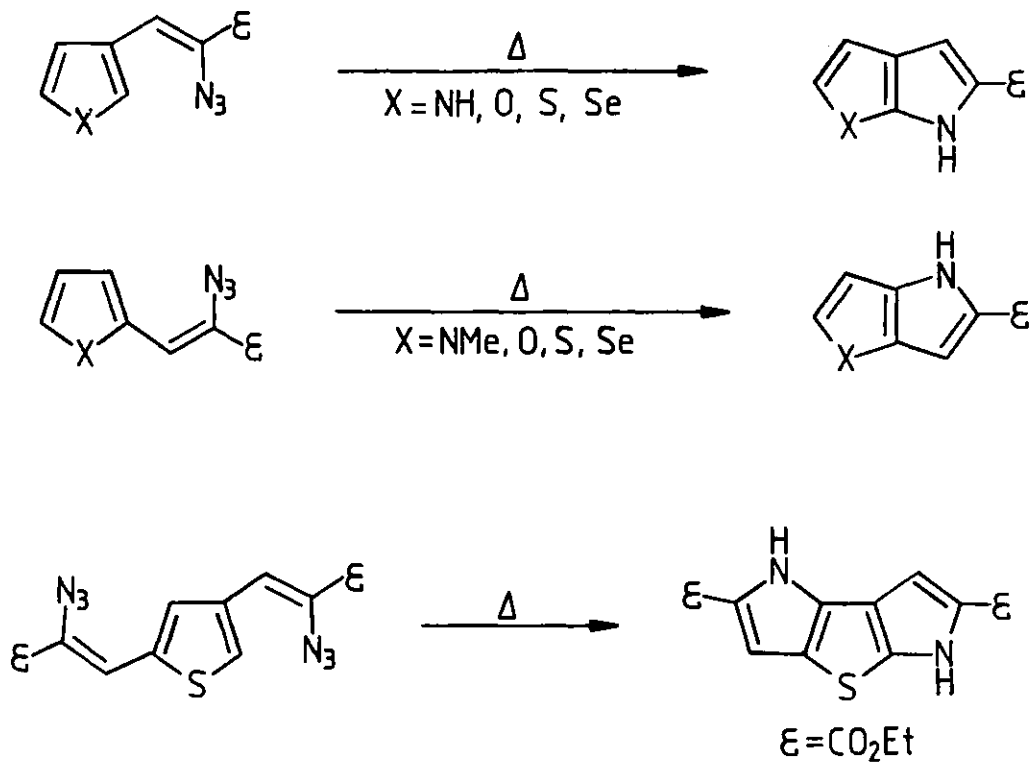
i Five membered ring formation

Thermolysis of a number of α-azidocinnamates (146) gives indoles (147) in excellent yields.[87] This reaction requires at least one of the o-positions in the phenyl ring to be unsubstituted. In contrast with β-azidostyrene, no nitrile formation has been observed in this system (SCHEME 38). The mechanism to give indole has been described in Section 1.7.



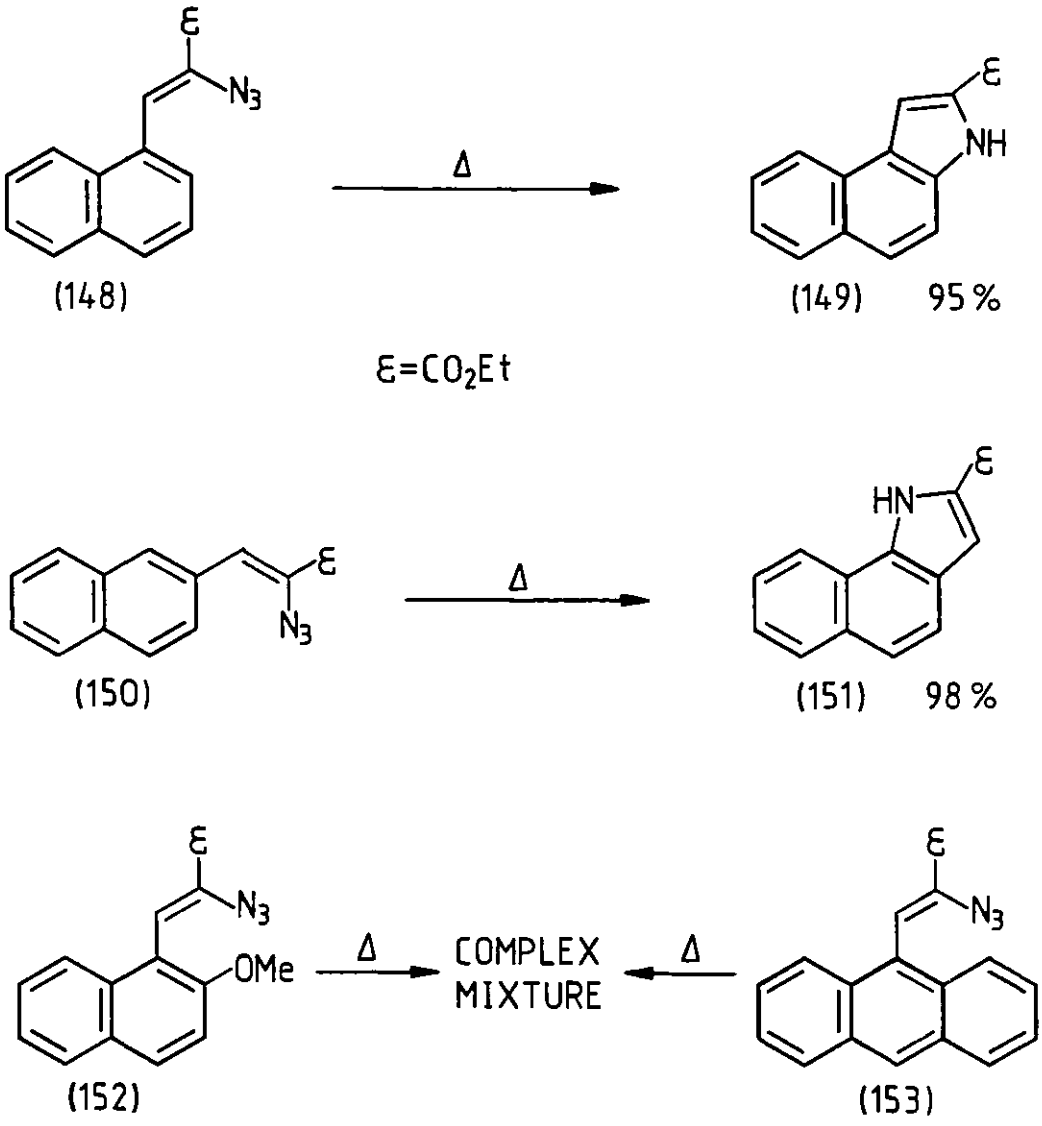
Scheme 38

This reaction also provides an excellent synthesis for various fused heterocyclic pyrroles.[28,31,32,84,88] Some examples are outlined in SCHEME 39. The only limitation to this heterocyclic synthesis is perhaps the availability of the starting vinyl azide.



Scheme 39

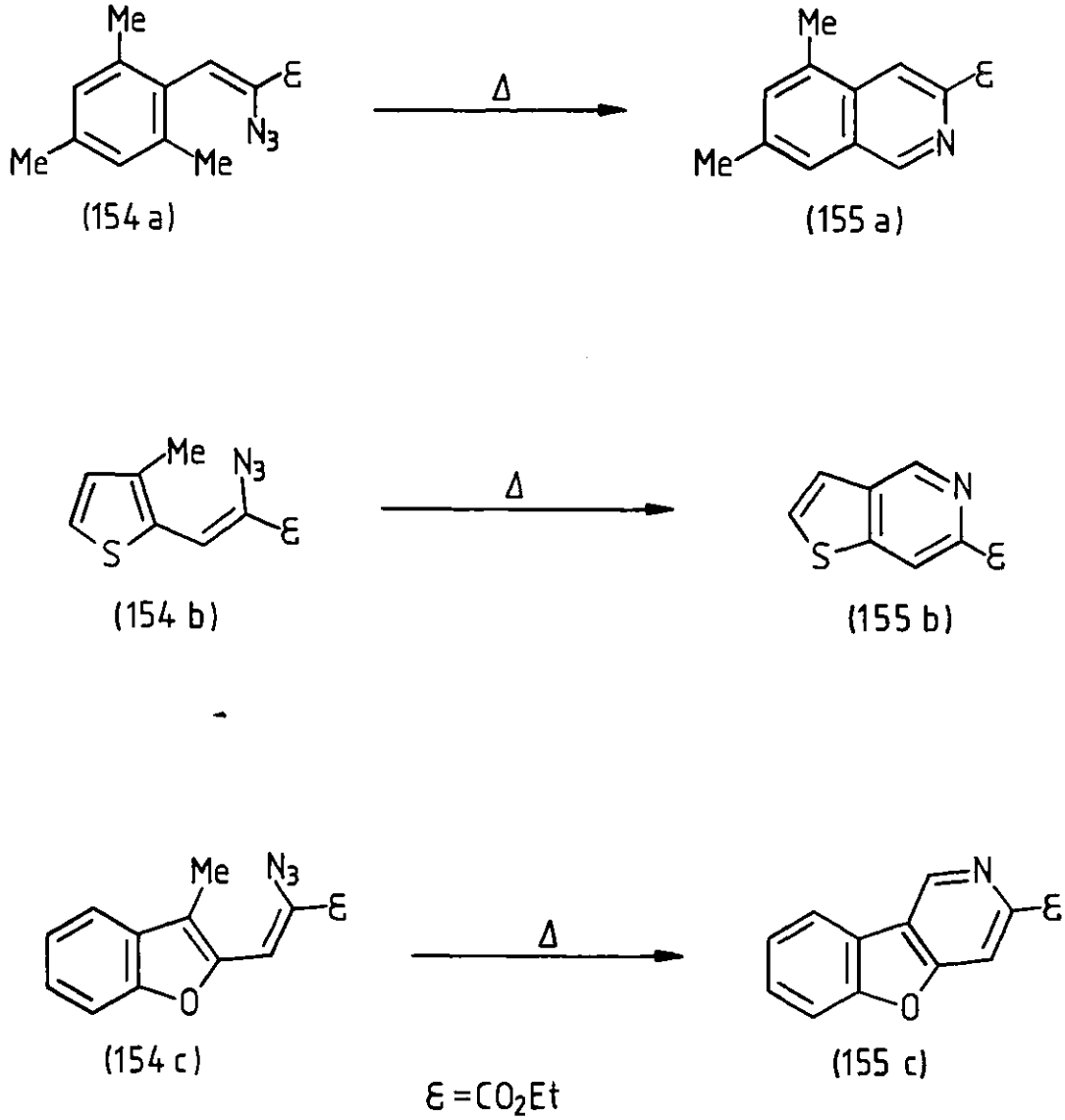
In addition, thermolysis of the corresponding 3-(1-naphthyl) (148) and 3-(2-naphthyl) (150) α-azidoacrylates gives the 3H-benz[e]indole (149) and the benz[g]indole (151) respectively. However, no characterizable product is obtained from (152) and (153) (SCHEME 40).[28]



Scheme 40

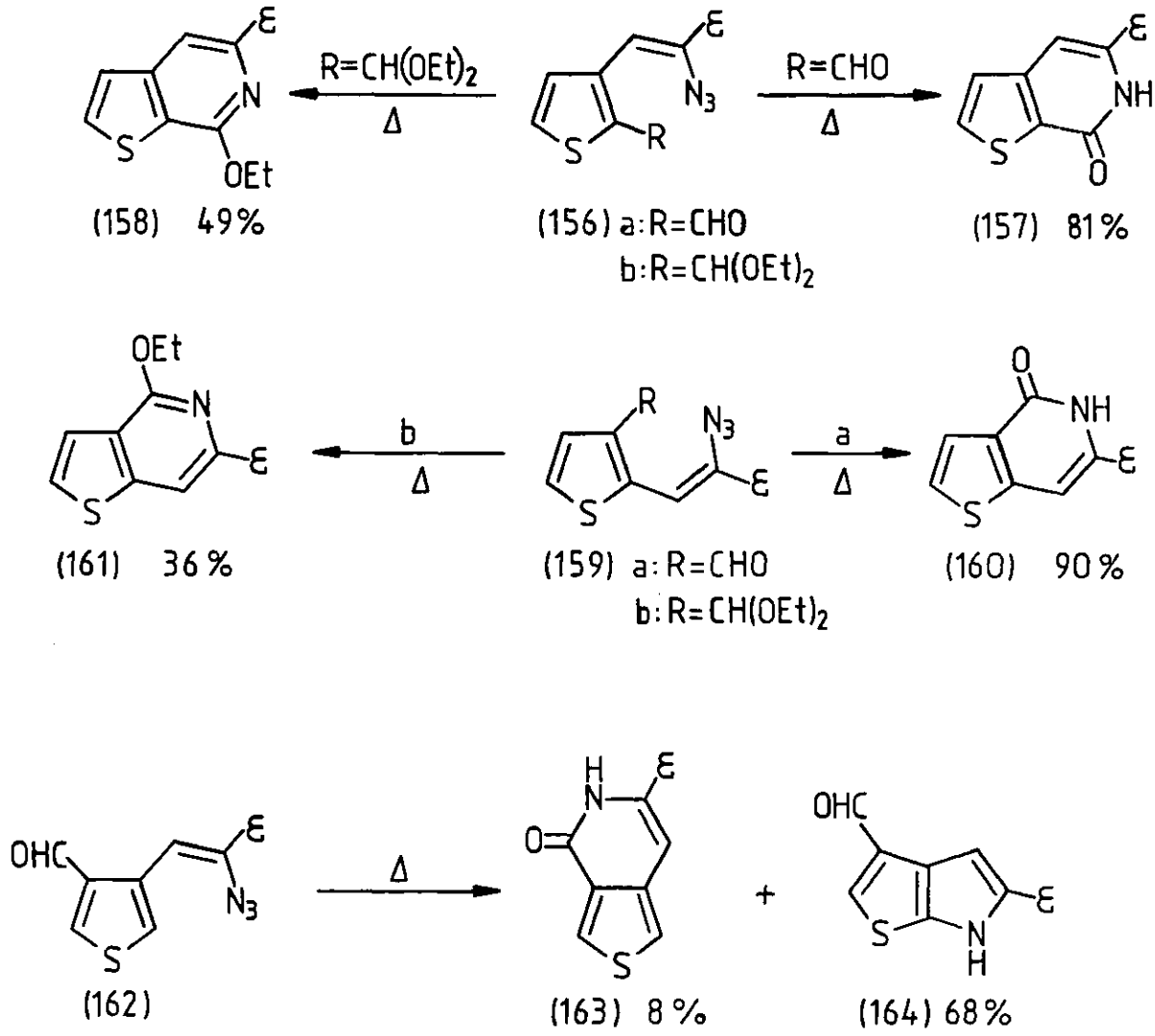
ii Six-membered ring formation

Under the thermolysis of the 1-azido-1,3-butadiene system, pyridine can be formed if a methyl group is placed at a suitable position within the molecule. Thus, a number of fused pyridines (155a-c) have been prepared by the thermolysis of various methyl-substituted α-azidocinnamates (154a-c) (SCHEME 41).[84,89]



Scheme 41

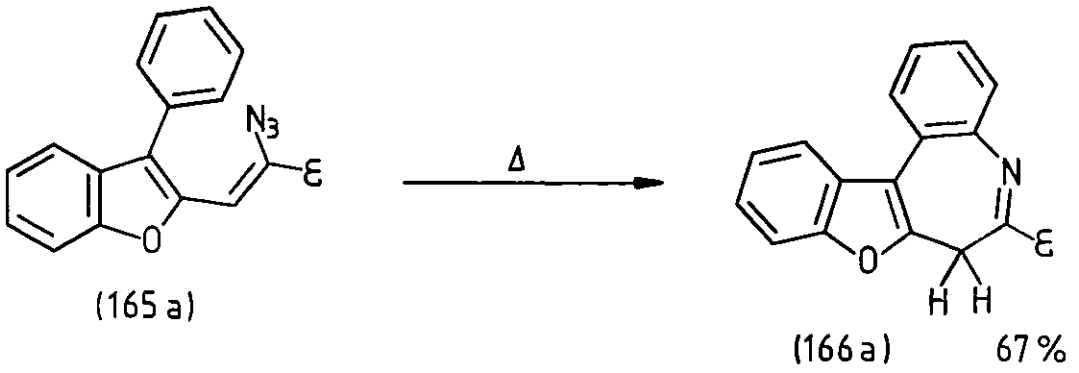
Substituents other than methyl have also been examined, in particular the formyl group as in (156a), (159a) and (162); this gives rise to the fused 1H-pyridones (157), (160) and (163) respectively. The acetal group as in (156b) and (159b), produces the fused pyridines (158) and (161) respectively (SCHEME 42).[29,30]



Scheme 42

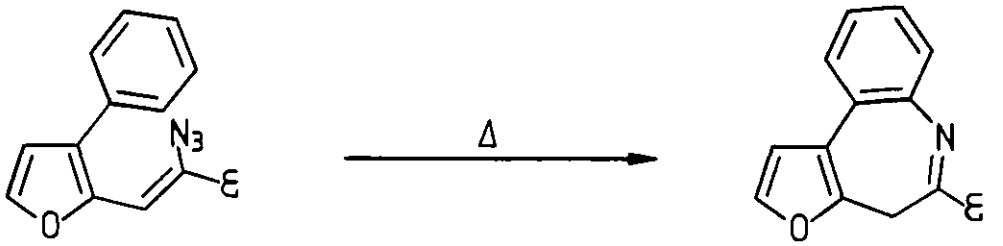
iii Seven-membered ring formation

There are only two examples in the literature where thermolysis of α-azidoacrylates result in the formation of a seven-membered ring product. Pyrolysis of the vinyl azides (165a) and (165b) give the fused azepines (166a) and (166b) respectively (SCHEME 43).[84,90]



(165 a) (166 a) 67 %

Ɛ = CO_2Et

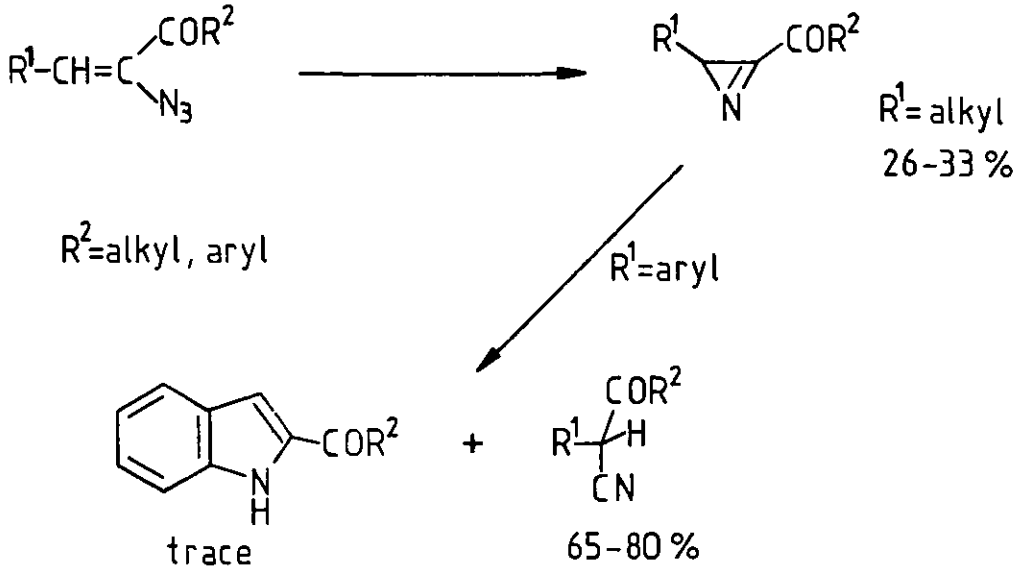


(165 b) (166 b)

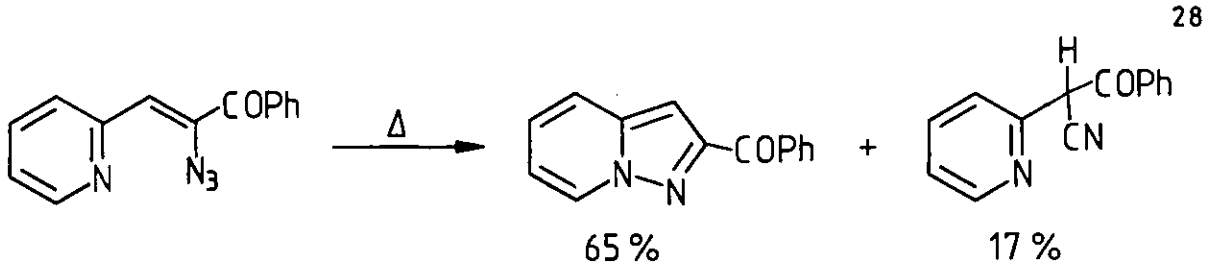
Scheme 43

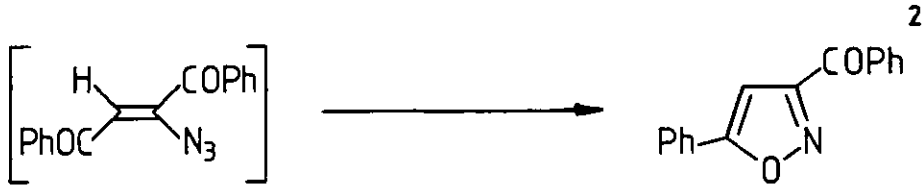
e α-Azidovinyl Ketones

β-Alkyl and aryl substituted α-azidovinyl ketones decompose to 2H-azirines, those with β-aryl substituents can further rearrange to ketonitriles as the major product and only trace amounts of indoles are detected.[35,91]



Unlike the corresponding esters, no "C-H insertion" has been observed and ring formation appears to be an unfavourable process. Exceptions to the latter are exemplified in SCHEME 44.



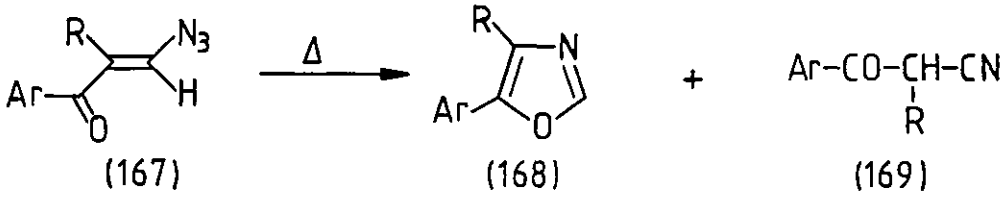


Scheme 44

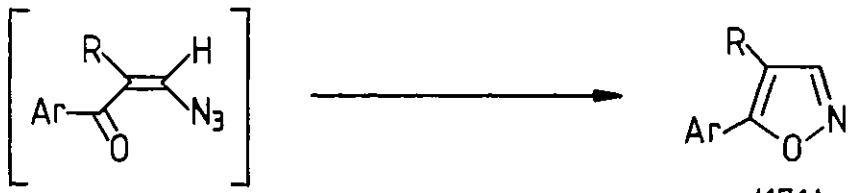
To summarize, the order of stability of 2H-azirines is: 3-unsubstituted < 3-keto or 3-carboxylate derivatives < 3-alkyl or aryl substituted 2H-azirines. Furthermore, in the case of 3-keto substituted azirine, the corresponding 2-alkyl substituted is more stable than the 2-aryl substituted one.

f β-Azidovinyl Ketones and Esters

Pyrolysis of trans-β-azidovinyl ketones (167) gives a mixture of oxazole (168) and nitrile (169).[92] On the other hand, the cis isomers (170) are unstable at room temperature and decompose to isoxazoles (171).[22,92-94]



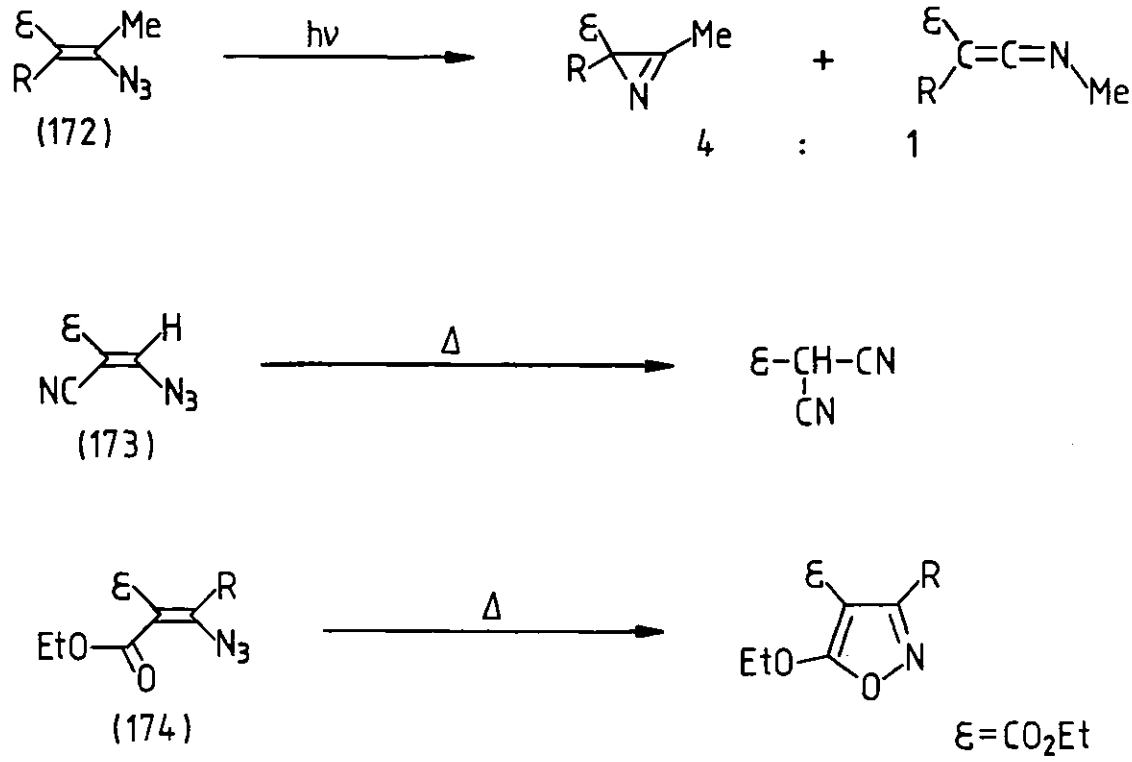
(167) (168) (169)



(170) (171)

The decomposition of β-azidovinyl esters depends largely on the precise constitution of the molecule. Internal vinyl azides (172) furnish azirines and/or ketenimines,[4,13,95] terminal vinyl azides (173) give nitriles,[95] and cis-β-azidovinyl esters (174) give isoxazoles.[95] Some of these reactions are outlined

in SCHEME 45.

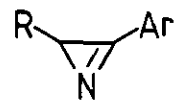


Scheme 45

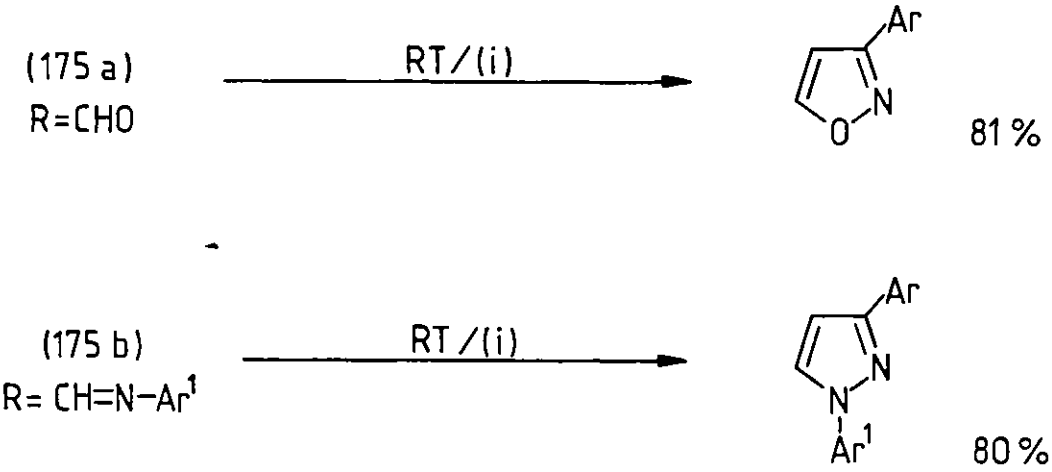
1.8 Metal Induced Reactions of 2H-Azirines

Recent studies have revealed that transition metal compounds can induce ring cleavage reactions of 2H-azirines by complexation. The reaction is normally carried out under very mild conditions. For example, treatment of 2-formyl-3-phenyl-2H-azirine (175) with molybdenum hexacarbonyl, $Mo(CO)_6$, at room temperature for 5 h gave 3-phenylisoxazole in 81% yield.[96] In contrast, the previously required conditions were 200°C in toluene, in a sealed tube for 3 days.[73] Other similar $Mo(CO)_6$ induced reactions

of 2H-azirines are outlined in SCHEME 46; they all result from initial C-N bond cleavage of the azirine ring. However, C-C bond cleavage cannot be ruled out in the dimerization leading to the formation of pyrazines (176).[96]

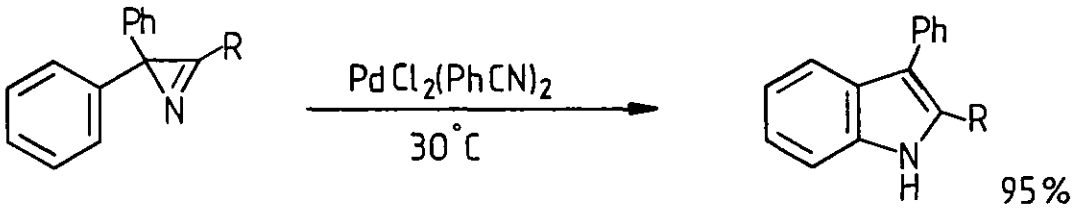


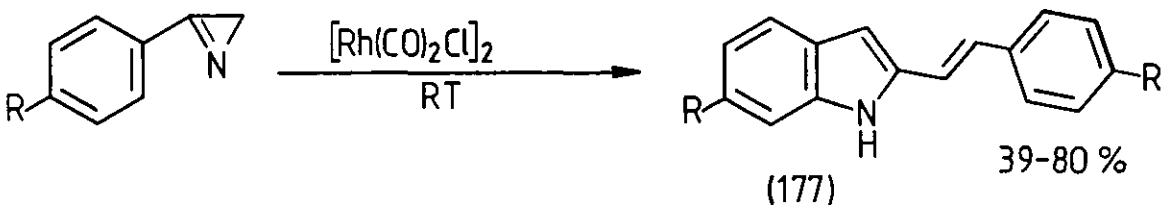
(175)



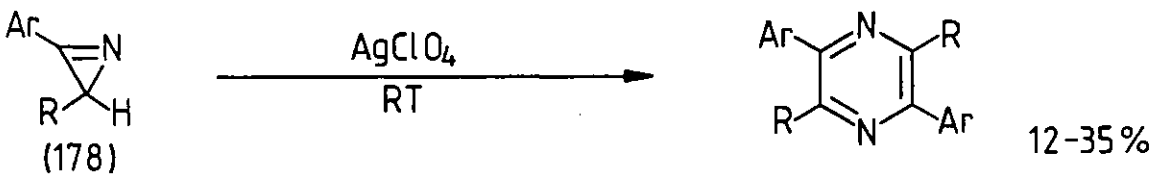
Scheme 46

Other metal compounds such as $PdCl_2(PhCN)_2$,[97] $[Rh(CO)_2Cl]_2$,[98] $AgClO_4$,[99] $TiCl_4$,[96] and $CuBr_2$[100] have also been reported to catalyse the decomposition of 2H-azirines. Examples of their reactions are shown in SCHEME 47.

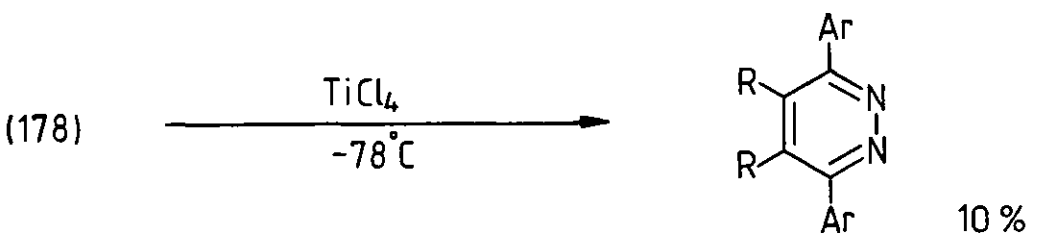


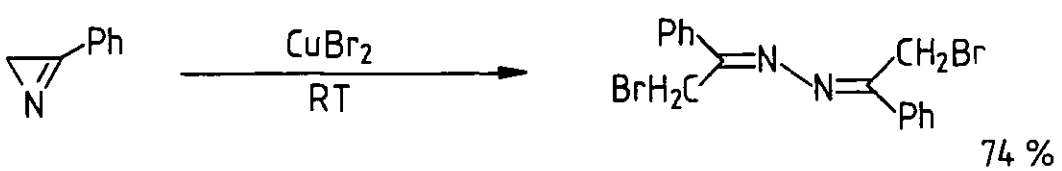


(177)



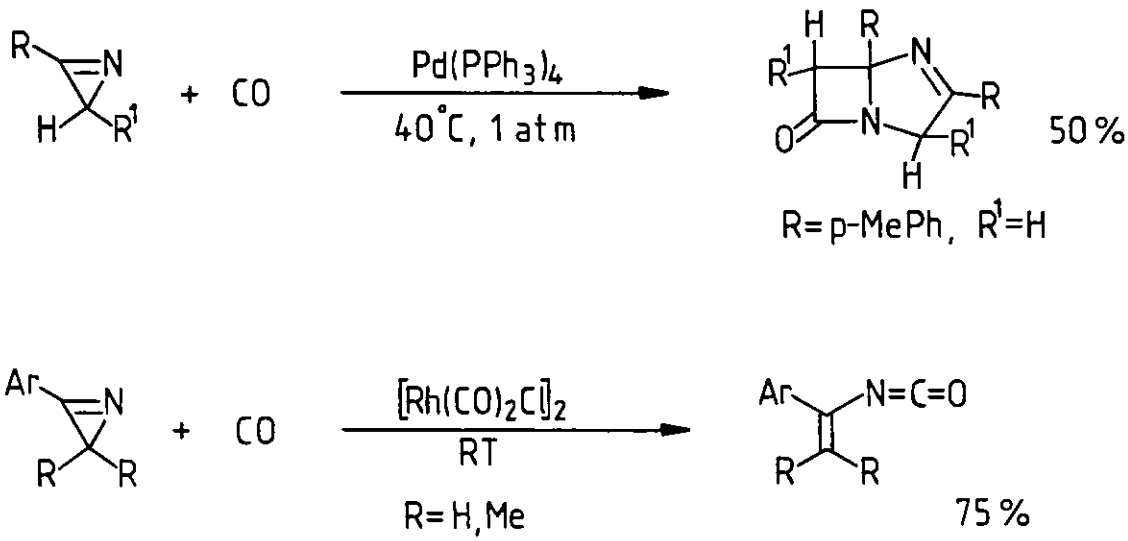
(178)





Scheme 47

A novel β-lactam synthesis involving palladium (0) catalysed carbonylation of azirines has been reported.[101] However, rhodium (I) induced carbonylation of 2H-azirines give isocyanates (SCHEME 48).[102]



Scheme 48

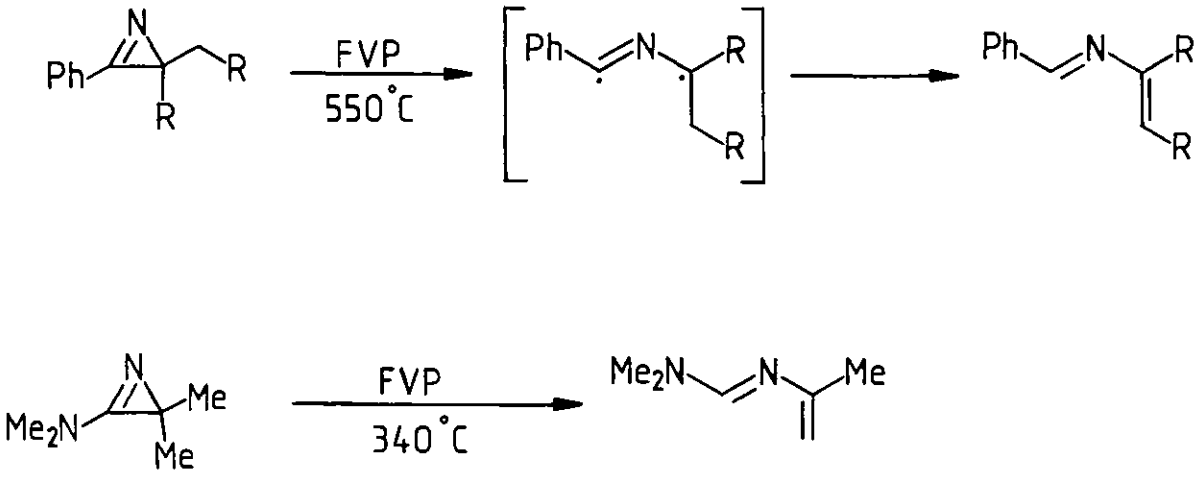
1.9 Miscellaneous Reactions

Vinyl azides, as well as the analogous 2H-azirines, can undergo electrophilic, nucleophilic and various cycloaddition reactions. Several recent reviews on these topics are available in the literature,[46,47,53,54,103-105] and only a few selected reactions will be mentioned here.

a Thermal C-C Bond Cleavage of 2H-Azirines

Unambiguous evidence for thermal C-C bond cleavage has been obtained in the vapour phase pyrolysis of several azirines.[106,107] A diradical species, generated from C-C bond fission followed by a

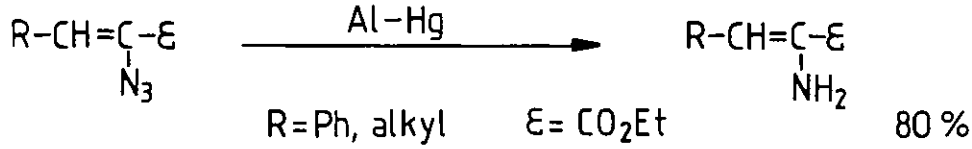
[1,4]-hydrogen shift to an azadiene, is postulated. Examples are given in SCHEME 49.



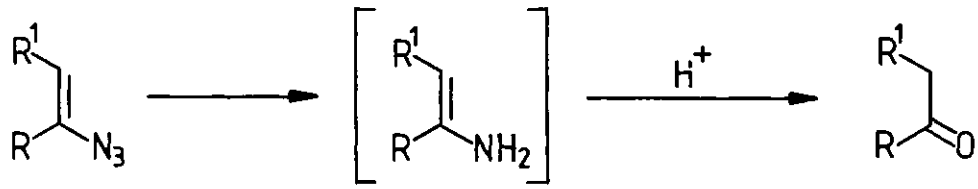
Scheme 49

b Reduction of Vinyl Azides

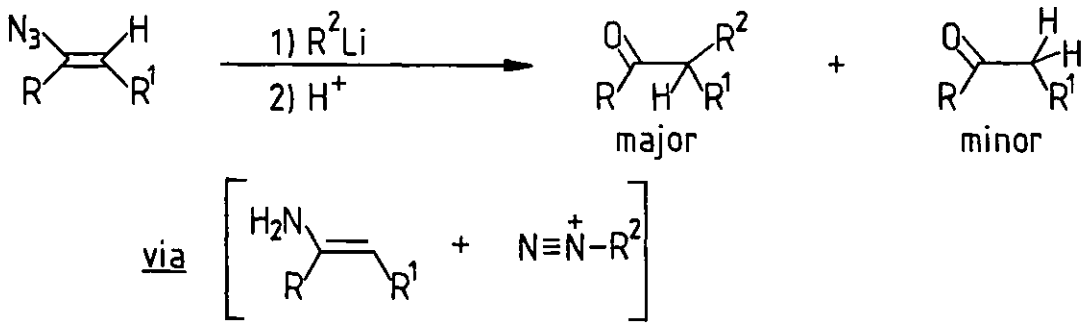
Reduction of α-azidoacrylate with aluminium amalgam gives the corresponding esters of dehydroamino acids in excellent yield.[37]



Conversion of other vinyl azides to aldehydes or ketones have been accomplished by various reducing agents, such as, zinc-acetic acid,[11] triphenyl phosphite,[38] and sodium sulphide,[108] presumably via enamine derivatives.



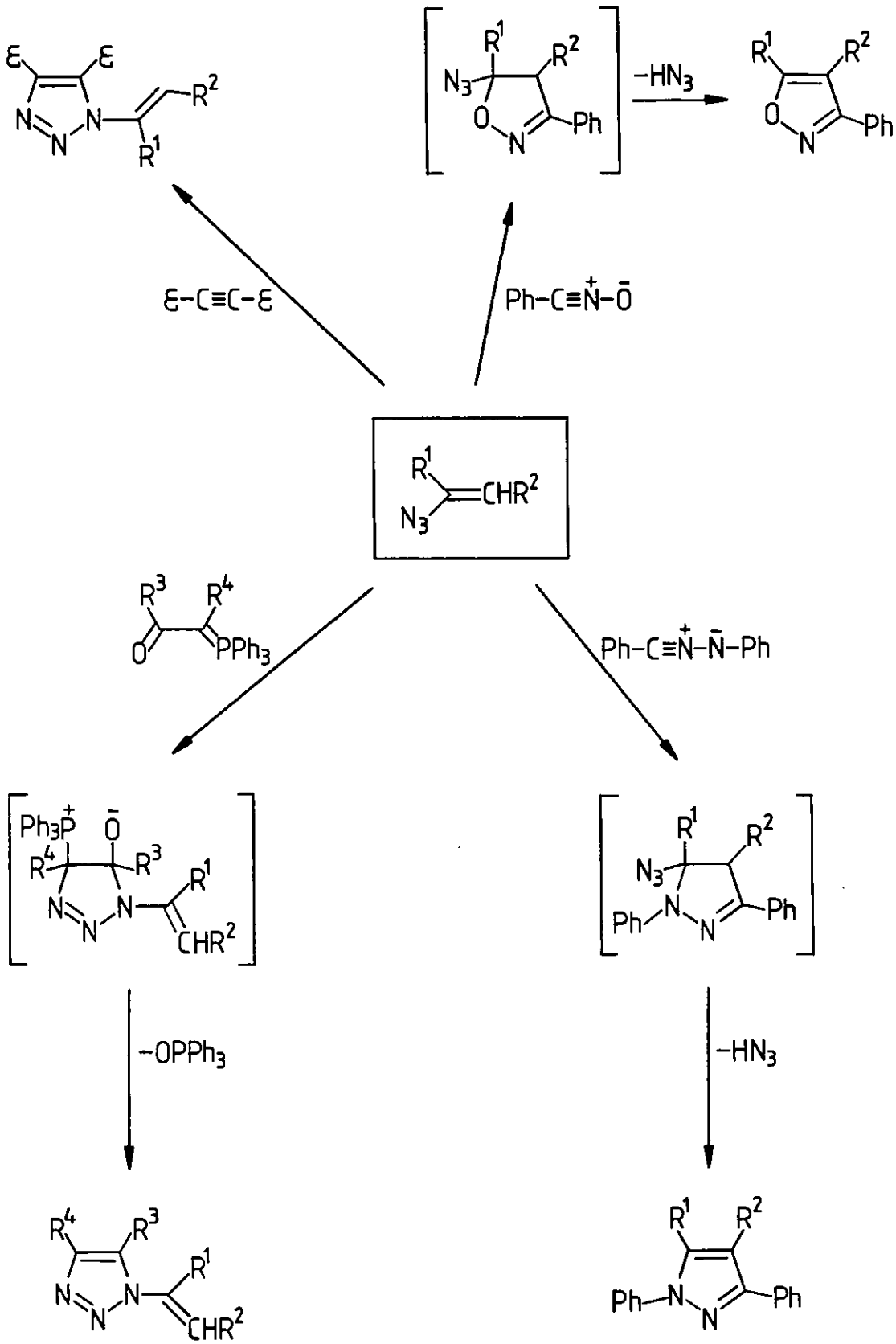
A related conversion of vinyl azides into ketones, in which simple alkyl anions are transformed into alkyl cation equivalents has been observed.[109]



c Intermolecular Cycloaddition with External Reagents

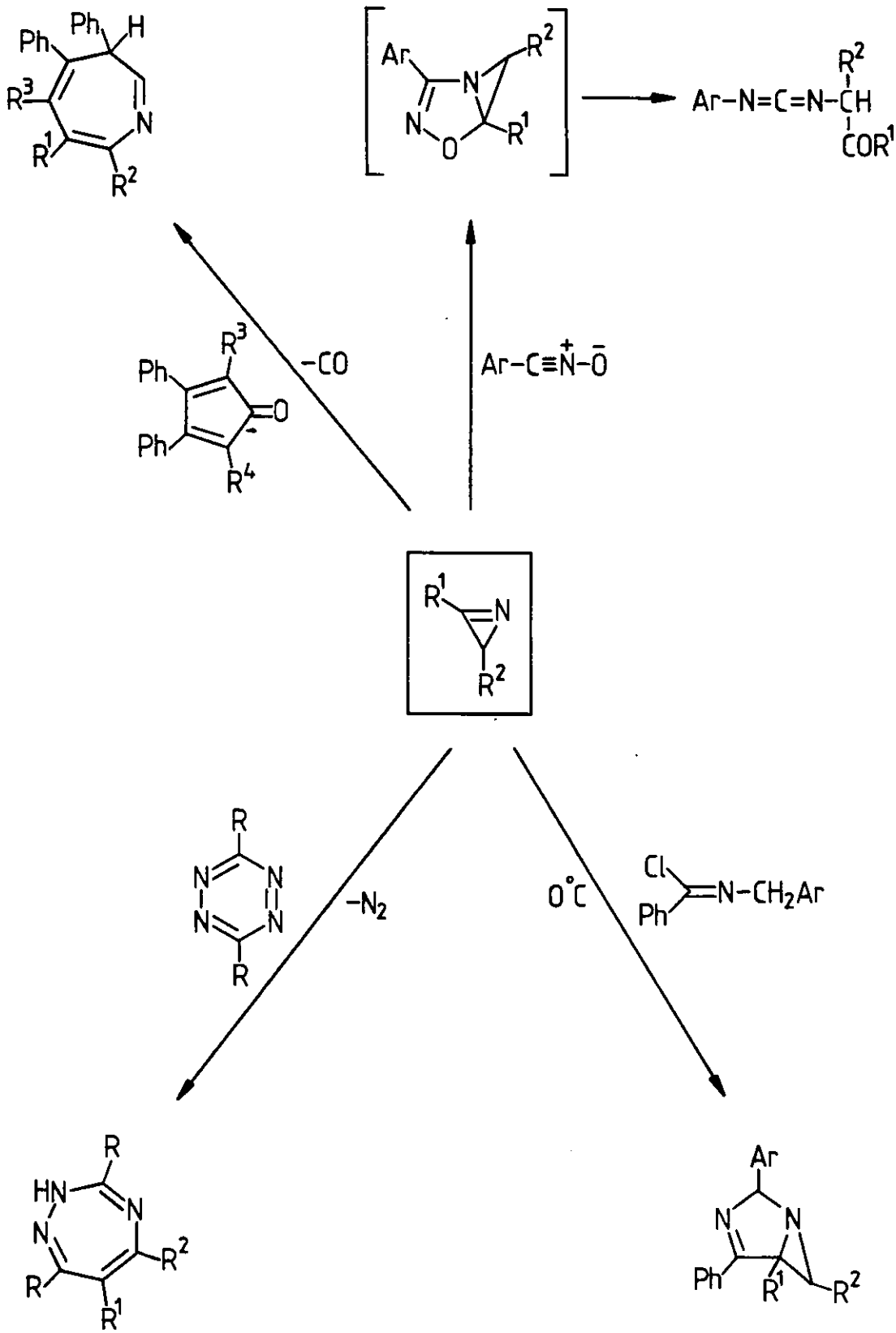
In vinyl azides, the azide function can react with various dipolarophiles to give 1,2,3-triazoles. However, the vinyl moiety can behave as dipolarophile and reacts with dipoles with the eventual elimination of HN_3 (SCHEME 50).[46]

In 2H-azirines, the 2π-electrons can participate in thermally allowed [$\pi_4s+\pi_2s$]- cycloadditions as dienophiles or as dipolarophiles.[46,103-105] Some examples are outlined in SCHEME 51.



Scheme 50

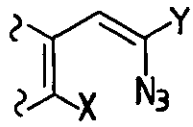
Under photolytic conditions, 2H-azirines react as nitrile ylides with a variety of dipolarophiles.[47, 53,54]



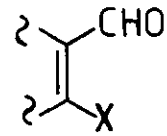
Scheme 51

2. DISCUSSION

The decomposition of vinyl azides has given rise to some interesting reactions and useful heterocyclic syntheses. The aim of this project was to examine the scope of the intramolecular reactions, and to investigate the possible interactions of various substituents X in vinyl azide decompositions, and in particular, systems such as (179).



(179)

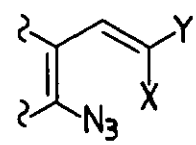


(180)

The most direct method available for preparing (179) is by the procedure of Hemetsberger.[26,36] The method involves the condensation of an aromatic or α,β-unsaturated aldehyde (180) with an α-azido ester or ketone (181). However, if an azide function is already in the aldehyde fragment (180, X = N_3), condensation with a variety of active methylene compounds will produce the adduct (182), a system which is similar to (179).

$COR-CH_2-N_3$

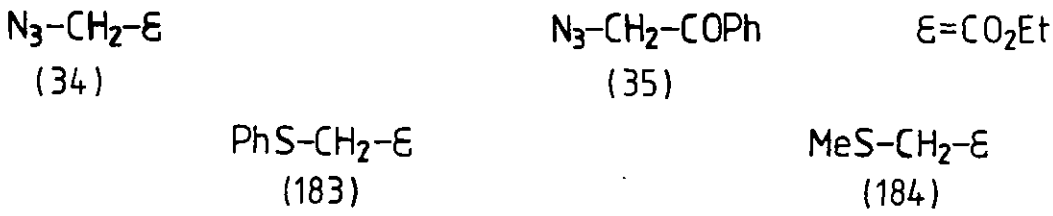
(181)



(182)

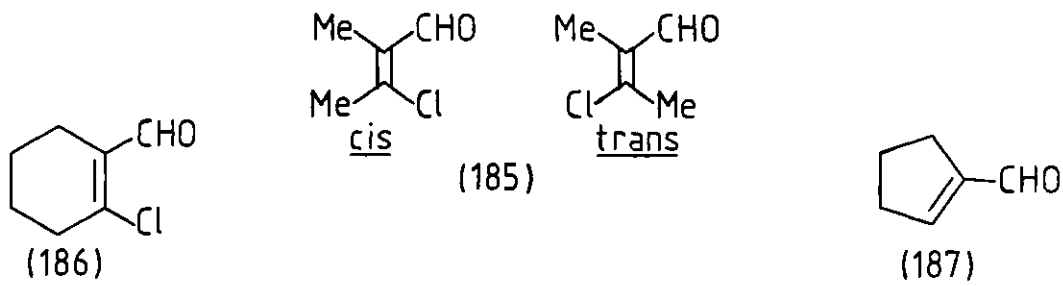
2.1 Preparation of Synthetic Intermediates

The active methylene compounds (34),[110] (35)[111] and (183)[112] were prepared according to their literature methods. Ethyl methylthioacetate (184) was prepared from esterification of mercaptoacetic acid followed by methylation of the resulting ester.



2.2 Preparation of Aldehydes

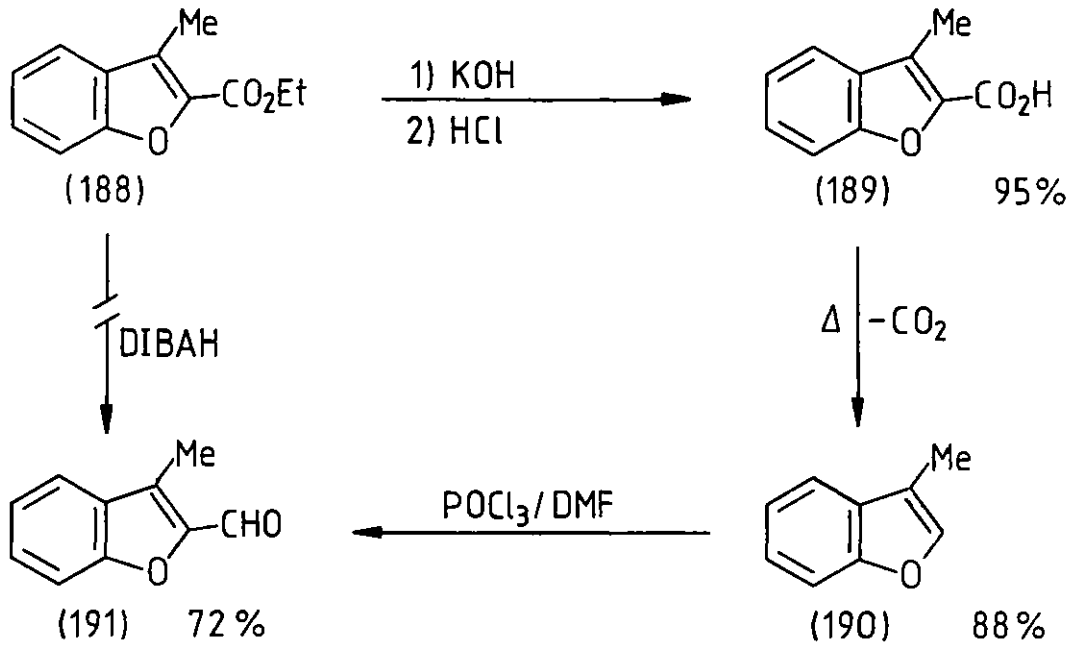
Aldehyde (185) was prepared according to the literature method as a mixture of cis and trans isomers in the ratio of 3:7.[113] Aldehydes (186)[113] and (187)[114] were also prepared by their respective known procedures.



The benzofuran aldehyde (191) was prepared according to the procedure outlined in SCHEME 52.[115,116] It has been reported that diisobutylaluminium hydride (DIBAH) is the reagent of choice for converting esters into the corresponding aldehydes in one step.[117-119] However, this reagent failed to react with the ester (188).

The aldehydes (192-195) were prepared by the method of Gronowitz as shown in SCHEME 53.[120-123] The literature procedure for converting the bromoaldehyde (192) into the azidoaldehyde (193) involved reaction

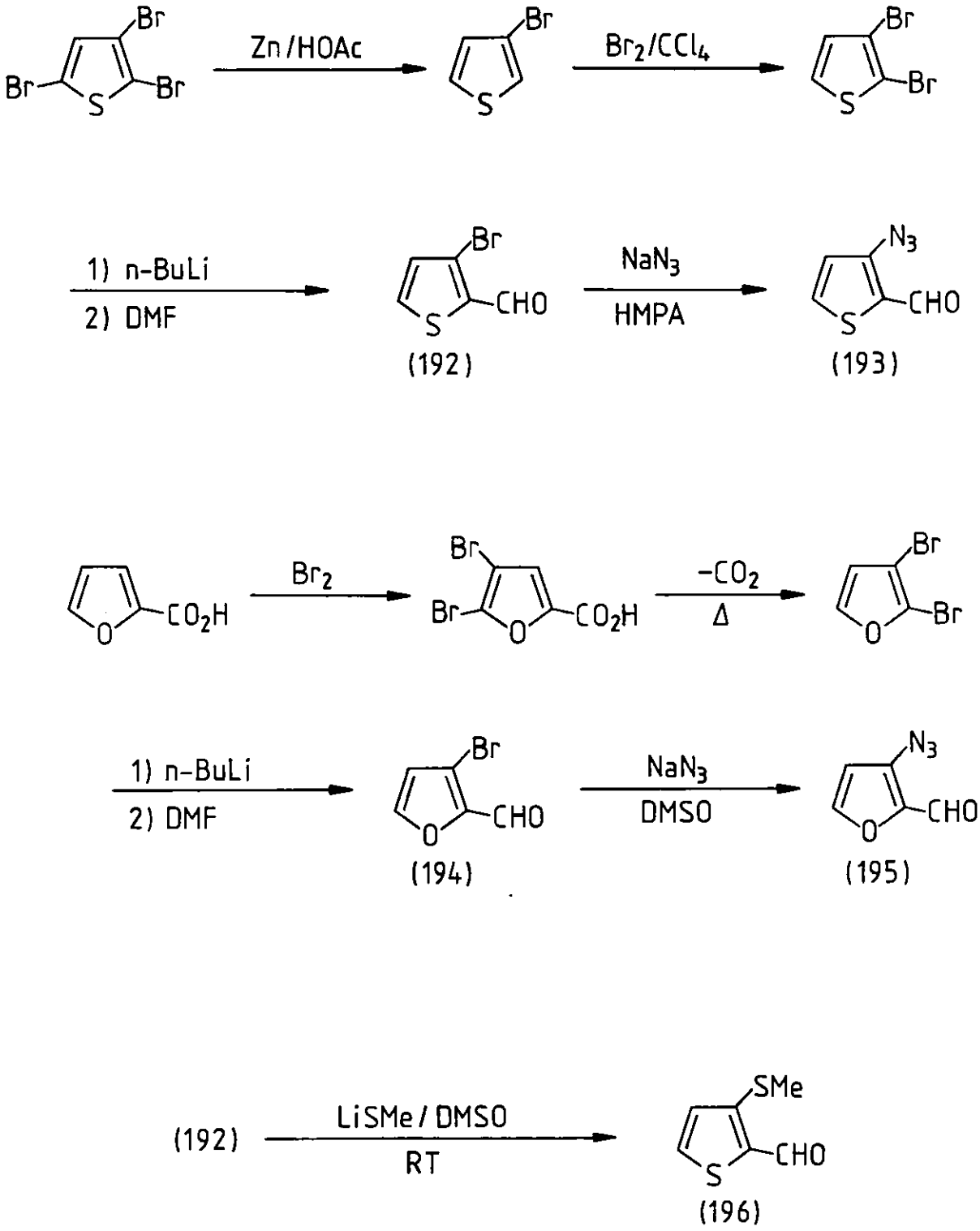
of (192) with sodium azide in DMSO at 65°C for 24 h;[121] a literature



Scheme 52

yield of 45% was obtained. However, when the bromoaldehyde (192) was treated with the more organic soluble lithium azide in DMF under the same conditions, the product (193) was isolated in 63% yield, indicating that solubility of the azide is an important factor. An even higher yield of the azidoaldehyde (193) was obtained (75%) with the use of sodium azide in HMPA at 30°C for 2 days. These results reflected the superiority of HMPA as a solvent in this type of substitution reaction. However, when the bromoaldehyde (194) was treated with NaN_3 in HMPA under the same conditions, only a 16% yield of (195) was obtained. The literature NaN_3/DMSO procedure gave the same product (195) in 50% yield.[123]

The methylmercapto aldehyde (196) was prepared in 58% yield by stirring a mixture of the aldehyde (192) and lithium thiomethoxide in dry DMSO at room temperature.


Br
Br
Br
S
Zn/HOAc
Br
S
Br2/CCl4
Br
Br
S
1) n-BuLi
2) DMF
Br
CHO
S
(192)
NaN3
HMPA
N3
CHO
S
(193)
CO2H
O
Br2
Br
Br
CO2H
O
-CO2
Δ
Br
Br
O
1) n-BuLi
2) DMF
Br
CHO
O
(194)
NaN3
DMSO
N3
CHO
O
(195)
(192)
LiSMe / DMSO
RT
SMe
CHO
S
(196)

Scheme 53

2.3 Preparation of Vinyl Azides

a α-Azidoacrylates

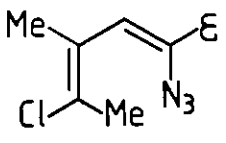
The literature procedure required the condensation to be carried out in four-fold excess of ethyl azidoacetate and sodium ethoxide, in ethanol at 0°C.[26] However, poor yields of vinyl azides were obtained from less reactive aldehydes. It was felt that there was a need for improvement in this reaction and the effect of base, solvent and temperature were investigated. However, attempts to condense the aldehydes (185), (186), (193), o-tolualdehyde and mesitylaldehyde with ethyl azidoacetate under a variety of conditions failed. The conditions and results are summarized in Table 2.

