SOME ASPECTS OF

THE

CHEMISTRY OF DIAZOALKANES

Thesis submitted to the University of Stirling

for the

Degree of Doctor of Philosophy

by

Josef A. Rechka

Department of Chemistry
University of Stirling

June 1985

ABSTRACT

The discussion of the research reported in this thesis is prefaced by a review on diazoalkane chemistry.

The initial object of this work was to continue and expand upon the work previously reported on thiophenium ylids.

3-Substituted thiophenium ylids had not previously been synthesized. Attempts to synthesize these compounds using reported conditions met with limited success, only low yields of the desired ylids were obtained.

The use of rhodium-(II)-hexanoate as a catalyst in the ylid forming reactions was found to be more effective in certain circumstances.

The thermal rearrangement of thiophenium ylids to thiophen-2-malonates was found to proceed via a 2(H)-thio-pyran intermediate.

Nmr studies of the substituted ylids showed non equivalent ester signals with a barrier to their exchange of 47-60 kJ mole^{-1}. Two exchange processes were found to be taking place, inversion at sulphur and rotation about the ylid bond, with inversion at sulphur having the lower barrier. The rotation about the ylidcarbon-carbonylcarbon bond was also hindered, this having a barrier of 38 kJ mole^{-1}.

Reaction of dimethyl diazomalonate with aliphatic amines resulted in the formation of 1,2,3-triazoles in good yield. However, the reaction of other diazoesters with the amines did not give the corresponding triazoles.

An attempt was made to synthesize the phytoalexin Wyerone using the rearrangement of an α-diazomethylthiophen to generate the <u>cis</u>-ene-yne side chain. The intermediate diazoalkane could not be prepared in sufficient yield to allow further transformation. The rhodium-(II)-acetate catalysed reaction of a closely related model compound resulted in the formation of the corresponding ketone.

ACKNOWLEDGEMENTS

CONTENTS

REVIEW

SOME NEW DEVELOPMENTS

IN THE

CHEMISTRY OF DIAZOALKANES

INTRODUCTION

Diazoalkanes have been useful intermediates in organic chemistry over the last 50 years. In recent years, due to their ready availability by new methods of synthesis, they have become very widely used.

This review is intended to cover developments in the field of diazoalkanes in organic synthesis, in the last two years.

Diazoalkanes are best represented as a resonance hybrid comprising linear structures with opposing dipoles (Scheme 1).

| I | II | III | IV |
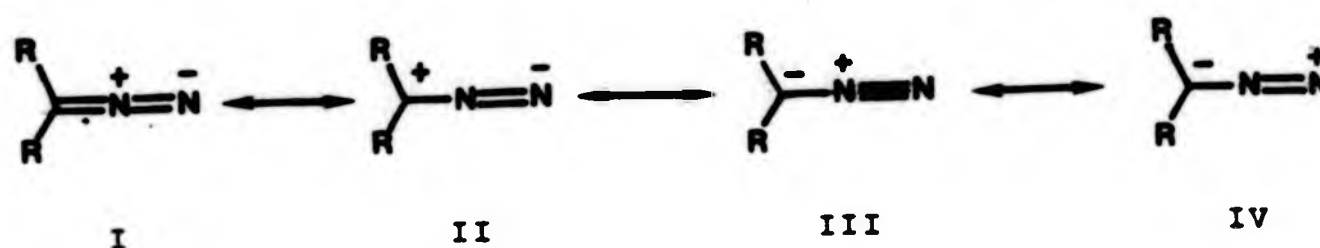
Scheme 1

Under the appropriate conditions diazoalkanes will act as acids or bases, as electrophiles or nucleophiles, as 1,3 dipoles and as carbene sources.

Nmr studies of diazoalkanes[1,2] show that a proton attached to the diazo carbon atom is shielded in a range 3.5-7 ppm depending on the substituents. For example, electron withdrawing substituents favour resonance structures having a formal carbanion e.g. III or IV (Scheme 1), whereas electron donors favour resonance structures having a formal carbonium ion, e.g. II (Scheme 1).

Preparation of diazoalkanes

There are a number of methods for the preparation of diazoalkanes which have been developed in recent years, perhaps reflecting the interest shown in them.

Diazotization of Amines

Amines when treated with nitrous acid will yield diazoalkanes but only if elimination of H^+ can compete with the decomposition of the diazonium ion, e.g. when there is an adjacent carbonyl group. The diazotisation of α-aminoesters by this method is well known. A recent example is the diazotization of 6-aminobenzylpenicillin[3] (Scheme 2).

Scheme 2
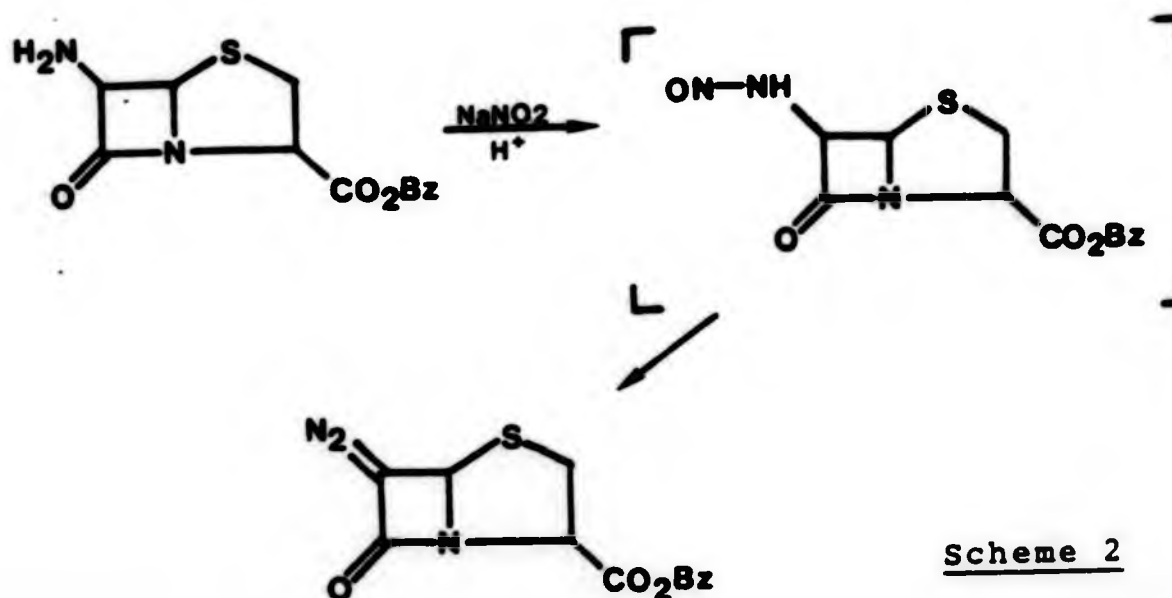
The Forster reaction

The Forster reaction involves the formation of an oxime followed by treatment with chloramine solution. The oxime reacts with the chloramine to yield the diazo group. This method was used by Trost[4] to obtain α,α'-bis-diazocyclohexanone (Scheme 3).

Scheme 3
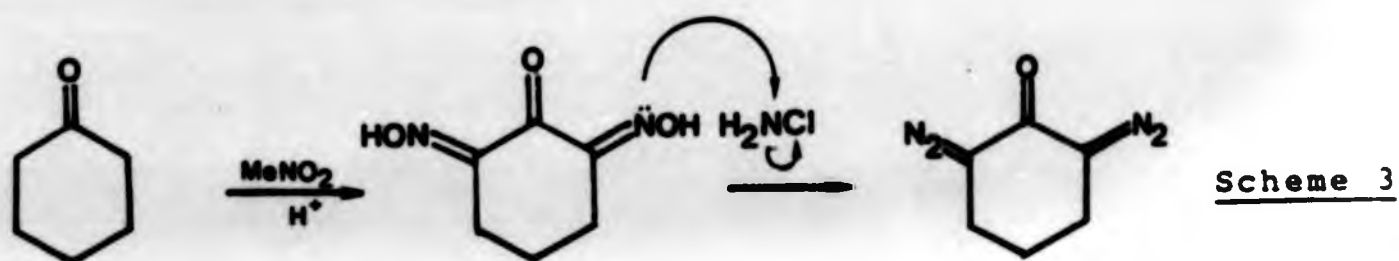
The Bamford-Stevens reaction[5]

The Bamford-Stevens reaction is important in
that it can be used to generate unstable diazoalkanes "in situ"
and thus affords a route to carbenes and carbonium ions via
fragmentation of the intermediate diazoalkanes. The reaction
involves treatment of a 4-toluenesulphonylhydrazone with a
base (Scheme 4). If R is alkyl, a relatively strong base is
required (e.g. KOH). However, if R is acyl, then basic alumina
will suffice.

Scheme 4
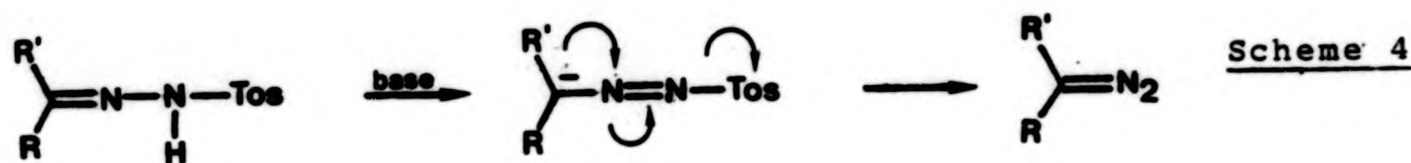
Deacylation of nitrosocarboxamides and sulphonamides

This type of reaction is probably the most important
method for the preparation of non-acylated diazoalkanes.
However, it is little used for the preparation of acylated
diazoalkanes. The starting materials have the general structure
shown (1). X may be $-CO_2R$, $-COR$, $-CONH_2$ or SO_2R. Probably the
most well-known example of this reaction is the 'Diazald'
preparation of diazomethane[6] (Scheme 5).

(1)

Scheme 5

The base hydrolysis of the nitrososulphonamide is normally carried out with ether as the solvent, the diazomethane is then co-distilled out of the reaction mixture with the ether. An example of an acylated diazoalkane prepared by this method is seen in the preparation of 3-diazo-5-methyl-2-hexanone[7] (Scheme 6).

Scheme 6
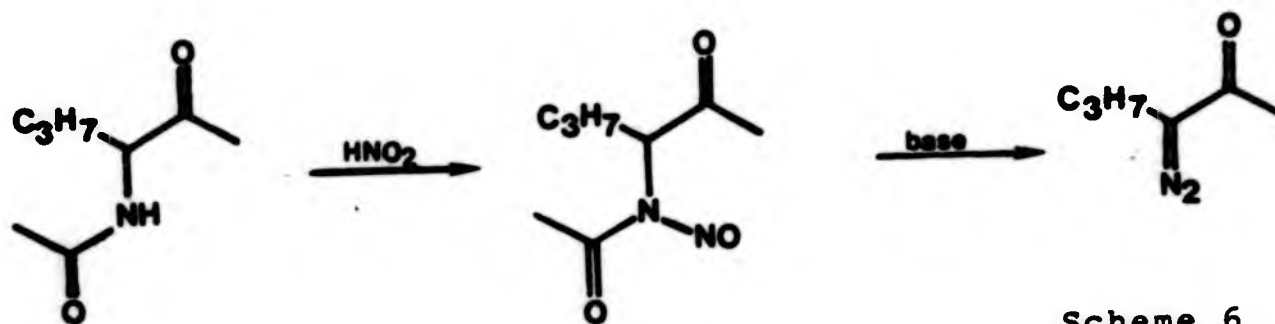
Dehydrogenation of hydrazones

The dehydrogenation of hydrazones is the oldest diazoalkane synthesis known[8]. Yellow mercuric-oxide, silver oxide and manganese dioxide are commonly used in the preparation of both diazoalkanes and acyldiazoalkanes. A recent example of the preparation of a diazoalkane by this method is that of bis(adamantyl)diazomethane[9] (Scheme 7).

Scheme 7
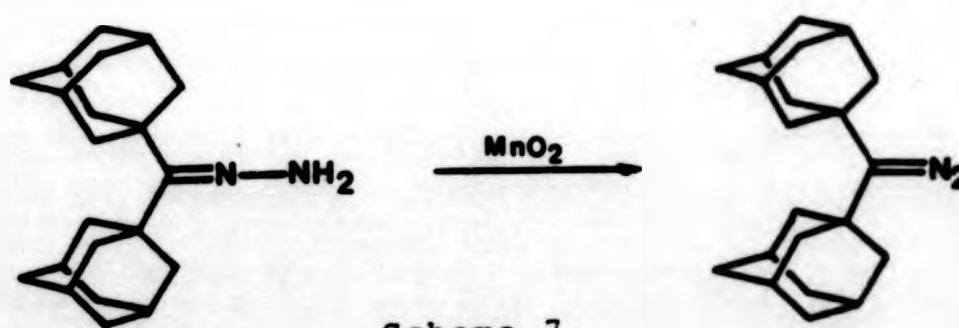
This method is less used in the synthesis of acylated diazoalkanes. However it has been used in the preparation of 3-diazo-D-camphor[10]. (2).

(2)
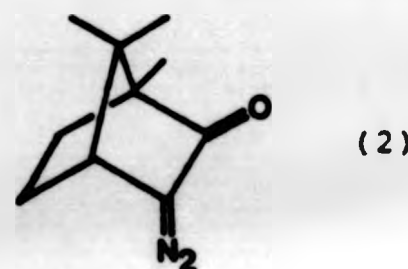
Diazo group transfer

Diazo group transfer has become the method of choice for the preparation of diazoalkanes from alkanes with an activated methylene group. The complete diazo group is transferred from a donor to the substrate. 4-Toluenesulphonyl-azide (tosylazide) is the most frequently used donor. The reaction probably proceeds via a triazene mechanism[11,12,13] (Scheme 8).
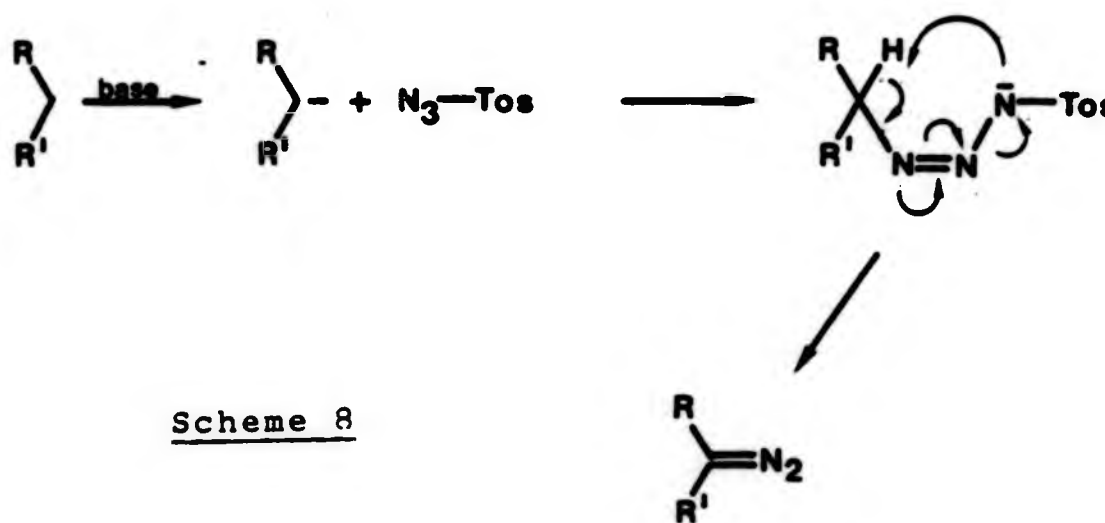
Scheme 8

The use of tosylazide or other sulphonylazides is highly dependent on the ability to use a suitable base. However, azidinium salts[14] for example, 2-azido-3-ethylbenzo-thiazolium fluoroborate (3, Scheme 9) transfers the diazo-group in neutral to acid media. The triazene type of intermediate can be again assumed[15].

Deformylating diazo transfer[11,12,13]

The methylene group in monocarbonyl compounds is usually not sufficiently activated to allow diazo transfer. However, it is possible to further activate the methylene group with a formyl group, via a Claisen ester condensation, and then conduct the transfer. The formyl group is lost during

the transfer (Scheme 10). The precise mechanism is not known at the present time.
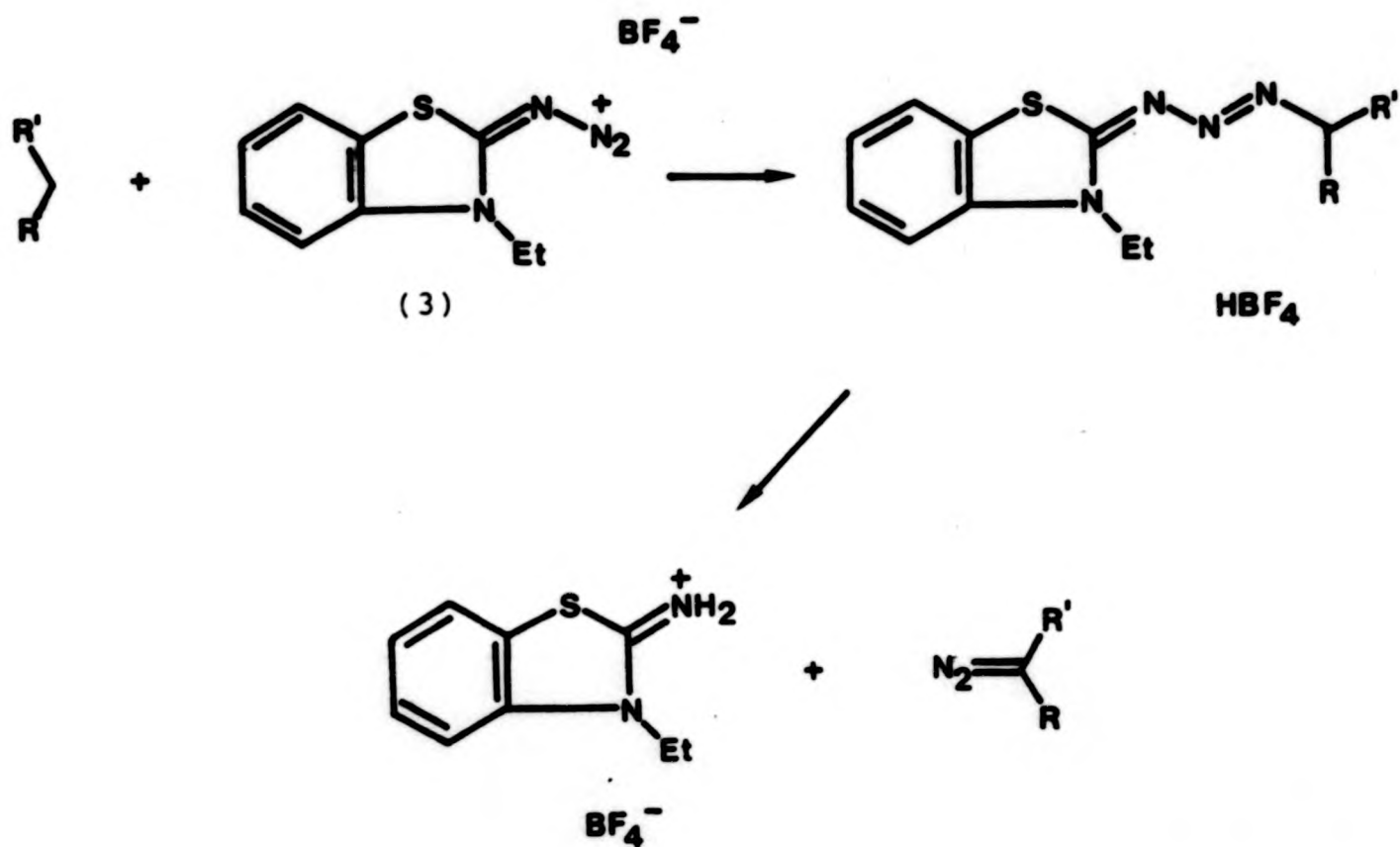
Scheme 9
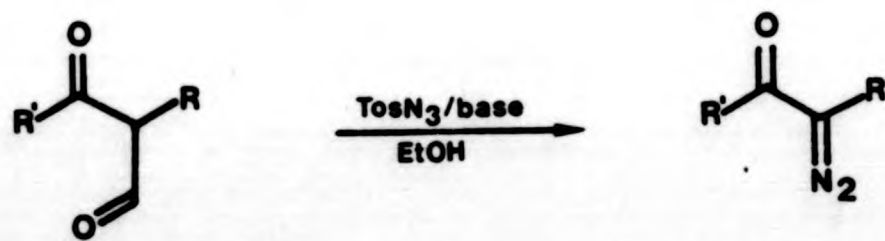
Scheme 10

Substitution reactions

The diazo group is stable under quite drastic reaction conditions. It is often possible to obtain a desired diazo-alkane by reacting a simpler diazoalkane with a substrate which will substitute the hydrogen on the diazo carbon. In the classical Ardnt-Eistert reaction[16] diazomethane is reacted with an acylhalide (Scheme 11). If only one equivalent of diazo-methane is used the HCl liberated reacts further to produce an α-chloroketone. A second mole of diazomethane is usually added to remove the excess HCl. It can be replaced by organic amines[7,17,18,19].
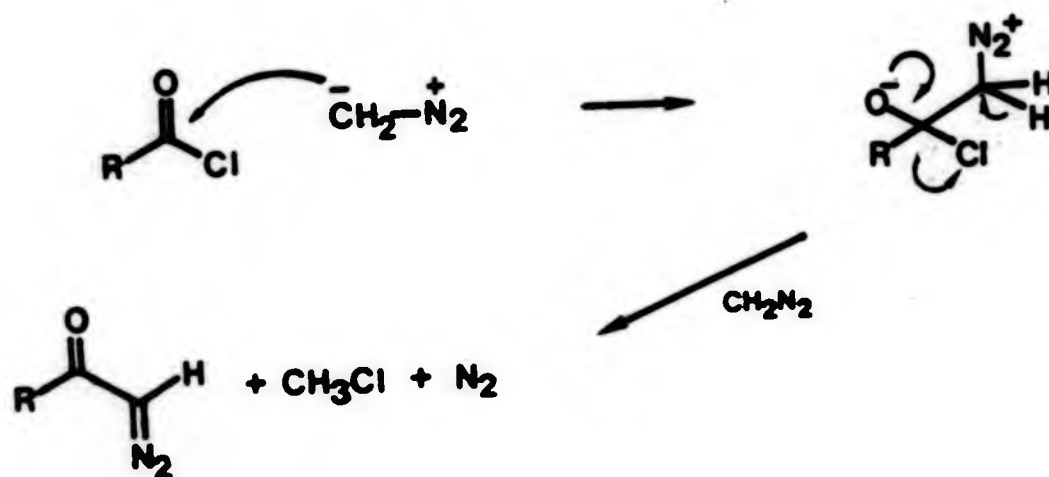
Scheme 11

Mixed anhydrides can also acylate diazoalkanes. For example, those of ethyl carbonates[20] (Scheme 12).
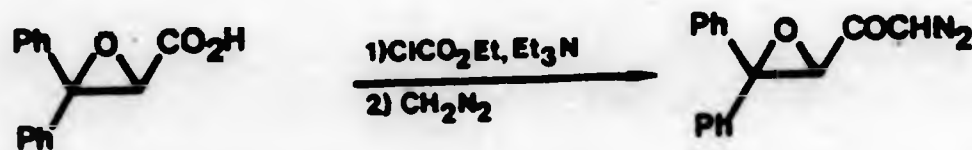
Scheme 12

The hydrogen on the diazocarbon is quite acidic and can be displaced by a metal from a suitable base, e.g. n-butyllithium in the case of diazomethane, or potassium hydroxide in the case of an acyldiazoalkane.

Diazoalkanes can also react in an aldol-like manner with suitable ketones (Scheme 13)[21].
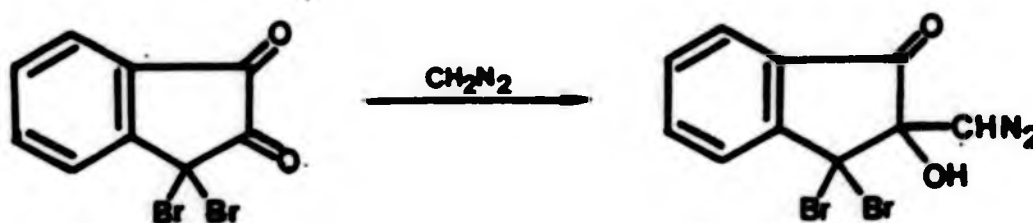
Scheme 13

Metal derivatives of diazoalkanes can be reacted with suitable substrates for example, the mercury derivative of ethyl α-diazoacetate has been reacted with bromine to give ethyl α-bromo-α-diazoacetate[22]   (Scheme 14).
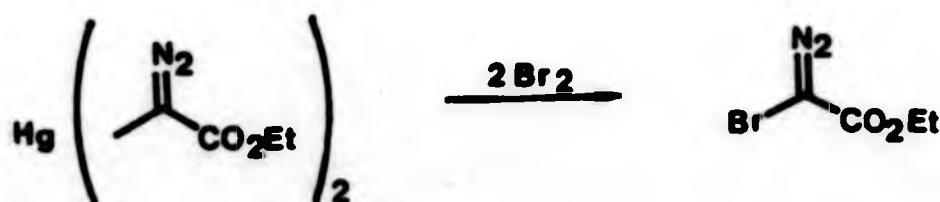
Scheme 14

New methods for the preparation of diazoalkanes

The new methods for the preparation of diazoalkanes are mainly those involving diazo transfer reactions.

Azidochloromethylenedimethylammonium chloride is a new diazo transfer donor[23] which diazotizes Meldrums acid in good yield (Scheme 15).

Phase transfer conditions with the use of tosylazide has been used in the preparation of diazoindole[24] (Scheme 16).
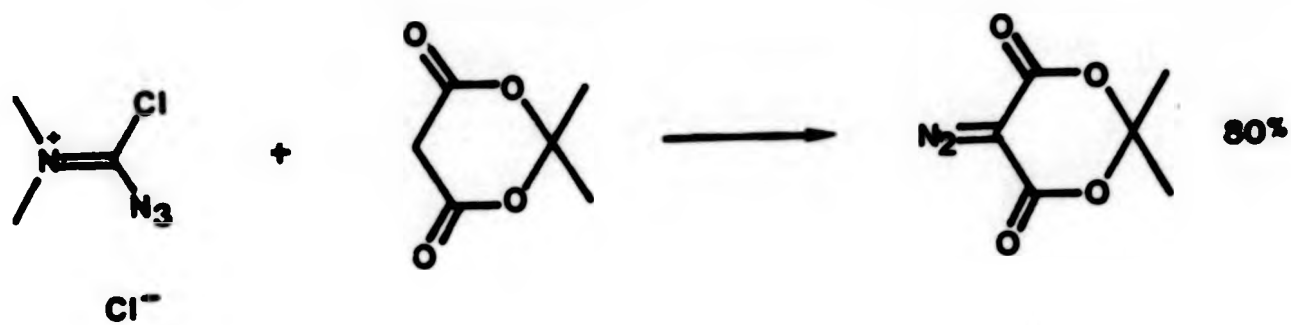
Scheme 15
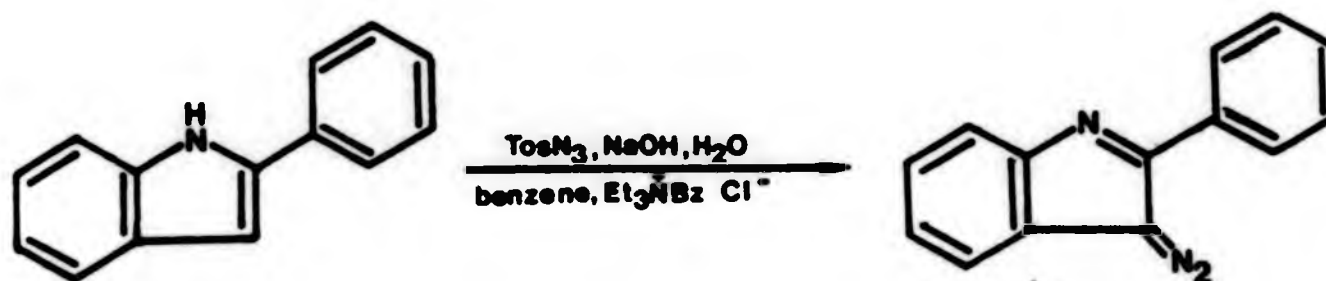
Scheme 16

The use of triisopropylbenzenesulphonylazide under phase transfer conditions has allowed the formation of α-diazo-ketones where the α-position is too hindered for prior formylation[25] (Scheme 17).
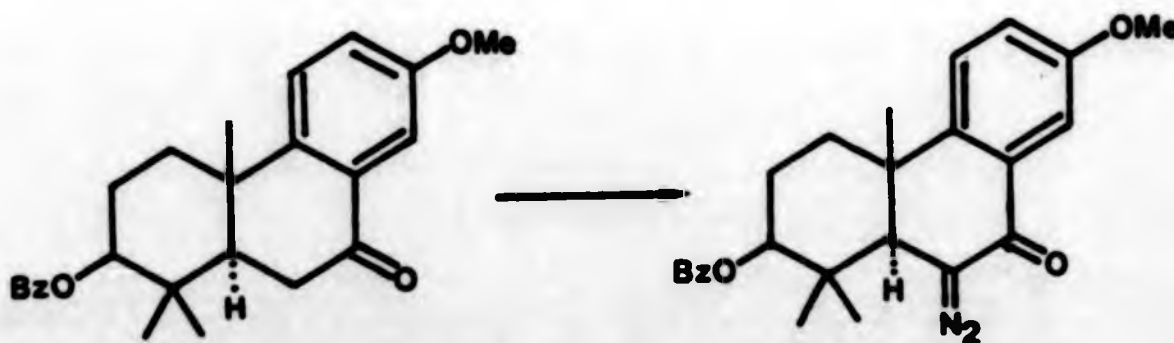
Scheme 17

The reactions of diazoalkanes

Diazoalkanes are being used increasingly in organic synthesis. This is probably due to improved methods of synthesis and because their reputation as being dangerously toxic and explosive, is being overcome.

Carbene and carbenoid insertion into double bonds

There are two common methods of activating diazoalkanes so that they will react with multiple bonds. These are via photolysis and via metal-catalysed thermolysis. The catalytic approach is generally preferred[26]. However, if the most highly substituted of two possible products is required, then photolysis may be the only possible method[27] (Scheme 18).

X_2CN_2 + (hv) ... (Δ +cat)
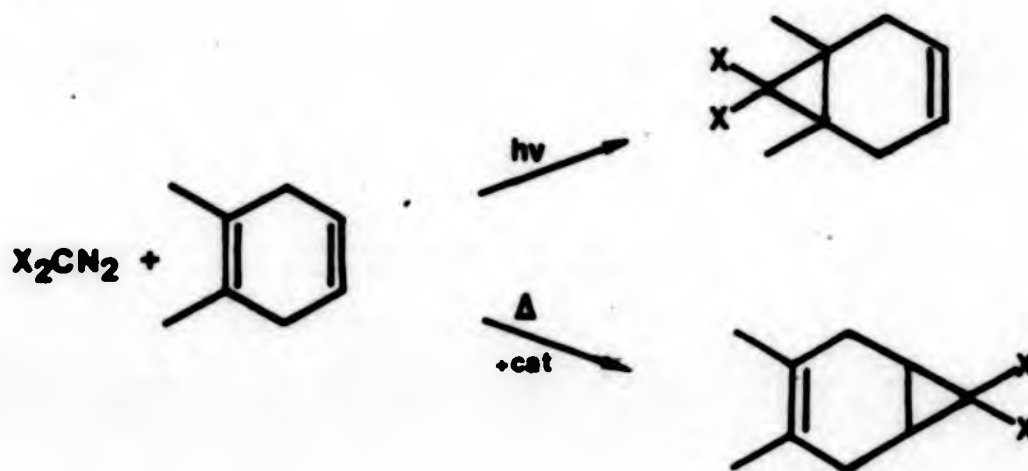
Scheme 18

The reluctance of catalytically activated diazoalkanes to react with highly substituted double bonds is attributed to the steric repulsion between the alkene and the carbene/diazoalkane catalyst complex[27].

Photolytically generated carbenes generally add to olefins stereospecifically, particularly so in the presence of oxygen[28]. However, if sensitizers such as benzophenone[29,30]

are added, both possible products are formed.   This difference
is attributed to the formation of carbenes with different spin
states.   Singlet carbenes are thought to add to double bonds
in a single step and thus preserve their stereochemistry.
Triplet carbenes on the other hand, cannot form a singlet ground
state cyclopropane in a single fast step and must therefore
react via a two step addition.   Rotation about single bonds in
the diradical intermediate could then result in non-stereo-
specific addition.   This interpretation of stereospecificity in
terms of spin state is known as the Skell rule[31].   Others[33]
have argued that only a single electronic state of methylene
is responsible for its reactions, and that the energy of the
methylene is responsible for the variation in products formed.

Recently it has been found that the irradiation of
Meldrums diazo-compound at 253nm gives high yields of cyclo-
propanes[32] (Scheme 19).
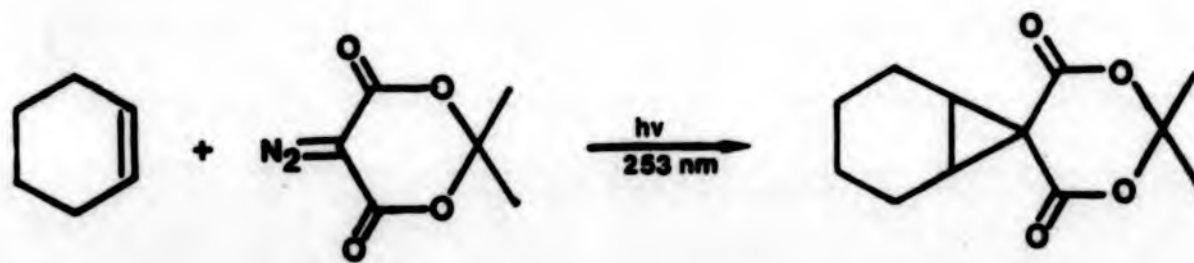
Scheme 19

The wavelength used corresponds to the $\pi \to \pi^*$
transition of the diazoalkane at 249nm.   The intermediate
is considered to be a singlet carbene.

Photochemical decompositions are extensively used

when the final product of the reaction is likely to be
thermally labile. Photolysis of the diazoalkane allows
reactions to be carried out at lower temperatures for
example, cyclopropene (4) was prepared by photolysis at 25°C [34]
(Scheme 20).

(4)

Scheme 20

Uncatalysed thermal reactions of diazoalkanes may
take place via thermolysis of the diazoalkane followed by
reaction of the resultant carbene with the substrate[35], or
the reaction may be concerted with the diazoalkane 'masquerading'
as a carbene[36]. In the case of metal-catalysed thermolysis both
carbene-metal and diazoalkane-metal complexes have been
isolated[37], and it seems likely that both are involved in metal-
catalysed thermolysis of diazoalkanes.

Doyle and Davidson[38] investigated the catalytic
properties of molybdenum hexacarbonyl because of its affinity
for dinitrogen and the reactivity of molybdenum-carbene com-
plexes. They found that it catalysed the cyclopropanation of
α,β-unsaturated esters and nitriles (Scheme 21).

Scheme 21
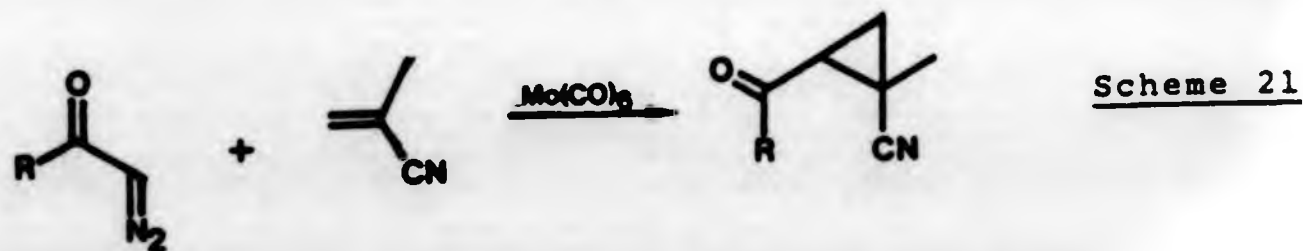
Rhodium-(II)-salts of carboxylic acids have proved to be very efficient catalysts for the insertion of diazo-alkanes into double bonds. In the Buchner reaction the use of rhodium-(II)-trifluoroacetate produces 100% yield of the cycloheptatriene when ethyl diazoacetate is reacted with benzene[38] (Scheme 22).
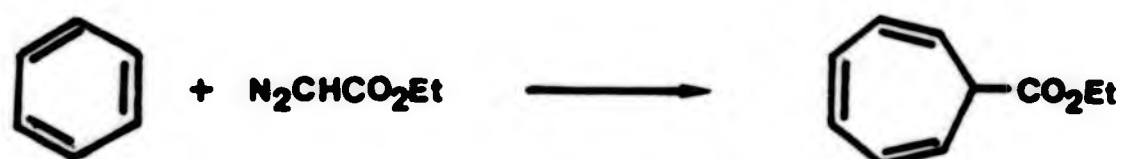
Scheme 22

In the field of penicillin chemistry rhodium-(II)-acetate has been used in the reaction between benzyl 6-diazo-penicillanate and furan[40] to give the dienal side-chain at C-6 (Scheme 23).
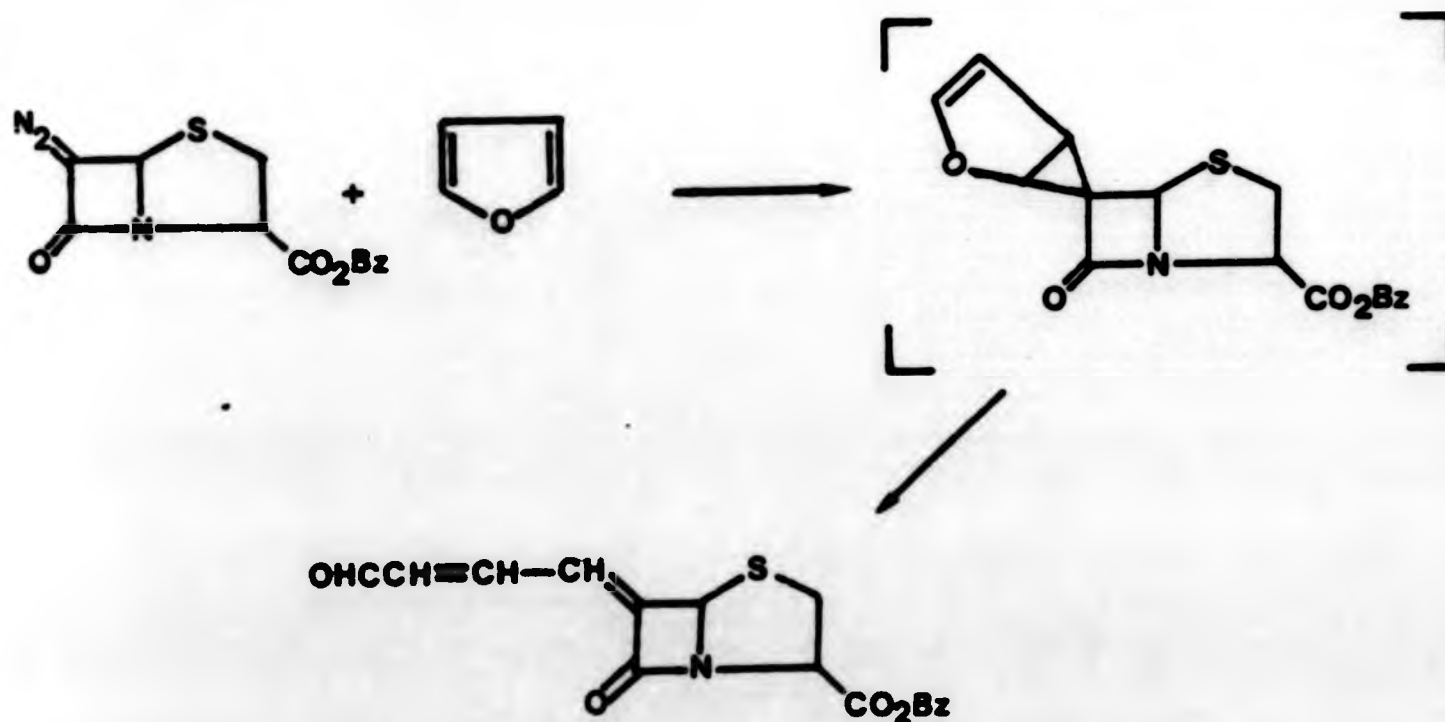
Scheme 23

Shankar and Shechter[41] have shown that the catalyst iodorhodium-(III)-tetraphenylporphyrin, a very large species, gives improved selectivity in the formation of _cis_-1,2-diaryl ethylenes from aryldiazomethanes over that of rhodium-(II)-acetate, thus showing that steric effects play a major part in stereoselectivity of this type of reaction.

Palladium-(II)-acetate is a highly specific catalyst with an affinity for olefins. It has been used in the preparation of α,β-epoxycyclopropyl ketones[42] (Scheme 24). Copper catalysis fails to give the cyclopropane.
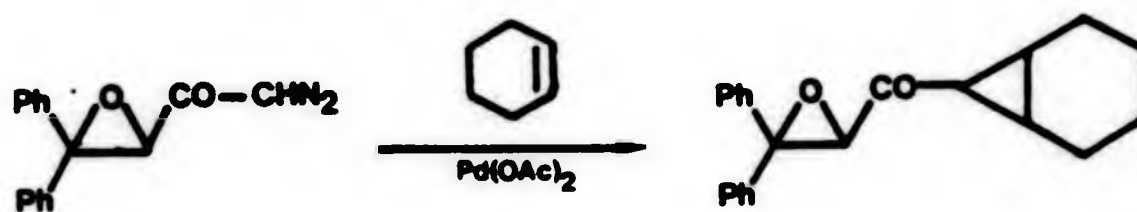
Scheme 24

Hubert and co-workers have shown that although palladium-(II)-acetate is a very specific catalyst[43], it is sensitive to steric crowding and works best in activated systems. Its selectivity is attributed to the formation of an intermediate catalyst-olefin-carbene complex[44]. It can be used to specifically cyclopropanate terminal double bonds with diazomethane[45] (Scheme 25).

Scheme 25

Copper catalysts have been used for many years in the field of diazoalkanes. Prior to the appearance of the group-8-metal catalysts copper was the dominant metal used and it is still used to a very large extent. For example, copper-(II)-acetylacetonate was used to catalyse the intra-molecular cyclopropanation of the diazoketone (4) (Scheme 26). Thermal vinyl-cyclopropane rearrangement of the resultant cyclopropane[46] yielded the cyclopentene (5) which was used in the synthesis of hirsutene[47].

(4)

(5)
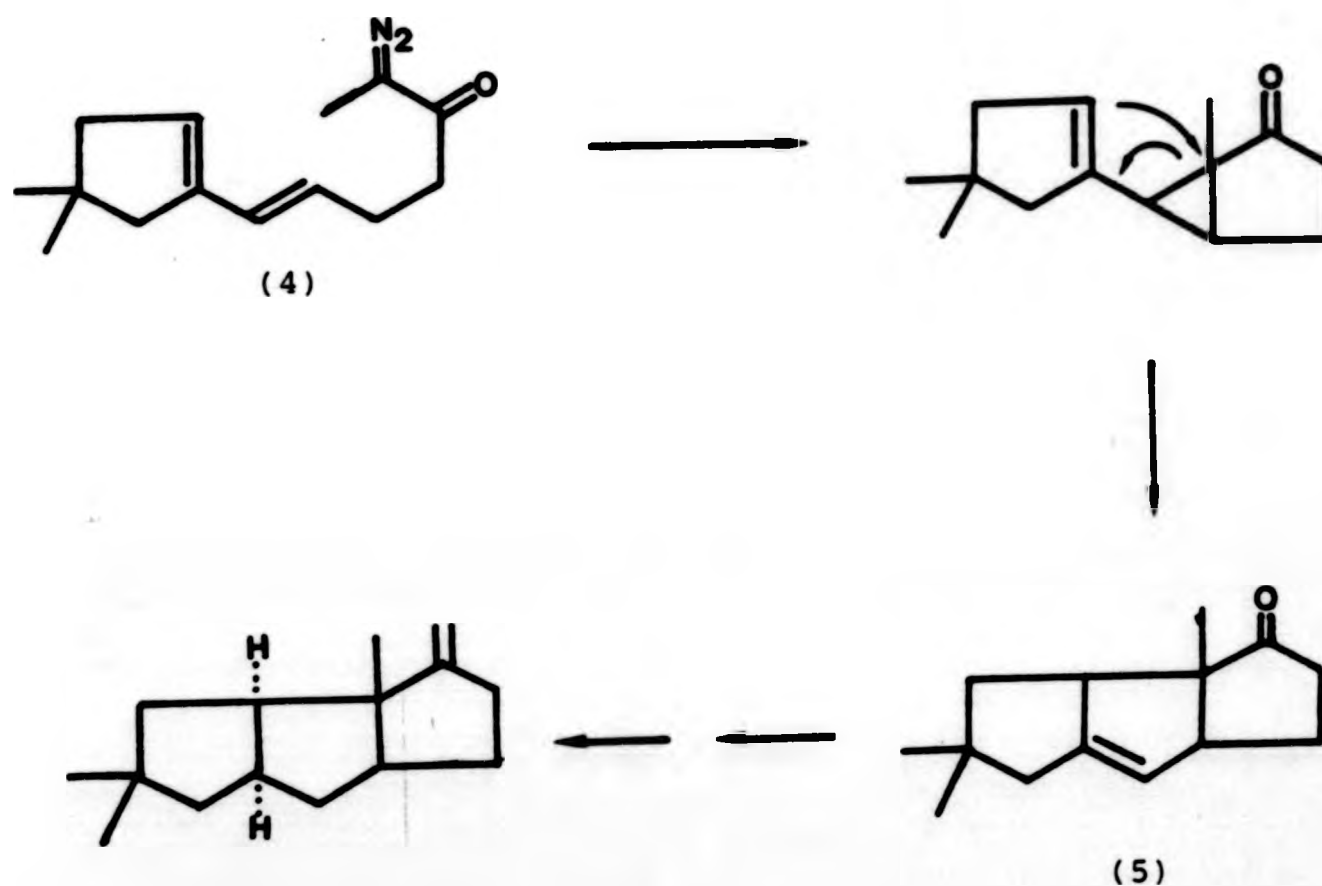
Scheme 26

This method has also been applied to the synthesis of bicyclononanes[48] and octanes[49].

Another recent example of the use of copper catalysis is in the field of penicillin chemistry. Mara et al.[50] used

copper-(II)-acetylacetonate to catalyse the reaction between the thiazoloazetidinone (6) and ethyl diazoacetoacetate (Scheme 27).

(6)
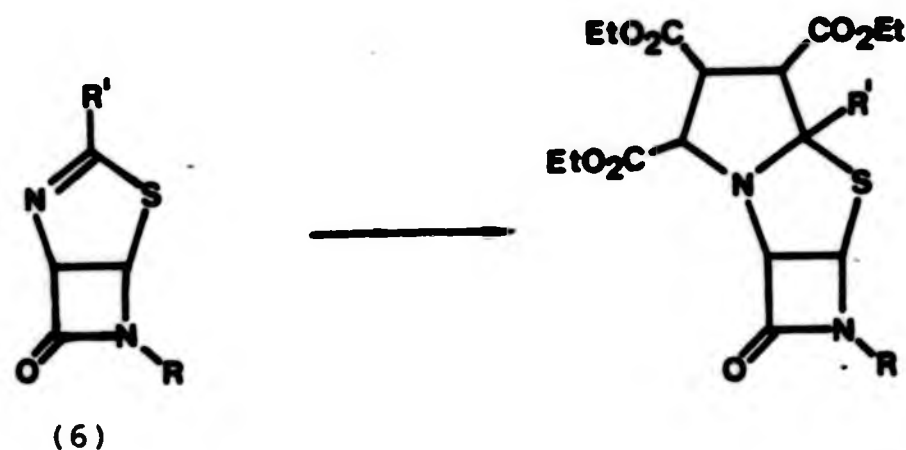
<u>Scheme 27</u>

The reaction is believed to proceed via the dipole (7).

(7)
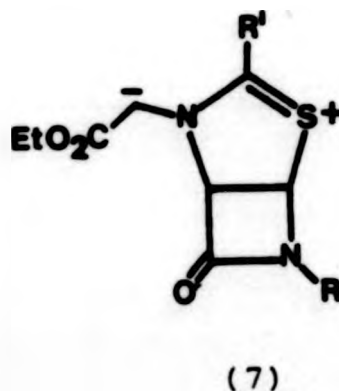
<u>1,3 Dipolar cycloadditions of diazoalkanes</u>

Diazoalkanes can add over many types of double bonds, although the rate and/or equilibrium of the reaction may not always be favourable. Changing solvent[51] and increasing pressure[52] can speed up the reaction and increase yield.

The addition of diazoalkanes to double bonds can occur in two senses even when the double bond is strongly polarised[53] (8) and (9). The rationalization of this regio-selectivity is obtained by consideration of the HOMO-LUMO interaction[54] of the diazoalkane-dipolarophile respectively.
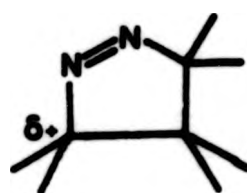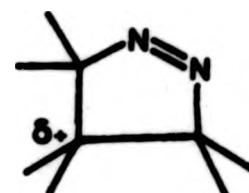
(8)   (9)

Thus, if the diazoalkane possess electron donating groups (lowering its HOMO), and the dipolarophile possess electron withdrawing groups (raising its LUMO), then the reaction will be rapid, because the frontier orbital separation is small.

A recent example of 1,3 dipolar cyclo-addition was in the reaction of diazomethane with silylated ethylenes[55], to give, after thermolysis, <u>trans</u>-1,3-bis(trimethylsilyl) propenes. Oxidation of the intermediate pyrazolines yields the corresponding pyrazoles (Scheme 28).
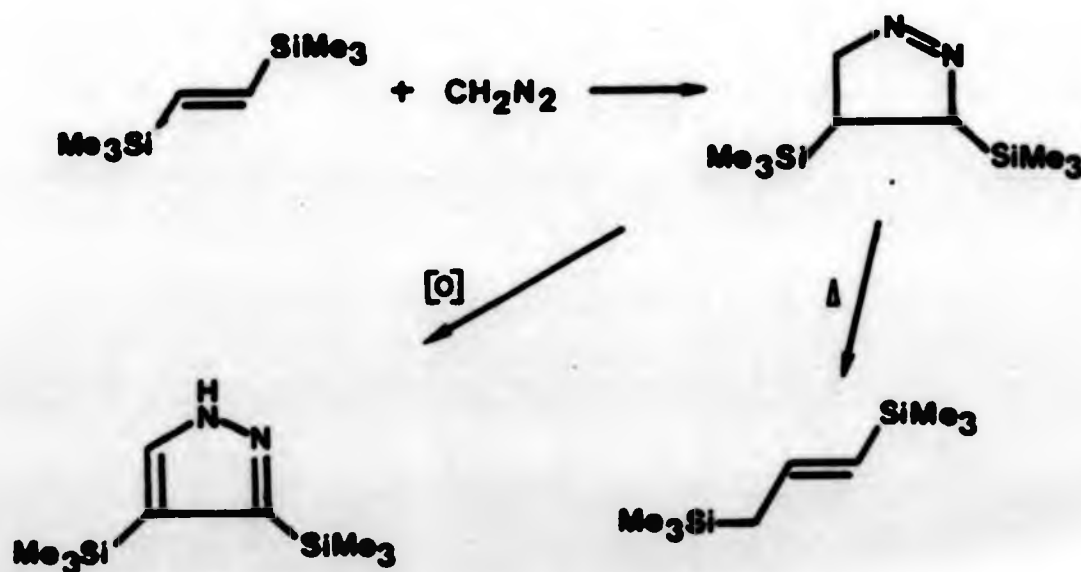
<u>Scheme 28</u>

Diazoalkanes add much more readily to strained
double bonds, thus Burgert et al.[56] reacted several 9-diazo-
fluorenes and benzyne to obtain spiro[fluorene-9,3'-pyrazoles]
in fair yield (Scheme 29).
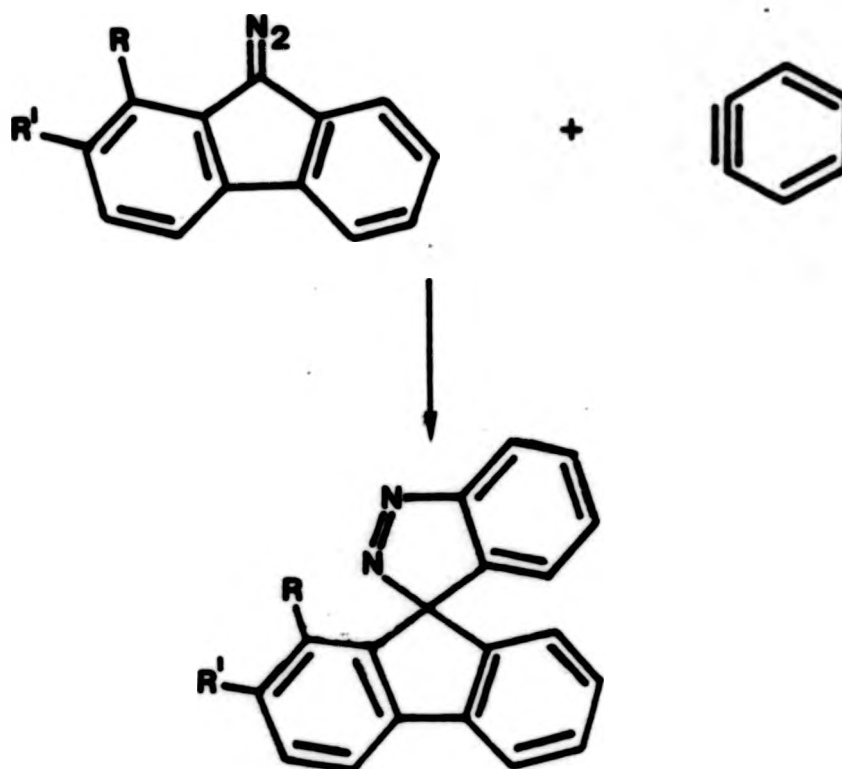
Scheme 29

Gallagher and Storr[57] found that the reaction of
diazomethane with chloroazirines forms 1,2,3 triazines. The
reaction proceeds by way of the intermediate dipolar cyclo-
addition product (Scheme 30). This reaction is of interest
in that 1,2,3-triazines are normally inaccessible by other
methods.
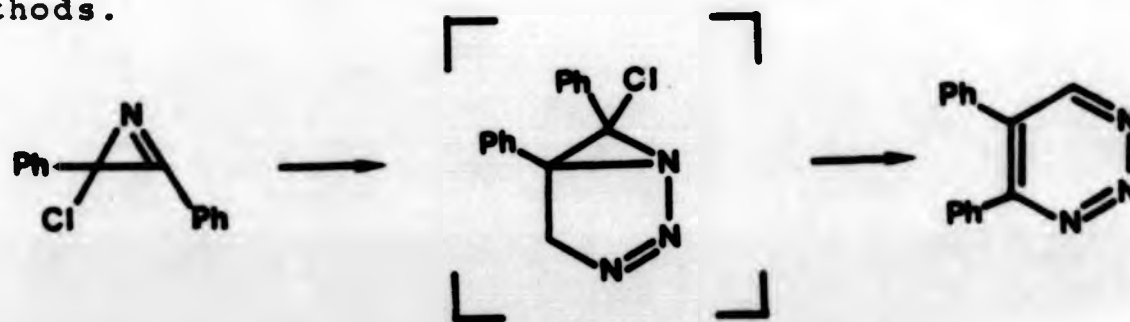
Scheme 30

Diazomethane rarely undergoes dipolar additions to 5-membered heterocyclic systems such as imidazoles. However when the double bond is activated and localized, as in the case of 2-dichloroacetamido-1-methyl-5-nitroimidazole, addition can occur[58] (Scheme 31).

R = Cl$_2$HCO

−HNO$_2$
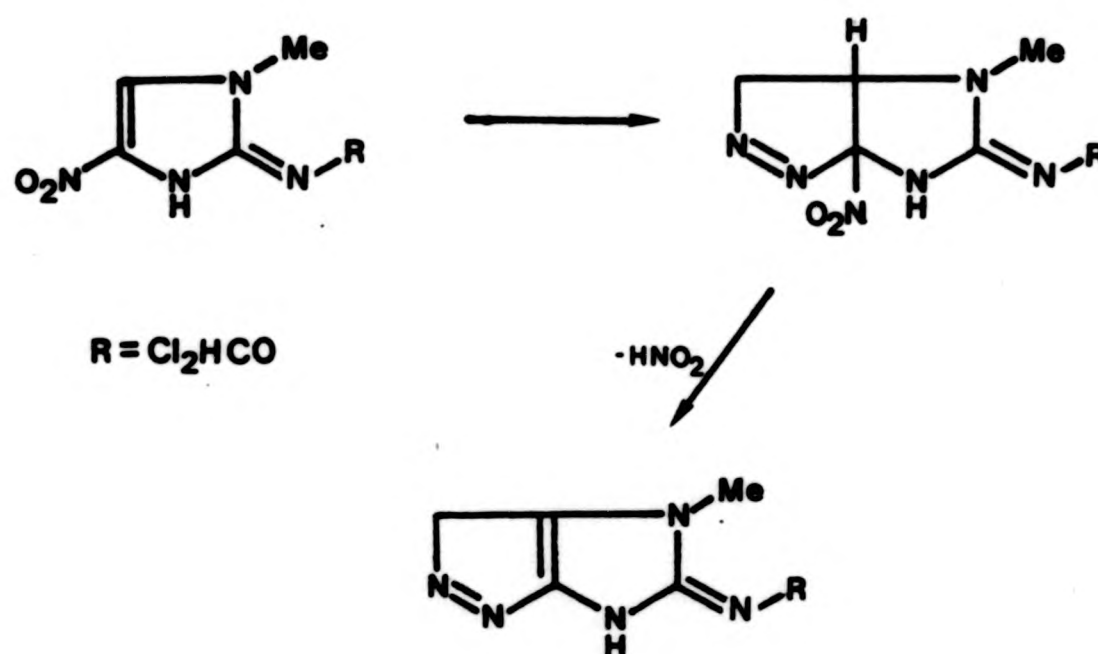
Scheme 31

Huisgen and co-workers[59] investigated the reaction between diazomethane and thiocarbonylcompounds at -78°C. The dipolar cycloaddition product was obtained, which formed the ylid (10) upon warming. The ylid was trapped by various dipolarophiles (Scheme 32).

(10)
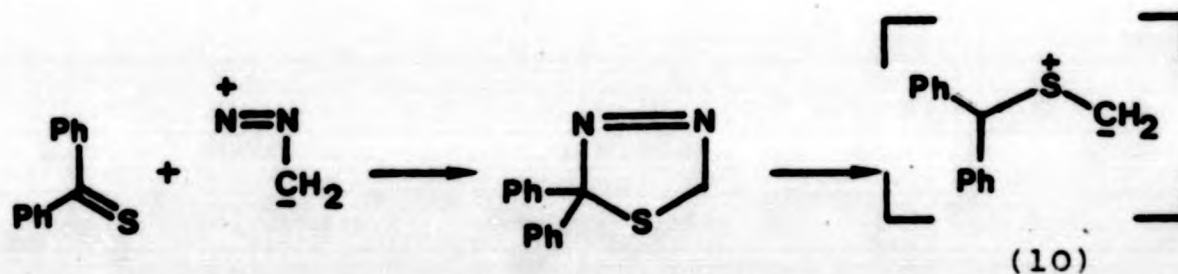
Scheme 32

The 1,3-dipolar cycloaddition of diazoalkanes to acetylenes may be used to prepare 3H-pyrazoles   for example, Huisgen[60] et al. added dimethyl diazomalonate to 1-(diethyl-amino)propyne to give the 3H-pyrazole. This rearranged by a 1,5-sigmatropic shift of an ester group to give the 2H-pyrazole. This aromatization is known as the Van Alphen-Huttle rearrangement[61] (Scheme 33).
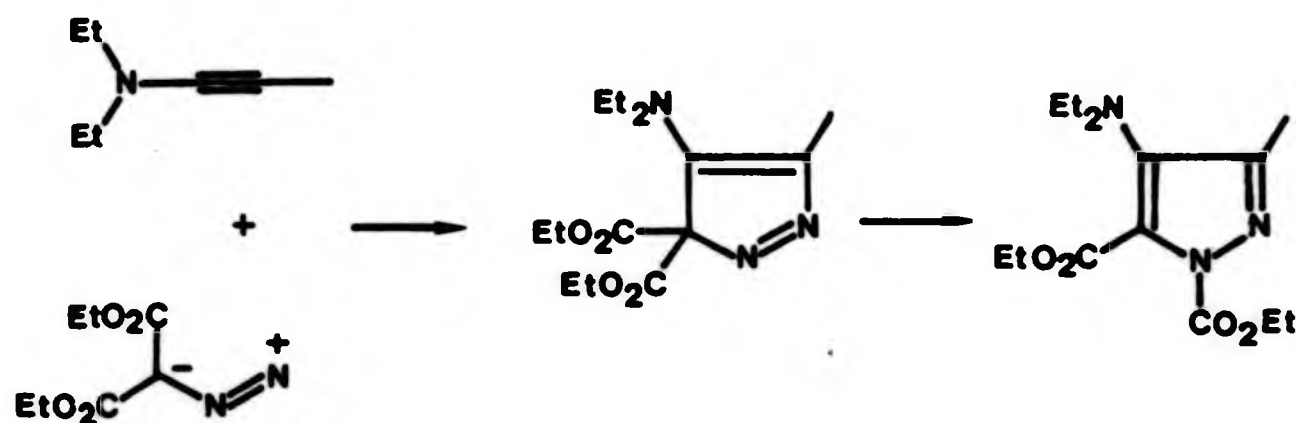
Scheme 33

Padwa et al.[62] reacted diazopyrazolines with electron deficient acetylenes. They obtained a number of products each of which was derived from an intermediate 3H-pyrazole (Scheme 34).

E. Schaumann et al.[63] obtained a 3H-pyrazole from the reaction of 2-diazopropane and allyl(silyl)thioketene (11). The 3H-pyrazole is in fact derived from the tautomer of the thioketen (Scheme 35).

Enamines are inert towards diazomethane. However, Huisgen and Reissig[64] found that α-diazocarbonyl compounds undergo 1,3-dipolarcycloaddition with enamines at room

Scheme 34

(11)
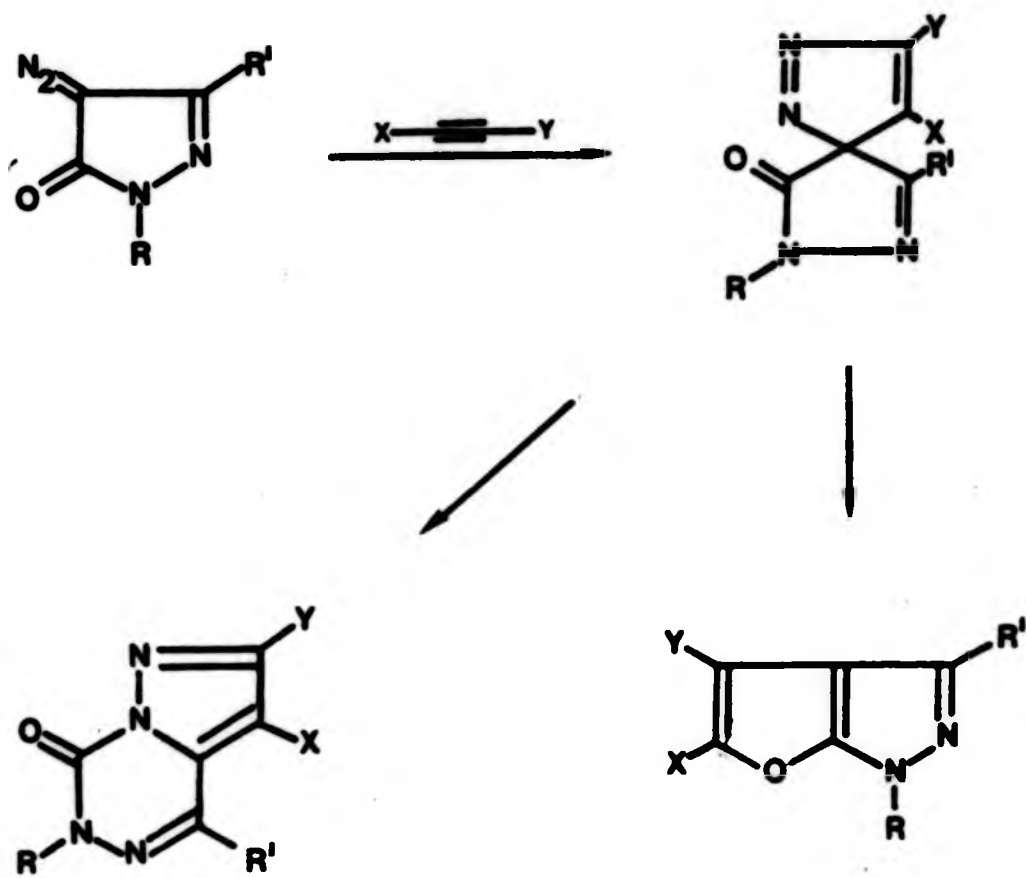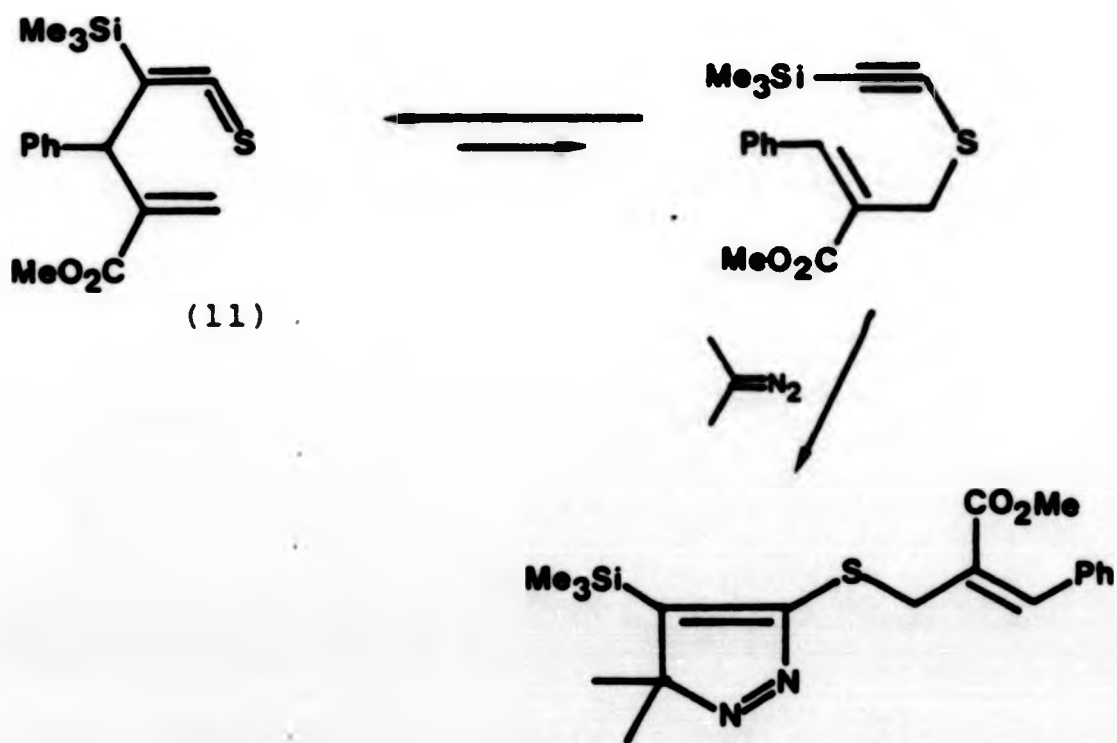
Scheme 35

temperature. For example methyl diazoacetate reacts with N(1-propenyl)pyrrolidine to give the pyrazole (13). The pyrazoline (12) is the intermediate (Scheme 36).
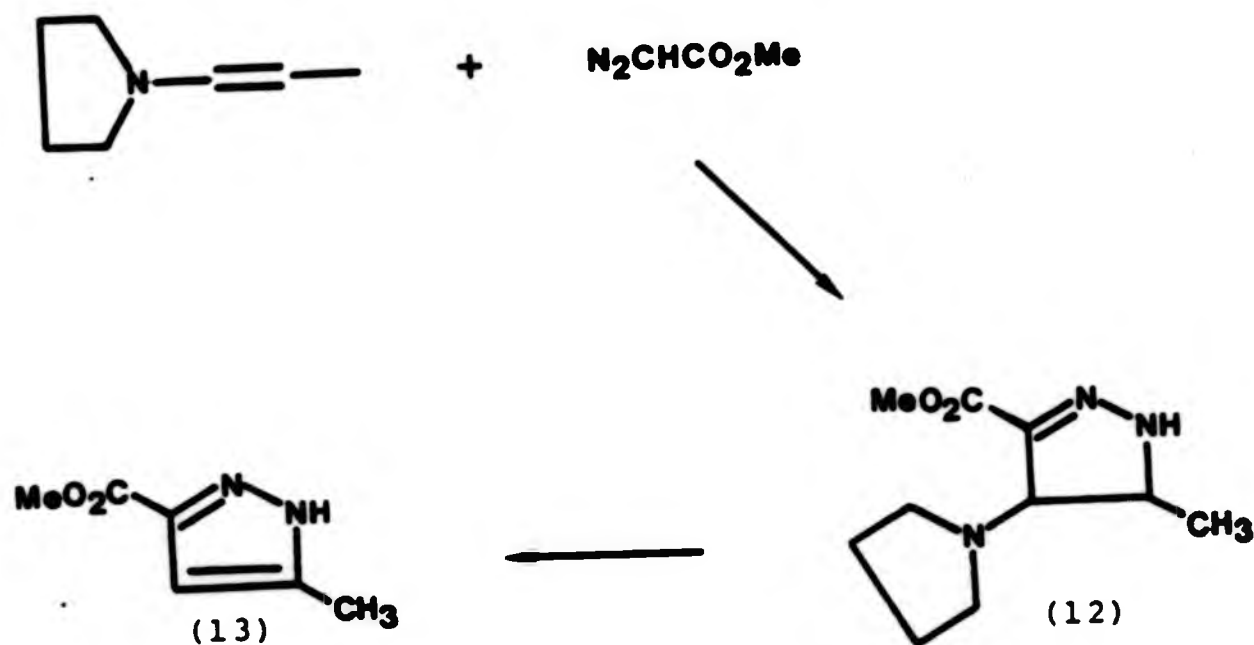
Scheme 36

Keto- or Imino-carbene cycloadditions

α-Diazocarbonyl or imino compounds can act as precursors to 1,3-dipoles. The carbene generated by the elimination of the diazo-group can be regarded as a 1,3-dipole (Scheme 37).

Scheme 37

These dipoles can undergo cycloaddition, for example, ethyl diazoacetate when thermolysed in the presence of copper-(II)-hexafluoroacetylacetonate gives (14) a 1,3-dipolar addition product with crotonaldehyde[65] (Scheme 38).

(14)
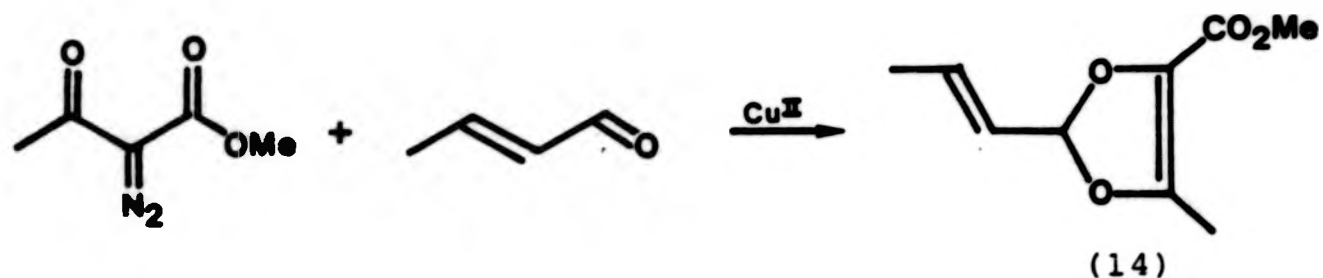
Scheme 38

Doyle et al.[66] found that Lewis acids effectively
catalyse the decomposition of α-diazocarbonyl compounds in
nitriles to give the 1,3-dipolar addition product. BF_3-etherate
for example, has been used in the preparation of a number of
substituted oxazoles[67] (Scheme 39).
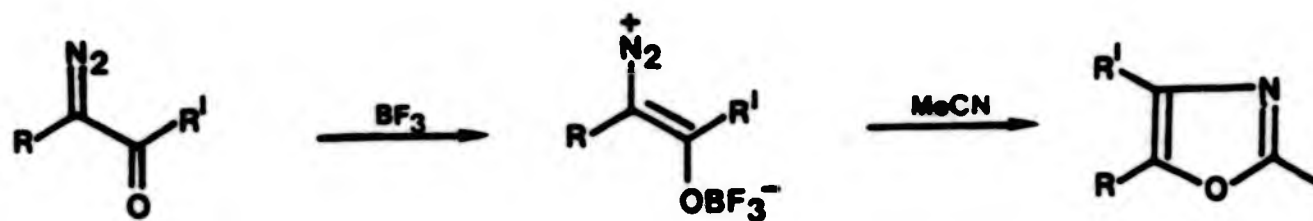
Scheme 39

If an electron-rich benzene derivative is present in
the above reaction mixture the intermediate nitrilium betaine
can be captured[68] (Scheme 40).
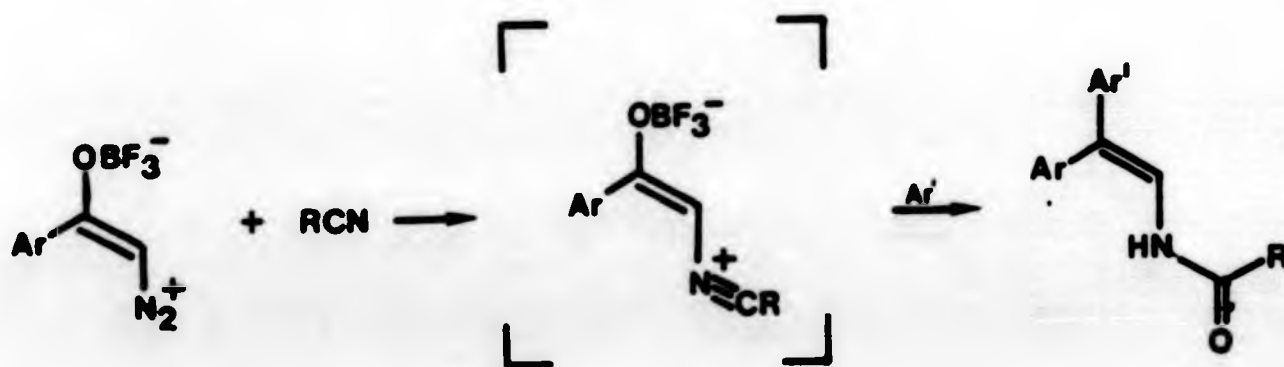
(Ar = 2,4,6-trimethoxy-
benzene)

Scheme 40

Wenkert et al.[69] reacted ethyl diazopyruvate (15)
with the alkoxycyclohexene (16) and obtained the "unexpected"
dihydrofuran (Scheme 41).

(16)
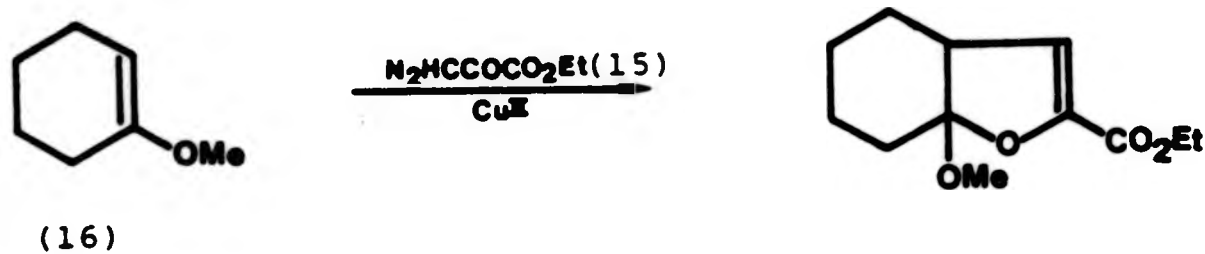
Scheme 41

Reaction of ethyl diazopyruvate with cyclohexene
yielded only the cyclopropane (17).

α-Diazocyanoimines also undergo 1,3-dipolar type
cycloadditions when thermolysed[70,71], for example, when
triazole (18) is heated in acetonitrile or benzene the
corresponding addition products are formed[70] (Scheme 42).

(18)
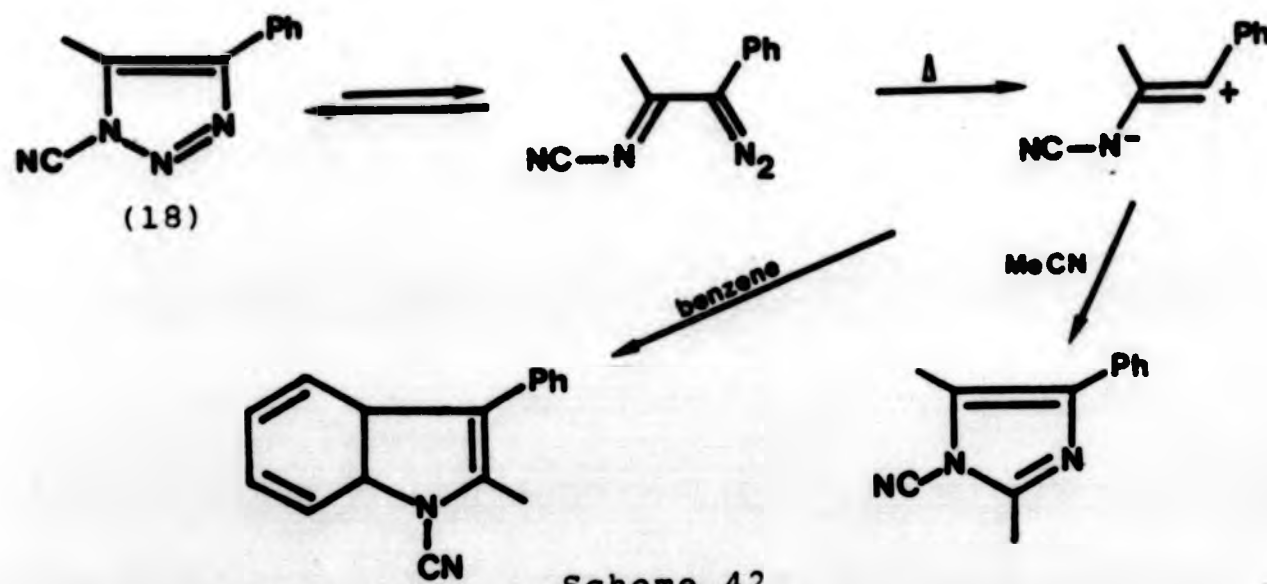
Scheme 42

It should be noted that acylcyclopropanes undergo
a thermal vinyl-cyclopropane type rearrangement to give the
same product that would arise from 1,3-dipolar cycloaddition[72]
(Scheme 43). If the rearrangement is facile, it is probable that
the cyclopropane would not be detected.

Scheme 43

Insertion into single bonds

Most insertions of diazoalkanes into single bonds
involve the loss of N_2. They can therefore be considered carbene
or carbenoid type reactions. In reality however, radicals,
carbonium ions, and ylids may be involved.

The most common insertion reaction involves X-H
bonds where H is somewhat acidic, for example, the esterifica-
tion of carboxylic acids using diazoalkanes. The reaction is
essentially a nucleophilic displacement of nitrogen from the protonated
diazoalkane (Scheme 44).
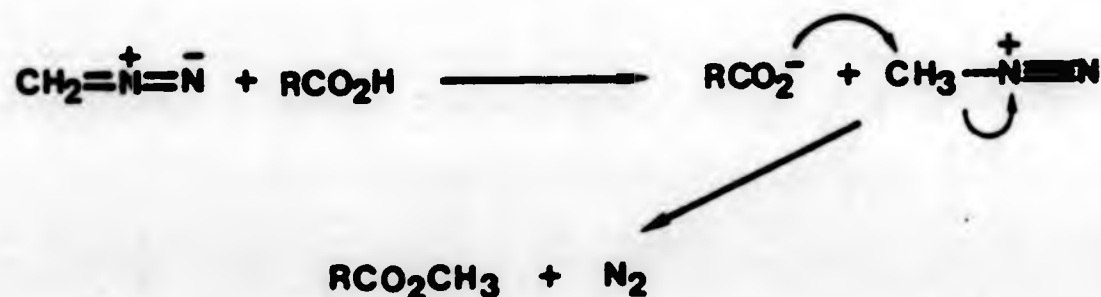
Scheme 44

In the case of photolysis of diazoalkanes in the presence
of alcohols, the carbene is believed[36] to be the reactive
species and it is this that is protonated by the alcohol to
form a carbonium ion which is then solvolysed, for example,
the novel phosphonium diazoalkane (19) inserts into the OH bond
of methanol when photolysed in that solvent[73] (Scheme 45).

(19)
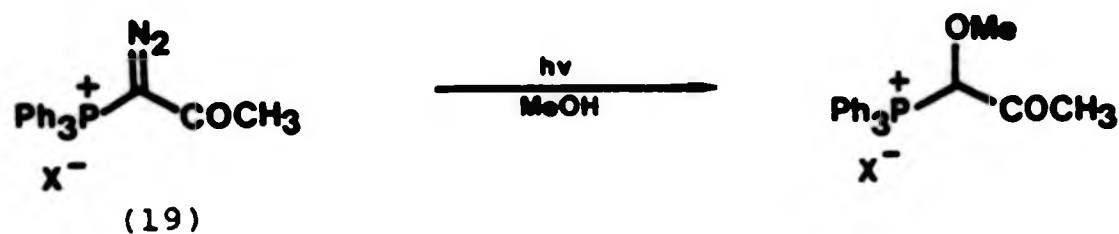
Scheme 45

Enolic hydrogen-oxygen bonds are also reactive
towards insertion. BF_3 catalysed decomposition of ethyl diazo-
acetate in the presence of a β-dicarbonyl compound gives the
monoenolether[74] (Scheme 46).
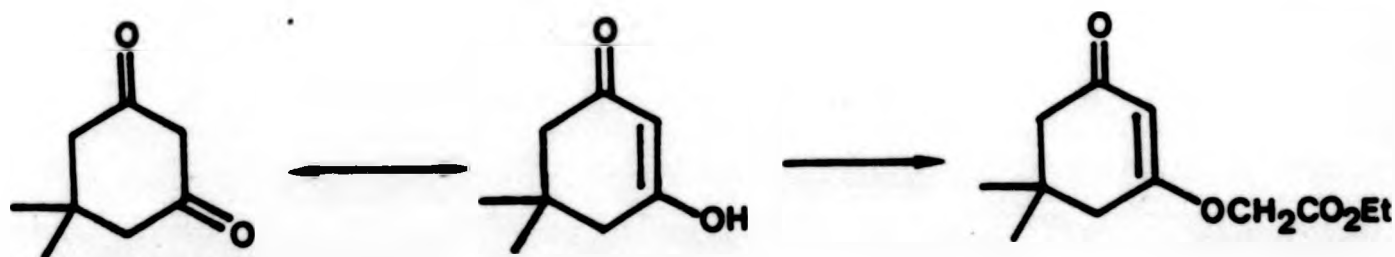
Scheme 46

Insertion into single bonds can also be catalysed by
metal catalysts, for example, Cu-(II)-acetylacetonate was
used to catalyse the reaction between α,ω-bisdiazoketones and

diols, to form macrocyclic oxo crown ethers[75] (Scheme 47).