Aldehyde	EAA (eq)	Reagent	Solvent	Temp. (°C)	Time (h)	Result
(185)	1.1	NaH,.1.1 eq.	DME	0	2	NR
(185)	1.1	NaH,1.1 eq.	DME	20	24	NR
(185)	3.0	KO^tBu,3.0 eq.	THF	-20	0.5	PM
(185)	3.0	KO^tBu,3.0 eq.	THF	-78	0.5	PM
(185)	1.1	n-BuLi,1.1 eq.	THF	-78	4	PM
(186)	1.0	LiI,5 eq.	Et_2O	20	48	NR
(186)	1.0	K_2CO_3,1.1 eq.	DMF	20	72	NR
(193)	1.0	PA,1.0 eq.	EtOH	20	18	NR
o-Tolu-	1.1	Na_2CO_3	EtOH	20	48	NR
o-Tolu-	0.9	PA, cat.	C_6H_6	80	17	RSM/PM
o-Tolu-	1.0	PA,4 eq.[26]	EtOH/Ch	20	24	NR
Mesityl-	1.0	$TiCl_4/Py$[124]	THF	0-20	72	NR

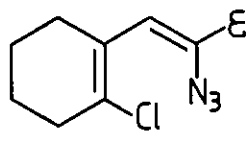
EAA = Ethyl azidoacetate
PA = Piperidine acetate
DME = 1,2-Dimethoxyethane
Py = Pyridine
Ch = Cyclohexane
NR = No reaction
PM = Polymeric mixture
RSM = Recovered starting material

Table 2

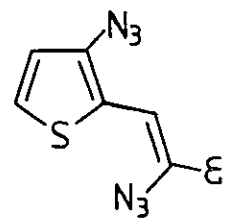
A simple modification of the Hemetsberger procedure gave an improved yield of vinyl azide. For example, the yield of the vinyl azide (197) was improved from 12.6% to 55% using the modified procedure. The modification essentially comprised lowering the reaction temperature to between -15 and -10°C and monitoring the reaction by t.l.c. until all the aldehyde had been consumed. At that temperature, the anion of ethyl azidoacetate was stable enough not to undergo extensive decomposition,[27] but reaction with the aldehyde could still occur. In order to optimize the final yield of vinyl azide, the alkaline reaction mixture should be kept at low temperature and the excess of ethyl azidoacetate should be destroyed to avoid complication in the isolation process. Since the base-induced decomposition of ethyl azidoacetate is an exothermic process, its decomposition should be carried out in a controlled manner. This was achieved by allowing the reaction mixture to warm up slowly to between -5 and +5°C, until the evolution of nitrogen ceased. Thus, a number of vinyl azides were prepared in moderate to good yield.



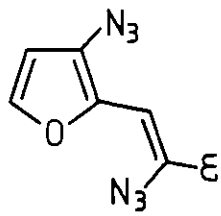
(197) 55%



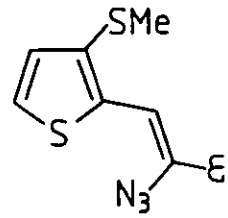
(198) 56%



(199) 63%



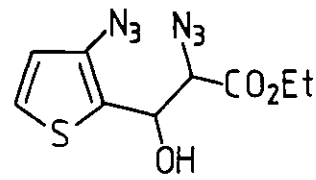
(200) 25%



(201) 52%

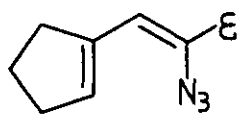
E=CO_2Et

During the preparation of the bis-azide (199), t.l.c. of the reaction mixture showed that apart from the starting aldehyde (R_f 0.4), two other components (R_f 0.7 and 0.2) were observed. However, when the reaction was completed and was worked up, t.l.c. of the crude mixture showed only the presence of the compound with R_f 0.7, which corresponded to the bis-azide (199); some highly polar material was also observed. The component with R_f 0.2 observed earlier had disappeared; it could be the initial hydroxy adduct (202) which on elimination of water, gives the final product (199). As shall be seen later, the hydroxy intermediate was isolated in a similar condensation reaction.

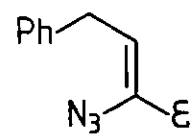


(202)

Attempts to condense the aldehydes (187) and phenylacetaldehyde with ethyl azidoacetate over a temperature range of -40 to 0°C, failed to produce the required vinyl azides (203) and (204). In both cases, either no reaction or polymerization of the aldehydes occurred. This was probably due to the low reactivity of ethyl azidoacetate at temperatures below -20°C and the rapid self-condensation of the aldehydes under the reaction conditions.



(203)



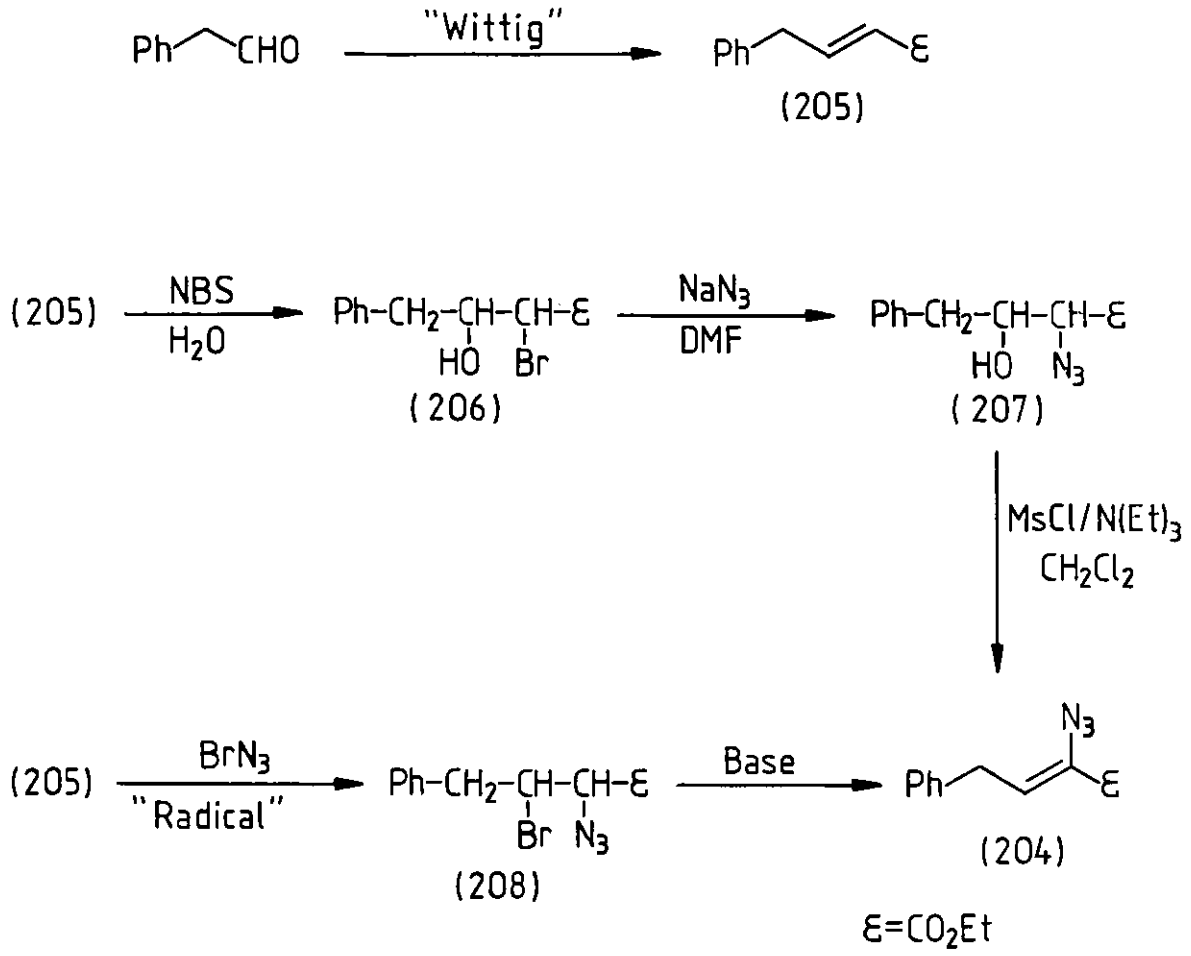
(204)

E=CO_2Et

Two possible alternative routes to the vinyl azide (204) are shown in SCHEME 54. Both methods require the acrylate (205) as the key intermediate which can readily be prepared from phenylacetaldehyde. The first method is to adapt the general procedure developed by Shin and co-workers;[5,37] it involves the formation of bromohydrin (206) from the acrylate (205), followed by substitution to give the β-hydroxy azide (207); treatment of (207) with mesyl chloride and triethylamine in dichloromethane should give the vinyl azide (204). The second method is Hassner's radical addition of bromine azide or chlorine azide to olefins.[5,8-10] The addition of azide radical to olefins is governed by the formation of the most stable radical intermediate, and in this case (208) would be the expected adduct from (205). Base elimination of (208) should produce the required product (204).

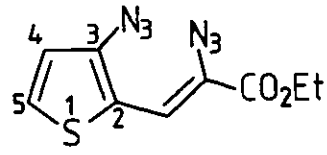
The ^{1}H n.m.r. spectra of the vinyl azides (197-201) indicated that only one of the two possible geometric isomer was present. On thermodynamic grounds, the cis configuration with respect to the ester group and the olefinic proton as shown in structures (197-201) was assumed.[26] The n.m.r. evidence supporting the single isomeric structure in compounds (197) and (198), came from the olefinic proton signal in which a one proton singlet was observed. In the case of vinyl azide (197), Z and E configurations about the chlorine bearing double bond were also possible, because the precursor aldehyde (185) contained a mixture of Z and E isomers in the ratio of 3:7. In order to account for the 55% yield from the reaction, the product must come from the E isomer of the aldehyde (185) and hence the product structure of (197).

In the ^{1}H n.m.r. spectra of (199) and (201), the olefinic protons were shown to couple to the H-5 thiophen ring-proton, with a coupling constant of about 0.8 Hz. This was due to the long range



Scheme 54

"zig-zag" coupling through the heteroatom between the two protons; this implies that, in solution, the molecule on average exists as that particular conformation as shown in (199) and (201). If the molecule existed as in (209), a long range "zig-zag" coupling between the higher field H-4 ring-proton and the side chain olefinic proton would be observed. The "zig-zag" coupling in these systems is well documented[29,88,123,125] and provides a useful means for many structural assignments in the later part of this work. However, in the case of (200), the coupling constant was so small that only a slight broadening of the olefinic and the H-5 proton signal was observed.

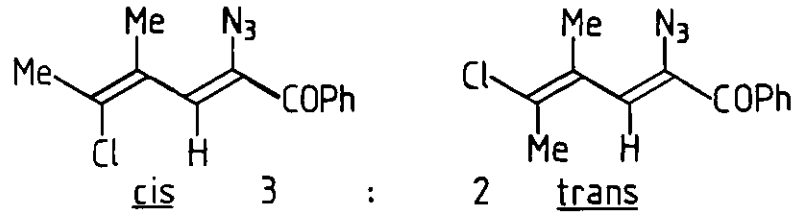


(209)

b 2-Azido-1-phenylpropenones

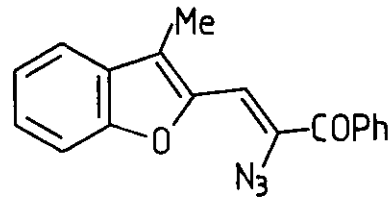
Vinyl azides (210-212) were prepared according to the literature procedure from the appropriate aldehydes and α-azidoacetophenone in the presence of piperidine acetate at room temperature.[36] Only one isomer of (210) and (212) were observed from their ^{1}H n.m.r. spectra, and the thermodynamically most stable Z configuration was observed. This assumption was supported by other α-azidochalcones prepared by the same procedure.[2,36]

The ^{1}H n.m.r. spectrum of compound (211) showed that it contained a mixture of two geometrical isomers. By assuming the Z configuration about the azide bearing double bond, there remained two possible geometrical isomers, the cis and the trans isomers of (211) as shown. In this context, the cis and trans refer to the relative position of the two methyl groups. The chemical shifts of the olefinic protons of (211) were 6.28 and 6.69 ppm, and by analogy to the literature assignment of the cis and trans β-chlorovinyl aldehyde (185),[113] the lower field signal was assigned to the cis isomer and the higher field to the trans.

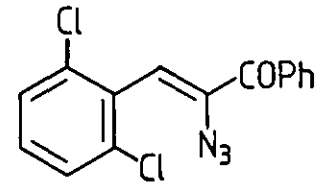


cis 3 : 2 trans

(211) 36%



(210) 89%

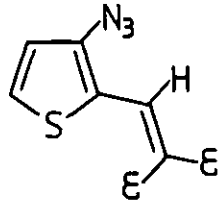


(212) 60%

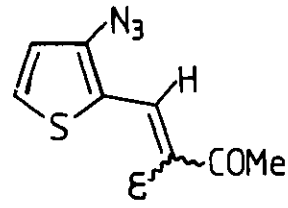
2.4 Preparation of 3-(3-azidothien-2-yl)propenoates

Compound (213) was prepared in 96% yield by reaction of the azidoaldehyde (193) with diethyl malonate in the presence of piperidine acetate. Attempted preparation of (214) by the same method, using ethyl acetoacetate as the active methylene fragment failed to produce the required product; a polymeric mixture was obtained instead.

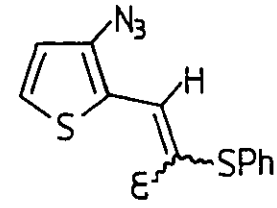
Compound (215) was prepared in 85% yield by condensation of (193) with ethyl phenylthioacetate (183) in ethanolic sodium ethoxide at $0^{\circ}C$. Compound (216) was similarly prepared from (193) and ethyl methylthioacetate (184) in 82% yield. In the preparation of (216), the hydroxy intermediate (217) was isolated in 5% yield; its structural assignment was based on evidence of elemental analysis, i.r., n.m.r. and mass spectroscopy.



(213)

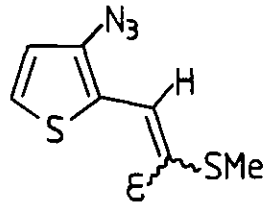


(214)

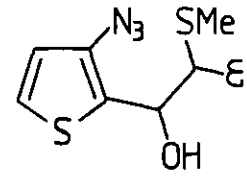


(215)

E=CO_2Et



(216)



(217)

Compounds (213), (215) and (216) each showed a long range "zig-zag" coupling between the olefinic proton and the H-5 of the thiophen ring, indicating the compounds in solution have conformations as shown. However, the configuration about the olefinic double bond in (215) and (216) remained unclear. Attempts to reveal the configuration of (216) by n.m.r. nuclear Overhauser effect difference experiments failed to produce a clear answer. The results are shown in the Appendix, (Figure 1).

2.5 Decomposition of Vinyl Azides

It has been reported that thermolysis of the α-azido-β-(benzofuran-2-yl)acrylate (154c) (see page 58) in refluxing xylene gave quantitatively the corresponding benzofuropyridine (155c).[84] However, thermolysis of the α-azidocinnamate (154a) under similar conditions gave the isoquinoline (155a) in 45% yield.[89] The cause of the large difference in the yield between the two reactions, was thought to be that of the double bond in the five-membered ring of benzofuran being less aromatic, and hence capable of greater participation in other reactions. Moreover, this type of ring formation has not been observed in the decomposition of 2-azido-1-phenylpropenones, they generally gave the 2H-azirines or further rearranged to the corresponding nitriles.[35,91] So, it was decided to investigate the decomposition of the vinyl azide (210), hoping that it might provide the first example of a six-membered ring formation in the decomposition of 2-azido-1-phenylpropenone. However, both thermal and photochemical decomposition of (210) gave a complex mixture with no characterizable product isolated.

The readily available β-chlorovinyl aldehyde (185) provided a direct route to the vinyl azide system (179) where X = Cl, CH_3. This would allow one to examine the effect of the chlorine substituent in the decomposition of vinyl azide.

Although the exact configuration of the vinyl azides (197-201) was not unambiguously confirmed, it was considered to be relatively unimportant in the thermolysis of vinyl azides. During thermolysis, the transient vinyl nitrene which was thought to be in thermal equilibrium with the initially formed 2H-azirine, could delocalize the conjugated system and rotation throughout the system was permitted. This proposed delocalization in vinyl nitrenes is best illustrated by

the racemization of an optically active 2H-azirine (see page 34).[56]

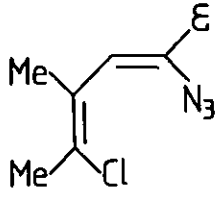
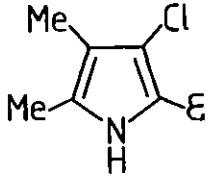
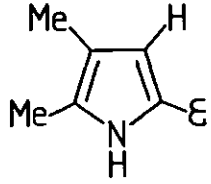
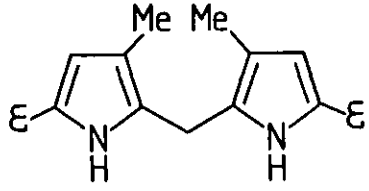
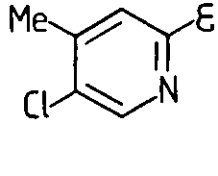
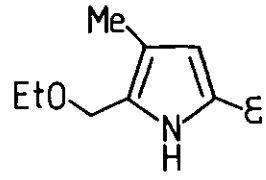
Thermolysis of the α-azidoacrylate (197) under various conditions gave a variety of products in low yield. The conditions and results are summarized in Table 3.

Formation of the pyrroles (218), (219), (222) and the dipyrrolemethane (220) could be rationalized as involving a common reaction intermediate (223) which resulted from an electrocylic ring closure of the vinyl nitrene generated from the azide (197) (SCHEME 55).

From the intermediate (223), migration of the chlorine atom would give the 3-chloropyrrole (218); on the other hand, methyl migration would produce the 5-chloropyrrole (224). The assigned structure of (218) as opposed to (224) was based on the n.m.r. n.O.e. difference experiments, in that pre-irradiation of the N-H proton showed a 1.25% enhancement of the 5-methyl protons and only a 0.21% enhancement of the 4-methyl signal, (see Figure 2 in the Appendix). If the 5-chloropyrrole (224) was the correct structure, one would expect a very similar enhancement of the two methyl signals by presaturating the N-H proton.

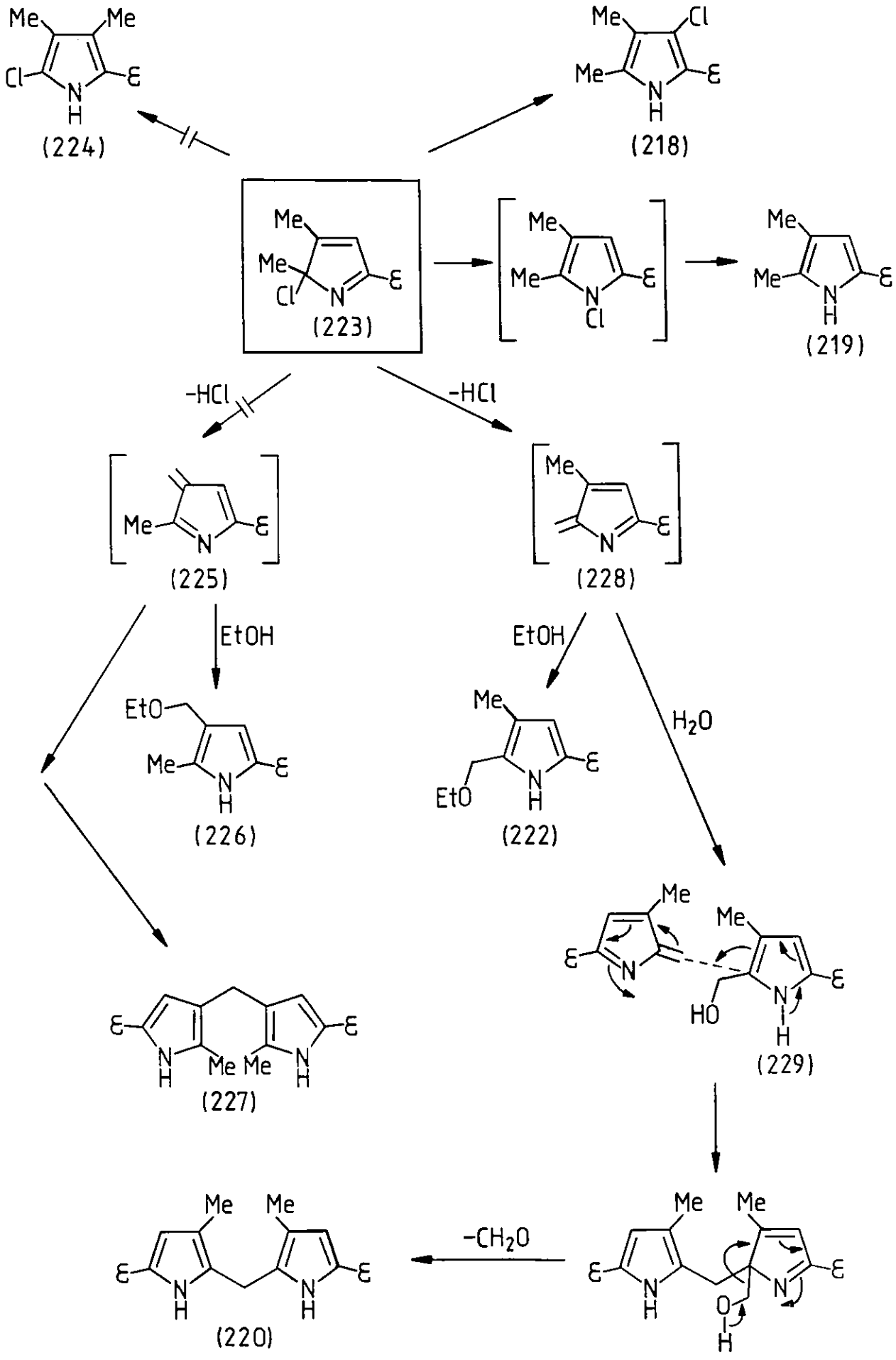
The structure of the dimethylpyrrole (219) was assigned on the basis of its spectroscopic data and by comparison with the literature melting point of the known structure. The reaction pathway is outlined in SCHEME 55.

Formation of the 5-ethoxymethylpyrrole (222) involved elimination of HCl from the intermediate (223) in which the proton was lost from the 5-methyl group, followed by addition of ethanol to give the observed product (SCHEME 55). However, if the proton of the eliminated HCl was derived from the 4-methyl group, addition of ethanol to this new intermediate (225) would produce the 4-ethoxymethylpyrrole (226). The structure of (226) was ruled out on the basis

 (197)	 (218)	 (219)	 (220)	 (221)	 (222)	
Conditions	Yield (%)					Total Yield (%)
Toluene/15min	4	-	6	9	-	19
Benzene/2 h	8	-	16	-	-	24
BrPh (90°C)/2.5h	4	3	3	17	-	27
$CHCl_3$/24 h	2	-	-	11	9	22
Toluene/I_2/20min	1	2.5	-	24	-	27.5

$\mathcal{E}=CO_2Et$

Table 3


(224)
(218)
(223)
(219)
-HCl
-HCl
(225)
(228)
EtOH
EtOH
(226)
(222)
H_2O
(227)
(229)
$-CH_2O$
(220)

Scheme 55

of the melting point and n.m.r. data of the known ethyl 4-ethoxymethyl-5-methylpyrrole-2-carboxylate (Table 4).

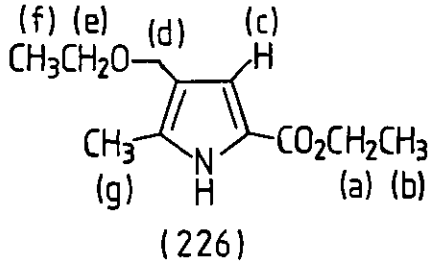
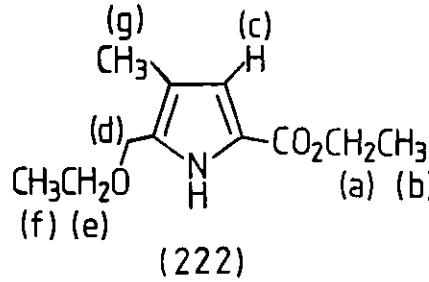
 (226)	 (222)
Literature data:[126]	Observed data:
M.p. 42-44°C	M.p. 62-64°C
δ (ppm): (a) 4.30	δ (ppm): (a) 4.33
(b) 1.35	(b) 1.35
(c) 6.72	(c) 6.75
(d) 4.25	(d) 4.50
(e) 3.40	(e) 3.53
(f) 1.13	(f) 1.20
(g) 2.28	(g) 2.06

Table 4

The 5-ethoxymethylpyrrole (222) was only isolated from the thermolysis of (198) in chloroform. The chloroform was later found to contain 2% (V/V) ethanol as stabilizer from the manufacturer. So, this accounted for the presence of ethanol in the reaction mixture. However, when the thermolysis was carried out in ethanol, the reaction was less clean, and no preference was observed for the formation of (222).

The formation of the 5,5'-methylenepyrrole (220) was rationalized as shown in SCHEME 55. Nucleophilic addition of water to the intermediate (228), which could have originated from atmospheric moisture, gave the 5-methanol pyrrole (229). Under the reaction

conditions, the 5-methanol pyrrole (229) further reacted with the intermediate (228), which followed by elimination of formaldehyde to give the final product (220). The formation of dipyrrolmethanes from α-methanol pyrrole under similar conditions, are well precedented in the literature.[127,128]

As with the formation of 5-ethoxymethylpyrrole (222), elimination of HCl with loss of the proton from the 4-methyl group, would accordingly give the 4,4'-methylenepyrrole (227). The structure of the 5,5'-methylenepyrrole (220) was assigned on the basis of the elemental analysis and spectroscopic data. The position of the methylene linkage and the relative position of the other substituents were further established by n.m.r. n.O.e. difference experiments. The results are summarized in the Appendix (Figure 3), and confirm unambiguously the structure (220).

It is worth noting, that in the formation of product (220) and (222), the elimination of HCl from the intermediate (223) proceeded *via* the 5-methyl proton instead of the allylic 4-methyl proton.

Formation of the pyridine (221) could be envisaged as a formal C-H insertion of the vinyl nitrene, into the adjacent methyl group followed by oxidation to give the observed product. The detailed mechanism of this reaction shall be discussed later.

From the results summarized in Table 3, the pyridine formation was favoured by higher temperature, and the reaction could also be promoted by halogenated solvents or addition of iodine. This heavy atom effect has also been reported,[89] but the exact role played by the heavy atom was not clear.

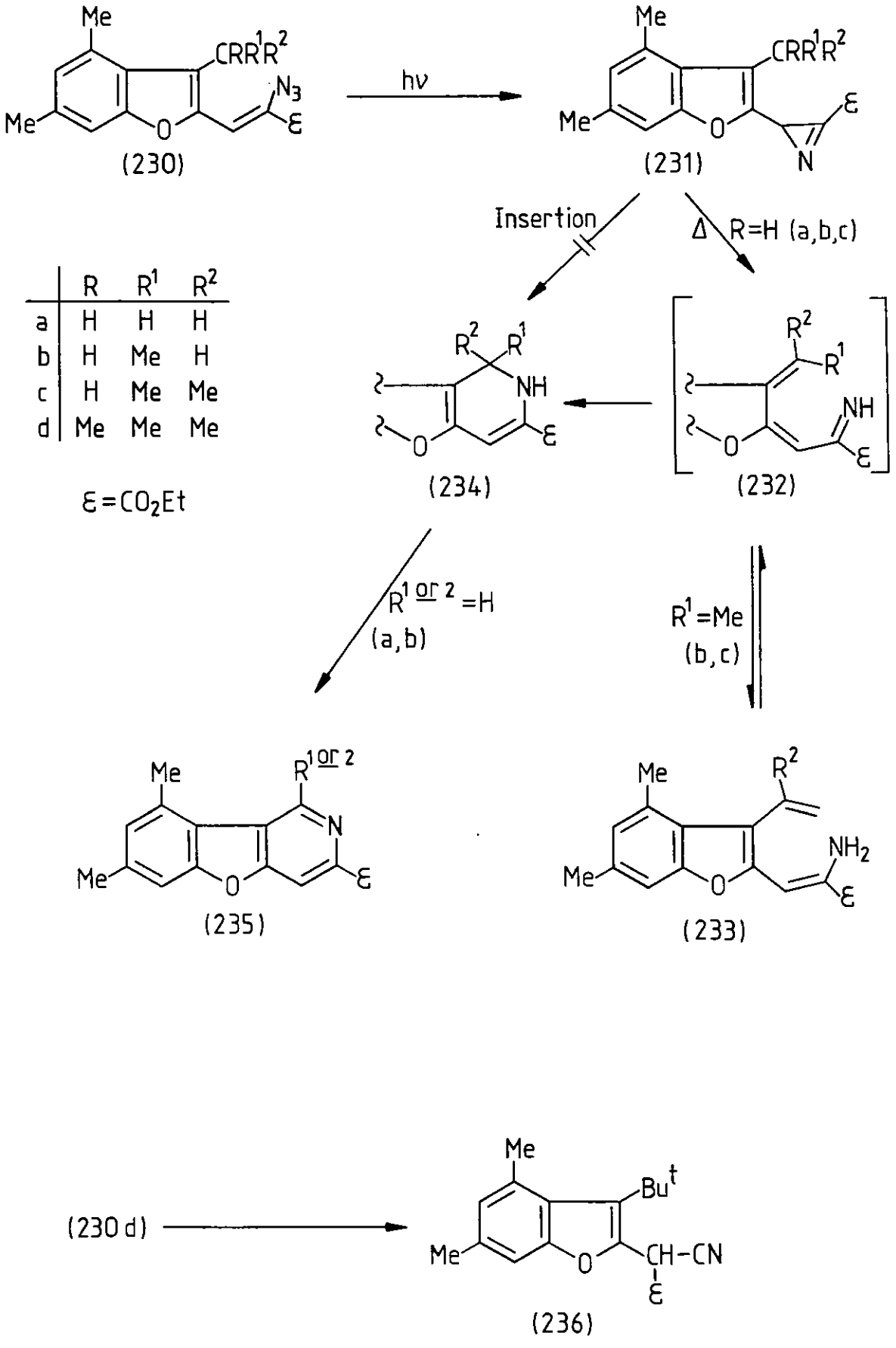
Mechanism of Pyridine Formation from Vinyl Nitrene

The formation of pyridine type compounds from the thermolysis of vinyl azides was generally considered as an insertion reaction of a vinyl nitrene into the C-H bond of the adjacent methyl group. However, recent studies of a number of β-(3-substituted benzofuran-2-yl) vinyl azides (230 a-d) have suggested that the reaction proceeded by a hydrogen abstraction of the vinyl nitrene, followed by an electrocyclic ring closure and aromatization to give the product (SCHEME 56).[129]

The initial hydrogen abstraction of the vinyl nitrene would give the imine (232) as the key intermediate, which is also in equilibrium with the enamine (233). The intermediacy of the imine was supported by the isolation of the enamines (233b) and (233c). Furthermore, thermolysis of the enamine (233b) gave the fused pyridine (235b), whereas thermolysis of (233c) produced the dihydropyridine (234c). The isolation of (234c) in turn provided evidence for the dihydropyridine as an intermediate in the formation of the pyridine. Interestingly, the t-butyl substituted vinyl azide (230d) rearranged to the nitrile (236) on thermolysis.

The process of forming a fused pyridine product is of higher energy than the cyclization to give five-membered ring product. This is best illustrated by the pyrolysis of o-tolyl azidocinnamate (237) in which exclusive indole (238) formation was observed (SCHEME 57).[87]

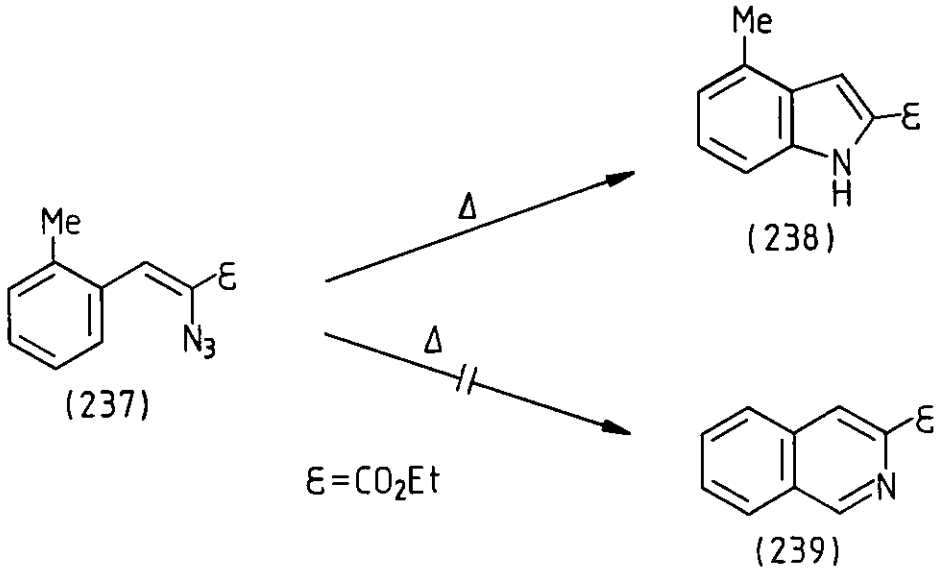
However, thermolysis of the 2-(2-naphthyl)-2H-azirine (240) gave the isoquinoline (241) as the major product, no benz[f]indole (243) was obtained (SCHEME 58).[130] This observation suggested that the fused pyridine formation process is of lower energy than the disruption of the aromatic system (242), which was required in the formation of (243).



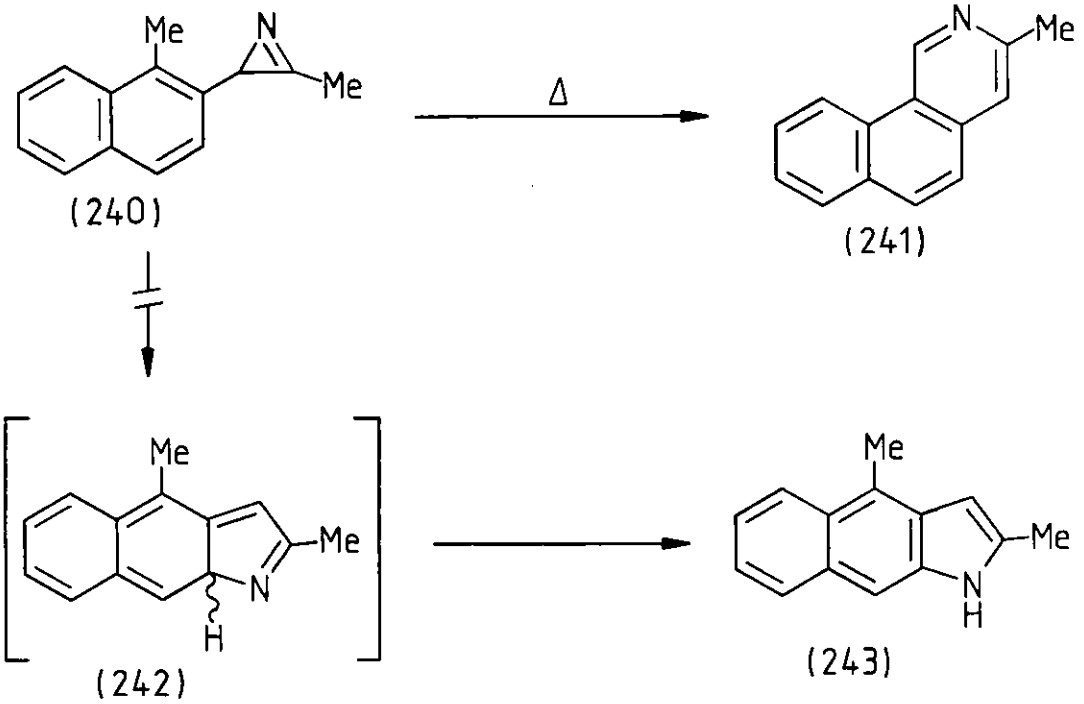
	R	R^1	R^2
a	H	H	H
b	H	Me	H
c	H	Me	Me
d	Me	Me	Me

ε = CO_2Et

Scheme 56

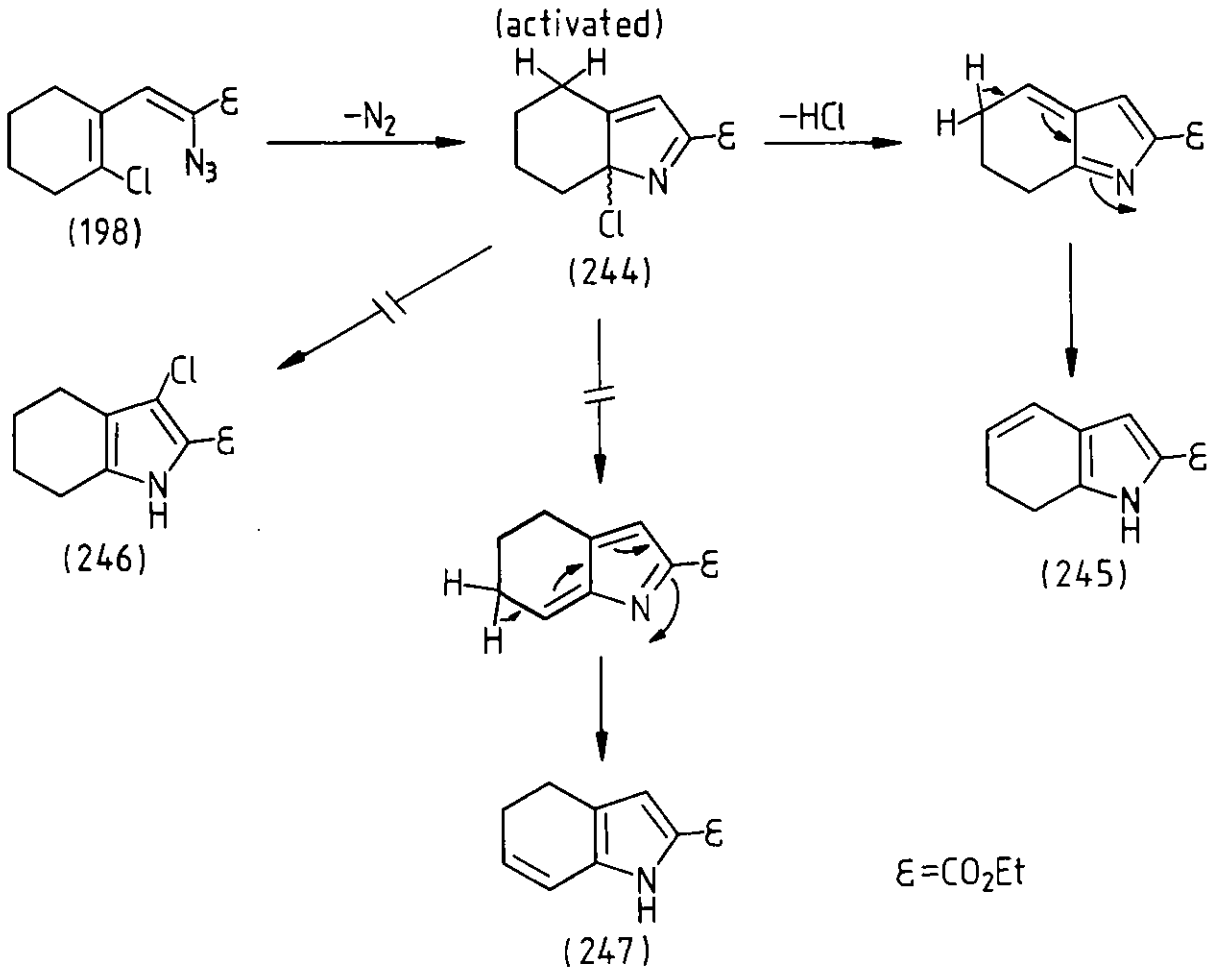


Scheme 57



Scheme 58

In continuation of the study of chlorine substituent effects in vinyl azide decomposition, the thermolysis of the vinyl azide (198) was investigated. The thermolysis was carried out in a number of solvents, including chloroform, 1,2-dichloroethane, benzene, toluene and bromobenzene. However, all the experiments gave a complex mixture, from which the dihydroindole (245) was the only characterizable product, isolated in low yield. The expected tetrahydroindole (246) was not isolated. A mechanism for the formation of the dihydroindole (245) is shown in SCHEME 59.



Scheme 59

The elimination of HCl from the intermediate (244), as expected, resulted from the loss of an allylic proton and hence gave the

dihydroindole (245) and not (247). In contrast, the analogous intermediate (223) eliminated HCl from the non-activated proton to give the corresponding products (SCHEME 55).

Attempts to improve the reaction condition by way of carrying out the thermolysis in presence of triethylamine failed. The idea was to assist the elimination of HCl and to remove it by formation of a salt. However, the reaction resulted in a complex mixture with no characterizable product, apart from triethylamine hydrochloride.

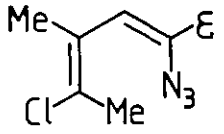
The assigned structure of the dihydroindole (245) was supported by elemental analysis and spectroscopic data. The position of the unsaturation in the six-membered ring was unambiguously confirmed by n.m.r. n.O.e. difference experiments. The results are summarized in Figure 4 in the Appendix. If the double bond was in the 6-position as in (247), one would expect an enhancement of the olefinic proton rather than the ring-methylene protons from the pre-irradiation of the N-H. Similarly, pre-irradiation of H-3 in structure (247) would produce an enhancement of the methylene protons, but not the olefinic proton.

The structure of the dihydroindole (245) was also in agreement with the findings of the n.m.r. lanthanide shift experiments. The lanthanide shift reagent was tris(2,2,6,6-tetramethyl-3,5-heptanedionate) europium (III) ($Eu(thd)_3$), the results are summarised in Table 5.

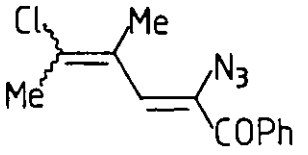
	$Eu(thd)_3$	
$\Delta\delta$	0.2 eq.	0.3 eq.
H-4	+0.15	+0.3
H-7	-0.19	-0.44

Table 5

In contrast with the thermolysis of the α-azidoacrylate (197), thermolysis of the corresponding 2-azido-1-phenylpropenone (211) failed to produce any characterizable product.

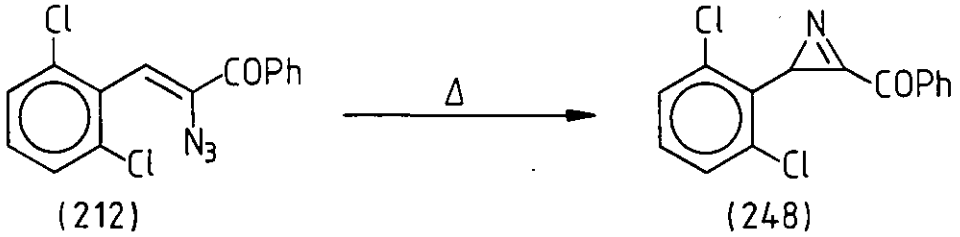


(197)

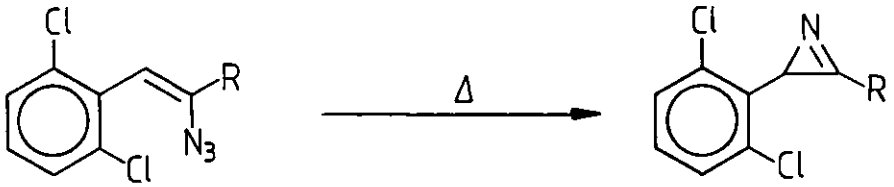


(211)

Pyrolysis of 2-azido-3-(2,6-dichlorophenyl)-1-phenylpropenone (212) gave the expected 2H-azirine (248) in excellent yield. Similar reaction of the corresponding 1-(4-chlorophenyl)propenone (249a)[91] and the arcylate (249b)[89] have also been reported.



(212) (248)



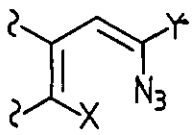
(249) (250)

a: R = COp-ClPh

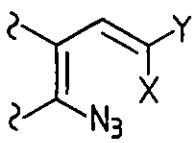
b: R = CO_2Et

2.6 Decomposition of Bis-Azides

In the study of substituent interaction in vinyl azide decomposition, it was thought that having substituent X as an azido group in the vinyl azide system (179), or (182) would be of interest. Decomposition of such systems could lead to a novel synthesis of pyridazines in which the two nitrogen atoms were brought together by the formation of a double bond between them. Furthermore, the synthesis of six membered heteroaromatic compounds which contain at least two hetero atoms rarely involves the formation of a bond between two hetero atoms as the ring closure step.



(179)

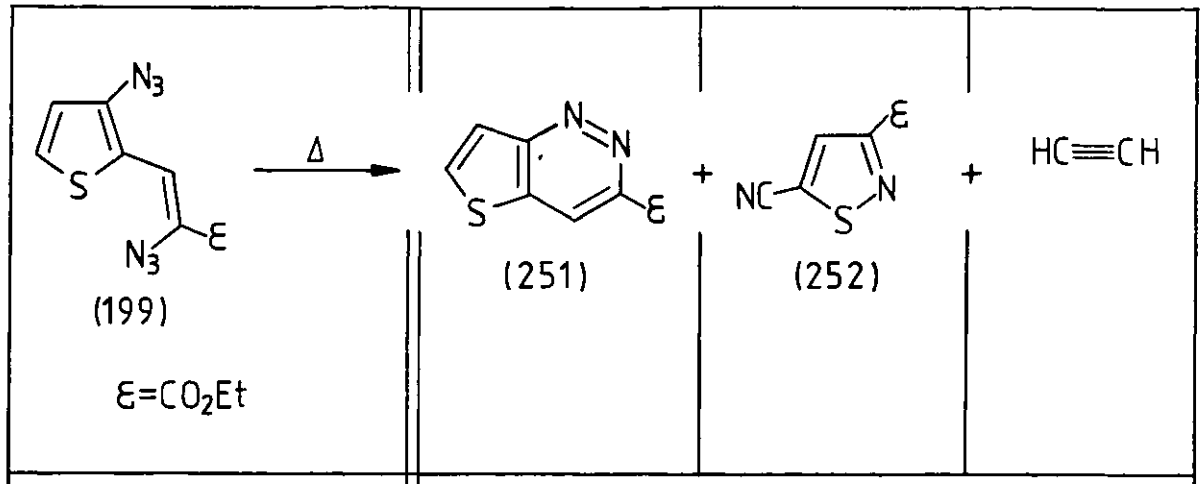


(182)

The readily accessible 3-azidothiophen-2-carbaldehyde provided a suitable starting material for this investigation. Thus the bis-azide (199) was prepared.

Thermolysis of the bis-azide (199) in a number of boiling solvents gave the expected thienopyridazine (251) and the unexpected isothiazole (252), both in rather low yields. The results are summarized in Table 6 .

The structure of ethyl thieno[3,2-c]pyridazine-3-carboxylate (251) was assigned on the basis of elemental analysis and spectroscopic data. The position of the ester group could only be at the 3-position, because a "zig-zag" coupling between H-4 and H-7 was observed. The structure of (251) was further confirmed by hydrolysis and decarboxylation to give the known thieno[3,2-c]pyridazine.[131]



	Yield (%)		
Benzene (80°C)/1.5h	13	14	X
Toluene (110°C)/0.5h	17	19	15
Xylene (140°C)/0.5h	26	27	21
PhBr (156°C)/0.15h	9	9	X

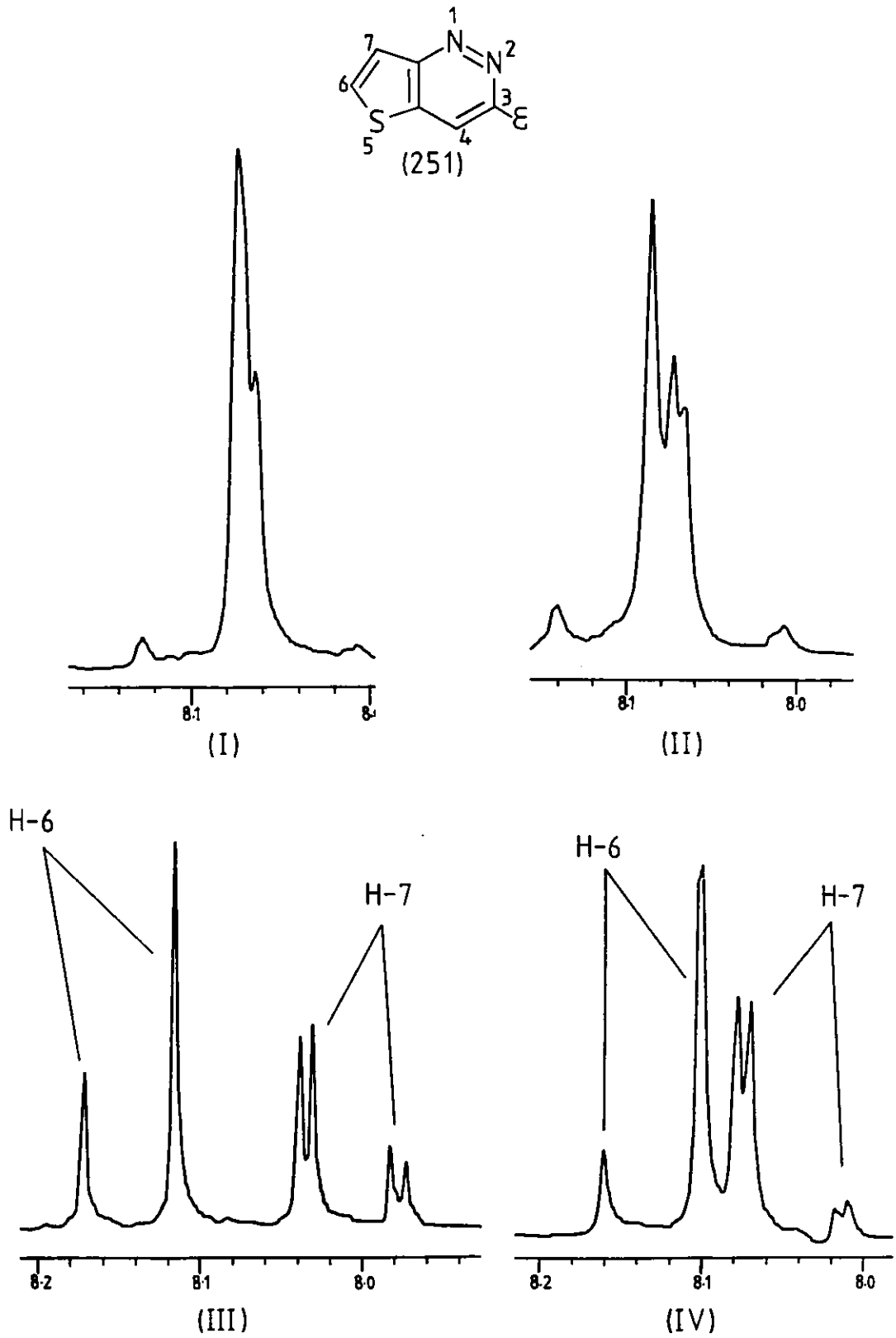
X - where qualitative method was used, the acetylene was detected as copper acetylide but was not quantified.

Table 6

Independent synthesis of (251) was attempted but failed; the details are discussed later.

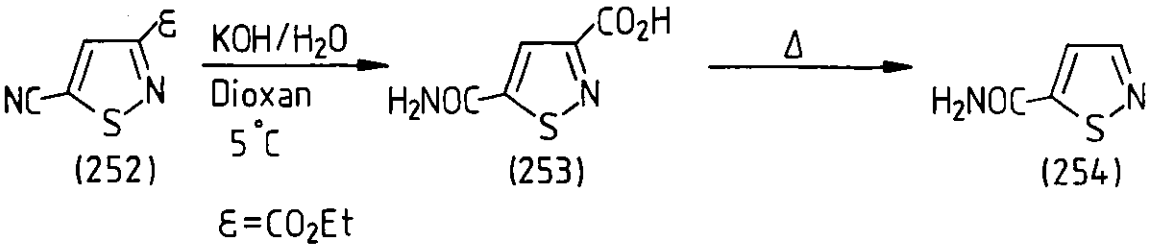
It is worth pointing out that the thienopyridazine (251) exhibits a marked concentration effect in the n.m.r. chemical shifts of the AB quartet of H-6 and H-7. The observed effect is illustrated in Figure 5. The process was also shown to be reversible.

The structure of the isothiazole (252), expected on mechanistic grounds (see below), was confirmed by hydrolysis and decarboxylation to give the known isothiazole-5-carboxamide (254).[132] The melting point of the acid amide (253) did not correspond to the known 5-carbamyliso-thiazole-4-carboxylic acid,[133] therefore re-affirming the position of the ester group in (252).

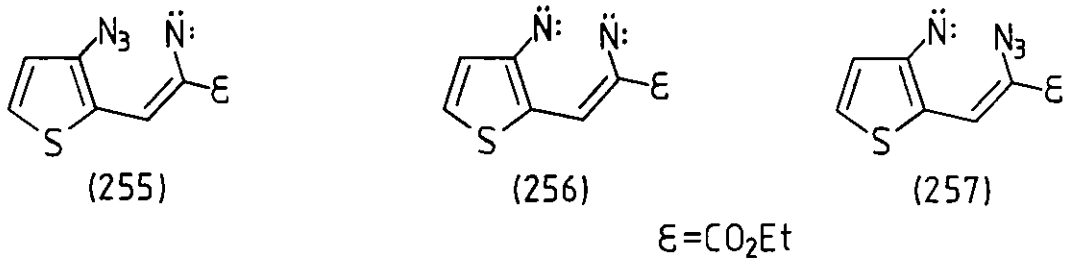


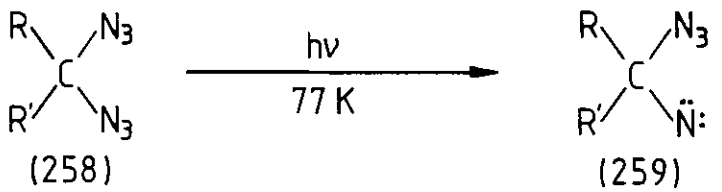
^{1}H n.m.r. spectra of (251) showing the H-6 and H-7 signals in increasing concentration from (I) to (IV).

Figure 5



The formation of the thienopyridazine (251) could be interpreted as an intramolecular coupling of the two azide groups with loss of nitrogen. The exact mechanism is uncertain; it is conceivable that an azidonitrene (255) and/or a dinitrene (256) are involved. The azidonitrene (257), which was also a possible intermediate, was thought to be unlikely, because vinyl azides are generally more thermally unstable than aryl azides.

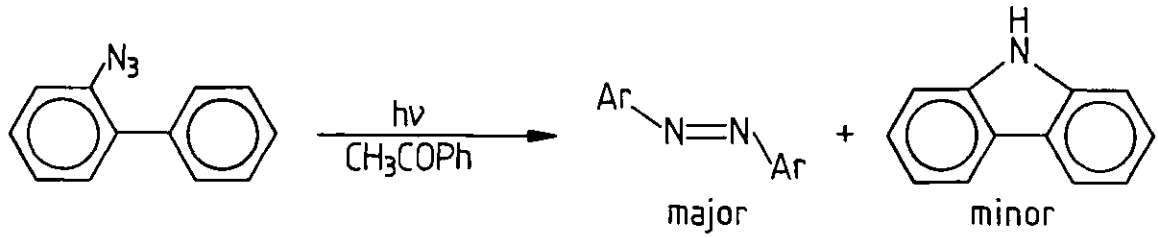




E.p.r. spectroscopic evidence of azidonitrenes has been obtained from sensitized photolysis of geminal diazides (258) at 77K in rigid matrices.[134]

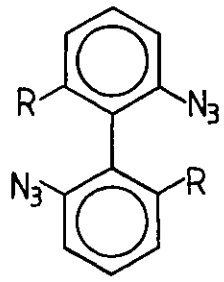
There are a number of examples in which azo derivatives are formed

by intermolecular dimerization of aryl nitrenes, the photolytic process are also enhanced by presence of triplet sensitizers (e.g. SCHEME 60).[135,136] However, the corresponding intramolecular process

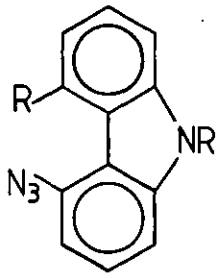


Scheme 60

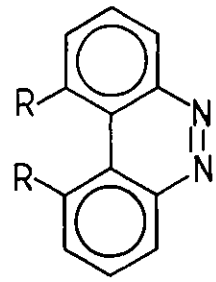
is rare. Pyrolysis of 2,2'-diazidobiphenyl (260, R = H) produced the carbazole (261) in about 10% yield, and no benzo[c]cinnoline (262) was detected.[137] Sensitized and unsensitized photolysis of the bis-azide (260, R = H) at room temperature gave mainly the carbazole (261) and trace amounts of benzo[c]cinnoline (262).[137,138] In contrast, low temperature (77 K) photolysis of (260, R = H, Me) in a rigid matrix gave good yields of the benzo[c]cinnolines (262) and (263);[138,139] however, thermolysis of the bis-azide (260, R = Me) only produced tarry material (Table 7).[140] In the above cases, where R = Me in (260), the expected 4,9-diazapyrene (263) was not observed. Spectroscopic evidence for benz[cd]indazole (265) was obtained from similar photolysis of 1,8-diazidonaphthalene (264),[141] where other methods of decomposition of (264) had failed (SCHEME 61).[142]



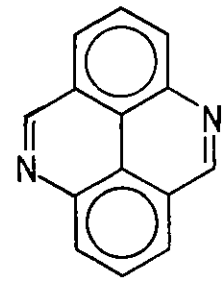
(260)



(261)



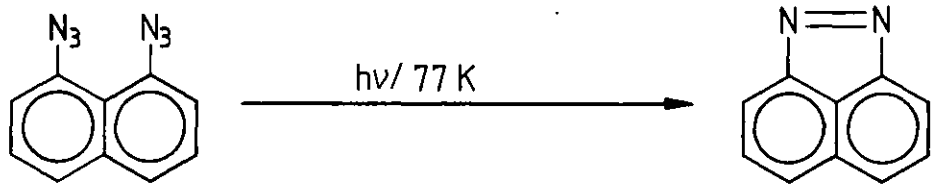
(262)



(263)

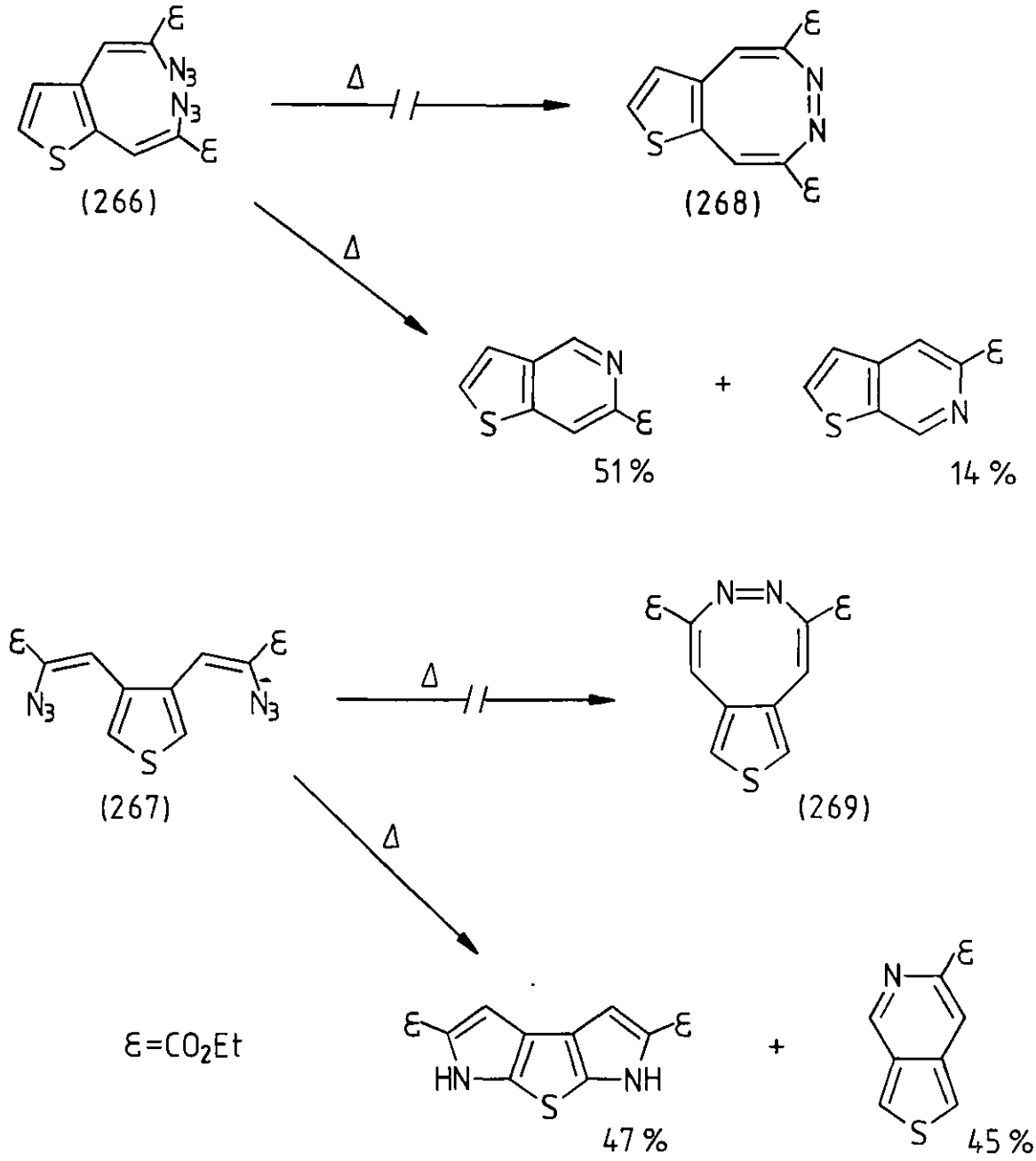
R	conditions	Yields/%	Yields/%	Yields/%
H	Δ	10	0	-
H	hν/RT	50	Trace	-
H	hν/77K	0	98	-
Me	hν/77K	-	60	0
Me	Δ	-	0	0

Table 7



Scheme 61

Similar coupling of two azide groups is also possible in the decomposition of the bis-azides (266) and (267), but such a reaction would result in the formation of eight-membered cyclic azo derivatives (268) and (269). This did not occur and the reactions shown were observed, (SCHEME 62).[29,30]



Scheme 62

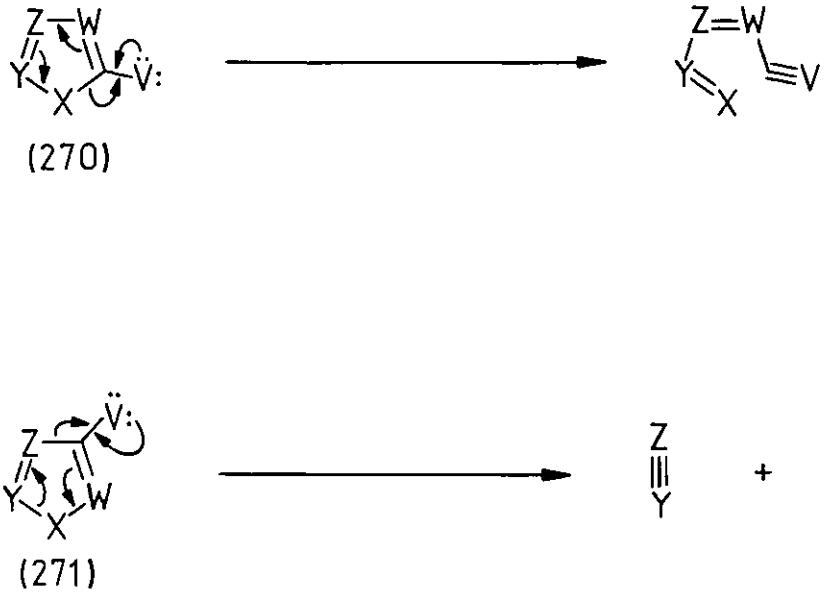
There are some reports of metal induced decomposition of 2H-azirines giving pyridazines, pyrimidines, or acyclic azine derivatives as the dimerization products (see Section 1.8). It was felt that there might be a possibility of diverting the reaction pathways of the thiophen bis-azide (199), to solely the formation of the thieno-pyridazine (251), by metal induced decomposition. However, no reaction

was observed when a benzene solution of the thiophen bis-azide (199) was stirred in presence of a catalytic amount of copper (I) chloride or palladium acetate or copper(II) acetylacetonate at room temperature When the above three reaction mixtures were heated to reflux, each resulted in a complex mixture with only trace amounts of the thienopyridazine (251) and the isothiazole (252).