Macrocycles
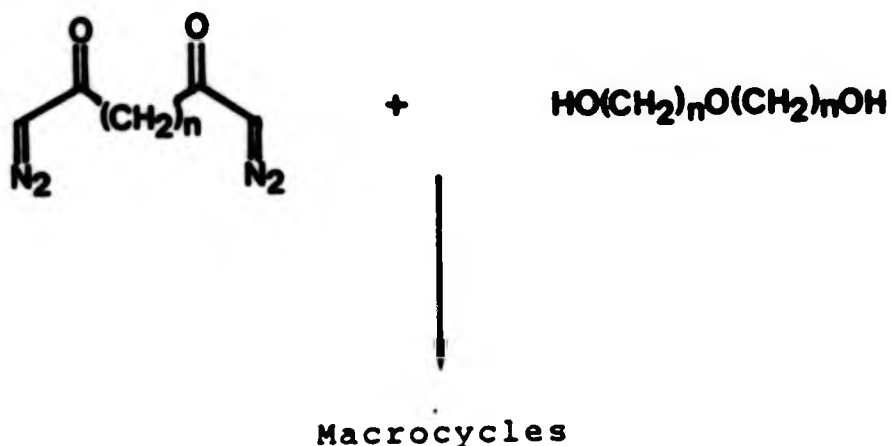
Scheme 47

Diazoalkane insertion into N-H bonds is quite commonly used, particularly in the field of β-lactam chemistry. Rhodium-(II)-acetate has been used to catalyse the intra-molecular insertion to form the carbapen-2-em system[76,77] (Scheme 48).
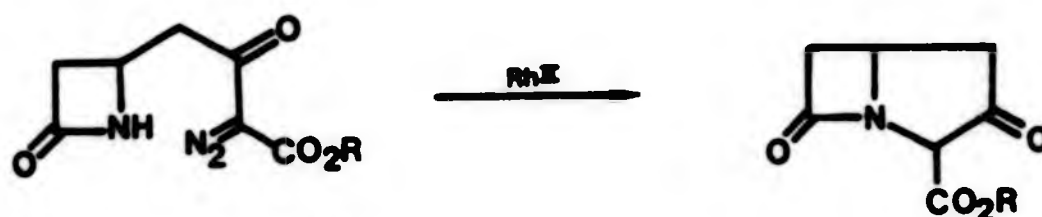
Scheme 48

Copper catalysed decomposition of diazomalonate and diazoacetate in the presence of imidazole gives mixtures of N-methylimidazole, ethylimidazole-1-ylacetate, and diethyl imidazole-1-yl malonate[78].

Acidic C-H bonds also give insertion products. The allylic position of an olefin can give troublesome side reactions when cyclopropanation is being attempted[27]. Examples of the use of C-H insertion reactions include the construction

of β-lactams by insertion of a diazoalkane α to an amide nitrogen[79] (Scheme 49).
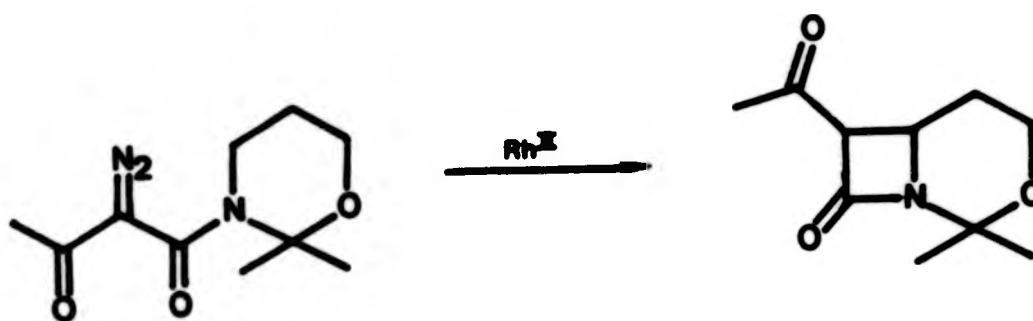
Scheme 49

α,β-Unsaturated carboxylic acids may be obtained from α-diazocarboxylic acids using rhodium-(II)-acetate catalysis. The reaction involves a 'hydride shift' or an insertion into a C-H bond[80] (Scheme 50).

Scheme 50

Lithiodiazoalkane (20) may be reacted with aldehydes, and the product then converted to a β-diketone via a hydride shift[81] (Scheme 51).
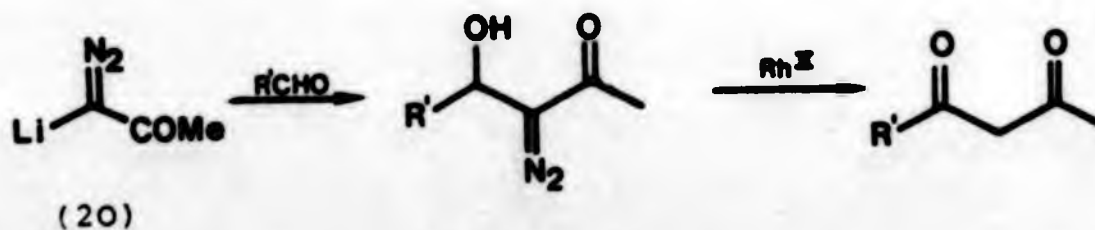
Scheme 51

Other examples of insertion into single bonds by diazoalkanes include insertion into the diselenide bond[82] (Scheme 52), the selenium-chlorine bond[83] (Scheme 53), and the fluorine-fluorine bond[84] (Scheme 54).

$$N_2CHCO_2Et \ + \ PhSeSePh \longrightarrow (PhSe)_2CHCO_2Et$$
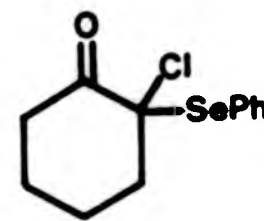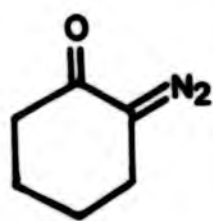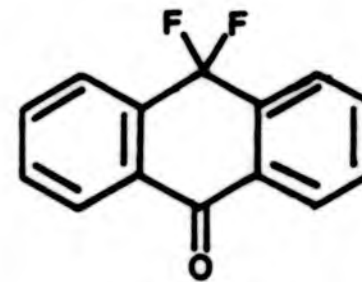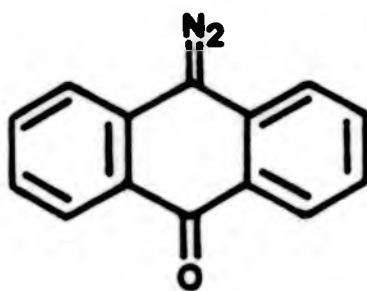
<p align="center">Scheme 52</p>

<p align="center">Scheme 53</p>

<p align="center">Scheme 54</p>

Preparation of ylids

The formation of a carbene or a carbenoid from a diazoalkane means that it can form ylids with nucleophilic atoms (carbenes being electrophilic), for example a possible mechanism for the insertion of diazoalkanes into O-H bonds is via formation of an oxonium ylid followed by proton transfer[85] (Scheme 55).
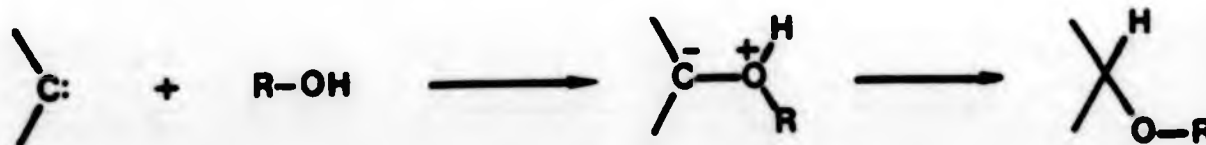
<p align="center">Scheme 55</p>

Recent examples of ylid formation from diazoalkanes all involve sulphur ylids. The formation of ylids as intermediates in the preparation of novel β-lactams has been reported[86,87,88,89], for example, Prased et al.[88] obtained the β-lactams (21) and (22) from the thermal decomposition of diazoketone (23) (Scheme 56).

(23)

(21)   (22)
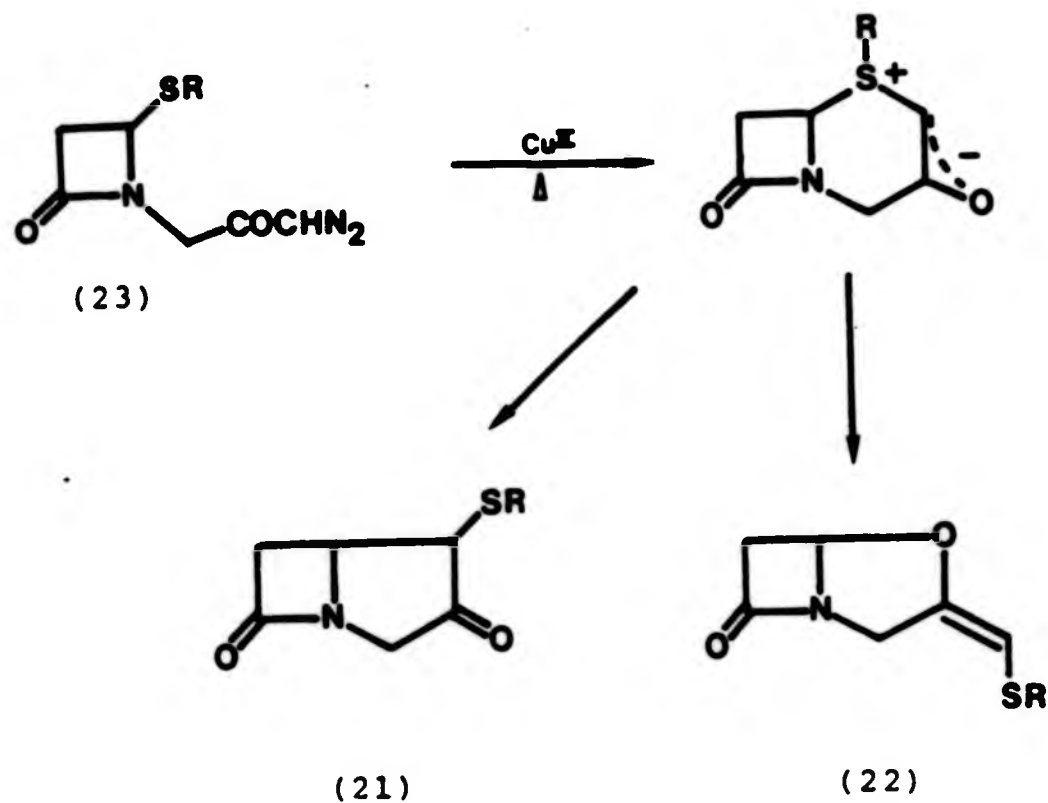
Scheme 56

Kalwinsch and Huisgen[90] invoke a sulphur ylid intermediate in the reaction of diazoacetic ester with thiobenzophenone (Scheme 57) as is done in the reaction of diazomethane with thiobenzophenone[59] (p. 20).
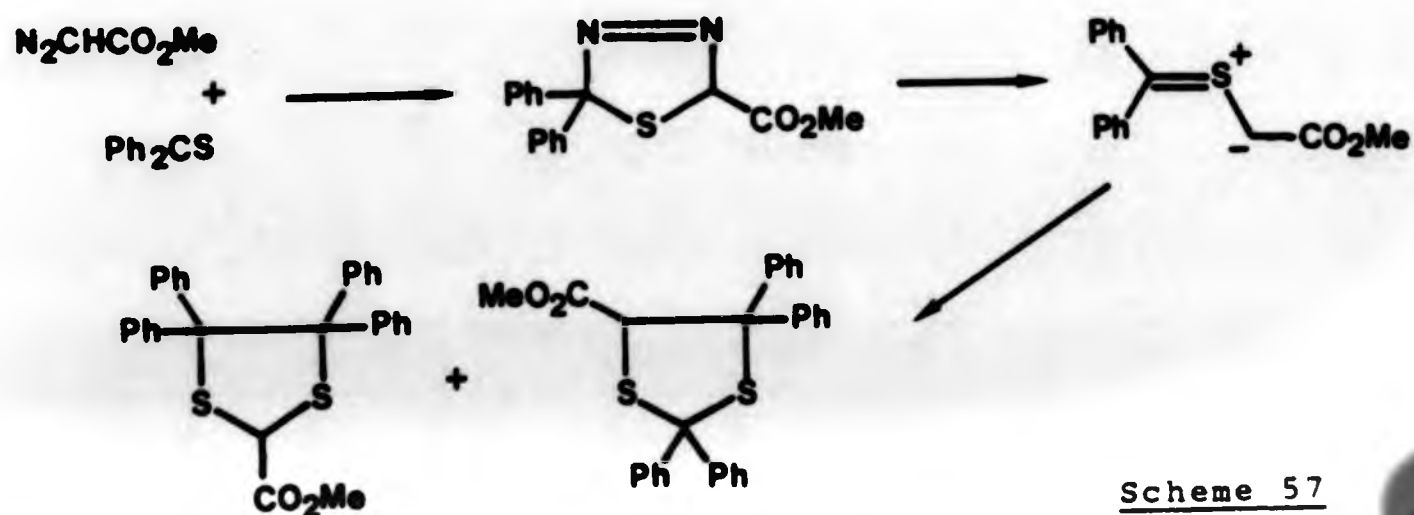
Scheme 57

Treatment of thiochroman-4-one with dimethyl diazo-malonate in the presence of copper-(II)-sulphate gives the ylid. Treatment of the ylid with triethylamine gives the corresponding tetrahydro-1-benzothiepin-5-one. The rearrangement takes place via a β-elimination followed by an intramolecular Michael addition[91] (Scheme 58).
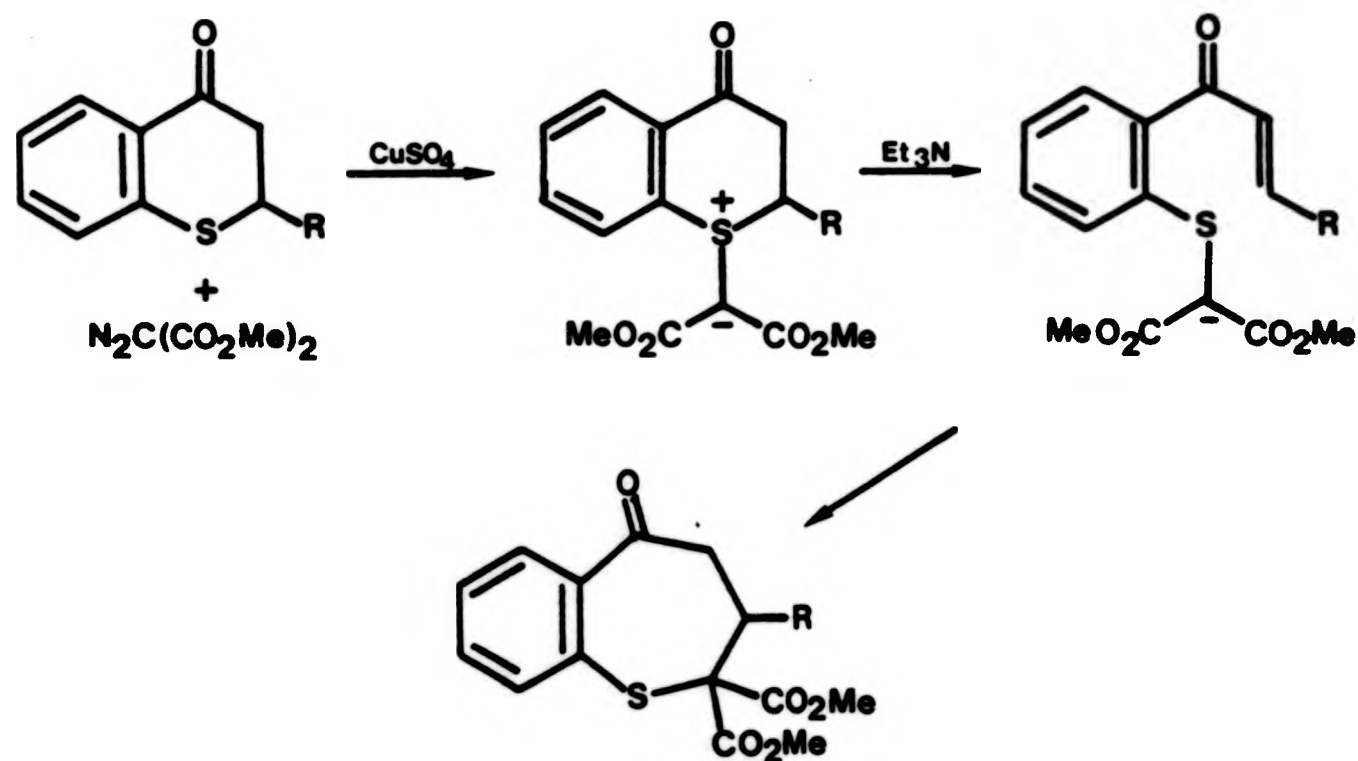
Scheme 58

Rearrangement of diazoalkanes

By far the most common rearrangement of diazoalkanes is the Wolff rearrangement[92], in which α-diazoketones furnish a ketene or a ketene-derived product (Scheme 59). It is used in the Arndt-Eistert homologation of acids and in ring contractions.
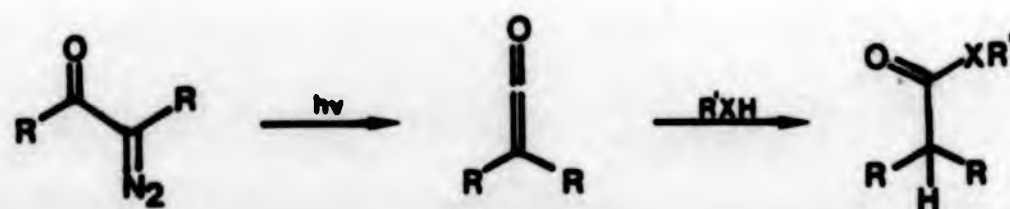
Scheme 59

The Wolff rearrangement can be induced by thermolysis, catalysis, and photolysis. The processes are not always equivalent and usually one particular method is preferable. Silver catalysis is frequently used in acid homologation, the use of the $Ag_2O/Na_2S_2O_3/Na_2CO_3$ system being common practice[93]. Photochemical methods are more common for the preparation of strained ring systems since this enables the reaction to be carried out at low temperatures, for example, the preparation of acenaphthyne[94] was carried out using photolysis at 15°K (Scheme 60).
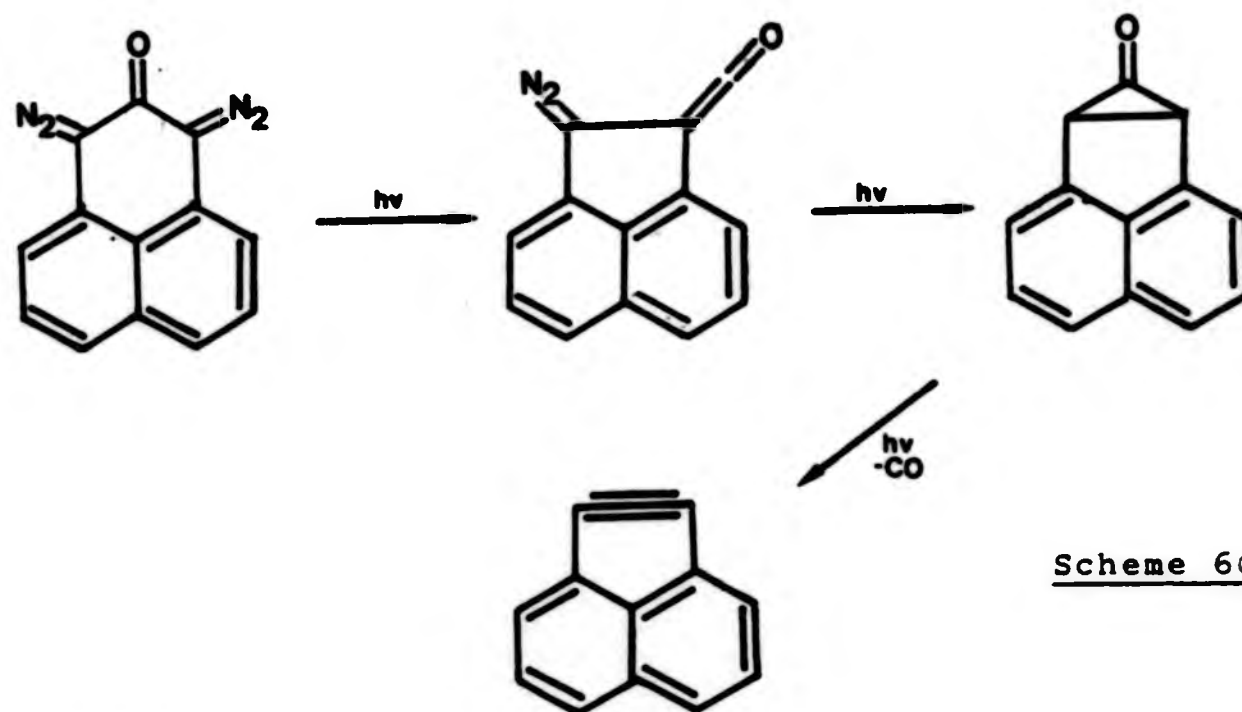
Scheme 60

Wolff and Agosta[95] used a Wolff rearrangement to contract the ring of tricyclic ketone (24) to obtain the corresponding tricyclo[4.2.0.0^{1,4}] octane carboxylates (Scheme 61). The two isomers were obtained in the ratio of 11:2 respectively, the major one resulting from attack by the methanol from the less hindered side of the ketene.

Ketenes can undergo cycloadditions, therefore the thermolysis of α-diazoketones in the presence of suitable substrates

can afford the corresponding cycloadducts (Scheme 62)[96], and
(Scheme 63)[97].
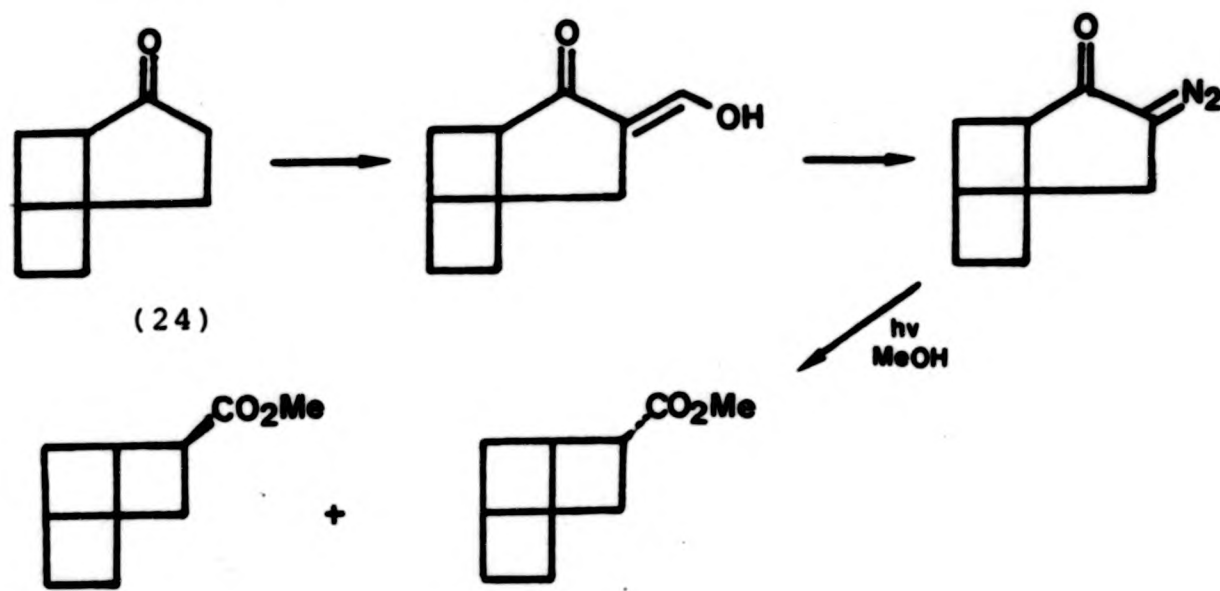
Scheme 61
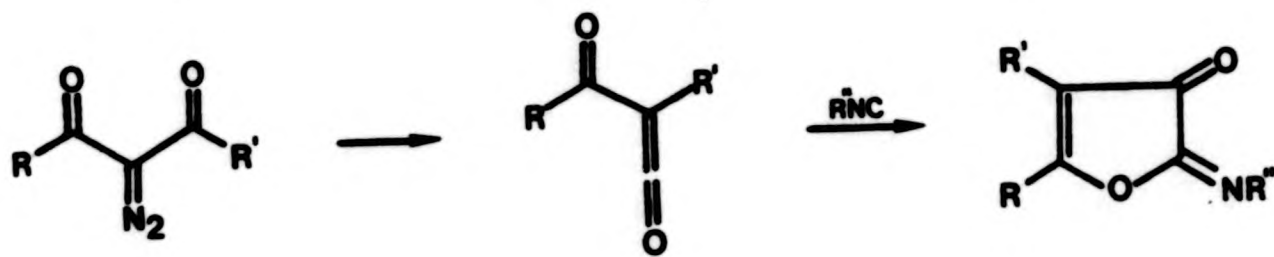
Scheme 62
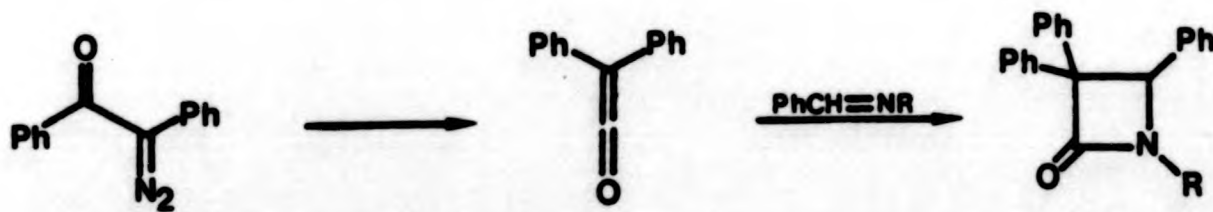
Scheme 63

Acid catalysed intramolecular C-alkylations with diazoketones

Recently a great deal of interest has been shown in reactions of this type[98,99], for example, Satyanarayna et al.[100] used it to form pentaleno-annelated polycyclic systems (Scheme 64). The mechanism involves the protonation of the diazo-group and generation of a carbonium ion like intermediate, as illustrated by the alkylation of dienic-diazoketones in the synthesis of (±)Filifolone[101] (Scheme 65).
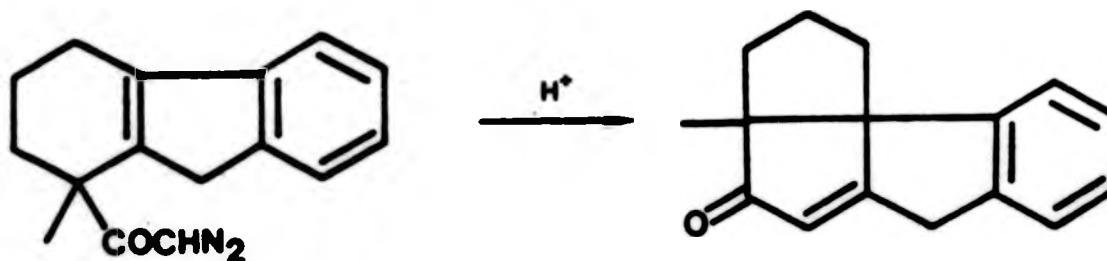
Scheme 64

Scheme 65

Satyanarayana et al.[102] have shown that acid-catalysed cyclization of rigid β,γ-unsaturated diazomethylketones[103] proceeds via the cyclobutanone carbinyl cation (Scheme 66).

Scheme 66

Depending on the polarity of the solvent this cation may lose a proton (non polar solvent) or may undergo Wagner-Meerwein shifts (polar solvent).

Other examples of the use of this reaction include the synthesis of a number of methoxy-tricyclic dienones[104] (Scheme 67), the construction of the A ring of gibberellins[105], and in the cyclization of polyolefins[106] (Scheme 68).

Scheme 67

Scheme 68
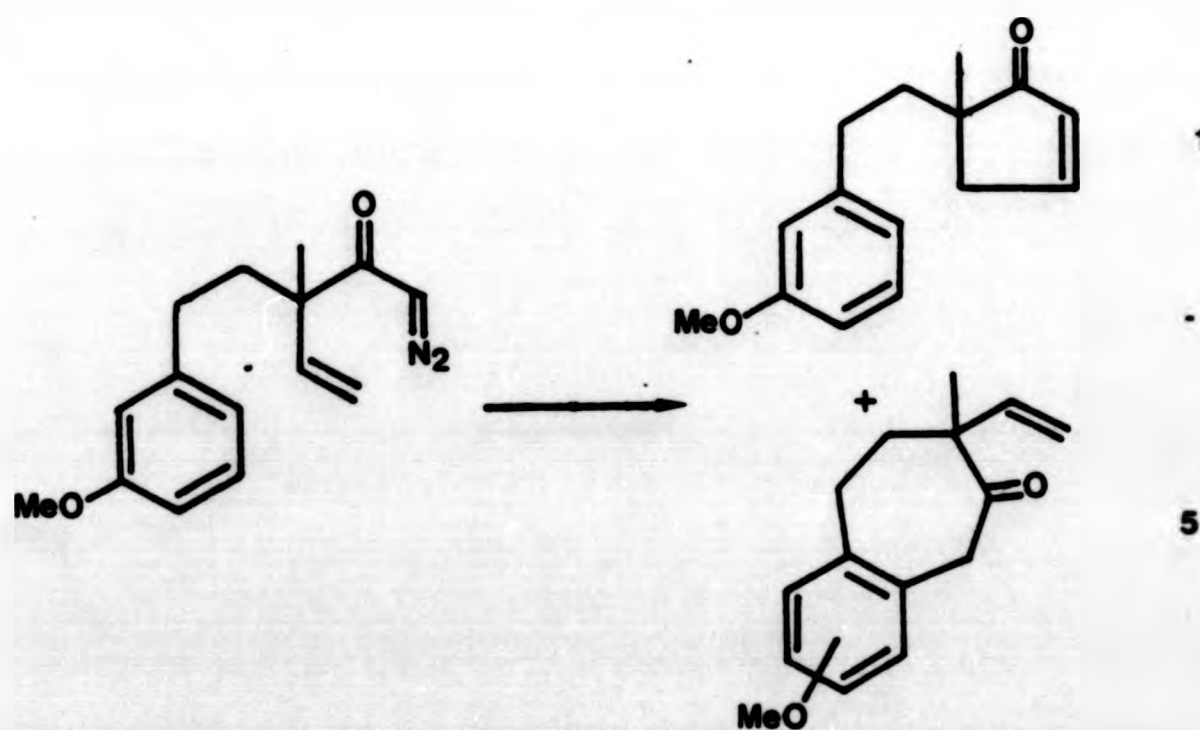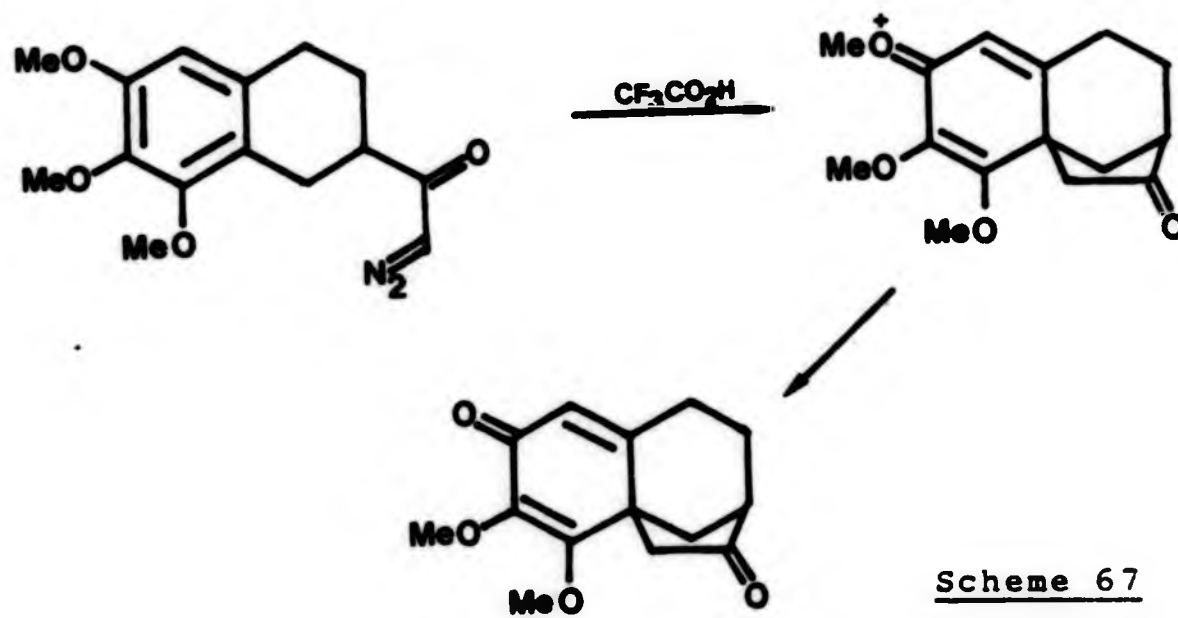
Selected recent developments in diazoalkane chemistry

Since the initial preparation of this review a number
of papers have appeared which are relevant to the work described
in this thesis.

In the field of thiophenium ylid chemistry Meth-Cohen
et al.[107] found that tetrachlorothiophen forms stable ylids (24)
with both nitrenes and carbenes, that are not formed with thiophen
and 2,5-dichlorothiophen.
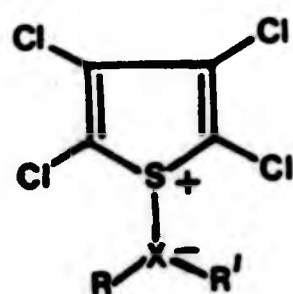
X	R	R'
N	-	CO_2Et
C	COMe	CO_2Et
C	$CO_2(Me)$	$_2O_2C$

(24)

Skramstaad et al.[108] have attempted to prepare cyclic
thiophenium ylids using diazoalkanes (25) and (26) (Scheme 69
and 70), however only the corresponding azine, 3-insertion product
or ring expanded thiophen (27) were formed.

(25)

Scheme 69

(26)

(27)
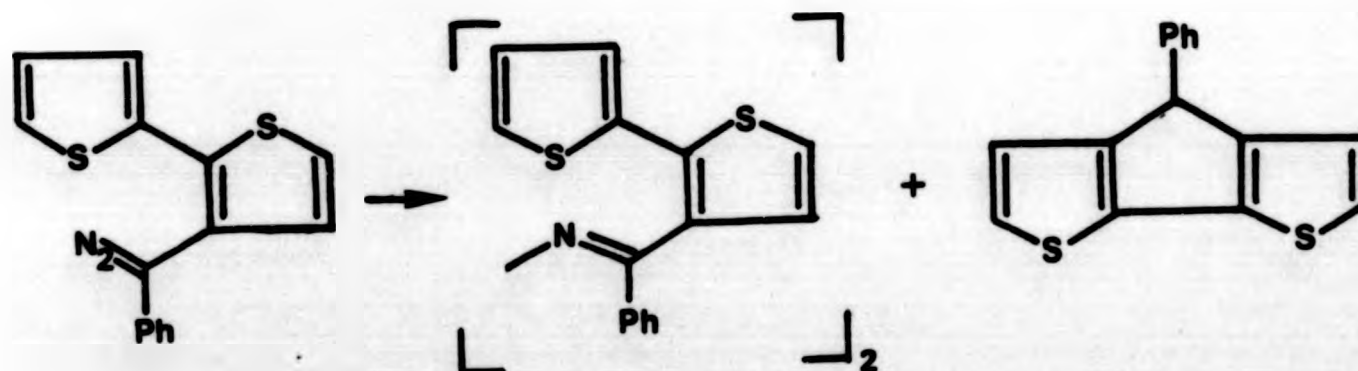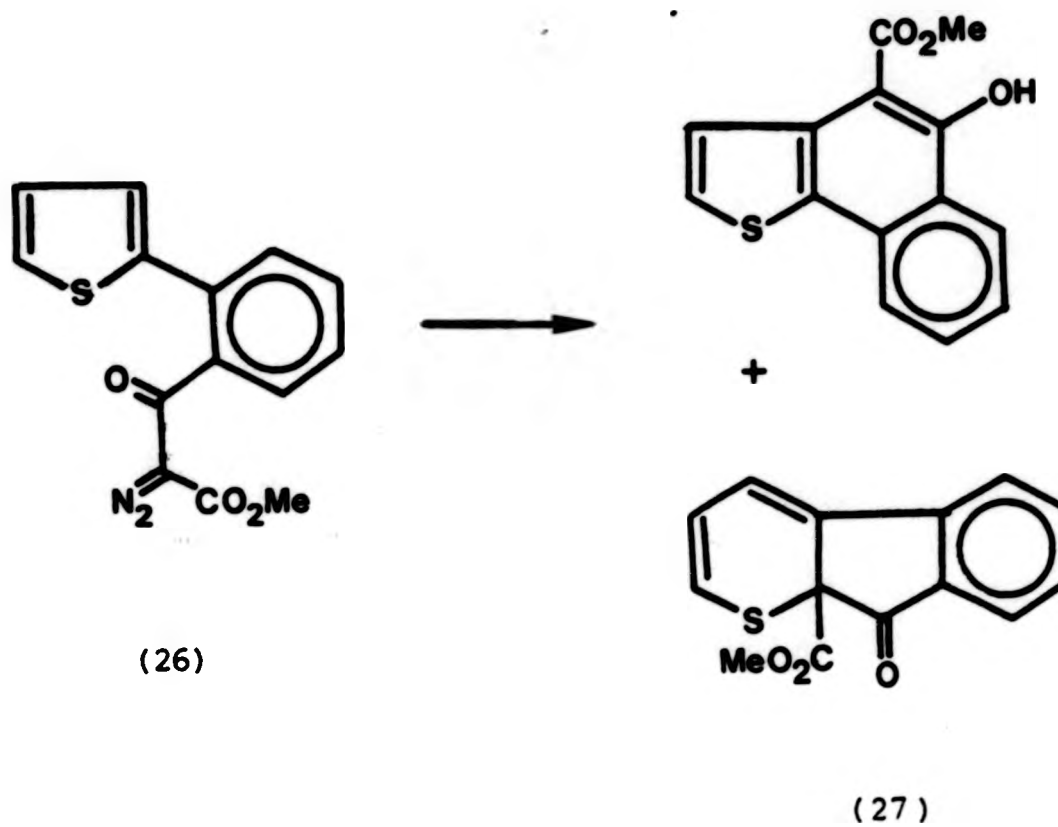
Scheme 70

The rearrangement of certain 2-(1-diazoalkyl)-thiophens was found by Munro and Sharp[109] to give the corresponding 2-ene-yne system in the same way as that observed by Orphanides and Shechter.[110] (Scheme 71).

Scheme 71
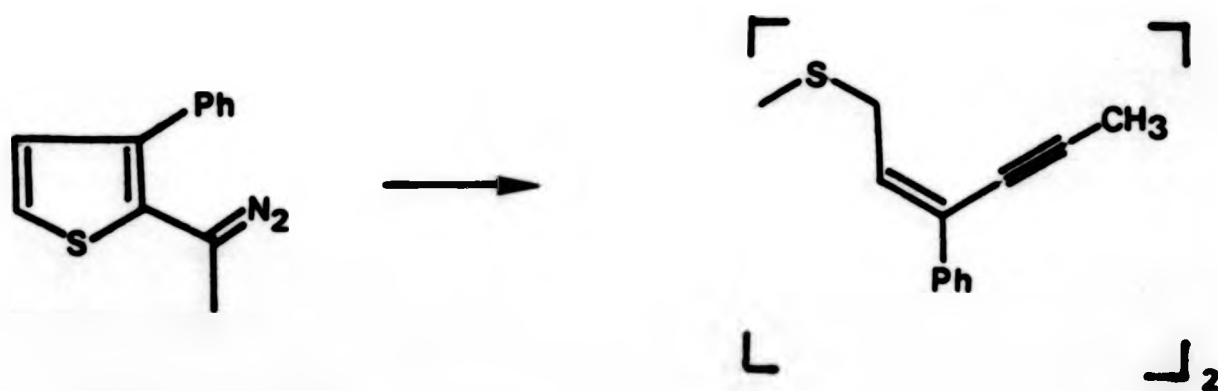
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DISCUSSION

SOME ASPECTS OF THE CHEMISTRY OF DIAZOALKANES

THE FORMATION AND REACTIONS OF SUBSTITUTED THIOPHENIUM YLIDS

Thiophen and its derivatives are important inter-
mediates in the manufacture of pharmaceuticals.[1] Thiophen-2-
acetic acid is used in the antibiotic Cephalothin (1) and
thiophen-3-malonate in the antibiotic Ticarcillin (2) one of
the principal new thiophen based semi-synthetic penicillins.[2]

(1)

(2)
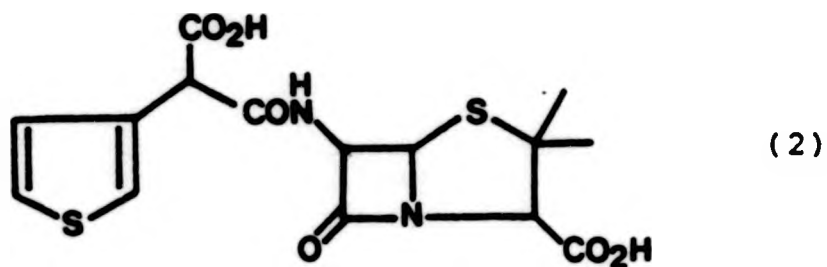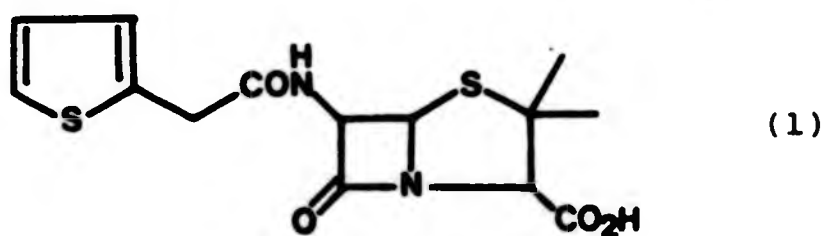
During the course of research into the preparation
of thiophen-3-malonate Gillespie et al. found that the reaction
of dimethyl diazomalonate with certain thiophens, in the
presence of rhodium-(II)-acetate, resulted in the formation of
the corresponding thiophenium ylids[3] (3).

(3)

R^1	H	H	H	H	H	Br	Cl	Cl	H
R^2	H	H	Br	CH_3	CH_2OH	Br	Cl	Cl	Br
R^3	H	H	H	H	H	H	H	H	CH_3
R^4	CH_3	C_2H_5	CH_3	CH_3	CH_3	CH_3	CH_3	C_2H_5	CH_3

Thiophens with deactivating substituents, e.g. CN,CHO did not give the corresponding ylids.

The initial objective of this work was to investigate the scope of these reactions further. The ylids previously synthesized were almost exclusively prepared from 2 and 2,5-disubstituted thiophens.

In order to test the effect of 3-substitution on ylid formation 3-methyl, 3-bromo and 3-hydroxymethylthiophen were reacted with dimethyl diazomalonate in the presence of rhodium-(II)-acetate. Initially the thiophens were reacted under the conditions used for the preparation of 2-substituted thiophenium ylids.[3] Dimethyl diazomalonate was added to a 10-fold excess of the thiophen containing ca. 1g mole^{-1} of rhodium-(II)-acetate and the mixture stirred at room temperature until the diazo band (ir) had disappeared. In the case of 2-substituted thiophens the reactions were usually complete in 2-3 days, however in the case of the 3-substituted thiophens the reaction mixtures became dark and the diazoband persisted for several weeks. When the reaction mixtures were worked up none of the 3-substituted thiophenium ylids could be detected.

It was found that if the reactions were carried out at 0°C over several weeks, the desired ylids were obtained in low yield (10-25%). The ylids were unstable, they decomposed over several days at room temperature. Attempted recrystallisation also resulted in decomposition. However, the ^{1}H nmr, ir and mass spectra were consistent with those expected for ylidic products. 3-Ethylthiophen was also reacted with dimethyl diazomalonate in the presence of rhodium-(II)-acetate. A solid product

precipitated from the reaction mixture, but this decomposed on attempted purification. All attempts to repeat this reaction failed.
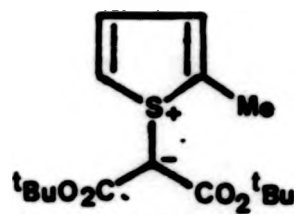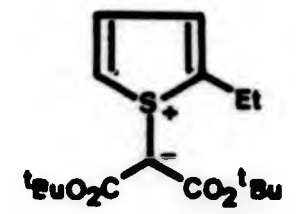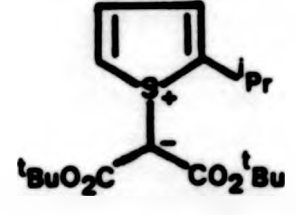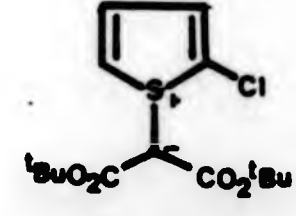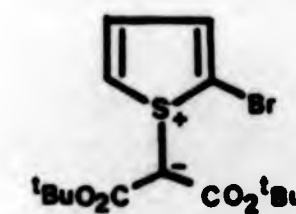
It would appear that ylid formation is very sensitive to substitution of the thiophen. The ylids derived from 3-substituted thiophens are considerably less stable than those derived from 2- and 2,5-disubstituted thiophens. It is probably this instability combined with the long reaction times required that result in the poor yields obtained.
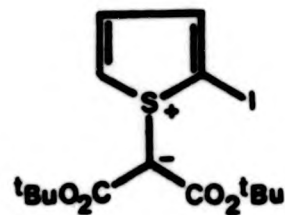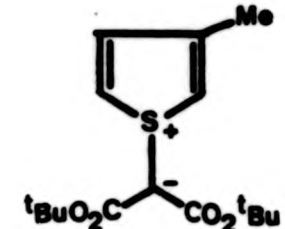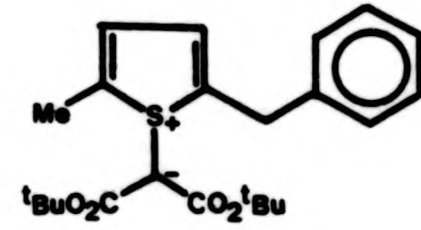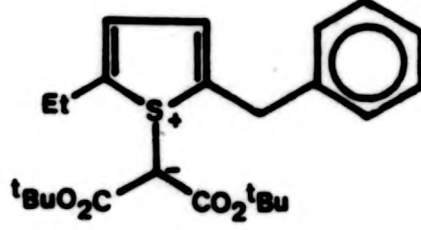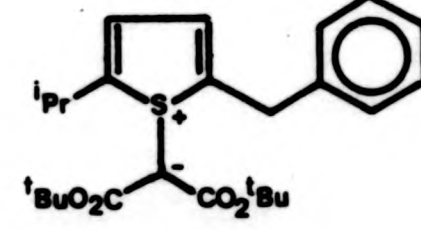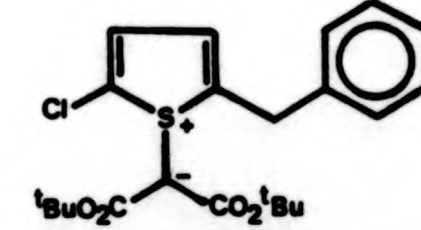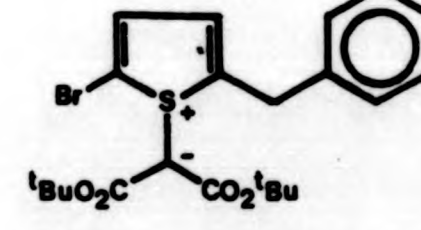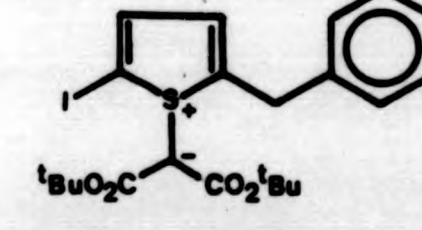
During the course of work to prepare thiophenium bis(t —butoxycarbonyl) methylides for nmr studies it was found to be convenient to conduct the ylid forming reactions in methylcyclohexane with only one equivalent of the thiophen (Method A). This allowed isolation of the products by filtration in most cases and avoided the problem of removing the high-boiling thiophens. These reactions were rather slow however and this was attributed to the low solubility of rhodium-(II)-acetate in methylcyclohexane. The hydrocarbon-soluble salt rhodium-(II)-hexanoate was therefore prepared and used in place of rhodium-(II) acetate (Method B). The effect of this catalyst was remarkable. Reaction times were reduced from 2-3 days to a matter of hours. The catalyst also proved to be more resistant to poisoning. Occasionally when preparing ylids using rhodium-(II) acetate as the catalyst, the green colour of the reaction mixture would change to a dark red or brown. This was associated with a great slowing, or halting of the reaction. However, with rhodium-(II)-hexanoate, if a red or brown colour did form when the catalyst was added to the thiophen solution it invariably gave way to a
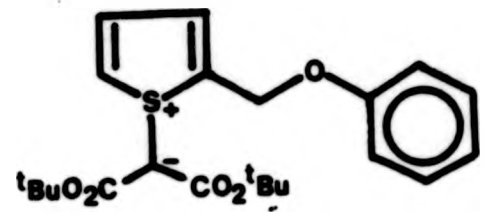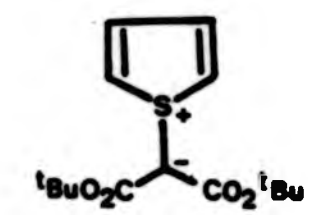
green colour when the di-t-butyl diazomalonate was added. The
reaction then proceeded as normal. Because of the effectiveness
of this catalyst it was decided to attempt the reaction of 3-
methylthiophen with di-t-butyl diazomalonate under these conditions.
Nitrogen evolution was immediate on addition of the diazomalonate
and within 30 minutes a solid began to form. After 3 hours the
ylid was filtered off and washed with methylcyclohexane. The
yield of (10) was 72%.

TABLE 1

Ylid		Method	Yield %
(4)		A	37
		B	92
(5)		A	38
(6)		A	25
(7)		B	42
(8)		B	66

Ylid		Method	Yield %
	(9)	B	75
	(10)	B	72
	(11)	B	44
	(12)	B	73
	(13)	B	56
	(14)	B	51
	(15)	B	49
	(16)	B	67

Ylid		Method	Yield %
	(17)	B	64
	(18)	B	80

The bulk of the above ylids were prepared for dynamic nmr studies (page 80)., 14, 15, and 16 have substituents which vary both in their steric and electronic effects, whilst 11, 12, 13 have those which vary principally in their steric effects. Compounds 4, 5, 6, 7, 8, and 9 provide a direct comparison of the effect of the benzyl group in each case.

The thiophen precursors required for the preparation of these ylids were synthesized as shown in Scheme 1. The 2-benzyl 5-halothiophens were prepared by halogenation of 2-benzyl-thiophen. Initially an attempt was made to prepare them via benzoylation of the corresponding 2-halothiophens but it was found that the benzoyl group displaced the halogen to give 2-benzoyl-thiophen under the reaction conditions ($SnCl_4$, benzene). The 2-alkylthiophens were relatively accessible. However the preparation of 2-isopropylthiophen via catalytic hydrogenation of 2-iso-propenylthiophen proved somewhat variable in yield, probably because of catalyst poisoning. In the preparation of the 2-alkyl-

(i) SO_2Cl_2, (ii) NBS/DMF, (iii) I_2/HNO_3, (iv) N_2H_2/KOH, (v) PhCOCl, (vi) Ac_2O, (vii) PhO^-, (viii) CH_3MgI, (ix) H_2/Pd, (x) NBS.
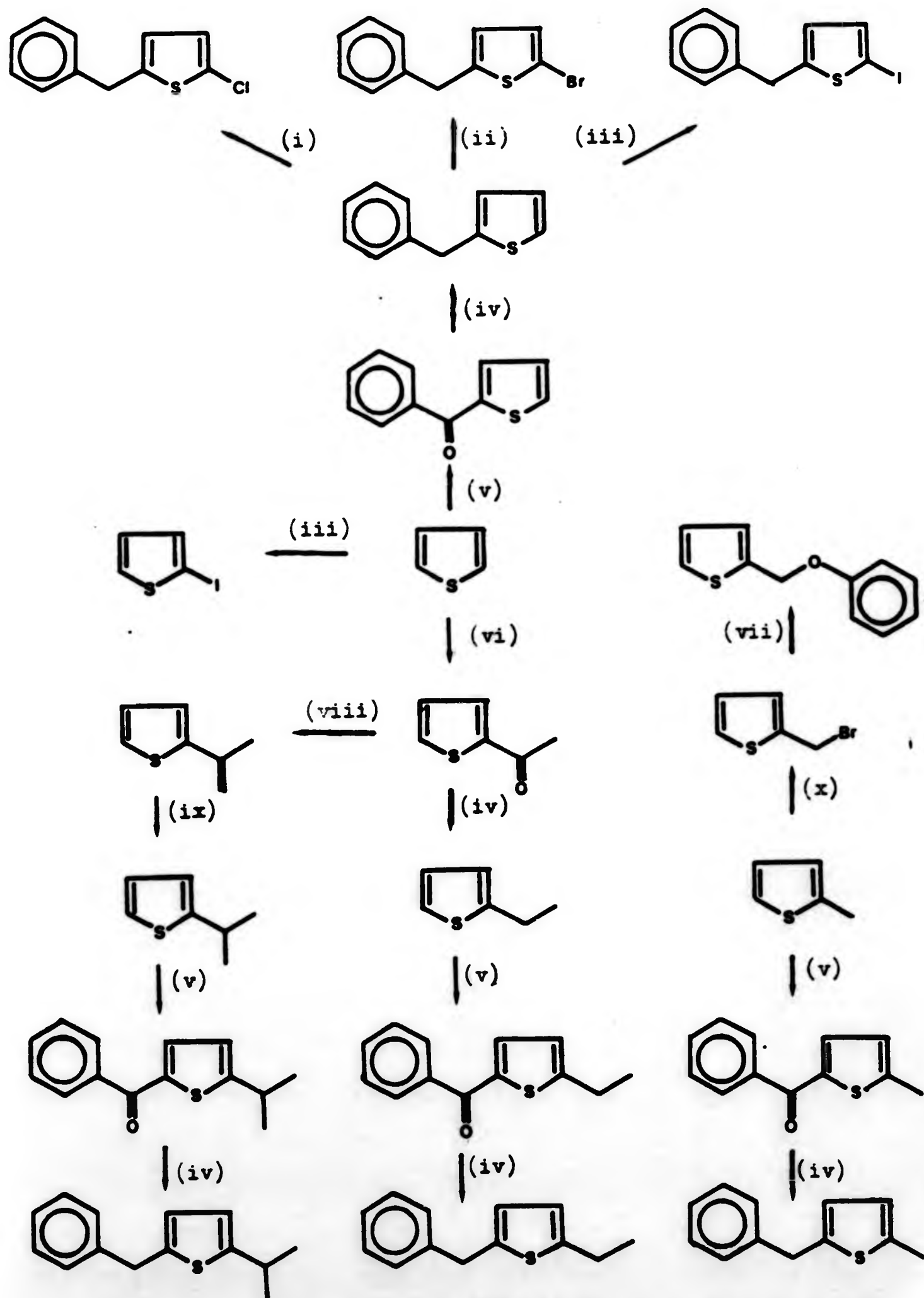
Scheme 1

5-benzylthiophens the 2-alkyl-5-benzoylthiophens proved too involatile for easy distillation and were reduced without prior isolation. 2-(Phenoxymethyl)thiophen was prepared as shown:- the 2-(bromomethyl)thiophen was reacted with sodium phenoxide immediately on its isolation in order to avoid decomposition of the unstable bromo compound. The remainder of the thiophens were obtained commercially.

The method used for the preparation of each ylid is shown in Table 1. In the case of the 2-benzyl-5-substituted thiophens, because of their relatively high boiling points and the small quantities being distilled, some impurities were present in the final products. The ylid forming reactions although changing colour in these cases were completed in a reasonable time and in fair yield, thus demonstrating the efficacy of rhodium-(II)-hexanoate as a catalyst.

The 2-alkyl-5-benzylthiophenium ylids were unusual in that after chromatography of the reaction mixtures they were isolated as gums. The 2-methyl-5-benzylthiophenium ylid did crystallize after storage at low temperature for several days, but attempted recrystallization transformed the solid back to a gum.

The mass spectra of the bis(butoxycarbonyl)methylide ylids did not in general give molecular ions. The highest significant mass was usually that due to the M-73, (C_4H_9O) fragment.

2-$\underline{t}$-Butylthiophen was also prepared and reacted with di $\underline{t}$-butyl diazomalonate. Initially an attempt was made to produce 2-$\underline{t}$-butylthiophen from 2-$\underline{t}$-butylfuran via the γ-keto-aldehyde (Scheme 2), however this proved unsuccessful.
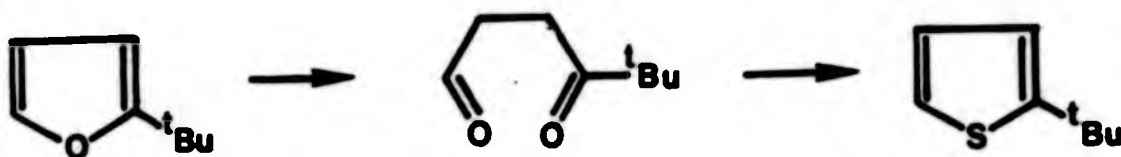
Scheme 2

2-t-butylthiophen was eventually prepared by fractional distillation of a mixture of isomeric t-butylthiophens. The reaction of this with di t-butyl diazomalonate using method B failed to give a product identifiable as the corresponding ylid. Tlc examination of the reaction mixture did however reveal a product considerably less polar than would be expected for a thiophenium ylid. After chromatography and crystallization from methylcyclohexane a white crystalline solid was obtained which had a mass spectrum and elemental analysis consistent with the formula $C_{30}H_{48}O_8S$ i.e. an adduct of 2-t-butylthiophen and two molecules of bis(t-butoxycarbonyl)carbene. The 250 MHz ^{1}H nmr spectrum of this compound showed 5 non-equivalent t-butyl reso-nances and an ABX system with signals at 6.1 (1H) and 3.45δ (2H) ($J_{AB} = 7$, $J_{AX} = 0.7$, $J_{BX} = 3$ Hz). This data was consistent with the structures (19) and (20).
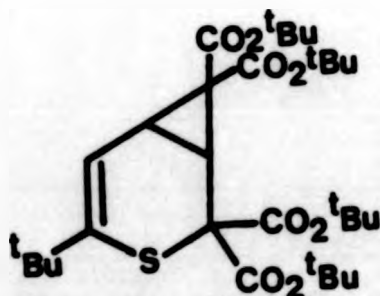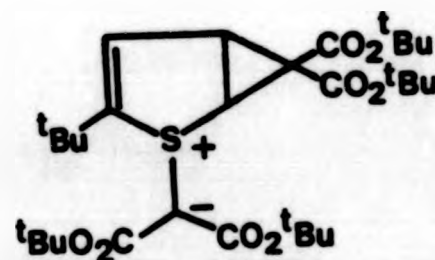
(19)   (20)

The mass spectra of thiophenium ylids normally show a peak at the mass of the parent thiophen. This was not seen with this compound. Since (20) is not a normal thiophenium ylid however, the assignment of structure (19) to the product can only be tentative.[59]

In an effort to assess the effects of activating groups on ylid formation, thiophen-2-acetamide[4] (21) and 2-methoxythiophen were prepared from thiophen and reacted with dimethyl diazomalonate in the presence of rhodium-(II)-acetate.

(21)
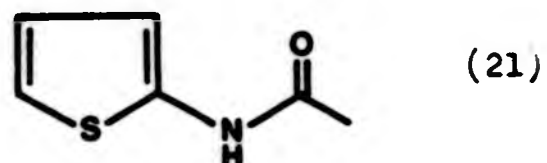
The reaction of thiophen-2-acetamide was carried out in N,N-dimethyl formamide, this being the only aprotic solvent in which (21) was reasonably soluble. No ylid was formed, the only characterized product was a small amount of the carbene dimer tertramethyl ethylene-1,1,2,2-tetra-carboxylate (22).

(22)
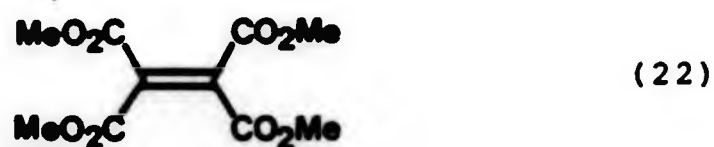
2-Methoxythiophen[5] was reacted with dimethyl diazomalonate in the usual manner[3]. No ylid was obtained, however dimethyl 2-methoxythiophen-5-malonate (23) was obtained in 43% yield.

(23)
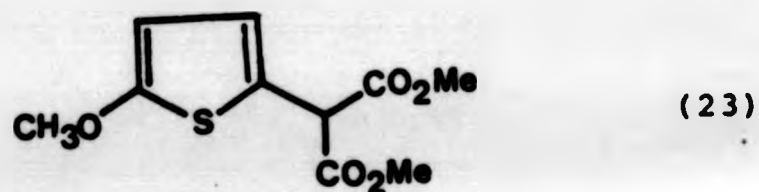
Two further 2-substituted thiophens were reacted with dimethyl diazomalonate. Dimethyl thiophen-2-malonate[6] was treated with 0.4 equivalents of dimethyl diazomalonate in 2 portions with an interval of 3 weeks. The reaction was extremely slow with complete disappearance of the diazo band (ir) requiring 6 weeks. The whole reaction mixture was then chromatographed on silica gel.

The first product eluted proved to be highly crystalline. The ^{1}H nmr spectrum showed two methyl ester signals and a symmetrical multiplet centered at 7.25δ. The two groups of signals were in the ratio of 3:1. The mass spectrum gave a M^+ of 312. The infrared spectrum showed absorptions at 1725 and 1620 cm^{-1}. The ultraviolet spectrum showed a λmax at 317 nm. On this basis the compound was assigned the structure (24).

(24)
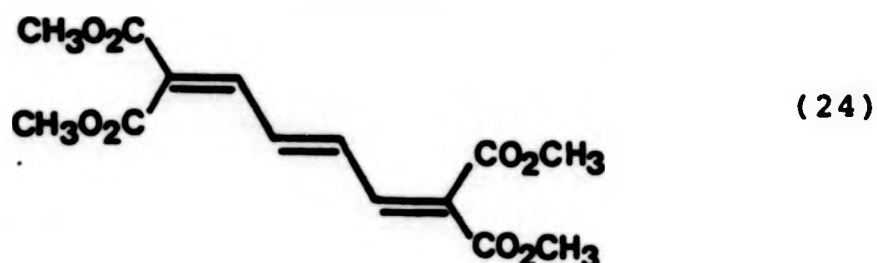
The _trans_ geometry was assigned after computer iteration of trial parameters for the chemical shifts and coupling constants of the olefinic hydrogens. The multiplet at 7.25δ is an AA'BB' system. The coupling constant between the two central protons is 14.9 Hz. Typical values of H-H coupling constants in

Observed
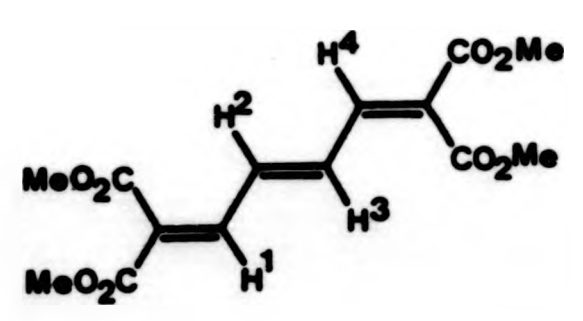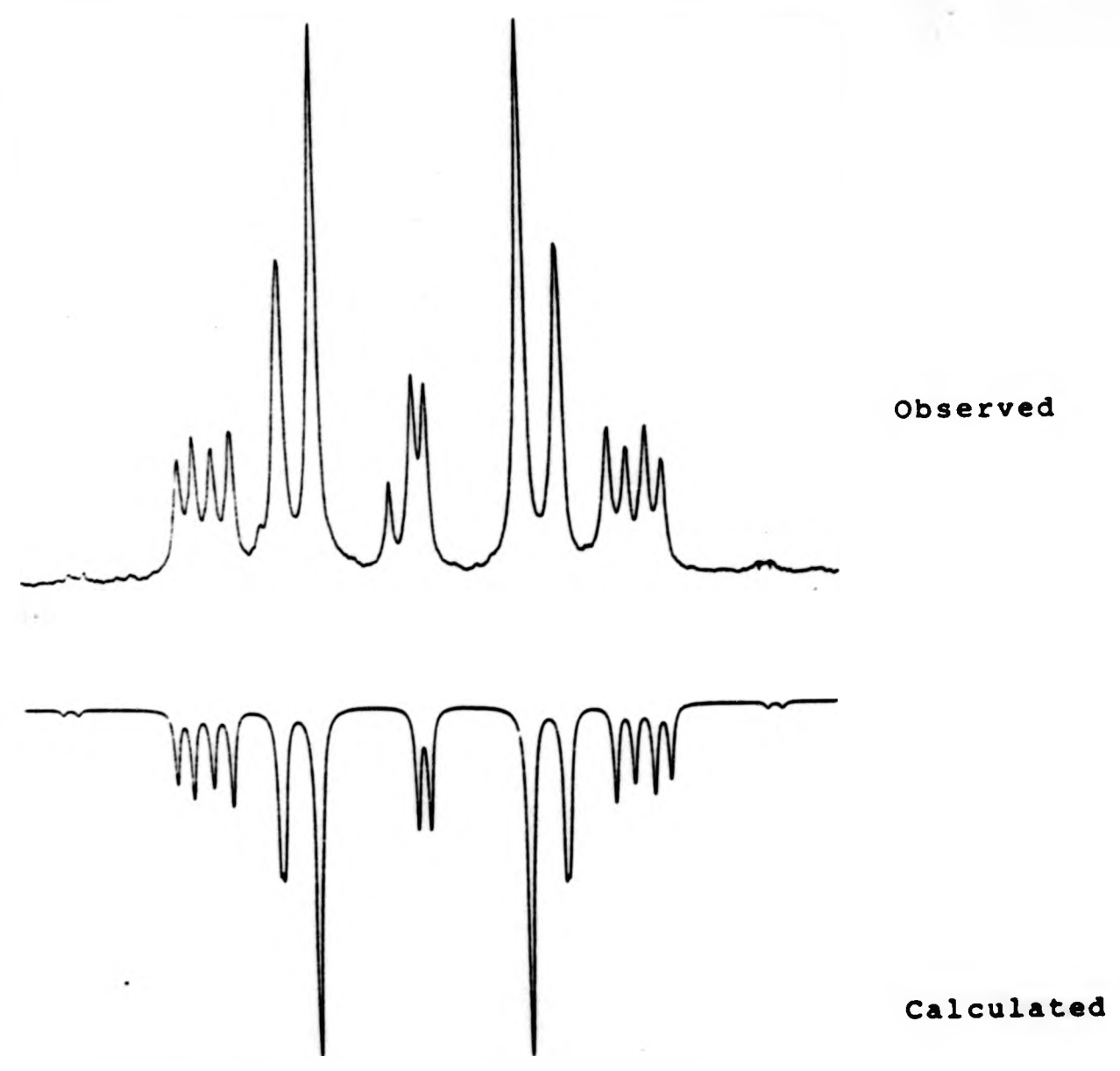
Calculated

Coupling Constants Hz

$J_{1,2} = J_{3,4} = 11.81$

$J_{1,3} = J_{2,4} = -0.71$

$J_{1,4} = 0.18$

$J_{2,3} = 14.85$

Chemical shift (δ)

$H_1 = H_4 = 7.43$

$H_2 = H_3 = 7.18$

Figure 1

olefins are 6-14 Hz for a <u>cis</u> relationship and 11-18 Hz for <u>trans</u> compounds[7]. The observed and calculated spectra for the olefinic protons of (24) are shown in Figure 1.

The second material to be eluted was a mixture of the chromatographically identical thiophen dimalonates (25) and (26).
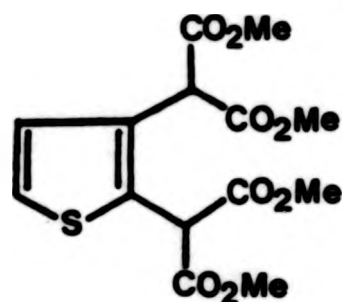
(25)
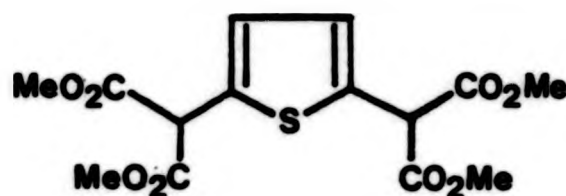
(26)

It was possible to obtain pure (25) by fractional crystallization of the mixture from ethanol. The nmr spectrum of (25) showed signals at 7.2δ (2H,AB quartet, J = 6 Hz), 5.1 and 4.9δ (both 1H singlets) and 3.75δ (two, 6H singlets) with a separation of $\sim$ 1 Hz. The nmr spectrum of (26) was obtained by the subtraction of the spectrum of (25) from that of the mixture. The spectrum showed signals at 6.72δ (2H,s), 4.85 (2H,s) and 3.75δ (12H,s). Both the mass spectrum of (25) and that of the mixture gave the expected m/e of 342.

A mechanism for the formation of the three products

of this reaction involves the two cyclopropanes (27) and (28).
The two dimalonates (25) and (26) can then be obtained by simple
cyclopropane ring opening of these compounds.   The hexatriene
(24) can be formed from (28) by the mechanism shown in Scheme (3).

(27)

(28)

(24)
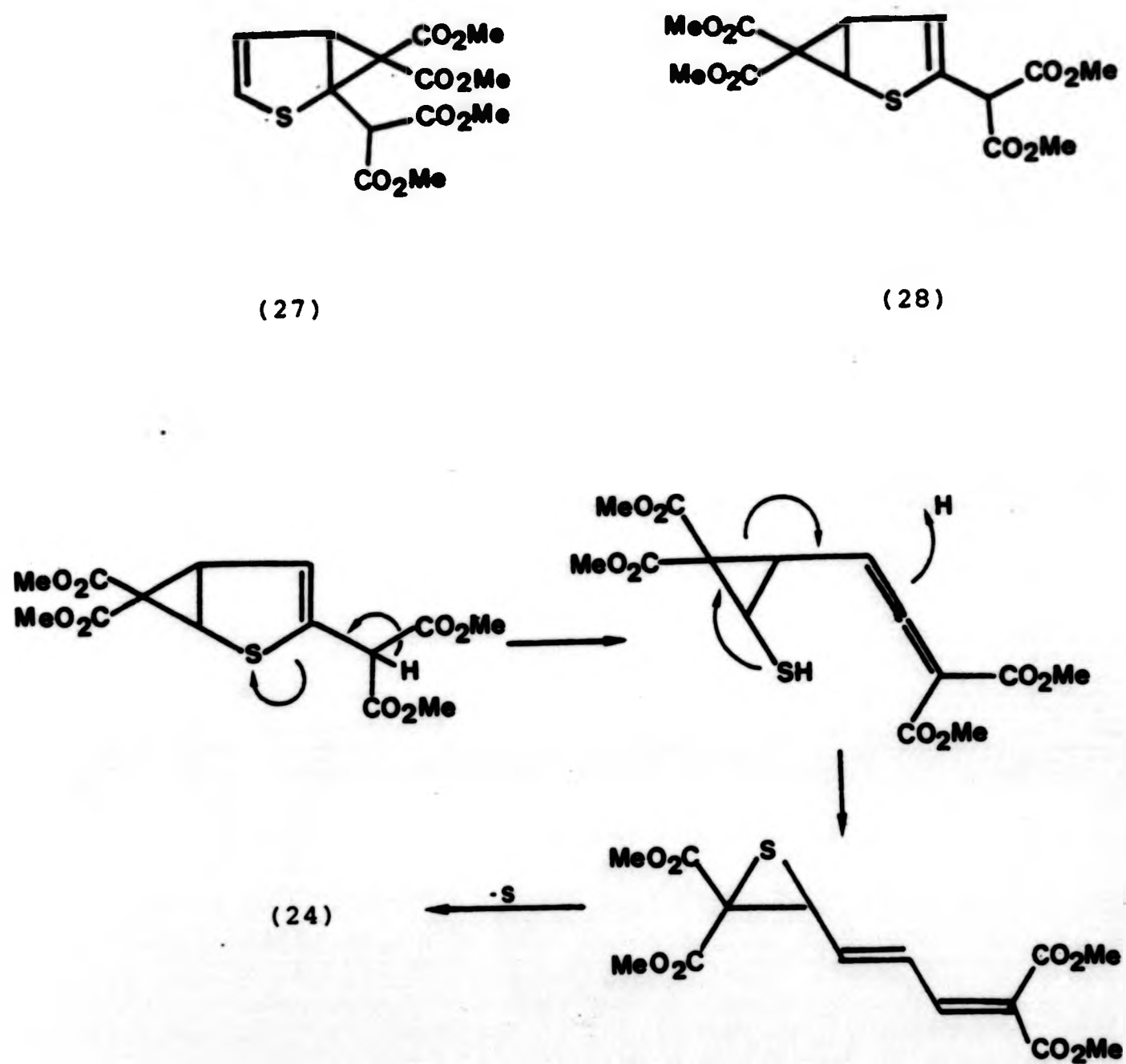
Scheme 3

The final step to compound (24) may take place via sulphur extrusion or via the thiranium ylid (29). The extrusion of sulphur from ylids similar to (29) is a well known phenomenon.[8]

(29)
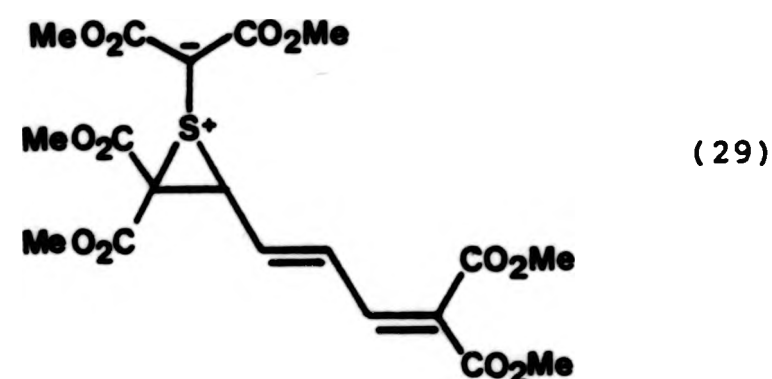
The _trans_ stereochemistry of (24) may be due to bond rotation during the rearrangement or by isomerisation of the _cis_ isomer. Systems such as (30) are known to isomerise to the all _trans_ isomer very readily,[9] (Scheme 4).
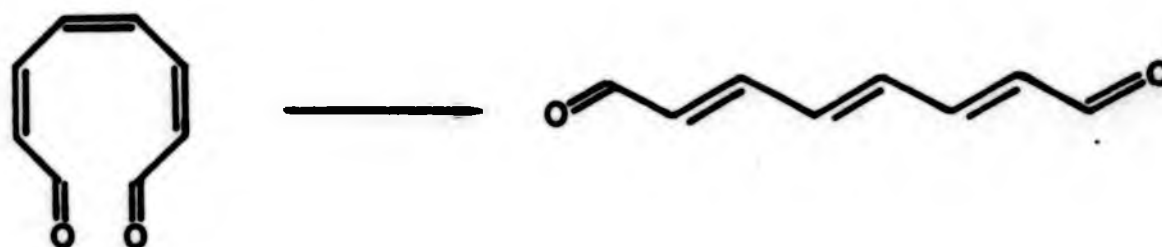
(30)

Scheme 4

Dithenylmethane (31) was prepared by the method of Gol'dfarb et al.[10]. Two equivalents of this material were dissolved in methylcyclohexane containing rhodium-(II)-acetate, and dimethyl diazomalonate was added. After 3 days an oily precipitate had formed after chromatography and crystallization

(32) was obtained in 44% yield.

(31)

(32)
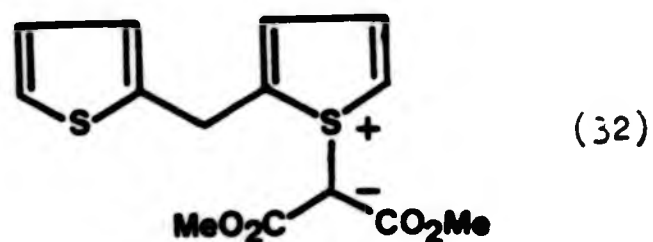
Ylid (32) showed the expected 6H multiplet (6.9δ), 2H singlet (4.0δ) and 6H singlet (3.4δ). The mass spectrum gave the expected molecular ion.

Thermolysis of the thiophenium ylids

In the attempted synthesis of thiophen-2 and 3-malonates, Gillespie et al.[5] had hoped to form the cyclopropane (33) which could be rearranged to form the 2- and 3-malonates by treatment with base or acid. However, reaction of dimethyl diazomalonate with various thiophens resulted only in the formation of the corresponding ylids. Thermolysis of the mono-substituted thiophenium ylids or the addition of dimethyl diazomalonate at higher temperatures resulted in exclusive formation of the 2-malonates.

(33)
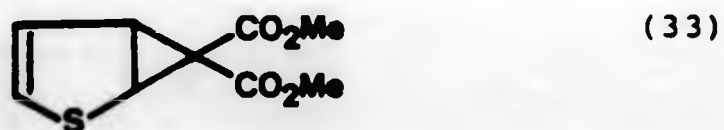
2-Bromothiophenium bis(methoxycarbonyl)methylide had not been thermolysed before. When it was heated in refluxing toluene for 2 hours and then chromatographed a red oil was obtained. The ^{1}H nmr spectrum of this compound showed a singlet at 4.25δ and an ABX multiplet between 6.5 and 5.8δ with couplings 6 Hz, 10 Hz, and 1.5 Hz. The integral ratios were 2:1 respectively. The infra-red spectrum showed absorptions at 3000, 2950, and 1740 cm^{-1} and the mass spectrum gave a molecular ion at 291.9413 which is consistent with the molecular formula $C_9H_9BrO_4S$.

Thermolysis of a number of other ylids (34a-c) gave products with analogous spectral characteristics. In the case of (34d) the reaction was particularly facile and attempted recrystallization from methylcyclohexane (110°, 2 minutes) resulted in quantitative conversion to the corresponding product.

(34)   (35)
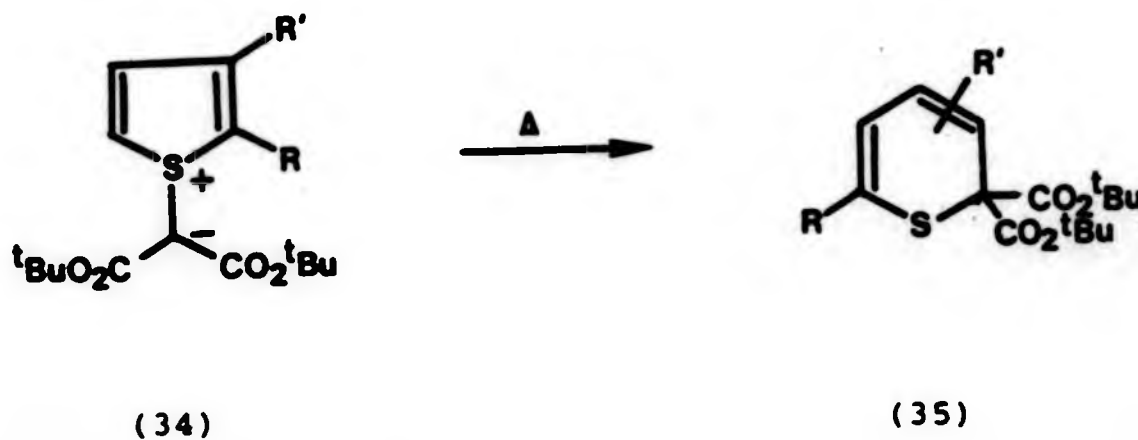
	R	R'
a	H	CH_3
b	I	H
c	CH_2OPh	H
d	H	H
e	Br	H

In view of these results the thermolysis of thiophenium bis(methoxycarbonyl)methylide was re-examined. After heating a solution of the ylid in refluxing toluene for 10 minutes approximately 25% of the starting material had been converted to a less polar product. The reaction time was kept short to obviate the formation of thiophen-2-malonate. Analysis of the 250 MHz ^{1}H nmr spectrum of this compound suggested that it was the 2(H)-thiopyran (36). Computer analysis of the ABCX system gave the spectral parameters. Figure 2 shows the observed and calculated spectra for the olefinic protons together with the chemical shifts and coupling constants obtained. It will be noted that there is some discrepancy in the observed and calculated spectra. This is probably due to an impurity in the compound.