The stoichiometry for the formation of the isothiazole (252) from the bis-azide (199) required the extrusion of two molecules of nitrogen and one molecule of acetylene. The extrusion of acetylene was confirmed by the formation of copper acetylide when the exit gases from the thermolysis were bubbled through ammoniacal copper (I) chloride. The yield of acetylene was estimated by the silver nitrate method (see Table 6). Details of the qualitative and quantitative methods of acetylene detection are described in the Experimental Section.

In general, there are two main types of ring-opening reactions of five-membered heterocyclic carbenes or nitrenes.[143,144] The first is the α-carbene or nitrene derivatives of the general type (270), which yield one product in the manner shown in SCHEME 63. The second is the β-carbene or nitrene derivatives of the general structure (271), which fragment to give two products. The former is by far the more common of the two reactions.

However, all the reported examples of fragmentation of 5-membered heterocyclic carbenes or nitrenes, involved the production of the fragment Z ≡ Y, either as molecular nitrogen or as a nitrile; a recent example is shown in SCHEME 64.[145]



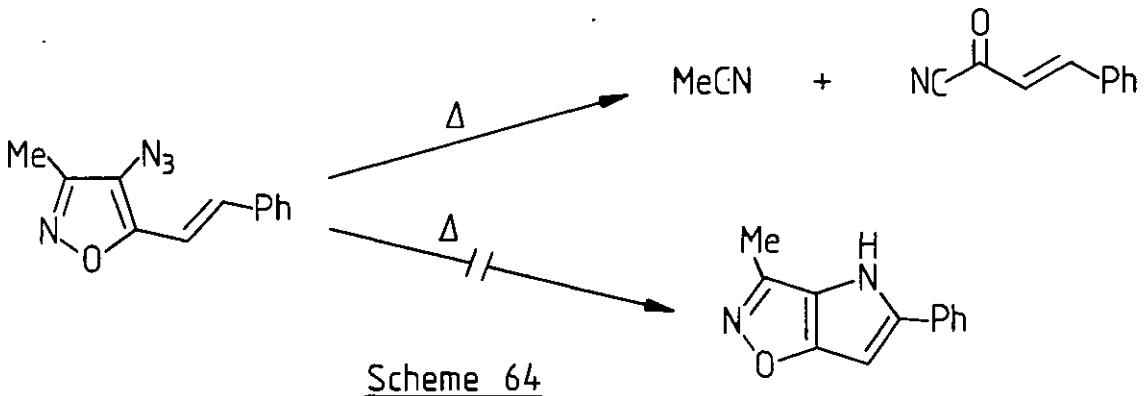
(270)

(271)

W,X,Y,Z = any heteroatom in its appropriate valence state.

$\ddot{V}$ = $\ddot{C}$-R or $\ddot{N}$:

Scheme 63

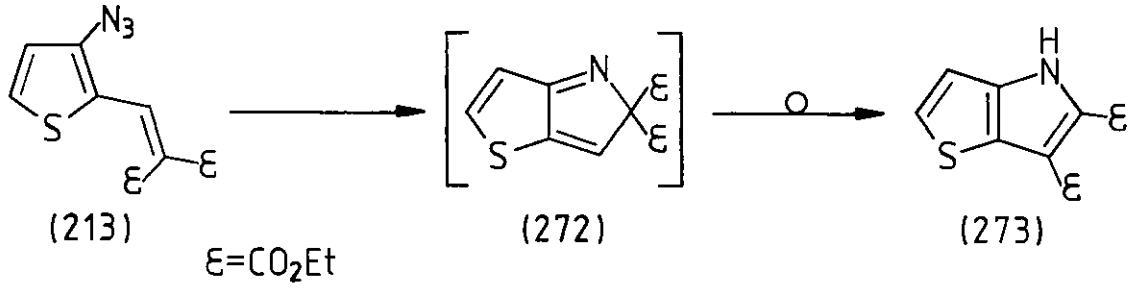


Scheme 64

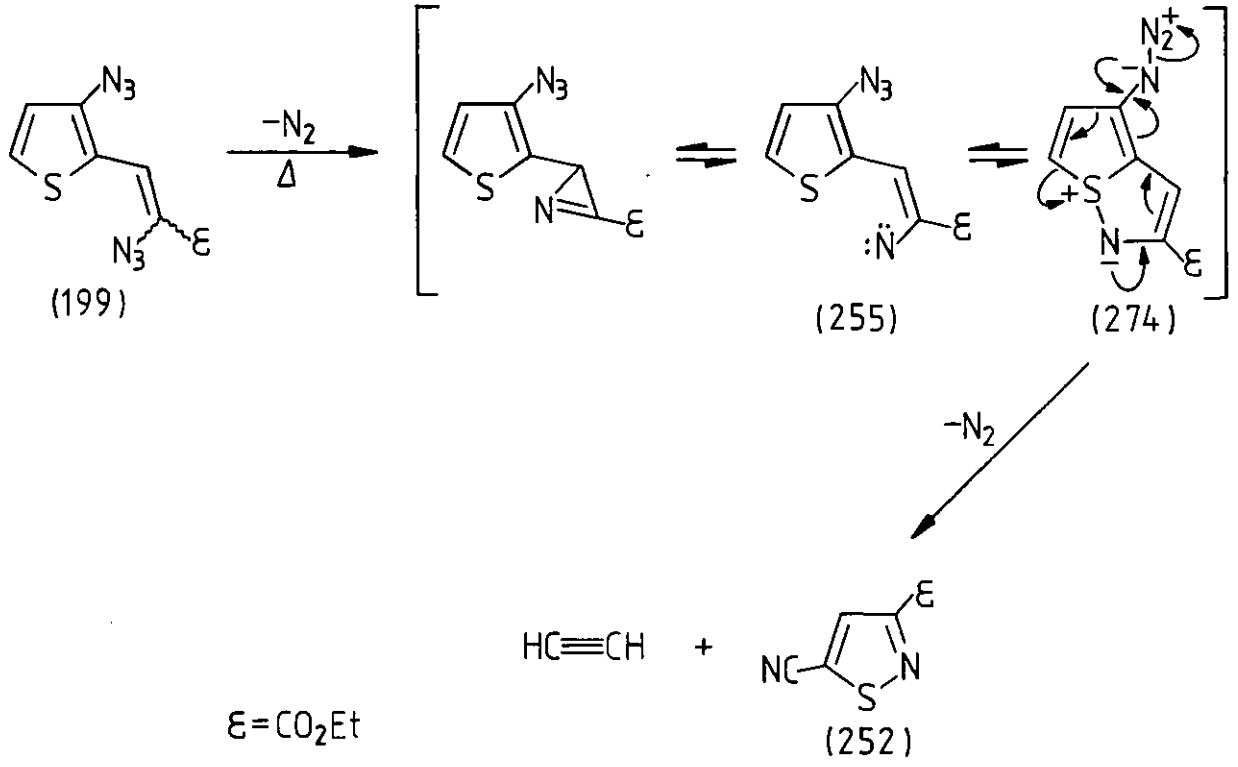
Fragmentation of 3-azidothiophen or other heterocycles (271) to give an acetylene (Z = Y = CR) has not been observed.

Furthermore, we have shown that decomposition of the 3-azidothiophen (213) in refluxing toluene gave the thienopyrrole (273) as the only product; no acetylene nor ring-cleavage products were detected.

The formation of the thienopyrrole (273) presumably resulted from a [1,5] ester shift in the intermediate formed by cyclization of the nitrene (272) (SCHEME 65). So it seems reasonable that the vinyl azide function of the bis-azide (199) did play an important role in the fragmentation of the thiophen ring. A possible mechanism is outlined in SCHEME 66. Initial decomposition of the vinyl azide would give rise



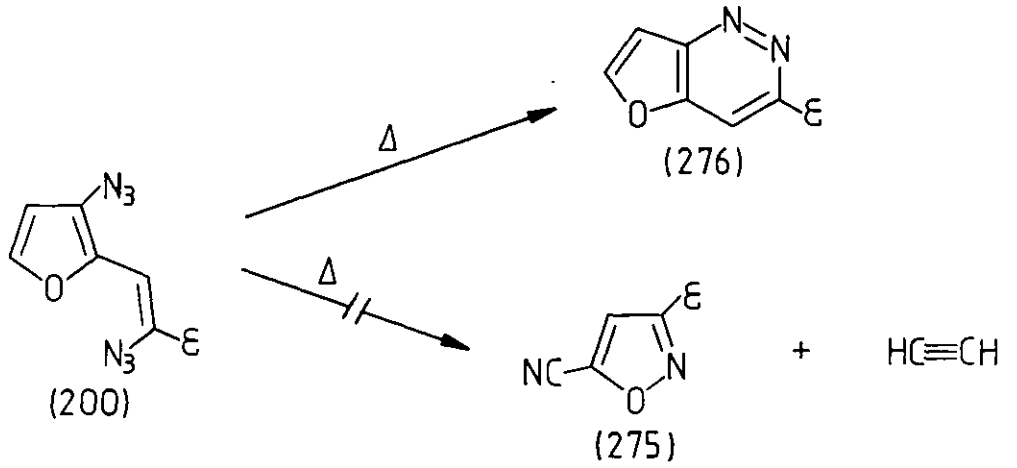
Scheme 65



Scheme 66

to an azirine, which is presumably in thermal equilibrium with the azidonitrene (255). Interception of the vinyl nitrene with the thiophen sulphur would lead to the formation of the intermediate (274). This ylidic nature of intermediate (274) would cause the thiophen ring to weaken considerably, and hence the observed fragmentation from the decomposition of the second azide group becomes possible.

Further support for this proposed mechanism was sought. It was thought that by replacing the thiophen ring with the oxygen analogue, the furan oxygen atom would be less capable of participating in an ylide structure like (274), and hence the ring cleavage reaction would be suppressed. Indeed, thermolysis of the furan bis-azide (200) under similar conditions gave no acetylene nor the ring cleavage product (275). The reaction only produced the furo[3,2-c]pyridazine (276) in 19% yield and a large amount of tarry material (SCHEME 67).



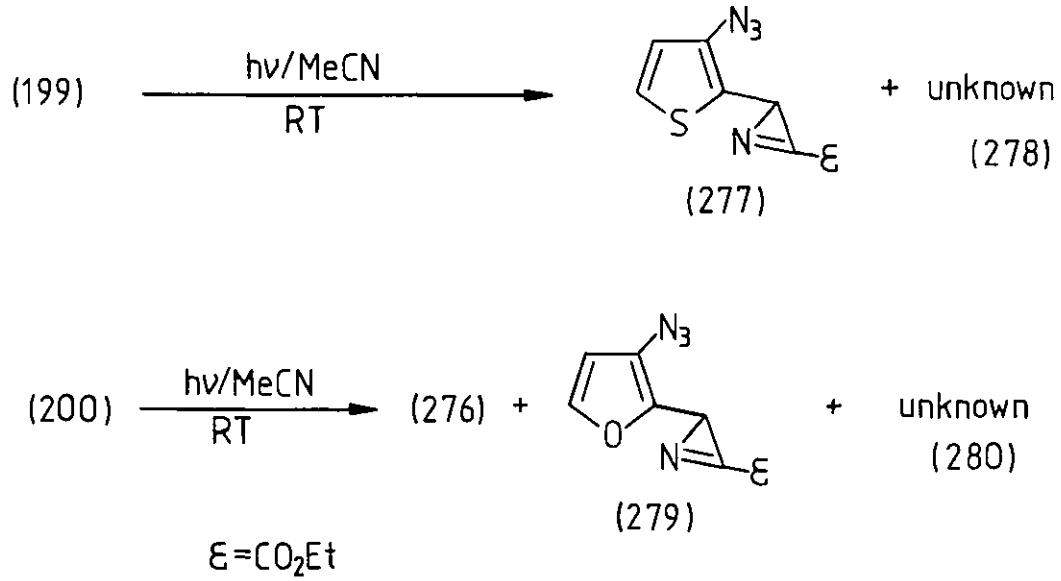
Scheme 67

Flash vacuum pyrolysis of the thiophen bis-azide (199) was unsuccessful; the bis-azide did not vaporize under the experimental conditions, and decomposed in the solid state.

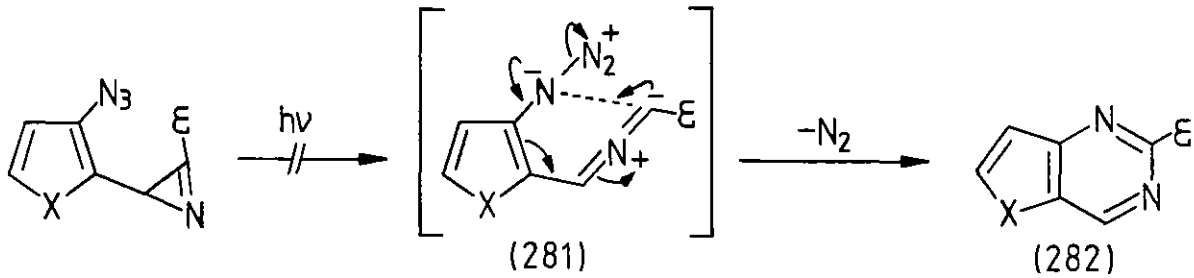
Photolysis of the thiophen bis-azide (199) at room temperature gave the unstable azidoazirine (277) as the major product. No acetylene nor the isothiazole (252) nor the thienopyridazine (251) was observed. Purification of the crude mixture by silica gel chromatography gave an unknown orange/red solid (278) in 7% (ω/ω) yield. The azidoazirine (277) was not isolated, but presumably decomposed or polymerized.

A similar result was obtained from the photolysis of the furan bis-azide (200). In this case, the azidoazirine (279) again decomposed on column chromatography, but the furopyridazine (276) was isolated in 5% yield and an unknown yellow/orange solid (280) in 4% (w/w) yield.

The azidoazirines (277) and (279) both exhibit a characteristic one proton singlet at about 3.6 ppm corresponding to an azirine H-2 methine proton; their i.r. spectra also featured a strong stretching frequency at 2120 cm^{-1}, which is an indication of an azide function present in the molecules. Thus, the above spectral data support the azidoazirine structures.



A possible photochemical reaction that could occur with the two azidoazirine (277) and (279) was the generation of the azido-nitrile ylides (281 a,b) which could then collapse to give the corresponding fused pyrimidines (282 a,b) (SCHEME 68). However, the spectral data of the two unknown products (278) and (280) do not fit the corresponding fused pyrimidine structures.



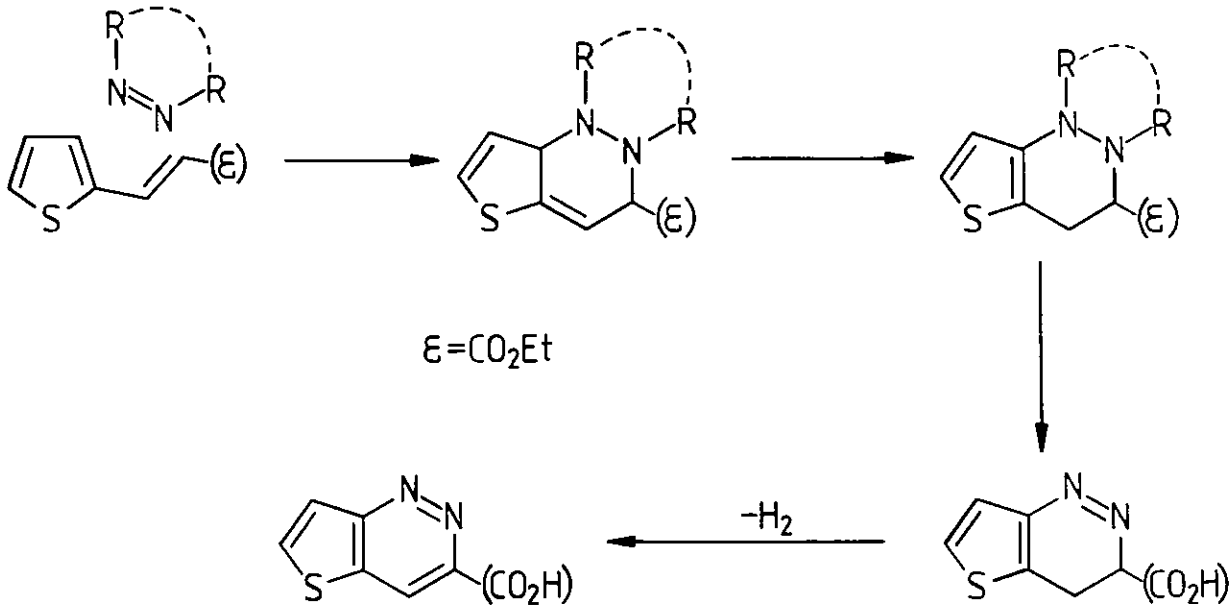
a: X=S, b: X=O

Scheme 68

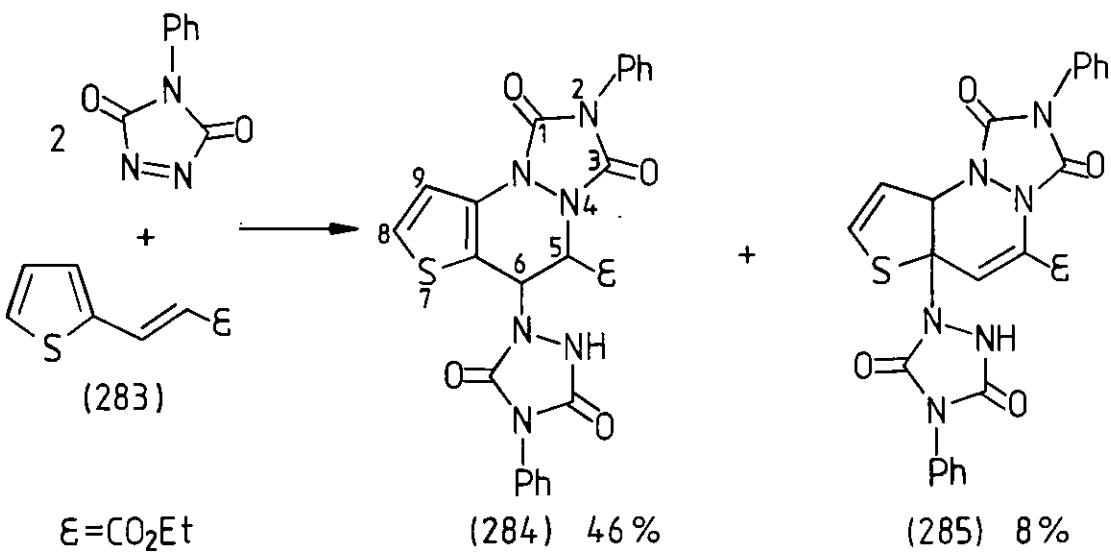
2.7 Attempted Independent Synthesis of Thieno[3,2-c]-pyridazines

The literature procedure for preparing thieno[3,2-c]pyridazine was thought to be very long and inefficient.[131] We devised a synthesis that would enable us to construct the fused ring system from readily available starting materials in one step. It is based on a Diels-Alder cycloaddition of 2-vinylthiophen or the acrylate (283) with azo dienophiles. Once the ring system is formed, it will be a matter of cleaving off the dienophile's side substituents and then dehydrogenating to the aromatic system. The synthetic route is outlined in SCHEME 69.

We first turned to one of the most reactive azo dienophiles, 4-phenyl-1,2,4-triazole-3,5-dione (PTAD). Addition of one equivalent of PTAD to a solution of the acrylate (283) at room temperature gave two products in the yields indicated. They were assigned as two



Scheme 69



different adducts of structure (284) and (285).

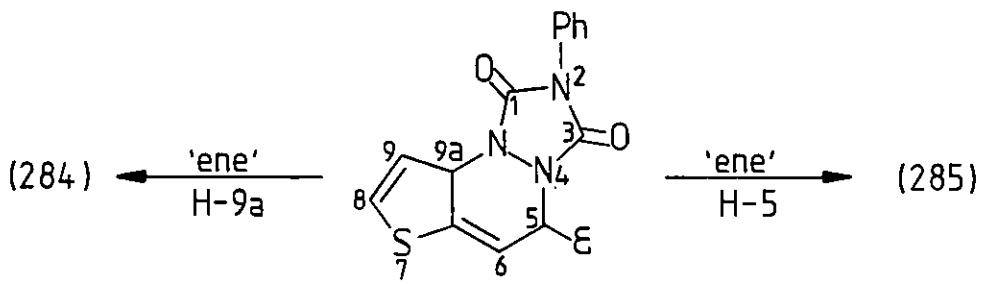
The structure of the adducts (284) and (285) were tentatively assigned on the basis of their elemental analysis and spectroscopic data. The mass spectra of the two adducts have very similar features. Each showed a low intensity molecular ion, the first major loss was the elimination of 4-phenylurazole; a strong urazole ion of 177 mass units was also observed. This suggested the presence of a urazole side chain and a readily available proton which could be eliminated. The base peak of 136 m.u. corresponded to the parent thieno[3,2-c]-pyridazine system; this, together with the presence of a strong ion of 119 m.u. due to PhNCO, supported the proposed tricyclic thieno-triazolopyridazine system of (284) and (285). The n.m.r. spectrum of the adduct (284) showed that the protons H-5 and H-6 were coupled with a coupling constant of 1.8 Hz; the methylene protons of the ethyl ester group appeared to be an AB quartet of quartets, which suggested the ester group might be at an asymmetric centre; the protons H-8 (δ = 7.61) and H-9 (hidden among the protons of the two phenyl groups, δ 7.3-7.5) appeared at the chemical shifts where normal aromatic thiophen protons would appear. In the case of the adduct (285), the methylene protons of the ethyl ester group appeared as a single quartet; the protons H-8 and H-9 have shifted upfield and no longer resonate as aromatic thiophen protons; however the signals due to protons H-6, H-8, H-9 and H-9a could not be firmly assigned due to the incompatibility of their chemical shifts with the splitting patterns revealed by proton decoupling experiments. The results of the decoupling experiments are summarised in Table 8.

δ	6.95	6.45	6.24	5.84
J/Hz	H-a	H-b	H-c	H-d
H-a	-	3.3	1.7	1.3
H-b	3.3	-	1.6	-
H-c	1.7	1.6	-	6.2
H-d	1.3	-	6.2	-

Results of the Proton Decoupling Experiments on Adduct (285) - Chemical Shifts and Coupling Constants.

Table 8

The adducts (284) and (285) were presumably derived from the initially formed Diels-Alder intermediate (286), followed by an ene reaction with a second molecule of PTAD. Ene reactions involving H-9a or H-5 would produce the adduct (284) or (285) respectively.

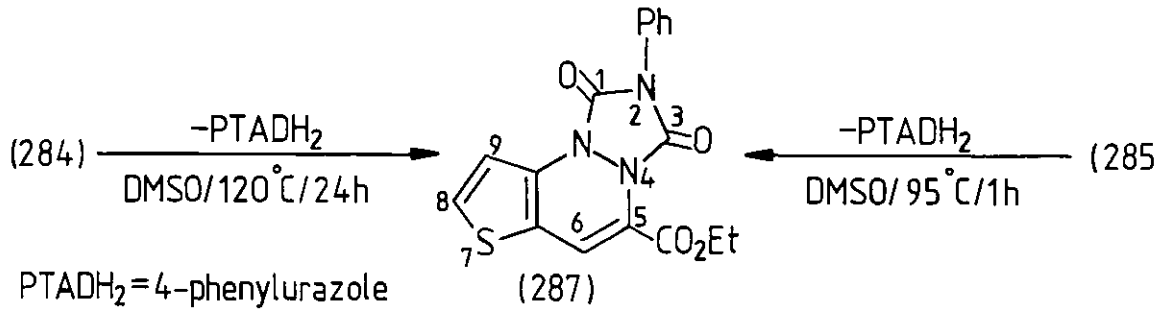


(286)

Addition of the diene (283) to a solution of two equivalents of PTAD, again produced the 2 : 1 adducts (284) and (285) in similar yields. Treatment of adduct (284) in refluxing hydrazine hydrate gave a complex mixture.

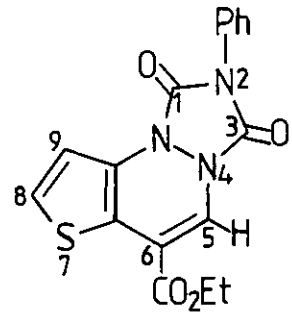
In recording the n.m.r. spectrum of the 2 : 1 adduct (285), the compound was found to be particularly unstable in DMSO. The colourless solid (285) on dissolving in DMSO gave a pale yellow solution. After about half an hour at room temperature, a bright yellow solution was obtained, and the n.m.r. spectrum was different. When a solution of

the adduct (285) in DMSO was heated at 95°C for 1 h, a single yellow crystalline solid was isolated in quantitative yield. A small amount of 4-phenylurazole was also obtained. Similarly, heating a solution of the 2:1 adduct (284) in DMSO at 120°C for 24 h, gave the same yellow solid in quantitative yield. On the basis of elemental analysis and spectroscopic data, this yellow compound was tentatively assigned as the product derived from the elimination of one molecule of 4-phenylurazole, the tricyclic thienotriazolopyridazine (287).



This elimination reaction was also catalysed by boron trifluoride diethyl etherate, but in much lower yield (40%). No reaction was observed when the adduct (284) was refluxed in chlorobenzene for one day.

The mass spectrum of the eliminated product (287) again showed a base peak corresponding to the unsubstituted thieno [3,2-c]pyridazine and a strong PhNCO ion derived from the triazole ring. These fragmentation patterns are consistent with the proposed tricyclic structure (287). However, the n.m.r. spectrum seemed to be more in favour of the isomeric structure (288), but mechanistically it is difficult to account for the formation of (288). The lower field doublet of the thiophen AB quartet, usually assigned to the α-proton on the thiophen ring, in this case H-8, shows a long range coupling (0.6Hz) to an olefinic proton which can be explained by H-5 of structure (288).



(288)

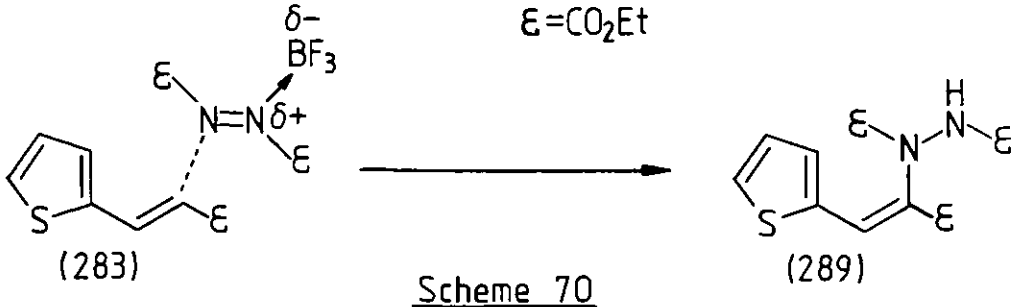
On the other hand, this long range coupling could not be explained by structure (287) because the 5-position is now substituted. Unless, for some unknown reason, the chemical shifts of H-8 and H-9 have become inverted and the long range coupling is that of H-9 and H-6.

Assuming the structure (287) was correct, our next step would be to cleave the triazole ring. It is well documented that hydrolytic cleavage of the triazole ring in a fused ring system, followed by oxidation would give the required cyclic azo compound.[146-149] A wide range of hydrolytic conditions were carried out in an attempt to cleave the triazole ring of the tricyclic compound (287), but all the experiments resulted in either a complex mixture or extensive decomposition of the starting material with the loss of hydrogen sulphide during the acid work up. The reaction conditions are summarized in the Experimental Section.

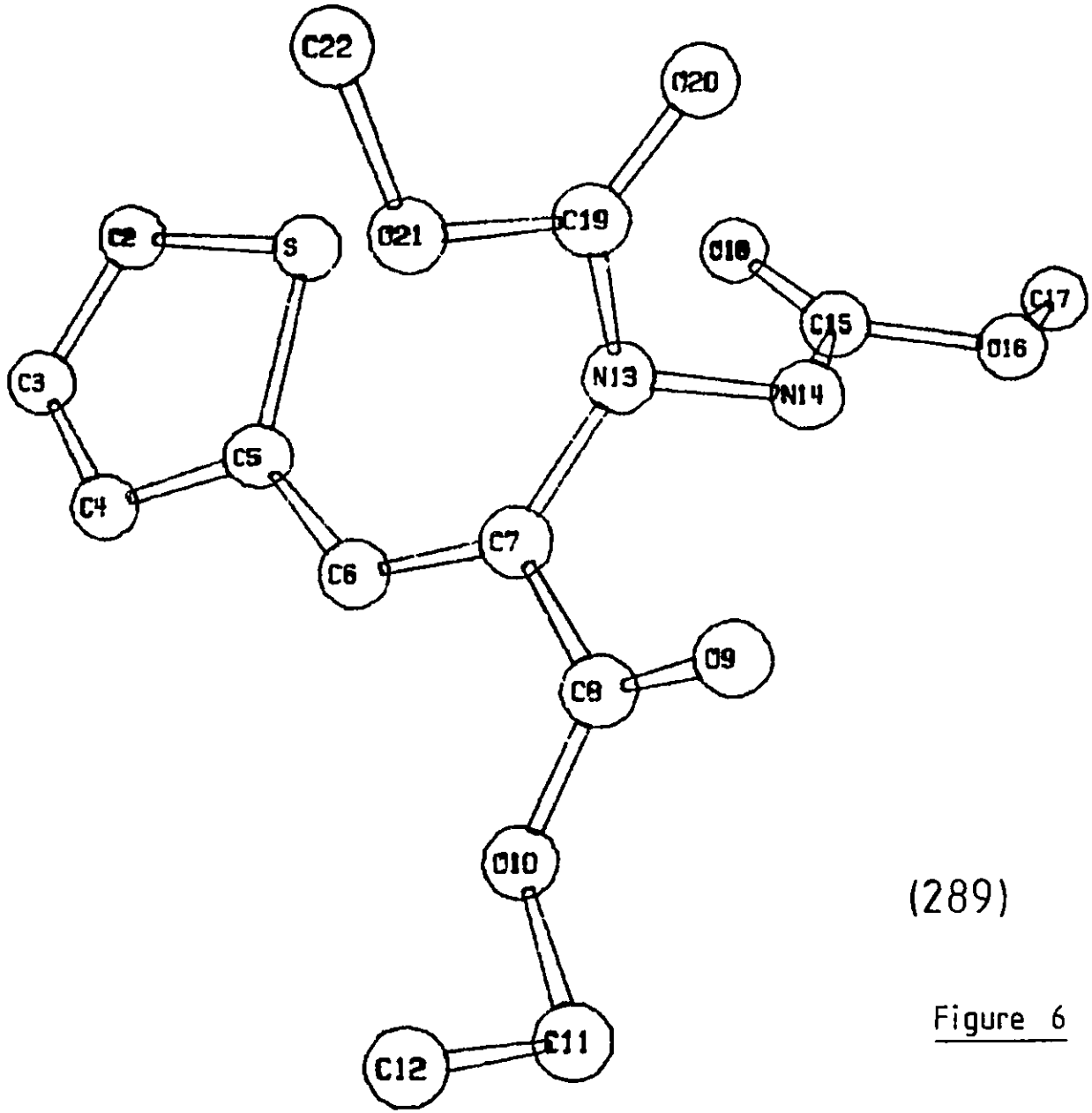
In view of the difficulties experienced in cleaving the triazole ring at the final stage of the synthesis, it was decided to use diethyl azodicarboxylate (DEAZD) as the dienophile in the same synthetic approach. When a mixture of the acylate (283) and DEAZD was refluxed in toluene or bromobenzene for 24 h, apart from polymerization of the starting materials, no reaction was observed. A similar result was reported with methyl β-(2-pyridyl)acrylate.[150]

It has been reported that the cis isomer of DEAZD, which can be generated by irradiation of the normal trans isomer, is more reactive towards Diels-Alder reactions.[151] However, when a mixture of the acrylate (283) and DEAZD was irradiated for 15 h, no reaction was observed.

Some Diels-Alder reactions are known to be catalysed by Lewis acids.[152] In an attempt to react the acrylate (283) with DEAZD, a catalytic amount of $BF_3.Et_2O$ was added to the reaction mixture in toluene. After heating under reflux for 3 h, the reaction resulted in the polymerization of the dienophile. When the same reaction was carried out at room temperature, using $BF_3.Et_2O$ as solvent, a 15% yield of the 1:1 adduct (289) was isolated. The structure was assigned on the basis of elemental analysis and spectropic data. The structure of the adduct (289) was later confirmed by X-ray crystallography (Figure 6). The observed reaction was probably initiated by the complexation of BF_3 onto the nitrogen of DEAZD. DEAZD-BF_3 complex is more electrophilic than DEAZD itself, and addition to the acrylate (283) followed by proton abstraction gives the observed product (SCHEME 70). This result was rather unexpected, because the acrylate is not particularly electron rich, and this type of reaction by DEAZD or DEAZD-BF_3 has only been observed with electron rich aromatics or olefins.[153,154]



Scheme 70


C22
O20
C19
O21
C2
S
O18
C17
C15
O16
C3
N13
N14
C5
C4
C7
C6
O9
C8
O10
C11
C12

(289)

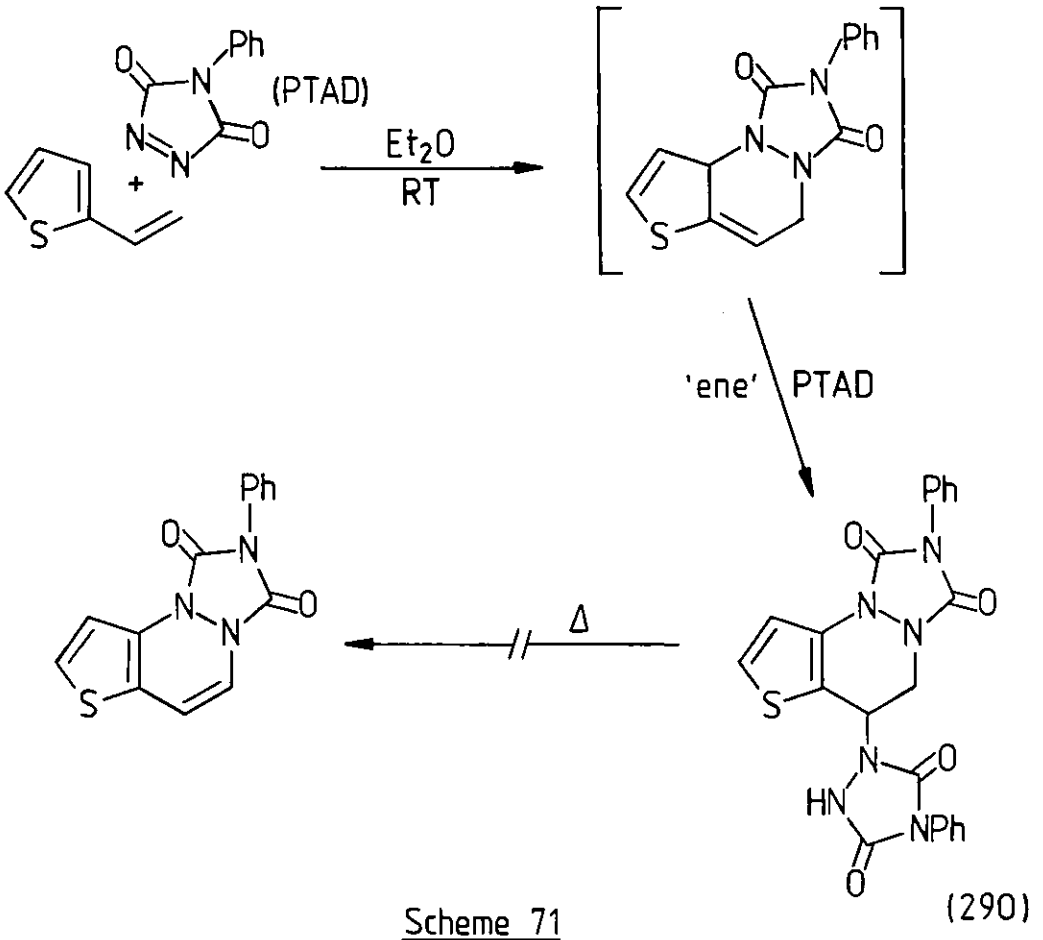
Figure 6

It was next decided to attempt to synthesise the unsubstituted thieno[3,2-c]pyridazine, thus enabling a more reactive diene, 2-vinylthiophen to be used. Reaction of 2-vinylthiophen with one equivalent of PTAD in diethyl ether at room temperature gave a single product (290) in 66% yield.

The mass spectrum of the product showed a low intensity molecular ion which corresponded to an adduct consisting of two PTAD to one 2-vinylthiophen. Its fragmentation pattern was similar to that of adducts (284) and (285). However, the first major loss from the molecular ion was 176 m.u. (PTAD + H) giving a base peak of 284 m.u. This implied that unlike adduct (284), the H-5 proton in (290) was not activated enough for the elimination of 4-phenylurazole to occur. The presence of the ion 138 which corresponds to dihydrothienopyridazine, and the fragment of PhNCO again suggested the tricyclic structure as in adduct (284). Thus, the structure of the product was assigned as (290). This structural assignment was further supported by the n.m.r. spectrum featuring the following signals: a two protons ABX splitting pattern at δ 4.3, a one proton multiplet (X of ABX) at δ 5.7, an α and β aromatic thiophen protons, a low field broad singlet of a D_2O exchangeable proton and the ten protons of the two phenyl groups. The mechanism of formation of (290) is outlined in SCHEME 71 and is parallel to that for adduct (284).

Treatment of the adduct (290) with $BF_3.Et_2O$ in refluxing dioxan for two days gave no reaction. Again, no elimination of 4-phenylurazole from adduct (290) was observed when a DMSO solution was heated at 120°C for two days. This result was probably attributed to the absence of an ester group at the 5-position, which served as an activating group to the H-5 proton in the elimination of 4-phenylurazole.

Attempted hydrolysis of the adduct (290) in a refluxing solution

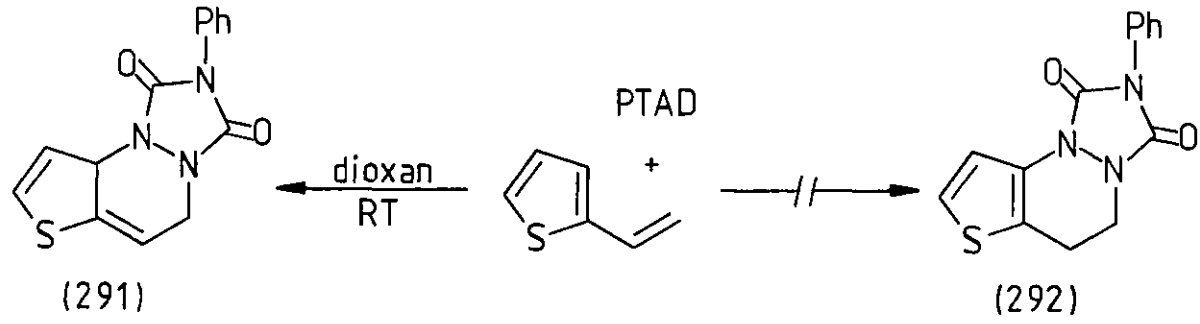


Scheme 71

of potassium hydroxide, water and dioxan, produced a complex mixture with extensive decomposition of the starting material.

When the reaction between 2-vinylthiophen and 1 equivalent of PTAD was carried out in dioxan at room temperature, a good yield of the Diels-Alder adduct (291) was obtained (94% crude yield) (SCHEME 72). This compound was reported to have been prepared by a similar reaction, but no physical nor spectral data on the product were quoted.[155]

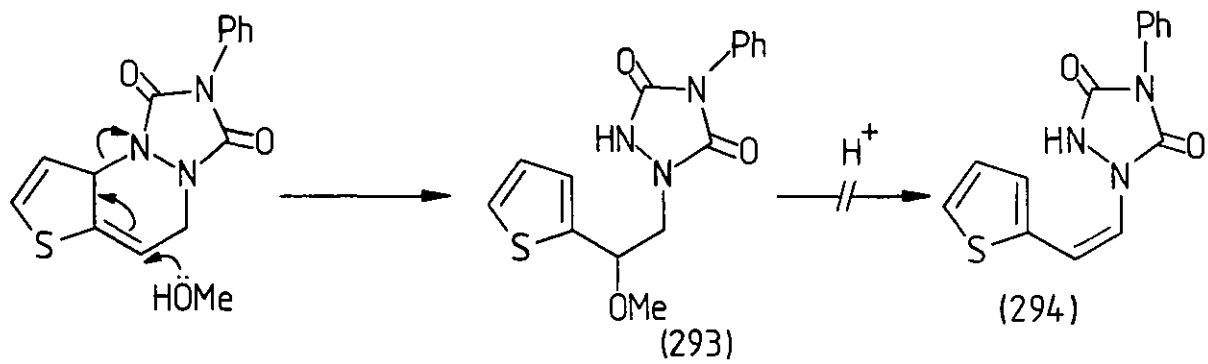
The assignment of the non-aromatic thiophen structure (291) rather than the aromatized thiophen structure (292), was supported by the n.m.r. data. The observed splitting pattern and the chemical shifts of the two thiophen protons were considered to be too complex and higher field than would be expected from structure (292). Evidence in favour for the tricyclic thienotriazolopyridazine system, was again obtained from the mass spectral fragmentation pattern.



Scheme 72

Acid or base hydrolysis of adduct (291) resulted in a complex mixture with no characterizable product.

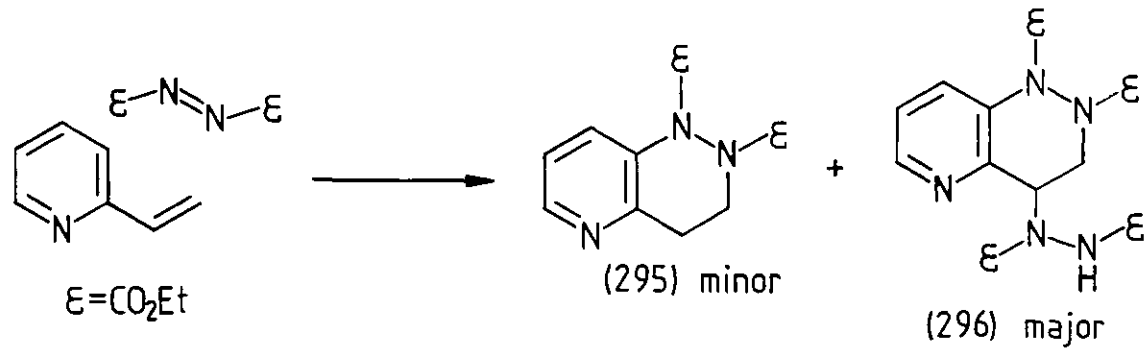
Attempts to purify the adduct (291) by silica gel chromatography led to an inseparable mixture. However, an attempt to recrystallize the adduct (291) from hot methanol led to the isolation of a methanol adduct (293) (SCHEME 73). The structure of (293) was assigned on the basis of elemental analysis and spectroscopic data. Several attempts



Scheme 73

to eliminate methanol from the new product (293) failed. It was hoped that one might be able to reform the tricyclic system from (294).

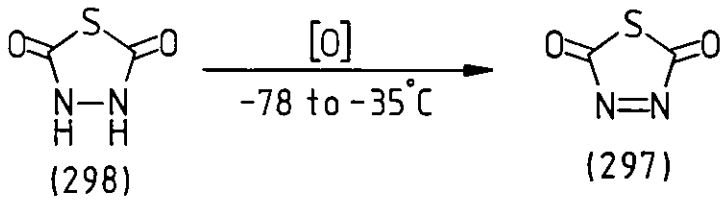
It has been reported that 2-vinylpyridine reacts with dimethyl azodicarboxylate to give a minor 1:1 and a major 2:1 adduct, (295) and (296) respectively (SCHEME 74).[150] By analogy, 2-vinylthiophen



Scheme 74

might react with DEAZD in the same manner. When the reaction was carried out at room temperature in dioxan, no reaction was observed; however, upon reflux for 1.5 h, a complex mixture was obtained. From the mixture, there was isolated in low yield an unstable sticky solid which showed a molecular ion in the mass spectrum corresponding to a 2:1 adduct of DEAZD and 2-vinylthiophen. The product polymerized easily and was not characterized.

Recently, 1,3,4-thiadiazole-2,5-dione (TDAD) (297) has been described as a very reactive dienophile.[156,157] It has the advantage over PTAD of being more readily hydrolysed to a 1,2-disubstituted hydrazine under mild conditions. The dienophile (TDAD) is not stable at room temperature, it has to be generated in situ at low temperature by oxidation of its dihydro precursor (298). Therefore, the use of TDAD is restricted to low temperature reactions only (-35°C or below).



(298) (297)

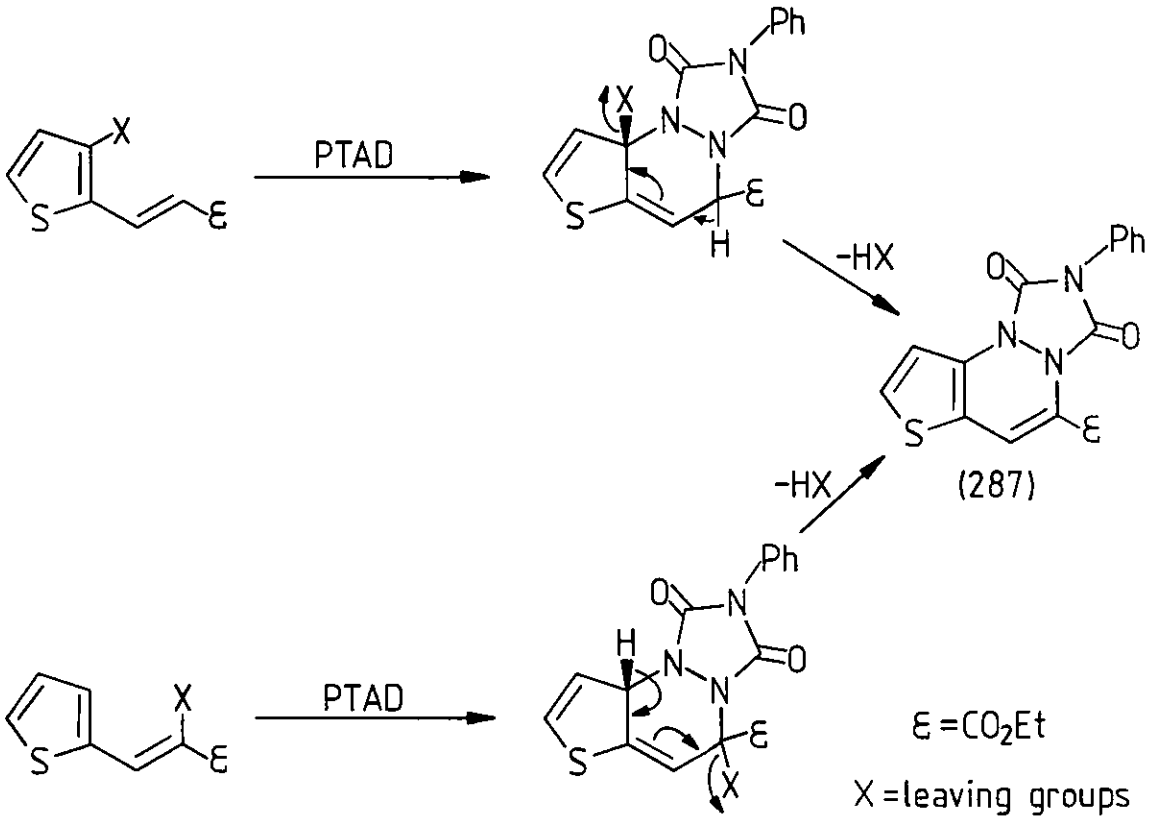
[O] = LTA, $CuCl_2$, ^tBuOCl

Reaction of 2-vinylthiophen with TDAD was investigated. A range of experimental conditions, such as variation in temperature, oxidant, solvents and order of additions were tried; however, all resulted in a complex mixture of inseparable products which were difficult to purify and characterize. The reaction conditions are described in the Experimental Section.

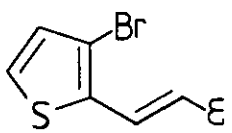
By analogy with the elimination of 4-phenylurazole from the 2:1 adduct (284), one could make use of the idea of cycloaddition - elimination reaction in such a way that the eliminated product, the the tricyclic compound (287), could be prepared by the approaches shown in Scheme 75.

So, the acrylates (299), (300) and (301), were prepared and treated with PTAD at room temperature and at 90°C for several hours. There were either no reaction, or an inseparable mixture containing mainly the starting dienes. Steric congestion presented by the extra substituent might be the cause of the failure in these reactions.

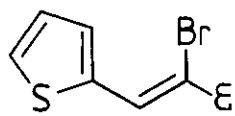
However, reaction of 3-bromo-2-vinylthiophen with PTAD at room temperature, followed by treatment with potassium carbonate in refluxing dioxan, produced the expected product (302) in 46% yield. A similar reaction involving the bromovinylpyridine (303) and PTAD has been reported (SCHEME 76).[154]



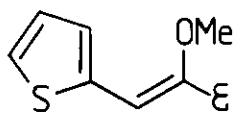
Scheme 75



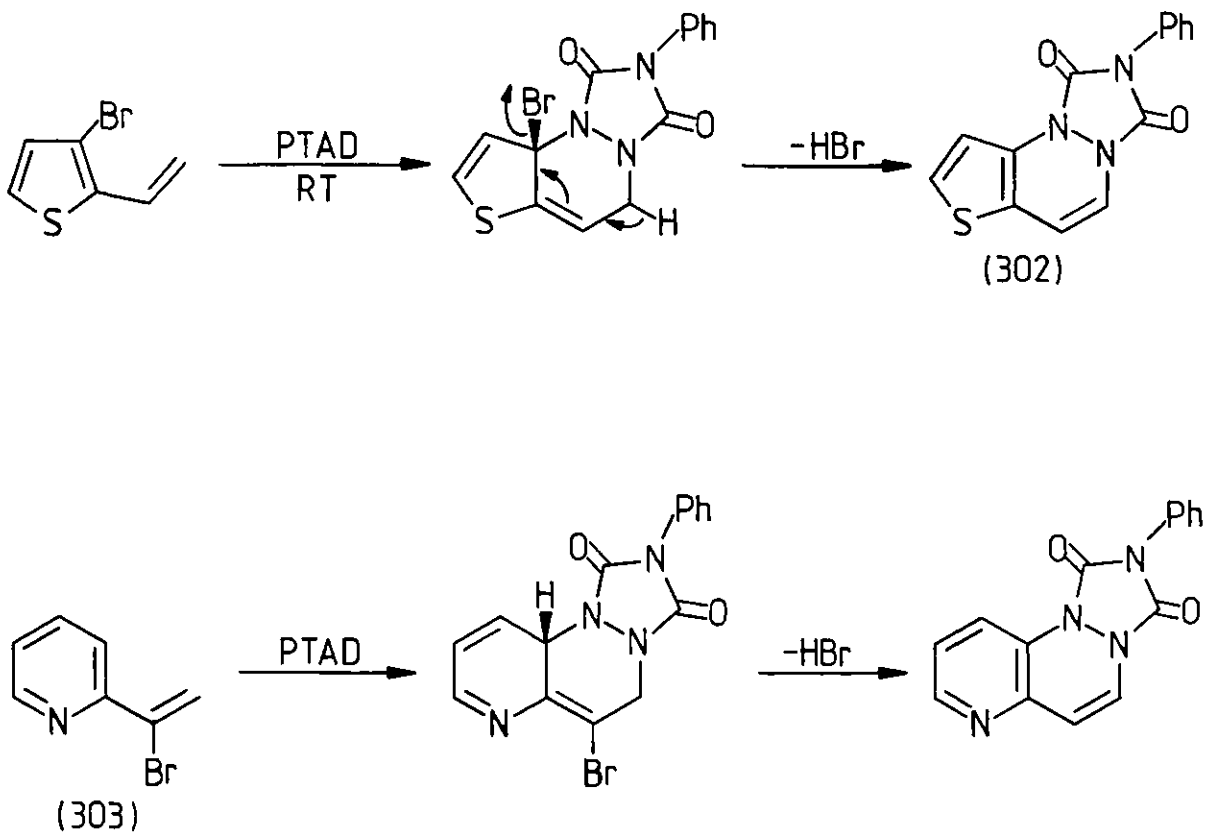
(299)



(300)



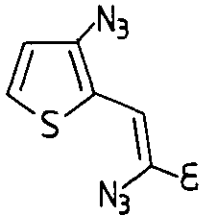
(301)



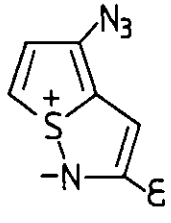
Scheme 76

2.8 Preparation of Cyclic Sulphimides

In the decomposition of the thiophen bis-azide (199), we have postulated that the thiophen ring fragmentation was made possible by the coordination between the vinyl nitrene and the sulphur atom of the thiophen ring, giving the $\overset{+}{S}\text{-}\overset{-}{N}$ ylidic intermediate (274).



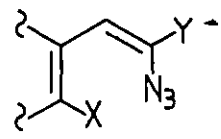
(199)



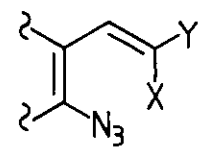
(274)

E=CO_2Et

In order to provide evidence for the intermediacy of the cyclic ylide, and also forming part of the investigation into substituent interactions with vinyl nitrenes, it was decided to study the decomposition reactions of the vinyl azide systems (179) and (182), where X = SR. So, by having a suitably positioned nucleophilic sulphur substituent, we hoped to intercept the nitrene intermediate intramolecularly and form a sulphimide system which would provide a novel synthesis of the almost unknown azathiabenzene system (304).[158] The chemistry of the acyclic sulphimides (305) is well documented and



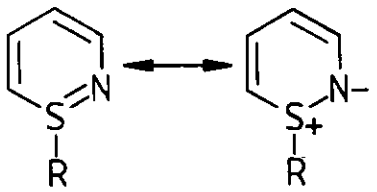
(179)



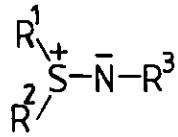
(182)

a recent review on the topic is available.[159] Examples of the closely related benzothiadiazines (306) have also been reported.[160]

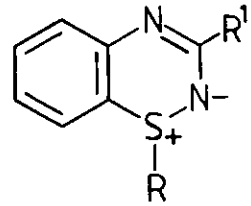
The vinyl azide (201) and the 3-azidothiophens (215) and (216) were prepared. Thermolysis of the vinyl azide (201) in refluxing toluene gave the expected S-methyl cyclic sulphimide (307) in excellent yield. Similarly, thermolysis of the 3-azidothiophen (216) produced the isomeric S-methyl cyclic sulphimide (308) in 84% yield (SCHEME 77). This is the first example of such an isomeric pair of cyclic sulphimides being isolated. A small amount of the thienopyrrole (309) was also isolated from the later reaction; its formation and structural assignment will be discussed in Section 2.10. When a bright yellow solution of the 3-azidothiophen (215) was refluxed in toluene, the reaction mixture gradually turned orange and eventually into deep red when the decomposition was completed. From this mixture,



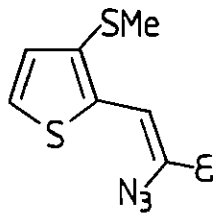
(304)



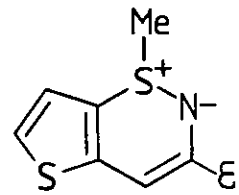
(305)



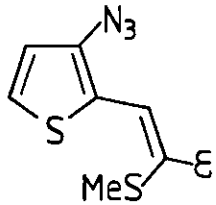
(306)



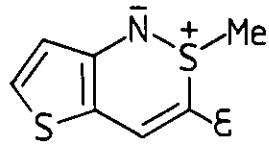
(201)



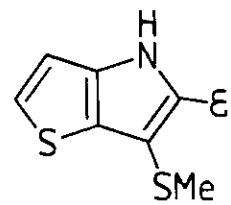
(307) 89%



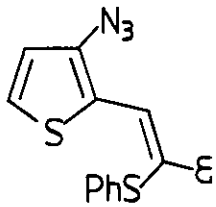
(216)



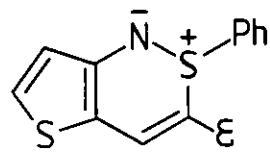
(308) 84%



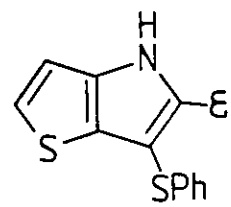
(309) 8%



(215)

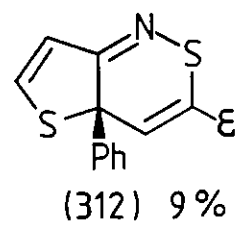


(310) 89%



(311) 1%

+



(312) 9%

$E = CO_2Et$

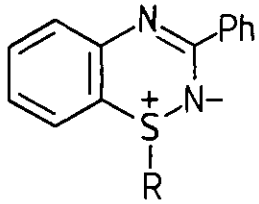
Scheme 77

the S-phenyl cyclic sulphimide (310) was isolated in 89% yield, and in addition, the thienopyrrole (311) and the 4aH-thieno [3,2-c] thiazine (312) were also isolated in 1 and 8% yield respectively. The formation and the structural assignments of the two minor products (311) and (312) will be discussed in Section 2.10 and 2.9c respectively.