(36)
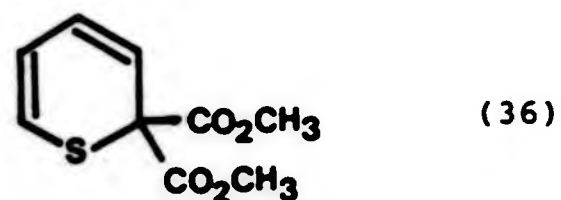
The pattern of the major couplings is consistent with the butadiene type structure, as is the equivalence of the ester signals. The upfield shift of Ha may be attributed to shielding by the ester carbonyl groups. By analogy the products of the thermolysis of (34a-c) were assigned structures (35a-c). The products are drawn with the substituents in the 6-position on the basis that one of the ring protons in these compounds is significantly shielded (i.e. the substituent is not in place of

Calculated

Observed
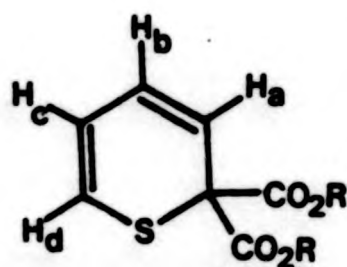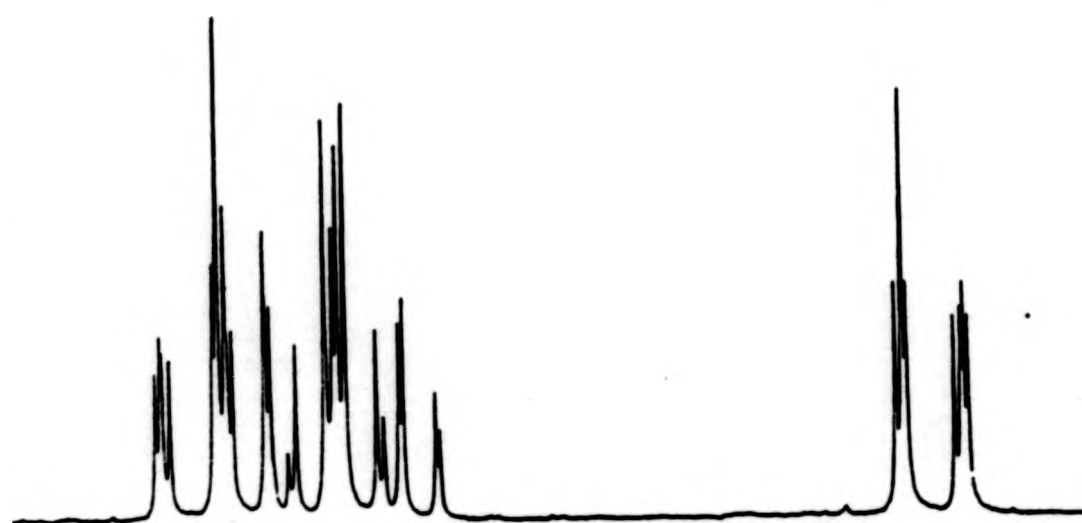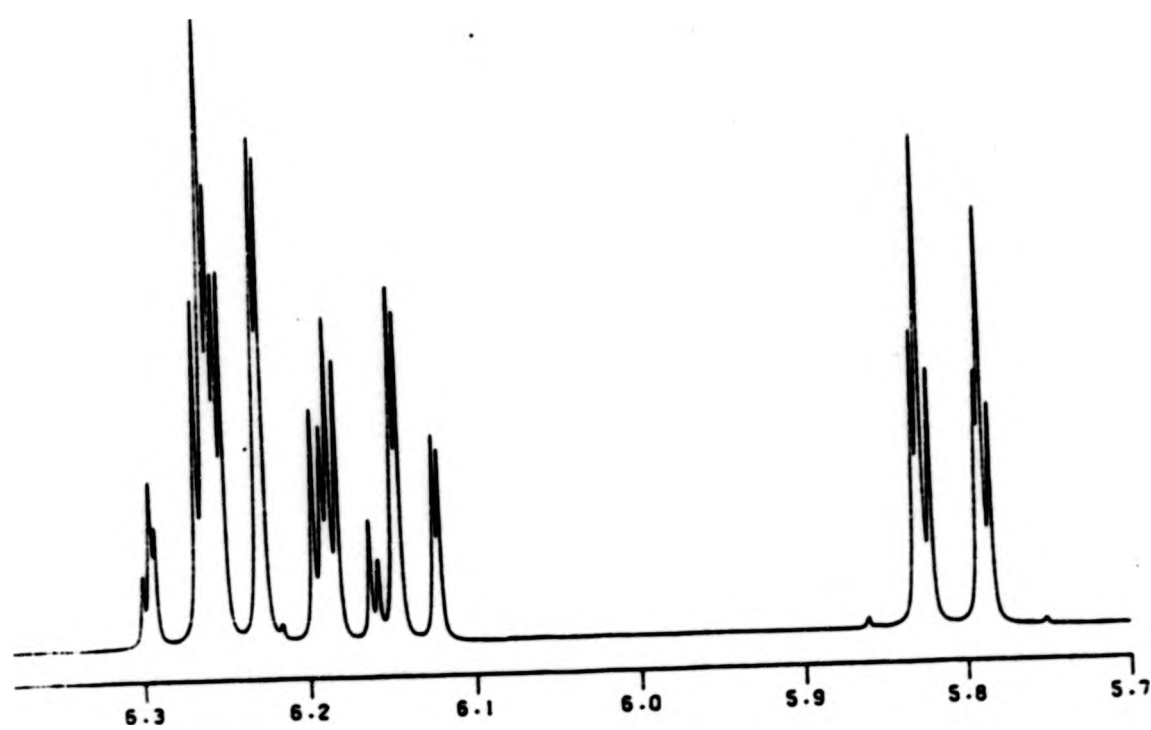
Chemical Constants Hz		Chemical Shift δ	
J_{AB}	9.94	Ha	5.81
J_{AC}	0.53	Hb	6.62
J_{AD}	1.20	Hc	6.23
J_{BC}	7.04	Hd	6.26
J_{BD}	−0.37		
J_{CD}	9.86		

Figure 2

Ha) and because these compounds rearrange to the 2,5-substituted thiophens. In the case of (35a) the position of the methyl group is not clear.

It would appear that the thiopyrans are the kinetic products of the thermolysis of these ylids and that the 2-substituted thiophens are the thermodynamic products. Heating the ylids at lower temperatures, e.g. in refluxing thiophen, for longer periods[9] results in the formation of the 2-malonates, presumably because thiopyrans rearrange as rapidly as they form. At higher temperatures particularly when the ylid is somewhat destabilized, by a bulky ester group for example, the concentration of the thiopyran can build up appreciably.

It was decided to prepare a crystalline derivative of (36) in order that complete characterization could be carried out. Attempts to de-esterify (36) with trimethylsilyl iodide[11] at room temperature failed. Tertiary butyl ester are known to be more labile to cleavage by trimethylsilyl iodide[12]. Thiophen bis(t — butoxycarbonyl)methylide (34d) was therefore prepared and thermolysed. In view of the fact that high temperatures appear to favour thiopyran ring formation this reaction was carried out in refluxing xylene. After 3 minutes 100% conversion had taken place, and after chromatography the thiopyran (35d) was obtained as a crystalline solid in 84% yield. The low field portion of the ^{1}H nmr spectrum (250 MHz) of this product was virtually identical to that of (36). In addition a ^{13}C nmr spectrum was obtained which showed 4 resonances in the olefinic carbon region at 115.8, 118.7, 119.9, and 125.4 ppm.

An x-ray structure analysis was carried out on

thiopyran[13] (35e) in order to confirm the structure and establish that the substituent was indeed in the 6 position.

Crystals of the product $C_{13}H_{21}BrO_4S$ Mr 353 were monoclinic space group $\underline{P}2/\underline{n}$ a = 10.013(7), b = 10.969(5), c = 16.633(13) Å, α = 90.00°, β = 100.43(6)°, γ = 90.00°, U = 1797 Å³. 2183 independent reflections were collected with $|\underline{F}_o| > 3\sigma (|\underline{F}_o|)$.

The structure (Figure 3) consists of the expected 6-bromo substituted 2H-thiopyran. The ring bond lengths (S_1-C_2) 1.733 Å, (C_2-C_3) 1.327 Å, (C_3-C_4) 1.461 Å, (C_4-C_5) 1.306 Å, (C_5-C_6) 1.525 Å, and (C_6-S_1) 1.836 Å are consistent with the alternating bond pattern.

A number of mechanisms may be drawn for the formation of the thiopyrans and the 2-malonates (Scheme 5). Both the thiopyran and the 2-malonate may be formed through a common intermediate such as the bicyclic system (37) or the thioaldehyde (38). Alternatively a Stevens type rearrangement could yield the thiopyran directly and the 2-malonate could be formed via (37) or (38).

The thiopyrans slowly decompose to the 2-malonates at room temperature. This would therefore tend to rule out (37) as being too high in energy. The thiopyran derived from 2-bromothiophenium bis(methoxycarbonyl)methylide shows no sign of reacting with alcohols which one would expect if the bromo derivative of (38) were formed.

Molecular orbital calculations are currently being carried out in an effort to map out the energy surface of the thiophenium ylids and products thereof including (37) and (38).[14]

68.

Figure 3

(37)

(38)
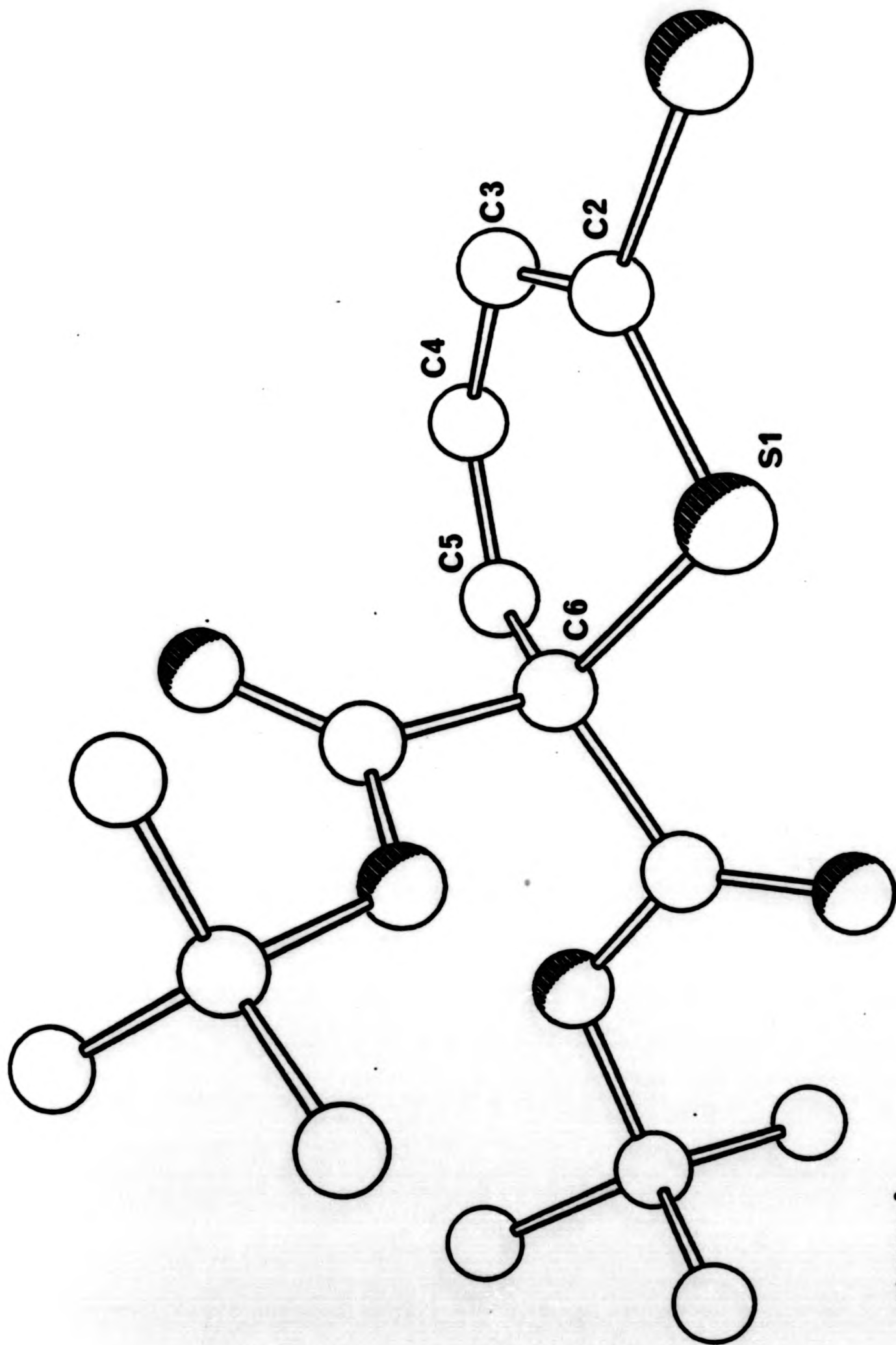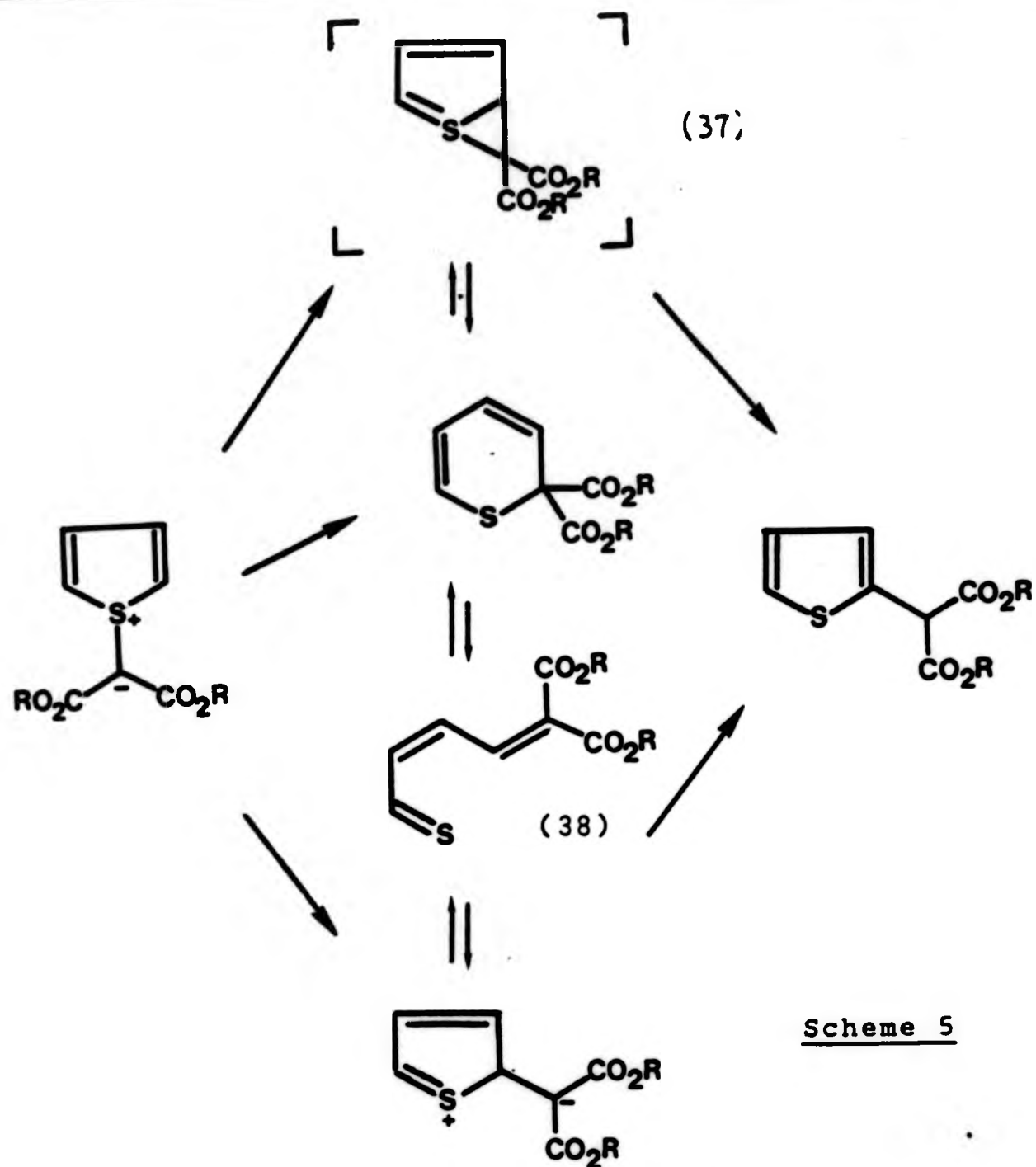
Scheme 5

The reaction of 2,5-dichlorothiophenium bis(methoxycarbonyl)-methylide with substituted thiophens

2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide (39) is known to be an effective reagent in the introduction of the malonate moiety into the thiophen ring and other systems.[15] It was decided to investigate the reaction of (39) with various substituted thiophens in an effort to produce the corresponding substituted thiophen malonates.

(39)
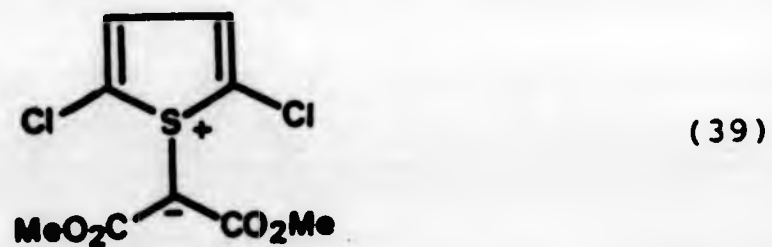
The substituted thiophens (40a-g) were heated in refluxing toluene with one equivalent of (39) and a catalytic amount of copper-(II)-acetylacetonate, until no more ylid remained.
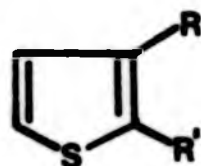
	R	R'
a	-H	$-CH_2NH_2$
b	-H	$-NHCOCH_3$
c	-H	-Br
d	-H	$-CH(CO_2CH_3)_2$
e	-H	$-CH_3$
f	$-CH_3$	-H
g	-Br	-H

(40)

The reaction gave mixtures of products (between 5 and 10) without any obvious major product. The thermolyses were then carried out at lower temperatures in an attempt to reduce the number of products. Although the reactions were slower similar mixtures were produced. A thermolysis was carried out using refluxing 2-methylthiophen as the solvent. In this case 2-methylthiophen-5-malonate was obtained, but only in 29% yield.

The reason for the failure of these reactions is unclear. It may be due to the reactivity of the thiophen nucleus. The reaction of thiophens with highly reactive electrophiles is known to give both 2- and 3-substituted products[16]. Activating substituents increase this reactivity to a large extent. For example 2,5-dimethylthiophen competes

effectively with thiophen in electrophilic substitution reactions. It is therefore possible for a number of products to be formed in each case.

Mechanistic studies

Diazoacetic esters have been reacted with thiophen in the presence of rhodium-(II)-acetate to give the cyclopropyl derivatives (41) which may then be rearranged to the 2-acetates[17].

(41)

No ylid formation is observed. In view of the thermal rearrangement of the thiophenium ylids to give the corresponding 2-malonates or thiopyrans, it is of interest to ascertain whether (41) is formed via an unstable ylid intermediate or not.

In order to establish whether the formation does proceed through an unstable ylid, attempts have been made to de-esterify thiophenium bis(methoxycarbonyl)methylide (42), (Scheme 6).
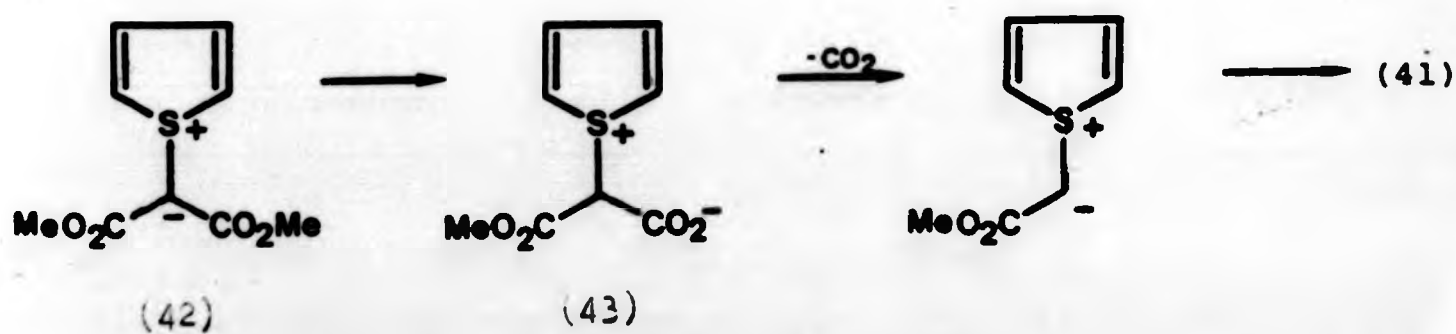
Scheme 6

The mono ester (43) obtained would be expected to rearrange to give either the 2-acetate or the cyclopropane (41). The ester group has proved remarkably stable to hydrolysis. Even trimethylsilyl iodide cannot effect de-esterification[17]. The contribution of structures (44) and (45) to that of (42) could account for this stability.

(42)

(44)   (45)
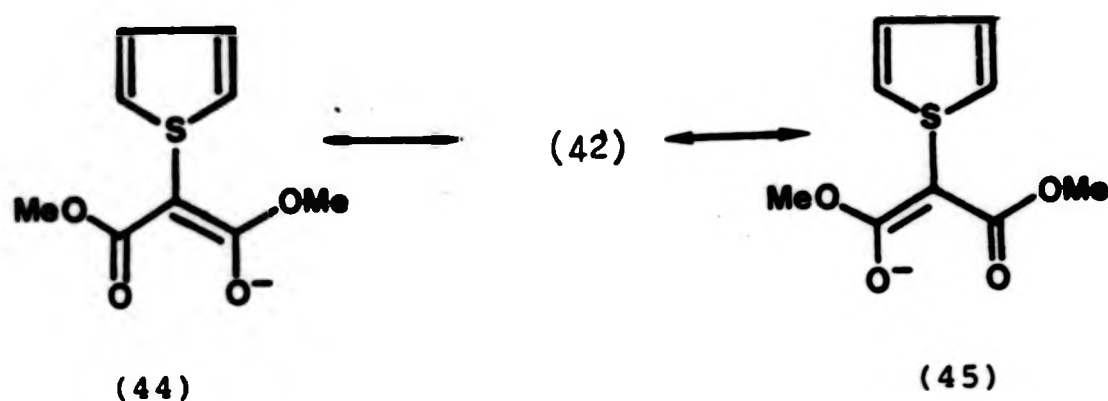
The delocalization of the negative charge over the carbonyl groups would tend to make them less susceptible to electrophilic attack.

In an effort to generate the mono-ester derivative the preparation of thiophenium methoxycarbonyl(benzyloxycarbonyl)-methylide (46) was undertaken. It was hoped that hydrogenolysis would effect a mild deprotection of the carboxylate group. The ylid was prepared by the route outlined in (Scheme 7).

Attempted hydrogenolysis of the benzyl group in ylid (46) using palladium on charcoal as a catalyst left the ylid unchanged. It is probable that the catalyst was poisoned, this is not unknown in thiophen chemistry.

The 4-nitrobenzyl ester group can be easily cleaved with sodium sulphide in aqueous THF[18], thus avoiding hydrogenation. It was therefore decided to synthesise the ylid (47) by the route

shown in (Scheme 8).

(46)

Scheme 7

(47)

(PNB=paranitrobenzyl)
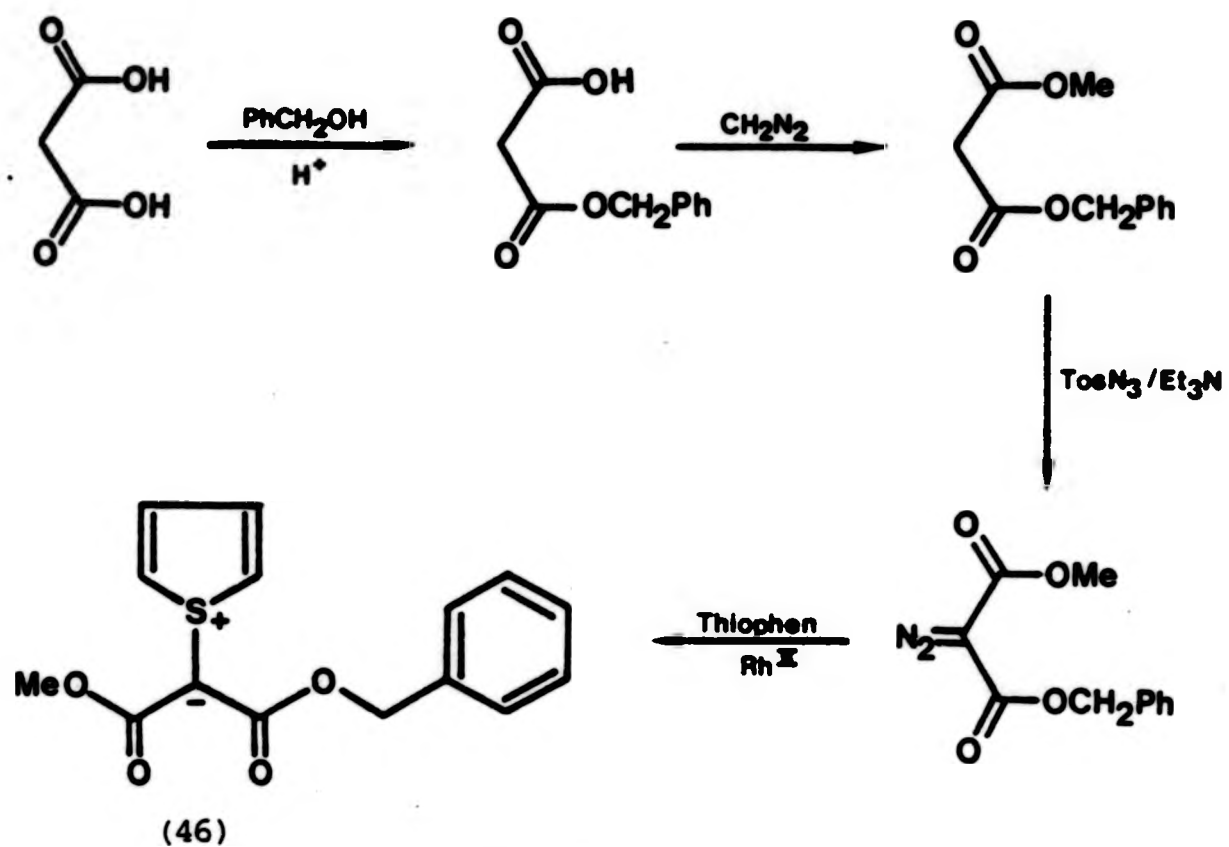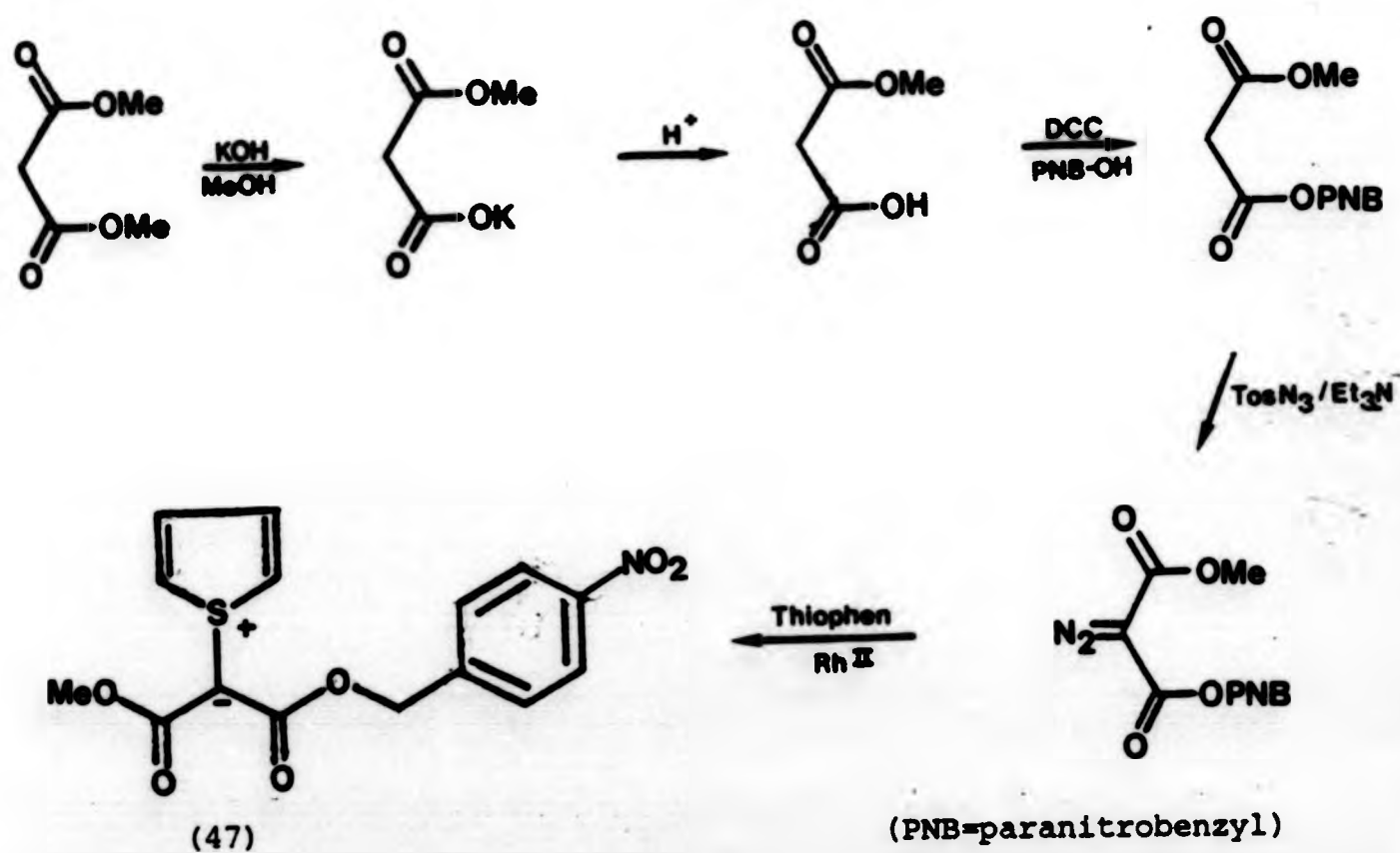
Scheme 8

Treatment of the ylid (47) with one equivalent of sodium sulphide at 0°C in aqueous THF for 20 minutes in the same way as for the deprotection of penicillin esters[18], gave no reaction. The treatment of the ylid with a two-fold excess of sodium sulphide at room temperature also left the ylid unchanged. Leaving the reaction for longer periods resulted in slow decomposition of the ylid. The solid ylid also showed signs of decomposition if left at room temperature for periods of over a week. Higher temperatures could not be used because of this instability.

Unfortunately lack of time prevented further study of this problem.

Rotational energy barriers in substituted thiophenium ylids

During the recording of the ^{13}C nmr spectra of 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (48) (R' = R" = Cl, R = CH_3) it was noted that the carbonyl-carbon atoms were non-equivalent. A number of spectra were recorded at various temperatures and it was found that the coalescence temperature for the carbonyl-carbon signals was 315° ± 5°K and that the energy barrier was 60.6 ± 2 KJ mole^{-1} at that temperature.

(48)
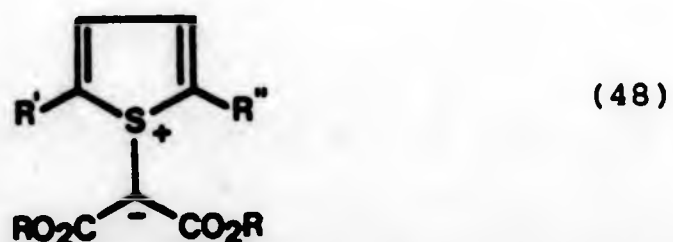
A number of substituted thiophenium ylids were synthesized by the method of Gillespie et al.[3], and their ^{1}H nmr spectra recorded at various temperatures. The spectra were

recorded in $CDCl_3$ and $CDFCl_2$ in dilute solution to avoid association effects, those in $CDCl_3$ at 25 mg ml^{-1} and those in $CDFCl_2$ at 5-10 mg ml^{-1}.

The values of $\Delta G^{\neq}$ were obtained using the approximation:-

$$Kc = \frac{\pi \delta \nu}{\sqrt{2}} = 2.22\delta\nu$$

Using this approximation in the Eyring equation[19] gives:-

$$\Delta G^{\neq}_{tc} = 19.14\ Tc(9.97 + \log Tc/\delta\nu)\ J\ mole^{-1}$$

Initially two temperature dependent processes were observed; one at 'high' temperature where coalescence occurred between 240-315°K and one at 'low' temperature where coalescence occurred between 190-200°K.

Figure 4 shows the signals due to the methyl esters in ^1H spectrum of 2-bromothiophenium bis(methoxycarbonyl)-methylide in the high temperature region.

The values of $\Delta G^{\neq}$ for the various ylids studied are shown in Table 2.

There are three processes which could account for the temperature dependent spectra; rotation about the ylid bond, inversion at sulphur, and rotation about the methylidecarbon-carbonylcarbon bond.

Nozaki et al.[20] found that dimethyl sulphonium bis(acetyl)methylide (49) showed a 1:1 doublet in its ^1H nmr spectrum at -60°C. The coalescence temperature was ca. -25°C
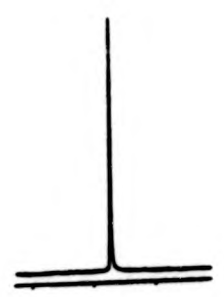
310 K
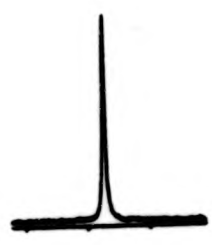
273 K

265 K

263 K

261 K

259 K

230 K
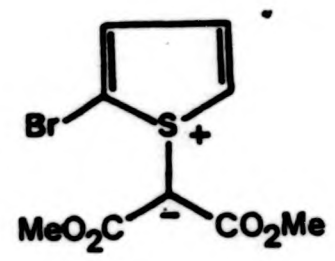
Figure 4

TABLE 2

Compound (46)			T_c (°K)	$\delta\nu$ (Hz)	$\Delta G^{\neq b}$ (KJ mole^{-1})
R	R'	R"			
Cl	Cl	Me	315 ± 5	34.1	60.1 ± 2 [a]
Cl	Cl	Et	309 ± 2	7.0	61.1 ± .5
H	Br	Me	263 ± 2	7.6	51.8 ± .3
Br	Br	Me	293 ± 2	7.2	57.8 ± .4
H	Me	Me	240 ± 2	7.2	47.3 ± .3
Me	Me	Me	257 ± 2	7.0	50.8 ± .4

a. This value was obtained from ^{13}C nmr data

b. $\Delta G^{\neq}$ value are only valid at the respective
    coalescence temperature

and the barrier was <u>ca</u>. 48 KJ mole^{-1}.

$$(49)$$

Of the three possibilities, rotation about the methylidecarbon-carbonylcarbon bond was discounted on the basis that it would affect the signals due to the S-methyl groups. These did not vary with temperature. Of the other two possibilities, inversion at sulphur was considered most likely.

Campbell and Dawlish[21] found that cooling chiral (50) in ^{1}H nmr experiments resulted in broadening identical to that found for (51). They therefore ascribed the broadening to hindered rotation about the ylid bond. The barrier to inversion for (50) was found to be <u>ca</u>. 100 KJ mole^{-1}.
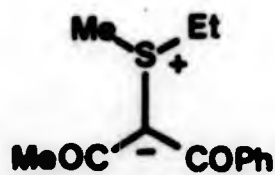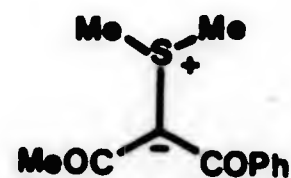
$$(50) \qquad (51)$$

In the case of thiophenium ylids rotation about the methylidecarbon-carbonylcarbon bond can also be discounted. The signal due to α-hydrogen in the mono-substituted thiophenium

ylids shows no change in the high temperature region. Of the other two possibilities it is not clear which is responsible for the observed barrier. It is however clear that both processes must have a barrier which is greater or equal to that observed. The possibilities are as follows:-

	Rotation barrier	Inversion barrier
A	very high	as observed
B	as observed	very high
C	slightly higher than observed	slightly higher than observed

NB. In this instance very high means > 10 KJ mole^{-1} higher than the observed barrier.

These possibilities represent the extremes, any intermediate state is of course possible.

Table 3 shows the $\Delta G^{\neq}$ values for the ester exchanges with the Van der Waals radii and σ values for the thiophen substituents. The change of $\Delta G^{\neq}$ with steric effects should indicate which process is occurring.

It seems likely that when R = R' = H the rotational barrier is low i.e. ≤ 37 KJ mole^{-1} and thus situation B is observed. When an α-substituent is introduced, the barrier to rotation is raised such that any alternative is possible. The trends in terms of electronic and steric effects tend to suggest that B/C predominates. The barrier increases with the number of substituents and with electron withdrawing effect of the substituent. One would expect the ylid bond order and therefore the barrier to rotation to increase with the withdrawal of electrons from the thiophen ring.

TABLE 3

Compound (46)			Van der Waals[22] radii of R/R' (Å)	σ [23]	σ^+ [24]	$\Delta G^{\neq}$ (KJ mole^{-1})
R	R'	R"				
H	H	CH$_3$	1.2	0	0	$\leqslant$ 37
Cl	Cl	CH$_3$	1.8	0.232	0.035	61
H	Br	CH$_3$	1.95			52
Br	Br	CH$_3$	1.95	0.227	0.025	58
H	CH$_3$	CH$_3$	2.0			47
CH$_3$	CH$_3$	CH$_3$	2.0	-0.17	-0.26	51

It is clear that merely by examining the signals due to the ester groups one cannot be definitive about the exchange mechanisms.

The inversion barrier

It is possible to obtain exclusive information about the inversion barrier in the thiophenium ylids by observing the temperature dependence of the signals due to a prochiral group in the α-position of the thiophen ring. We adopted this approach using the ylid (52).[25]
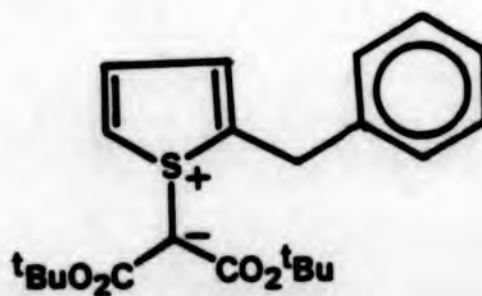
(52)

At temperatures of <u>ca</u>. 240°K the benzyl-methylene protons show up as an AB quartet in the ^{1}H 250 MHz nmr spectrum, with a coupling of <u>ca</u>. -16 Hz and a shift difference of <u>ca</u>. 30 Hz. In the dimethyl ester derivative of (52), the quartet is partially obscured by the ester signal. The di <u>t</u>-butyl ester derivative avoids this problem and gives similar but more accurate values for the activation parameters. The rates of exchange were obtained by visual comparison of the line shapes obtained experimentally with spectra generated by computer. The Eyring plot of these rates against temperature yielded the activation parameters. These were:-

$\Delta H^{\neq}$ 70.6 ± 1.2 KJ mole^{-1}, $\Delta G^{\neq}_{298}$ 51.7 ± 1.1 KJ mole^{-1}, and $\Delta S^{\neq}$ 63.5 ± 0.3 J mole^{-1} K^{-1} for the inversion process, and $\Delta H^{\neq}$ 56.1 ± 2.2 KJ mole^{-1}, $\Delta G^{\neq}_{298}$ 53.3 ± 2 KJ mole^{-1} and $\Delta S^{\neq}$ 9.3 ± 0.6 J mole^{-1} K^{-1} for the ester signal exchange. It was noted that the $\Delta S^{\neq}$ value for the inversion process was surprisingly high, values normally being closer to zero.

In order to confirm this result and to investigate the effect of thiophen substitution on the inversion and rotation processes a number of 5- and 2,5-substituted ylids (4-9, 11-17) were prepared for study.

The first ylid to be studied was 2-(phenoxymethyl)-thiophenium bis(<u>t</u>-butoxycarbonyl)methylide (17).
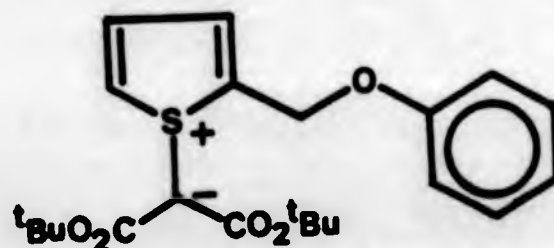
(17)

It was hoped that the replacement of the benzene ring in (52) by the phenoxy group would remove the line broadening of the methylene group signal that is due to coupling with the phenyl group. This would lead to more accurate determination of the rates of exchange, in particular at the extremes of the temperature range where the correlation between broadening and the effects of exchange are very high.

The ^{1}H nmr of (17) at 240°K showed an AB quartet with considerable asymmetry (Figure 5) which remained throughout the temperature range (until coalescence). This asymmetry is probably due to coupling with the thiophen protons, and it precluded a good fit to the computer generated spectra (Figure 6). This asymmetry showed itself in all the spectra recorded of these compounds to a greater or lesser extent, and no doubt contributed to the errors in the activation parameters obtained. Since the purpose of studying (17) was to obtain more accurate values of the rates, and thus the activation parameters, no further work was done with this compound.
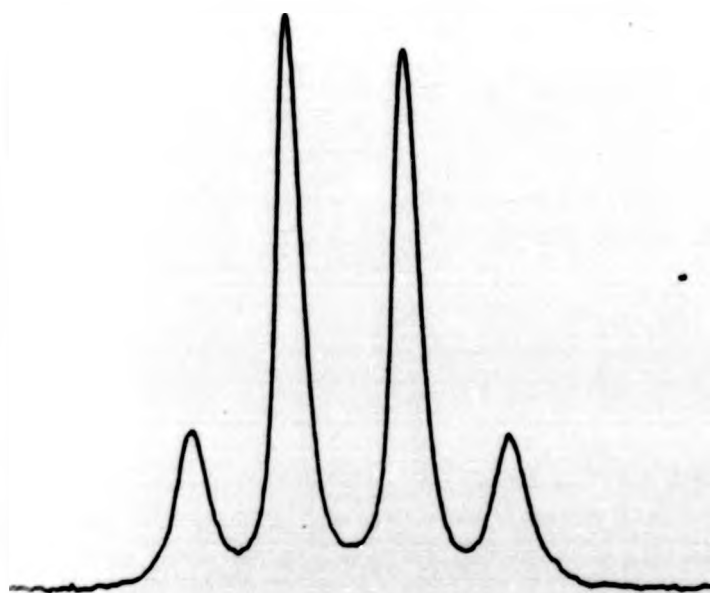
Figure 5
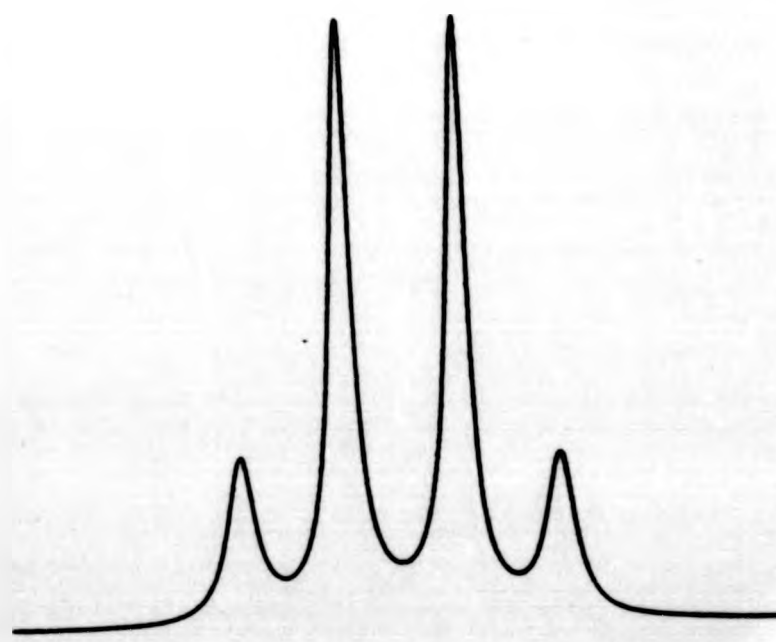
Figure 6

The next ylid to be studied was 2-benzyl-5-ethylthio-
phenium bis(t-butoxycarbonyl)methylide (12). As well as allowing
the study of the effect of an additional alkyl group in the
molecule the prochiral ethyl-methylene group can act as an
internal check on the rates obtained from the benzyl group.

(12)
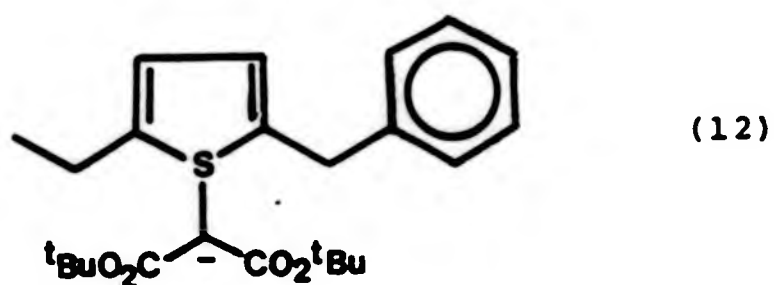
Both the signals due to the prochiral groups showed
some asymmetry and broadening of the signals. After an initial
attempt at fitting them to computer generated spectra it was
decided to attempt to decouple the protons in the 3- and 4-
positions of the thiophen. This was successful and a considerable
improvement in the signals was observed, however the ethyl-methylene
signal was still asymmetrical (Figure 7).
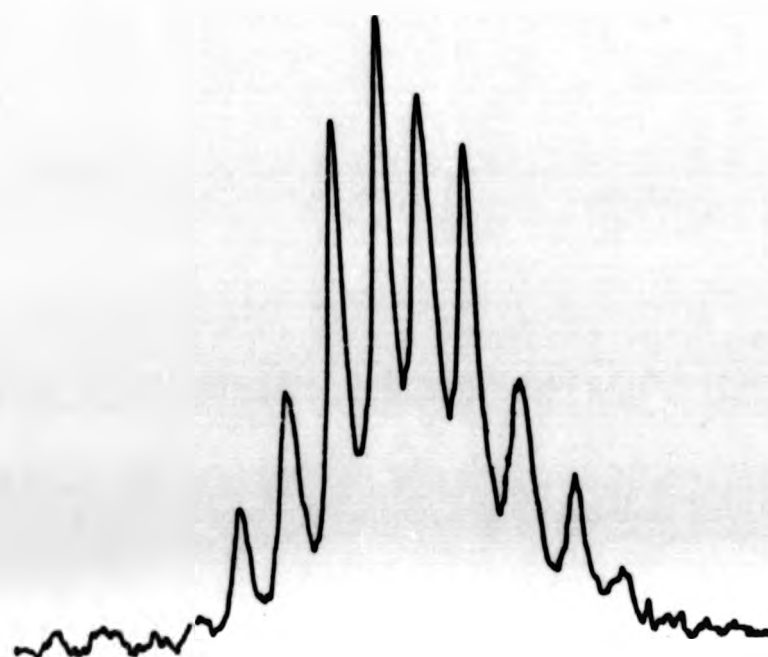
Figure 7

The fitting of the computer generated spectra to the ethyl-methylene proved to be rather difficult, partially because of asymmetry and also because the static parameters (i.e. coupling constants and $\delta\nu$) were less easy to obtain. A fully iterative fit was made using digitised spectra at two temperatures but these did not give rates which were appreciably different from those obtained from visual fitting.

The benzyl-methylene spectra in contrast, were relatively symmetrical and fitted well to the computer generated spectra (Figure 8) above 240°K.

A further three compounds were studied (14-16). These provided a range of electronic as well as steric effects.

	R
14	Cl
15	Br
16	I
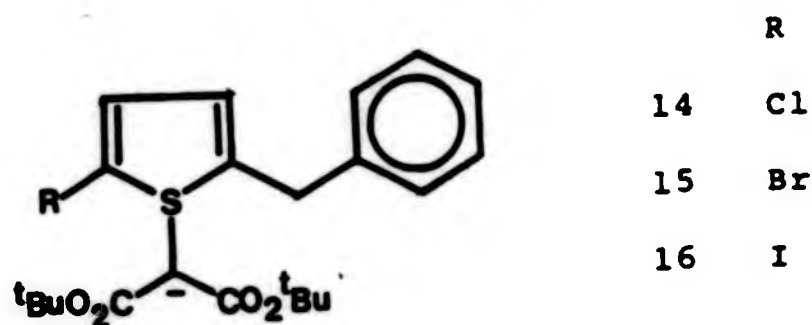
Unfortunately instrumental problems and lack of time prevented the recording of these spectra with the thiophen protons decoupled and the methylene signals of these compounds showed the clearest evidence of coupling with a clear splitting of one half of the AB quartet at low temperature (Figure 9).

The spectra were nevertheless analysed by comparison of half the quartet with the computer generated spectra.

The temperature settings were checked by running spectra of methanol at the various temperatures as in the method of Van Geet.[26]
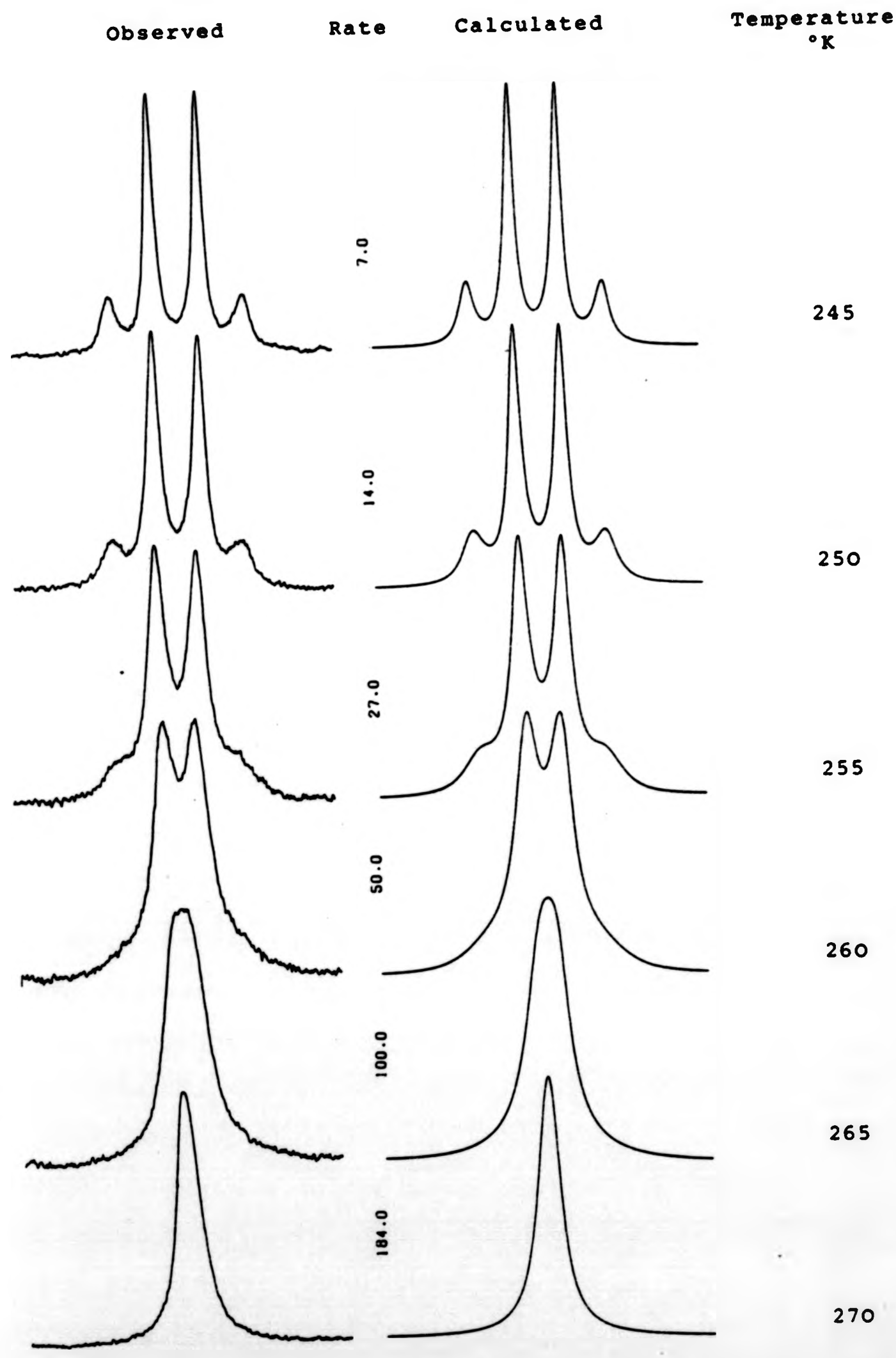
Figure 8
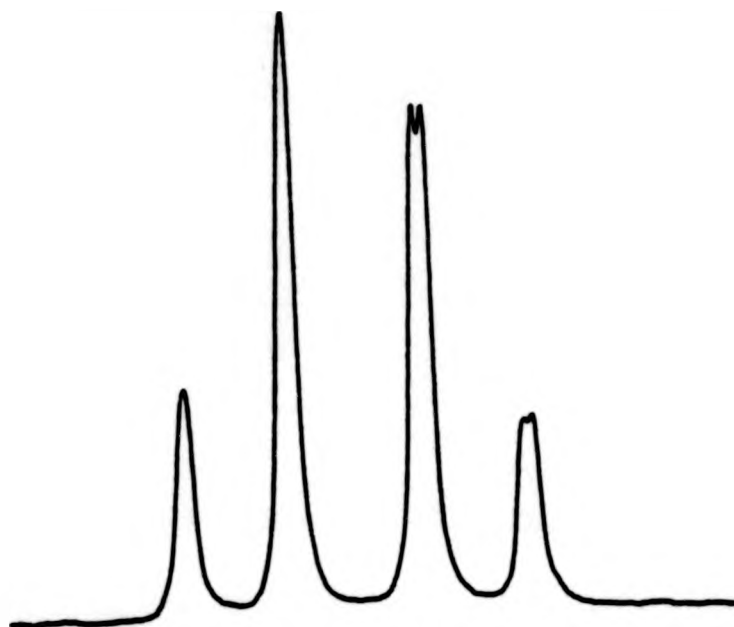
Figure 9

There was not sufficient time to study all the ylids synthesized for this work. Of the remainder (page 50), the mono-substituted ylids (4-9) can be used to investigate the effect of the benzyl group on ester exchange (one would expect a higher rate of exchange because of decreased hindrance to rotation). Ylids 5, 11, and 13 possess prochiral methylene groups which can be investigated as above and the two isopropyl substituted ylids 6, and 13 offer the opportunity of analysis of the pro-chiral isopropyl carbons by ^{13}C nmr. The Forsen-Hoffman spin saturation method for slow rates may be used.[27] In this method one of the signals is saturated and the time dependence of the other signal intensity is observed. This provides accurate rates at one extreme of the temperature range thus improving the accuracy of $\Delta S^{\neq}$ and $\Delta H^{\neq}$.

The activation parameters for the ylids studied are

listed in Table 4.   The values of $\Delta H^{\neq}$ and particular $\Delta S^{\neq}$ are included for the sake of completeness but their values must be regarded with suspicion.   The value of $\Delta G^{\neq}$ however, is relatively insensitive to errors in the individual rates and may thus be viewed with some confidence.

TABLE 4

Ylid R	$\Delta H^{\neq}$ KJ mole^{-1}	$\Delta S^{\neq}$ J mole^{-1} K^{-1}	$\Delta G^{\neq}_{298}$ KJ mole^{-1}
(12) Et (ethyl-methylene)	63.1 ± 11	28.0 ± 3	54.8 ± 11
(benzyl-methylene)	74.2 ± .5	71.4 ± .1	52.9 ± 0.5
(14) Cl	74.4 ± 4.9	49.8 ± 1.4	59.6 ± 4.9
(15) Br	70.2 ± 3.0	38.2 ± .8	58.8 ± 3.0
(16) I	68.8 ± 7.1	40.4 ± 1.9	56.7 ± 7.1

What can be said about $\Delta S^{\neq}$ is that it appears to remain significantly positive as was found originally.   It is also of interest that the value of $\Delta G^{\neq}$ increases with the electronegativity of the substituent.   This is the opposite of what one would intuitively expect on the grounds of thiophenium ion stability.

The rates of ester exchange were also obtained by line shape analysis.   The 2-benzyl-5-ethylthiophenium ylid (12) was not analysed because of the overlap of the ethyl and t-butyl groups.   The activation parameters obtained are listed in Table 5.

TABLE 5

Ylid R	$\Delta H^{\neq}$ KJ mole^{-1}	$\Delta S^{\neq}$ J mole^{-1} K^{-1}	$\Delta G^{\neq}_{298}$ KJ mole^{-1}
(14) Cl	69.6 ± 13.2	33.2 ± 3.6	59.7 ± 13.2
(15) Br	66.5 ± 6.0	25.4 ± 1.6	58.9 ± 6.0
(16) I	63.6 ± 6.3	22.0 ± 1.7	57.1 ± 6.4

Although the values of $\Delta G^{\neq}$ obtained for the ester-exchanges are similar to those for inversion, the Eyring plots are different at lower temperatures with the rates of ester exchange greater than those for inversion. This difference is not as great as that found in ylid (52), where the relatively greater rate of ester exchange may be attributed to the absence of a 5-substituent.

In principle it should be possible to obtain the rates of rotation about the ylid-bond by manipulation of the data obtained from the inversion and ester-exchange processes. Unfortunately the errors in this instance are such that this was not possible.

In summary, the unsubstituted thiophenium ylids have a low barrier to rotation about the ylid bond which is increased by α-substitution of the thiophen. The benzyl- and ethyl-substituted thiophenium ylids have a barrier to inversion at sulphur which is in the range 50-60 KJ mole^{-1} and which increases with the electronegativity of the substituents.

The x-ray structure of thiophenium bis(methoxycarbonyl)-
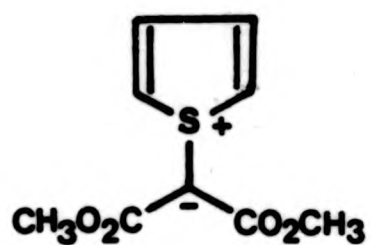
(53)
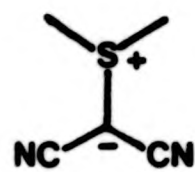
(54)
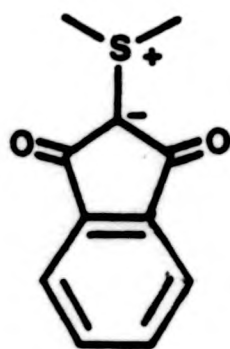
(55)

(56)
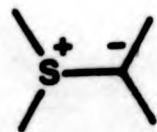
(57)
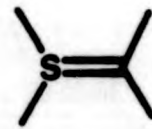
(58)

methylide (53)[3] gives a ylid-bond length of 1.712Å with
pyramidal sulphur. This is similar to the structure of other
ylids studied by x-ray diffraction. The ylids 54, 55, and 56
have ylid-bond lengths of 1.73, 1.71, and 1.712Å respectively,[28]
and all are pyramidal at sulphur. The ylid-bond lengths are all
significantly shorter than other C-S bonds, and this has been
attributed to the contribution of structure (58) to that of
the ylid (57).[29]

Comparing the thiophenium ylids with the ylid (50),
the inversion barriers are ca. 52 KJ mole^{-1} and 100 MJ mole^{-1}
respectively, although the ylid bond orders are similar. This
may be due to the angular constraints of the thiophen ring.

The low temperature process

.At temperatures in the region of 200°K the signals
due to the methyl esters of the ylids (48) (R = CH$_3$) had resolved
into either 3 or 4 peaks (Figures 10 and 11). Distortion of the
benzylic AB quartet was also visible in the benzylthiophenium
ylids at low temperatures (Figure 12). Table 6 gives the values
of Tc, δν, and $\Delta G^{\neq}$ for the various ylids studied, the values
of $\Delta G^{\neq}$ were obtained using the approximation on page 75.

The values of $\Delta G^{\neq}$ for these compounds are very similar.
In fact they are the same within experimental error. The
process is therefore not influenced to any appreciable extent
by the substitution on the thiophen ring. Hindered rotation
of the methylidecarbon-carbonylcarbon bond would seem to be
the most likely origin of these signals. As mentioned earlier,
one would expect the signals due to the thiophen α-hydrogens to

TABLE 6

| Compound (48) | | | | | |
R	R'	R"	Tc (°K)	δν (Hz)	$\Delta G^{\neq}$ (KJ mole^{-1})
H	H	CH$_3$	190 ± 2	6.6	37.5 ± 0.4
Cl	Cl	CH$_3$	193 ± 5	20.8	37.2 ± 1
Cl	Cl	C$_2$H$_5$		a	
H	Br	CH$_3$	195 ± 5	35	37.5 ± 1
Br	Br	CH$_3$	193 ± 5	33.4	37.1 ± 0.9
CH$_3$	H	CH$_3$	200 ± 5	38.3	38.4 ± 1
CH$_3$	CH$_3$	CH$_3$	200 ± 5	36.9	38.4 ± 1

a   The signals due to the ethyl groups were not sufficiently resolved to give an accurate measure of δν.
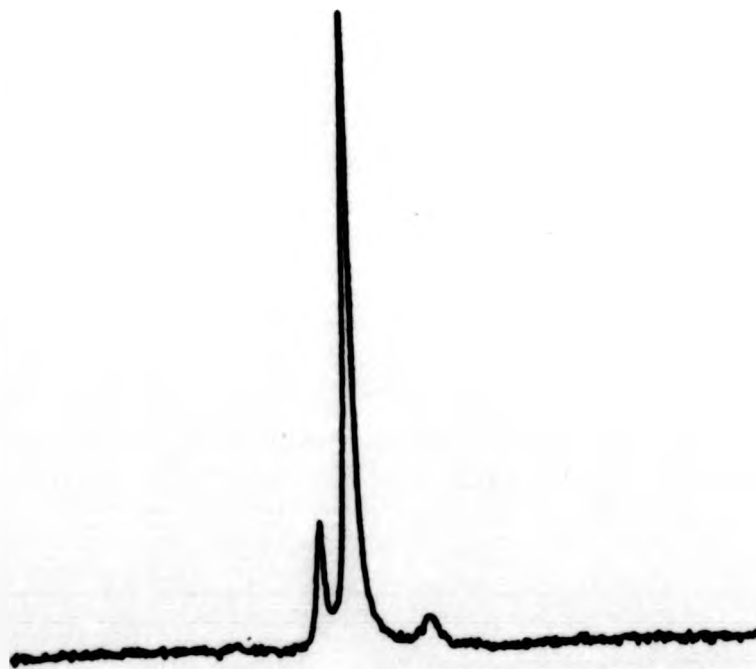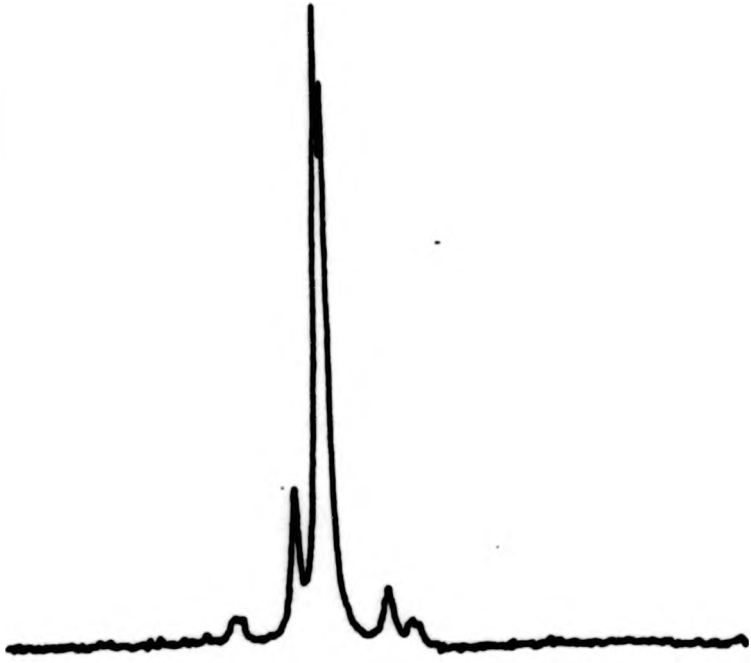
Figure 10

Figure 11
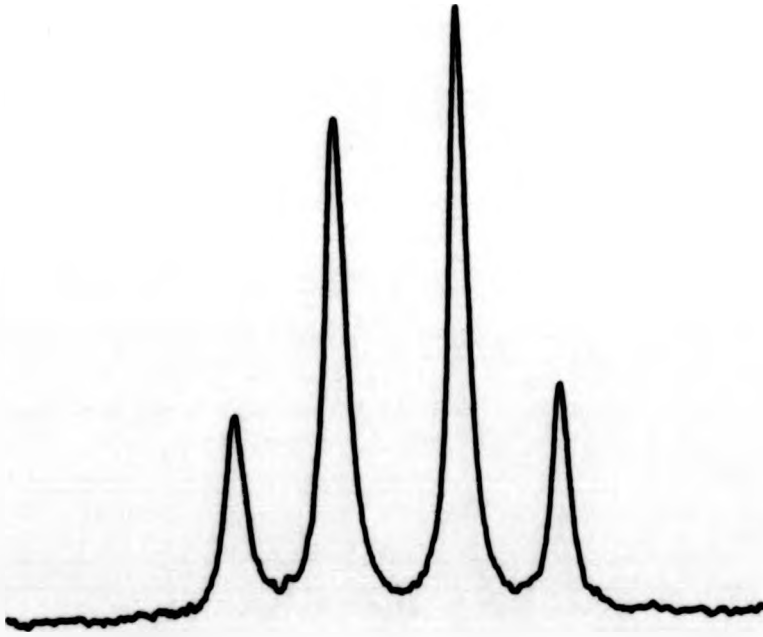
Figure 12

be affected by this process. The spectra of the thiophen rings do indeed change to some extent, but the broadening of the spectra make it impossible to be definite. One might expect the substituents on the thiophen ring to affect the rotation via steric interactions. Changes in the ylid bond order would also tend to affect the barrier to rotation via the resonances seen in Figure 13. The x-ray structure of ylid (53) shows the ester groups to be staggered with respect to the thiophen ring. This would reduce the steric interaction with the substituents.
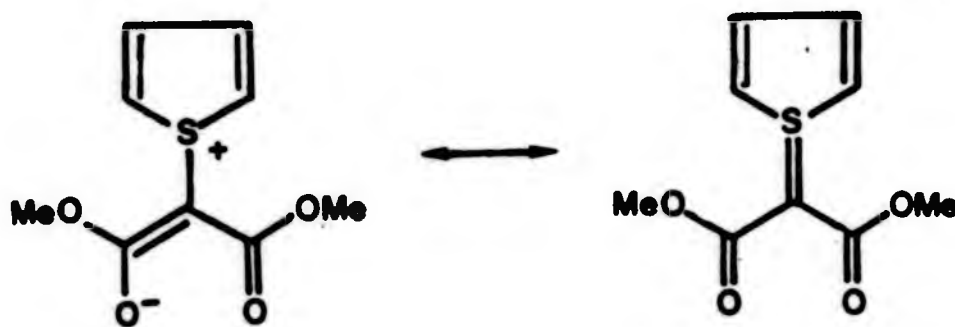
<u>Figure 13</u>

In conclusion one can say that this barrier is probably due to hindered rotation of the carbonyl groups due to increased bond order of the methylidecarbon-carbonylcarbon bond or possibly interaction between the ester group and the thiophen ring.

The formation of 1,2,3-triazoles

During the investigation of the reactions of dimethyl diazomalonate with substituted thiophens, 2-aminomethyl-thiophen was reacted with dimethyl diazomalonate in the presence of rhodium-(II)-acetate. A white crystalline solid was obtained which had no diazo band in the IR. The nmr spectrum showed the presence of two methyl thiophens and a methyl ester. The elemental analysis was consistent with the formula $C_{14}H_{16}N_4O_3S$. However, the mass spectrum indicated a molecular formula of $C_9H_8N_3O_3S$. An X-ray structure analysis was carried out to establish true structure.

Crystals of the product $C_{14}H_{16}N_4O_3S_2$ Mr 352.85 were triclinic, space group PI   a = 10.89(2), b = 8.41(1), c = 10.40(2)$\overset{\circ}{A}$ α=92.20(5)$^\circ$, β=106.39(5)$^\circ$, γ = 111.40(2)$^\circ$, U = 840.7 $\overset{\circ}{A}{}^3$, z = 2, Dm = 1.394g cm^{-3} (Dc = 1.393g cm^{-3}). Mo-Kα radiation (λ 0.7107 $\overset{\circ}{A}$) μ = 2.86 cm^{-1}, 1999 reflections (h0-6ℓ) with θ < 25° were collected on a STADI-2 diffractometer of which 1223 with I > 3σ (I) were used. The structure was solved by direct methods and all hydrogen atoms were located. Full-matrix refinement with anisotropic thermal parameters for heavy atoms converged at R = 0.057.

The structure (Figure 14) (64) consists of 2-thienyl-ammonium cations hydrogen bonded to the heterocyclic anions. The ring bond lengths (N_1-N_2 = 1.378(7) $\overset{\circ}{A}$, N_2-N_3 = 1.312(7) $\overset{\circ}{A}$, N_3-C_4 = 1.375(8) $\overset{\circ}{A}$, C_4-C_5 = 1.416(9) $\overset{\circ}{A}$, C_5-N_1 = 1.382(8) $\overset{\circ}{A}$, C_5-O = 1.261(8) $\overset{\circ}{A}$) are consistent with the enol form.

The reaction probably proceeds via an amination of dimethyl diazomalonate followed by nucleophilic attack by the amide nitrogen (Scheme 9).

Figure 14

<div align="right">Scheme 9</div>
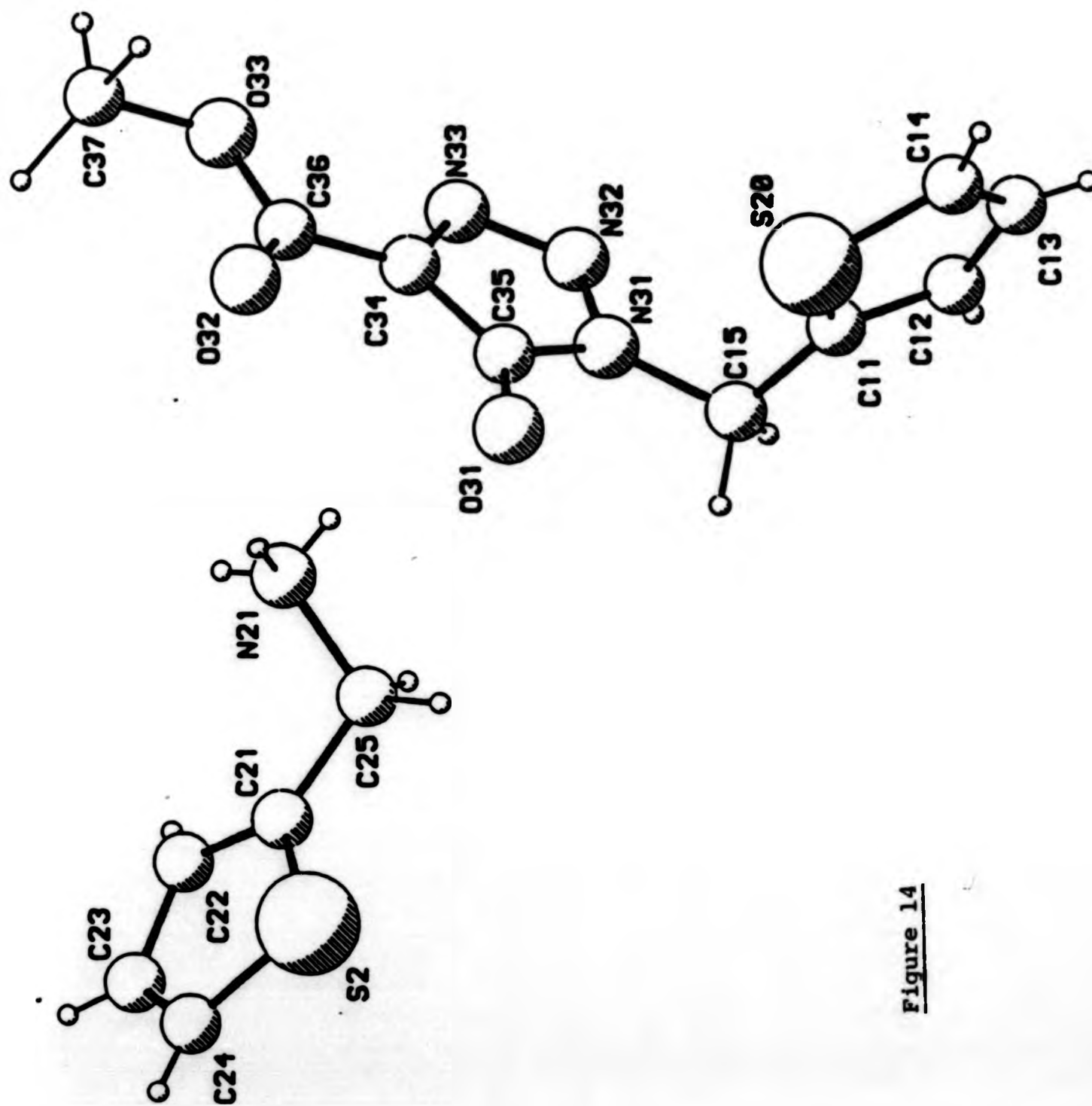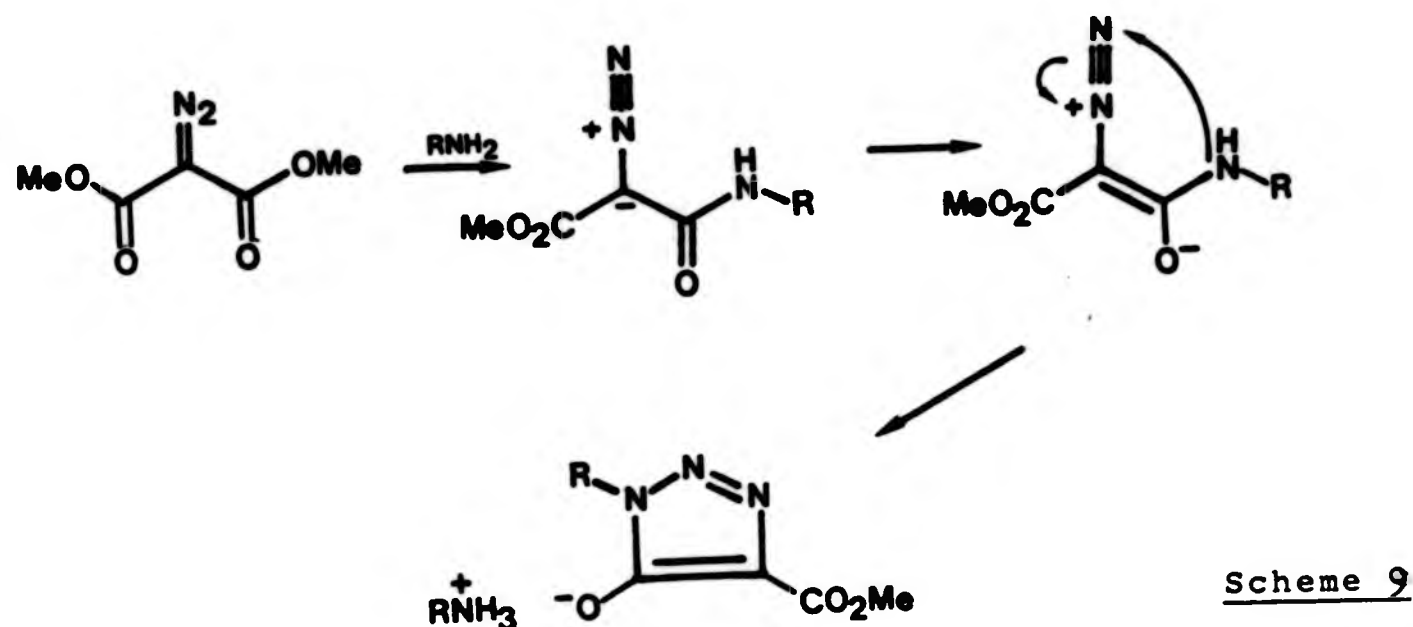
The alkali catalysed isomerisation of α-diazoamides into 4-hydroxy-1,2,3-triazoles is known as the Dimroth rearrangement.[30,31] Dimroth reacted diethyl malonate with phenyl azide in the presence of sodium ethoxide to give 1-phenyl-4-carboethoxy-5-hydroxy 1,2,3-triazole[32] (59).

(59)
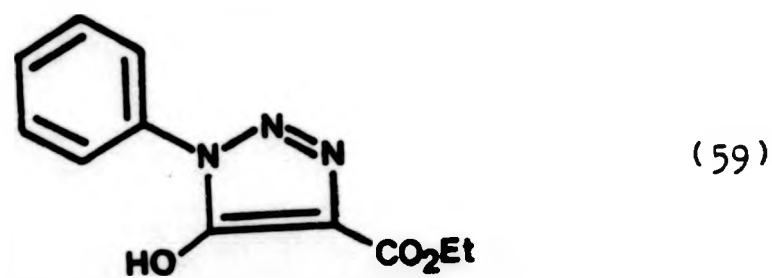
He also found that the reaction of malonamide with phenyl azide gave the triazole (60) and aniline[31]. (Scheme 10).

(60)

<div align="center">Scheme 10</div>

Triazine (61) is the assumed intermediate.[33]

(61)
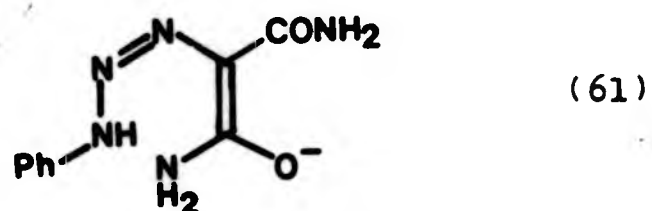
Begtrup and Pedersen have shown[33] that this is the case and that the enolate structure must predominate in this reaction. When 2-methylmalonamide was used this enolization was not possible, and thus the alternative product was formed (Scheme 11).
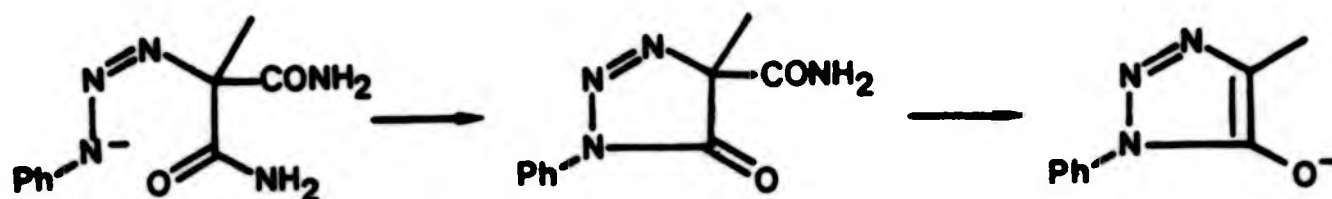
<u>Scheme 11</u>

The reaction of amines with dimethyl diazomalonate represents a potentially useful method of obtaining 5-hydroxy-4-alkoxycarbonyl triazoles, in that it avoids the preparation of azides. In order to test the generality of this reaction dimethyl diazomalonate was reacted with a 2-3-fold excess of several amines in toluene or THF at room temperature. After 2-3 days the triazoles were filtered off and recrystallized. The results are tabulated below.

Amine	Triazole	Yield (%)

(62) — 82

(63) — 70

Figure 14

(64) — 66

(65) — 98

(66) — 79
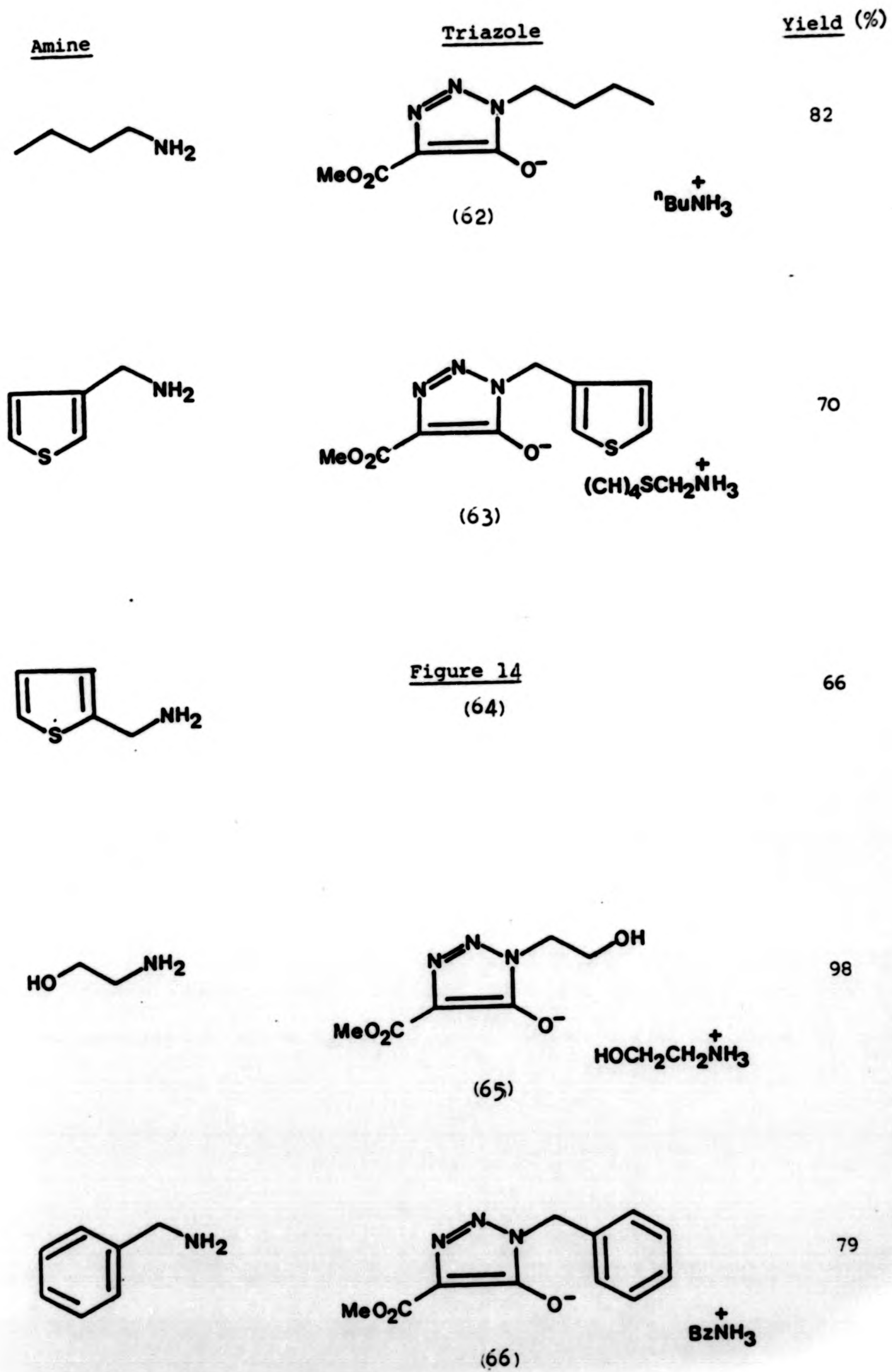
Aniline did not give a triazole, probably
because aniline does not readily form the amide. Reactions of this
type are dependent on the basicity of the amine[34].

The reaction between ethanolamine and dimethyl
diazomalonate was carried out in THF. The formation of the
triazole tended to 'salt out' unreacted ethanolamine if toluene
was used as a solvent. The benzylamine reaction required 2 to
3 times the amount of amine to go to completion. This is
probably because the triazole was appreciably soluble in toluene
and thus facilitated the equilibrium in the reverse direction.

The treatment of the triazole salts with dilute acid
followed by extraction with a suitable solvent yields the
corresponding hydroxy compounds (67).

(67)

These compounds are unstable and standing at room
temperature for several days, or heating briefly at 100°C,
resulted in the formation of the linear α-diazoamides. The
compounds obtained from the treatment of the triazoles with
acid and their corresponding diazoamides are listed below.

It proved impossible to obtain elemental analyses
of the hydroxytriazoles and diazoamides. The hydroxytriazoles
were not sufficiently stable for recrystallization, and the
diazoamides were not sufficiently volatile to be distilled
without decomposition. It was possible to obtain accurate

masses for these compounds with exception of amides (71) and (73), which did not give molecular ions.