The sulphimides (308) and (310) can also be prepared by photolysis of the corresponding azides, although this is less satisfactory because the sulphimides themselves are photo-labile. On the other hand, irradiation of the vinyl azide (201) did not produce the cyclic sulphimide (307) but gave a different product. The photochemistry of these azides and cyclic sulphimides will be described in Section 2.10.

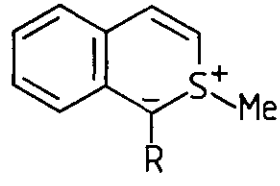
The thermolysis of the vinyl azide (201) was complete in boiling toluene in 10 minutes, whereas under the same conditions, decomposition of the 3-azidothiophen (216) took about 3 hours, therefore giving some indications of the differences in reactivities or stabilities between vinyl azides and aryl azides in general.

All three cyclic sulphimides (307), (308) and (310) were isolated by silica gel chromatography. However, it has been reported that the closely related $1\lambda^4$, 2,4-benzothiadiazines (313a), where R = Me or Et, could not be isolated by silica gel chromatography. The corresponding aryl substituted benzothiadiazines (313b) are stable towards silica.[160]



(313) a: R=alkyl

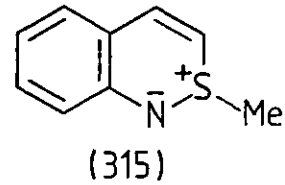
b: R=aryl



(314)

a: R=Ph, isoproyl;

b: R= C_6F_6 ; c: R=H



(315)

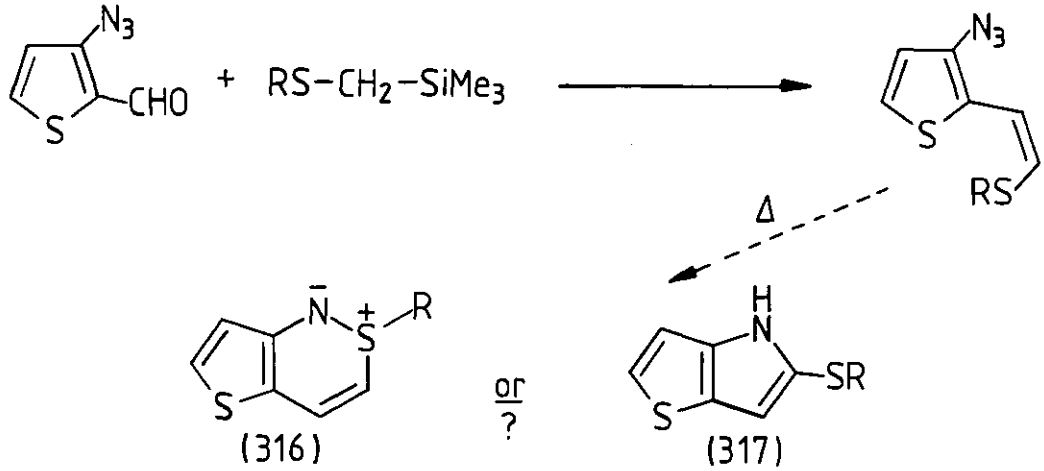
The isomeric pair of S-methyl cyclic sulphimides (307) and (308) were initially obtained as yellow gums. On storage at 0°C, both compounds solidified rather reluctantly giving a yellow/brown sticky solids; they both produced a bright yellow colour in solutions, with the colour of the sulphimide (308) being more intense. The S-phenyl cyclic sulphimide (310) was isolated as a highly crystalline solid. The colours of the above three cyclic sulphimides are not unreasonable when compared with the thianaphthalenes (314a) which are reported as being purple,[161,162] and the benzothiazine (315) as being yellow.[158] The difference in colour intensity between the isomeric pair of S-methyl cyclic sulphimides, was probably due to the extra delocalization of the negative charge onto the ester carbonyl of the cyclic sulphimide (308). The phenyl group in (310) probably provided an extended chromophore in the cyclic sulphimide system and hence further colouration of the compound.

The thermal stability of the three cyclic sulphimides increase in the order: (307) < (308) ⩽ (310). The sulphimide (307) decomposed slowly at room temperature, but could be stored in the dark at 0°C for up to two months. The sulphimides (308) and (310) are stable indefinitely at room temperature provided that they are kept in the dark. However, these cyclic sulphimides (307), (308) and (310) do undergo thermal rearrangement at temperatures above 120°C and their thermal reactions will be discussed in Section 2.9.

The difference in stability between the two isomeric S-methyl cyclic sulphimides was probably due to the delocalization of the negative charge onto the ester carbonyl. This delocalization is possible in sulphimide (308) and (310), but is not possible for sulphimide (307). A similar substituent stabilization effect has also been observed from the 1,2-disubstituted 2-thianaphthalenes (314).

In this case, the 1-pentafluorophenyl substituted derivative (314b) is more stable than the 1-phenyl derivative (314a), and 1-unsubstituted system (314c) is unstable even at -65°C.[162] In addition to the stabilization of the negative charge on the nitrogen of the sulphimides (308) and (310), the lone pair of electrons on the sulphur atom of the thiophen ring could flow via the β-position, which is normally the more nucleophilic site of the thiophen system, onto the positive charge of the thiazine sulphur and hence further stabilize the system.

From the above arguments, one would expect the corresponding thienothiazine (316) to be less stable without the 3-carboxylate substituent. A possible synthetic route to such a molecule is outlined in SCHEME 78. A possible undesirable side reaction would be the formation of the thienopyrrole (317).



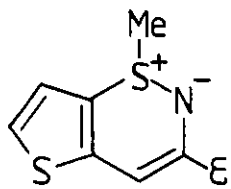
Scheme 78

Therefore, the thermal stability of these azathiabenzene systems can be generalized as follows: structural elements that can delocalize or stabilize a positive charge on sulphur and/or a negative charge on nitrogen, will contribute to the stabilization of the system. This generalization is also consistent with the observed thermal stability within thiabenzene systems.

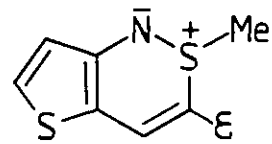
Since nitrogen can accommodate a negative charge much better than carbon, the effect of having one or more nitrogen atoms at the appropriate positions within the ylidic system will increase its stability; hence the observed thermal stability of thiabenzenes < 1,2-azathiabenzenes < 1,2,4-diazathiabenzenes.

The structures of the three cyclic sulphimides (307), (308) and (310) were assigned on the basis of their elemental analysis and spectroscopic data. Further structural evidence was obtained by comparing the data with the two literature examples of azathiabenzene derivatives.[158]

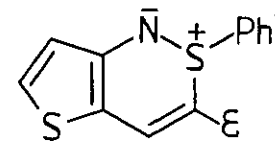
As expected from the colour of the thieno cyclic sulphimides, their u.v. spectra exhibited an absorption at long wavelength. The S-methyl cyclic sulphimide (307) has an absorption at 400 nm (log ε 3.81), whereas the reverse isomeric S-methyl and S-phenyl cyclic sulphimides (308) and (310) show absorptions at 457 nm (log ε 3.64) and 459 nm (log ε 3.63) respectively.



(307)



(308) E=CO_2Et

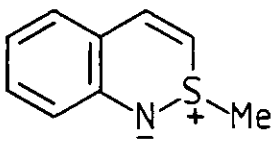


(310)

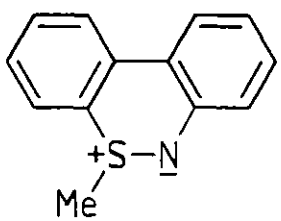
An interesting feature was observed when the i.r. spectra of the three thieno cyclic sulphimides were compared. The S-methyl cyclic sulphimide (307) showed an ester carbonyl stretching frequency at 1695 cm^{-1}, which is within the normal range of stretching frequency of α,β-unsaturated esters. However, the reverse isomeric S-methyl and S-phenyl cyclic sulphimides (308) and (310) showed their ester carbonyl stretches at 1675 and 1670 cm^{-1} respectively; these are unusual for α,β-unsaturated esters. This observation could be explained by delocalization of the nitrogen's negative charge onto the carbonyl function of the ester group; this has an effect of lengthening the C=O

double bond, and hence lowering the vibrational frequency of the carbonyl.

In comparing the ^{1}H n.m.r. spectra of the azide precursors and the cyclic sulphimides, there was an upfield shift of the S-methyl singlet in going from the vinylazide (201) to the corresponding sulphimide (307), and also from the 3-azidothiophen (216) to the S-methyl cyclic sulphimide (308). However, the S-methyl chemical shifts of (307) and (308) compared favourably with the literature examples (Table 9), but are surprisingly close to the "textbook" value of normal saturated methyl sulphide (δ_{S-CH_3} = 2.1).[163]



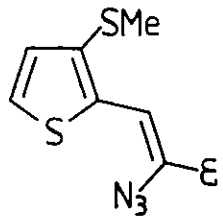
(315)



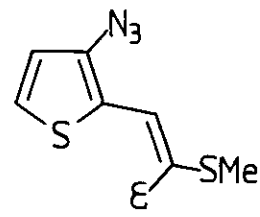
(318)

Azide precursors δ_{SMe}	Cyclic Sulphimides δ^{+}_{SMe}
(201) 2.47	(307) 2.27
(216) 2.37	(308) 2.28
-	(315) 2.20[158]
-	(318) 2.34[158]

Table 9



(201)



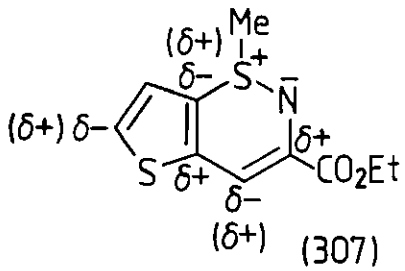
(216)

The chemical shifts of the H-4, H-6 and H-7 of the three cyclic sulphimides are shown in Table 10. The slight differences in these chemical shifts between the two isomeric type of cyclic sulphimides (307) vs (308) and (310), could be explained by the difference in charge distribution as shown in SCHEME 79. Again the long range "zig-zag" couplings between H-4 and H-7 are observed.

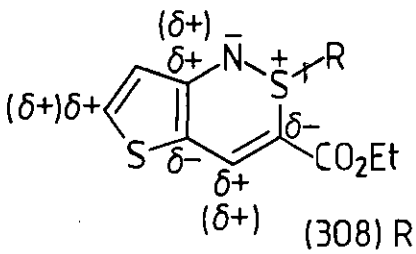
Chemical Shifts/δ

Cyclic sulphimides	H-4 ($J_{4,7}$)		H-6 ($J_{6,7}$)		H-7	($J_{7,6}$; $J_{7,4}$)	
(307)	7.17	(0.8Hz)	7.30	(5.1Hz)	6.90	(5.1;	0.8Hz)
(308)	8.02	(0.8Hz)	7.62	(5.4Hz)	6.79	(5.4;	0.8Hz)
(310)	8.12	(0.8Hz)	7.59	(5.5Hz)	6.89	(5.5;	0.8Hz)

Table 10



(307)



(308) R=Me
(310) R=Ph

(δ+)=contribution from the ester group

Scheme 79

The remaining interesting feature in the ^1H n.m.r. spectra of the three thieno cyclic sulphimides lies in the splitting patterns of the methylene component of the ethyl ester group. In the sulphimide (307), the methylene protons appeared as a quartet of quartets; on the other hand, the reverse isomeric analogue (308) showed a single quartet for the methylene protons. This is opposite to what was expected, because the chiral sulphur is closer to the ester group in structure

(308) than in structure (307). In the S-phenyl cyclic sulphimide (310), the methylene protons appeared as multiple quartets. In view of the single quartet observed in the sulphimide (308), the multiplicity observed here in (310) is considered to result from restricted rotation of the ethyl group imposed by the adjacent phenyl group.

The broad-band noise-decoupled ^{13}C n.m.r. spectra of the three thieno cyclic sulphimides are shown in Figures 7,8 and 9 in the Appendix. The carbon assignments were tentatively made, wherever possible, on the basis of the available data.

The ^{13}C n.m.r. spectrum of the S-methyl cyclic sulphimide (307) in $CDCl_3$ features only nine signals when there are ten carbon atoms in the molecule, however, by using benzene-d_6 as the solvent, all 10 carbons were observed. The S-methyl carbon for the sulphimides (307) and (308) were assigned to the signals at 31.4 and 28.5 ppm respectively. These chemical shifts are close to the reported value of 31.9 ppm for the S-methyl of the benzothiabenzene (314a).[162] The chemical shifts for the ring carbons of the three cyclic sulphimides are listed in Table 11; their assignments were based on the charge distribution models shown in SCHEME 79. The excellent shift correlation between sulphimides (308) and (310) has provided good evidence for their identical fused ring system. The large differences in the chemical shifts between sulphimide (307) and the other two sulphimides (308) and (310) reflected the two dissimilar structural arrangements.

The mass spectral evidence was also consistent with the structure of the three thieno cyclic sulphimides. Each sulphimide showed a strong molecular ion in the mass spectrum, and they all have a base peak corresponding to M-R, where R is the substituent on the four valent sulphur atom. In addition, only the S-methyl cyclic sulphimide (307) showed a strong M+2 peak in the mass spectrum, this

Compound/ Solvent	Chemical Shifts/δ						
	sp^2 quarternary carbons			sp^2 methine carbons			
	C-3	C-4a	C-7a	C-4	C-6	C-7	S-Me
(307)/$CDCl_3$	142.8	142.8	105.0	102.4	121.2	124.5	31.4
(307)/C_6D_6	143.4 or 144.7		104.5	101.6	121.5	123.7	30.8
(308)/$CDCl_3$	85.2	114.0	162.0 or 162.7	135.8 or 136.7		124.2	28.5
(310)/$CDCl_3$	85.5	116.2	163.4 or 163.7	136.8 or 137.0		123.9	-

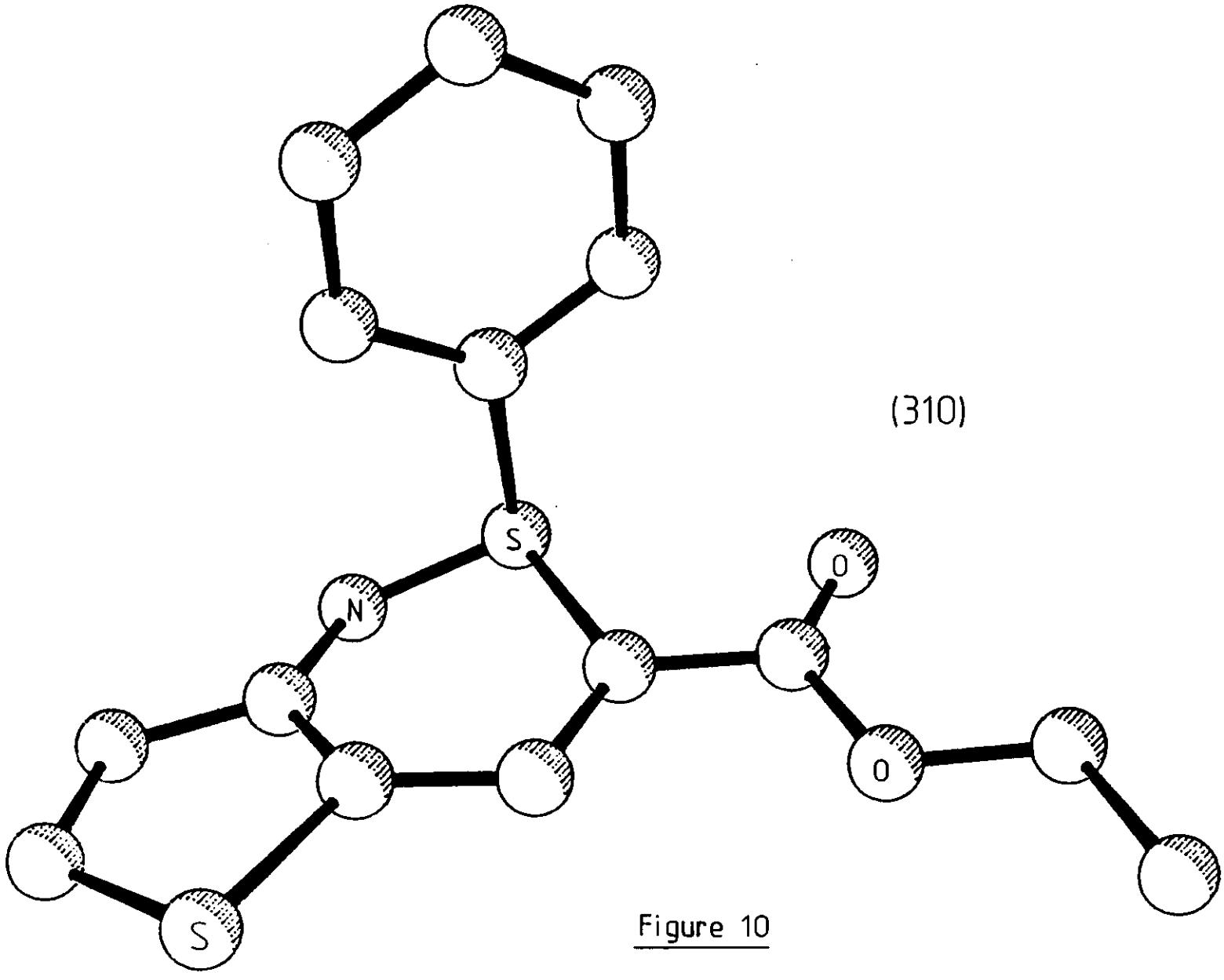
^{13}C n.m.r. data for some Thieno Cyclic Sulphimides

Table 11

might suggest a relatively weaker S-N bond and hence the compound was less stable than its reverse isomeric cyclic sulphimides (308) and (310).

Since there has been no report of any X-ray crystallographic study of this rare class of compounds, the azathiabenzenes, it would be of interest to determine the S-N bond length and the geometry at the four valent sulphur atom, hence providing further indications of its ylidic structure. The highly crystalline S-phenyl cyclic sulphimide (310) was the only suitable choice for single crystal X-ray crystallographic examination. The X-ray crystal structure of the cyclic sulphimide (310) is shown in Figure 10, and further confirmed the earlier structural assignment. Bond length measurements of the compound revealed the S-N bond length is 1.63Å, which is within the range for acyclic sulphimides, and is intermediate between the single S-N (1.74Å) and the double S=N (1.53Å) bond distance.[159] The geometry of the four valent sulphur was tetrahedral with the phenyl group pointing out of the plane. These findings are consistent with the suggested ylidic nature of the azathiabenzen system.

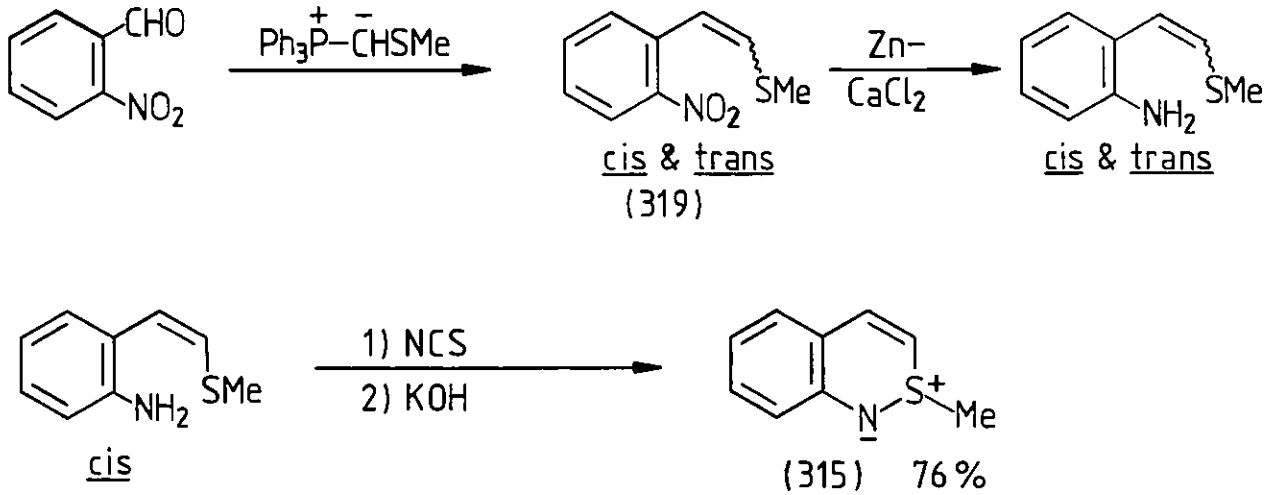
Apart from the three thienoazathiabenzenes already described, there are only two other azathiabenzene derivatives known in the literature, the azathianaphthalene (315) and the azathiaphenanthrene (318).



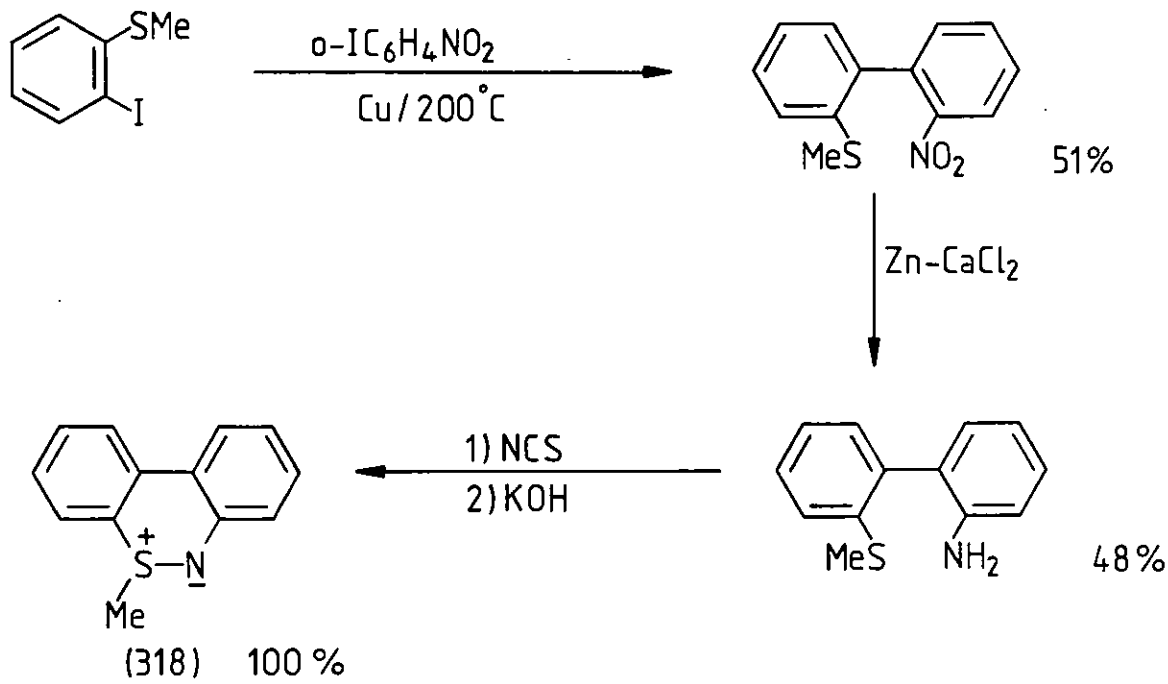
(310)

Figure 10

The preparation of these two compounds was reported by Hori and co-workers and their syntheses are outlined in SCHEMES 80 and 81.



Scheme 80



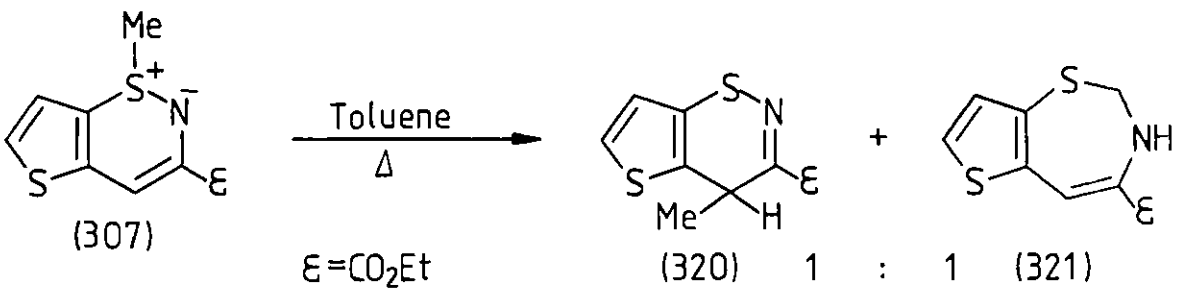
Scheme 81

The synthesis of the azathianaphthalene (315) shown in SCHEME 80 has a major disadvantage in that the o-nitrostyrene (319) was formed as a 1:1 cis and trans isomeric mixture, and only the cis isomer could subsequently be converted into the required cyclic sulphimide (315).

2.9 Thermolysis of Cyclic Sulphimides

a Ethyl 1-methylthieno[2,3-e][1λ^4,2]thiazine-3-carboxylate (307).

The cyclic sulphimide (307) was heated under reflux in dry toluene until it had all decomposed (2h). After removal of the solvent, the residual oil was analysed by t.l.c. The oil was shown to consist of a complex mixture with two of the components appearing in larger quantity. The two major products have very similar R_f values, and were initially isolated by column chromatography as a mixture together with a third minor component in a total yield of 40%. A reasonably pure sample of the two major products was only obtained after double purification by p.l.c. with multiple elutions. The two products were assigned as the 4H-thieno[2,3-e][1,2]thiazine (320) and the 2,3-dihydrothieno[2,3-f][1,3]thiazepin (321) (SCHEME 82). The ring system of (321) appears to be unknown in the literature, and that of (320) is known only as the S-dioxide.[164]

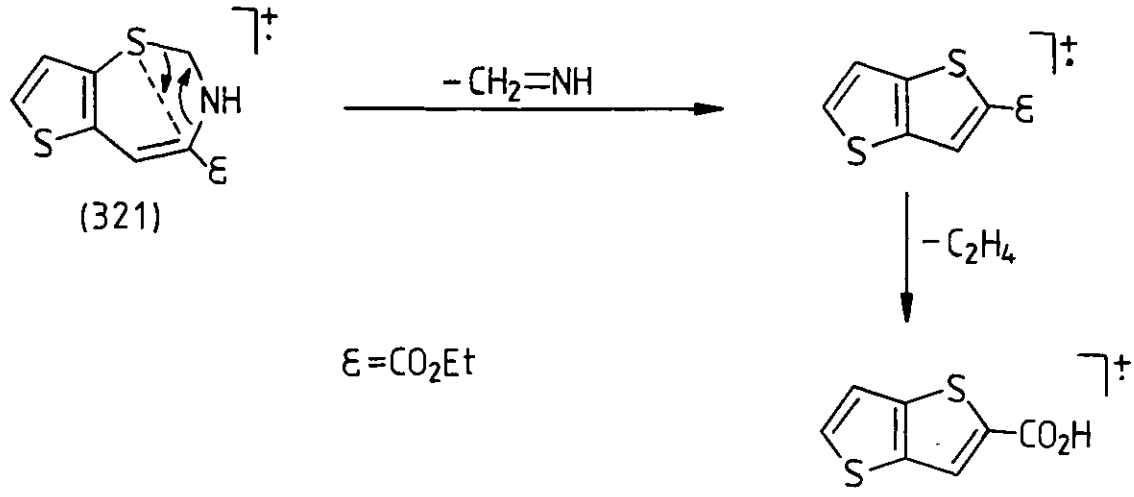


Scheme 82

The structure of the thienothiazine (320) was supported by spectral evidence: the ^{1}H n.m.r. contained a three proton doublet at δ1.31 with a coupling constant of 7.7Hz; this coupling constant corresponded to that of the one proton quartet at δ4.77 and their coupling was further confirmed by a decoupling experiment. Hence they were assigned to the C-4 methyl and the C-4 proton. The one proton doublets at δ7.30 and δ6.80 were assigned to the α and β protons of the aromatic thiophen system respectively. The i.r. spectrum indicated a carbonyl stretch of an α,β-unsaturated ester at 1710 cm^{-1}. The mass spectrum showed a molecular ion of 241 with a base peak of 226 which corresponded to the loss of the 4-methyl group.

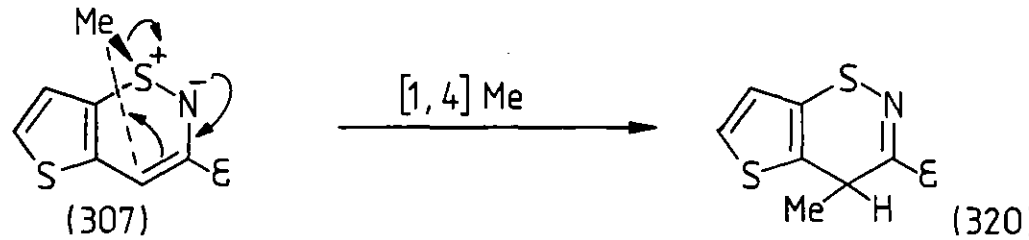
The assignment of the thiazepin (321) was made on the basis of spectral evidence: the i.r. spectrum indicated a N-H stretching frequency at 3400 cm^{-1} and an α,β-unsaturated ester carbonyl at 1705 cm^{-1}. The ^{1}H n.m.r. showed the C-2 methylene protons as a doublet at δ4.48 with coupling constant $J_{2,N-H}$ = 6.8Hz; the N-H proton resonated at δ5.79 and appeared as D_2O exchangeable broad multiplet. The olefinic proton H-5 appeared as a double doublet at δ6.82 with coupling constants $J_{5,N-H}$ = 1.3Hz and $J_{5,8}$ = 0.4Hz; the H-7 and H-8 protons resonated at 7.18 and 6.82 ppm respectively, their coupling constant was 5.3Hz. H-8 was further split by H-5 through a long range "zig-zag" coupling with $J_{8,5}$ = 0.4Hz; the couplings between N-H and H-5, and N-H and H-2 were confirmed by decoupling experiments. The mass spectrum was also consistent with the proposed structure. The 1,3-thiazepin (321) showed a molecular ion of 241 as the base peak, a loss of 29 from the molecular ion gave 212 and was followed by a further loss of 28 to give an ion at 184; both fragmentations were accompanied by a metastable ion. Fragmentations are proposed in SCHEME 83.

The formation of the thienothiazine (320) from the cyclic sulphimide



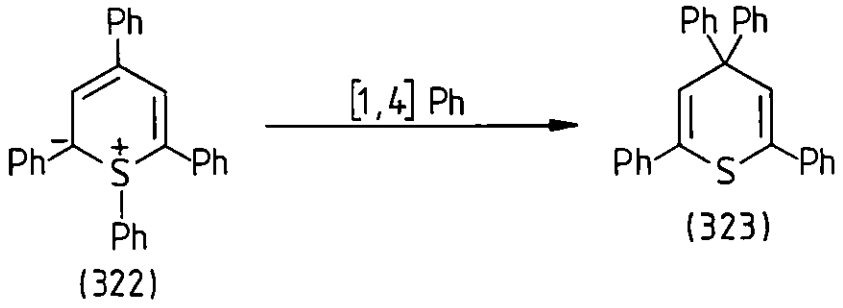
Scheme 83

(307) may be formally described as a six-electron [1,4] sigmatropic shift of the methyl group (SCHEME 84).

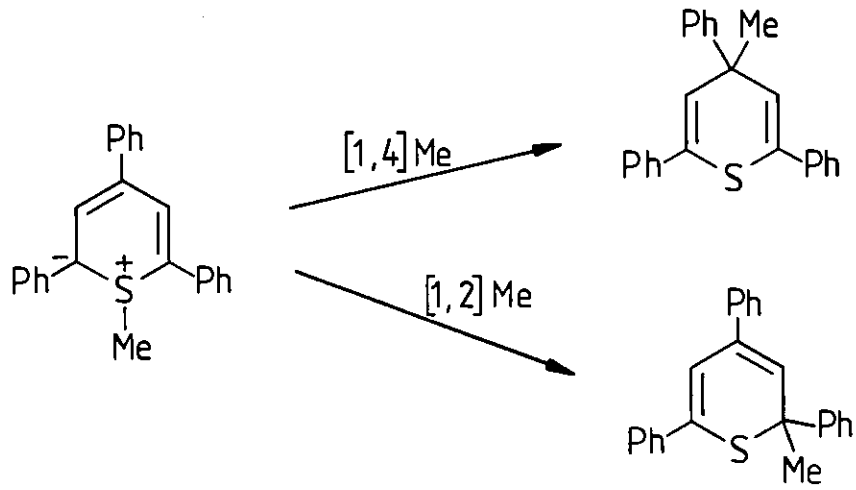


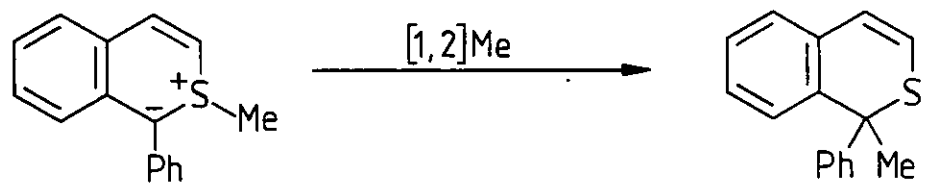
Scheme 84

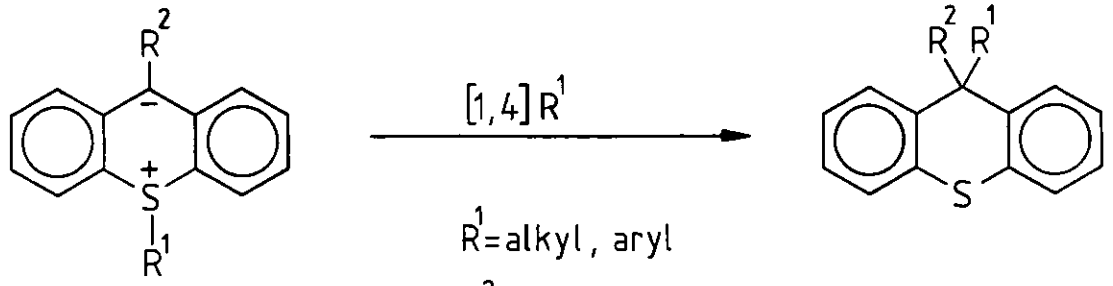
This type of [1,4] shift is analogous to an extended version of the [1,2] shift recognized in a variety of carbanionic species including acyclic sulphonium ylides.[165] In thiabenzene chemistry, thermal rearrangement involving a six-electron [1,4] migration of an aryl or alkyl group from sulphur to carbon has also been established.[162,166-169] For example, the first thiabenzene ever prepared, 1,2,4,6-tetraphenylthiabenzene (322) was reported to undergo thermal rearrangement to give the thiopyran (323) via a [1,4]phenyl shift, in 25% yield.[170] In the S-alkyl thiabenzene, in addition to the [1,4] alkyl shift, a



(322) (323)







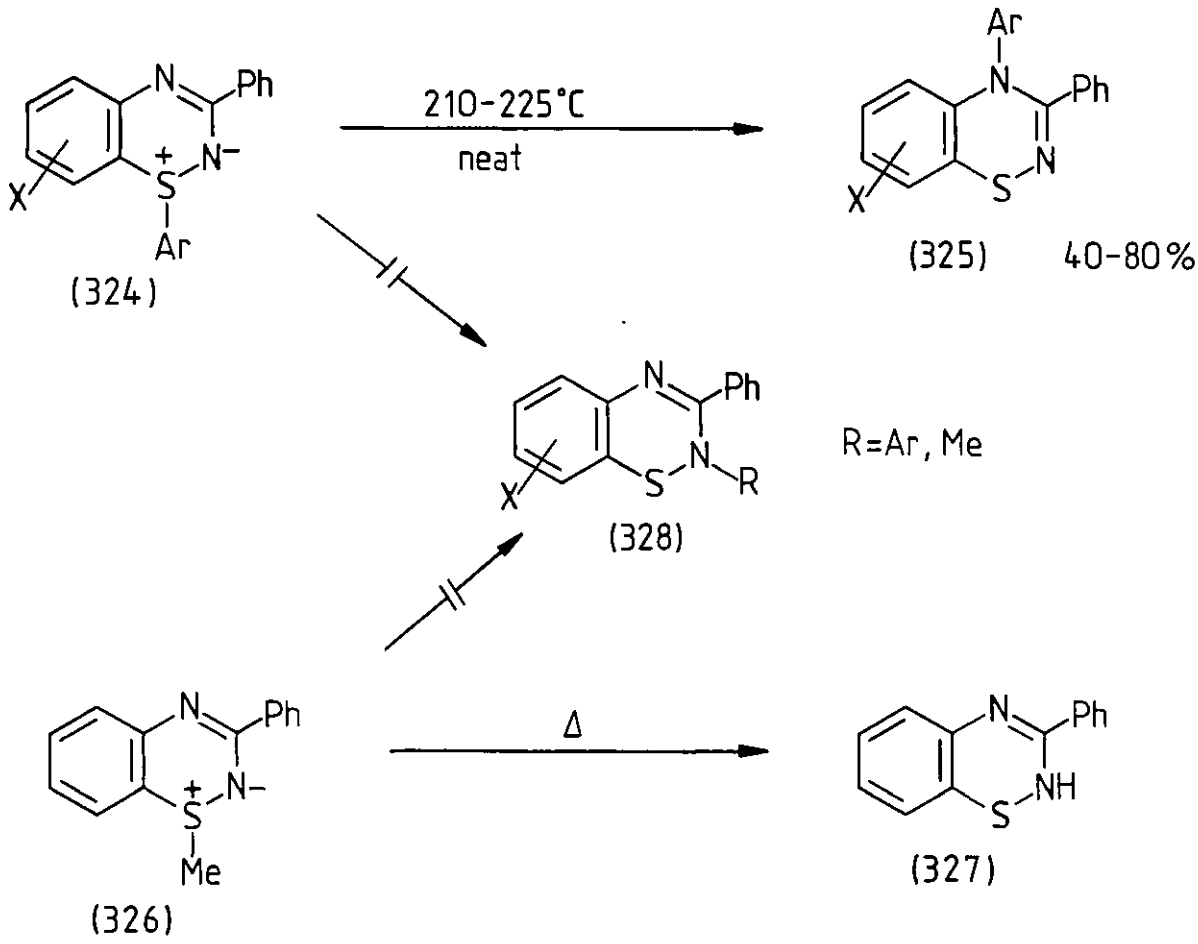
R^1 = alkyl, aryl

R^2 = H, aryl, CN

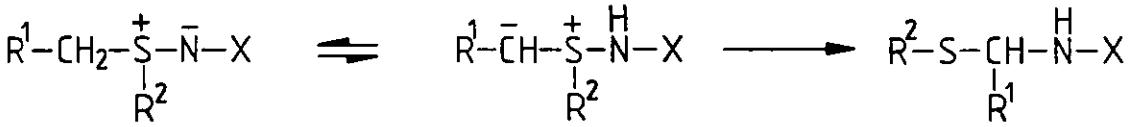
Scheme 85

four-electron [1,2]shift was also observed in equal proportion. Similar thermal rearrangements were also reported in thianaphthalene and thiaanthracene systems; the former underwent exclusive [1,2] shift and the latter a [1,4] rearrangement (SCHEME 85).

It has been reported that thermolysis of some S-aryl-1λ^4,2,4-benzothiadiazines(324) gave rise to the 4-aryl-1,2,4-benzothiadiazines (325) which were derived by a [1,4]aryl migration from sulphur to nitrogen. Thermolysis of the S-methyl-1λ^4,2,4-benzothiadiazine (326) however produced the 2H-1,2,4-benzothiadiazine (327) in 52% yield. The mechanism by which the product (327) was formed still remained unclear.[171]

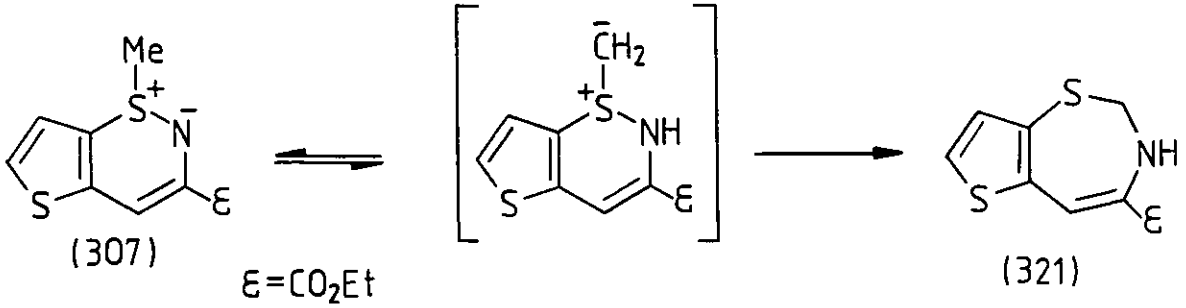


It is interesting to note that a simple [1,2] migration of a substituent from sulphur to nitrogen in the $1\lambda^4$,2,4-benzothiadiazine system (324,326), which would produce the 2-substituted-1,2,4-benzothiadiazine (328), was never observed. This finding is in accordance with the acyclic sulphimide system. However, with acyclic sulphimides, a Pummerer-type [1,2] shift was observed. It was postulated as the initial step in many thermal reaction of S-alkylsulphimides (SCHEME 86), and in a few cases the primary products of the Pummerer rearrangement have also been isolated.[159]

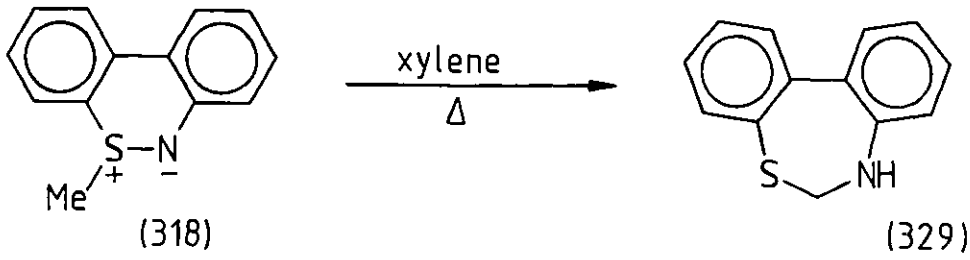


Scheme 86

The mechanism by which the 1,3-thiazepin (321) resulted from the thermal ring expansion of the cyclic sulphimide (307) could be envisaged as a Pummerer-type rearrangement described earlier (SCHEME 87). This type of thermal ring expansion has also been observed in the thermolysis of azathiaphenanthrene (318).[158] The 1,3-thiazepin (329) was isolated as the only product in 26% yield; the [1,4]methyl shift from sulphur to carbon was not observed (SCHEME 88). The azathianaphthalene (315) on the other hand, produced a complex mixture on standing at room temperature.[158]



Scheme 87

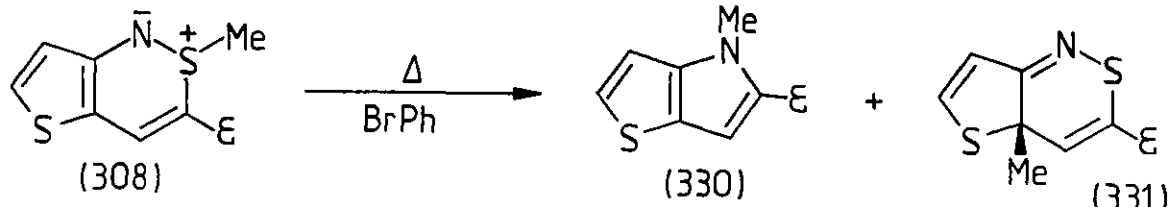


(318) (329)

Scheme 88

b Ethyl 2-methylthio[3,2-c][1λ⁴,2]thiazine-3-carboxylate (308)

Thermolysis of the cyclic sulphimide (308) in refluxing bromobenzene (2h) gave the N-methylthieno[3,2-b]pyrrole (330) and the 4aH-thieno[3,2-c]thiazine (331) in 9 and 40% yield respectively (SCHEME 89).

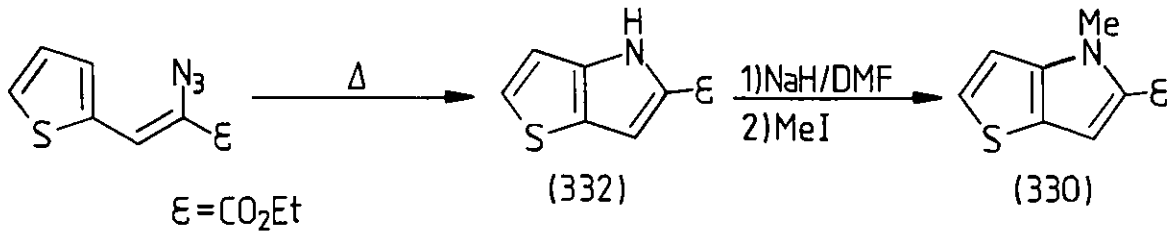


(308) (330) (331)

Scheme 89

The structure of N-methylthienopyrrole (330) was assigned on the basis of its elemental analysis and spectroscopic data. The elemental analysis showed a loss of one sulphur atom from the starting sulphimide. The i.r. appeared to have no N-H stretching; the ^{1}H n.m.r. showed a three proton singlet at 4.03 ppm and was assigned to the N-methyl group. The thiophen β-proton absorbed at δ6.91 as a double doublet with coupling constants of 5.1 and 0.7Hz. The 5.1Hz coupling constant was to the thiophen α-proton and the 0.7Hz coupling was explained by a long range "zig-zag" coupling to the pyrrolic proton (H-3) which resonated at δ7.17. The ^{13}C n.m.r. also showed a N-methyl carbon signal at δ34.5. The structure of the N-methylthienopyrrole (300) was further confirmed by an independent synthesis as depicted in SCHEME 90. The thienopyrrole (332) was prepared according to the method of

Hemetsberger,[28] N-methylation of the thienopyrrole (332) gave the required product (330) in 75% yield.

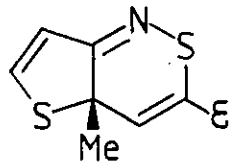


Scheme 90

The major product resulting from the thermolysis of the cyclic sulphimide (308) was confirmed by elemental analysis, to be an isomer of the starting sulphimide. The i.r. showed a carbonyl stretching frequency at 1720 cm^{-1}, which falls between an α,β-unsaturated ester and a saturated ester group. No N-H stretch was observed in the i.r. spectrum. In the ^{1}H n.m.r. spectrum, there was a three proton singlet resonation at δ1.19 which suggested a methyl group attached to a sp^3 quarternary carbon centre; the two doublets at δ6.30 and 7.28, forming an AB quartet with coupling constant of 5.9Hz, were assigned as a thiophen AB quartet; the upfield shift of the thiophen β-proton from δ6.79 in the starting sulphimide (308) to δ6.30 in the major product, implied the thiophen ring no longer remained aromatic; there was also a singlet at δ7.02 suggesting an olefinic proton. The ^{13}C n.m.r. was consistent with the proton spectrum, the presence of a sp^3 quarternary carbon was confirmed by the weak signal at 53.1 ppm; the strong signal at 20.3 ppm provided further evidence of a methyl group bonded to a sp^3 quarternary carbon (see Figure 11 in the Appendix).

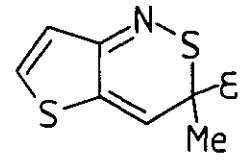
On the basis of the above information, the thienothiazines (331) and (333) were proposed as possible structures for the major product. Because of the inconclusive carbonyl stretching frequency observed in

the i.r., it was not possible to distinguish between these structures.



(331)

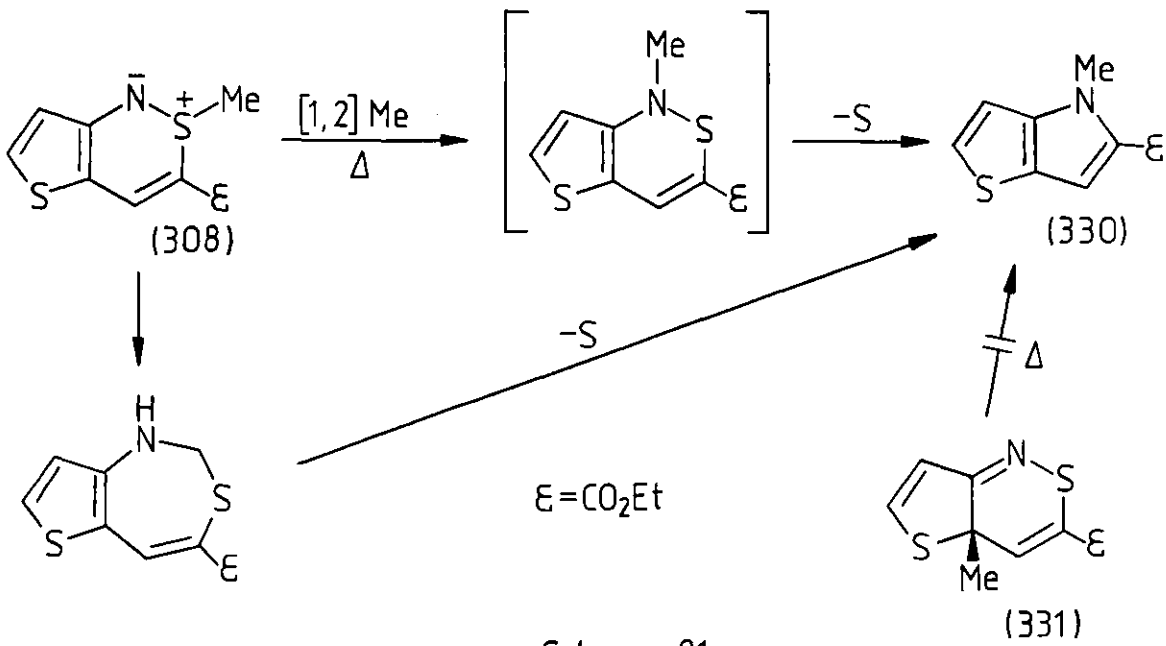
Ɛ=CO_2Et



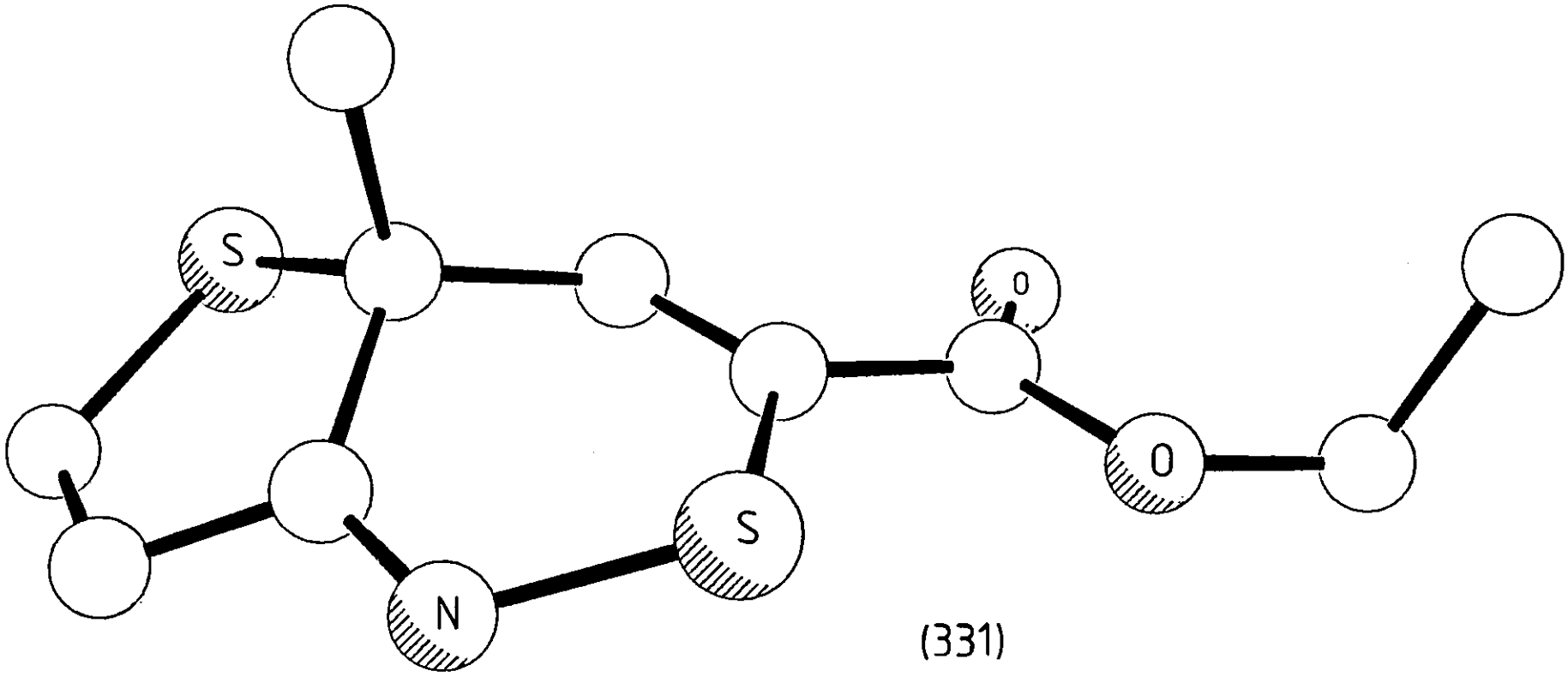
(333)

However, the structure of the product was later unambiguously confirmed to be that of (331) by single crystal X-ray crystallography. A picture of the structure is shown in Figure 12.

The formation of the N-methylthienopyrrole (330) could be envisaged as a [1,2]methyl shift from sulphur to nitrogen, followed by the loss of elemental sulphur to give the observed product, or via the 1,3-thiazepin intermediate (SCHEME 91). It was further shown that the 4aH-thienothiazine was not an intermediate in the formation of the N-methylthienopyrrole. Thermolysis of the 4aH-thienothiazine (331) in refluxing bromobenzene gave a complex mixture with no detectable N-methylthienopyrrole (330).



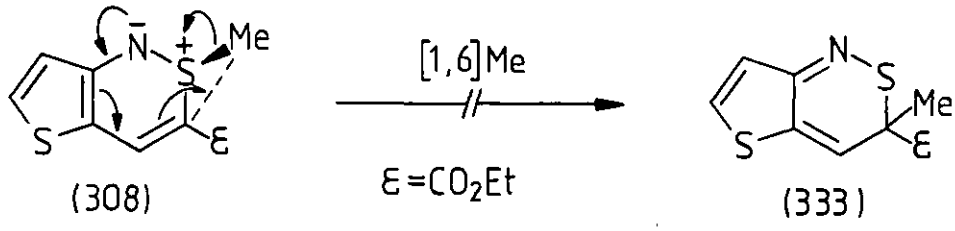
Scheme 91



(331)

Figure 12

The mechanism by which the 4a<u>H</u>-thienothiazine (331) was formed could formally be described as a six-electron [1,4]methyl shift; it is infact analogous to the [1,4] shift observed in the <u>S</u>-methyl cyclic sulphimide (307). However, it also seems possible that an eight-electron [1,6]methyl shift could give rise to the 3-methyl-thienothiazine (333), which was considered as one of the possible structures, but was not observed (SCHEME 92).



(308) (333)

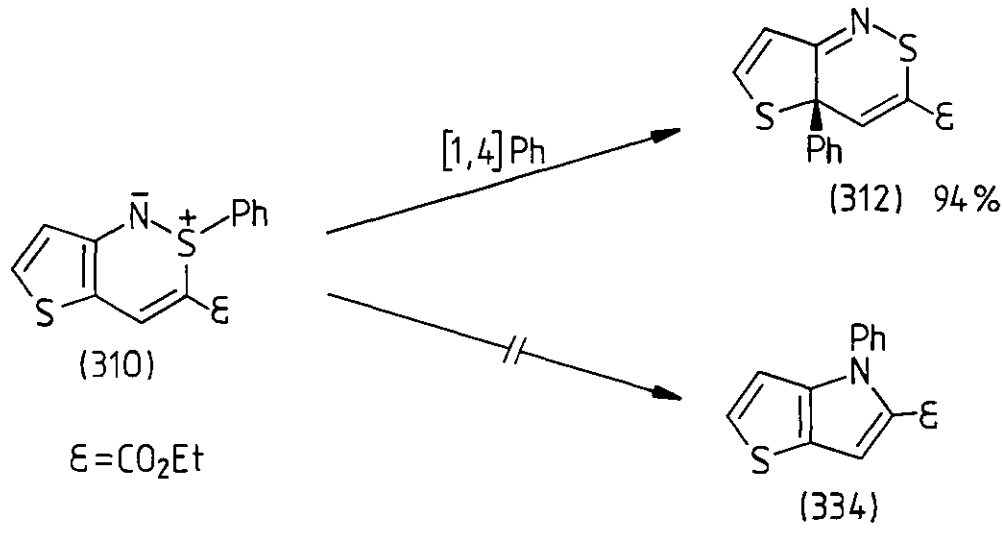
Scheme 92

The formation of (331) as the major product of thermal rearrangement of (308) was quite unexpected since it requires disruption of the thiophen ring aromaticity.

c Ethyl 2-phenylthieno[3,2-<u>c</u>][1λ^4,2]thiazine-3-carboxylate (310)

Thermolysis of the <u>S</u>-phenyl cyclic sulphimide (310) in boiling xylene for 10h gave the pale yellow 4a<u>H</u>-thienothiazine (312) in 94% yield. The <u>N</u>-phenylthienopyrrole (334), which would be analogous to the formation of the <u>N</u>-methylthienopyrrole (330) from the sulphimide (308), was not observed (SCHEME 93). It is worth noting that the [1,4]phenyl shift proceeds far more cleanly than the corresponding [1,4]methyl shift; this is to be expected, as phenyl migrates more easily than methyl.

The structure of the 4a<u>H</u>-thienothiazine (312) was assigned on the basis of its elemental analysis and spectral data. All its spectral properties were consistent with those expected by comparison with its methyl analogue (331); in particular, the i.r. showed a carbonyl

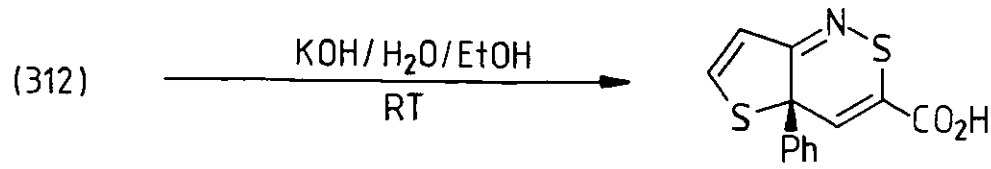


Scheme 93

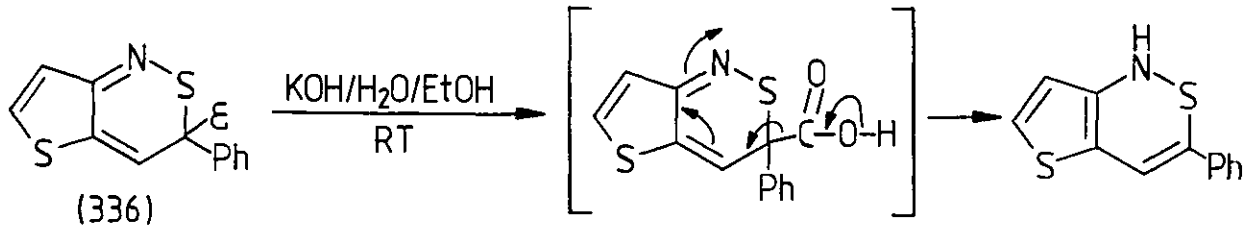
stretch at 1725 cm^{-1}; the u.v. spectrum of the two 4aH-thienothiazine (312) and (331) both have a characteristic broad and complex absorption between 250 and 350 nm; its ^{1}H n.m.r. spectrum again showed a non-aromatic thiophen β-proton at δ6.50, as a doublet with coupling constant of 5.8Hz; in the ^{13}C n.m.r. spectrum, a low intensity signal at δ59.3 indicated a sp^3 quarternary carbon which was assigned to the bridgehead C-4a carbon (see Figure 13 in the Appendix).

Hydrolysis of the 4aH-thienothiazine (312) in aqueous ethanolic potassium hydroxide at room temperature gave the corresponding acid (335) as a stable solid in 97% yield. The apparent stability of this acid (335) further supported the assigned structure and not the alternative isomer (336), because the acid (337) would be expected to decarboxylate very readily (SCHEME 94).

A small amount of the 4aH-thienothiazine (312) was also isolated during the preparation of the cyclic sulphimide (310) from the azide precursor (215); this presumably resulted from the thermal rearrangement of the cyclic sulphimide (310) via a [1,4]phenyl shift.