Hydroxytriazole	Amide
(68)	(69)
(70)	(71)
(72)	(73)
(74)	(75)
(76)	(77)
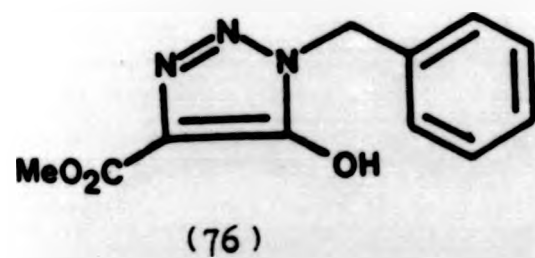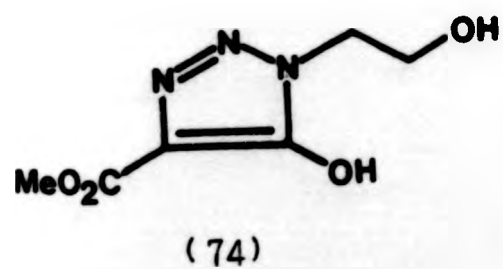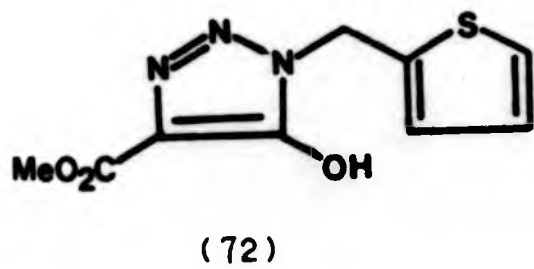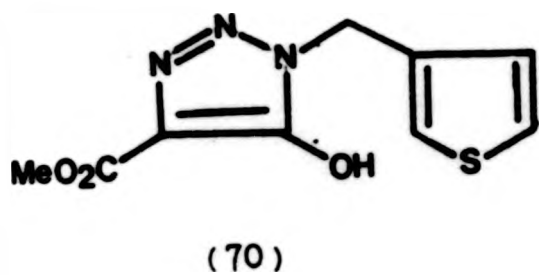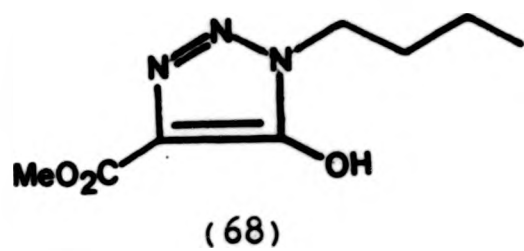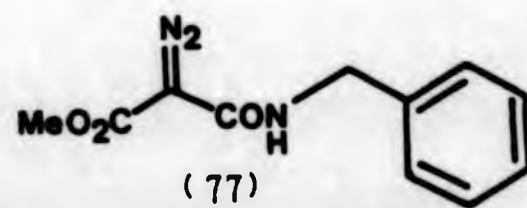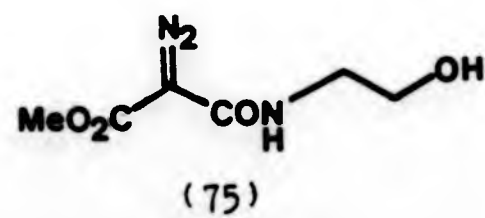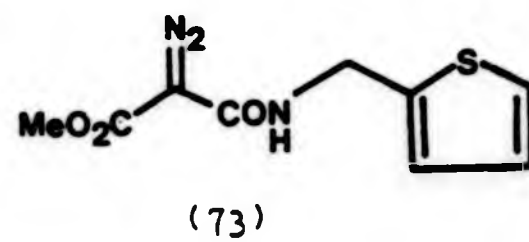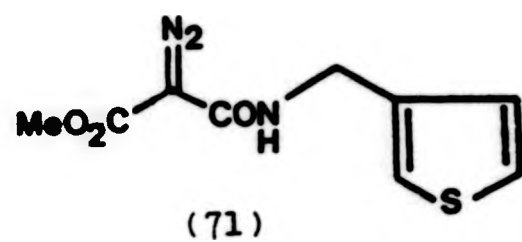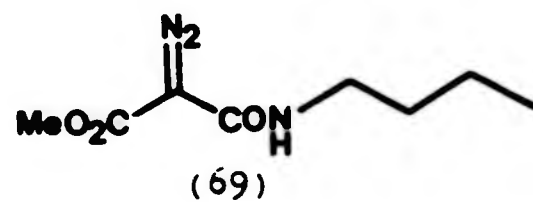
In order to investigate the reaction of other diazoesters with these amines ethyl diazoacetoacetate[35] (78), ethyl diazoacetate[36] (79), methyl diazophenylacetate[37] (80) and methyl diazocyanoacetate[38] (81) were prepared.
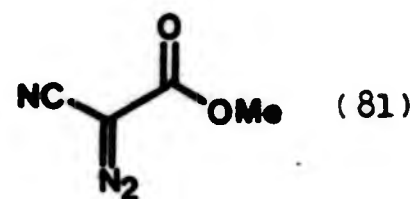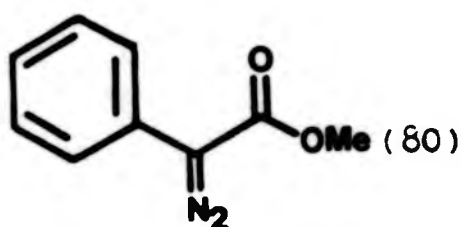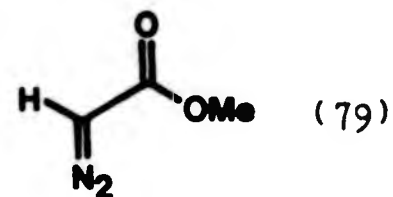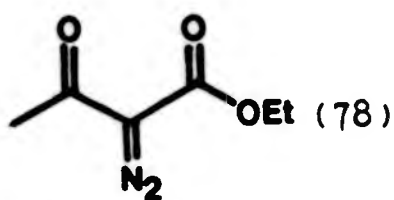
Compounds (79) and (80) were prepared by diazotization of the corresponding amino acids, whilst (78) and (81) were prepared by diazo-transfer reactions. Some problems were encountered in the preparation of (81). Initially 4-toluene-sulphonylazide and triethylamine were used as reagents, but this only resulted in the formation of a black tar. However, the use of 2-azido-3-ethylbenzothiazolium fluoroborate (82) under acidic conditions in aqueous-ethanol yielded the desired product.
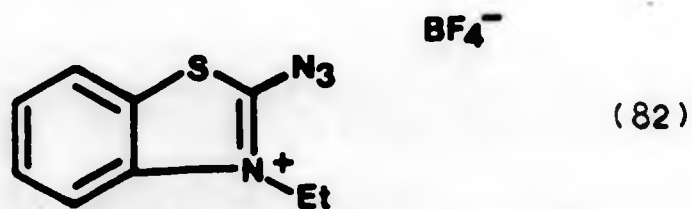
These diazocompounds were reacted with butylamine in toluene, and with ethanolamine in THF, as described previously. Ethyl diazoacetoacetate, methyl diazophenylacetate, and ethyl diazoacetate gave no triazoles. The diazo-band (ir) was still present after several weeks at room temperature although some colour change was apparent. It was thought that perhaps the diazoamides had formed, but the enolate anions were too basic to form under the reaction conditions. In an effort to generate the anion and thus facilitate triazole formation, sodium methoxide was used as a base.

When butylamine was reacted with methyl diazoacetate in the presence of sodium methoxide the reaction resulted in the formation of a black tar.

Methyl diazocyanoacetate gave a red oil on treatment with butylamine. The infrared spectrum of the oil showed a weak diazo adsorption. This suggested some triazole had been formed but that the remainder of the diazo compound had been 'salted out'. The use of more polar solvents and long reaction times gave no improvement. It proved impossible to characterize any definite products.

In view of the fact that 1,2,3-triazoles are readily available from the corresponding esters and azides it was decided to abandon this line of work.

Attempted synthesis of methyl 3[5-(hept-cis-4-ene-ynoyl)-
2-furyl] prop-trans-2-enoate, (Wyerone), (83) using diazoalkanes

(83)
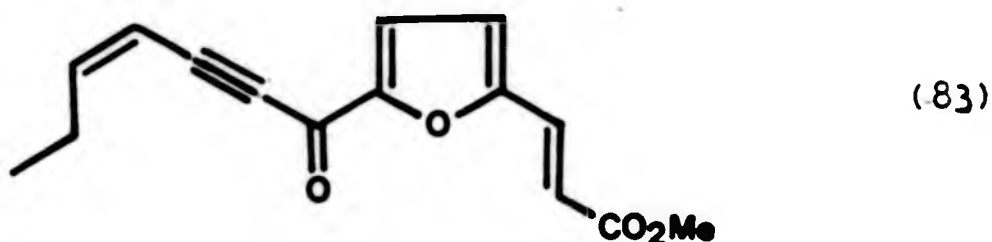
Wyerone[39] is a phytoalexin produced by the broad bean
(Vicia faba L.) when it is infected with Botrytis fabae and
Botrytis cinerea.[40,41]   It is a member of the acetylenic
metabolites found in many plants and it gives the plant some
ability to resist fungal attack.   There has been considerable
experimental interest in Wyerone,[42] which is normally obtained
by extraction of infected plants with diethyl ether followed by
chromatography.[43]   A method of preparing Wyerone in reasonable
quantity would therefore be of some interest.

Wyerone has been synthesised by the condensation of
methyl 3-(5-formyl-2-furyl)acrylate (84) and cis-hex-3-ene-1-
yne magnesiumbromide (85).[39]   (Scheme 12).

(84)   (85)   Scheme 12
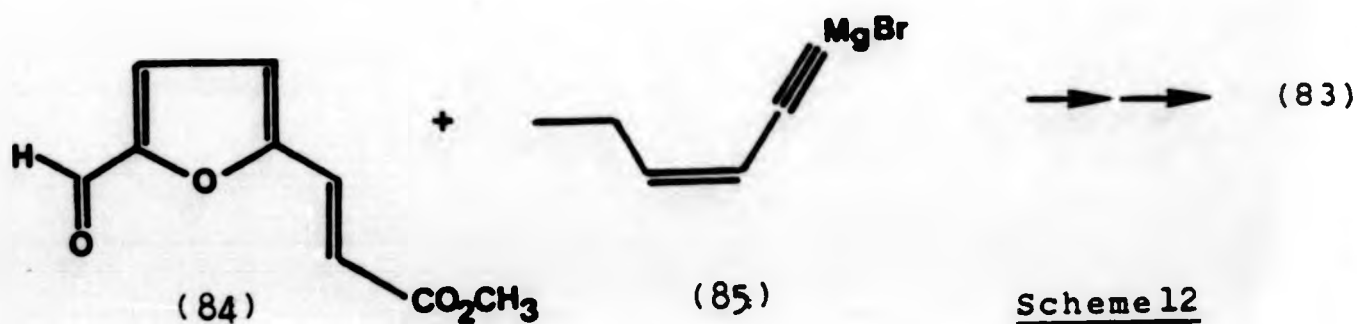
More recently it has been prepared by the condensation
of the dianion of 3-(2-furyl)-acrylic acid (86) with cis-hept-4-
ene-2-ynal[44] (87). (Scheme 13)

(83)

(86)   (87)   Scheme 13
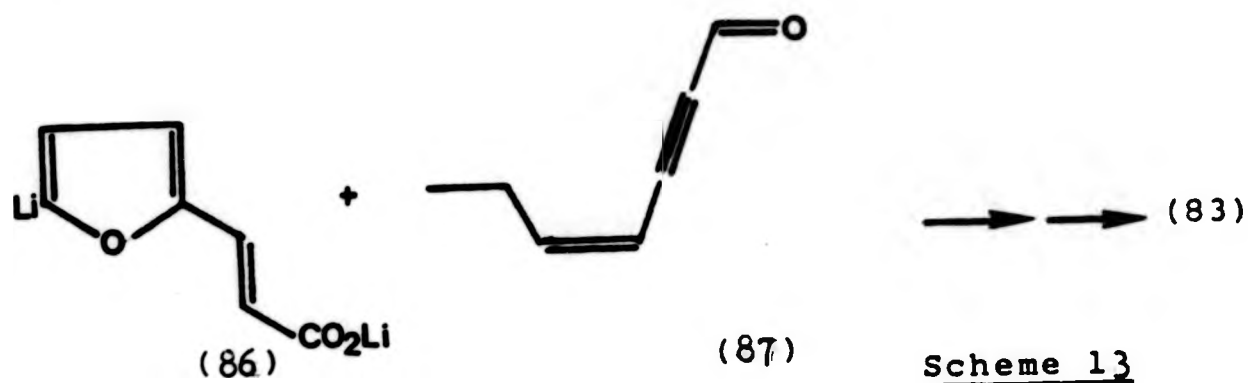
Diazoalkanes offer a method of avoiding the preparation of the cis-hexene-yne side chain. Hoffman and Shechter[45] have shown that warming of ethyl(2-furyl)diazoacetate (88) results in the formation of ethyl cis-hex-4-ene-2-ynoate (89) in 100% yield. Scheme (14).

(88)

Scheme 14

(89)
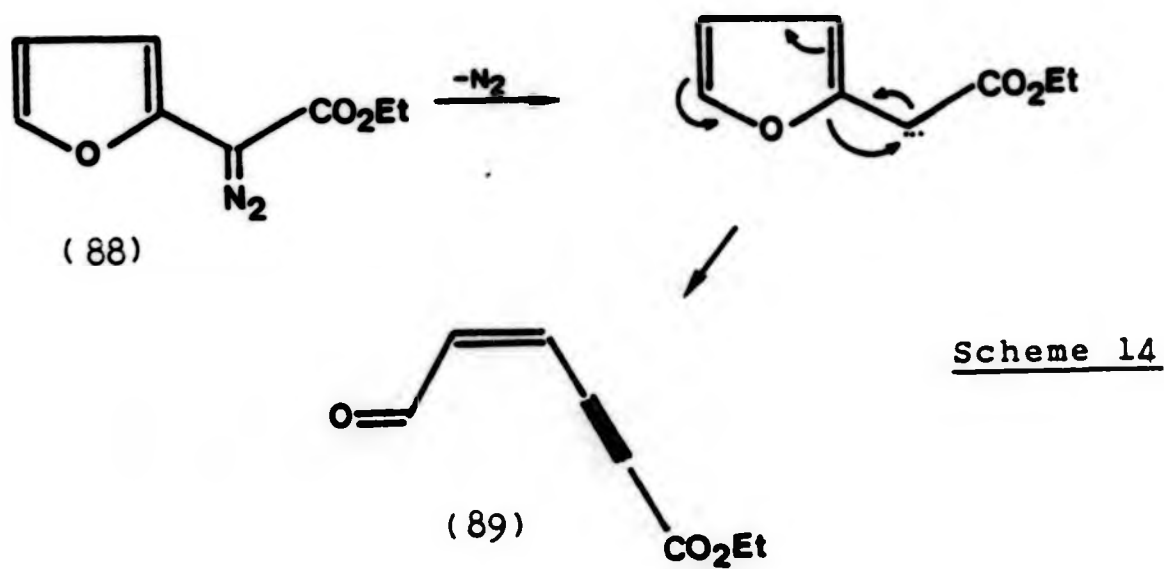
In an earlier paper[46] it had been shown that thermolysis of the tosyl hydrazone (90) (R=H) results in a similar product. The yield was lower however, (60%) and some of the trans-isomer was formed.

(90)
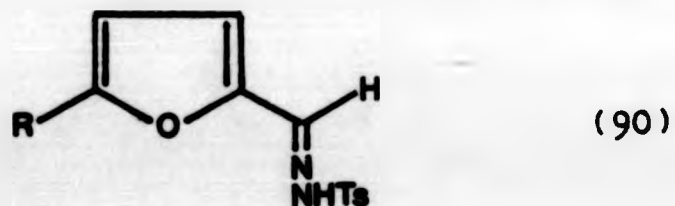
In this series of reactions the analogous thiophen compound (R=CH$_3$) was also thermolysed to give the carbene dimer (91) in 21% yield and the polysulphide (92) in 8% yield.
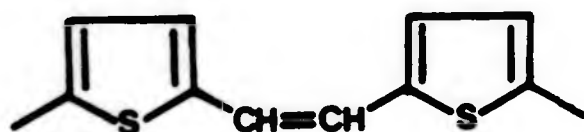
(91)
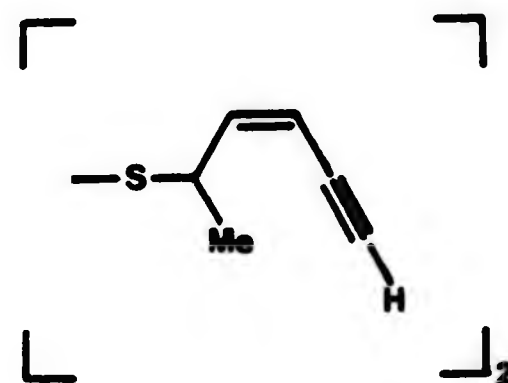
(92)

The formation of the dimer was ascribed to the relative stability of the thiophen ring compared to that of furan.

· It was hoped that the synthesis of compound (93) and the generation of the carbene under mild conditions, possibly with rhodium-(II)-acetate catalysis, would yield the desired intermediate (94), which on reduction would yield Wyerone (Scheme 15).

(93)

(83)

(94)
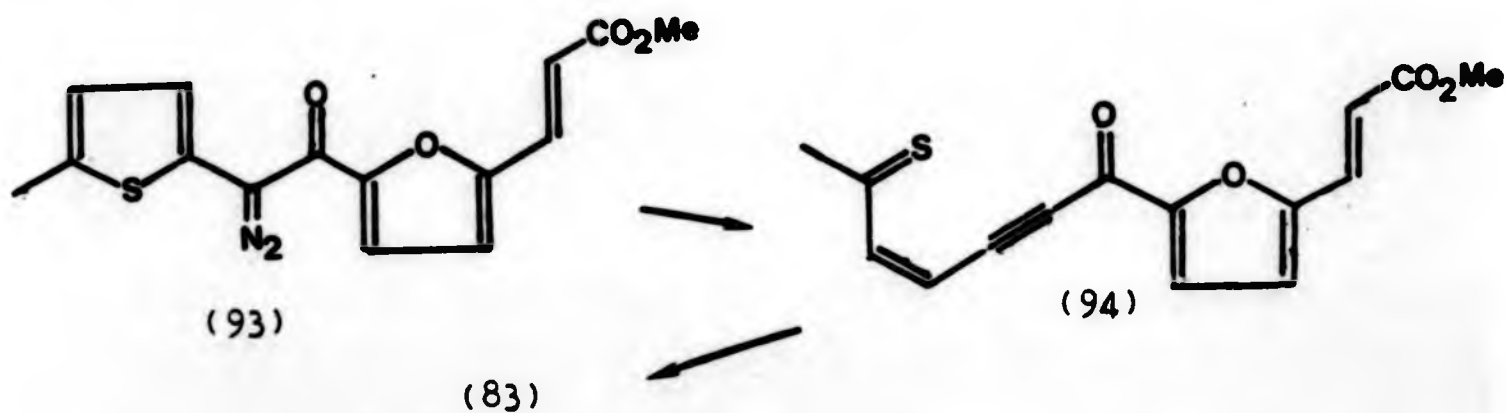
Scheme 15

If polysulphides were formed from the thioketone (94), suitable reducing agents would still give the desired product. The mild conditions together with the increased steric hindrance, possibly with high dilution, would reduce dimer formation.

(95)

(84)

(96)

(97)

(93)
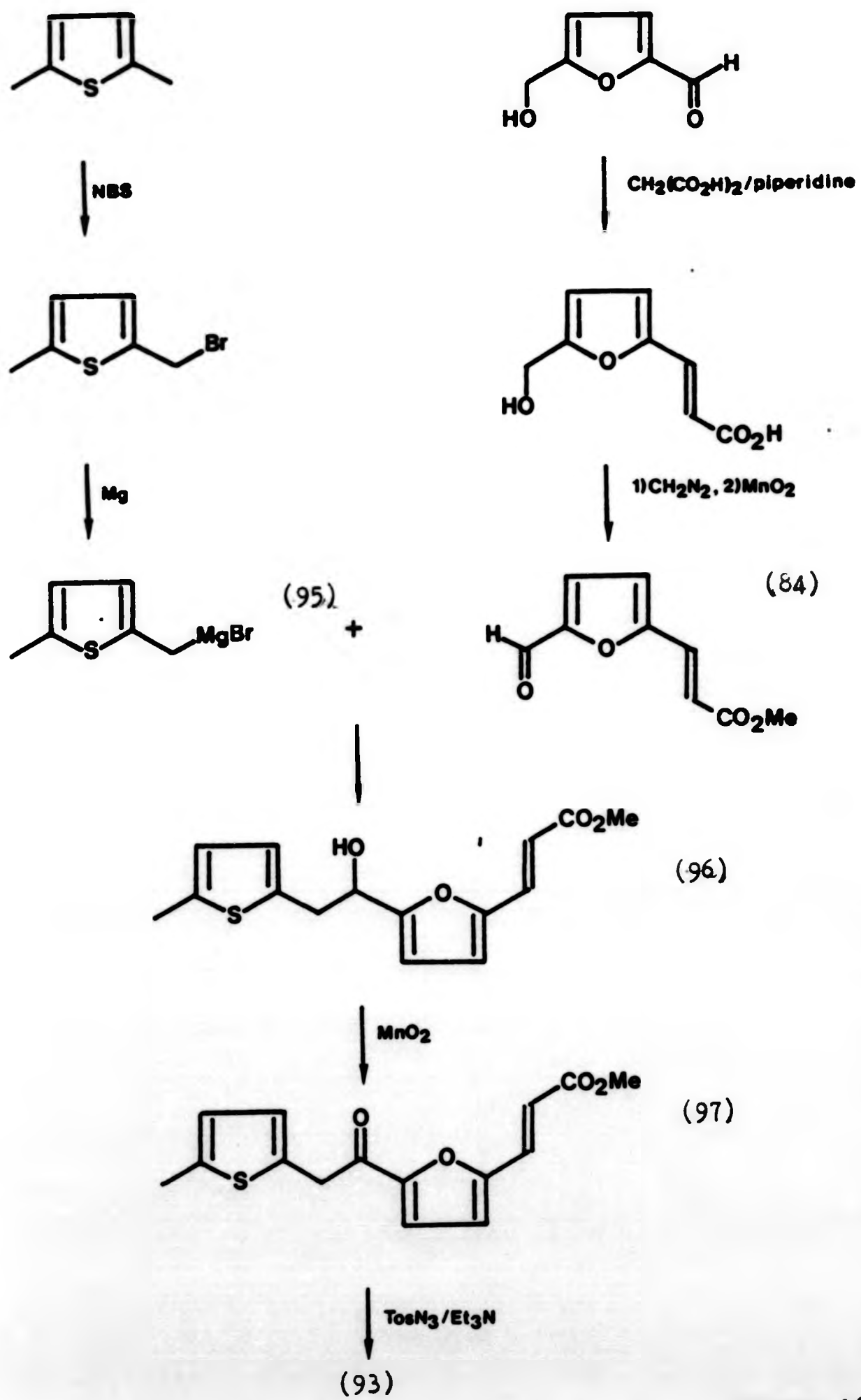
Scheme 16

The initial route to compound (93) was to be via the condensation of 5-methyl-2-thienylmagnesium bromide (95) with methyl 3-(5-formyl-2-furyl)-acrylate (84). (Scheme 16).

The route to (84) is a modification of that of Fawcett et al.[39] 5-(Hydroxymethyl)furfural was prepared by the oxidation of sucrose with iodine in DMF. This was then condensed with malonic acid in a Stobbe condensation followed by decarboxylation, esterification, and oxidation of the alcohol with manganese dioxide.

2-Bromomethyl-5-methylthiophen was prepared from 2,5-dimethylthiophen via a radical bromination with N-bromo-succinimide. The bromo compound proved to be extremely unstable. The first preparation was stored over calcium carbonate as recommended for 3-thienylbromide.[47] However the compound underwent self-catalysed decomposition, which resulted in a minor explosion. Subsequently the material was prepared, distilled and reacted immediately with magnesium turnings. When the purple Grignard reagent was added to the aldehyde (84) none of the desired alcohol was obtained. The only identifiable product was the recovered aldehyde (84) in 50% yield. Further attempts at this reaction also proved fruitless.

An attempt was made to generate the lithium adduct of 2,5-dimethylthiophen (98) via a method analogous to that for the formation of benzyllithium.[48]

(98)
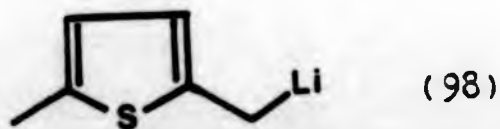
Butyllithium was added to a solution of 2,5-dimethyl-thiophen in THF containing N,N,N,N-tetramethylethylenediamine at -20°C. After 5 minutes the mixture was cooled to -78°C and the solution was added to the furanaldehyde (84) under N_2. After 10 minutes, the mixture was allowed to warm up to room temperature and was stirred for 20 minutes. No product was obtained. The starting furan has been consumed, but no significant products were observed on tlc under uv light. Further attempts using higher or lower temperatures and different reaction times also met with no success.

A report[49] was later found which showed that little of compound (98) is in fact formed in the reaction of butyllithium with 2,5-dimethylthiophen.

An alternative route to the alcohol (96) is via the condensation of 5-methylthiophen-2-magnesium bromide (99) and methyl 3-[5-(1,2-epoxyethyl)-2-furyl]acrylate (100) (Scheme 17).

(99)   (100)   Scheme 17
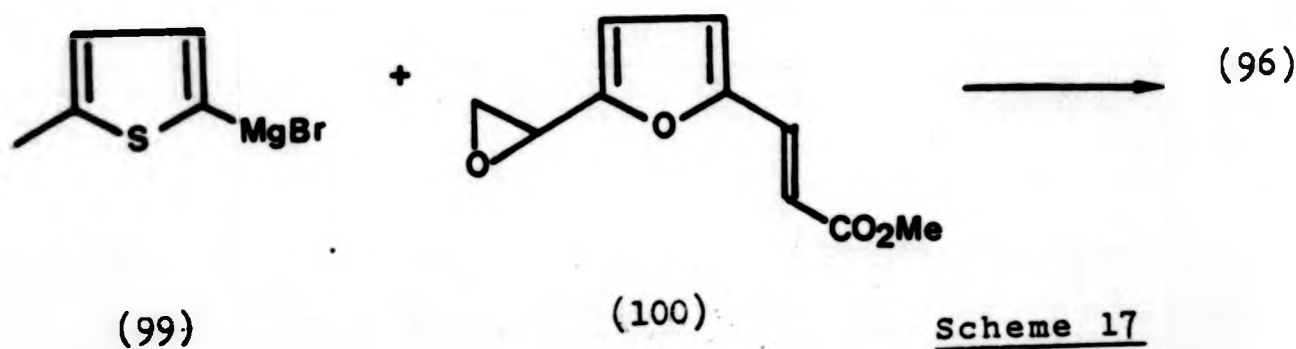
Attempts to synthesise epoxide (100) from the furan aldehyde (84) using trimethylsulphonium iodide/sodium hydride resulted in the formation of a black solid from which the starting aldehyde was recovered in 50% yield.

It would appear that the aldehyde is particularly unstable to basic/nucleophilic reagents. Diazomethane was

considered as a possible epoxidising agent. However the literature[50] suggests that only the corresponding methylketones are formed when furylaldehydes are reacted with diazomethane.

Another possible route to the intermediate ketone (97) is the direct acylation of methyl-2-furyl acrylate (101) with a derivative of 5-methylthiophen acetic acid (102), (Scheme 18).

Mixed anhydrides of toluene-4-sulphonic acid and carboxylic acids are known to acylate furans in high yields.[51] Furan (101) is readily available from furfural via a Stobbe condensation with malonic acid[52], followed by esterification with diazomethane. Thiophen (102) may be obtained by the reaction of dimethyl diazomalonate with 2-methylthiophen followed by hydrolysis and decarboxylation.

(102)   +   (101) $\longrightarrow$ (97)
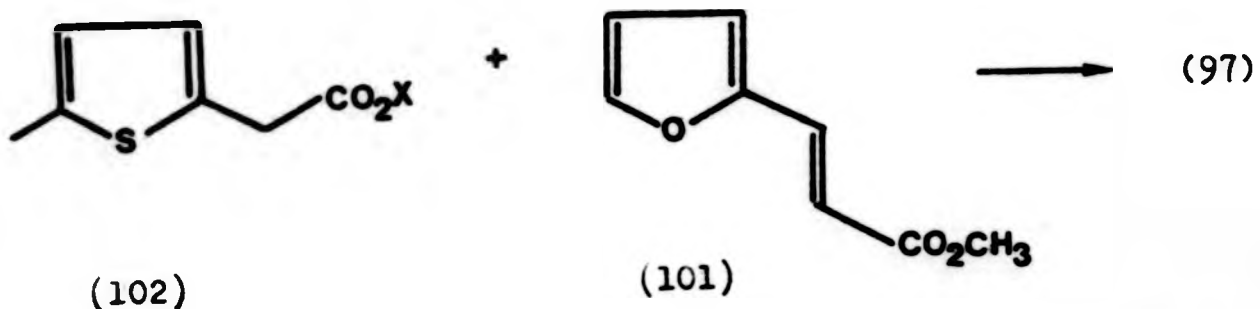
Scheme 18

In order to test the feasibility of using the mixed anhydride of toluene-4-sulphonic acid as the acylating agent, phenylacetic-4-toluenesulphonic anhydride (103) was reacted with furan in refluxing anhydrous toluene (Scheme 19).

(103)   (104)
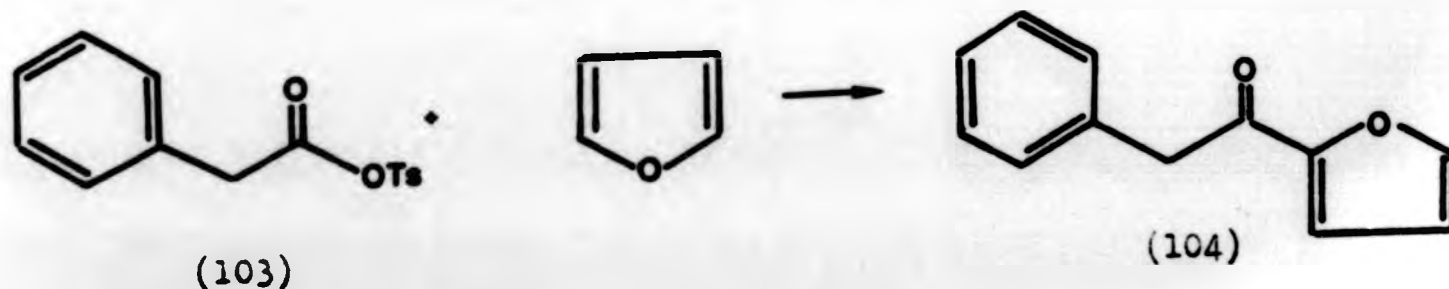
Scheme 19

The published method for the preparation of the mixed anhydrides requires the reaction of excess of the carboxoyl chloride with anhydrous 4-toluenesulphonic acid followed by the removal of the excess acid chloride under vacuum. These mixed anhydrides are unstable at the elevated temperatures required to remove 5-methylthiophen-2-acetylchloride under vacuum. A modified method was therefore adopted. Equivalent amounts of phenyl-acetylchloride and toluene sulphonic acid were reacted and then the mixture was added to a solution of furan in toluene. No product identifiable as the acylatedfuran (104) was formed.

Mixed anhydrides of trifluoroacetic acid are known to acylate furans and thiophens.[53] Phenylacetic acid was treated with trifluoroacetic anhydride at 100°C followed by a two-fold excess of furan. The reaction became very dark almost instantly. After 30 seconds the mixture was quenched with ice cold sodium bicarbonate solution and the mixture was extracted with diethyl ether. After chromatography the acylated furan (104) was obtained as a reddish oil in 80% yield. The ^{1}H nmr gave the correct spectrum for a 2-substituted furan, the infrared spectrum gave an absorption at 1670 cm^{-1} consistent with a furylketone and the mass spectrum gave the molecular ion at M^+ 186 with a base peak for the furylaldehyde ion $C_4H_4O.CO^+$, M^+ 95.

Methyl furylacrylate was prepared and using the same procedure as above was acylated with phenylacetic acid. The reaction time in this case was 3 minutes. The desired product (105) was obtained in 25% yield.

The ^{1}H nmr spectrum showed the expected AB quartets for the <u>trans</u>-propenoic acid (J_{AB}=16Hz) and for the 3,4-protons
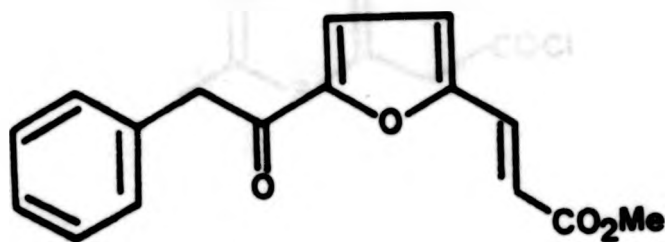
(105)

of the furan ($J_{3,4}$=4Hz). The mass spectrum gave the molecular ion at M^+ 270 with the base peak at M^+ 179.

Attempts to optimise this reaction using trifluoro-acetic anhydride as the solvent (i.e. a 10-fold excess) gave no acylated product. The use of various solvents at lower reaction temperatures for longer periods gave no improvement.

5-Methylthiophen-2-acetic acid (102 X=H) was prepared from dimethyl 5-methylthiophen-2-malonate, and was reacted with trifluoroacetic anhydride and the furan (101) in the same way as phenylacetic acid. After workup and chromatography the desired product (97) was obtained, but only in ∿ 1% yield.

The ^{1}H nmr spectrum showed signals at 7.5-6.3δ, 3 AB-quartets with J=4Hz, 16Hz and 9Hz, a signal for the methylene group at 4.15δ and signals for the methyl ester and methyl side chain at 3.7δ, and 2.34δ respectively. The infrared spectrum showed absorptions at 1710, 1670, and 1640 cm^{-1}, and the mass spectrum gave a molecular ion at M^+ 290.

In an effort to produce workable amounts of the acylated furan (97), 5-methylthiophen-2-acetylchloride (106) was prepared by the method advocated for activated methylene compounds.[54]

(106)
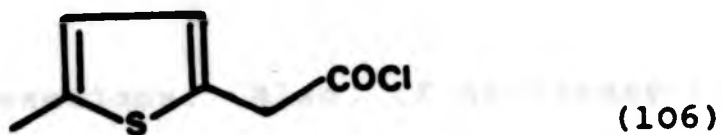
It was then reacted with methyl 2-furylacrylate under various conditions. Benzene and 1,2-dichloroethane were used as solvents, with tin-(IV)-chloride[55] and zinc chloride[56] as catalysts. None of the desired product was obtained in any of the reactions. The reactants invariably decomposed under the reaction conditions to form a black tar.

In order to test whether the α-diazothiophen system would yield the desired 2-ene-yne side chain as hoped (Scheme 20), it was decided to prepare a model diazoketone which would behave similarly to compound (93). Thus 5-methylthiophen-2-acetic acid was reacted with trifluoroacetic anhydride followed by furan.
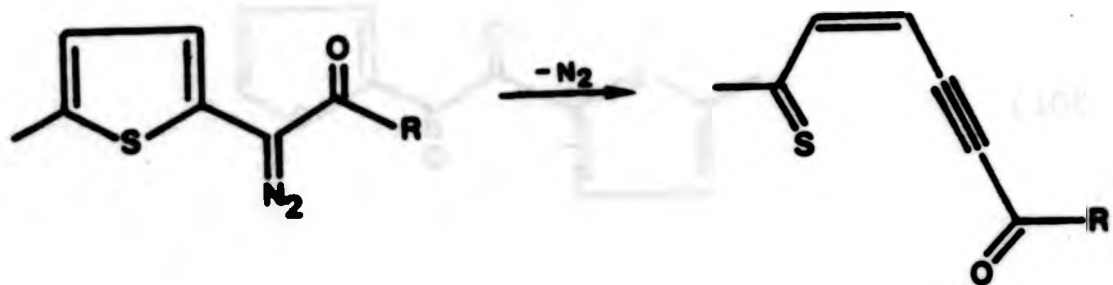
Scheme 20

After chromatography the desired furylketone (107) was obtained in 18% yield.

(107)
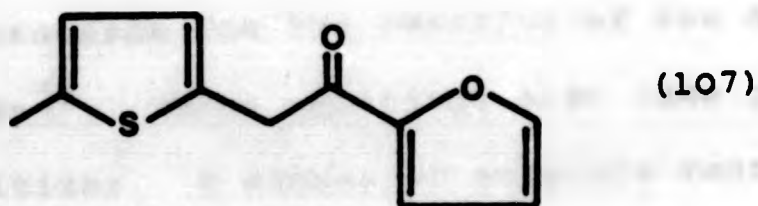
Ketone (107) closely resembles the desired ketone (97) and would be expected to behave similarly in the diazo-transfer

and rearrangement reactions. Also, if necessary it could be
elaborated to the acrylic ester.

Compound (107) was treated with a slight excess of
4-carboxybenzenesulphonylazide and triethylamine in acetonitrile
overnight. Tlc showed a yellow compound had formed which ran
slightly slower than the starting ketone. ^{1}H nmr of the purified
product showed a similar spectrum to that of the starting ketone
with a shifting of the thiophen AB-quartet and loss of the methy-
lene signal. The infrared spectrum however contained no diazo
or acetylenic absorptions. It did however contain an adsorption
at 1640 cm^{-1}. The mass spectrum gave a molecular ion at M$^+$ 220
with a base peak at M$^+$ 125. It was therefore concluded that the
oxidized.product (108) had been formed.
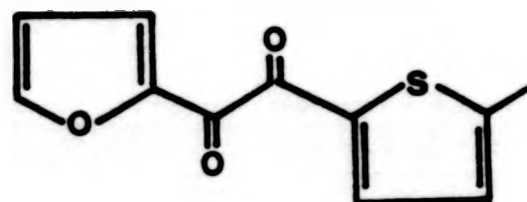
(108)

The photolysis of 2-diazo-3-butanone in the presence
of oxygen and a sensitizer gives biacetal in 55% yield.[57] This
type of reaction proceeds via the reaction of the diazo compound
with singlet oxygen[58]. These reactions also take place in the
absence of a sensitizer. A number of possible routes to the
dione are shown in (Scheme 21).

Since the diazo-transfer reaction on compound (107)
was conducted in air in daylight it seems likely that this
mechanism also accounts for the formation of compound (108).

R–C(=O)–C(N₂)–R →[¹O₂]→ ... →[−N₂O]→ R–C(=O)–C(=O)–R

Scheme 21

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14. This work is currently being carried out by Dr. H. S. Krepha at Imperial College, London.

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59. Since the completion of this work an X-ray structure analysis has been carried out on this compound which shows it to be di-*t*-butyl 3-*t*-butylbicyclo[3,1,0]-hex-2-ene-4-sulphonium bis(*t*-butoxycarbonyl)methylide (20). Details may be obtained from Dr. A.E.A. Porter, Department of Chemistry, University of Stirling, Scotland.

EXPERIMENTAL

General

^{1}H nmr spectra were recorded as dilute solutions in the given solvent on a Perkin-Elmer R24 at 60 MHz or a Perkin-Elmer R32 at 90 MHz. ^{13}C and variable temperature nmr were recorded on a Brüker WP80, the accuracy of the temperature settings were checked with a thermocouple inserted into the nmr tube. 250 MHz ^{1}H nmr spectra were recorded on a Brüker WM250.

The iterative fit of trial nmr spectra to those obtained experimentally was carried out using the program PANIC 800425 and an Aspect 2000 Computer from Brüker Spectrospin, or a program developed by Dr. H. Rzepha, Department of Chemistry, Imperial College, London, and the Cyber 180/885 Computer at Imperial College Computer Centre. The synthetic line shapes used in the variable temperature nmr work were obtained using the program DNMR 3H, W. Stempfle, J. Klein, and E. G. Hoffman, Quantum Chemistry Program Exchange, 1977, 11, 450, and the Cyber 180/855 Computer at Imperial College Computer Centre. Infrared spectra were recorded on a Perkin-Elmer 577 Grating Infrared Spectrophotometer. Melting points were recorded on a Köfler block and are uncorrected. Analytical tlc was carried out using glass plates coated with Merck Kieselgel GF254 (Type 60) and column chromatography was carried out using Merck Kieselgel HF254 in an adaption of the pressure method of Still.[1]

3-Methylthiophenium bis(methoxycarbonyl)methylide

Dimethyl diazomalonate (0.79g, 5mMole) was added to a solution of rhodium-(II)-acetate (5mg) in 3-methylthiophen (5ml). After 21 days at 0°C the excess 3-methylthiophen was evaporated off under vacuum at ambient temperature. The residue was chromatographed on 50g of silica eluted with 1-5% ethanol in dichloromethane. The appropriate fractions were combined and the solvent was evaporated at 30°C. The resultant yellow oil was taken up in ethanol (2ml) and stored at 0°C. After 4 days the crystalline product was filtered and dried under vacuum. Yield 0.58g (25%), m.p. (ethanol) 93-96°C.

ν_{max} (KBr) 3100,2940,1650, and 1430 cm^{-1}.

δ(CDCl$_3$) 7.3-6.5 (3H,m); 3.6 (6H,s); and 2.25 (3H,d,J = 1 Hz).

Found: M$^+$, 228.0450. C$_{10}$H$_{12}$O$_4$S requires M. 228.0456.

3-Hydroxymethylthiophenium bis(methoxycarbonyl)methylide

Dimethyl diazomalonate (0.79g, 5mMole) was added to a solution of rhodium-(II)-acetate (5mg) in 3-hydroxymethyl-thiophen (5ml). After 8 days at 0°C, the whole reaction mixture was chromatographed on 50g of silica eluted with a gradient of 0-10% ethanol in dichloromethane. The fractions containing the ylid were evaporated at room temperature to yield a yellow oil. The oil was taken up in ethanol (2 ml) and stored at 0°C for 3 days. The resultant suspension was filtered and the crystalline product dried under vacuum. Yield 0.186g (15%), m.p. (ethanol) 102-106°C.