(335)



(336)

(337)

Scheme 94

Thermolysis of the cyclic sulphimide (310) in refluxing bromobenzene for 2.5 h, produced an inseparable mixture containing the 4a<u>H</u>-thienothiazine (312) and another product in 5:1 ratio (by n.m.r.). However, on prolonged thermolysis, the mixture was converted into this minor product in 80% yield. The same product was obtained in 82% yield from the thermolysis of the 4a<u>H</u>-thienothiazine (312), thus confirming that the product was derived from the thermal reaction of the 4a<u>H</u>-thienothiazine. In both cases, elemental sulphur was also isolated. The second experiment gave a 63% isolated yield of sulphur.

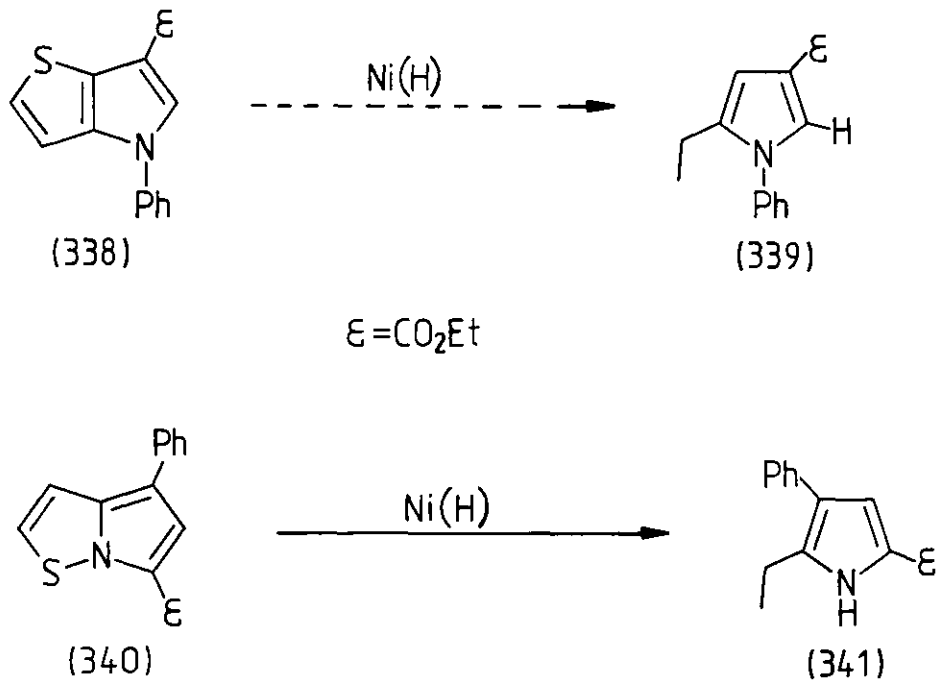
The organic product from the reaction was found to be unstable on silica gel as indicated by two-dimensional t.l.c. analysis. The product was therefore purified by vacuum distillation, and from the distillate sulphur was precipitated out by addition of cold dichloromethane. The residue from the dichloromethane solution was recrystallized from petrol to give the pure product as a pale yellow solid.

The isolation of roughly one equivalent of elemental sulphur has led to the suggestion that, one of the sulphur atoms in the 4a*H*-thienothiazine (312) might have been extruded during the course of reactions. This suggestion was borne out by the elemental analysis and mass spectrometry, and the product was indeed found to contain one sulphur atom less than the 4a*H*-thienothiazine (312). The i.r. spectrum featured an α,β-unsaturated ester carbonyl absorption at 1670 cm^{-1}. The u.v. spectrum bears no resemblance to that of the *N*-methylthienopyrrole (330), but it has the characteristic absorptions at 226, 261, 310 and 345 nm; these absorptions were more distinct and have lost the broad and complex character of its precursor.

In the ^{1}H n.m.r. spectrum, apart from the phenyl and the ethyl ester signals, there showed interestingly a single proton doublet at δ7.14 (*J* = 6Hz), a one proton fine doublet at δ7.48 (*J* = 1Hz) and a one proton double doublet at δ7.68 (*J* = 6 and 1Hz). The couplings of the double doublet were confirmed to be associated with the two doublets at δ7.14 and δ7.48, by decoupling experiments. From these chemical shift data and splitting patterns, the double doublet was considered to be a thiophen α-proton which coupled to both the thiophen β-proton (δ7.14) and also by a long range "zig-zag" coupling to an olefinic proton (δ7.48). This immediately ruled out the *N*-phenylthienopyrrole (334) as the structure, because in this case it would be the thiophen β-proton that experiences a long range coupling to the pyrrolic proton (H-3). The ^{13}C spectrum showed that the sp^{3} quarternary carbon and the C = N carbon were no longer present in the new product (see Figure 14 in the Appendix).

Taking into account all the above information, we arrived at two structures that could satisfy the observed data. One is the *N*-phenylthienopyrrole (338) with the ethyl ester group at the 3-position,

and the second is the pyrrolo[1,2-b]isothiazole (340). If the N-phenylthienopyrrole (338) were the correct structure, one would expect to see a M-Ph peak in the mass spectrum. However, the mass spectrum of the product did not show a M-Ph peak at 194 m.u., therefore this observation seems to rule against the structure (338). So, by the process of elimination, the remaining pyrrolo[1,2-b]isothiazole (340), was assigned as the thermal rearrangement product from the 4aH-thienothiazine (312). Further evidence in support of the structure (340) was obtained by desulphurization with Raney nickel. Successful desulphurization of the pyrrolo[1,2-b]isothiazole (340) would produce the 1H-pyrrole (341). On the other hand, desulphurization of the N-phenylthienopyrrole (338) would give the N-phenylpyrrole (339) (SCHEME 95).

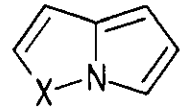


Scheme 95

When the desulphurization reaction was carried out with an excess of freshly prepared Raney nickel[172] in refluxing ethanol, the 1H-pyrrole (341) was indeed isolated in excellent yield. This confirmed the product as the pyrrolo[1,2-b]isothiazole (340).

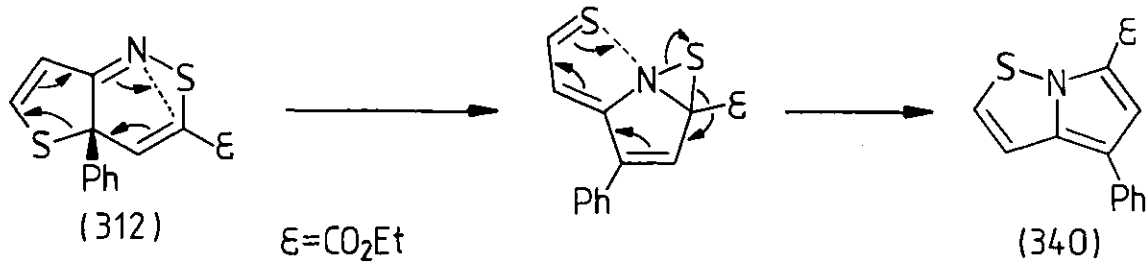
The structure of the pyrrole (341) was assigned on the basis of elemental analysis and spectroscopic data. The relative positions of the substituents were confirmed by n.m.r. n.O.e. difference experiments. The results are summarized in Figure 15 in the Appendix.

Although there are many examples of the hexahydropyrrolo[1,2-b]-isoxazole and a few examples of pyrrolo[1,2-b]isothiazole of different oxidation levels reported in the literature, these fully unsaturated systems (342) are not known.[173,174]



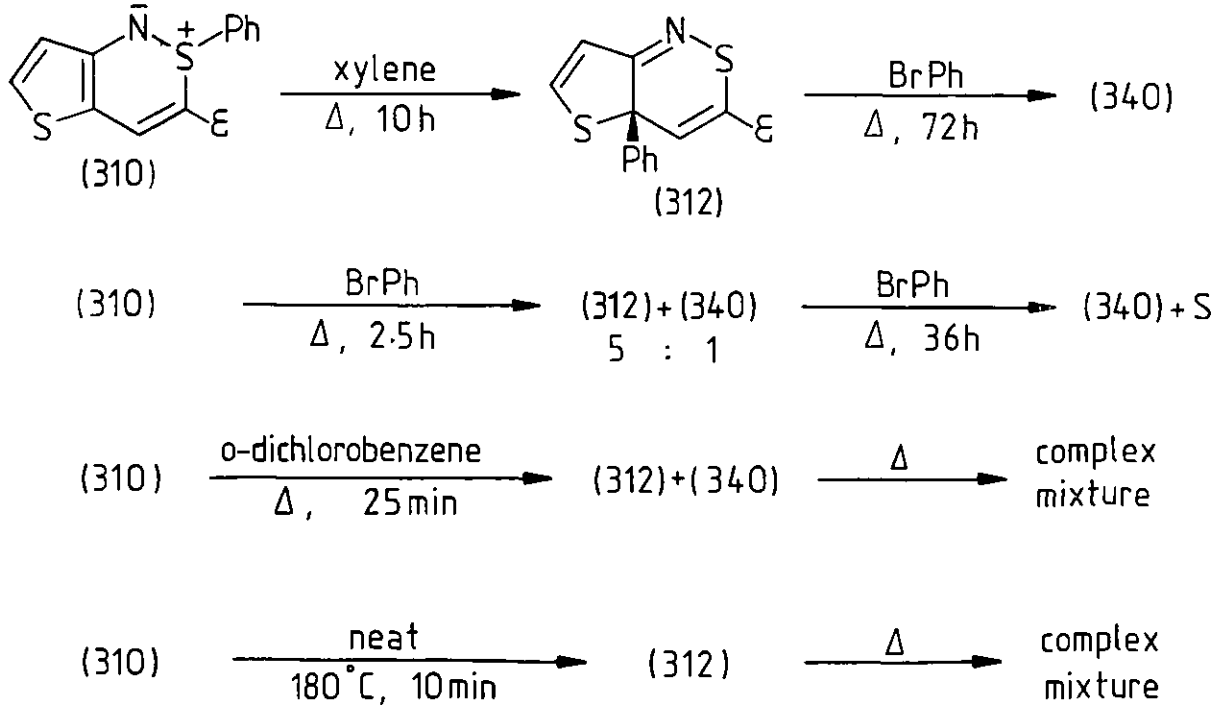
(342) X=O,S

The mechanism by which the pyrrolo[1,2-b]isothiazole (340) was formed remains uncertain. However, it is clear that at some stage along the reaction pathway, a sulphur atom has to be extruded from the molecule. The sulphur atom adjacent to the nitrogen in the 4aH-thienothiazine (312) seems more likely to be involved in the extrusion reaction. It is also clear that the C-S bond between the thiophen sulphur and the bridgehead carbon has to be broken in order to form a new N-S bond. A possible reaction mechanism is therefore proposed in SCHEME 96.



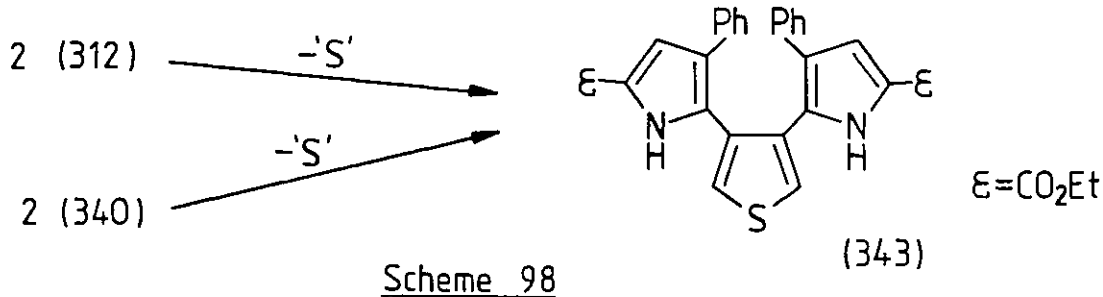
Scheme 96

Thermolysis of the cyclic sulphimide (310) in refluxing o-dichlorobenzene for 25 minutes produced a mixture of the 4aH-thienothiazine (312) and the pyrrolo[1,2-b]isothiazole (340) as indicated by t.l.c. analysis. However, on further heating, the reaction resulted in a complex mixture with much polymerization. Similar results were obtained when the cyclic sulphimide (310) was pyrolysed neat at 180°C. This series of thermal reactions of the cyclic sulphimide (310) is summarized in SCHEME 97.



Scheme 97

Thermolysis of the 4a<u>H</u>-thienothiazine (312) in refluxing <u>o</u>-dichlorobenzene for 15 hours furnished the thiophen (343) in 28% yield, a 0.85 mole equivalent of elemental sulphur was also isolated from the reaction (SCHEME 98). Under similar conditions, thermolysis of the pyrrolo [1,2-<u>b</u>] isothiazole (340) itself a thermal decomposition product of the 4a<u>H</u>-thienothiazine (312), also produced the same thiophen (343) as the only product in 49% yield. This latter reaction was carried out under a nitrogen balloon, and when the reaction was over, a strong odour of hydrogen sulphide was detected, and its presence was confirmed by moist lead acetate paper.

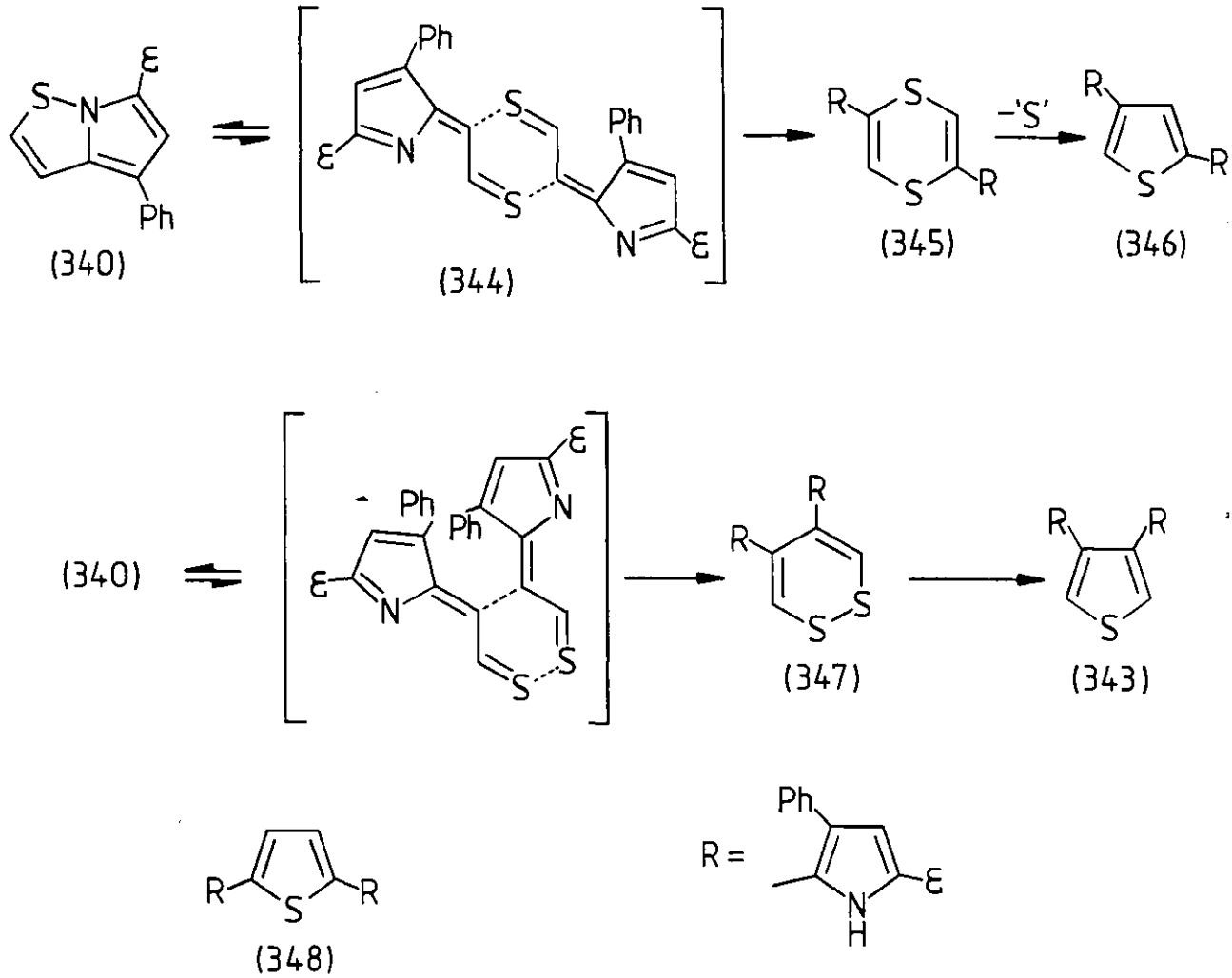


Scheme 98

The thiophen (343) structure was assigned on the basis of spectroscopic data and in conjunction with a mechanistic rationale. The mass spectrum showed a molecular ion of 510 mass units which corresponds to a molecular formula of twice the pyrrolo[1,2-<u>b</u>]-isothiazole (340) less one sulphur. The molecular formula was further confirmed by accurate mass measurement.

In terms of reaction mechanism, the pyrrolo [1,2-<u>b</u>] isothiazole (340) might be considered to be in thermal equilibrium with a species such as (344), presumably as a result of cleavage of the S-N bond which is the weakest bond in the molecule. This intermediate (344) could then dimerize either in a head to tail fashion to give the dithiin (345), or in a head to head fashion to give the cyclic disulphide (347). Extrusion of either one of the sulphur atoms from the dithiin (345) or the cyclic

disulphide (347) would produce the thiophens (346) and (343) respectively (SCHEME 99). A third possible structure is that of the thiophen (348), though its formation is not mechanistically obvious.

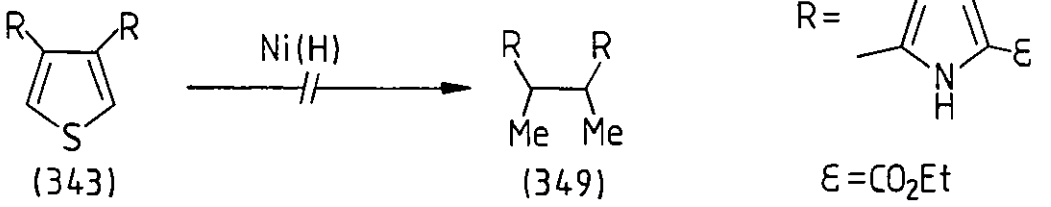


Scheme 99

The relative integration ratio and the simple resonances shown on the ^{1}H n.m.r. spectrum together with the mass spectral data, made it necessary for the compound to possess a symmetrical structure. This requirement immediately eliminates the thiophen structure (346). The remaining structure (343) was consistent with all the observed spectral data, and was therefore assigned as being the correct structure for the reaction product. The n.m.r. spectrum was assigned as follows: the three proton triplet at δ1.30 and the two proton quartet at δ4.23 were

assigned to the ethyl signals for the ester group; the doublet of a single proton with coupling constant of 2.6Hz was assigned to H-3 of the pyrrole ring, this proton was coupled to the N-H of the same pyrrole ring which resonated at δ11.27 as broad doublet, the coupling of these two protons was confirmed by decoupling experiments; the five proton multiplet at δ7.15 and the one proton singlet at δ7.58 were assigned to the phenyl protons and the thiophen α-proton respectively. The i.r. spectrum showed an N-H stretch at 3280 cm^{-1} and a carbonyl stretch at 1685 cm^{-1}.

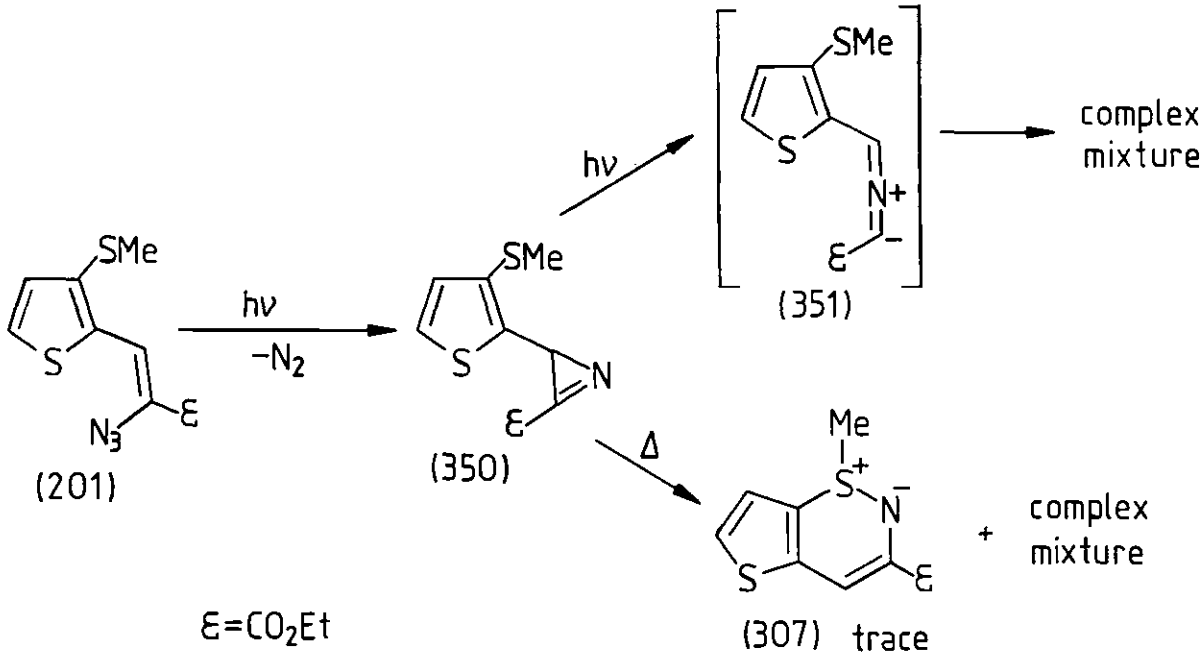
Attempts to desulphurize the thiophen (343) with Raney nickel failed to produce the expected product (349). In all cases, the starting material remained unchanged. Hence the structure of (343) was only tentatively assigned.



(343) (349)

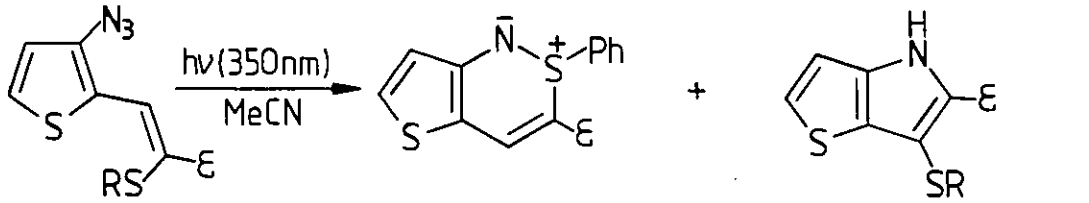
2.10 Photolysis of Cyclic Sulphimides and their Azide Precursors

Photolysis of the vinyl azide (201) in acetonitrile at 350 nm for 5 minutes afforded the expected 2H-azirine (350) as the major product. However, the cyclic sulphimide (307) was not detected and no other characterizable product was isolated (SCHEME 100). The azirine (350) was identified by its characteristic H-2 resonance at δ3.70 in the ^{1}H n.m.r. spectrum. No attempt to purify the azirine was made because of its unstable nature towards heat and silica gel. Further irradiation of the azirine gave a complex mixture which might have resulted from the polymerization of the nitrile ylide (351). Thermolysis of the azirine again produced a complex mixture and trace amount of the cyclic sulphimide (307) (SCHEME 100).



Scheme 100

Irradiation of the azide (216) in acetonitrile solution at 350 nm for 25 minutes until all the starting material has been consumed, gave a mixture of the cyclic sulphimide (308) and the thienopyrrole (309) in 40% and 53% yields respectively. Prolonged irradiation of the reaction mixture, after 2 h, gave the thienopyrrole (309) in 79% as the only product. Similar results were obtained from the irradiation of the azide (215) (Table 12).



(215) R=Ph (310) (311)

(216) R=Me (308) (309)

$\varepsilon = CO_2Et$

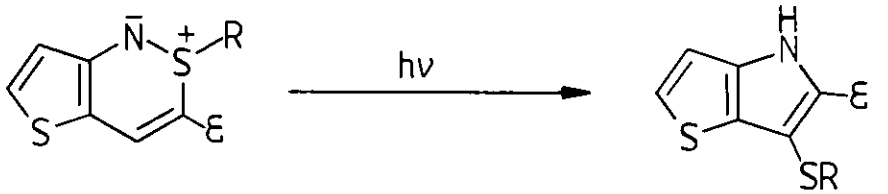
Azide	R	Time (min)	Cyclic Sulphimide	Yield/%	Thienopyrrole	Yield/%
(216)	Me	30*	(308)	40	(309)	53
(216)	Me	120	(308)	0	(309)	79
(215)	Ph	25*	(310)	56	(311)	41
(215)	Ph	180	(310)	0	(311)	80

* Irradiation time required for complete decomposition of the azide.

Table 12

From these results, it was apparent that the cyclic sulphimides were photochemically converted into the corresponding thienopyrroles. However, it was not clear whether the thienopyrroles were solely derived from the cyclic sulphimides or whether they were also formed directly from the azides.

In the search for further information on this question, the cyclic sulphimides (308) and (310) were irradiated under various conditions. In all cases, the corresponding thienopyrrole was isolated as the main reaction product. The conditions and results are summarized in Table 13.



(308) R=Me (309)
(310) R=Ph (311) E=CO_2Et

Sulphimide	Solvent	λ/nm	Time/ Min	Thieno-pyrrole	Yield/%	Recovered Sulphimide/%
(308)	MeCN	350	30	(309)	34	58
(308)	MeCN	300	300*	(309)	50	0
(308)	MeCN/DMSO 10:1	300	300*	(309)	58	0
(308)	DMSO	300	300*	(309)	63	0
(310)	MeCN	350	25	(311)	15	83
(310)	MeCN	350	120*	(311)	83†	0

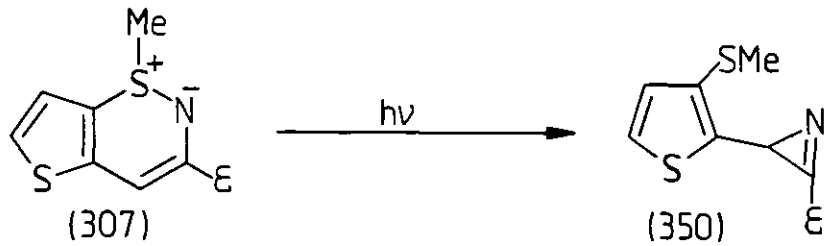
* Irradiation time required for complete decomposition of cyclic sulphimide.

† A minor product of unknown structure was also isolated.

Table 13

From the results shown in Tables 12 and 13, the photo-conversions of the cyclic sulphimides to the thienopyrroles were confirmed. Furthermore, it also became clear that when the irradiations were carried out under identical conditions, the formation of the thienopyrroles from the azides far exceeded that resulting from the cyclic sulphimides, and that the thienopyrroles were also formed directly from the azides without going through the sulphimides as intermediates. The rates of thienopyrrole formation from the azides were also faster than from the cyclic sulphimides.

Unlike the two cyclic sulphimides just described, photolysis of the sulphimide (307) in acetonitrile at 350 nm for 10 minutes afforded the azirine (350) as a major product (SCHEME 101).



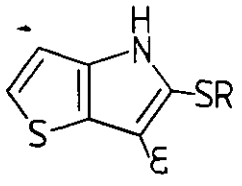
(307) (350)

Scheme 101

Evidence for the structures of the thienopyrroles (309) and (311) was obtained from their elemental analyses and spectroscopic data. The i.r. spectra showed a N-H stretch at 3275 cm^{-1} and an ester carbonyl at 1675 cm^{-1}. In the ^{1}H n.m.r. spectra, the N-H proton resonated at δ9.6 as broad singlets and were shown to exchange slowly with D_2O; the two doublets forming an AB quartet of the thiophen α and β-protons resonated at around 7.2 and 6.9 ppm respectively; the S-methyl protons of (309) appeared as a singlet at δ = 2.68 and the S-phenyl of (311) as multiplet at δ = 7.30-7.55. Broad band decoupled ^{13}C n.m.r. spectra were partially assigned and are shown in Figures 16 and 17 in the Appendix. The mass spectra showed the corresponding molecular ions for the two

thienopyrroles; these two spectra showed a fragmentation of M-46 (EtOH) followed by a further loss of 28 mass unit (CO); both of these fragmentations were accompanied by metastable ions. The thienopyrrole (309) showed a further loss of 15 mass units (CH_3) whereas (311) indicated a further loss of 77 mass units (C_6H_5).

However, the exact position of the ethyl ester group and the S-R substituent could not be determined from the above information. The thienopyrroles (352a,b) were also considered as the likely alternative structures to (309) and (311). Attempts to resolve the structural differences between (309) and (352a) by n.m.r. n.O.e. experiments were



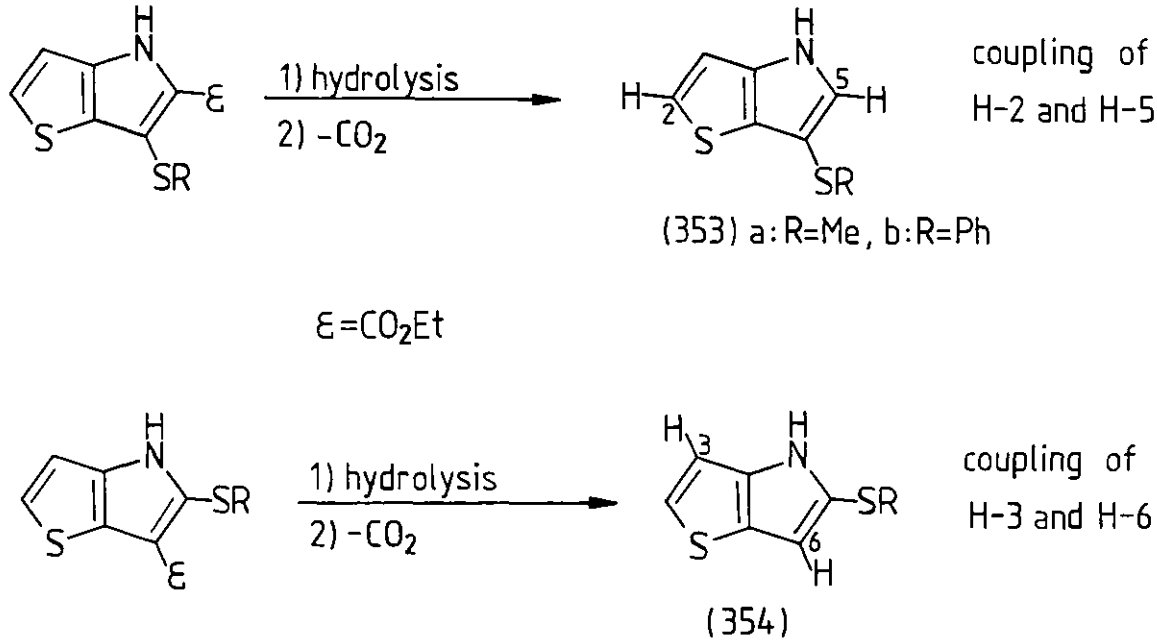
E=CO_2Et

(352) a: R=Me, b: R=Ph

inconclusive. The results are summarized in Figure 18 in the Appendix. However, these data seem to be more in favour of structure (309) in that presaturation of the N-H proton produced a small enhancement from the methylene protons of the ethyl ester group and a large increase (3.88%) of the H-3 signal; although the enhancement of the methylene protons was not large enough to confirm the ester group at the 5-position, nevertheless the absence of an enhancement from the S-methyl protons by presaturating the N-H has ruled against the structure (352a).

In order to obtain unambiguous structural evidence for the two thienopyrroles, it was decided to remove their ester substituents by hydrolysis and decarboxylation, thus converting them to the corresponding mono-substituted derivatives. By observing the ^1H n.m.r. spectra of the two resulting mono-substituted thienopyrroles, one could determine the

original position of the ester group by virtue of a H-2 and H-5 coupling or a H-3 and H-6 coupling; the former coupling would indicate the 5-position was originally occupied by the ester substituent and vice-versa (SCHEME 102). N.m.r. of the two mono-substituted



Scheme 102

thienopyrroles both showed a coupling between H-2 and H-5 of 1.3 Hz, thus confirming the structures (309) and (311). The above couplings were further supported by decoupling experiments.

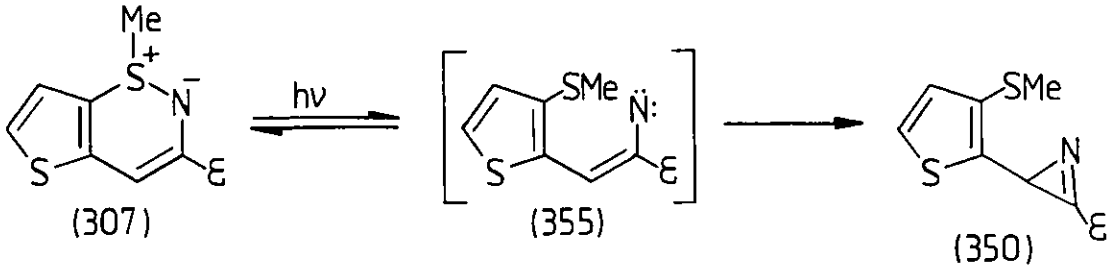
The n.m.r. n.O.e. difference experiments of the two mono-substituted thienopyrroles (353a,b) together with that of the thienopyrrole (332) of known structure, has provided further proof for their assigned structures (see Figures 19-21 in the Appendix). By comparing the presaturated N-H experiment of each of the above three compounds, and by using the H-3 enhancement as an internal reference, the H-6 enhancement of the known compound (332) was 3.2 times smaller than that of its H-3 enhancement, whereas the pyrrolic proton enhancement of the thienopyrroles (309) and (311) were 4.3 times and 3.6 times greater than

that of their respective H-3 enhancement. This observation leads to the conclusion that the pyrrole C-H proton in the two thienopyrroles is closer to the N-H proton than H-3 is to the N-H proton, and hence is in agreement with the structures (309) and (311).

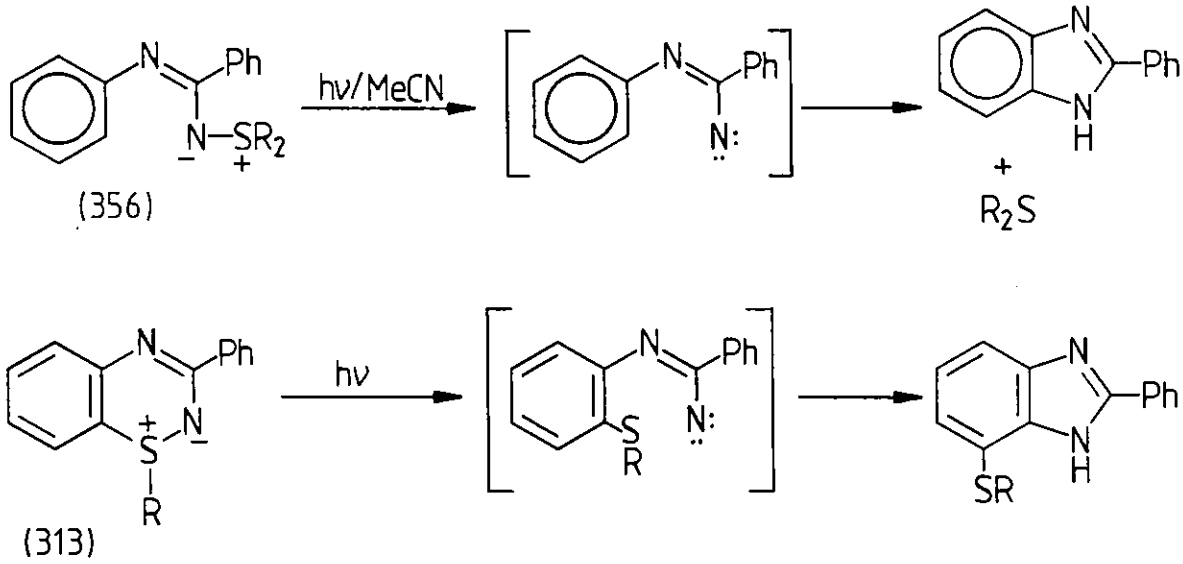
Formation of the azirine (350) from photolysis of the cyclic sulphimide (307) was envisaged to proceed *via* the vinyl nitrene intermediate (355) (SCHEME 103). This photochemical reaction is analogous to that of *N*-arylbenzimidoyl-sulphimides (356)[175,176] and $1\lambda^4$,2,4-benzothiadiazine (313)[177] in that they all involve S-N bond cleavage to give a nitrene (SCHEME 104). Similarly, photolysis of the sulphimides (308) and (310) might involve the nitrene precursor (357) which then cyclized to the bicyclic intermediate (358); a [1,5] shift of the ester or the SR substituent to carbon could lead to the formation of a thienopyrrole (SCHEME 105). As the thienopyrroles (309) and (311) were confirmed to be the products, the migratory aptitude of *S*-methyl and *S*-phenyl substituents must be greater than that of the ester group. Little is known about the sigmatropic migrations of SR groups, though formal [1,7]SR shifts have been reported to proceed rapidly.[178] It is interesting to see that they migrate, at least in our structures, faster than the ester group which is known to migrate rather rapidly.[179]

Attempts to obtain evidence for the nitrene intermediate were unsuccessful. Irradiation of the cyclic sulphimide (308) in excess of DMSO or in DMSO as solvent failed to produce the sulphoximide (359) as the intercepted nitrene product. Instead, a higher yield of the thienopyrrole was observed (Table 13) and this can probably be attributed to a solvent effect.

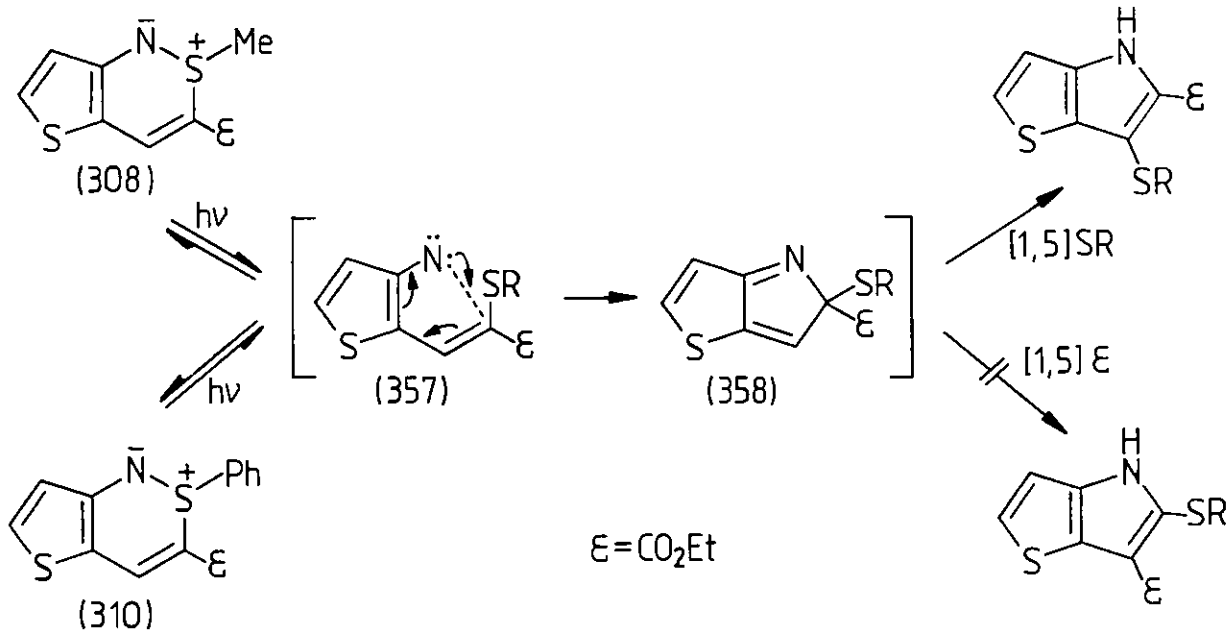
Nitrenes have been known to react with DMSO to form sulphoximides,[180] an example of which is shown in SCHEME 106.[181] In this example, the



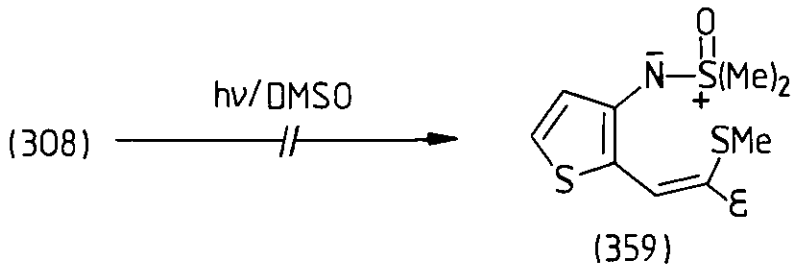
Scheme 103



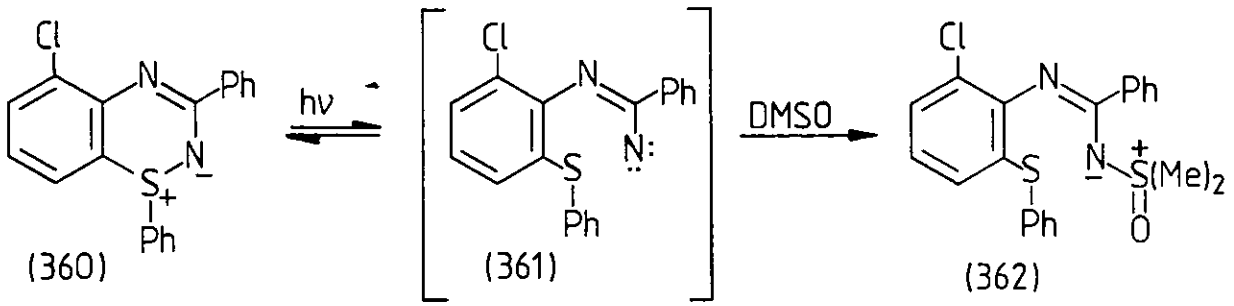
Scheme 104



Scheme 105

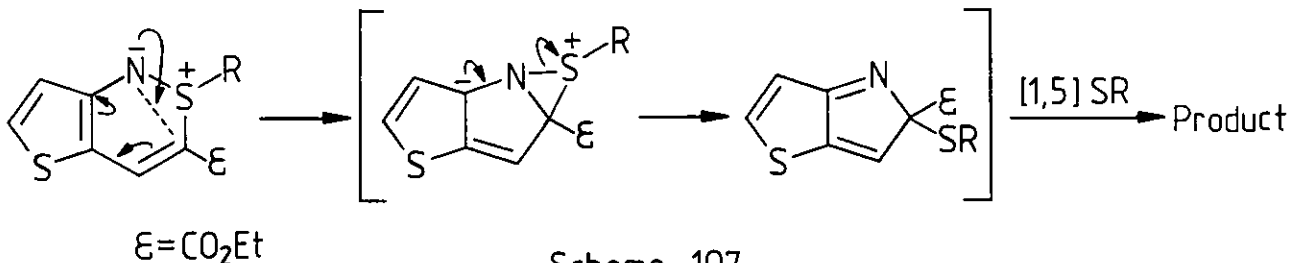


sulphimide (360) was postulated to be in photo-equilibrium with the imidoyl nitrene (361) and attack of the nitrene by the nucleophilic sulphur of DMSO gave the sulphoximide (362). In the case of sulphimide



Scheme 106

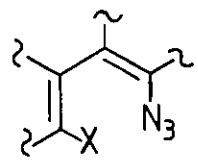
(308), nucleophilic attack of the nitrene (357) by DMSO might be a much slower and less favourable process than the nitrene cyclization reaction, and hence no sulphoximide was isolated. An alternative explanation would be that the reaction does not proceed <u>via</u> a nitrene intermediate and that a different mechanism is involved. A possible reaction pathway is illustrated in SCHEME 107, but it seems less reasonable than the nitrene mechanism.



Scheme 107

CONCLUSION

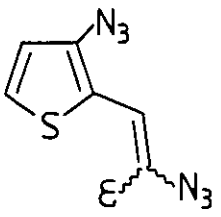
We have made a number of studies into the interaction of substituents in vinyl azide decomposition. In all cases, the substitiuents are conjugated 1,4 to the azide function:



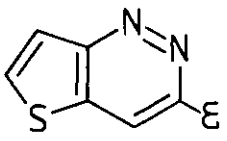
In the chlorine substituted system, little or no interaction was observed. Chlorine simply acts as a blocking group and increases the energy barrier for the cyclization of the nitrene to form five-membered ring heterocycles. As a result of this, the formal C-H insertion reaction to give pyridine type product was also observed along with other five-membered ring products.

When X = N_3, the pyridazine formation did not occur as readily as might have been expected; in the case of the thiophen bis-azide (199) only 17% yield of the thienopyridazine (251) was obtained. This low yield became less surprising when it was discovered in the literature that intramolecular coupling of two azido functions with the loss of two nitrogen molecules is very rare. However, apart from pyridazine formation, a novel extrusion of acetylene from the aromatic thiophen ring was observed when the thiophen bis-azide (199) was heated. In order to rationalize this fragmentation, we postulate a sulphur-nitrogen ylide intermediate (274) in which the thiophen ring is very much weakened decomposition

of the second azide group led to the extrusion of acetylene and the formation of the isothiazole (252).

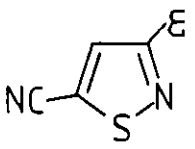


(199)

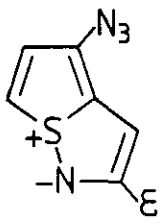


(251)

$\mathcal{E}=CO_2Et$

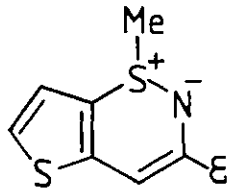


(252)

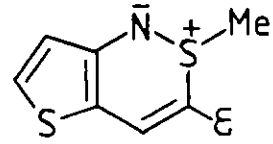


(274)

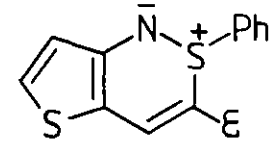
As a result of the above observation, we set out to prove that such sulphur-nitrene interactions do occur,and thus the decomposition of the vinyl azide system where X = SR was investigated. Our findings have shown that this S-N interaction is indeed correct and have led us to discover a convenient synthesis of derivatives of the relatively unknown heterocyclic system azathiabenzene, which is a cyclic sulphimide. The new cyclic sulphimides (307), (308) and (310) were prepared by this method in excellent yield.



(307)



(308)



(310)

$E = CO_2Et$

The sulphimides themselves also undergo thermal and photochemical rearrangements. Under thermolytic conditions the R substituent on the 4-valent sulphur undergoes a [1,4] sigmatropic shift, whereas photolytically the S-N bond cleaves to generate the corresponding nitrene which then cyclizes to give thienopyrrole.

3. EXPERIMENTAL

Spectra

Infrared spectra (i.r.) were recorded in the range of 600-4000 cm^{-1} using Perkin Elmer 257 and 298 spectrophotometers and calibrated against polystyrene. Spectra of solids were taken as Nujol mulls or potassium bromide discs, and liquids as thin films between sodium chloride plates unless otherwise stated. Abbreviations used are strong (s), medium (m), weak (w), broad (br) and shoulder (sh).

Ultra-violet and visible spectra (u.v.) were recorded in the range 200-700 nm using a Pye Unicam SP 800 recording spectrophotometer and calibrated against holmium glass. Solvents used are indicated in the experimental data. Abbreviation used is shoulder (sh).

Proton nuclear magnetic resonance spectra (n.m.r.) were recorded using Varian T60 (operating at 60 MHz), Perkin Elmer R32 (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). All spectra given in the text are from the Bruker 250 MHz spectrometer unless otherwise stated. Carbon-13 nuclear magnetic resonance spectra (^{13}C n.m.r.) were recorded using a Bruker WM250 (operating at 62.9 MHz) instrument.

Low and high resolution mass spectra were recorded on A.E.I. MS 12 and VG Micromass 7070 B instruments. Spectra were recorded at 70 or 12 eV using a direct insertion probe.

Melting Points

Melting points were carried out on a Kofler Hot Stage apparatus and are uncorrected.

Solvents

Petrol refers to petroleum ether, b.p. 40-60°C unless otherwise stated, and was distilled before use. Dichloromethane was distilled prior to use. Acetonitrile, dimethylformamide and dimethyl sulphoxide were dried by refluxing over calcium hydride, followed by distillation directly into the reaction vessel. Tetrahydrofuran and dioxan were dried by refluxing over sodium wire followed by distillation directly into the reaction vessel under dry nitrogen. Bromobenzene was distilled prior to use. Hydrocarbon solvents were dried by standing over sodium wire. Acetone, chloroform, ethyl acetate, ethanol and methanol were used as supplied commercially unless otherwise stated.

Chromatography

Column chromatography was carried out on silica gel H Art. 7736 (Merck), under pump pressure. Thin layer chromatography (t.l.c.) was used extensively as a qualitative analytical technique for following the progress of reactions and assessing the purity of compounds; silica gel GF_{254} (Merck) or alumina GF_{254} (Merck) or aluminium sheets pre-coated with Kieselgel 60 F_{254} Art. 5554 (Merck) were used.

Preparative layer chromatography was carried out on 20 X 20 or 20 X 40 cm glass plates coated with a 2 mm layer of silica gel GF_{254} (Merck). All plates were observed under ultra-violet light (254 nm).

Photolysis

Photochemical reactions were carried out using a Rayonet photochemical reactor with lamps of 253.7, 300 or 350 nm wavelength. The solvent used was dry, degassed acetonitrile unless otherwise stated.

3.1 Preparation of Synthetic Intermediates

Ethyl azidoacetate (34)

Prepared according to the literature method[110a] from ethyl bromoacetate and sodium azide, b.p. 66-68°C/12 mmHg (lit.,[110b] 63°C/12 mmHg).

α-Azidoacetophenone (35)

Prepared according to the literature method from α-bromoacetophenone and sodium azide, m.p. 17-19°C (lit.,[111] 17°C).

Ethyl phenylthioacetate (183)

Prepared by the literature method from ethyl bromoacetate and sodium thiophenoxide b.p. 144-145°C/14 mmHg (lit.,[112] 130-135°C/10 mmHg).

Ethyl methylthioacetate (184)

A mixture of thioacetic acid (30 g, 0.326 mol) and concentrated sulphuric acid (10 cm^3) in ethanol (46 g, 1 mol) was heated to reflux for 24 h. After cooling to room temperature the mixture was diluted with ether (100 cm^3), washed with saturated sodium chloride solution (2 X 50 cm^3), followed by saturated sodium bicarbonate solution (2 X 50 cm^3) and water (2 X 50 cm^3). The organic layer was dried over magnesium sulphate and the solvent carefully removed in vacuo (below 40°C) to give a crude oil. Vacuum distillation of the crude oil gave ethyl thioacetate (26.6 g, 68%), b.p. 64-65°C/18 mmHg (lit.,[182] 43°C/8 mmHg).

A solution of ethyl thioacetate (6 g, 0.05 mol) and sodium ethoxide (1.21 g, 0.053 g-atom of sodium) in ethanol (20 cm^3) was refluxed for 0.5 h. After cooling to about 35°C, methyl iodide (7.81 g, 0.055 mol)

was added to the mixture and was left stirring at room temperature for 16 h. The mixture was then poured into water, extracted with diethyl ether, dried over sodium sulphate and the solvent removed *in vacuo* to give a yellow liquid. Vacuum distillation of the yellow liquid gave ethyl methylthioacetate (184) (5 g, 75%), b.p. 69°C/17 mmHg (lit.,[183] 66°C/12 mmHg).

3.2 Preparation of Aldehydes

3-Chloro-2-methylbut-2-enals (185)

The aldehyde was prepared as a mixture of *cis* and *trans* isomers (*cis* : *trans* 3 : 7), by the method of Lloyd, *et al.*,[113] from butan-2-one, *N*,*N*-dimethylformamide and phosphoryl chloride, b.p. 56-58°C/20 mmHg (lit.,[113] 57-59°C/21 mmHg).

2-Chlorocyclohex-1-enecarbaldehyde (186)

Prepared according to the method of Lloyd, *et al.*,[113] from cyclohexanone, b.p. 101-102°C/16 mmHg (lit.,[113] 96°C/14 mmHg).

Cyclopent-1-enecarbaldehyde (187)

Prepared by the literature method from cyclohexene in three steps b.p. 56-57°C/12 mmHg (lit.,[114] 50°C/10 mmHg).

Ethyl 3-methylbenzofuran-2-carboxylate (188)

Prepared according to the literature procedure ,[115] m.p. 50-52°C (lit.,[115] 49-51°C).

3-Methylbenzofuran (190)

Hydrolysis and decarboxylation of ethyl 3-methylbenzofuran-2-carboxylate (188) by the literature method,[115] gave 3-methylbenzofuran (190), b.p. 195-197°C (lit.,[115] b.p. 195-197°C).

3-Methylbenzofuran-2-carbaldehyde (191)

Prepared by the literature method *via* the Vilsmeier formylation of 3-methylbenzofuran, m.p. 65°C (methanol) (lit.,[116] 64°C).

Attempt to reduce ethyl 3-methylbenzofuran-2-carboxylate (118) to the aldehyde (191) with diisobutylaluminium hydride, using the literature procedure[117-119] was unsuccessful.

3-Bromothiophen-2-carbaldehyde (192)

Treatment of 2,3,5-tribromothiophen with zinc dust in acetic acid by the literature method gave 3-bromothiophen, b.p. 159-160°C (lit.,[120] 159-160°C). Bromination of 3-bromothiophen with bromine in dry benzene gave 2,3-dibromothiophen, b.p. 95-98°C/18 mmHg (lit.,[121] 89-91°C/13 mmHg). 2,3-Dibromothiophen was treated with n-butyllithium at -78°C followed by *N*,*N*-dimethylformamide, to give 3-bromothiophen-2-carbaldehyde (192), b.p. 120-122°C/15 mmHg (lit.,[122] 113-115°C/10 mmHg).

3-Azidothiophen-2-carbaldehyde (193)

A mixture of 3-bromothiophen-2-carbaldehyde (192) (7.17 g, 37.5 mmol) and sodium azide (9.75 g, 150 mmol) in dry hexamethylphosphoramide (80 cm^3) was stirred at 30-35°C, under nitrogen, for two days. The mixture was poured into ice/water (300 cm^3) and the yellow/brown precipitate was filtered and washed with ice/water. The solid was taken up into ether, washed three times with saturated sodium chloride solution, dried over magnesium sulphate and the solvent removed *in vacuo*. The original aqueous mixture was extracted with diethyl ether

(3 X 150 cm^3), washed with saturated sodium chloride solution (3 X 100 cm^3), dried over magnesium sulphate and the solvent removed in vacuo. The combined crude product was purified by column chromatography (silica H, 100 g; gradient elution from 30% dichloromethane in petrol) to give 3-azidothiophen-2-carbaldehyde (193) (4.32 g, 75%), m.p. 57-58°C (lit.,[121] 56-57°C).

Alternatively, the azido aldehyde (193) can also be prepared from the bromoaldehyde (192) using lithium azide in DMF at 60°C for 24 h (63%), or the literature method[121] of sodium azide in dimethyl sulphoxide at 65°C for 24 h (48%).

3-Bromofuran-2-carbaldehyde (194)

Furan-2-carboxylic acid was brominated with bromine, according to the method of Gronowitz, et al.,[184] to give 4,5-dibromofuran-2-carboxylic acid, m.p. 167-170°C (lit.,[184] 168-170°C). Decarboxylation of the resultant acid in a mixture of quinoline and copper bronze at 190°C afforded 2,3-dibromofuran in 53% yield, b.p. 80-85°C/75 mmHg (lit.,[184] 79%, 75-80°C/75 mmHg). Treatment of 2,3-dibromofuran with n-butyllithium at -78°C followed by N,N-dimethylformamide gave, 3-bromofuran-2-carbaldehyde (194), b.p. 94-96°C/12 mmHg (lit.,[184] 97-98°C/13 mmHg).

3-Azidofuran-2-carbaldehyde (195)

Prepared in 50% yield by the method of Gronowitz, et al.,[184] from 3-bromofuran-2-carbaldehyde (194) and sodium azide in dimethyl sulphoxide, m.p. 114-115°C (lit.,[184] 115°C). A much lower yield of (195) (16%) was obtained when hexamethylphosphoramide was used as the solvent instead of dimethyl sulphoxide under the same conditions.

3-Methylthiothiophen-2-carbaldehyde (196)

To a stir solution of 3-bromothiophen-2-carbaldehyde (3.2 g, 16.6 mmol) in dry dimethyl sulphoxide (110 cm^3) was added a 1 : 1 mixture of lithium bromide and lithium thiomethoxide[185] (10 g, 70 mmol) with some external cooling. The mixture was allowed to stir at room temperature under nitrogen for 16 h. The mixture was poured into ice/water (600 g), extracted with diethyl ether (5 X 100 cm^3) and the combined extracts were washed with saturated sodium chloride solution (2 X 100 cm^3). After drying over magnesium sulphate, the solvent was removed in vacuo, to give a crude yellow oil. Purification of the crude oil by column chromatography (silica H, 25 g; gradient elution from 35% dichloromethane in petrol) gave the product (196) as a yellow solid (1.51 g, 58%), m.p. 31-33°C (lit.,[186] 32-33.5°C); ν_{max} (melt) 1660 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 2.60 (3H, s), 7.15 (1H, d, J 5.0 Hz), 7.75 (1H, dd, J 5.0 and 0.8 Hz), and 10.05 (1H, d, J 0.8 Hz); m/e 158 (M^+), 143, 124 and 45 (base).

3.3 Preparation of Vinyl Azides

a 1-Substituted Ethyl 2-azidopropenoate

General Procedure:

An ethanolic sodium ethoxide solution (approximately 1.6 M) prepared from sodium (4 eq.) and ethanol (AR grade) was cooled to -20°C (CCl_4/CO_2) under dry nitrogen. A mixture of ethyl azidoacetate (4 eq.) and the aldehyde (1 eq.) (if necessary, dissolved in a minimum amount of ethanol or other dry solvent) was added dropwise, with stirring. The addition was carried out at such a rate that effective stirring could be maintained (prevent excessive foaming) and the temperature kept

below -10°C. After the addition had been completed (varied between 0.5 to 1 h depending on the scale of the preparation), the mixture was stirred at -15°C and the reaction monitored by t.l.c. When all the aldehyde had been consumed as confirmed by t.l.c., the reaction mixture was allowed to warm up to temperature between -5 and 5°C in order that the excess ethyl azidoacetate could be decomposed in a controlled manner. When all the excess ethyl azidoacetate had decomposed (evolution of nitrogen ceased), the mixture was poured into ice/water (approximately ten times the volume of the reaction mixture) and extracted with diethyl ether or dichloromethane. The organic extracts then washed with saturated ammonium chloride solution (equal volume) followed by water (equal volume), dried over magnesium sulphate and the solvent removed in vacuo below 45°C. The crude product was then purified by column chromatography and the vinyl azide isolated was stored at 0°C in the dark.

The following vinyl azides were prepared by the above method.

Ethyl 2-azido-5-chloro-4-methylhexa-2,4-dieneonate (197)

Prepared from 3-chloro-2-methylbut-2-enal (185) and purified by column chromatography (gradient elution from 20% dichloromethane in petrol) as a yellow oil (55%), ν_{max} (neat) 2130 (s) and 1720 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.37 (3H, t, J 7.0 Hz) 2.10 (3H, m), 2.23 (3H, m), 4.38 (2H, q, J 7.0 Hz), and 6.82 (1H, s); m/e 231/229 (M^+), 203/201, 186/184, 167, 158/156, 131/129 (base), 130/128, 104/102, and 103/101.

Ethyl 2-azido-3-(2-chlorocyclohex-1-enyl)propenoate (198)

Prepared from 2-chlorocyclohex-1-enecarbaldehyde and purified by column chromatography (gradient elution from 30% dichloromethane in petrol) as a pale yellow solid (56%), m.p. 44-45°C (Found: C,

51.69; H, 5.60; N, 16.10. $C_{11}H_{14}ClN_3O_2$ requires C, 51.67; H, 5.52; N, 16.43%); ν_{max} (melt) 2120 (s) and 1720 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.35 (3H, t, J 7.0 Hz), 1.70 (4H, m), 2.54 (4H, m), 4.33 (2H, q, J 7.0 Hz), and 7.09 (1H, s); m/e 257/255 (M^+), 212/210, 185/183, 157/155, 129/127, 120/118, 93/91 (base), and 79/77, m* (183→155) 131.3, (155→120) 92.9, and (118→91) 70.2.

Ethyl 2-azido-3-(3-azidothien-2-yl)propenoate (199)

Prepared from 3-azidothiophen-2-carbaldehyde (193) and purified by column chromatography (20% dichloromethane in petrol) as pale yellow needles (63%), m.p. 67-68°C (from petrol) (Found: C, 41.14; H, 3.00; N, 31.51. $C_9H_8N_6O_2S$ requires C, 40.90; H, 3.05; N, 31.80%); ν_{max} (Nujol) 2130 (s), 2105 (s), 1705 (s), 1605 (w), and 1515 (m) cm^{-1}; λ_{max} (EtOH) 205 (log ε 4.00), 236 (3.97), 250 sh (3.89), and 349 (4.31) nm; δ($CDCl_3$) 1.38 (3H, t, J 7.0 Hz), 4.39 (2H, q, J 7.0 Hz), 6.98 (1H, d, J 5.2 Hz), 7.17 (1H, d, J 0.8 Hz), and 7.50 (1H, dd, J 7.0 and 0.8 Hz); m/e 264 (M^+), 236, 164, 136 (base) and 109, m* (136→109) 87.4.

Ethyl 2-azido-3-(3-azidofuran-2-yl)propenoate (200)

Prepared from 3-azidofuran-2-carbaldehyde (195) and purified by column chromatography (gradient elution from 30% dichloromethane in petrol) as a yellow solid (25%), m.p. 85-86°C (from ethanol/water) (Found: C, 43.83; H, 3.25; N, 33.80. $C_9H_8N_6O_3$ requires C, 43.55; H, 3.25; N, 33.86%); ν_{max} (Nujol) 2130 (s), 2102 (s), 1710 (s), 1625 (m), and 1562 (m) cm^{-1}; λ_{max} (EtOH) 203 (log ε 3.79), 225 (3.83), 244 sh (3.75), and 346 (4.31) nm; δ($CDCl_3$) 1.38 (3H, t, J 7.1 Hz), 4.35 (2H, q, J 7.1 Hz), 6.47 (1H, d, J 2.1 Hz), 6.66 (1H, s), and 7.52 (1H, d, J 2.1 Hz); m/e 248 (M^+), 220, 203, 148, 147, 120 (base)

119, 92 and 91.

Ethyl 2-azido-3-(3-methylthiothien-2-yl) propenoate (201)

Prepared from 3-methylthiothiophen-2-carbaldehyde (196) and purified by column chromatography (gradient elution from 20% dichloromethane in petrol) as pale yellow needles (52%), m.p. 61-64°C (from petrol) (Found: C, 44.55; H, 4.09; N, 15.41. $C_{10}H_{11}N_3O_2S_2$ requires C, 44.59; H, 4.12; N, 15.60%) ν_{max} (Nujol) 2140 sh (s), 2120 (s), 1710 (s), and 1610 (m) cm^{-1}; λ_{max} (EtOH) 204 (log ε 3.87), 230 (3.73), and 355 (3.97) nm; δ($CDCl_3$) 1.40 (3H, t, J 7.2 Hz), 2.47 (3H, s), 4.38 (2H, q, J 7.2 Hz), 7.07 (1H, d, J 5.3 Hz), 7.46 (1H, d, J 0.7 Hz), and 7.48 (1H, dd, J 5.3 and 0.7 Hz); m/e 269 (M^+), 243, 241, 226 (base), 198, 168, 154, 141, 128 , 109, and 97, m* (269→226) 189.9, (226→198) 173.5, and (168→141) 118.3.

The following aldehydes failed to produce the desired vinyl azides under the above conditions.

Cyclopentene-1-carbaldehyde (187)

The reaction was also carried out at -40 and 0°C. In all three cases, complex polymeric mixtures were obtained.

Phenylacetylaldehyde

The reaction resulted in a polymeric mixture with no identifiable product.

Alternative Procedure

Ethyl 2-azido-5-chloro-4-methylhexa-2,4-dieneonate (197) was prepared using the method of Hemetsberger, et al.[26] as outlined below.

To a solution of sodium ethoxide (1.84 g, 0.08 g-atom of sodium)

in ethanol (AR grade, 55 cm^3) at 5 to 10°C, was added a mixture of ethyl azidoacetate (10.32 g, 0.08 mol) and 3-chloro-2-methylbut-2-enal (185) (2.37 g, 0.02 mol) over a period of 30 min and with rapid stirring. The solution was maintained at this temperature, with stirring, until the evolution of nitrogen diminished (1 h). Half the solvent was then removed under reduced pressure at temperature below 40°C. The residual mixture was then treated with solid ammonium chloride and diluted with ice/water (500 cm^3). The mixture was extracted with diethyl ether (4 X 200 cm^3). The combined organic extracts were washed with water (400 cm^3), separated, dried over sodium sulphate and the solvent removed *in vacuo*. The crude product was purified by column chromatography (silica H, 40 g; gradient elution from 20% dichloromethane in petrol) to give ethyl 2-azido-5-chloro-4-methylhexa-2,4-dieneonate (197) (0.58 g, 12.6%).

b *3-Substituted 2-azido-1-phenylprop-2-en-1-one.*

General Procedure:

The vinyl azides were prepared according to the method of Hemetsberger, *et al.*,[36] as outlined below.

α-Azidoacetophenone (0.02 mol) was added to a stirred mixture of piperidine acetate (0.01 mol) and the appropriate aldehyde (0.025 mol) in ethanol (AR grade, 20-40 cm^3) at room temperature. The reaction mixture was kept in the dark for two days. The mixture was diluted with water (100-150 cm^3), extracted with diethyl ether, dried over sodium sulphate and the solvent removed *in vacuo* to give the crude product. Purification of the crude product by column chromatography yielded the required vinyl azide.

The following vinyl azides were prepared by the above method.

2-Azido-3-(3-methylbenzofuran-2-yl)—1-phenylprop-2-en-1-one (210)

Prepared from 3-methylbenzofuran-2-carbaldehyde (191) as a yellow solid (89%), m.p. 112-114°C; ν_{max} (CCl_4) 2110 (s), 1660 (s), and 1610 (s) cm^{-1}; λ_{max} (EtOH) 209 (log ε 4.28), 254 (4.16), 278 sh (3.98), 285 sh (3.94), and 381 (3.76) nm; δ(90 MHz, $CDCl_3$) 2.23 (3H, S), 6.58 (1H, S), and 7.30-7.95 (9H, m).

2-Azido-5-chloro-4-methyl-1-phenylhexa-2,4-diene-1-one (211)

Prepared from 3-chloro-2-methylbut-2-enals (185) as a yellow oil (36%), ν_{max} (neat) 2120 (s) and 1660 (s) cm^{-1}; δ(90 MHz, $CDCl_3$), 2.00-2.28 (6H, m) 6.28 (0.63H, S), 6.69 (0.37H, S), 7.33-7.62 (3H, m), and 7.63-7.85 (2H, m).

2-Azido-3-(2,6-dichlorophenyl)-1-phenylprop-2-en-1-one (212)

Prepared from 2,6-dichlorobenzaldehyde as a solid (60%), m.p. 101-103°C; ν_{max} (CCl_4) 2120 (s) and 1670 (s) cm^{-1}; δ(60 MHz, $CDCl_3$) 6.52 (1H, S), 7.50 (6H, m), and 8.10 (2H, m).

3.4 Condensation of 3-Azidothiophen-2-carbaldehyde with various 'Active Methylene' Compounds.

a With diethyl malonate

Following the general procedure as described in section (3.2 b), diethyl malonate was condensed with 3-azidothiophen-2-carbaldehyde to give diethyl[(3-azido-2-thienyl)methylene]propanedioate (213) as a yellow solid (96%), m.p. 39-41°C (from dichloromethane/petrol) (Found:

C, 49.15; H, 4.47; N, 14.15. $C_{12}H_{13}N_3O_4S$ requires C, 48.80; H, 4.44; N, 14.23%); ν_{max} (melt) 2115 (s), 2105 (s), 1725 (s), and 1618 (s) cm^{-1}; λ_{max} (EtOH) 206 (log ε 4.01), 244 (3.82), and 338 (4.32) nm; δ(90 MHz, $CDCl_3$) 1.36 (6H, m, 2 X t), 4.36 (4H, 2 X q), 7.01 (1H, d, J 5.0 Hz), 7.56 (1H, dd, J 5.0 and 0.8 Hz), and 7.90 (1H, d, J 0.8 Hz); m/e 295 (M^+), 268, 267, 250, 239, 222, 210, 193 (base), 139, 137, and 109, m* (295→268) 243.5, (267→239) 214.0, (239→193) 155.9, (193→165) 141.1, and (193→137) 97.2.

b With ethyl acetoacetate

Following the general procedure as described in section (3.3 a), the reaction gave a complex mixture with no identifiable product isolated.

c With ethyl phenylthioacetate

To a stirred solution of sodium ethoxide (0.243 g, 10.56 mg-atom of sodium) in ethanol (16 cm^3) was added slowly over a period of 0.5 h, a mixture of 3-azidothiophen-2-carbaldehyde (193) (1.47 g, 9.6 mmol) and ethyl phenylthioacetate (2.07 g, 10.55 mmol) in ethanol (8 cm^3) at 0°C under dry nitrogen. The reaction was followed by t.l.c. until all the aldehyde had disappeared (ca. 3 h). A suspension of yellow/orange solid was obtained, it was poured into ice/water (150 cm^3) and the yellow solid filtered and washed with water. The solid was dissolved up into dichloromethane, washed once with saturated sodium chloride solution, dried over magnesium sulphate and removal of the solvent in vacuo (below 50°C) gave essentially pure ethyl 3-(3-azidothien-2-yl)-2-(phenylthio)propenoate (215) as a yellow solid (2.88 g, 91%). Recrystallization from dichloromethane/petrol gave an analytically pure sample of (215)

(2.7 g, 85%), m.p. 106-108°C dec. (Found: C, 54.27; H, 3.89; N, 12.65. $C_{15}H_{13}N_3O_2S_2$ requires C, 54.36; H, 3.95; N, 12.68%); ν_{max} (Nujol) 2135 (s), 2120 (s) and, 1700 (s) cm^{-1}; λ_{max} (EtOH) 207 (log ε 4.17), 250 (4.11), and 344 (4.23) nm; δ($CDCl_3$) 1.13 (3H, t, J 7.0 Hz), 4.18 (2H, q, J 7.0 Hz), 7.00 (1H, d, J 5.0 Hz), 7.12-7.38 (5H, m), 7.53 (1H, dd, J 5.0 and 0.8 Hz), and 8.43 (1H, d, J 0.8 Hz); m/e 331 (M^+), 303, 274, 230, 226 (base), and 198, m* (331→303) 277.4, (226→198) 173.5, and (303→226) 168.6.

d With ethyl methylthioacetate

To a stirred solution of sodium ethoxide (0.7 g, 0.03 g-atom of sodium) in ethanol (25 cm^3) was added dropwise, over a period of 0.5 h, a mixture of 3-azidothiophen-2-carbaldehyde (1.53 g, 0.01 mol) and ethyl methylthioacetate (4.02 g, 0.03 mol) in ethanol (10 cm^3) at -5 to -10°C under dry nitrogen. The reaction was monitored by t.l.c. until all the aldehyde had disappeared (ca. 3 h). The mixture was poured into ice/water (200 cm^3) and extracted with diethyl ether (4 X 75 cm^3). The combined extracts were washed successively with ammonium chloride solution (100 cm^3) and water (100 cm^3), dried over magnesium sulphate and the solvent removed in vacuo (below 50°C). The crude mixture was separated by column chromatography (silica H, 40 g: gradient elution from 25% dichloromethane in petrol) to give ethyl 3-(3-azidothien-2-yl)-2-(methylthio)propenoate (216) as yellow needles (2.2 g, 82%), m.p. 54-55°C (from petrol) (Found: C, 44.47; H, 4.00; N, 15.47. $C_{10}H_{11}N_3O_2S_2$ requires C, 44.59; H, 4.12; N, 15.60%); ν_{max} (Nujol) 2120 (s), 2100 (s), and 1700 (s) cm^{-1}; λ_{max} (EtOH) 205 (log ε 3.94), 248 (3.79), and 353 (4.16) nm; δ($CDCl_3$) 1.38 (3H, t, J 7.1 Hz), 2.37 (3H, s), 4.33 (2H, q, J 7.1 Hz), 6.99 (1H, d, J 5.4 Hz), 7.55 (1H, dd, J 5.4 and 0.8 Hz), and 8.15 (1H, d, J 0.8 Hz); m/e 269 (M^+), 241, 226, 212, 198 (base), 154, and 101,

m* (226→198) 173.5.

Ethyl 3-(3-azidothien-2-yl)-3-hydroxy-2-(methylthio)propanoate (217) (0.15 g, 5%), m.p. 94-95°C (from dichloromethane/petrol) (Found: C, 41.87; H, 4.51; N, 14.56. $C_{10}H_{13}N_3O_3S_2$ requires C, 41.80; H, 4.56; N, 14.62%); ν_{max} (Nujol) 3475 (br. m), 2125 (sh, m), 2115 (s), and 1715 (s) cm^{-1}; λ_{max} (EtOH) 207 (log ε 3.73), 230 (3.94), 250 sh (3.94), 255 (3.96), and 259 sh (3.95); δ($CDCl_3$) 1.31 (3H, t, J 7.1 Hz), 2.17 (3H, s), 3.28 (1H, d, J 6.0 Hz, D_2O exchangeable), 3.61 (1H, d, J 8.3 Hz), 4.27 (2H, q, J 7.1 Hz), 5.27 (1H, dd, J 8.3 and 6.0 Hz, collapse to a doublet J 8.3 Hz upon D_2O exchange), 6.93 (1H, d, J 5.2 Hz), and 7.33 (1H, d, J 5.2 Hz); m/e 287 (M^+), 213, 184, 154, and 134 (base).

3.5 Decomposition of Vinyl Azides

Solution Thermolysis : General procedure

All thermolyses were carried out under dry nitrogen and with constant stirring, unless otherwise stated. An approximately 1% solution was generally used. The round bottom flask containing the solution and a magnetic stirrer, fitted with a condenser (water or air where appropriate), was flushed out with dry nitrogen. A nitrogen supply, as a nitrogen balloon or bubbler, was fitted to the top of the condenser. The flask was placed in an oil or Wood's metal bath, preheated to bewteen 20-30°C above the boiling point of the solvent. The solutions rapidly attained reflux temperature, and were then monitored by t.l.c. until all starting material had been consumed. The flask was allowed to cool and the solvent removed by short path distillation.

Photolysis: General Procedure

All the photolysis experiments were carried out in a quartz tube, using a Rayonet photochemical reactor fitted with a set of four lamps of wavelength 350, 300 or 254 nm. An approximately 0.1% solution of the substrate in dry and degassed solvent was used. The photolysis proceeded under a slow stream of dry nitrogen passing through the solution, at the temperature of the inside of the Rayonet reactor (30-40^{o}C depending on the reaction time). The course of the photolysis was monitored by t.l.c. until all starting material had been consumed, unless otherwise stated. When the reaction had completed, the solvent was removed in vacuo to yield the crude product.

2-Azido-3-(3-methylbenzofuran-2-yl)-1-phenylpropen-1-one (210)

Thermolysis of the vinyl azide (210) in boiling benzene, toluene, xylene and bromobenzene gave complex mixtures with no characterizable product. Photolysis of (210) at 254 nm in acetonitrile again resulted in a complex mixture.

2-Azido-5-chloro-4-methyl-1-phenylhexa-2,4-diene-1-one (211)

Thermolysis of the vinyl azide (211) in benzene solution gave a complex mixture with no identifiable product isolated.

2-Azido-3-(2,6-dichlorophenyl)-1-phenylpropen-1-one (212)

Thermolysis of this vinyl azide (212) (250 mg, 0.79 mmol) in toluene (30 cm^{3}) gave, after column chromatography (silica H, 10 g; 50% dichloromethane in petrol), 3-benzoyl-2-(2,6-dichlorophenyl)-2H-azirine (248) (190 mg, 83%), m.p. 85-86^{o}C (from diethyl ether/petrol); ν_{max} (CCl_4) 1725 (m) and 1680 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 3.78 (1H, s), 7.20-7.40 (3H, m), 7.41-7.70 (3H, m), and 8.35-8.62 (2H, m); m/e 291/289

(M^+), 257/255, 256/254, 169, 152/150, 125/123, 105 (base), and 77.

Ethyl 2-azido-5-chloro-4-methylhexa-2,4-dieneonate (197)

i) In toluene - Thermolysis of the vinyl azide (197) (500 mg, 2.18 mmol) in boiling toluene (60 cm^3) for 15 min gave, after p.l.c. (eluted with dichloromethane), ethyl 3-chloro-4,5-dimethylpyrrole-2-carboxylate (218) (17 mg, 4%) (R_f 0.4), m.p. 149-151°C (from dichloromethane/petrol) (Found: C, 53.60; H, 6.00; Cl, 17.58; N, 6.95. $C_9H_{12}ClNO_2$ requires C, 53.55; H, 6.01; Cl, 17.88; N, 6.88%); ν_{max} (KBr) 3290 (s) and 1665 (s) cm^{-1}; δ(60 MHz, $CDCl_3$) 1.40 (3H, t, J 7.0 Hz), 2.03 (3H, s), 2.30 (3H, s), 4.47 (2H, q, J 7.0 Hz), and 9.3 (1H, br. s, D_2O exchangeable); m/e 203/201 (M^+), 175/173, 158/156, 157/155 (base), 121/119, and 92, m^* (201→173) 148.9, (173→155) 138.9, and (155→92) 54.6, ethyl 5-chloro-4-methylpyridine-2-carboxylate (221) (40 mg, 9%) (R_f 0.2), m.p. 53-54°C (vacuum sublimation 45-60°C/0.1 mmHg) (Found: C, 53.97; H, 5.02; Cl, 18.03; N, 6.97. $C_9H_{10}ClNO_2$ requires C, 54.15; H, 5.05, Cl, 17.76; N, 7.01%); ν_{max} (CCl_4) 1755 (s) and 1725 (s) cm^{-1}; ν_{max} (Nujol) 1720 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.44 (3H, t, J 7.0 Hz), 2.45 (3H, s), 4.54 (2H, q, J 7.0 Hz), 8.09 (1H, s), and 8.67 (1H, s); m/e 201/199 (M^+), 157/155, 156/154, 129/127 (base), 101/99, and 92/90, diethyl 5,5'-methylenebis(4-methyl-1H-pyrrole-2-carboxylate) (220) (R_f 0.1) (25 mg, 6%), m.p. 192-193°C (vacuum sublimation 160-170°C/0.1 mmHg) (Found: C, 64.03; H, 7.01; N, 8.68. $C_{17}H_{22}N_2O_4$ requires C, 64.13; H, 6.96; N, 8.80%); ν_{max} (KBr) 3345 (s), 1705 (s), and 1660 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.30 (2 X [3H, t, J 7.3 Hz]), 2.05 (2 X [3H, s]), 3.90 (2 X [1H, br. s]), 4.30 (2 X [2H, q, J 7.3 Hz]), 6.75 (2 X [1H, d, J 2.4 Hz]), and 9.60 (2 X [1H, br. s]); m/e 318 (M^+, base), 303, 289, 273, 272, 257, 245, 227, 199, 165, and 120, m* (318→272) 232.7 and (273→227) 188.8.

ii) In benzene - The vinyl azide (197) (1.26 g, 5.5 mmol) in boiling benzene (200 cm^3) for 2 h gave, after column chromatography, ethyl 3-chloro-4,5-dimethylpyrrole-2-carboxylate (218) (85 mg, 8%) and the dipyrrolemethane (220) (136 mg, 16%).

iii) In bromobenzene at 90°C - The vinyl azide (197) (1.27 g, 5.5 mmol) in bromobenzene (150 cm^3) was thermolysed at 90°C for 2.5 h. After the usual work up gave ethyl 3-chloro-4,5-dimethylpyrrole-2-carboxylate (218) (40 mg, 4%), ethyl 4,5-dimethylpyrrole-2-carboxylate (219) (27 mg, 3%), m.p. 112-114°C (lit.,[187] 114-116°C); δ(60 MHz, $CDCl_3$) 1.32 (3H, t, J 7.0 Hz), 2.00 (3H, s), 2.20 (3H,s), 4.27 (2H, q, J 7 Hz), 6.60 (1H, d, J 2.3 Hz), and 9.16 (1H, br. s); m/e 167 (M^+, base), 139, 121, 93, 85, 71, and 57, m* (167→139) 115.7, (139→121) 105.3, and (121→93) 71.5, the pyridine (221) (170 mg, 17%) and the dipyrrolemethane (220) (30 mg, 3%).

iv) In toluene with iodine - A solution of the vinyl azide (197) (1.27 g, 5.5 mmol) and iodine (2.8 g, 11 mmol) in toluene (80 cm^3) was refluxed for 20 min. After cooling to room temperature, the mixture was washed with 10% sodium metabisulphite solution, dried over sodium sulphate and the solvent removed in vacuo. The crude mixture was separated by p.l.c. to give ethyl 3-chloro-4,5-dimethylpyrrole-2-carboxylate (218) (11 mg, 1%), ethyl 4,5-dimethylpyrrole-2-carboxylate (219) (22.6 mg, 2.5%) and the pyridine (221) (262 mg, 24%).

v) In chloroform - The vinyl azide (197) (260 mg, 1.1 mmol) in boiling chloroform (160 cm^3, AR grade) for 24 h gave, after chromatography, ethyl 3-chloro-4,5-dimethylpyrrole-2-carboxylate (218) (4.4 mg, 2%), the pyridine (221) (25 mg, 11%) and ethyl 5-ethoxymethyl-4-methylpyrrole-2-carboxylate (222) (23 mg, 9%), m.p. 62-64°C; ν_{max} (KBr) 3310 (m) and 1690 (s) cm^{-1}; δ(60 MHz, $CDCl_3$) 1.20 (3H, t, J 7 Hz), 1.33 (3H, t, J 7 Hz), 2.06 (3H, s), 3.53

(2H, q, J 7 Hz), 4.33 (2H, q, J 7 Hz), 4.50 (2H, s), 6.75 (1H, d, J 2.5 Hz), and 9.93 (1H, br. s); m/e 211 (M^+), 166 (base), 138, 120 and 92, m* (211→166) 130.6, (166→138) 114.7, and (138→120) 104.3.

vi) In ethanol - The vinyl azide (197) (76 mg) in ethanol (50 cm^3) was refluxed for 3 h. After work up, the crude mixture was analysed by t.l.c. and n.m.r. The following products (218), (220), (221) and (222) were shown to be present in the crude mixture in low yields. There was no distinct improvement on the yield of (222).

Ethyl 2-azido-3-(2-chlorocyclohex-1-enyl)propenoate (198)

The vinyl azide (198) (700 mg, 2.7 mmol) in boiling bromobenzene (70 cm^3) for 2 min gave a complex mixture. After separation by column chromatography, ethyl 6,7-dihydroindole-2-carboxylate (245) was isolated as the only identifiable product (90 mg, 17%), m.p. 109-111°C (vacuum sublimation) (Found: C, 68.88; H, 6.84; N, 7.27. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32%); ν_{max} ($CHCl_3$) 3450 (m) and 1690 (s) cm^{-1}; δ($CDCl_3$) 1.37 (3H, t, J 7.0 Hz), 2.43 (2H, m), 2.78 (2H, t, J 8.8 Hz), 4.32 (2H, q, J 7.0 Hz), 5.63 (2H, dt, J 9.6 and 4.4 Hz), 6.35 (2H, d, J 9.6 Hz), 6.68 (1H, d, J 3.5 Hz), and 9.90 (1H, D_2O exchangeable). Thermolysis of the vinyl azide (198) in 1,2-dichloroethane for 3 h also gave the dihydroindole (245) as the only product in 15% yield. Small scale thermolyses of (198) in toluene (20 min), benzene (1 h) and bromobenzene/triethyl amine (1 eq.) were carried out. The crude reaction mixtures were analysed by t.l.c. and n.m.r. No distinct improvement on the reaction was observed.

3.6 Decomposition of Bis-Azides

a Thermolysis of Azides with Detection of Acetylene

General Procedure

A three-neck round bottom flask containing a solution of the azide and a magnetic stirrer bar, was fitted with a condenser, a stopper and a rubber septum. At the top of the condenser, an adaptor with a gas inlet and outlet was fitted. The gas inlet system with a glass tube reaching down, through the condenser, just above the solution was connected to a nitrogen supply. The gas outlet was connected to a series of bubblers containing the reagent for detection of acetylene. A slow stream of nitrogen was allowed to sweep through the apparatus with the outlet at the top and through the bubblers. The reaction flask was then lowered into a preheated 'hot' bath, and the thermolysis was carried out in the usual manner. Samples of the reaction solution could be taken *via* a syringe for monitoring purposes (t.l.c. or i.r.).

Detection of Acetylene

Qualitative method[188]: Freshly prepared colourless ammoniacal solution of copper (I) chloride was used. A red/brown precipitate of copper (I) acetylide indicates the presence of acetylene. The reagent was prepared by combining two solutions (A) and (B) in the ratio of 1 : 2. Solution (A): A solution of copper (II) chloride (1.5 g) and ammonium chloride (3 g) in concentrate ammonia solution (SG 0.88 20 cm^3), diluted to 50 cm^3 with water. Solution (B): A solution of hydroxylamine hydrochloride (5 g) in water (50 cm^3).

Quantitative method[189]: Concentrated solution of silver nitrate (3 M) with methyl red as indicator (1 drop per 10 cm^3) was used. The initial

pink solution was neutralised with dilute alkali before use. A small sample of the 'neutralised' reagent was retained, and used as the reference for the 'end-point' of the titration. If acetylene is extruded during the thermolysis, it would react with silver nitrate to give silver acetylide, and the nitric acid generated would turn the indicator pink/red. At the end of the thermolysis, the combined trapping reagent was titrated with standard sodium hydroxide solution (0.1 M).

Calculation

$$HC{\equiv}CH + 3AgNO_3 \longrightarrow AgC{\equiv}CAg{\cdot}AgNO_3 + 2HNO_3$$

If the volume of 0.1 M NaOH required = χ cm^3. The amount of HNO_3 generated = $\chi/10$ mmol. Since 1 mmol of HNO_3 ≡ 1/2 mmol of acetylene therefore, the amount of acetylene reacted = $\chi/20$ mmol.

The following azides were thermolysed using the above procedures.

Ethyl 2-azido-3-(3-azidothien-2-yl)propenoate (199)

The bis-azide (199) (264 mg, 1 mmol) in boiling toluene (20 cm^3) for 0.5 h gave acetylene (15%), ethyl 5-cyanoisothiazole-3-carboxylate (252) as an oil which was purified by distillation (bulb to bulb) (35 mg, 19%), b.p. 100-104°C/0.2 mmHg (oven temperature) (Found: C, 46.40; H, 3.47; N, 15.33; S, 17.30. $C_7H_6N_2O_2S$ requires C, 46.14; H, 3.32; N, 15.38; S, 17.60%); ν_{max} (neat) 2240 (m), 1745 (s), and 1725 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.46 (3H, t, J 7.2 Hz) 4.55 (2H, q, J 7.2 Hz), and 8.30 (1H, s); m/e 182 (M^+), 155, 138, 137 (base), 110, 109 and 83, m* (182→138) 104.6, (137→110) 88.3, (137→109) 86.7, and (110→83) 62.6, and ethyl thieno[3,2-c]pyridazine-3-carboxylate (251) as a solid,

which was purified by vacuum sublimation (70-80°C/0.06 mmHg) (35.4 mg, 17%), m.p. 130-131°C (from dichloromethane/petrol) (Found: C, 51.59; H, 3.83; N, 13.13. $C_9H_8N_2O_2S$ requires C, 51.91; H, 3.87; N, 13.45%); ν_{max} (KBr) 3110 (m), 3080 (m), 1715 (s), and 1565 (m) cm^{-1}; δ(100 MHz, $CDCl_3$) 1.51 (3H, t, J 7.0 Hz), 4.61 (2H, q, J 7.0 Hz), 8.01 (1H, dd, $J_{7,6}$ 5.5 and $J_{7,4}$ 0.8 Hz), 8.13 (1H, d, $J_{6,7}$ 5.5 Hz), and 8.80 (1H, d, $J_{4,7}$ 0.8 Hz); m/e 208 (M^+), 164, 163, 136 (base), 135, 109, 92, 91, 84, and 63, m* (208→164) 129.3, (164→136) 112.8, (136→109) 87.4, and (136→92) 62.2. The two products (251) and (252) were initially isolated by column chromatography (silica H, 4 g; gradient elution from 40% dichloromethane in petrol).

The thieno[3, 2-c]pyridazine (251) (0.1 g, 0.48 mmol) was hydrolysed in aqueous ethanolic potassium hydroxide solution (0.6 cm^3 of 1 M KOH in 0.6 cm^3 of ethanol) at room temperature (24 h), to give thieno[3, 2-c]pyridazine-3-carboxylic acid as a solid (74 mg, 85%), m.p. 176-178°C (from ethyl acetate); ν_{max} (Nujol) 2800-2050 (br) and 1710 (m) cm^{-1}; m/e 180 (M^+), 136 (base), 109, and 90, m* (180→136) 102.8 and (136→109) 87.4. The above acid (24 mg, 0.13 mmol) was decarboxylated at 170-185°C (ca. 15 min) to give the known compound, thieno[3,2-c]pyridazine (15 mg, 83%), m.p. 95-96°C (lit.,[131] 97.5-98.5°C); ν_{max} (KBr) 1397 (s), 1032 (m), 882 (m), 850 (m), 793 (m), 733 (s), and 675 (m) cm^{-1}; m/e 136 (M^+, base), 108, 82, 69, and 63.

Ethyl 5-cyanoisothiazole-3-carboxylate (252) (100 mg, 0.55 mmol) was hydrolysed in a mixture of aqueous potassium hydroxide (0.6 cm^3, 1 M) and dioxan (0.6 cm^3) at 5°C (1 h) to give 5-carbamylisothiazole-3-carboxylic acid (253) (85 mg, 90%), m.p. 263-266°C dec.; ν_{max} (Nujol) 3600-2100 (br), 3500 (m), 3430 (m), 3360 (s), 3200 (m), 1710 sh (s), 1690 (s), and 1660 (s) cm^{-1}; δ(90 MHz, DMSO-d_6) 7.95 (1H, br. s, D_2O exchangeable), 8.38 (3H, comprised of (1H, s), and (2H, br. D_2O

exchangeable); m/e 172 (M^+), 156 (base), 128, 100, 84, and 57, m* (172→128) 95.3 and (128→100) 78.1. The acid (253) was heated over a free flame to give isothiazole-5-carboxamide (254) (35 mg, 55%), m.p. 169-172°C (from water) (lit.,[132] 172-174°C); ν_{max} (Nujol) 3365 (m), 3285 (w), 3185 (s), 3080 (w), 1672 (s), and 1615 (m) cm^{-1}; δ(acetone-d_6) 2.88 (2H, br. s, D_2O exchangeable), 7.81 (1H, d, J 1.8 Hz), and 8.56 (1H, d, J 1.8 Hz); m/e 128 (M^+), 112 (base), 84, and 57.

Similarly, the bis-azide (199) was decomposed in boiling benzene, xylene and bromobenzene, the results are summarized in Table 7 (Section 2.6).

Thermolysis of ethyl 2-azido-3-(3-azidothiophen-2-yl)propenoate (199) in presence of a transition metal ion.

Three separate thermolysese were carried out in refluxing benzene. A catalytic amount of one of the following compounds: copper (I) chloride, palladium acetate and copper (II) acetylacetonate, was added separately to the three thermolysis solutions. The reaction was monitored by t.l.c. and was completed in 1.5 h. Each reaction was worked up and analysed by t.l.c. and n.m.r. All three reactions were shown to give complex mixtures with traces of the thienopyridazine (251) and the isothiazole (252).

Diethyl [(3-azido-2-thienyl)methylene]propanedioate (213)

The azide (213) (203 mg, 0.69 mmol) in boiling toluene (20 cm^3) for 4 h gave diethyl thieno[3,2-b]pyrrole-5,6-dicarboxylate (273) after column chromatography (silica H, 5 g; gradient elution from 70% dichloromethane in petrol) (140 mg, 76%), m.p. 107-109°C (vacuum sublimation 90-100°C/0.05 mmHg) (Found: C, 54.23; H, 4.88; N, 5.20. $C_{12}H_{13}NO_4S$ requires C, 53.92; H, 4.90; N, 5.24%); ν_{max} (Nujol) 3280

(s), 1732 (s), 1660 (s), and 1525 (m) cm^{-1}; λ_{max} (EtOH) 205 sh (log ε 3.83), 235 (4.16), 247 sh (4.06), and 307 (4.17) nm; δ($CDCl_3$) 1.39 (3H, t, J 7.0 Hz), 1.43 (3H, t, J 7.3 Hz), 4.41 (2H, q, J 7.3 Hz), 4.42 (2H, q, J 7.0 Hz), 6.96 (1H, d, J 5.5 Hz), 7.35 (1H, d, J 5.5 Hz), and 10.31 (1H, br. s, D_2O exchangeable); ^{13}C δ($CDCl_3$) 14.3, 14.4, 60.8, 61.6, 111.2, 112.8, 126.9, 128.1, 130.7, 138.6, 160.9, and 162.7; m/e 267 (M^+), 221, 194, 193, 177, 176, 150, and 149 (base), m* (267→221) 182.9, (221→193) 168.5, (194→176) 159.7, (221→177) 141.8, (194→150) 116.0, (194→149) 114.4 and (221→149) 100.5. No acetylene was detected (qualitative method).

Ethyl 2-azido-3-(3-azidofuran-2-yl)propenoate (200)

The bis-azide (200) (100 mg, 0.4 mmol) in boiling toluene (10 cm^3) for 45 min gave ethyl furo[3,2-c]pyridazine-3-carboxylate (276) after column chromatography (silica H, 3 g; gradient elution from 2% diethyl ether in dichloromethane) (13 mg, 17%) as the only identifiable product, m.p. 111-112°C (from dichloromethane/petrol); ν_{max} (Nujol) 3140 (w), 3095 (w), and 1715 (s) cm^{-1}; δ($CDCl_3$) 1.52 (3H, t, J 7.0 Hz), 4.60 (2H, q, J 7.0 Hz), 7.46 (1H, dd, $J_{7,6}$ 2.2 and $J_{7,4}$ 1.1 Hz), 8.08 (1H, d, $J_{6,7}$ 2.2 Hz), and 8.33 (1H, d, $J_{4,7}$ 1.1 Hz); m/e 192 (M^+), 148, 147, 120 (base), 119, 93, and 92, m* (192→148) 114.1, (148→120) 97.3, (147→119) 96.3, (120→93) 72.1, and (120→92) 70.5. No acetylene was detected (qualitative method).

Two similar thermolyses of the bis-azide (200) were carried out in refluxing benzene (3 h) and xylene (20 min). Again no acetylene was detected (qualitative method) and ethyl furo[3,2-c]-pyridazine-3-carboxylate (276) was the only product isolated in 13% and 18% yield respectively.

b Flash Vacuum Pyrolysis (FVP) of Ethyl 2-azido-3-(3-azidothien-2-yl)propenoate (199)

The bis-azides (199) was vaporised at 60°C/0.04 mmHg, and the vapor passed through a quartz tube at 400°C. However, the bis-azide (199) sublimed rather slowly and extensive decomposition occurred in the solid phase. After 4h, only about 10% of the bis-azide had sublimed. T.l.c. of the pyrolysate showed both the isothiazole (252) and the thieno[3,2-c]pyridazine (251) as products.

c Photolysis of Ethyl 2-azido-3-(3-azidothien-2-yl)propenoate (199) with Detection of Acetylene

A solution of the bis-azide (199) (72 mg) in acetonitrile (75 cm^3) was irradiated at 350 nm for 5 min. The exit gases were bubbled through an ammoniacal copper (I) chloride solution for detection of acetylene. No copper (I) acetylide was observed. N.m.r. and i.r. of the crude mixture showed that the ethyl 2-(3-azidothien-2-yl)-2H-azirine-3-carboxylate (277) (δ 3.57 (methine proton), ν_{max} 2120 cm^{-1}) was the major product. After purification by column chromatography, a red solid (278) was isolated as the only product (5.2 mg), m.p. 110-113°C dec.; ν_{max} (Nujol) 2145 (s), 2115 (s), and 1700 (s) cm^{-1}; δ($CDCl_3$) 1.47 (3H, t, J 7.2 Hz), 4.45 (2H, q, J 7.2 Hz), 7.50 (1H, dd, J 5.3 and 0.8 Hz), 7.54 (1H, d, J 5.3 Hz), and 8.12 (1H, d, J 0.8 Hz); m/e 469, 354, 235, 221, 208, 189, 164, 136 (base), and 109. No structure assigned.

d Photolysis of Ethyl 2-azido-3-(3-azidofuran-2-yl)propenoate (200) with Detection of Acetylene

A solution of the bis-azide (200) (80 mg) in acetonitrile (75 cm^3) was irradiated at 350 nm for 10 min. The exit gases were bubbled through

an ammoniacal copper (I) chloride solution, but no copper acetylide was formed. N.m.r. of the crude reaction mixture indicated that the corresponding azirine (279) (characteristic methine proton at 3.7 ppm) constituted the major component. After column chromatography (silica H, 3 g; gradient elution from dichloromethane to 50% diethyl ether in dichloromethane), ethyl furo[3,2-c]pyridazine (276) (3 mg, 5%) and an unknown yellow/orange solid (280) (3 mg) was isolated. The unknown yellow/orange solid has R_f 0.5 (silica/dichloromethane); ν_{max} ($CHCl_3$) 2130 (s) and 1710 (m) cm^{-1}; δ($CDCl_3$) 1.42 (3H, t, J 7.2 Hz), 4.41 (2H, q, J 7.2 Hz), 6.87 (1H, d, J 2.2 Hz), 7.40 (1H, s), and 7.60 (1H, d, J 2.2 Hz); m/e 469, 323, 308, 279, 167, and 149.

3.7 Attempted Independent Synthesis of Thieno[3,2-c]-pyridazines

a Preparation of Dienes for Cycloaddition Reactions.

Ethyl (E)-3-(thien-2-yl)propenoate (283)

Prepared by the literature procedure from thiophen-2-carbaldehyde and ethyl bromoacetate in an overall yield of 41%,[190] b.p. 114-116°C/1 mmHg (lit.,[190] 115-116°C/1 mmHg); ν_{max} (neat) 1710 (s) cm^{-1}; δ($CDCl_3$) 1.32 (3H, t, J 7.0 Hz), 4.24 (2H, q, J 7.0 Hz), 6.23 (1H, d, J 15.7 Hz), 7.02 (1H, dd, J 5.1 and 3.8 Hz), 7.22 (1H, d, J 3.8 Hz), 7.34 (1H, d, J 5.1 Hz), and 7.77 (1H, d, J 15.7 Hz).

Ethyl 3-hydroxy-3-(3-bromothien-2-yl)propanoate

Prepared by the method of Schuetz et al.,[190] from 3-bromothiophen-

2-carbaldehyde and ethyl bromoacetate. The compound was isolated as an oil (78%), b.p. 131-133°C/0.5 mmHg; ν_{max} (neat) 3470 (br) and 1735 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.29 (3H, t, J 7.0 Hz), 2.47-3.02 (2H, m, AB of ABX), 3.81 (1H, d, J 3.8 Hz, D_2O exchangeable), 4.23 (2H, q, J 7.0 Hz), 5.39 (1H, m, splitting pattern simplified to X of ABX upon D_2O exchange, J 3.6 and 8.6 Hz), 6.93 (1H, d, J 5.0 Hz), and 7.24 (1H, d, J 5.0 Hz); m/e 280/278 (M^+), 235/233, 199, 193/191 (base), 192/190, 191/189, 115 and 111.

Treatment of ethyl 3-hydroxy-3-(3-bromothien-2-yl)propanoate with aqueous oxalic acid

The hydroxy ester (3 g, 10.75 mmol) in aqueous oxalic acid (6% w/v, 30 cm^3) was refluxed for 7 h, after which the mixture was extracted with ethyl acetate, dried over sodium sulphate and the solvent removed in vacuo.

The crude product was diluted with dichloromethane and a crystalline solid precipitated. The solid was filtered and washed with dichloromethane to give 3-(3-bromothien-2-yl)propenoic acid (67 mg, 3%), m.p. 172-175°C; ν_{max} (Nujol) 3500 (br), 3200-2300 (br), 1690 (s) and 1615 (s) cm^{-1}; δ(90 MHz, DMSO-d_6) 6.20 (1H, br. s, D_2O exchangeable), 6.34 (1H, d, J 16.6 Hz), 7.27 (1H, d, J 5.6 Hz), 7.74 (1H, d, J 16.6 Hz), and 7.85 (1H, d, J 5.6 Hz); m/e 234/232 (M^+), 217/215, 189/187, 153 (base), 125, 108, 97, and 82, m* (153→125) 102.1, (233→153) 100.5, (153→108) 76.2, and (108→82) 62.3.

The combined filtrate was concentrated and separated by column chromatography (silica H, 30 g; gradient elution from 5% dichloromethane in petrol) to give 3-bromo-2-ethenylthiophen as an oil (0.8 g, 39%), ν_{max} (neat) 3120 (w), 3100 (w), 1625 (s), 1510 (s), and 1348 (s); δ(90 MHz, CCl_4) 5.28 (1H, d, J 12.2 Hz), 5.65 (1H, d, J 19.6 Hz), and 6.7-7.2 (3H, m); m/e 190/188 (M^+, base), 164/162,

109 and 65, m* (188→109) 63.2, (190→109) 62.5, and (109→65) 38.8, ethyl 3-(3-bromothien-2-yl)propenoate (299) (0.364 g, 13%), m.p. 65-66°C (from carbon tetrachloride); ν_{max} (Nujol) 3105 (w), 3090 (m), 1705 (s), and 1625 (s) cm^{-1}; δ(90 MHz, CCl_4) 1.33 (3H, t, J 7.3 Hz), 4.26 (2H, q, J 7.3 Hz), 6.28 (1H, d, J 16.0 Hz), 7.06 (1H, d, J 5.0 Hz), 7.33 (1H, d, J 5.0 Hz), and 7.78 (1H, d, J 16.0 Hz); m/e 261/259 (M^+), 217/215, 189/187, 181, 153 (base), 136, 125, and 108, m* (181→153) 129.3 and (153→125) 102.1, and ethyl 3-(3-bromothien-2-yl)-3-ethoxypropanoate as an oil (58 mg, 2%), ν_{max} (neat) 1750 (s) cm^{-1}; δ(90 MHz, CCl_4) 1.04-1.37 (6H, 2 X t, J 7.0 Hz), 2.49-2.86 (2H, m, AB of ABX), 3.50 (2H, q, J 7.0 Hz), 4.15 (2H, q, J 7.0 Hz), 5.10 (1H, X of ABX, J 5.6 and 8.0 Hz), 6.92 (1H, d, J 5.0 Hz), and 7.26 (1H, d, J 5.0 Hz); m/e 308/306 (M^+), 279/277, 263/261, 227 (base), 221/219, and 193/191, m* (227→199) 174.5 (221→193) 168.5, and (219→191) 166.6. Recovered starting material (0.50 g, 17%).

Treatment of ethyl 3-hydroxy-3-(3-bromothien-2-yl)propanoate with phosphorus oxychloride in pyridine

A mixture of the hydroxy ester (100 mg, 0.36 mmol) and phosphorus oxychloride (0.16 cm^3, 1.8 mmol) in dry pyridine (2 cm^3), was stirred under nitrogen at room temperature for 24 h. The mixture was poured into ice/water, acidified with concentrated hydrochloride acid and extracted with ethyl acetate. After column chromatography, ethyl 3-(3-bromothien-2-yl)propenoate (299) (20 mg, 21%) was obtained as the only product from the reaction.

Ethyl 2,3-dibromo-3-(thien-2-yl)propanoate

Prepared by the literature procedure[191] from ethyl 3-(thien-2-yl)propenoate (283) in 72% yield, m.p. 67-69°C (from petrol) (lit.,[191]

68-70°C).

Ethyl 2-bromo-3-(thien-2-yl)propenoate (300)

Prepared from the adapted procedure in the literature.[191] A solution of ethyl 2,3-dibromo-3-(thien-2-yl)propanoate (30 mg, 0.09 mmol) in glacial acetic acid (2 cm^3) was heated to reflux for 1 h. The mixture was poured into water and extracted with ether. The ether extract was washed with sodium bicarbonate solution (10%, 10 cm^3) followed by water (10 cm^3), dried over sodium sulphate and the solvent removed in vacuo. The crude product was purified by column chromatography (silica H, 1 g; dichloromethane/petrol) to give (300) as an oil (17 mg, 72%).

Ethyl 2-methoxy-3-(thien-2-yl)propenoate (301)

Prepared by the method of Horner et al.,[192] from thiophen-2-carbaldehyde and ethyl methoxyacetate,[193] b.p. 77-80°C/0.01 mmHg (lit.,[192] 102-103°C/0.1 mmHg).

b Cycloaddition of Ethyl 3-(thien-2-yl)propenoate (283) with 4-Phenyl-1,2,4-triazole-3,5-dione (PTAD)

With one equivalent of PTAD

A solution of PTAD (0.65 g, 3.7 mmol) in dry dioxan (20 cm^3) was added dropwise to a stirred solution of the diene (283) (0.67 g, 3.7 mmol) in dry dioxan (15 cm^3) at room temperature under nitrogen. The red colouration of the PTAD was rapidly discharged to give a pale yellow solution. After removal of the solvent in vacuo, the residual yellow syrup was separated by column chromatography (silica H, 25g; gradient elution from 25% ethyl acetate in petrol) to give 5,6-dihydro-5-ethoxycarbonyl-2-phenyl-6-(4-phenyl-1,2,4-triazol-3,5-dion-1-yl)-1H-

thieno[3,2-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (284) (0.46 g, 46%) as a solid, m.p. 128-132°C (from dichloromethane/petrol) (Found: C, 56.04; H, 3.77; N, 15.68. $C_{25}H_{20}N_6O_6S$ requires C, 56.38; H, 3.79; N, 15.78%); ν_{max} (Nujol) 3170 (w), 3110 (w), 1785 (m), and 1725 (s) cm^{-1}; λ_{max} (EtOH) 223 (log ε 4.43) and 275 (4.04) nm; δ($CDCl_3$) 1.21 (3H, t, J 7 Hz), 4.21 (2H, m [AB quartet of quartets]), 5.35 (1H, d, J 1.8 Hz), 6.19 (1H, d, J 1.8 Hz), 7.3-7.5 (11H, m), 7.61 (1H, d, J 5 Hz), and 8.45 (1H, br. s, D_2O exchangeable); m/e 532 (M^+), 355, 177, 136 (base) and 119.

The second product eluted from the column was 6a, 9a-dihydro-5-ethoxycarbonyl-2-phenyl-6a-(4-phenyl-1,2,4-triazol-3,5-dion-1-yl)-1H-thieno[3,2-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (285) (0.08 g, 8%) as fine needles, m.p. 135-160°C (from ethyl acetate/petrol (b.p. 60-80°C)) (Found: C, 56.18; H, 3.77; N, 15.66. $C_{25}H_{20}N_6O_6S$ requires C, 56.38; H, 3.79; N, 15.78%); ν_{max} (Nujol) 3160 (w), 3080 (w), 1795 (m), 1780 (m), 1730 (s), and 1705 (s) cm^{-1}; λ_{max} (EtOH) 221 (log ε 4.44), 265 (4.26), and 273 (4.22) nm; δ(DMSO-d_6) 1.19 (3H, t, J 7 Hz), 4.21 (2H, q, J 7 Hz), 5.84 (1H, m), 6.24 (1H, m), 6.45 (1H, m), 6.95 (1H, m), 7.40-7.65 (10H, m), and 10.81 (1H, br. s, D_2O exchangeable); m/e 532 (M^+), 355, 177, 136 (base), and 119.

With two equivalent of PTAD

A solution of ethyl 3-(thien-2-yl)propenoate (283) (1.22 g, 6.69 mmol) in dry dioxan (10 cm^3) was added dropwise to a stirred solution of PTAD (2.34 g, 13.37 mmol) in dry dioxan (50 cm^3) at room temperature under nitrogen. At the end of the addition, the red colouration of the PTAD still persisted and the mixture was allowed to stir under the same conditions for two days. After removal of the solvent in vacuo, the residual red syrup was separated by column

chromatography (silica H, 50 g; gradient elution from 20% ethyl acetate in petrol) to give adduct (284) (1.54 g, 43%) and adduct (285) (0.26 g, 7.4%).

c Elimination Reaction of Adducts (284) and (285)

Adduct (284) in dimethyl sulphoxide (DMSO)

A stirred solution of the adduct (284) (0.85 g, 1.6 mmol) in DMSO (40 cm^3) was heated at 110-120°C for 24 h. The mixture was then poured into water and extracted with ethyl acetate. The combined extracts were washed with water (3 X 25 cm^3), dried over magnesium sulphate and evaporated *in vacuo*. The residual yellow solid was chromatographed (silica H, 15 g; gradient elution from 20% ethyl acetate in petrol) to give 5-*ethoxycarbonyl*-2-*phenyl*-1*H*-*thieno*[3,2-*c*]-[1,2,4]*triazolo*[1,2-*a*]*pyridazine*-1,3(2*H*)-*dione* (287) (0.56 g, 99%) as yellow needles, m.p. 175-176°C (ethyl acetate/petrol (b.p. 60-80°C)) (Found: C, 57.31; H, 3.83; N, 11.64. $C_{17}H_{13}N_3O_4S$ requires C, 57.46; H, 3.69; N, 11.83%); ν_{max} (Nujol) 1772 (m), 1732 (s), and 1714 (s) cm^{-1}; λ_{max} (EtOH) 220 (log ε 3.95), 242 (3.98), 283 (3.63), and 405 (3.46) nm; δ($CDCl_3$) 1.37 (3H, t, *J* 7 Hz), 4.38 (2H, q, *J* 7 Hz), 6.80 (1H, d, *J* 0.6 Hz), 7.35-7.60 (6H, m [containing H-6 (1H, d, *J* 5.4 Hz)]), 7.62 (1H, doublet of doublets, *J* 5.4 and 0.6 Hz); m/e 355 (M^+), 136 (base), and 119.

Adduct (285) in DMSO

A solution of the adduct (285) (37 mg, 0.07 mmol) in DMSO (2 cm^3) was heated at 90-95°C until all starting material disappeared (by t.l.c., 1 h). After similar work up and column chromatography gave the product (287) in 97% yield (24 mg).

Adduct (284) with boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$)

A stirred solution of the adduct (284) (45.6 mg, 0.086 mmol) and redistilled $BF_3 \cdot Et_2O$ (10 drops) in chlorobenzene (10 cm^3) was heated at 90-95°C for 1 h (the disappearance of starting material confirmed by t.l.c.). Removal of the solvent in vacuo followed by column chromatography gave (287) in 39% yield.

A similar reaction was carried out in the absence of $BF_3 \cdot Et_2O$ in refluxing chlorobenzene. No reaction was observed after 24 h.

d Attempted Hydrolysis of 5-Ethoxycarbonyl-2-phenyl-1H-thieno[3,2-c]-[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (287)

Several procedures were adapted from the literature, and these are summarised in Table 14. All experiments resulted in either a complex mixture with no isolatable product or extensive decomposition of the starting material with the loss of hydrogen sulphide during the acid work up.

Method	Ref.
1) KOH (40 eq.)/EtOH-H_2O (6 :1)/24 h/reflux (worked up at pH 1/$CuCl_2$)	146
2) KOH (30 eq.)/EtOH-H_2O (1 : 1, degassed)/24 h/refluxed under N_2 (worked up at pH7/$CuCl_2$)	147
3) KOH (30 eq.)/EtOH-H_2O (1 : 1, degassed)/15 h/refluxed under N_2 (worked up at pH 5/$CuCl_2$)	147
4) KOH (30 eq.)/EtOH-H_2O (1 : 1, degassed)/3 min./100°C under N_2 (worked up at pH 3)	147

5) KOH (90 eq.)/ethylene glycol-H_2O (1 : 1, degassed)/1½ h/ 160-170°C under argon (worked up at pH 7)	148
6) KOH (90 eq.)/ethylene glycol-H_2O (1 : 1, degassed)/1½ h/ 160-170°C under argon (worked up at pH 1)	148
7) KOH (90 eq.)/ethylene glycol-H_2O (1 : 1, degassed)/1½ h/ 160-170°C under argon (worked up at pH 3)	148
8) HCl (6 M, 4 cm^3)/EtOH (2 cm^3)/0.11 mmol of (286)/15 h/ reflux under N_2	-
9) ^tBuOK (3 eq.)/DMSO (dry)/3 h/RT	149

Table 14

e Reactions of Ethyl 3-(thien-2-yl)propenoate (283) with Diethyl azodicarboxylate (DEAZD)

In boiling toluene and bromobenzene

A solution of ethyl 3-(thien-2-yl)propenoate (283) (65 mg, 0.36 mmol) and DEAZD (60 mg, 0.34 mmol) in dry toluene (10 cm^3) was refluxed under nitrogen for 24 h. T.l.c. showed the presence of unreacted starting materials only. A similar reaction was carried out in refluxing bromobenzene for 24 h. T.l.c. again showed no sign of reaction.

Under U.V. irradiation

Method (i) A solution of the propenoate (283) (1.36 g, 7.5 mmol) and DEAZD (1.2 g, 6.9 mmol) in dry degassed cyclohexane (120 cm^3) was irradiated with a 125 W high-pressure mercury lamp in a quartz vessel

for 15 h. T.l.c. again showed no reaction and the n.m.r. of the crude mixture after work-up showed only the unreacted starting materials.

Method (ii) A solution of DEAZD (0.174 g, 1 mmol) in dry degassed benzene (100 cm^3) was pre-irradiated at 350 nm in a quartz tube under a slow stream of nitrogen. The isomerization was followed by u.v. and the λ_{max} shifted from 400 to 410 nm after 3.5 h. The u.v. spectrum did not change on further irradiation (4 h). The irradiation was then stopped and a solution of the propenoate (283) (0.182 g, 1 mmol) in dry benzene (5 cm^3) was added and the mixture was allowed to stir at room temperature under nitrogen. T.l.c. of the reaction mixture after 12 h showed no reaction.

In presence of boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$)

Method (i) To a stirred solution of the propenoate (283) (0.132 g, 0.72 mmol) and DEAZD (0.122 g, 0.70 mmol) in dry toluene (10 cm^3) was added boron trifluoride diethyl etherate (3 drops, freshly redistilled).[194] The mixture was then refluxed under nitrogen and the reaction followed by t.l.c. The mixture turned dark rapidly and after 3 h, t.l.c. showed a complex mixture with the starting propenoate (283) as the major component.

Method (ii) To a stirred mixture of the propenoate (283) (0.152 g, 0.83 mmol) and DEAZD (0.127 g, 0.73 mmol) under nitrogen was added $BF_3 \cdot Et_2O$ (2 cm^3, freshly redistilled) at room temperature. The reaction mixture turned dark immediately. T.l.c. of the reaction mixture showed no further changes after 2 h. The reaction mixture was poured into water, extracted with ethyl acetate, dried (sodium sulphate) and the solvent removed in vacuo. The crude product was chromatographed (silica H, 5 g; gradient elution from 2% ethyl

acetate in dichloromethane) to give ethyl 2-(N,N'-diethoxycarbonyl-hydrazino)-3-(thien-2-yl)propenoate (289) (40 mg, 15%) as a solid, m.p. 115-116°C (from chloroform/petrol (b.p. 60-80°C)) (Found: C, 50.39; H, 5.61; N, 7.78. $C_{15}H_{20}N_2O_6S$ requires C, 50.55; H, 5.66; N, 7.86%); ν_{max} (Nujol) 3290 (s), 1760 (s), 1730 (s), and 1695 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 1.10-1.45 (9H, m), 4.05-4.45 (6H, m), 7.05-7.20 (2H, m), 7.55-7.7 (2H, m), and 7.79 (1H, br. s); m/e 356 (M^+), 312, 311, 284, and 237 (base), m* (356→312) 273.4, (312→284) 258.5, and (356→284) 226.6.

f Cycloaddition Reactions of 2-Ethenylthiophen

i) With one equivalent of PTAD in diethyl ether

To a solution of 2-ethenylthiophen[195] (0.55 g, 5mmol) in dry ether (50 cm^3) was added PTAD (0.88 g, 5 mmol) as a solid at room temperature. The red colouration of the PTAD discharged rapidly as it dissolved. The mixture was allowed to stir for 2 days and the resultant precipitate was filtered and washed with more ether (15 cm^3) to give 5,6-dihydro-2-phenyl-6-(4-phenyl-1,2,4-triazol-3,5-dion-1-yl)-1H-thieno[3,2-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (290) (0.76 g, 66% (base on PTAD)), m.p. 257-258°C; ν_{max} (Nujol) 3160 (w), 1785 (m), 1725 (s), and 1705 (s) cm^{-1}; δ(90 MHz, DMSO-d_6) 3.95-4.70 (2H, AB of ABX, J_{AB} 14 Hz, J_{AX} 4 Hz, J_{BX} 3 Hz), 5.72 (1H, m, X of ABX), 7.3-7.65 (11H, m), 7.78 (1H, d, J 5.0 Hz), and 10.76 (1H, br. s, D_2O exchangeable); m/e 460 (M^+), 284 (base), 177, 165, 138, 119, 109, 91 and 77, m* (460→284) 175.3, (284→165) 95.9, (119→91) 69.6, and (284→138) 67.1.

Attempted elimination reactions of adduct (290)

No reaction was observed when a solution of the adduct (290) in DMSO was heated to 120°C for 2 days. Again, no reaction was observed when a mixture of the adduct (290) (50 mg, 0.11 mmol) and $BF_3 \cdot Et_2O$

(5 drops) in dry dioxan (6 cm^3) was stirred at room temperature for 2 days followed by reflux for 2 h.

Attempted hydrolysis of adduct (290)

A mixture of the adduct (290) (90 mg, 0.2 mmol) and potassium hydroxide solution (5 M, 2 cm^3) in dioxan (1 cm^3) was heated to reflux for 1.5 h. A complex mixture with no identifiable product was obtained. Hydrogen sulphide was evolved during the acid work-up.

ii) With PTAD in dioxan

To a stirred solution of 2-ethenylthiophen (0.88 g, 8 mmol) in dry dioxan (25 cm^3) was added dropwise a solution of PTAD (1.2 g, 6.86 mmol) in dry dioxan (30 cm^3) at room temperature. The red colouration of the PTAD was rapidly discharged to give a yellow solution. After 0.5 h, the solvent was removed in vacuo to give a yellow syrup. Trituration of the syrup with diethyl ether, followed by filtration and further washing with diethyl ether gave a solid which was tentatively assigned as 5,9a-dihydro-2-phenyl-1H-thieno[3,2-c][1,2,4]triazolo[1,2-a]-pyridazine-1,3(2H)-dione (291) (1.84 g, 94%), m.p. 101-104°C; ν_{max} (Nujol) 1770 (m) and 1715 (s) cm^{-1}; δ (90 MHz, DMSO-d_6) 4.30 (2H, m), 5.55 (1H, m), 6.02 (1H, m), 6.34 (1H, m), 6.90 (1H, m), and 7.53 (5H, m); m/e 285 (M^+), 166, 138, 119, and 110 (base).

Attempted purification of the adduct (291) by column chromatography (silica H, ethyl acetate/dichloromethane) led to a mixture of inseparable products. An attempt to purify the adduct (291) (0.92 g) by recrystallization from boiling methanol gave a compound which contained additionally the elements of methanol. This was assigned as 1-[2-methoxy-2-(thien-2-yl)ethyl]-4-phenyl-1,2,4-triazole-3,5-dione (293) (0.65 g, 60%), m.p. 142-143°C (from diethyl ether/chloroform) (Found: C, 56.72; H, 4.74; N, 13.29. $C_{15}H_{15}N_3O_3S$ requires C, 56.77; H, 4.76; N, 13.24%); ν_{max} (Nujol) 3200 (w), 1770 (w),

and 1697 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 3.27 (3H, s), 3.64-4.21 (2H, AB of ABX, J_{AB} 14 Hz, J_{AX} 3.6 Hz, and J_{BX} 8.0 Hz), 4.81 (1H, X of ABX, J_{XA} 3.6 Hz and J_{XB} 8.0 Hz), 6.98-7.14 (2H, m), 7.32-7.58 (6H, m), and 8.65 (1H, br. s, D_2O exchangeable); m/e 317 (M^+), 285, 140, 127 (base), 119, and 110, m* (317→285) 256.2.

Attempted hydrolysis of adduct (291)

Two attempts were made and are summarized in Table 15.

Conditions	Results
1) KOH (10 eq.)/dioxan-H_2O (3 : 1)/17 h/reflux	complex mixture
2) HCl (6N, 2 cm^3) - dioxan (2 cm^3)/0.35 mmol of (291), 30 min /100°C	complex mixture

Table 15

Attempted elimination reactions of (293)

Three attempts were made, their experimental conditions and results are summarized in Table 16.

Conditions	Results
1) PTSA/benzene/3.5 h/reflux under N_2	complex mixture
2) Conc. H_2SO_4-MeOH (1 : 1)/0°C/5 min.	no reaction
3) Conc. H_2SO_4/0-20°C/10 min.	complex mixture with evolution of H_2S

Table 16

iii) With diethyl azodicarboxylate (DEAZD)

To a stir solution of 2-ethenylthiophen (1.1 g, 10 mmol) in dry dioxan (6 cm^3) was added dropwise a solution of DEAZD (1.74 g, 10 mmol) in dry dioxan (8 cm^3) at room temperature. No appreciable reaction was observed after 1 h (by t.l.c.). The mixture was then heated to reflux for 1.5 h (until the disappearance of starting material confirmed by t.l.c.). Removal of the solvent in vacuo gave a yellow syrup containing a complex mixture. Purification of the crude product by column chromatography (silica H, gradient elution from 30% of diethyl ether in petrol) gave several fractions mostly containing unidentifiable mixtures. One of the fractions was isolated as a sticky solid (0.58g, 25%) with a molecular ion of 458 in the mass spectrum which corresponded to an 1:2 adduct of 2-ethenylthiphen and DEAZD. The compound was difficult to purify and easily polymerized. Both the i.r. and n.m.r. were unhelpful in determining the structure.

iv) With 1,3,4-thiadiazole-2,5-dione (297)

Several procedures were adapted from the literature in an attempt to react the dienophile (297) with 2-ethenylthiophen. The experimental conditions and the results are summarized in Table 17. All experiments resulted in either a complex mixture or inseparable products which were difficult to purify. (See over for Table 17).

g Miscellaneous Cycloaddition Reaction of PTAD With ethyl 3-(3-bromothien-2-yl)propenoate (299)

A solution of PTAD (45.5 mg, 0.26 mmol) in dry dioxan (1 cm^3) was added dropwise to a stirred solution of (299) (67.8 mg, 0.26 mmol) in dry dioxan (1 cm^3) at room temperature under nitrogen. A red solution was obtained. No reaction was observed after 1 h at room

Experimental Conditions *	Ref.
1) THF - DMF (1 : 3)/HOAc (1%)/(298) (1 eq.)/ET (3 eq.)/ -78°C/LTA (1.5 eq.)/4 h/ethylene glycol/RT	156
2) DMF/anhydrous $CuCl_2$ [196] (4.8 eq.)/0°C/ET (14.5 eq.)/ (298) (1 eq.)/20 min /RT	157
3) Acetone/(298) (1 eq.)/-78°C/^{t}BuOCl (5 eq.)/10 min / ET (10 eq.)/20min /RT	157
4) Acetone/(298) (1.2 eq.)/ET (1 eq.)/-78°C/^{t}BuOCl (until purple colour persist/½ h/RT	-

* The sequence of additions and manipulations were carried out in the order listed.

ET = 2-ethenylthiophen

LTA = Lead tetraacetate

Table 17

temperature. The mixture was then refluxed for 3 h which lead to a complex mixture with no identifiable product.

With ethyl 2-bromo-3-(thien-2-yl)propenoate (300)

A solution of PTAD (2.6 mg, 0.065 mmol) in dry dioxan (1 cm^3) was added dropwise to a stirred solution of (300) (17 mg, 0.065 mmol) in dry dioxan (1 cm^3) at room temperature under nitrogen. A red solution was obtained. No reaction was observed after 2 h and the mixture was then heated to 85-90°C for a further 2 h. T.l.c. analysis showed a complex mixture with the starting material (300) as the major component.

With ethyl 2-methoxy-3-(thien-2-yl)propenoate (301)

A solution of PTAD (0.175 g, 1 mmol) in dry dioxan (5 cm^3) was added dropwise to a stirred solution of (301) (0.212 g, 1 mmol) in dry dioxan (3 cm^3) at room temperature under nitrogen. A red solution was obtained. No reaction was observed after 2 h at room temperature and the mixture was heated to 90°C for 24 h.

The reaction gave an inseparable mixture with the starting material (301) as the main component.

With 3-bromo-2-ethenylthiophen

A solution of PTAD (92.6 mg, 0.53 mmol) in dry dioxan (4 cm^3) was added dropwise to a stirred solution of 3-bromo-2-ethenylthiophen (100 mg, 0.53 mmol) in dry dioxan (2 cm^3) at room temperature under nitrogen. The red colouration of the PTAD was discharged within 30 s as it was added. At the end of the addition, a bright yellow solution was obtained. Potassium carbonate (73 mg, 0.53 mmol) was added and the mixture was heated to reflux for 0.5 h.

The mixture was filtered and the solvent removed *in vacuo*, purification of the crude product by p.l.c. (silica, 20 X 40 cm; 1 : 1 ethyl acetate/petrol) gave 2-*phenyl*-1*H*-*thieno*[3,2-*c*][1,2,4]-*triazolo*[1,2-*a*]*pyridazine*-1,3(2*H*)-*dione* (302) as a yellow solid (69 mg, 47%), δ(90 MHz, $CDCl_3$) 5.87 (1H, d, $J_{6,5}$ 8.0 Hz), 6.95 (1H, d, $J_{5,6}$ 8.0 Hz), 7.24 (1H, d, $J_{9,8}$ 5.2 Hz), and 7.38-7.68 (6H, m); m/e 283 (M^+), 136 (base), and 119.

3.8 Preparation of Cyclic Sulphimides

Cyclic sulphimides were prepared by the decomposition of the appropriate azides. Thus the following sulphimides were prepared.

Ethyl 1-methylthieno[2,3-*e*][1λ⁴,2]thiazine-3-carboxylate (307)

Prepared by solution thermolysis of ethyl 2-azido-3-(3-methylthiothien-2-yl)propenoate (201) (350 mg, 1.3 mmol) in boiling toluene (30 cm^3) for 10 min. The crude product was purified by column chromatography (silica H, 10 g; gradient elution from 5% diethyl ether in dichloromethane) to give the cyclic sulphimide (307) as a yellow/brown gum (278 mg, 89%). The product solidified to a yellow/brown sticky solid at -5°C overnight, m.p. 58-62°C (from dichloromethane/petrol (b.p. 60-80°C)) (Found: C, 49.56; H, 4.54; N, 5.73; S, 26.69. $C_{10}H_{11}NO_2S_2$ requires C, 49.77; H, 4.59; N, 5.80; S, 26.57%); ν_{max} (Nujol) 1695 (s) cm^{-1}; ν_{max} (CCl_4) 1715 (s) cm^{-1}; λ_{max} (EtOH) 205 (log ε 3.95), 245 (3.93), and 400 (3.81) nm; δ($CDCl_3$) 1.38 (3H, t, *J* 7.3 Hz), 2.27 (3H, s), 4.35 (2H, quartet of quartets, *J* 7.3 Hz), 6.90 (1H, dd, $J_{7,6}$ 5.1 and $J_{7,4}$ 0.8 Hz), 7.17 (1H, d, $J_{4,7}$ 0.8 Hz), and 7.30 (1H, d, $J_{6,7}$ 5.1 Hz); ^{13}C δ($CDCl_3$) 14.4, 31.4,

61.5, 102.4, 105.0, 121.2, 124.5, 142.8, and 166.4; ^{13}C $\delta(C_6D_6)$ 14.3, 30.8, 61.0, 101.6, 104.5, 121.5, 123.7, 143.4, 144.7, and 166.4 (see Figure 7 in the Appendix); m/e 243 (M+2), 241 (M^+), 226 (base), 198, 168, 158, 154, 143, 141, 120, and 118, m* (226→198) 173.5.

Similarly, thermolysis of the vinyl azide (201) in refluxing benzene for 2 h gave the cyclic sulphimide (307) in 84% yield.

Ethyl 2-methylthieno[3,2-c][1λ^4,2]thiazine-3-carboxylate (308)

Prepared by solution thermolysis of ethyl 3-(3-azidothien-2-yl)-2-(methylthio)propenoate (216) (158 mg, 0.59 mmol) in boiling toluene (12 cm^3) for 3 h. After p.l.c. (20 X 40 cm, 7% diethyl ether in dichloromethane), the cyclic sulphimide (308) was isolated and further purified by vacuum distillation (b.p. 105-110°C/0.1 mmHg) to give an orange /red gum (119 mg, 84%), which solidified to a yellow/brown solid after standing at room temperature in the dark for 3 weeks. The title compound showed no changes in its spectroscopic properties on distillation. M.p. 72-73°C (Found: C, 49.46; H, 4.56; N, 5.71. $C_{10}H_{11}NO_2S_2$ requires C, 49.77; H, 4.59; N, 5.80%); ν_{max} (Nujol) 3120 (w), 3060 (w), 1675 (s), and 1555 (s) cm^{-1}; λ_{max} (EtOH) 209 sh (log ε 3.91), 217 (3.94), 268 (3.53), 321 (3.88), and 457 (3.64) nm; $\delta(CDCl_3)$ 1.35 (3H, t, J 7.1 Hz), 2.28 (3H, s), 4.31 (2H, q, J 7.1 Hz), 6.79 (1H, dd, $J_{7,6}$ 5.4 and $J_{7,4}$ 0.8 Hz), 7.62 (1H, d, $J_{6,7}$ 5.4 Hz), and 8.02 (1H, d, $J_{4,7}$ 0.8 Hz); ^{13}C $\delta(CDCl_3)$ 14.4, 28.5, 61.1, 85.2, 114.0, 124.2, 135.8, 136.7, 162.0, and 162.7 (see Figure 8 in the Appendix); m/e 241 (M^+), 226 (base), 198, 154, and 110, m* (226→198) 173.5.

A second product, ethyl 6-methylthio-4H-thieno[3,2-b]pyrrole-5-carboxylate (309) was isolated as a crystalline solid (12 mg, 8%),

m.p. 115-116°C (from ethanol/water) (Found: C, 49.89; H, 4.57; N, 5.82. $C_{10}H_{11}NO_2S_2$ requires C, 49.77; H, 4.59; N, 5.80%); ν_{max} (Nujol) 3280 (sh, s), 3270 (s), 1675 (s) and 1655 (s) cm^{-1}; λ_{max} (EtOH) 202 (log ε 3.82), 257 sh (4.01), 263 (4.03), 292 (4.38), and 329 sh (3.90); δ($CDCl_3$) 1.40 (3H, t, J 7.0 Hz), 2.68 (3H, s), 4.40 (2H, q, J 7.0 Hz), 6.89 (1H, d, $J_{3,2}$ 5.5 Hz), 7.28 (1H, d, $J_{2,3}$ 5.5 Hz), and 9.65 (1H, br. s, slowly exchangeable with D_2O); ^{13}C δ($CDCl_3$) 14.5, 16.5, 60.8, 111.3, 118.8, 122.9, 125.3, 129.8, 140.9, and 161.5 (see Figure 16 in the Appendix); m/e 241 (M^+), 195 (base), 167, and 152, m* (241→195) 157.8 and (195→167) 143.0.

Ethyl 2-phenylthieno[3,2-c][1λ⁴,2]thiazine-3-carboxylate (310)

Prepared by solution thermolysis of ethyl 3-(3-azidothien-2-yl)-2-(phenylthio)propenoate (215) (0.5 g, 1.51 mmol) in refluxing toluene (60 cm^3) for 2.5 h. After column chromatography (silica H, 15 g; gradient elution from 70% dichloromethane in petrol to 100% dichloromethane and finally up to 10% diethyl ether in dichloromethane), the cyclic sulphimide (310) was isolated as red crystals (0.41 g, 89.6 %), m.p. 128-129°C (from ethyl acetate/petrol (b.p. 60-80°C)) (Found: C, 59.31; H, 4.38; N, 4.64. $C_{15}H_{13}NO_2S_2$ requires C, 59.38; H, 4.32; N, 4.62%); ν_{max} (Nujol) 3105 (w), 3060 (w), 1670 (s), and 1555 (m) cm^{-1}; λ_{max} (EtOH) 220 (log ε 4.15), 262 sh (3.64), 326 (3.93), and 459 (3.63) nm; δ($CDCl_3$) 1.38 (3H, t, J 6.9 Hz), 4.38 (2H, q, J 6.9 Hz), 6.89 (1H, dd, $J_{7,6}$ 5.5 and $J_{7,4}$ 0.8 Hz), 7.31-7.44 (3H, m), 7.46-7.52 (2H, m), 7.59 (1H, d, $J_{6,7}$ 5.5 Hz), and 8.12 (1H, d, $J_{4,7}$ 0.8 Hz); ^{13}C δ($CDCl_3$) 14.5, 61.3, 85.5, 116.2, 123.7, 125.5, 129.0, 130.9, 136.8, 137.0, 139.6, 163.4, and 163.7 (see Figure 9 in the Appendix); m/e 303 (M^+), 258, 230, 226 (base), 198 and, 154, m* (226→198) 173.5, (303→226) 168.6, and (198→154) 119.8.

A second product, ethyl 6-phenylthio-4H-thieno[3,2-b]pyrrole-5-carboxylate (311) was also isolated (4.2 mg, 0.9%), m.p. 136-137°C (from ethanol/water) (Found: C, 59.16; H, 4.27; N, 4.56. $C_{15}H_{13}NO_2S_2$ requires C, 59.83; H, 4.32; N, 4.62%); ν_{max} (Nujol) 3275 (s) and, 1675 (s) cm^{-1}; λ_{max} (EtOH) 2.04 (log ε 3.99), 2.51 (3.59), 2.95 (4.13), and 330 sh (3.70) nm; δ($CDCl_3$) 1.38 (3H, t, J 6.8 Hz), 4.43 (2H, q, J 6.8 Hz), 6.88 (1H, d, $J_{3,2}$ 5.4 Hz), 7.21 (1H, d, $J_{2,3}$ 5.4 Hz), 7.30-7.38 (3H, m), 7.50-7.55 (2H, m) and, 9.58 (1H, br. s, slowly exchangeable with D_2O); ^{13}C δ($CDCl_3$) 14.5, 61.0, 110.9, 116.4, 123.4, 126.4, 127.9, 128.9, 130.6, 133.0, 140.3, 140.4, and 161.4 (see Figure 17 in the Appendix); m/e 303 (M^+), 257 (base), 229, 152, and 105, m* (303→257) 218.0 and (257→229) 204.1.

A third product, ethyl 4a-phenyl-4aH-thieno[3,2-c][1,2]thiazine-3-carboxylate (312), an oil, was further purified by vacuum distillation (38.8 mg, 8.5%) b.p. ∿140°C/0.02 mmHg (Found: C, 59.66; H, 4.37; N, 4.64; S, 21.27. $C_{15}H_{13}NO_2S_2$ requires C, 59.38; H, 4.32; N, 4.62; S, 21.14%); ν_{max} (CCl_4) 1725 (s) cm^{-1}; λ_{max} (EtOH) 207 (log ε 4.31), 260 sh (3.89), 267 (3.89), 272 sh (3.87), 296 (3.78), and 330 (3.82) nm; δ($CDCl_3$) 1.33 (3H, t, J 7.0 Hz), 4.26 (2H, q, J 7.0 Hz), 6.50 (1H, d, $J_{7,6}$ 5.8 Hz) 7.13-7.26 (5H, m), 7.34 (1H, d, $J_{6,7}$ 5.8 Hz), and 7.38 (1H, s); ^{13}C δ($CDCl_3$) 14.0, 59.3, 62.0, 120.2, 120.7, 125.6, 128.4, 128.5, 131.1, 137.9, 141.9, 162.4, and 165.6 (see Figure 13 in the Appendix); m/e 303 (M^+), 274, 230 (base), 226, 198, and 186, m* (303→274) 247.8, (303→230) 174.6, and (230→186) 150.4.

3.9 Thermolysis of Cyclic Sulphimides

a Ethyl 1-methylthieno[2,3-e][1λ^4,2]thiazine-3-carboxylate (307)

A solution of the cyclic sulphimide (307) (188 mg, 0.78 mmol) in toluene (18 cm^3) was refluxed for 2 h. T.l.c. (dichloromethane) of the crude mixture was shown to be complex. However, two major components were isolated together as a mixture of oils (74.7 mg) by column chromatography (silica H, 4 g; gradient elution from 50% dichloromethane in petrol). Further purification of this mixture by p.l.c. (35% ethyl acetate in petrol, double elutions) gave two partially overlapping bands, R_f 0.7 (34.1 mg) and R_f 0.6 (35.4 mg), which were individually subjected to further purification by p.l.c with multiple elutions. Thus, from the top band (R_f 0.7), ethyl 4-methyl-4H-thieno[2,3-e][1,2]thiazine-3-carboxylate (320) was isolated as an oil (7 mg, 4%), ν_{max} (neat) 2980 (m), 2930 (m), 2870 (w), 1710 (s), 1575 (w), and 1450 (w) cm^{-1}; δ($CDCl_3$) 1.31 (3H, d, $J_{4\text{-Me},4}$ 7.7 Hz), 1.40 (3H, t, J 7.5 Hz), 4.37 (2H, q, J 7.5 Hz), 4.77 (1H, q, $J_{4,4\text{-Me}}$ 7.7 Hz), 6.80 (1H, d, $J_{7,6}$ 5.0 Hz), and 7.30 (1H, d, $J_{6,7}$ 5.0 Hz), the coupling between H-4 and 4-Me was confirmed by decoupling experiment; m/e 241 (M^+), 226 (base), 198, 195, 167, 154, 141, and 97, m* (226→198) 173.5 and (241→195) 157.8; the rest of the material remained a mixture.

Further separation of the lower band (R_f 0.6) by p.l.c. (40% dichloromethane in petrol, 3 elutions) produced a broad band, from the bottom half of which was isolated an essentially pure sample of ethyl 2,3-dihydrothieno[2,3-f][1,3]thiazepin-4-carboxylate (321) (26.8 mg, 14%), ν_{max} (neat) 3400 (s), 3110 (w), 2980 (m), 2930 (m), 1705 (s), 1660 (m), 1610 (s), and 1505 (s) cm^{-1}; δ($CDCl_3$) 1.37 (3H, t, J 7.2 Hz), 4.32 (2H, q, J 7.2 Hz), 4.48 (2H, d, $J_{2,NH}$ 6.8 Hz), 5.79 (1H, br. m), 6.78 (1H, dd, $J_{5,NH}$ 1.3 Hz and $J_{5,8}$ 0.4 Hz), 6.82

(1 H, dd, $J_{8,7}$ 5.3 Hz and $J_{8,5}$ 0.4 Hz), and 7.18 (1 H, d, $J_{7,8}$ 5.3 Hz) the coupling between NH and H-5, and NH and H-2 were confirmed by decoupling experiments; m/e 241 (M^+, base), 212, 184, 167, 140, and 97, m* (241→212) 186.5 and (212→184) 159.7.

Thermolysis of the cyclic sulphimide (307) in xylene for 0.5 h gave similar results.

b Ethyl 2-methylthieno[3,2-c][1λ^4,2]thiazine-3-carboxylate (308)

The cyclic sulphimide (308) (176 mg, 0.73 mmol) in refluxing bromobenzene (10 cm^3) for 2 h gave, after p.l.c (20 X 40 cm, 10% petrol in dichloromethane), ethyl 4-methyl-4 H-thieno[3,2-b]pyrrole-5-carboxylate (330) as an oil (b.p. ca. 110°C/0.08 mmHg, bulb to bulb distillation, oven temperature) (14 mg, 9%), low temperature recrystallization of the oil gave a crystalline solid, m.p. 24-26°C (from petrol, 20-0°C) (Found: C, 57.19; H, 5.49; N, 6.66. $C_{10}H_{11}NO_2S$ requires C, 57.39; H, 5.30; N, 6.69%); ν_{max} (neat) 3105 (w), 3090 (w), and 1705 (s) cm^{-1}; λ_{max} (EtOH) 220 (log ε 3.74), 288 (4.41), and 299 sh (4.38) nm; δ($CDCl_3$) 1.37 (3 H, t, J 7.0 Hz), 4.03 (3 H, s), 4.32 (2 H, q, J 7.0 Hz), 6.91 (1 H, dd, $J_{3,2}$ 5.1 and $J_{3,6}$ 0.7 Hz), 7.17 (1 H, d, $J_{6,3}$ 0.7 Hz), and 7.30 (1H, d, $J_{2,3}$ 5.1 Hz); ^{13}C δ($CDCl_3$) 14.5, 34.5, 60.1, 109.0, 110.1, 121.9, 127.1, 128.9, 145.7, and 161.8; m/e 209 (M^+, base), 194, 181, 164, 136, 109, and 95, m* (209→181) 156.8, (181→164) 148.6, (164→136) 112.8, (181→136) 102.2, (136→109) 87.4, and (136→95) 66.4, and ethyl 4a-methyl-4aH-thieno[3,2-c][1,2] thiazine-3-carboxylate (331) (71 mg, 40%), m.p. 71-72°C (from petrol (b.p. 60-80°C)) (Found: C, 50.04; H, 4.58; N, 5.80; S, 26.59. $C_{10}H_{11}NO_2S_2$ requires C, 49.77; H, 4.58; N, 5.80; S, 26.57%); ν_{max} (Nujol) 3070 (w), 3050 (w), 1720 (s), and 1595 (m) cm^{-1}; λ_{max} (EtOH) 207 (log ε 3.90), 243 sh (3.58), 253 sh (3.59), 295 sh (3.57), 325 (3.63),

and 343 sh (3.57) nm; δ($CDCl_3$) 1.19 (3H, s), 1.36 (3H, t, J 7.0 Hz), 4.32 (2H, q, J 7.0 Hz), 6.30 (1H, d, $J_{7,6}$ 5.9 Hz), 7.02 (1H, s), and 7.28 (1H, d, $J_{6,7}$ 5.9 Hz); ^{13}C δ($CDCl_3$) 14.2, 20.3, 53.1, 62.0, 119.6, 121.8, 129.8, 141.5, 162.3, and 167.7 (see Figure 11 in the Appendix); m/e 241 (M^+), 226, 209, 198, 181, 168 (base), and 141, m* (226→198) 173.5 and (241→168) 117.1.

Independent synthesis of ethyl 4-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylate (330).

Ethyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (332) was prepared by the method of Hemetsberger, et al.,[28] m.p. 130-131°C (from dichloromethane/petrol (b.p. 60-80°C)) (lit.,[28] 131°C from benzene); ν_{max} (Nujol) 3300 (s) and 1672 (s) cm^{-1}; λ_{max} (EtOH) 217 (log ε 3.73), 287, (4.36), and 296 sh (4.35) nm; ^{13}C δ($CDCl_3$) 14.5, 60.7, 107.6, 111.2, 124.8, 127.1, 129.4, 141.6, and 162.0.

To a stirred suspension of sodium hydride (7 mg, 0.29 mmol) in dry DMF (1 cm^3) under dry nitrogen, was added the 4H-thienopyrrole (332) (46.7 mg, 0.24 mmol) in dry DMF (1 cm^3) at room temperature. After stirring for 0.5 h, an excess of methyl iodide was added. The mixture was stirred at room temperature for a further 2 h and then poured into water (5 cm^3). The mixture was extracted with ether (4 X 5 cm^3), washed with saturated sodium chloride solution, dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by column chromatography (silica H, 1 g; 20% dichloromethane in petrol) to give an oil (37.7 mg, 75%). The spectroscopic properties were identical to that of the thienopyrrole (330).

Thermolysis of ethyl 4a-methyl-4a*H*-thieno[3,2-*c*][1,2]thiazine-3-carboxylate (331).

The thermolysis was carried out on t.l.c. scale (*ca.* 10 mg) in refluxing bromobenzene (1 cm^3). No appreciable reaction was observed after 8h. After 2 days, t.l.c. of the reaction mixture showed only base-line material with no sign of the 4-methylthienopyrrole (330) was observed.

c Ethyl 2-phenylthieno[3,2-*c*][1λ^4,2]thiazine-3-carboxylate (310)

i) In xylene - A solution of the cyclic sulphimide (310) (98.6 mg, 0.33 mmol) in boiling xylenes (8 cm^3) for 10 h gave, after p.l.c. (25% petrol in dichloromethane), ethyl 4a-phenyl-4a*H*-thieno[3,2-*c*]-thiazine-3-carboxylate (312) (93 mg, 94%). Hydrolysis of the above 4a*H*-thienothiazine (312) (50 mg, 0.165 mmol) was carried out in a mixture of ethanol (0.6 cm^3) and aqueous potassium hydroxide solution (0.3 cm^3, 1 *M*, 0.3 mmol) at room temperature for 12 h. The mixture was then diluted with saturated sodium chloride solution (5 cm^3), acidified with conc. HCl to pH 1, extracted with ethyl acetate and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave 4a-phenyl-4a*H*-thieno[3,2-*c*][1,2]thiazine-3-carboxylic acid (335) (44 mg, 97%), m.p. 150-160°C (dec.); ν_{max} (Nujol) 3200-2200 (br) and 1700 (s) cm^{-1}; δ(90 MHz, $CDCl_3$) 6.58 (1H, d, $J_{7,6}$ 6.0 Hz), 7.10-7.30 (5H, m), 7.40 (1H, d, $J_{6,7}$ 6.0 Hz), 7.49 (1H, s), and 9.43 (1H, br. s, D_2O exchangeable); m/e 275 (M^+, base), 230, 198, and 186.

ii) In bromobenzene - A solution of the cyclic sulphimide (310) (177 mg, 0.58 mmol) in boiling bromobenzene (11 cm^3) for 2.5 h gave, after p.l.c. (25% petrol in dichloromethane, double elutions), an inseparable mixture of ethyl 4a-phenyl-4a*H*-thieno[3,2-*c*]thiazine-3-carboxylate (312) and a new product (total yield 164 mg) in the ratio

of about 5:1 (by n.m.r.). When this mixture was subjected to further thermolysis in bromobenzene for 36 h, a clean conversion of the 4a<u>H</u>-thienothiazine (312) to the new product, <u>ethyl 4-phenylpyrrolo[1,2-b]isothiazole-6-carboxylate</u> (340) (126 mg, 80%, based on the starting cyclic sulphimide (310)), was observed, m.p. 108-109°C (from petrol) (Found: C, 66.62; H, 4.85; N, 5.19. $C_{15}H_{13}NO_2S$ requires C, 66.40; H, 4.83; N, 5.16%); ν_{max} (Nujol) 1670 (s) and 1660 (s) cm^{-1}; λ_{max} (EtOH) 202 (log ε 4.11), 226 (4.04), 261 (4.32), 310 (4.19), and 345 sh (3.95) nm; δ($CDCl_3$) 1.43 (3H, t, <u>J</u> 6.8 Hz), 4.43 (2H, q, <u>J</u> 6.8 Hz), 7.14 (1H, d, $\underline{J}_{3,2}$ 6 Hz), 7.19-7.28 (1H, m), 7.36-7.45 (2H, m), 7.48 (1H, d, $\underline{J}_{5,2}$ 1.0 Hz), 7.56-7.62 (2H, m), and 7.68 (1H, dd, $\underline{J}_{2,3}$ 6.0 Hz, $\underline{J}_{2,5}$ 1.0 Hz); ^{13}C δ($CDCl_3$) 14.6, 60.6, 111.1, 117.3, 118.1, 120.2, 125.8, 125.9, 128.9, 129.8, 135.2, 143.2, and 161.1 (see Figure 14 in the Appendix); m/e 271 (M^+, base), 243, 226, 198, and 196, m* (271→243) 217.9. This pyrroloisothiazole (340) was unstable on silica as confirmed by two dimensional t.l.c. analysis.

iii) In 1,2-dichlorobenzene - A solution of the cyclic sulphimide (310) (100 mg) in 1,2-dichlorobenzene (9 cm^3) was heated to reflux for 25 min, after which all of the starting cyclic sulphimide (310) had disappeared to give a mixture of the 4a<u>H</u>-thienothiazine (312) and the pyrroloisothiazole (340) together with some highly polar material (by t.l.c). Prolonged thermolysis (16 h) gave a complex mixture with traces of (312) and (340).

iv) In a melt at 180-185°C - The cyclic sulphimide (310) (30 mg) was heated neat at 180-185°C and the reaction was monitored by t.l.c. and n.m.r. spectroscopy. After 10 minutes, the sulphimide was converted mainly to the 4a<u>H</u>-thienothiazine (312), but on further heating, a complex mixture was obtained.

Desulphurisation of ethyl 4-phenylpyrrolo[1,2-b]isothiazole-6-carboxylate (340)

A mixture of (340) (37 mg, 0.136 mmol) and freshly prepared Raney nickel[172] (ca. 0.5 g as wet paste) in ethanol (7 cm^3) was heated to reflux for 1 h with stirring. After cooling to room temperature, the mixture was filtered through celite and the residue washed with hot ethanol (10 cm^3). Removal of the ethanol *in vacuo* gave a fluorescent green oil, which on p.l.c (20% petrol in dichloromethane) gave ethyl 5-ethyl-4-phenylpyrrole-2-carboxylate (341) as a solid (26.7 mg, 81%), m.p. 113-114°C (from ethanol/water) (Found: C,73.93; H, 7.07; N, 5.71. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%); ν_{max} (Nujol) 3280 (s) 1685 (s), and 1603 (w) cm^{-1}; $\delta(CDCl_3)$ 1.29 (3H, t, J 7.8 Hz), 1.37 (3H, t, J 7.0 Hz), 2.83 (2H, q, J 7.8 Hz) 4.36 (2H, q, J 7.0 Hz), 7.01 (1H, d, $J_{3,1}$ 2.6 Hz), 7.20-7.29 (1H, m), 7.33-7.39 (4H, m), and 9.51 (1H, br S), coupling between H-1 and H-3 was confirmed by decoupling experiments; m/e 243 (M^+, base), 228, 215, 197, 182, 170, 169, 168, 166, and 154, m* (243→228) 213.9, (243→197) 159.7, and (228→182) 145.3.

Thermolysis of ethyl 4a-phenyl-4aH-thieno[3,2-c]thiazine-3-carboxylate (312)

i) In bromobenzene - A solution of (312) (92 mg, 0.304 mmol) in bromobenzene (10 cm^3) was refluxed for 72 h. After removal of the solvent under reduced pressure, the residue was subjected to bulb to bulb distillation under vacuum. During the distillation, a pale yellow solid sublimed out and the main distillate fraction was collected between 140-150°C/0.02 mmHg. The distillate was taken up into cold dichloromethane and the insoluble yellow solid filtered. Removal of the solvent from the filtrate gave the pyrrolo[1,2-b]isothiazole (340)

(68 mg, 82%) after recrystallization from petrol. The pale yellow solid obtained was identified as elemental sulphur (6.1 mg, 63%), m.p. 110-112°C (lit.,[197] 112.8°C); ν_{max} (Nujol) 725 (w) cm^{-1}; t.l.c. was identical to that of sulphur in all solvent systems tried.

ii) In 1,2-dichlorobenzene - A solution of the 4a<u>H</u>-thienothiazine (312) (180 mg, 0.59 mmol) in refluxing 1,2-dichlorobenzene (15 cm^3) for 15 h gave, after column chromatography (silica H, 10 g; dichloromethane), 3,4-<u>di</u>(2-<u>ethoxycarbonyl</u>-4-<u>phenylpyrrol</u>-5-<u>yl</u>)<u>thiophen</u> (343) (42.6 mg, 28%), m.p. 246-248°C (Found: M^+= 510.1616. $C_{30}H_{26}N_2O_4S$ requires 510.1613); ν_{max} (Nujol) 3280 (s) and 1685 (s) cm^{-1}; λ_{max} (EtOH) 211 (log ε 4.47), 242 (4.52), and 292 (4.45) nm; δ(DMSO-d_6) 1.30 (2 X 3H, t, <u>J</u> 7.0 Hz), 4.23 (2 X 2H, q, <u>J</u> 7.0 Hz), 6.75 (2 X 1H, d, <u>J</u> 2.4 Hz), 7.02 (10H, m), 7.58 (2 X 1H, s), and 11.26 (2 X 1H, br. d, <u>J</u> 2.4 Hz); m/e 510 (M^+, base), 464, 421, 418, 393, 391, 390, 365, 363, 336, and 285, m* (510→464) 422.1, (464→418) 376.6, and (421→393) 366.9.

<u>Attempted desulphurization of 3,4-di(2-ethoxycarbonyl-4-phenyl-pyrrol-5-yl)thiophen (343)</u>

Three separate attempts were carried out using less active Raney nickel in boiling ethanol,[172] W-5 Raney nickel in boiling ethanol/chloroform mixture and W-5 Raney nickel in boiling dioxan. In all three cases, only starting material was recovered.

<u>Thermolysis of 4-phenylpyrrolo[1,2-<u>b</u>]isothiazole-6-carboxylate (340)</u>

A solution of (340) (22 mg, 0.08 mmol) in 1,2-dichlorobenzene (2 cm^3) was refluxed for 20 h. After cooling to room temperature, the apparatus was opened to air and a strong smell of hydrogen sulphide was noted. A strip of filter paper moistened with lead acetate solution

turned dark when brought near to the reaction mixture. The crude product, after column chromatography (silica H, 0.6 g; dichloromethane) gave the thiophen (343) (10 mg, 49%).

3.10 Photolysis of Cyclic Sulphimides and their Azide Precursors

a Ethyl 2-azido-3-(3-methylthiothien-2-yl)propenoate (201)

A solution of the vinyl azide (201) (100 mg) in acetonitrile (90 cm^3) was irradiated at 350 nm for 5 min. The n.m.r. spectrum of the crude mixture indicated that it was mostly one product. The major product was tentatively assigned as ethyl 2-(3-methylthiothien-2-yl)-2H-azirine-3-carboxylate (350), δ(90 MHz, CCl_4) 1.42 (3H, t, J 7.0 Hz), 2.33 (3H, s), 3.70 (1H, s), 4.47 (2H, q, J 7.0 Hz) 6.98 (1H, d, J 5.0 Hz), and 7.18 (1H, d, J 5.0 Hz). No attempt was made to purify the crude product owing to its instability to silica and high temperatures.

Further irradiation of the above crude product at 300 nm in acetonitrile (50 cm^3) for 2.5 h gave a complex mixture.

Thermolysis of the crude azirine (350) in boiling toluene again gave a complex mixture containing a trace amount of the cyclic sulphimide (307).

b Ethyl 3-(3-azidothien-2-yl)-2-(phenylthio)propenoate (215)

Method (i) A solution of the azide (215) (161 mg, 0.49 mmol) in acetonitrile (120 cm^3) was irradiated at 350 nm until all of the starting azide had been consumed (25 min). The crude products were separated by p.l.c. (1% diethyl ether in dichloromethane) to give

ethyl 6-phenylthio-4H-thieno[3,2-b]pyrrole-5-carboxylate (311) (60 mg, 41%) and ethyl 2-phenylthieno[3,2-c][1λ^4,2]thiazine-3-carboxylate (310) (83 mg, 56%).

Method (ii) A solution of the azide (215) (113 mg, 0.34 mmol) in acetonitrile (85 cm^3) was irradiated at 350 nm until all the cyclic sulphimide (310) formed from the starting azide had disappeared (3 h). The crude product was purified by column chromatography (silica H, 3 g; dichloromethane) to give the thienopyrrole (311) (82 mg, 80%).

Hydrolysis and decarboxylation of ethyl 6-phenylthio-4H-thieno[3,2-b]-pyrrole-5-carboxylate (311)

A solution of the 4H-thieno[3,2-b]pyrrole (311) (50 mg, 0.165 mmol) in dioxan (0.4 cm^3) and aqueous potassium hydroxide (0.2 cm^3, 1 M) was refluxed for 1 h. After cooling to room temperature, the mixture was diluted with water (2 cm^3) and extracted with ethyl acetate (2 X 2 cm^3). The aqueous layer was acidified to pH 5 with dilute hydrochloric acid solution (the product tends to be unstable towards strong acidic conditions; a strong smell of thiophenol was once noticed when the mixture was acidified to pH 1 all in one action) and the mixture was extracted with ethyl acetate (2 X 5 cm^3). This procedure was repeated three times until the acidity of the aqueous layer became pH 1. The combined ethyl acetate extracts (after acidification) were washed with water (2 X 10 cm^3), dried over magnesium sulphate and the solvent removed in vacuo to give 6-phenylthio-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (45 mg, 99%), m.p. 134-136°C (dec.); ν_{max} (Nujol) 3440 (m), 3300-2200 (br), and 1655 (s) cm^{-1}; δ(90 MHz, acetone-d_6) 7.03 (1H, d, 5.2 Hz), 7.19 (1H, br. s, D_2O exchangeable), 7.30-7.60 (6H, m), and 11.14 (1H, br. s, D_2O exchangeable); m/e 275 (M^+), 257 and 231 (base). The above acid (20 mg, 0.073 mmol) was heated at 145°C for 30 sec (smell of thiophenol was

detected). The crude product was purified by column chromatography (dichloromethane) to give 6-phenylthio-4 H-thieno[3,2-b]pyrrole (353b) (12.3 mg, 73%), m.p. 131-132°C; ν_{max} (Nujol) 3420 (s) and 1580 (m) cm^{-1}; δ($CDCl_3$) 6.98 (1H, d, $J_{3,2}$ 5.2 Hz), 7.05-7.25 (7H, m, which constitute [7.14 (1H, dd, $J_{2,3}$ 5.2 Hz and $J_{2,5}$ 1.3 Hz), 7.24 (1H, dd, $J_{5,4}$ 2.5 Hz and $J_{5,2}$ 1.3 Hz) and 5H of Ph as broad multiplet]), and 8.48 (1H, br. d, D_2O exchangeable), the couplings between H-2 and H-3, H-2 and H-5, and H-4 and H-5 were confirmed by decoupling experiments; m/e 231 (M^+, base), 199, 198, 186, 171, 154, and 122, m* (231→199) 171.4 and (231→198) 169.7. The structure of the thienopyrrole (353b) was further confirmed by n.m.r. n.O.e difference experiments (see Figure 20 in the Appendix).

c Ethyl 3-(3-azidothien-2-yl)-2-(methylthio)propenoate (216)

Method (i) A solution of the azide (216) (100 mg, 0.37 mmol) in acetonitrile (90 cm^3) was irradiated at 350 nm for 0.5 h (until all the starting azide had disappeared). The crude mixture was purified by column chromatography (silica H, 2 g; gradient elution from 1% diethyl ether in dichloromethane) to give ethyl 6-methylthio-4H-thieno[3,2-b]pyrrole-5-carboxylate (309) (47 mg, 53%) and ethyl 2-methylthieno[3,2-c][1λ^4, 2]thiazine-3-carboxylate (308) (36 mg, 40%).

Method (ii) As in (i) except that the irradiation was continued until all of the cyclic sulphimide (308) formed from the starting azide had disappeared (2 h). After column chromatography (silica H, 1g; dichloromethane), the 4 H-thienopyrrole (309) (79%) was isolated as the only product.

Hydrolysis and decarboxylation of ethyl 6-methylthio-4 H-thieno[3,2-b]-pyrrole-5-carboxylate (309)

A solution of the thienopyrrole (309) (70 mg, 0.29 mmol) in

dioxan (0.4 cm^3) and aqueous potassium hydroxide (1 M, 0.35 cm^3) was heated to reflux for 1 h. After cooling to room temperature, the reaction mixture was worked up as described for the hydrolysis of the thienopyrrole (311), to give 6-methylthio-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (60 mg, 97%), m.p. 140-143°C; ν_{max} (Nujol) 3440 (s), 3385 (s), 3300-2100 (br), and 1655 (s) cm^{-1}; δ(90 MHz, acetone-d_6) 2.64 (3H, s) 6.59 (1H, br. s, D_2O exchangeable), 7.07 (1H, d, J 5.0 Hz), 7.50 (1H, d, J 5.0 Hz), and 10.95 (1H, br. s, D_2O exchangeable); m/e 213(M^+, base), 195, 180, and 152, m* (213→195) 178.5. The above acid (30 mg, 0.14 mmol) was heated at 130-145°C until all of the solid had melted. A strong smell of methanethiol was noted. After purification by column chromatography (silica H, 1.5 g; 40% dichloromethane in petrol), gave 6-methylthio-4H-thieno-[3,2-b]pyrrole (353a) as an oil (13 mg, 55%). The compound decomposed within a week at room temperature, giving off a strong smell of methanethiol. ν_{max} (neat) 3400 (s), 1560 (w), and 1500 (w) cm^{-1}; δ($CDCl_3$) 2.42 (3H, s), 6.95 (1H, d, $J_{3,2}$ 5.3 Hz), 7.35 (1H, dd, $J_{5,4}$ 2.3 and $J_{5,2}$ 1.3 Hz), 7.13 (1H, dd, $J_{2,3}$ 5.3 and $J_{2,5}$ 1.3 Hz), and 8.25 (1H, br. d, D_2O exchangeable), the couplings between H-2 and H-3, H-2 and H-5, H-4 and H-5 were confirmed by decoupling experiments; m/e 169 (M^+), 154 (base), 136, and 110, m* (169→154) 140.3, (169→136) 109.4, and (154→110) 78.6. The structure of the thienopyrrole (353a) was further confirmed by n.m.r. n.O.e. difference experiments (see Figure 19 in the Appendix).

d Ethyl 2-methylthieno[3,2-c][1λ^4,2]thiazine-3-carboxylate (308)

Method (i) A solution of the cyclic sulphimide (308) (35 mg) in acetonitrile (30 cm^3) was irradiated at 350 nm for 0.5 h. The crude mixture was separated by column chromatography to give ethyl 6-methyl-

thio-4H-thieno[3,2-b]pyrrole-5-carboxylate (309) (12 mg, 34%) and the starting material (308) (20 mg, 58%).

Method (ii) Irradiation of the cyclic sulphimide (308) in acetonitrile at 300 nm for 5 h, gave the thienopyrrole (309) (50%).

Method (iii) The cyclic sulphimide (308) (84 mg, 0.35 mmol) was irradiated in a mixture of dimethyl sulphoxide (5 cm^3) and acetonitrile (60 cm^3) at 300 nm for 5 h. The thienopyrrole (309) (48.7 mg, 58%) was obtained as the only product.

Method (iv) Irradiation of the cyclic sulphimide (308) in dimethyl sulphoxide at 300 nm for 3 h gave the thienopyrrole (309) in 63% yield.

e Ethyl 2-phenylthieno[3,2-c][1λ^4, 2]thiazine-3-carboxylate (310)

Method (i) A solution of the cyclic sulphimide (310) (65 mg, 0.216 mmol) in acetonitrile (50 cm^3) was irradiated at 350 nm for 25 min. The crude mixture was separated by column chromatography (silica H, 2 g; dichloromethane) to give ethyl 6-phenylthio-4H-thieno-[3,2-b]pyrrole-5-carboxylate (311) (10 mg, 15%) and the starting sulphimide (310) (54 mg, 83%).

Method (ii) A solution of the sulphimide (310) (180 mg, 0.59 mmol) in acetonitrile (150 cm^3) was irradiated at 350 nm until all of the starting material had disappeared (2 h). The crude mixture was separated by p.l.c. (dichloromethane) to give the thienopyrrole (311) (150 mg, 83%).

f Ethyl 1-methylthieno[2,3-e][1λ^4, 2]thiazine-3-carboxylate (307)

Irradiation of the cyclic sulphimide (307) (92 mg) in acetonitrile (100 cm^3) at 350 nm for 10 min , gave the azirine (350) as the major product (as indicated by n.m.r).

4 APPENDIX

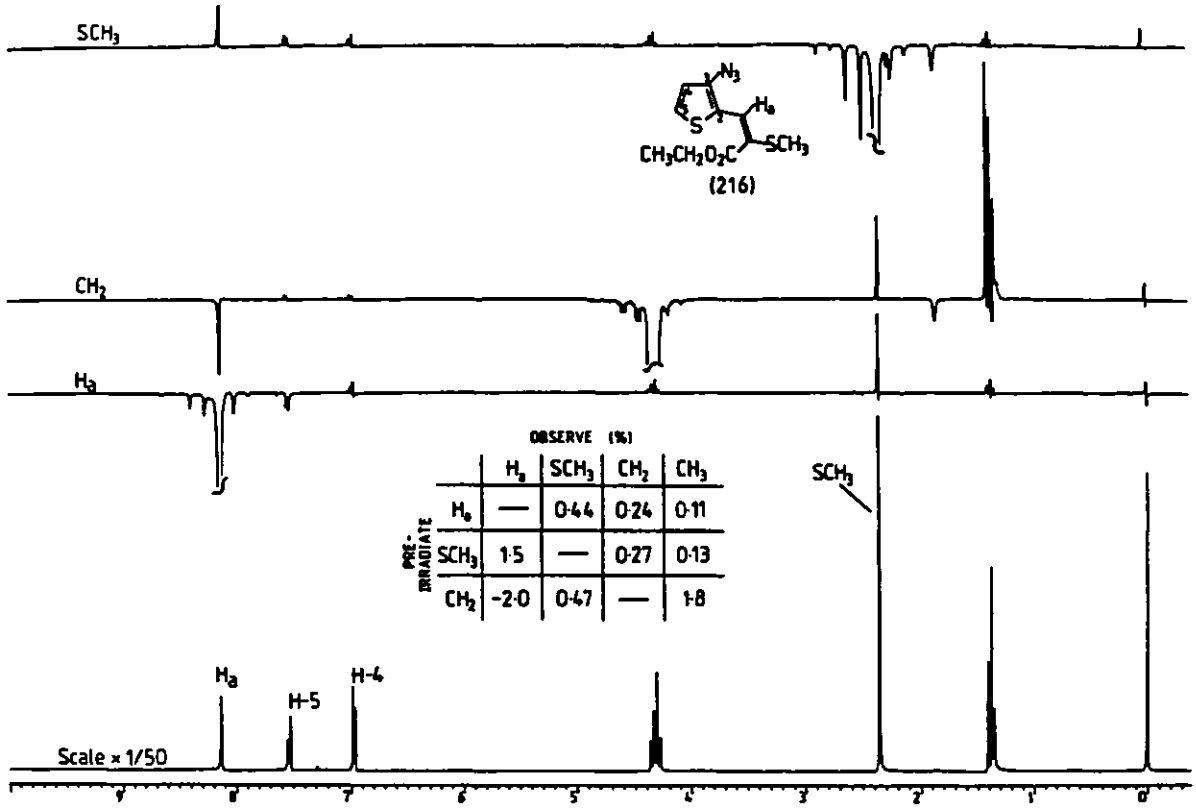


Figure 1

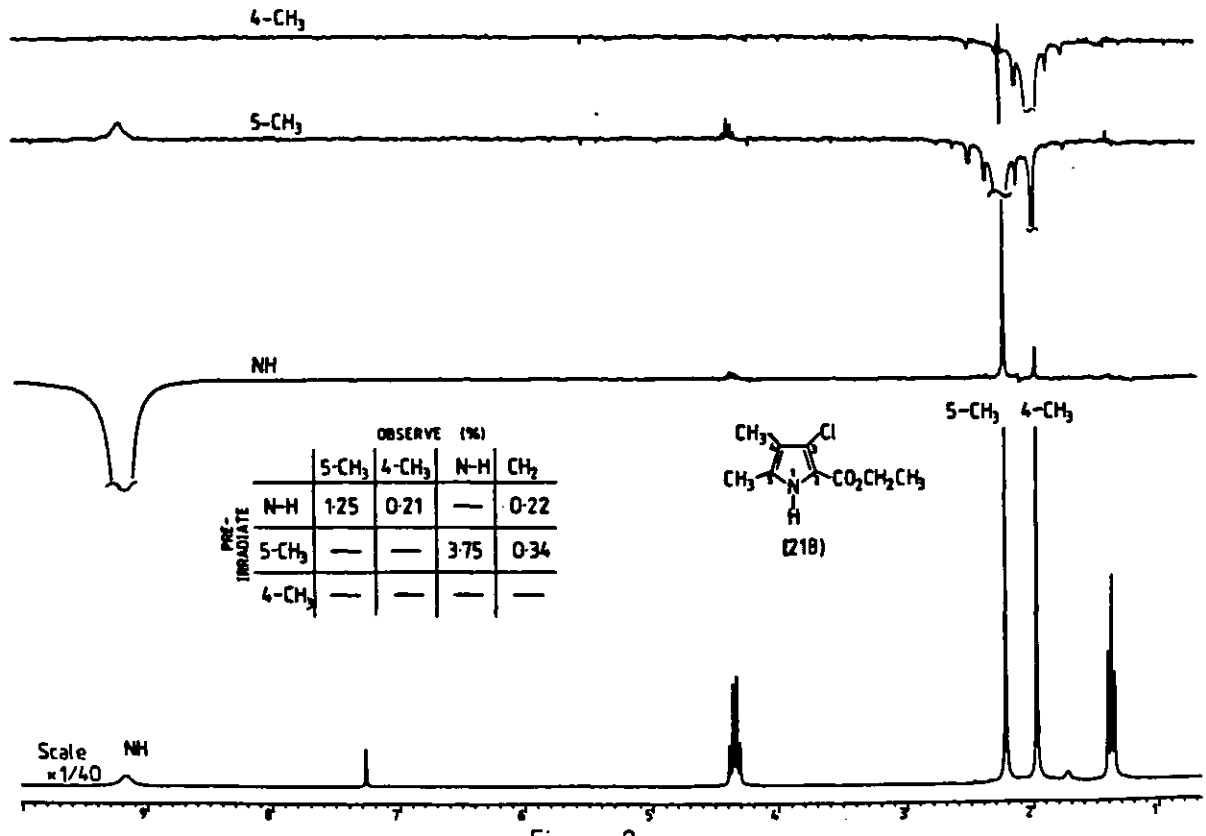
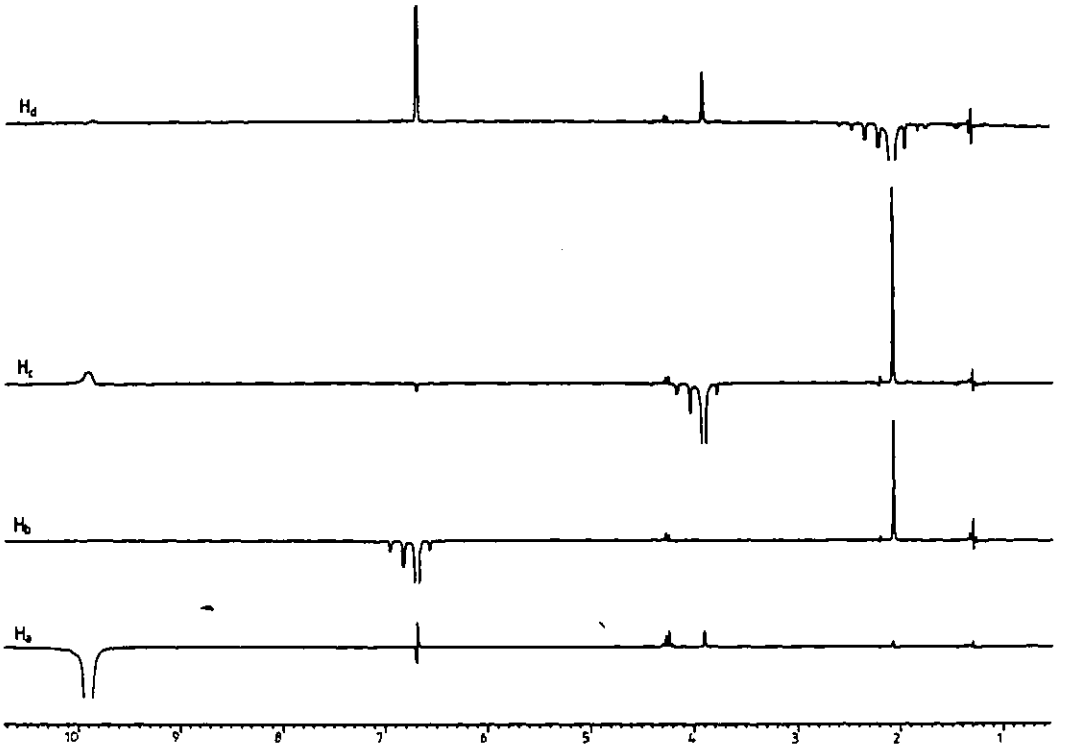
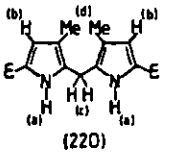


Figure 2



OBSERVE (%)

PRE-IRRADIATE	H_a	H_b	H_c	H_d	H_e
H_a	—	—	0·73	0·06	0·47
H_b	—	—	—	1·24	0·14
H_c	4·0	—	—	2·03	—
H_d	—	1·30	2·24	—	—



(220)

E=$CO_2CH_2CH_3$ (a)

Figure 3

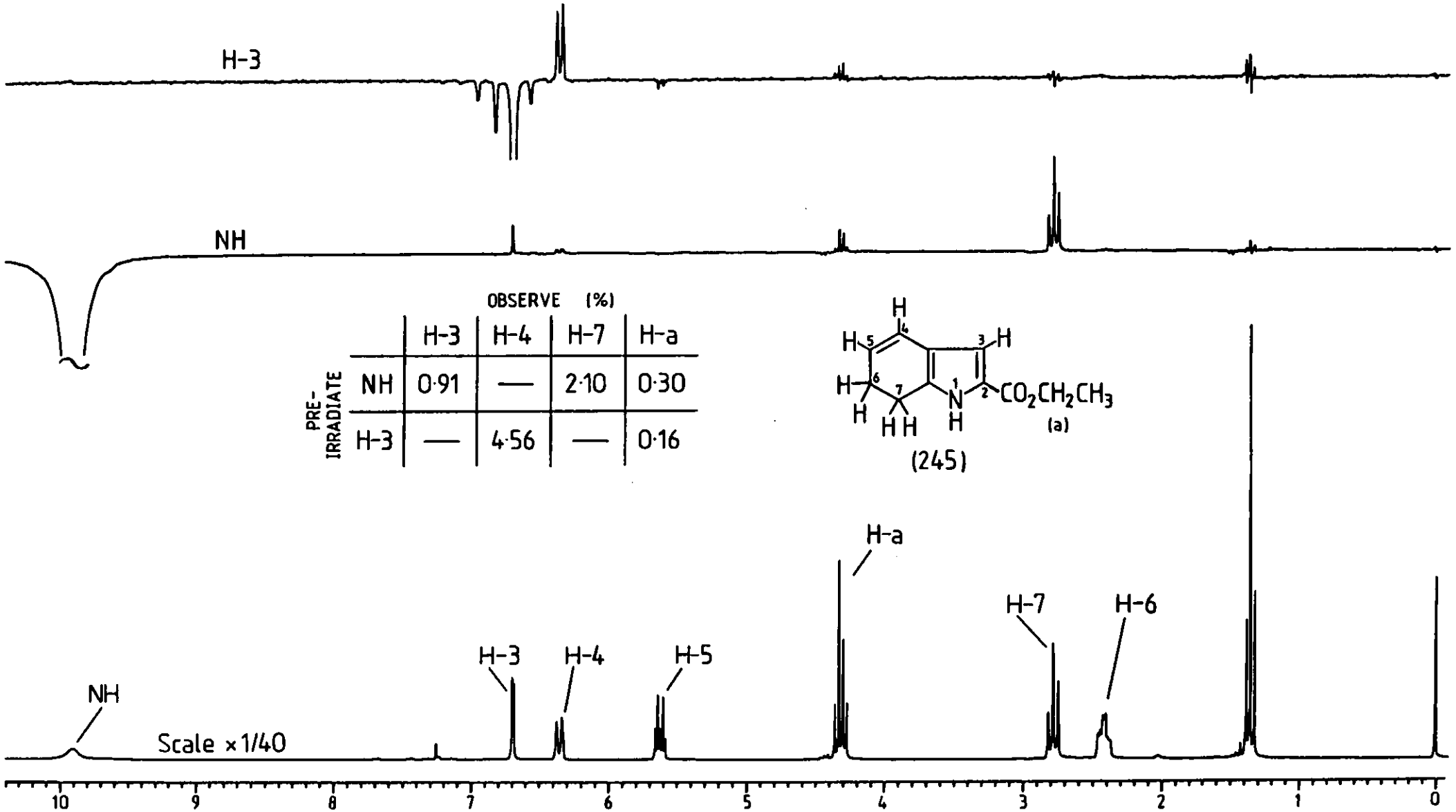
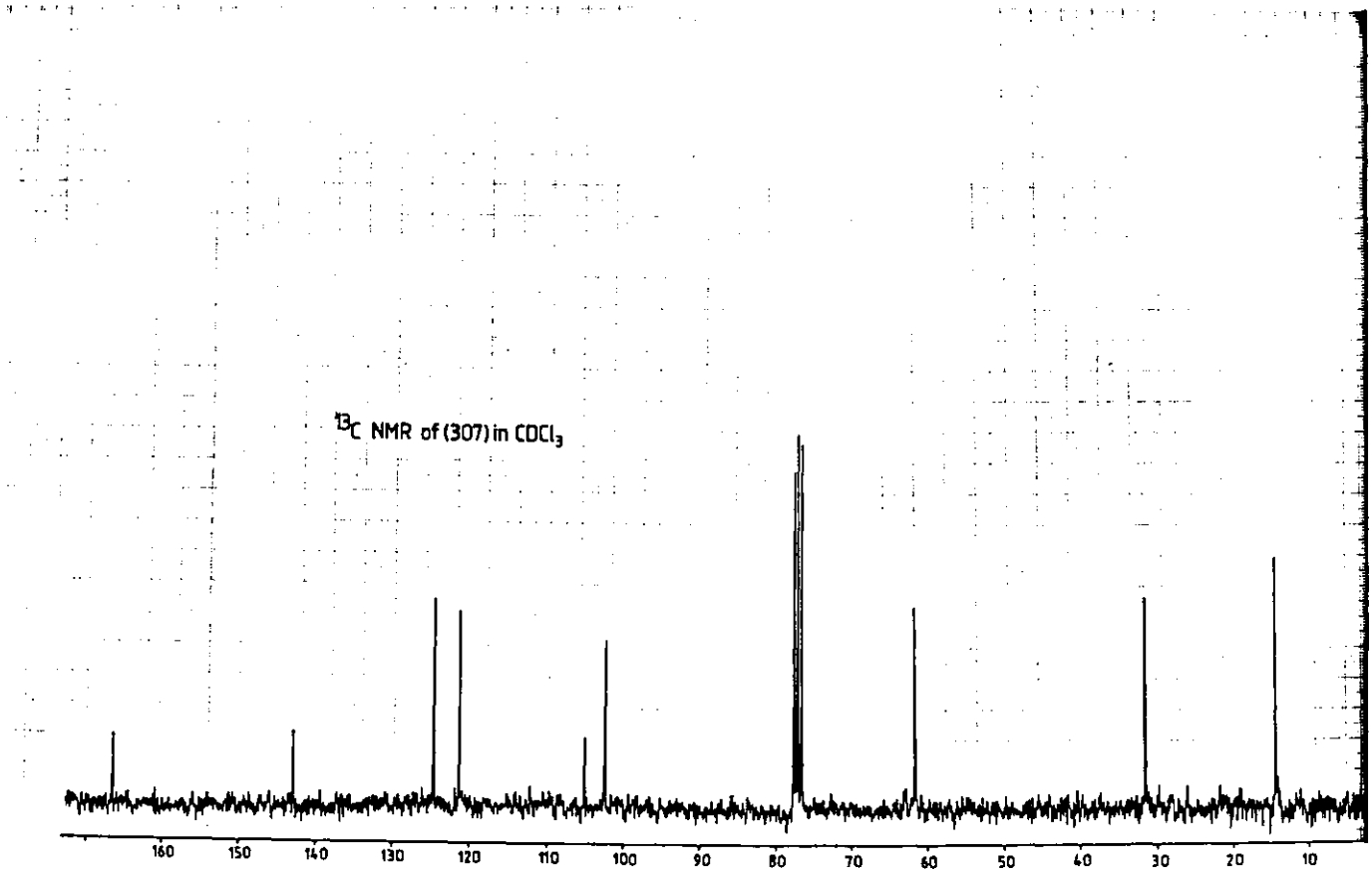

H-3
NH
OBSERVE (%)
PRE-IRRADIATE
H-3 H-4 H-7 H-a
NH 0·91 — 2·10 0·30
H-3 — 4·56 — 0·16
(245)
(a)
H-a
H-7
H-6
H-3
H-4
H-5
NH
Scale ×1/40
10 9 8 7 6 5 4 3 2 1 0

Figure 4


^{13}C NMR of (307) in $CDCl_3$
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

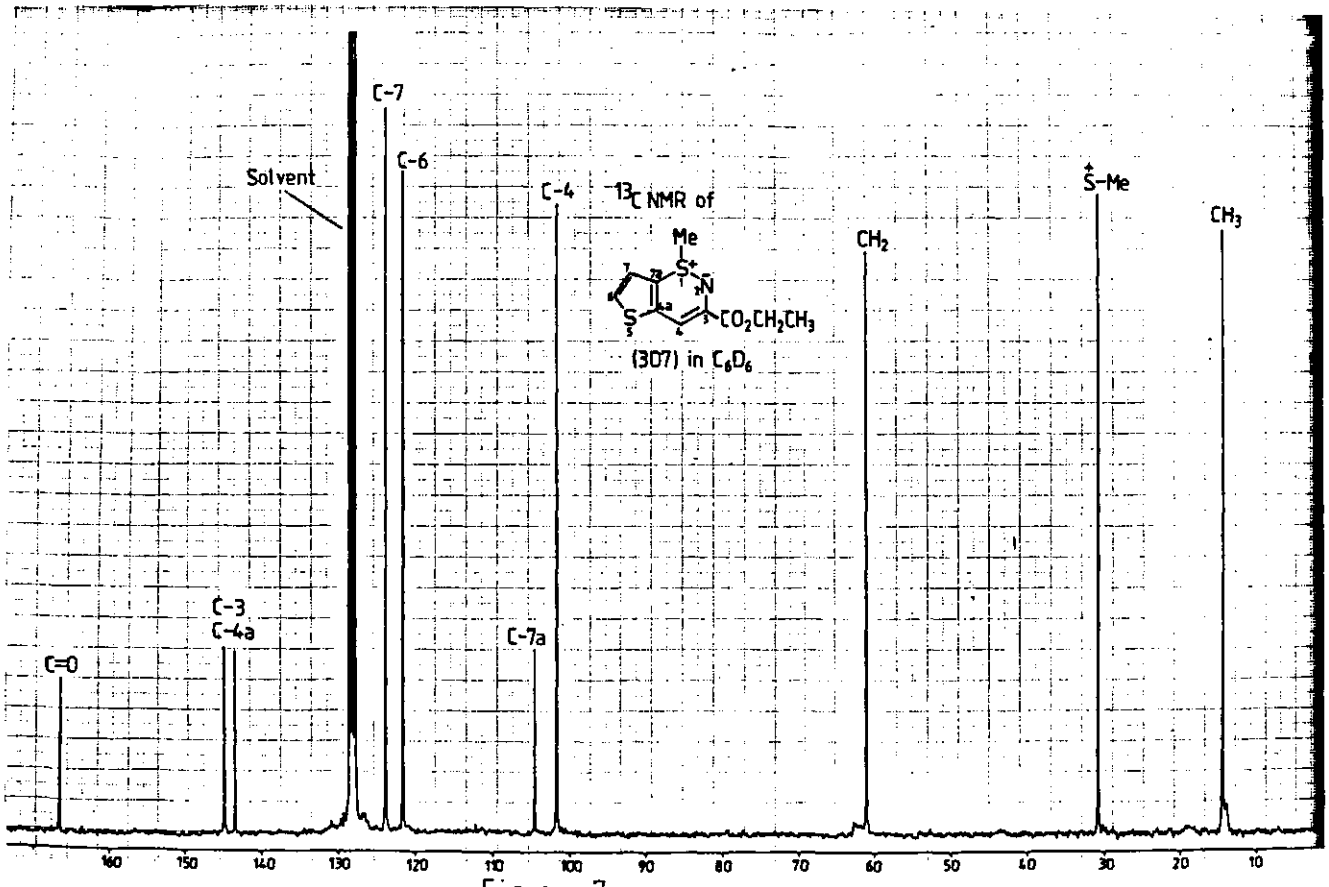

Solvent
C-7
C-6
C-4
^{13}C NMR of
Me
$CO_2CH_2CH_3$
(307) in C_6D_6
CH_2
S-Me
CH_3
C-3
C-4a
C-7a
C=O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

Figure 7

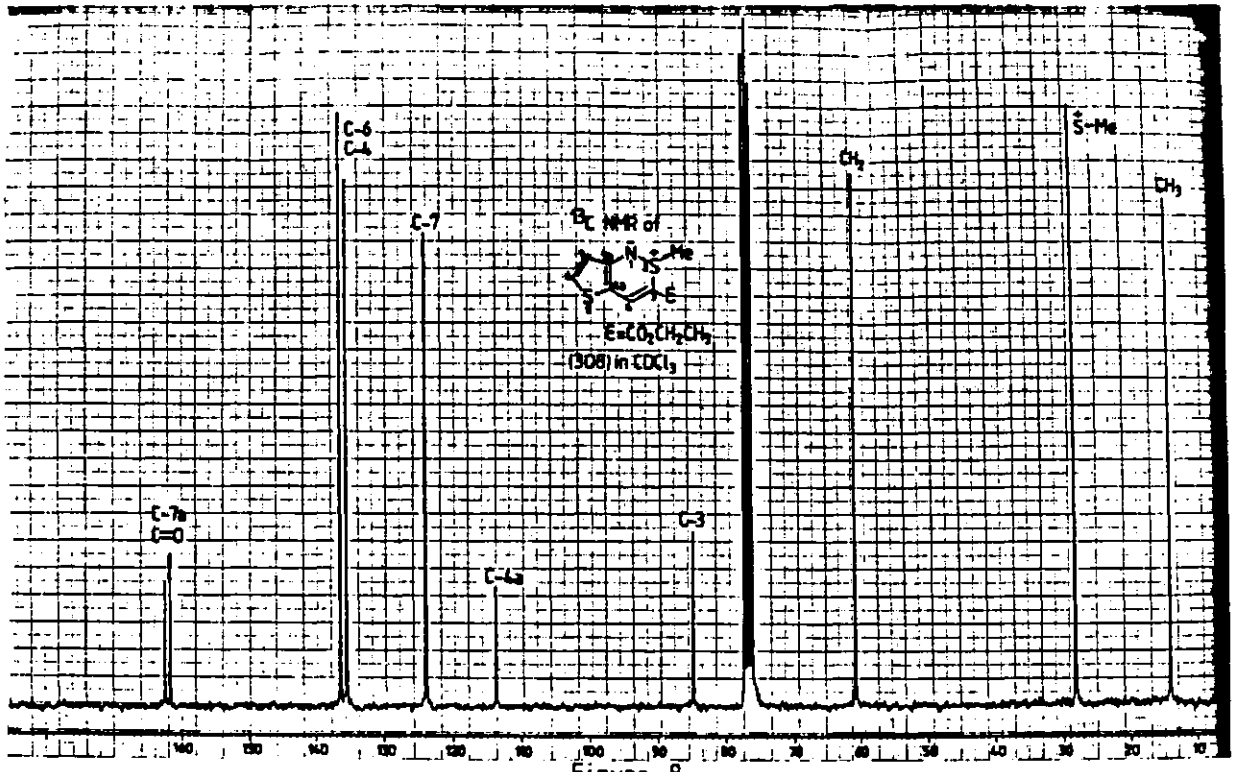


Figure 8

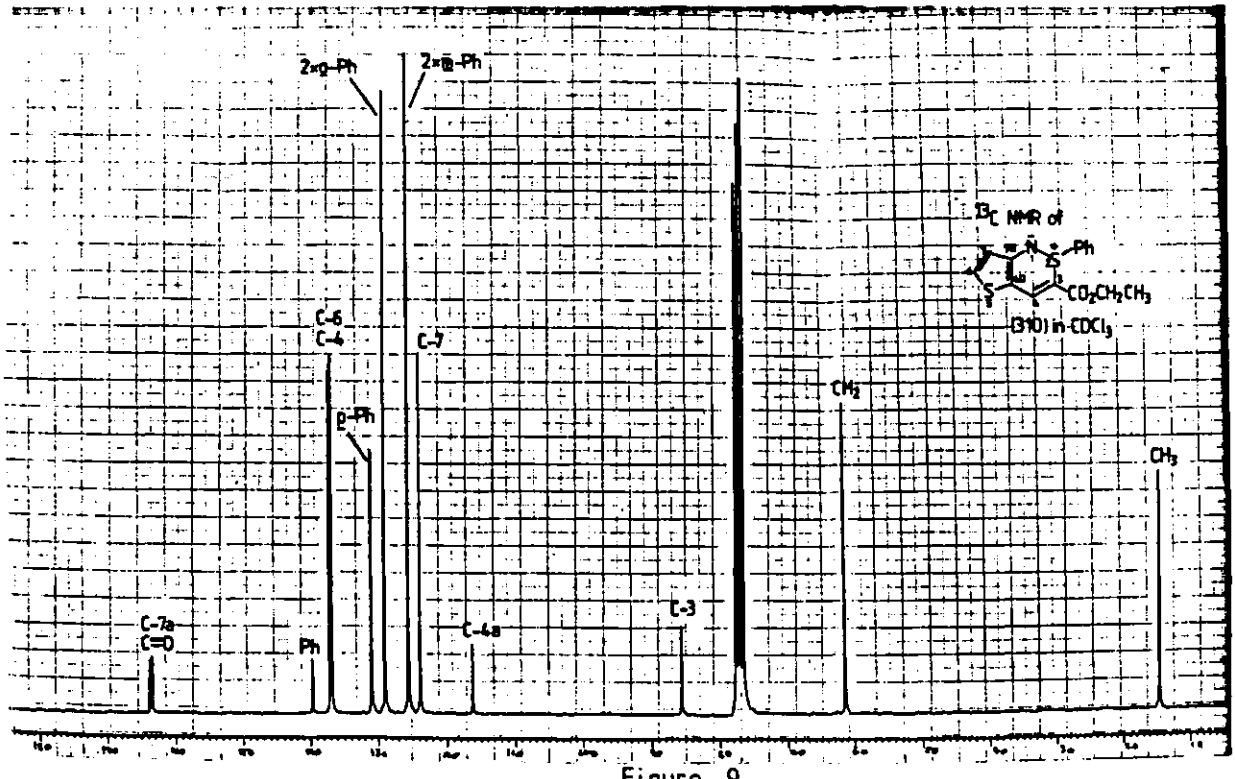


Figure 9

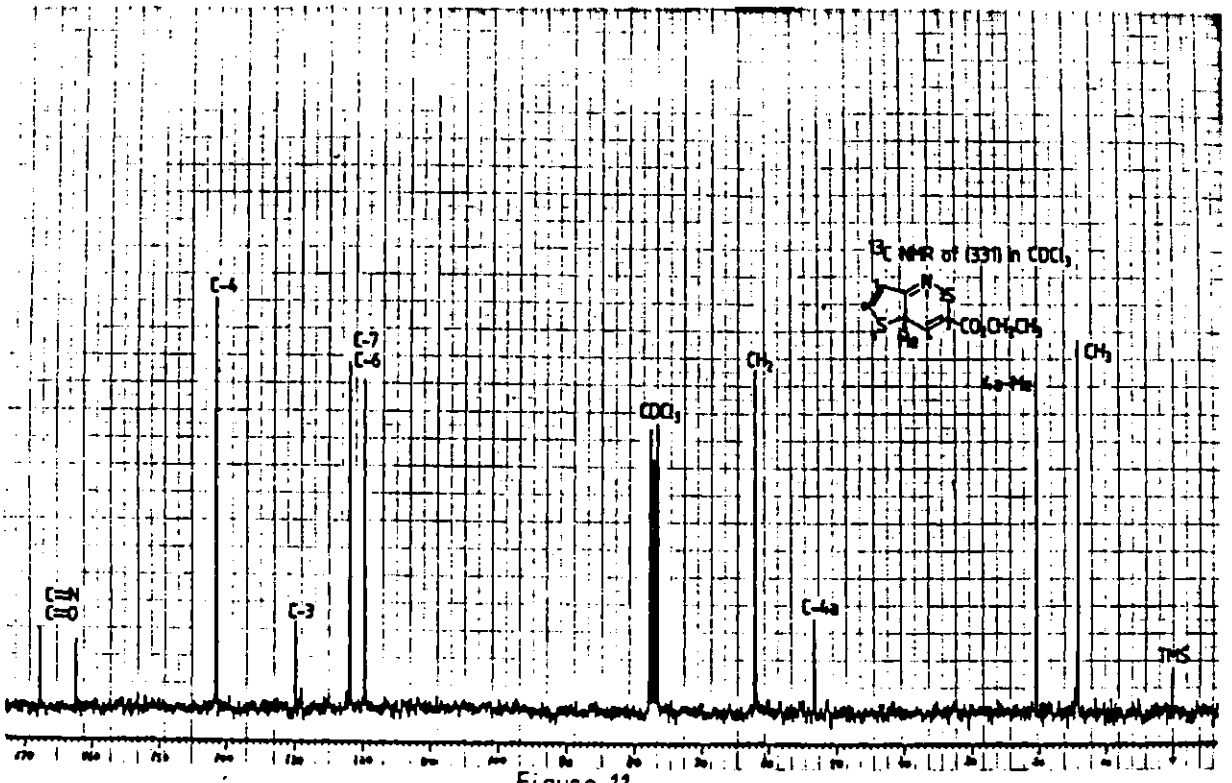


Figure 11

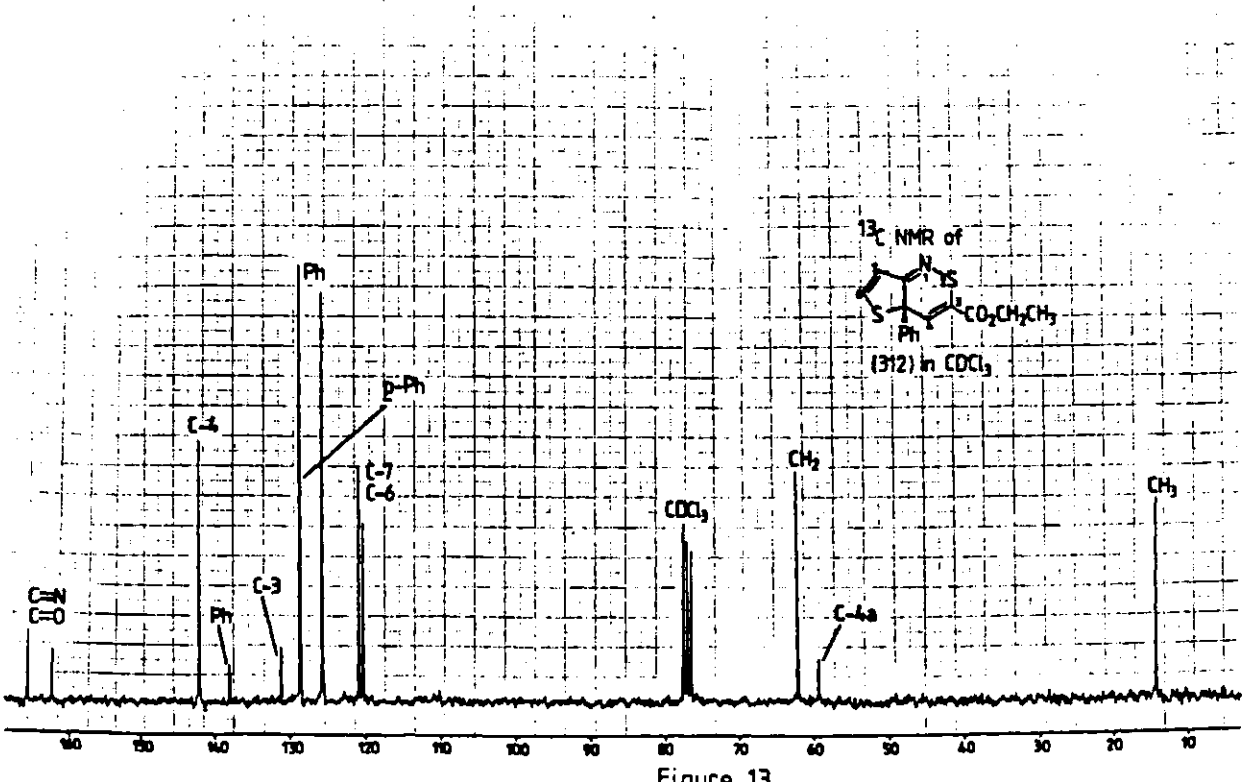


Figure 13

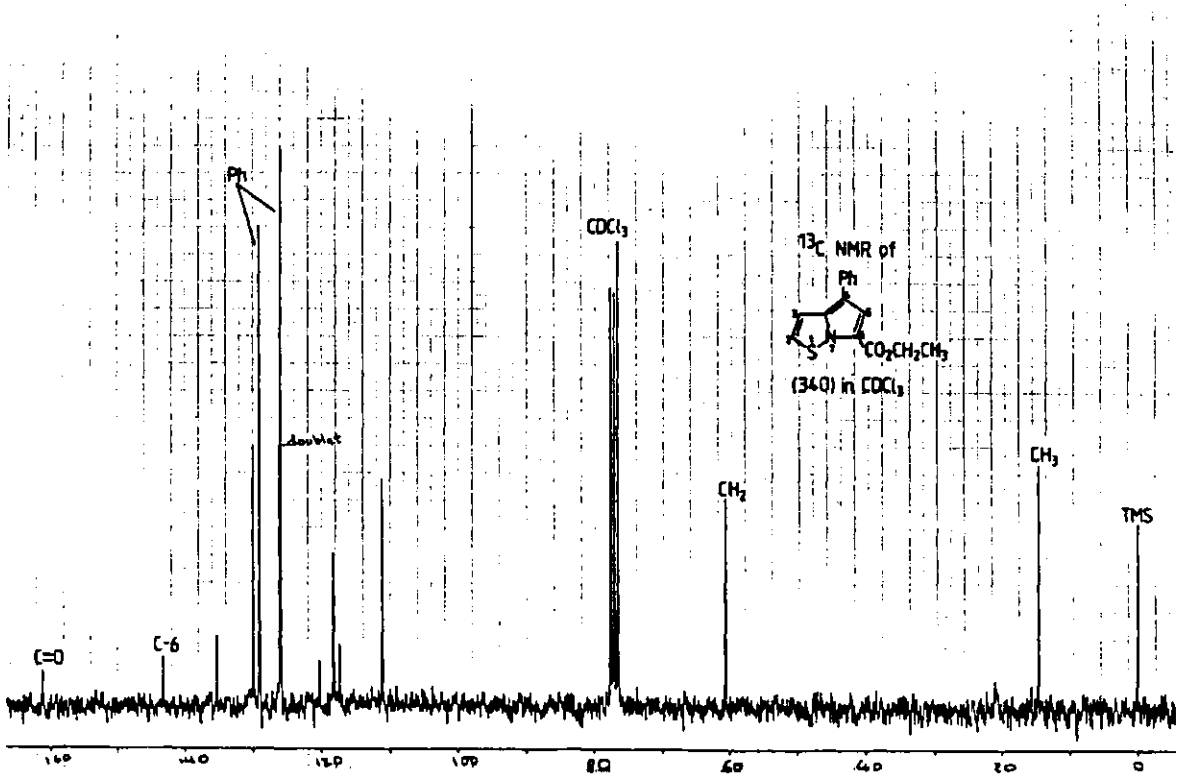


Figure 14

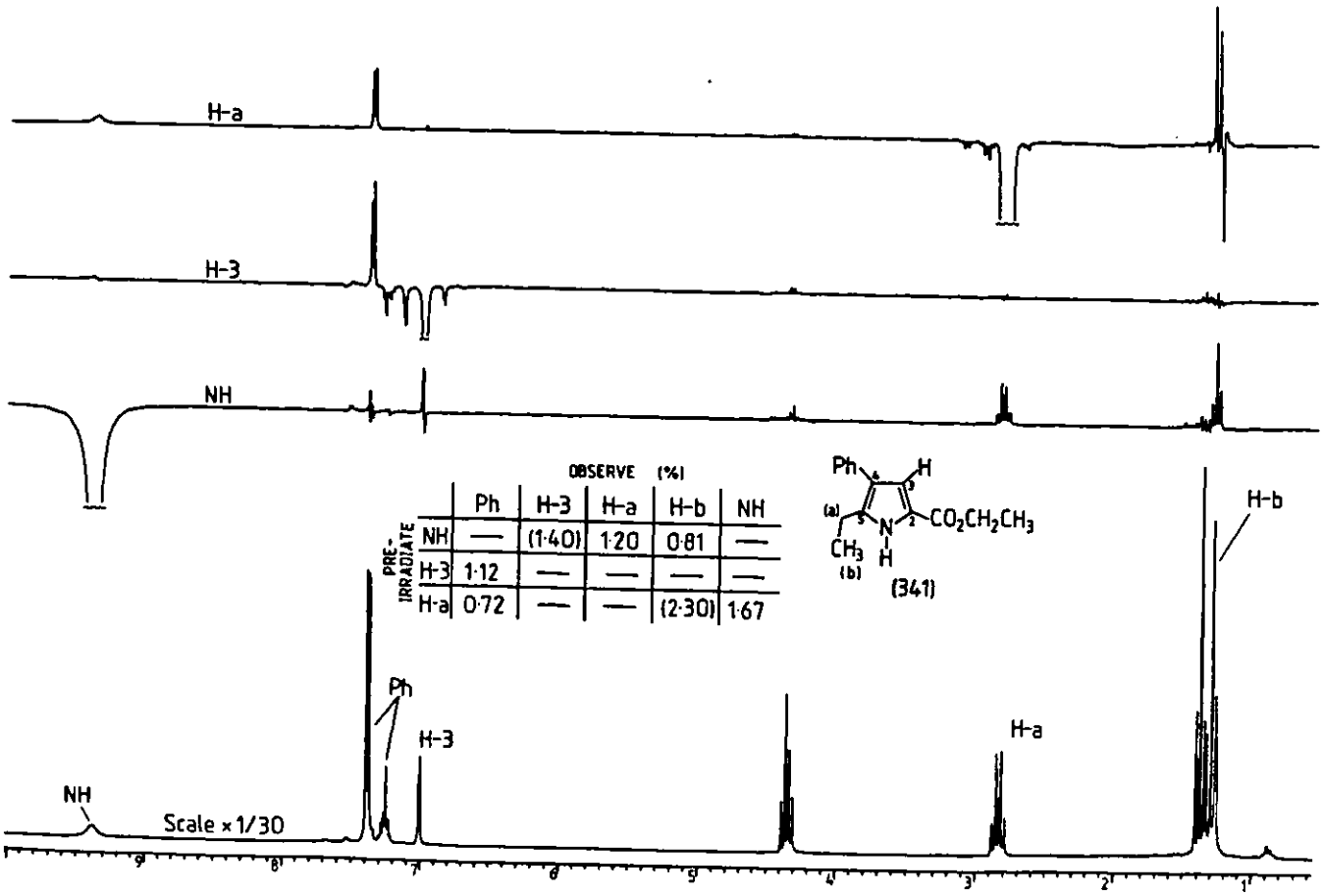


Figure 15

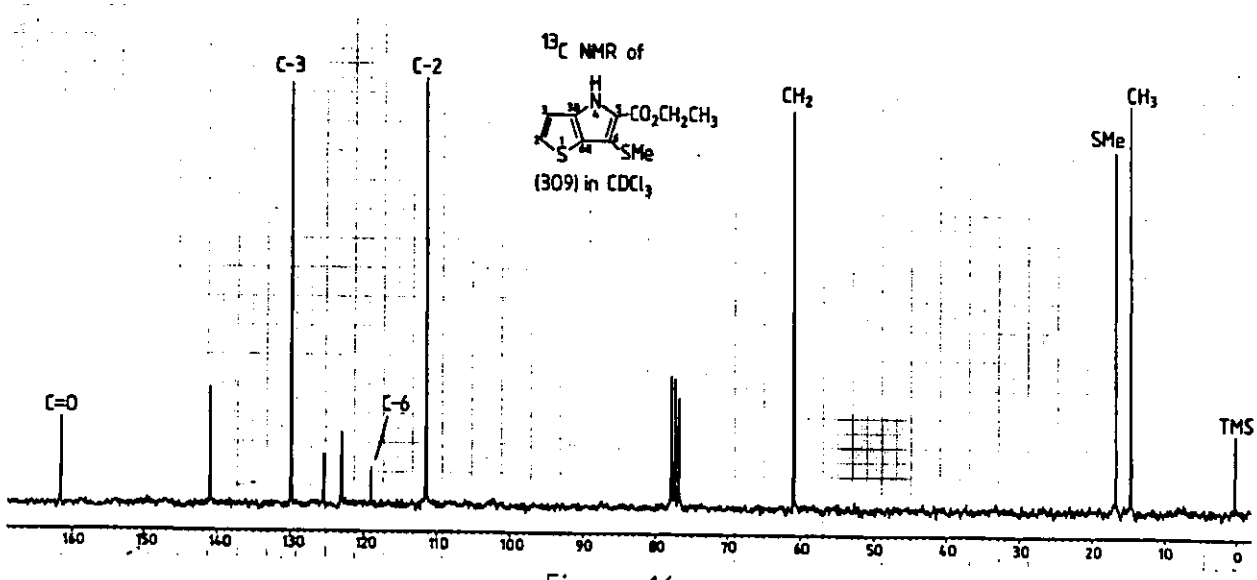


Figure 16

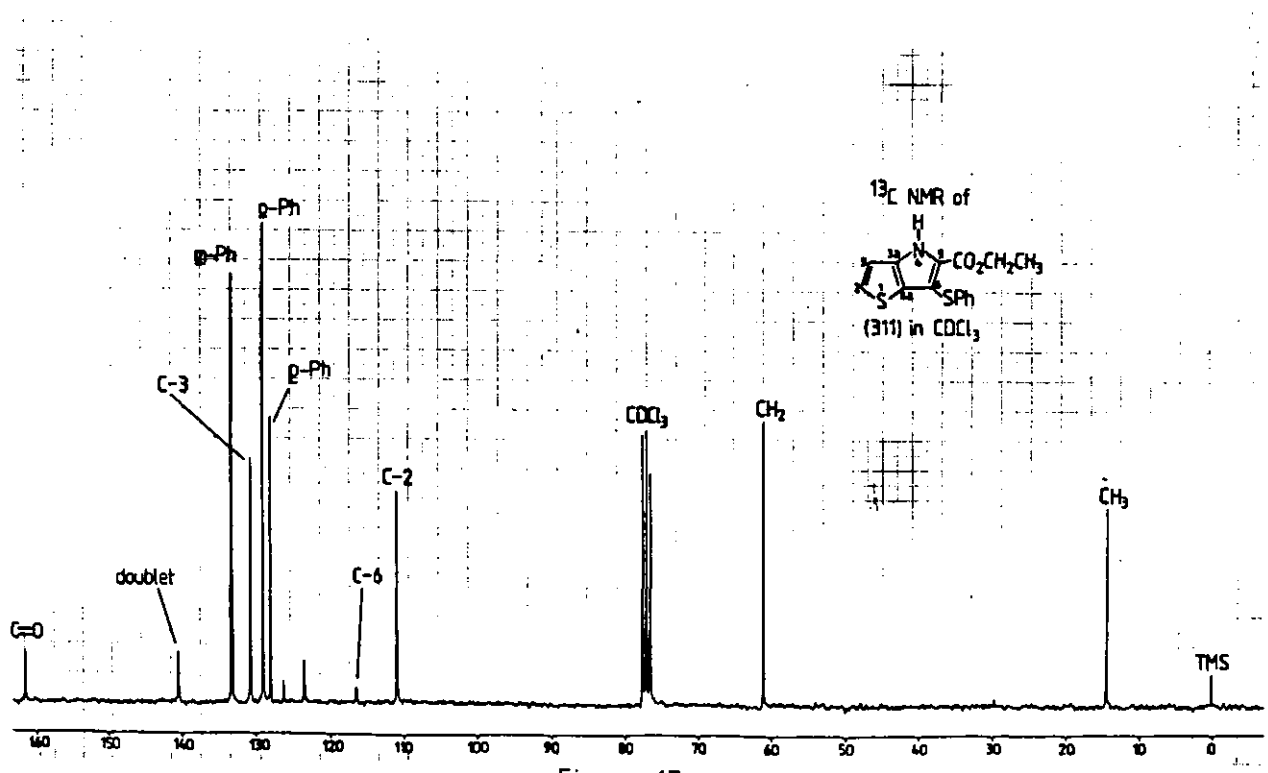


Figure 17

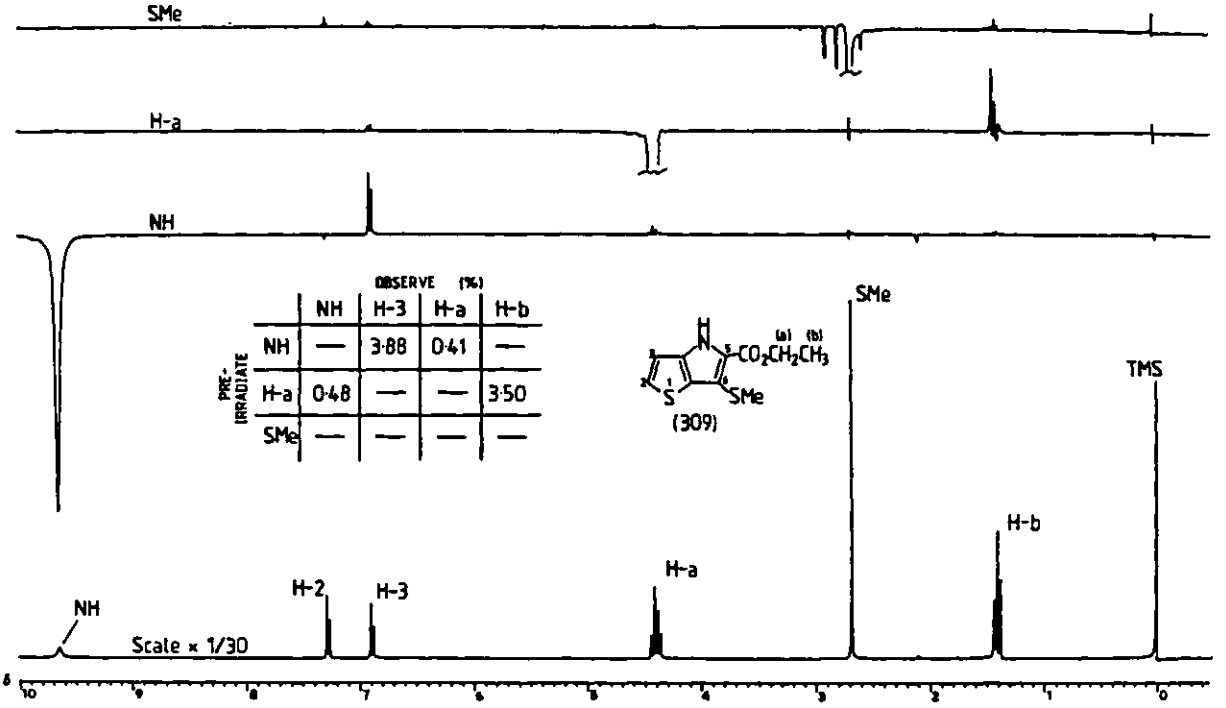


Figure 18

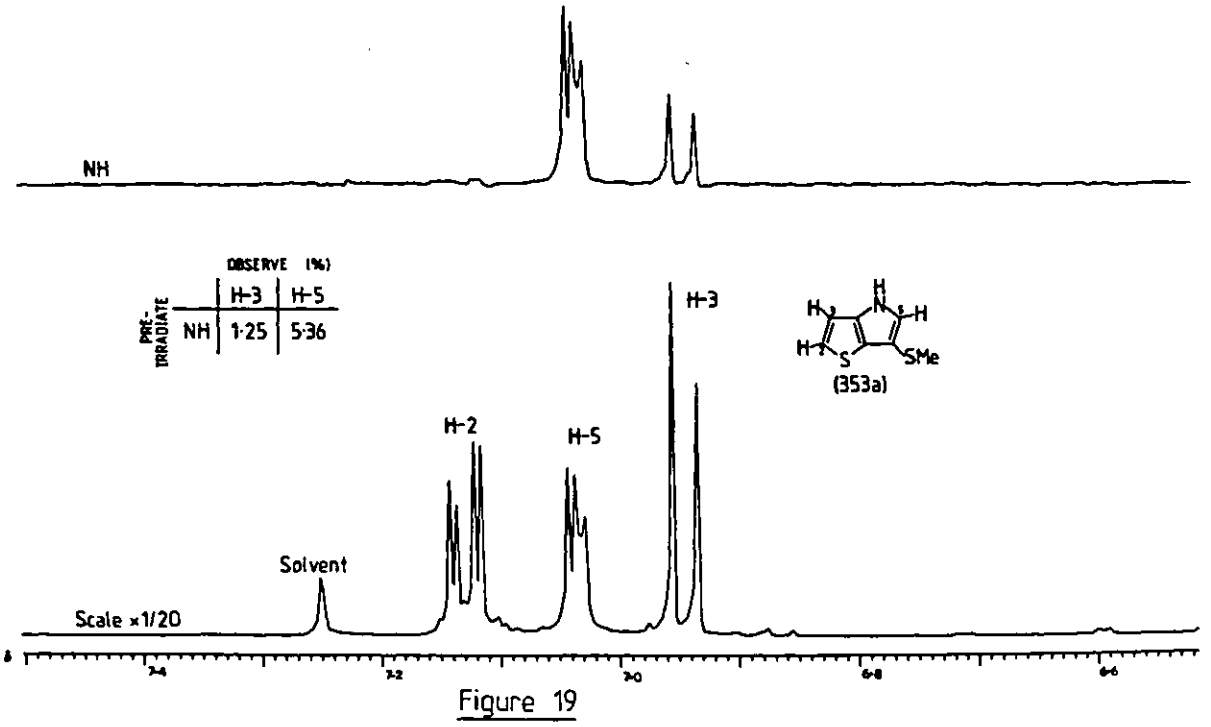


Figure 19

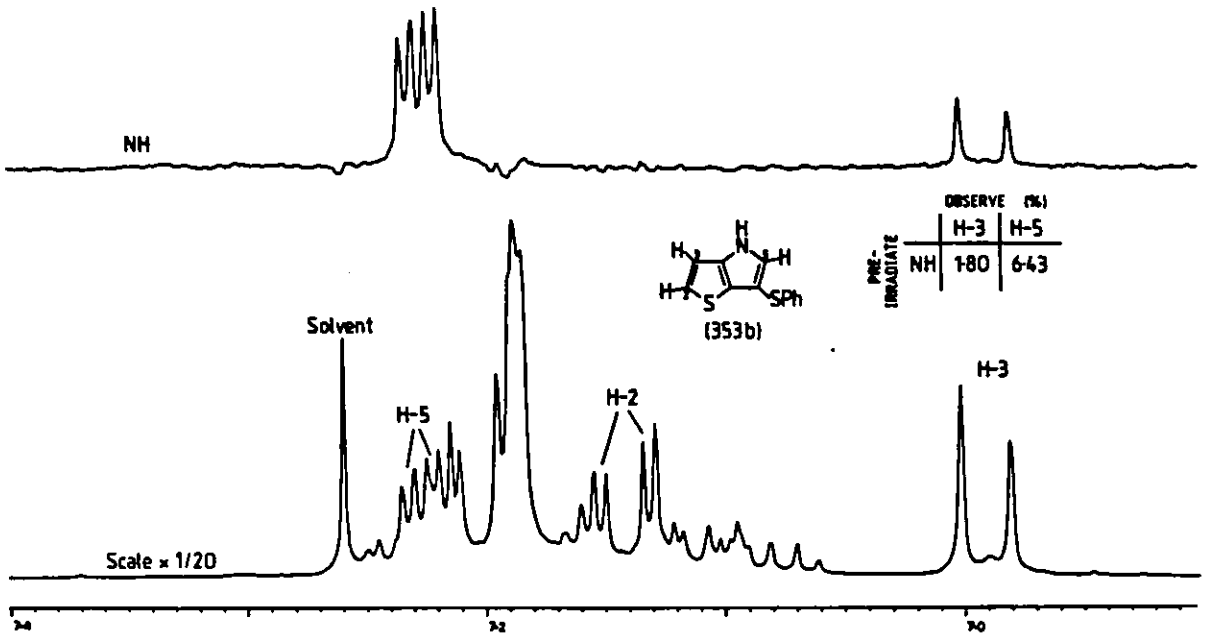


Figure 20

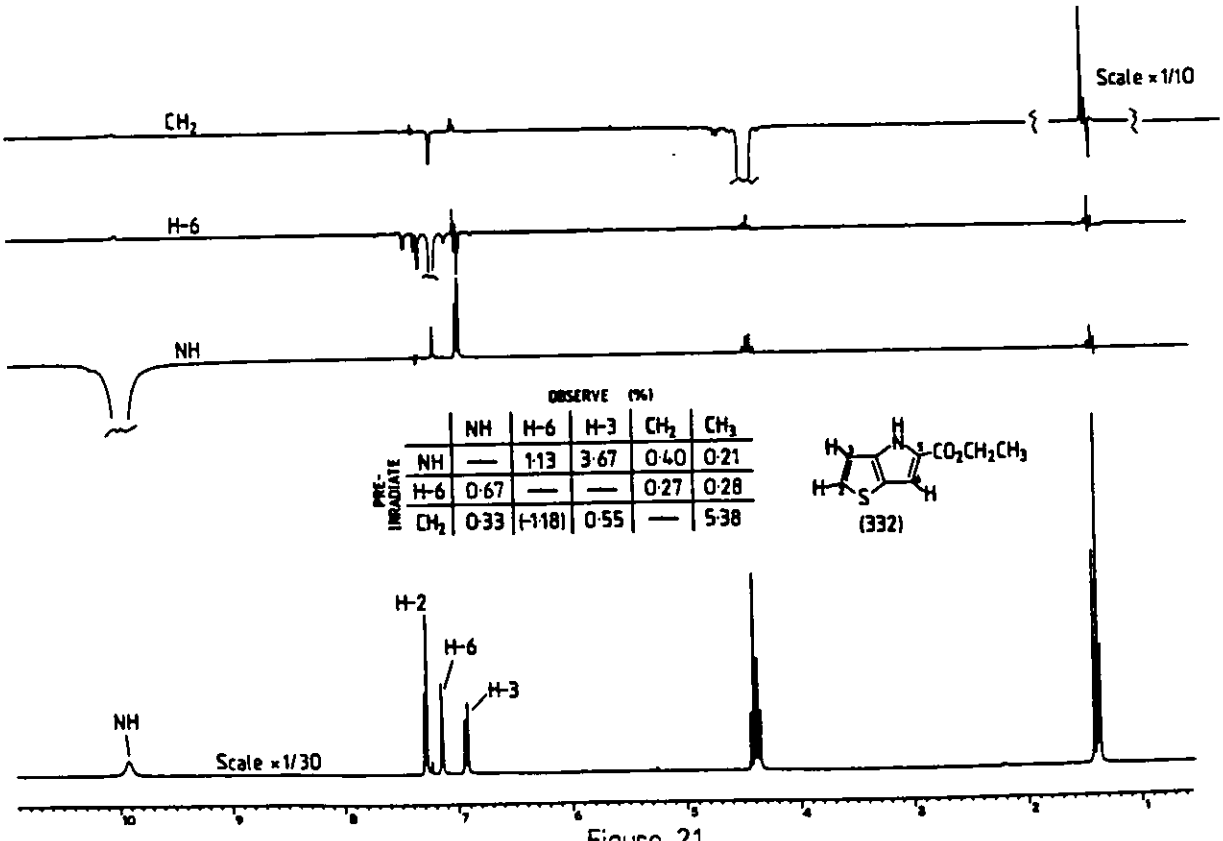


Figure 21

5 REFERENCES

1. M.O. Forster and S.H. Newman, J. Chem. Soc., 1910, 97, 2570.
2. G. L'abbe and A. Hassner, Angew. Chem., Int. Ed. Engl., 1971, 10, 98, and references therein.
3. A. Hassner and L.A. Lavy, J. Am. Chem. Soc., 1965, 87, 4203.
4. A. Hassner and F.W. Fowler, J. Org. Chem., 1968, 33, 2686.
5. A. Hassner, Acc. Chem. Res., 1971, 4, 9.
6. G. L'abbe and A. Hassner, J. Org. Chem., 1971, 36, 258.
7. F.W. Fowler, A. Hassner, and L.A. Levy, J. Am. Chem. Soc., 1967, 89, 2077.
8. A. Hassner, F. P. Boerwinkle, and A.B. Levy, ibid., 1970, 92, 4879.
9. A. Hassner and F. Boerwinkle, ibid., 1968, 90, 216.
10. A. Hassner and F. Boerwinkle, Tetrahedron Lett., 1969, 3309.
11. A. Hassner, R.J. Isbister, and A. Friederang, ibid., 1969, 2939.
12. A. Hassner and R.J. Isbister, J. Am. Chem. Soc., 1969, 91, 6126.
13. G.R. Harvey and K.W. Ratts, J. Org. Chem., 1966, 31, 3907.
14. C. Shin, Y. Yonezawa, and J. Yoshimura, Tetrahedron Lett., 1974, 7.
15. idem., Chem. Lett., 1976, 1063.
16. K. Friedrick, Angew. Chem., Int. Ed. Engl., 1967, 6, 959.
17. R.E. Banks and G.J. Moore, J. Chem. Soc. C, 1966, 2304.
18. J.S. Meek and J.S. Fowler, J. Org. Chem., 1968, 33, 985.
19. T.E. Stevens and W.D. Emmons, J. Am. Chem. Soc., 1958, 80, 338.
20. A.N. Nesmeyanov, M.I. Rybinskaya, and T.G. Kelekhsaeva, J. Org. Chem. USSR (Engl. Transl.), 1968, 4, 897.
21. K. Friedrick, G. Bock, and H. Fritz, Tetrahedron Lett., 1978, 3327.

22. A. Hassner, G. L'abbe, and M.J. Miller, J. Am. Chem. Soc., 1971. 93, 981.

23. G. Litkei, T. Mester, T. Patonay, and R. Bognar, Justus Liebigs Ann. Chem., 1979, 174.

24. G. Crass, Dissertation, ETH Zurich, 1979.

25. G. L'abbe, M.J. Miller, and A. Hassner, Chem. Ind. (London), 1970, 1321.

26. H. Hemetsberger, D. Knittel, and H. Weidmann, Monatsh. Chem., 1969, 100, 1599.

27. J.H. Boyer and F.C. Canter, Chem. Rev., 1954, 54, 1.

28. H. Hemetsberger and D. Knittel, Monatsh. Chem., 1972, 103, 194.

29. M. Farnier, S. Soth, and P. Fournari, Can. J. Chem., 1976, 54, 1066.

30. M. Farnier, S. Soth, and P. Fournari, ibid., 1976, 54, 1074.

31. S. Soth, M. Farnier, and C. Paulmier, ibid., 1978, 56, 1429.

32. A. Shafiee, A. Mazloumi, and V.I. Cohen, J. Heterocycl. Chem., 1979, 16, 1563.

33. H. Hemetsberger, I. Spira, and W. Schonfelder, J. Chem. Res. (S), 1977, 247.

34. J.P. Boukou-Poba, M. Farnier, and R. Guilard, Tetrahedron Lett., 1979, 1717.

35. H. Hemetsberger and D. Knittel, Monatsh. Chem., 1972, 103, 205.

36. D. Knittel, H. Hemetsberger, and H. Weidmann, ibid., 1970, 101, 157.

37. C. Shin, Y. Yonezawa, K. Unoki, and J. Yoshimura, Bull. Chem. Soc. Jpn., 1979, 52, 1657.

38. J.B. Hendrickson, K.W. Bair, and P.M. Keehn, J. Org. Chem., 1977, 42, 2935.

39. J.B. Hendrickson and P.L. Skipper, Tetrahedron, 1976, 32, 1627.

40. C. Shin, K. Nanjo, T. Nishino, Y. Sato, and J. Yoshimura, Bull. Chem. Soc. Jpn., 1975, 48, 2492.

41. K. Isomura, M. Okada, H. Ogawa, M. Ichiki, and H. Taniguchi, Org. Prep. Proced. Int., 1972, 4, 247.

42. G. Smolinsky and C.A. Pryde, J. Org. Chem., 1968, 33, 2411.

43. K. Ponsold and G. Schubert, J. Prakt. Chem., 1969, 311, 919.

44. G. Smolinsky, J. Am. Chem. Soc., 1961, 83, 4483.

45. G. Smolinsky, J. Org. Chem., 1962, 27, 3557.

46. G. L'abbe, Angew. Chem., Int. Ed. Engl., 1975, 14, 775, and references therein.

47. V. Nair and K.H. Kim, Heterocycles, 1977, 7, 353, and references therein.

48. W. Bauer and K. Hafner, Angew. Chem., Int. Ed. Engl., 1969, 8, 772.

49. K. Isomura, S. Kobayashi, and H. Taniguchi, Tetrahedron Lett., 1968, 3499.

50. K. Isomura, M. Okada, and H. Taniguchi, ibid., 1969, 4073.

51. D.J. Anderson and A.Hassner, J. Org. Chem., 1973, 38. 2565.

52. idem., ibid., 1974, 39, 3070.

53. A. Padwa, Acc. Chem. Res., 1976, 9, 371, and references therein.

54. idem., Chem. Rev., 1977, 77, 37, and references therein.

55. N. Kanehisa, N. Yasuoka, and N. Kasai, J. Chem. Soc., Chem. Commun., 1980, 98.

56. K. Isomura, G.-I. Ayabe, S. Hatano, and H. Taniguchi, ibid., 1980, 1252.

57. M. Komatsu, S. Ichijima, Y. Ohshiro, and T. Agawa, J. Org. Chem., 1973, 38,4341.

58. A. Padwa, M. Dharan, J. Smolanoff, and S.I. Wetmore, Jr., J. Am. Chem. Soc., 1973, 95, 1954, and references therein.

59. A. Padwa, J. Smolanoff, and S.I. Wetmore, Jr., J. Chem. Soc., Chem. Commun., 1972, 409.

60. J.H. Boyer, W.E. Krueger, and R. Modler, Tetrahedron Lett., 1968, 5979.

61. V. Nair and K.H. Kim, J. Heterocycl. Chem., 1976, 13, 873.

62. A. Padwa, A. Ku, H. Ku, and A. Mazzu, J. Org. Chem., 1978, 43, 66.

63. M.J. Pearson, J. Chem. Soc., Chem. Commun., 1981, 947.

64. A. Padwa, H. Ku, and A. Mazzu, J. Org. Chem., 1978, 43, 381.

65. A. Padwa, P.H.J. Carlsen, and A. Ku, J. Am. Chem. Soc., 1978, 100, 3494.

66. A. Padwa and A. Ku, ibid., 1978, 100, 2181.

67. J.S. Meek and J.S. Fowler, J. Org. Chem., 1968, 33 3418.

68. K. Isomura, M. Okada, and H. Taniguchi, Chem. Lett., 1972, 629.

69. A. Padwa, J.K. Rasmussen, and A. Tremper, J. Am. Chem. Soc., 1976, 98, 2605.

70. idem., J. Chem. Soc., Chem. Commun., 1976, 10.

71. A. Padwa, P.H.J. Carlsen, and A. Tremper, J. Am. Chem. Soc., 1978, 100, 4481.

72. A. Padwa, J. Smolanoff, and A. Tremper, Tetrahedron Lett., 1974, 29.

73. idem., J. Am. Chem. Soc., 1975, 97, 4682.

74. idem., J. Org. Chem., 1976, 41, 543.

75. A. Padwa and J. Smolanoff, Tetrahedron Lett., 1974, 33.

76. K. Isomura, T. Tanaka, and H. Taniguchi, Chem, Lett., 1977, 397.

77. A. Padwa and P.H.J. Carlsen, J. Org. Chem., 1978, 43, 2029, and references therein.

78. idem., Tetrahedron Lett., 1978, 433.

79. idem.,J. Am. Chem. Soc., 1975, 97, 3862.

80. idem., ibid., 1976, 98, 2006.

81. idem., ibid., 1977, 99, 1514.

82. idem., J. Org. Chem., 1978, 43, 3757.

83. A. Padwa and N. Kamigata, J. Am. Chem. Soc., 1977, 99, 1871.

84. K. Isomura, H. Taguchi, T. Tanaka, and H. Taniguchi, Chem. Lett., 1977, 401.

85. K. Isomura, S. Noguchi, M. Saruwatari, S. Hatano, and H. Taniguchi, Tetrahedron Lett., 1980, 3879.

86. D.M.B. Hickey, C.J. Moody, C.W. Rees, and D.J. Williams, J. Chem. Soc., Chem. Commun., 1982, 4.

87. H. Hemetsberger, D. Knittel, and H. Weidmann, Monatsh. Chem., 1970, 101, 161.

88. A. Krulošiková, J. Kováč, and J. Kristofčák, Coll. Czech. Chem. Commun. 1979, 44, 1799.

89. T.L. Gilchrist, C.W. Rees, and J.A.R. Rodrigues, J. Chem. Soc., Chem. Commun., 1979, 627.

90. K. Yakushijin, S. Yoshina, and A. Tanak , Heterocycles, 1977, 6, 721.

91. H. Hemetsberger, D. Knittel, R. Leipert, and H. Weidmann, Tetrahedron Lett., 1970, 1459.

92. M.I. Rybinskaya, A.N. Nesmeyanov, and N.K. Kochetov, Russ. Chem. Rev. (Engl. Transl.), 1969, 38, 433.

93. U. Türck and H. Behringer, Chem. Ber., 1965, 98, 3020.

94. L.K. Dyall and J.E. Kemp, J. Chem. Soc. B, 1968, 976 and references cited therein.

95. K. Friedrich and H.K. Thieme, Chem. Ber., 1970, 103, 1982.

96. H. Alper, J.E. Prickett, and S. Wollowitz, J. Am. Chem. Soc., 1977, 99, 4330.

97. K. Isomura, K. Uto, and H. Taniguchi, J. Chem. Soc., Chem. Commun., 1977, 664.

98. H. Alper and J. E. Prickett, J. Chem. Soc., Chem. Commun., 1976, 483.

99. idem., ibid., 1976, 983.

100. K. Hayashi, K. Isomura, and H. Taniguchi, Chem. Lett., 1975, 1011.

101. H. Alper and C.P. Perera, J. Am. Chem. Soc., 1981, 103, 1289.

102. T. Sakakibara and H. Alper, J. Chem. Soc., Chem. Commun., 1979, 458.

103. D.J. Anderson and A. Hassner, Synthesis, 1975, 8, 483, and references therein.

104. A. Hassner and V. Alexanian, New Trends in Heterocycl. Chem., 1979, 3, 178, and references therein.

105. A. Hassner, Heterocycles, 1980, 14, 1517, and references therein.

106. L.A. Wendling and R.G. Bergman, J. Org. Chem., 1976, 41, 831.

107. A. Demoulin, H. Gorissen, A.-M. Hesbain-Frisque, and L. Ghosez, J. Am. Chem. Soc., 1975, 97, 4409.

108. B.A. Belinka, Jr., and A. Hassner, J. Org. Chem., 1979, 44, 4712.

109. idem., J. Am. Chem. Soc., 1980, 102, 6185.

110. a) A.T. Moore and H.N. Rydon, Org. Synth., Coll. vol. 5, 1973, 586. b) A. Darapsky and M. Prabhakar, Chem. Ber., 1912, 45, 1654.

111. J. H. Boyer and D. Straw, J. Am. Chem. Soc., 1952, 74, 4506.

112. H. Dressler and J.E. Graham, J. Org. Chem., 1967, 32, 985.

113. J.M.F. Gagan, A.G. Lane, and D. Lloyd, J. Chem. Soc. C, 1970, 2484.

114. J.B. Brown, H.B. Henbest, and E.R.H. Jones, J. Chem. Soc., 1950, 3634.

115. W.R. Boehme, Org. Synth., Coll. vol. 4, 1963, 590.

116. D.S. Deorha and P. Gupta, Chem. Ber., 1964, 97, 3577.

117. L.I. Zakharkin and I.M. Khorlina, Tetrahedron Lett., 1962, 619.

118. G. Quéguiner and P. Pastour, Bull. Soc. Chim. Fr., 1968, 4117.

119. E. Winterfeldt, Synthesis, 1975, 617 and references cited therein.

120. S. Gronowitz and T.R. Raznikiewicz, Org. Synth., Coll. vol. 5, 1973, 149.

121. S.-O. Lawesson, Ark. Kemi., 1957, 11, 373.

122. S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Hakansson, Ark. Kemi., 1961, 17, 165.

123. S. Gronowitz, C, Westerlund, and A.-B. Hörnfeldt, Acta Chem. Scand., Sect. B, 1975, 29, 224.

124. W. Lehnert, Tetrahedron Lett., 1970, 4723; idem., Tetrahedron, 1972, 28, 663.

125. S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, Acta Chem. Scand., Sect. B., 1976, 30, 391.

126. P.E. Sonnet, J. Heterocycl. Chem., 1970, 7, 1101.

127. R.A. Jones and G.P. Bean, 'The Chemistry of Pyrroles,' Academic Press, London, 1977, p.356, and references cited therein.

128. R.M. Acheson, 'An Introduction to the Chemistry of Heterocyclic Compounds,' 3rd edn., Interscience, London, 1976, p.108, and references cited therein.

129. K. Isomura, S. Noguchi, M. Saruwatari, S. Hatano, and H. Taniguchi, Tetrahedron Lett., 1980, 3879.

130. H. Taguchi, M. Yamano, K. Isomura, and H. Taniguchi, Heterocycles, 1975, 3, 63.

131. A.J. Poole and F.L. Rose, J. Chem. Soc. C, 1971, 1285.

132. M.P.L. Caton, D.H. Jones, R. Slack, S. Squires, and K.R.H. Wooldridge, J. Med. Chem., 1965, 8, 680.

133. A. Adams and R. Slack, J. Chem. Soc., 1959, 3061.

134. L.B.E. Wasserman and W.A. Yager, J. Am. Chem. Soc., 1967, 89, 3931.

135. L. Horner and A. Christmann, Angew. Chem. Int. Ed. Engl., 1963, 2, 599.

136. 'The Chemistry of the Azido Group,' ed. S. Patai, Interscience, New York, 1971, p.310, 355, and references cited therein.

137. J. H. Boyer and G.J. Mikol, J. Chem. Soc., Chem. Commun., 1969, 734.

138. A. Yabe and K. Honda, Tetrahedron Lett., 1975, 1079.

139. A. Yabe, Bull. Chem. Soc. Jpn., 1980, 53, 2933.

140. B. Coffin and R.F. Robbins, J. Chem. Soc., 1965, 1252.

141. H. Nakanishi, A. Yabe, and K. Honda, J. Chem. Soc., Chem. Commun., 1982, 86.

142. S. Bradbury, C.W. Rees, and R.C. Storr, J. Chem. Soc., Perkin Trans. 1, 1972, 68.

143. D.P.J. Pearson, Ph.D. Thesis, University of Liverpool, 1976.

144. S.-I. Hayashi, M. Nair, D.J. Houser, and H. Shechter, Tetrahedron Lett., 1979, 2961.

145. G. Kumar, K. Rajagopalan, S. Swaminathan, and K.K. Balasubramanian, Tetrahedron Lett., 1979, 4685.

146. T.J. Katz and N. Acton, J. Am. Chem. Soc., 1973, 95, 2738.

147. M. Korat and D. Ginsburg, Tetrahedron, 1973, 2373.

148. T.J. Levek and E.F. Kiefer, J. Am. Chem. Soc., 1976, 98, 1875.

149. J.A. Pincock and L.M. Druet, Tetrahedron Lett., 1980, 3251.

150. P.B. Terent'ev, V.G. Kartsev, I.K. Yakushenko, L.N. Prostakova, A.N. Kost, and I.P. Gloriozov, Chem. Heterocycl. Compd. (Engl. Transl.), 1979, 15, 518.

151. R. Askani, Chem. Ber., 1965, 98, 2551.

152. T.L. Gilchrist and R.C. Storr, 'Organic Reactions and Orbital Symmetry,' 2nd. edn., Cambridge University Press, London, 1979, p.122 and references cited therein.

153. R.B. Carlin and M. S. Moores, J. Am. Chem. Soc., 1962, 84, 4107.

154. P.B. Terent'ev, N.G. Kotova, and A.N. Kost, Chem. Heterocycl. Compd. (Engl. Transl.), 1978, 14, 534.

155. W.A. Pryor, J. H. Coco, W. H. Daly, and K.N. Houk, J. Am. Chem. Soc., 1974, 96, 5591.

156. E.J. Corey and B.B. Snider, J. Org. Chem., 1973, 38, 3632.

157. S.W. Mojé and P. Beak, J. Org. Chem., 1974, 39, 2951.

158. M. Hori, T. Kataoka, H. Shimizu, and K. Matsuo, Tetrahedron Lett., 1979, 3969.

159. T.L. Gilchrist and C.J. Moody, Chem.Rev., 1977, 77, 409, and references cited therein.

160. D. Vaughan, Ph.D. Thesis, University of Liverpool, 1980, p.47.

161. C.C. Price and D.H. Follweiler, J. Org. Chem., 1969, 34, 3202.

162. B.E. Maryanoff, J. Stackhouse, G.H. Senkler, and K. Mislow, J. Am. Chem. Soc., 1975, 97, 2718 and references cited therein.

163. 'Vogel's Textbook of Practical Organic Chemistry,' 4th edn., Longman, London, 1978, p.1284.

164. R. Pfister and P. Zeller, Swiss Patent, 617,705, 1980 (Chem. Abstr., 1980, 93, 220761 j).

165. U. Schöllkopf, Angew. Chem., Int. Ed. Engl., 1970, 9, 763.

166. M. Hori, T.Kataoka, and H. Shimizu, Chem. Lett., 1974, 1117.

167. F. Ogura, W.D. Houshell, C.A. Maryanoff, W.J. Richter, and K. Mislow, J. Am.Chem. Soc., 1976, 98, 3615.

168. H. Pirelahi, Y. Abdoh, and A.Afzali, Tetrahedron Lett., 1976, 4609.

169. M. Hori, T. Kataoka, H. Shimizu, S. Ohno, and K. Narita, ibid., 1978, 251.

170. C.C. Price and G. Suld, J. Am. Chem. Soc., 1961, 83, 1770.

171. D. Vaughan, Ph.D. Thesis, University of Liverpool, 1980, p.65.

172. L.F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, p.729.

173. B.G. Murray and A.F. Turner, J. Chem. Soc. C, 1966, 1338; J.J. Tufariello and G.B. Mullen, J. Am. Chem. Soc., 1978, 100, 3638; J.J. Tufariello, G.B. Mullen, J.J. Tegeler, E.J. Trybulski, S.C. Wong, and S.A. Ali, ibid., 1979, 101, 2435.

174. T. Kobayashi, S. Kajigaeshi, and S. Kanemasa, Heterocycles, 1976, 4, 1281; S. Rajappa, B.G. Advani and R. Sreenivasan, Indian J. Chem., Sect. B, 1977, 15, 886.

175. T.L. Gilchrist, C.J. Moody, and C.W. Rees, J. Chem. Soc., Perkin Trans. 1, 1975, 1964.

176. T.L. Gilchrist, C.J. Moody, and C.W. Rees, ibid., 1979, 1871.

177. D. Vaughan, Ph.D. Thesis, University of Liverpool, 1980, p.72.

178. M. Cavazza, G. Morganti, and F. Pietra, J. Chem. Soc., Chem. Commun., 1978, 945.

179. C.W. Spangler, Chem. Rev., 1976, 76, 187.

180. J. Sauer and K.K. Mayer, Tetrahedron Lett., 1968, 319.

181. D. Vaughan, Ph.D. Thesis, University of Liverpool, 1980, p.78.

182. R.A. Gregg, D.M. Alderman, and F.R. Mayo, J. Am. Chem. Soc., 1948, 70, 3740.

183. A. Schonberg and K. Praefcke, Chem. Ber., 1966, 99, 2371.

184. S. Gronowitz and U. Michael, Ark. Kemi., 1970, 32, 283.

185. T.R. Kelly, H.M. Dali, and W.-G. Tsang, Tetrahedron Lett., 1977, 3859.

186. Y.L. Gol'dfarb, M.A. Kalik, and M.L. Kirmalova, Chem. Heterocycl. Compd. (Engl. Transl.), 1967, 3, 50.

187. P.S. Clezy, A.J. Liepa, A.W. Nichol, and G.A. Smythe, Aust. J. Chem., 1970, 23, 589.

188. F. Feigl, 'Spot Tests in Organic Analysis,' 6th edn., Elsevier, Amsterdam, 1960.

189. S. Siggia, 'Quantitative Organic Analysis via Functional Groups,' ch. 9, Wiley, New York, 1963.

190. R.D. Schuetz and W.H. Houff, J. Am. Chem. Soc., 1955, 77, 1836.

191. H. Keskin, R.E. Miller, and F.F. Nord, J. Org. Chem., 1951, 16, 199.

192. L. Horner and E.-O. Renth, Justus Liebigs Ann. Chem., 1967, 703, 37.

193. R.C. Fuson and B.H. Wojcik, Org. Synth., Coll. vol. 2, 1943, 260.

194. 'Vogel's Textbook of Practical Organic Chemistry,' Longman, London, 4th edn., 1978, p.283.

195. W.S. Emerson and T.M. Patrick, Jr., Org. Synth., Coll. vol. 4, 1963, 980.

196. A.R. Pray, Inorg. Synth., 1957, 5, 153.

197. 'Handbook of Chemistry and Physics,' 58th edn., ed. R.C. Weast, CRC Press, Ohio, 1977, p. B-165.