ν_{max} (KBr) 3420,3080,1620, and 1440 cm^{-1}.

δ(DMSO d^6) 7.5-6.9 (3H,m); 4.4 (2H,s); and 3.45 (6H,s).

Found: M$^+$, 244.0399. C$_{10}$H$_{12}$O$_5$S requires M. 244.0406.

Preparation of the 3-substituted thiophens

3-Bromothiophen was prepared by the method of Gronowitz et al.[3] 3-Aminomethylthiophen was prepared from 3-bromothiophen via reduction[4] of 3-cyanothiophen[5]. 3-Hydroxymethylthiophen was prepared from 3-cyanothiophen via reduction[6] of thiophen-3-carboxylic acid[7].

Preparation of thiophenium ylids (general)

The remainder of the thiophenium ylids were all prepared by the same general method. Dimethyl diazomalonate (1.58g, 10mMole) was added dropwise to a stirred solution of rhodium-(II)-acetate (10mg) in the thiophen (10ml). The reaction was followed by observing the disappearance of the diazoband (ir). After the reaction was complete the ylid was filtered from the reaction mixture and recrystallized.

Thiophenium bis(methoxycarbonyl)methylide

After 4 days. Yield 2.0g (93%), m.p. (acetonitrile) 144-146°C (lit.[8] 145-146°C).

ν_{max} (CHCl$_3$) 1650,1435, and 1330 cm^{-1}.

δ(CDCl$_3$) 7.9 (4H,m); and 3.65 (6H,s).

Thiophenium bis(ethoxycarbonyl)methylide

After 5 days. Yield 2.2g (90%), m.p. (acetonitrile) 110-111°C (lit.[8] 111-111.5°C).

ν_{max} (CCl$_4$) 1690,1660, and 1440 cm^{-1}.

δ(CDCl$_3$) 7.1 (4H,m); 4.05 (4H,q); and 1.2 (6H,t).

2-Bromothiophenium bis(methoxycarbonyl)methylide

After 7 days the excess thiophen was removed under vacuum (T ≤ 30°C) prior to recrystallisation.

Yield 2.1g (73%), m.p. (acetonitrile) 135-148°C, (lit.[8] 138-148°C).

ν_{max} (KBr) 1680,1660,1435, and 1330 cm^{-1}.

δ(CDCl$_3$) 7.2 (1H,m); 7.1 (2H,m); and 3.7 (6H,s).

2-Hydroxymethylthiophenium bis(methoxycarbonyl)methylide

After 14 days. Yield 0.73g (30%), m.p. (acetonitrile) 133-134°C (lit.[8] 133-133.5°C).

ν_{max} (KBr) 3400 br, 1675,1630, and 1435 cm^{-1}.

δ(CDCl$_3$) 7.0 (2H,m); 6.85 (1H,m); 4.55 (2H,d,J = 6HZ); 3.65 (6H,s); and 3.45 (1H,t,J = 6Hz).

2-Methylthiophenium bis(methoxycarbonyl)methylide

After 5 days. Yield 2.0g (89%), m.p. (ethyl acetate) 145.5-147°C (lit.[8] 146-146.5°C).

ν_{max} (CCl$_4$) 1680,1650,1435, and 1330 cm^{-1}.

δ(CDCl$_3$) 7.1 (1H,m); 6.85 (2H,m); 3.67 (6H,s); and 2.25 (3H,s).

2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide

After 3 days. Yield 2.5g (90%), m.p. (acetonitrile) 174-175°C (lit.[8] 174-174.5°C).

ν_{max} (KBr) 1690,1650,1435, and 1330 cm^{-1}.

δ(CDCl$_3$) 6.9 (2H,s); and 3.7 (6H,s).

2,5-Dichlorothiophenium bis(ethoxycarbonyl)methylide

After 2 days. Yield 2.6g (82%), m.p. (acetonitrile) 111-111.5°C (lit.[8] 111-111.5°C).

ν_{max} 1690,1650, and 1370 cm^{-1}.

δ(CDCl$_3$) 6.9 (2H,s); 4.1 (2H,q,broad); and 1.3 (3H,t,broad).

2,5-Dibromothiophenium bis(methoxycarbonyl)methylide

After 2 days. Yield 1.7g (46%), m.p. (acetonitrile) 189-190°C (lit.[8] 190-190.5°C).

ν_{max} 1690-1660,1440, and 1330 cm^{-1}.

δ(CDCl$_3$) 7.1 (2H,s); and 3.75 (6H,s).

2,5-Dimethylthiophenium bis(methoxycarbonyl)methylide

After 5 days. Yield 1.9g (80%), m.p. (benzene) 125-126.5°C.

ν_{max} 1640,1520,1440, and 1290 cm^{-1}.

δ(CDCl$_3$) 6.6 (2H,s); 3.7 (6H,s); and 2.2 (6H,s).

Found: C, 54.56; H,5.98.

$C_{11}H_{14}O_4S$ requires C, 54.55; H,5.78.

Preparation of dimethyl thiophen-2-malonate[8]

Dimethyl diazomalonate (12.64g 80mMole) was added dropwise to a stirred refluxing solution of rhodium-(II)-acetate (10mg) in thiophen over a period of 2 hours. After a further 30 minutes the excess thiophen was evaporated and the residue was chromatographed on 150g of silica eluted with 9:1 40-60 petroleum ether/ethyl acetate. Dimethyl thiophen-2-malonate was obtained in 65% yield.

ν_{max} (film) 2955,1735,1432, and 1240 cm^{-1}.

δ(CDCl$_3$) 7.4-6.8 (3H,m); 4.95 (1H,s); 3.7 (6H,s).

Reaction of dimethyl thiophen-2-malonate with dimethyl diazomalonate

A solution of dimethyl thiophen-2-malonate (9.9g 50mMole), dimethyl diazomalonate (3.16g 20mM) and rhodium-(II)-acetate (10mg) in toluene (10ml) was stirred at room temperature. After six weeks the diazoband (ir) had disappeared. A

further 3.16g (20mM) of dimethyl diazomalonate was added and
stirring was continued until the diazoband again disappeared
(3 weeks).

The toluene was evaporated under vacuum and
the residue was chromatographed on 150g of silica eluted 3:7
ethyl acetate/petroleum ether (40-60). The first compound
eluted was dimethyl thiophen-2-malonate 4.3g (43%). The
next compound eluted was tetramethyl 1,3,5-hexatriene-1,1,6,6-
tetracarboxylate (0.53g, 4.3%). m.p. (ethanol) 137-143°C
(lit.[9] 153°C).

ν_{max} (KBr) 2880,2310,2260,1725,1620, and 1440 cm^{-1}.

δ(CDCl$_3$) 7.25 (4H,AA'BB' quartet) $J_{AB} = A'B' = 11.81$,
$J_{AB'} = J_{A'B} = -0.77$, $J_{AA'} = 0.176$, $J_{BB'} = 14.85$);

3.88 (6H,s); and 3.85 (6H,s).

Found: M$^+$ 312.0824. C$_{14}$H$_{16}$O$_8$ requires M 312.0846.

The final compounds to be eluted were a mixture of
tetramethyl thiophen-2,3-dimalonate and tetramethyl
thiophen-2,5-dimalonate. Yield 5.6g (41%). On recrystallization
from ethanol a mixture was again obtained. However, on standing
the mother liquors yielded tetramethyl thiophen-2,3-dimalonate
in a pure form. m.p. (ethanol) 90-91°C.

ν_{max} (KBr) 2970,1760,1730,1720, and 1430 cm^{-1}.

δ(CDCl$_3$) 7.2 (2H,q,J = 6Hz); 5.05 (1H,s); 4.9 (1H,s);

3.75 (6H,s), and 3.73 (6H,s).

Found: M$^+$ 344.0565. C$_{14}$H$_{16}$O$_8$S requires M 344.0566.

Dimethyl 6-bromo-2(H)-thiopyran 2,2-dicarboxylate

2-Bromothiophenium bis(methoxycarbonyl)methylide
(0.488g) was stirred in refluxing toluene until no more ylid
remained (tlc 2:1 petroleum ether (40-60/ethyl acetate), (2h).
The toluene was evaporated and the residue was chromatographed
on 40g of silica to yield 0.44g (90%) of a red oil.

ν_{max} (film) 2950,1740,1540, and 1430 cm^{-1}.

δ(CDCl$_3$) 6.5-5.8 (3H,m ABX $J_{4,5}$ = 6Hz, $J_{4,7}$ = 1.5Hz,
$J_{5,7}$ = 10Hz); and 5.75 (6H,s).

Found: M$^+$ 291.9413. C$_9$H$_9$BrO$_4$S requires M 291.9406.

Thermolysis of 2,5-dichlorothiophenium bis(methoxycarbonyl)-methylide in the presence of 2-methylthiophen

A solution of 2,5-dichlorothiophenium bis(methoxy-
carbonyl)methylide (1g, 3.5mMole) in 2-methylthiophen (9ml)
containing copper-(II)-acetylacetonate (10mg) was stirred and
heated at 95-100°C for 16 hours. The excess methylthiophen
was evaporated off at 40°C and the residue chromatographed
on 30g of silica eluted with 3:17 ethyl acetate/petroleum ether
(40-60). The fractions containing the major product were
combined and evaporated to yield 0.23g (29%) of dimethyl
2-methylthiophen-5-malonate[8].

ν_{max} (film) 2960,1750, and 1440 cm^{-1}.

δ(CDCl$_3$) 6.7 (2H,q); 4.8 (1H,s); 3.7 (6H,s), and 2.4 (3H,s).

Benzyl(methyl) malonate

Malonic acid (26g 0.25 Mole) and benzyl alcohol
(27g 0.25 Mole) was dissolved in dichloromethane (150ml).
Hydrogen chloride gas was bubbled through the solution until
it was saturated and it was then left stirring overnight.

The solution was washed with water (3 x 100ml), and then extracted with sodium bicarbonate solution until the extracts were basic. The combined extracts were acidified and extracted with diethyl ether (2 x 100ml). The ether extracts were dried (MgSO$_4$) and evaporated to yield 7.2g (15%) of benzyl(hydrogen) malonate.

Without further purification the benzyl(hydrogen) malonate was dissolved in diethyl ether (50ml) and treated with diazomethane (3g, 71mMole) in diethyl ether, at 0°C. The solution was allowed to stand for 1h, and was then treated with glacial acetic acid to destroy the residual diazomethane. The ether solution was then washed with sodium bicarbonate solution (20ml) and was dried over magnesium sulphate. The filtered solution was evaporated to dryness to yield 7.5g (97%) of benzyl(methyl) malonate[10].

ν_{max} (film) 3040,2960,1960,1760,1740,1500,1450, and 1440 cm^{-1}.

δ(CDCl$_3$) 7.3 (5H,s); 5.1 (2H,s); 3.6 (3H,s), and 3.45 (2H,s). m/e 208.

Benzyl(methyl) diazomalonate[10]

A mixture of benzyl(methyl) malonate (7g, 34mMole), 4-toluenesulphonylazide (6.7g, 34mMole), and triethylamine (4.8, 3mMole) in toluene (30ml) was stirred for 3 days. The mixture was then filtered to remove 4-toluenesulphonamide and the solvent was evaporated. The residue was chromatographed on 150g of silica eluted with 4:1 petroleum ether (40-60)/ ethyl acetate. The fractions containing the diazo-compound were combined and the solvent evaporated off. Yield 5.4g (71%).

ν_{max} (film) 3030,2600,2130,1740, and 1700 cm^{-1}.

δ(CDCl$_3$) 7.4 (5H,s); 5.3 (2H,s), and 3.9 (3H,s).

Found: M$^+$ 234.0649. C$_{11}$H$_{10}$N$_2$O$_4$ requires 234.0641.

Thiophenium benzyloxycarbonyl(methoxycarbonyl)methylide

A mixture of freshly distilled thiophen (10ml), benzyl(methyl) diazomalonate (2g 8.5mMole) and rhodium-(II)-acetate was stirred for 24 hours. The excess thiophen was evaporated off and the residue was chromatographed on 40g of silica eluted with 1% ethanol in dichloromethane. The fractions containing the ylid were combined and evaporated.

Yield 1.4g (57%) m.p. (ethanol) 114-115°C.

ν_{max} (KBr) 3100,2950,1680,1640,1590, and 1500 cm^{-1}.

δ(CDCl$_3$) 7.3 (5H,s); 7.0 (4H,m); 5.1 (2H,s); 3.6 (3H,s).

Found: C, 62.23; H, 5.12. C$_{15}$H$_{14}$O$_4$S requires C, 62.07; H, 4.82.

Methyl(4-nitrobenzyl) malonate

Potassium hydroxide (46g 0.82 Mole) in anhydrous methanol was added dropwise to a solution of dimethyl malonate (100g 0.75 Mole) in a mixture of methanol (250ml) and diethyl ether (100ml). The resultant suspension was stirred for 1h and filtered. The solid was washed with diethyl ether then dissolved in water (140ml), cooled to 0°C and acidified with 10 molar hydrochloric acid (82ml). The aqueous solution was then extracted with diethyl ether (4 x 100ml), the ether extracts were dried over magnesium sulphate and the solvent was evaporated off. The residue was distilled to yield 21g (23%) of methyl(hydrogen) malonate b.p. 85-90°C (0.2mm Hg) (lit.[11] 84°C. 18mm Hg).

ν_{max} (film) 3500-2900 broad, and 1740 cm^{-1}.

δ(CDCl$_3$) 11.2 (1H,s); 3.7 (3H,s), and 3.4 (2H,s).

Thiophenium benzyloxycarbonyl(methoxycarbonyl)methylide

A mixture of freshly distilled thiophen (10ml), benzyl(methyl) diazomalonate (2g 8.5mMole) and rhodium-(II)-acetate was stirred for 24 hours. The excess thiophen was evaporated off and the residue was chromatographed on 40g of silica eluted with 1% ethanol in dichloromethane. The fractions containing the ylid were combined and evaporated.

Yield 1.4g (57%) m.p. (ethanol) 114-115°C.

ν_{max} (KBr) 3100,2950,1680,1640,1590, and 1500 cm^{-1}.

δ(CDCl$_3$) 7.3 (5H,s); 7.0 (4H,m); 5.1 (2H,s); 3.6 (3H,s).

Found: C, 62.23; H, 5.12. C$_{15}$H$_{14}$O$_4$S requires C, 62.07; H, 4.82.

Methyl(4-nitrobenzyl) malonate

Potassium hydroxide (46g 0.82 Mole) in anhydrous methanol was added dropwise to a solution of dimethyl malonate (100g 0.75 Mole) in a mixture of methanol (250ml) and diethyl ether (100ml). The resultant suspension was stirred for 1h and filtered. The solid was washed with diethyl ether then dissolved in water (140ml), cooled to 0°C and acidified with 10 molar hydrochloric acid (82ml). The aqueous solution was then extracted with diethyl ether (4 x 100ml), the ether extracts were dried over magnesium sulphate and the solvent was evaporated off. The residue was distilled to yield 21g (23%) of methyl(hydrogen) malonate b.p. 85-90°C (0.2mm Hg) (lit.[11] 84°C. 18mm Hg).

ν_{max} (film) 3500-2900 broad, and 1740 cm^{-1}.

δ(CDCl$_3$) 11.2 (1H,s); 3.7 (3H,s), and 3.4 (2H,s).

Dicyclohexylcarbodiimide (8g 39mMole) in dichloro-methane (50ml) was added over 10 minutes to a stirred solution of methyl(hydrogen) malonate (5g 42mMole) and 4-nitrobenzyl alcohol (6g 39mMole) in dichloromethane (100ml). After 20 hours the mixture was filtered to remove dicyclohexylurea and evaporated to dryness. The brown crystalline solid obtained was chromatographed on 100g of silica eluted with 4:1 petroleum ether (40-60)/ethyl acetate. The fractions containing the ester were evaporated to dryness to yield 8.4g (85%) of methyl(4-nitrobenzyl) malonate. m.p. (ethyl acetate) 66-68°C.

ν_{max} (KBr) 2950,1840,1730,1600,1500, and 1425 cm^{-1}.

δ(CDCl$_3$) 7.9 (4H,q); 5.3 (2H,s); 3.75 (3H,s), and 3.5 (2H,s).

Found: C, 52.02; H, 4.58; N, 5.26. C$_{11}$H$_{11}$NO$_6$ requires C, 52.17; H, 4.35; N, 5.53.

Methyl(4-nitrobenzyl) diazomalonate

A mixture of methyl(4-nitrobenzyl) malonate (7.6g 30mMole), triethylamine (2.2ml, 30mMole), and 4-toluenesulphonylazide (5.9g, 30mMole) in toluene (100ml) was stirred for 48 hours. The toluene was then evaporated and the mixture was taken up in dichloromethane. The bulk of the 4-toluenesulphonamide was removed by filtration of the solution through 25g of silica. The dichloromethane was then evaporated and the residue chromatographed on 150g of silica eluted with 2:1 petroleum ether (40-60)/ethyl acetate. The fractions containing the diazocompound were combined and evaporated to dryness. The residue was then extracted with water for 5 hours in a Soxhlet apparatus to remove residual

4-toluenesulphonamide.

Yield 4.48g (54%), m.p. (ethyl acetate) 97-99.5°C.

ν_{max} (KBr) 2950,2140,1740,1700,1600, and 1525 cm^{-1}.

δ(CDCl$_3$) 7.9 (4H,q); 5.4 (2H,s), and 3.8 (3H,s). M$^+$, 279.

Found: C, 47.04; H, 3.16; N, 15.10. C$_{11}$H$_9$N$_3$O$_6$ requires
C, 47.31; H, 3.23; N, 15.05.

Thiophenium methoxycarbonyl (4-nitrobenzyloxycarbonyl)methylide

Methyl(4-nitrobenzyl) diazomalonate (1.39g, 5mMole)
was dissolved in thiophen (5ml) containing rhodium-(II)-acetate
(5mg). The solution was stirred at room temperature until the
diazoband (2140 cm^{-1}) had disappeared (6 days). The excess
thiophen was evaporated at room temperature and the oily solid
remaining was washed with diethyl ether and dried.

Yield 0.6g (36%), m.p. (ethanol) 120.5-122°C.

ν_{max} (KBr) 3080,2940,1710,1630,1600, and 1510 cm^{-1}.

δ(CDCl$_3$) 7.2 (4H,m); 7.0 (4H,m); 5.1 (2H,s); and 3.6 (3H,s).

Found: C, 53.84; H, 4.03; N, 4.20. C$_{15}$H$_{13}$NO$_6$S requires
C, 53.73; H, 4.18; N, 4.18.

Preparation of 1,2,3-triazole salts (general)

The 1,2,3-triazole salts were all prepared by the
same general method. Dimethyl diazomalonate (1.58g 10mMole) was
added to a solution of the amine (20-50mMole) in toluene (10ml)
and the solution was stirred until the diazoband in the infrared
had disappeared. The product was then collected by filtration
and then recrystallized.

1-(2-Thienylmethyl)-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole 2-thienylmethylammonium salt

Yield 2.36g (66%), m.p. (acetonitrile/methanol) 160-161°C (dec).

ν_{max} (KBr) 3650-3250 broad, 3150-2700 broad, 1690,1640,1610, 1520, and 1460 cm^{-1}.

δ(DMSO d^6) 8.7 (3H,broad); 7.5-7.2 (3H,m); 7.1-6.8 (3H,m); 5.2 (2H,s); 4.25 (2H,s); and 3.6 (3H,s).

Found: C, 47.46; H, 4.61; N, 15.95. $C_4H_{16}N_4O_3S_2$ requires C, 47.72; H, 4.55; N, 15.91.

1-Butyl-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole butylammonium salt

Yield 2.22g (82%), m.p. (ethyl acetate) 111-113°C.

ν_{max} (KBr) 3200-2400 broad, 1690,1570,1460, and 1415 cm^{-1}.

δ(CDCl$_3$) 8.4 (3H,br,s); 3.9 (2H,m); 3.65 (3H,s); 3.0 (2H,t); 2.0-1.2 (8H,m), and 1.1-0.8 (6H,m).

Found: C, 52.91; H, 9.07; N, 20.92. $C_{12}H_{24}N_4O_3$ requires C, 52.95; H, 8.82; N, 20.59.

1-Benzyl-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole benzylammonium salt

Yield 2.68g (84%), m.p. (ethanol) 153-156°C dec.

ν_{max} (KBr) 3200-2500 broad, 1960,1690,1580,1520,1460, and 1410 cm^{-1}.

δ(CDCl$_3$) 7.2 (5H,s); 7.1 (5H,s); 5.05 (2H,s); 3.95 (2H,s). and 3.7 (3H,s).

Found: C, 63.49; H, 5.89; N, 16.66. $C_{18}H_{20}N_4O_3$ requires C, 63.53; H, 5.88; N, 16.47.

1-(3-Thienylmethyl)-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole 3-thienylmethylammonium salt

Yield 1.24g (70%), m.p. (acetonitrile) 160-162° dec.

ν_{max} (KBr) 3200-2500 broad, 1690,1645,1620,1550,1460,1410, and 1320 cm^{-1}.

δ(DMSO d^6) 7.65 (3H,broad,s); 7.4-6.7 (6H,m); 4.8 (2H,s); 3.85 (2H,s), and 3.5 (3H,s).

Found: C, 47.52; H, 4.45; N, 16.06. $C_{14}H_6N_4O_3S_2$ requires C, 47.59; H, 4.82; N, 15.86.

1-(2-Hydroxyethyl)-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole 2-hydroxyethylammonium salt

Yield 2.45g (98.7%), m.p. (ethanol) 119-124°C dec.

ν_{max} (KBr) 3500-2500 broad, 1700,1630,1580,1530, and 1450 cm^{-1}.

δ(DMSO d^6) 5.5 (3H,broad,s); 3.7-3.2 (11H,m).

Found: C, 38.66; H, 6.67; N, 22.84. $C_8H_8N_4O_5$ requires C, 38.71; H, 6.45; N, 22.58.

Preparation of hydroxy-1,2,3-triazoles (general)

In general the hydroxy-1,2,3-triazoles were prepared by stirring the 1,2,3-triazole salts (1g) in 1 molar hydrochloric acid (5ml) for a few minutes followed by extraction with dichloromethane (2 x 10ml). The extracts were combined, dried over magnesium sulphate and the solvent evaporated. The yields were quantitative.

1-(2-Thienylmethyl)-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole

m.p. (dichloromethane) 104-106°C.

ν_{max} (KBr) 2950,1725,1600,1530,1460,1410, and 1330 cm^{-1}.

δ(CDCl$_3$/DMSO d^6) 7.3-6.9 (3H,m); 5.5 (2H,s); and 3.9 (3H,s).

Found: M$^+$ 239.0374. $C_9H_9N_3O_3S$ requires 239.0365.

1-(3-Thienylmethyl)-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole

Gum. ν_{max} (KBr) 3090,2960,2500-2300 broad,2000-1800 broad, 1720,1600,1530, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.3-7.0 (3H,m); 5.3 (2H,s); 4.3 (1H,s); and 3.85 (3H,s).

Found: M$^+$ 239.0367. C$_9$H$_9$N$_3$O$_3$S requires 239.0365.

1-Butyl-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole

Oil. ν_{max} (CHCl$_3$) 3300 broad,2980,1720,1590,1550, and 1460 cm^{-1}.

δ(CDCl$_3$) 4.2 (3H,m); 3.65 (3H,s); 3.4 (2H,q); and 2.0-0.7 (5H,m).

Found: M$^+$ 199.0953. C$_8$H$_{13}$N$_3$O$_3$ requires 199.0957.

1-Benzyl-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole

m.p. (dichloromethane) 109-111°C.

ν_{max} (KBr) 3010,1690,1600,1530,1450, and 1290 cm^{-1}.

δ(CDCl$_3$) 7.2 (5H,s); 5.25 (2H,s); and 3.8 (3H,s).

Found: M$^+$ 233.0791. C$_{11}$H$_{11}$N$_3$O$_3$ requires 233.0800.

1-(2-Hydroxyethyl)-4-methoxycarbonyl-5-hydroxy-1,2,3-triazole

This triazole was obtained by passing an aqueous solution of the triazole salt through strongly acidic ion exchange resin, followed by evaporation of the water.

m.p. (water) 109-114°C.

ν_{max} (KBr) 3320 broad,2970,1720,1660,1600,1520, and 1450 cm^{-1}.

δ(DMSO d^6) 4.3 (2H,t); 3.95 (2H,t); and 3.9 (3H,s).

Found: M$^+$ 187.0585. C$_6$H$_9$N$_3$O$_4$ requires 187.0593.

Preparation of diazoacetamides (general)

The diazoacetamides were prepared from the corresponding 5-hydroxy-1,2,3-triazoles by warming them at 100°C for 2-3 minutes. The resultant liquids were distilled at high

vacuum (0.1-0.05τ) in a Kugelrohr distillation apparatus at an oven temperature of 130-180°C. There was some decomposition in all cases.

N-(2-thienylmethyl)-2-methoxycarbonyl-2-diazoacetamide

Yield 42%.

ν_{max} (film) 3350,3100,2980,2140,1700,1650,1530, and 1440 cm^{-1}.
δ(CDCl$_3$) 8.1 (1H,broad,s); 7.3 (1H,m); 7.0 (2H,m);
4.8 (2H,d); and 3.9 (3H,s). m/e 211 5.2%, 181 75.7%,
97 100%.

N-(3-thienylmethyl)-2-methoxycarbonyl-2-diazoacetamide

Yield 47%.

ν_{max} (film) 3350,3100,2980,2140,1690,1640,1540, and 1440 cm^{-1}.
δ(CDCl$_3$) 7.9 (1H,broad,s); 7.2 (3H,m); 4.5 (2H,d); and 3.8
(3H,s). m/e 211 35%, 181 75.0%, 97 100%.

N-butyl-2-methoxycarbonyl-2-diazoacetamide

Yield 71%.

ν_{max} (film) 3360,2960,2140,1700,1660,1540,1440, and 1330 cm^{-1}.
δ(CDCl$_3$) 7.6 (1H,broad,s); 4.15 (1H,t); 3.8 (3H,s);
3.3 (2H,m); 1.5 (4H,m); and 0.9 (3H,m).
Found: M$^+$ 199.0950. C$_8$H$_{13}$N$_3$O$_3$ requires M 199.0952.

N-(2-hydroxyethyl)-2-methoxycarbonyl-2-diazoacetamide

Yield 53%.

ν_{max} (film) 3350,2960,2140,1700,1640,1540, and 1440 cm^{-1}.
δ(CDCl$_3$) 8.0 (1H,broad,s); 3.9 (3H,s); 3.75 (2H,t);
and 2.85 (1H,s).
Found: M$^+$ 187.0597. C$_6$H$_9$N$_3$O$_4$ requires 187.0594.

N-benzyl-2-methoxycarbonyl-2-diazoacetamide

Yield 57%.

ν_{max} (film) 3356,2950,2130,1690,1645,1525, and 1440 cm^{-1}.

δ(CDCl$_3$) 8.0 (1H,broad,s); 7.15 (5H,s); 4.45 (2H,d);
and 3.6 (3H,s).

Found: M$^+$ 233.0806. C$_{11}$H$_{11}$N$_3$O$_3$ requires M 233.0801.

Methyl-3-(5-formyl-2-furyl)prop-trans-2-enoate

Hydroxymethylfurfural[12] (10g, 79mMole) was
dissolved in a solution containing pyridine (32ml), malonic
acid (16.5g, 160mMole) and piperidine (1.2ml, 12mMole).
The mixture was stirred and heated for 90 min. at 80-85°C,
then refluxed for one hour. The solution was then allowed
to cool and the pyridine was evaporated. The residue was
treated with hydrochloric acid (5 molar) until strongly acid
and then cooled in ice for 2 hours. The resulting yellow
solid was filtered off, washed with water (4 x 15ml) and
dried at 60°C under vacuum. Yield 10.1g (76%) of
(hydroxymethylfuryl) acrylic acid.

The solid was dissolved in diethyl ether (100ml)
and treated with diazomethane (4.5g) in diethyl ether. The
solution was left standing overnight. The following day the
solvent was evaporated under reduced pressure and the
residue was chromatographed on 100g of silica eluted with
2:1 petroleum ether (40-60)/ethyl acetate. Yield 7.3g (67%)
of methyl hydroxymethylfurylacrylate.

The solid was dissolved in dry distilled chloroform
(300ml) and 3g of manganese dioxide was added. After 1 hour

the remaining manganese dioxide (27g) was added and the reaction mixture was then left stirring for 16 hours. Tlc showed approximately 20% of starting material remaining. A further 12g of manganese dioxide was added and the mixture was stirred for 2 days. The suspension was then filtered through celite and the solvent evaporated. The residue was sublimed at 100-110°C (3mm Hg). Yield 5.04g (68%), (35% overall). m.p. 93-98°C (lit.[12] 106-106.5).

ν_{max} (KBr) 3120,1710,1670,1640, and 1500 cm^{-1}.

δ(CDCl$_3$) 9.7 (1H,s); 7.45 (1H,d J=17Hz); 7.25 (H,d J=4Hz); 6.75 (1H,d J=4Hz); 6.6 (1H,d J=17Hz); and 3.8 (3H,s).

2-Furyl-benzylketone

· Phenylacetic acid (1g 7.4mMole) was heated in trifluoroacetic anhydride (2ml, 14mMole) for 5 minutes at 100°C. Furan (1ml, 14mMole) was then added in one portion. The reaction became dark red almost immediately, after 30 seconds ice cold saturated sodium bicarbonate solution was added. The mixture was stirred for 10 minutes and then extracted with diethyl ether (2 x 10ml). The ether extracts were washed with water (10ml) and then dried over magnesium sulphate. The filtered solution was evaporated down and the residue was chromatographed on 40g of silica eluted with 9:1 petroleum ether (40-60)/ethyl acetate. On evaporation 2-furyl-benzylketone[13] was obtained as a red oil.

Yield 1.1g (80%).

ν_{max} (film) 3110,2900,1640,1560, and 1460 cm^{-1}.

δ(CDCl$_3$) 7.55 (1H,m); 7.3 (5H,s); 7.2 (1H,m); 6.4 (1H,m); and 4.1 (2H,s).

Found: M^+ 186.0688. $C_{12}H_{10}O_2$ requires M 186.0681.

Methyl 2-furylacrylate

A mixture of redistilled furfuraldehyde (9.6g 0.1 Mole), malonic acid (20.8g, 0.2 Mole), piperidine (1ml, 10mMole) and pyridine (30ml) was heated for 90 minutes at 80-85°C then refluxed for one hour. The solution was allowed to cool and the pyridine was evaporated off. The residue was made strongly acid with hydrochloric acid (5 Molar) and was left standing at 0°C overnight. The resulting solid was filtered, washed with water and dried under vacuum. Yield 12.7g (92%), m.p. 135-140°C (lit.[14] 141°C).

δ(CDCl$_3$) 7.6 (1H,d J=16Hz); 7.55 (1H,m); 6.8 (1H,m); 6.5 (1H,m); and 6.3 (2H,d J=16Hz).

Without further purification the solid was dissolved in diethyl ether (100ml) and was treated with ethereal diazo-methane (4.5g). After 10 minutes glacial acetic acid (2ml) was added to the solution. After a further 10 minutes the solution was extracted with saturated sodium bicarbonate solution (3 x 50ml) and then dried over magnesium sulphate. The ethereal solution was evaporated and the residue was distilled under vacuum.

Yield 14.1g (80%), b.p. 83°C (0.5mm Hg), (lit.[14] 112°C 15mm).

ν_{max} (film) 3130,2960,1720,1640,1560,1490, and 1440 cm^{-1}.

δ(CDCl$_3$) 7.5 (1H,m); 7.3 (1H,d J=16Hz); 6.6 (2H,m); 6.45 (1H,m); and 6.3 (1H,d J=16Hz).

Methyl-2-(3-trans-propenoate)-5-(1-oxo-2-phenylethyl)furan

Phenylacetic acid (0.34g, 2.5mMole) was heated at 100°C in trifluoroacetic anhydride (0.5ml, 3.5mMole) for

5 minutes.   Methyl 2-furylacrylate (0.38g, 2.5mMole) was
then added in one portion.   After 3 minutes the dark reaction
mixture was quenched with saturated sodium bicarbonate solution
(3ml).   The mixture was stirred for 5 minutes and then extracted
with dichloromethane (2 x 10ml).   The dichloromethane solution
was washed with water (10ml), dried over magnesium sulphate
and evaporated to dryness.   The residue was chromatographed
on 20g of silica eluted with 3:17 ethyl acetate/petroleum
ether (40-60).   Methyl 2-furylacrylate was eluted first in
40% yield.   Methyl 2-(3-_trans_-propenoate)-5-(1-oxo-2-phenyl-
ethyl)furan was eluted fourth (after two minor products).
Yield 0.16g (25%), m.p. (ethanol) 112-112.5°C.
ν_{max} (KBr) 3050,1710,1670,1640,1550, and 1490 cm^{-1}.
δ(CDCl$_3$) 7.4 (1H,d J=16Hz);   7.2 (5H,s);   7.1 (1H,d J=4Hz);
6.55 (1H,d J=4Hz);   6.4 (1H,d J=16Hz);   4.0 (2H,s); and
3.7 (3H,s).
Found: M$^+$ 270.0920.   C$_{16}$H$_{14}$O$_4$ requires M 270.0893.
Found: C, 71.20%;   H, 4.85%.   C$_{16}$H$_{14}$O$_4$ requires C, 71.11%;
H, 5.18%.

2-Methylthiophen-5-acetic acid

Dimethyl diazomalonate (12.64g, 80mMole) was
added dropwise to a stirred refluxing solution of rhodium-
(II)-acetate (50mg) in 2-methylthiophen (100ml) over 1 hour.
After refluxing for a further 30 minutes the excess 2-methyl-
thiophen was evaporated.   The residue was poured into a
solution of potassium hydroxide (50g) in water (50ml).   The
mixture was refluxed for 3 hours then cooled in an ice bath.

Hydrochloric acid (10M) (100ml) was added and the mixture was again refluxed, for 3 hours. The solution was then cooled and extracted with dichloromethane (4 x 100ml). The dark dichloromethane extracts were combined and evaporated. After drying under vacuum a dark brown solid was obtained. Yield 7.2g (58%). On recrystallisation (twice) from hexane/charcoal a white crystalline solid was obtained m.p. (hexane) 55-56°C (lit.[15] 56°C).

ν_{max} 3300-2700 broad, 1700,1490,1410, and 1400 cm^{-1}.

δ(CDCl$_3$) 6.7 (1H,d J=4Hz); 6.58 (1H,m); 3.75 (2H,s); and 2.4 (3H,s).

Methyl 2-(3-trans-propenoate)-5-(1-oxo-2-[5-methylthienyl]-ethyl)furan

2-Methylthiophen-5-acetic acid (1.56g, 10mMole) and trifluoroacetic anhydride (2ml, 14mMole) was stirred and heated at 100°C for 2 minutes, the mixture became dark. Methyl 2-furylacrylate (1.52g, 10mMole) was added in one portion and the mixture was heated for 3 minutes. The dark reaction mixture was then treated with saturated sodium bicarbonate solution (30ml) and diethyl ether (20ml). After stirring for 5 minutes the ether layer was separated, the aqueous layer was extracted with a further portion of diethyl ether (20ml) and the extracts were combined. After washing with sodium bicarbonate solution the ether extracts were dried over magnesium sulphate and evaporated to dryness. The residue was chromatographed on 60g of silica eluted with 3:17 ethyl acetate/petroleum ether (40-60). Methyl 2-furylacrylate was eluted first in 50% yield. Methyl 2-(3-trans-propenoate)-5-

(1-oxo-2-[5-methylthienyl]ethyl)furan was eluted fourth
(after 2 minor products). Yield 58mg (1.4%).

ν_{max} (KBr) 2950,1710,1670,1640,1500, and 1430 cm^{-1}.

δ(CDCl$_3$) 7.35 (1H,d J=16Hz); 7.1 (1H,d J=4Hz); 6.6 (3H,m);
6.45 (1H,d=16Hz); 4.15 (2H,s); 3.7 (3H,s); and 2.35 (3H,s).

Found: M$^+$ 290.0621. C$_{15}$H$_{14}$O$_4$S requires M$^+$ 290.0614.

2-Methylthiophen-5-acetylchloride

2-Methylthiophen-5-acetic acid (0.5g, 3.2mMole)
and thionylchloride (0.25ml, 3.4mMole) was heated at 40°C for
6 hours. The brown liquid was then allowed to cool and all
volatile material was removed under vacuum. The acid chloride
was distilled in a Kugelrohr distillation apparatus at
ca. 120°C (0.5mm Hg). Yield 0.26g (43%).

ν_{max} (film) 2940,1800,1490,1450,1400 cm^{-1}.

δ(CDCl$_3$) 6.65 (1H,d J=4Hz); 6.5 (1H,m); 4.1 (2H,s);
and 2.45 (3H,s).

2-(1-oxo-2-[5-methylthienyl]ethyl)furan

A mixture of 2-methylthiophen-5-acetic acid
(0.156g, 1mMole) and trifluoroacetic anhydride (0.2ml) was
heated at 100°C in an oil bath. Furan (0.5ml) was added in
one portion. After one minute sodium bicarbonate solution
(5ml) was added and the mixture was stirred for 5 minutes.
The mixture then extracted with diethyl ether (2 x 10ml).
The combined extracts were dried over magnesium sulphate and
evaporated to dryness. The residue was chromatographed on 20g
of silica eluted with 9:1 petroleum ether (40-60)/ethyl
acetate. Yield 0.86g (31%) of a yellow oil.

ν_{max} (film) 3120,2920,1670,1560,1460, and 1400 cm^{-1}.

δ(CDCl$_3$) 7.55 (1H,m); 7.2 (1H,m); 6.7 (1H,d J=4Hz);

6.5 (2H,m); 4.2 (2H,s); and 2.4 (3H,s).

Found: M$^+$ 206.0396. C$_{11}$H$_{10}$O$_2$S requires 206.0401.

2-(1,2-dioxo-2-[5-methylthienyl]ethyl)furan

2-[5-(2-methylthienyl)]-1-oxo-1-furylethane
(0.056g, 0.27mMole) was dissolved in a solution of benzene-
sulphonylazide-4-carboxylic acid (0.065g, 29mMole) in
acetonitrile (1.2ml). Triethylamine (0.12 ml, 0.87mMole) was
added in one portion and the reaction mixture was stirred for
2 days at room temperature. The resulting suspension was
taken up in diethyl ether (25ml) and was washed with sodium
bicarbonate solution (3 x 10ml). The ether layer was dried
over magnesium sulphate and the solvent evaporated. The
residue was chromatographed on 20g of silica eluted with 9:1
petroleum ether (40-60)/ethyl acetate. The major product was
collected as a yellow crystalline solid.

Yield 36mg (57%). m.p. (ethanol) 92-94°C.

ν_{max} (KBr) 3110,2950,1650 shoulder at 1640,1450 and 1400 cm^{-1}.

δ(CDCl$_3$) 7.8 (1H,d J=4Hz); 7.7 (1H,m); 7.55 (1H,m);

6.85 (1H,m); 6.6 (1H,m); and 2.6 (3H,s).

Found: M$^+$ 220.0194. C$_{11}$H$_8$O$_3$S requires 220.0194.

2-Benzylthiophen

A mixture of 2-benzoylthiophen[16] (94g, 0.5M),
potassium hydroxide (90g, 1.6M), and hydrazine hydrate
(90g, 1.8M) in digol (700ml) was refluxed for 1½ hours.
The water and excess hydrazine were distilled from the

reaction mixture until the pot temperature reached 200°C.
After a further 2 hours reflux the reaction mixture was
cooled, poured into water (2 dm^3) and extracted with diethyl
ether (2 x 100ml) and dried over magnesium sulphate. The
solvent was then evaporated and the residue was dried over
calcium hydride. Distillation yielded 71g (81%) b.p. (water
pump) 135°C (lit[18] 257-262°C).

ν_{max} (film) 3060,3010,2900,1600,1490, and 1430 cm^{-1}.

δ(CDCl$_3$) 7.2 (5H,s); 7.0 (3H,m); and 5.9 (2H,s).

2-Ethylthiophen

A mixture of 2-acetylthiophen[16] (63g, 0.5M),
potassium hydroxide (90g, 1.6M) and hydrazine hydrate
(90g, 1.8M) in digol (700ml) was refluxed for 3 hours.
The ethylthiophen, water, and excess hydrazine were distilled
until the pot temperature reached 200°C. The organic layer
of the distillate was then separated, washed with 2M HCl
solution and then dried, first over magnesium sulphate and
then calcium hydride. Distillation yielded 42g (75%), b.p.
134-135°C (lit[16] 132-134°C).

ν_{max} (film) 2960,1460, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.9 (3H,m); 2.9 (2H,q); and 1.3 (3H,t).

Attempted preparation of 2-t-butylthiophen from 2-t-butylfuran

2-t-Butylfuran was prepared by a modification of
the method of Newman et al.[17] 2-t-Butyl-5-furoic acid
(70g, 0.4M) was heated with stirring at 210°C and 2-t-butyl-
furan was distilled. Yield 44g (80%) b.p. 119-120°C (lit[17] 119-120°C).

ν_{max} (film) 2960,1580,1510, and 1460 cm^{-1}.

δ(CDCl$_3$) 7.15 (1H,m); 6.1 (1H,m); 5.9 (1H,m); and 1.2 (9H,s).

(a)   2-t-Butylfuran (1g) was dissolved in diethyl ether (20ml) containing 4-toluenesulphonic acid (10mg) and a trace of hydroquinone. Hydrogen sulphide was bubbled through the mixture for 2 hours at 0°C. No product was formed (G.C.). Water (1ml) and 4-toluenesulphonic acid (100mg) were added and the stream of hydrogen sulphide was continued for a further 2 hours. No product was evident on G.C. analysis.

(b)   2-t-Butylfuran (1g) was dissolved in 90% ethanol (4ml) and trifluoroacetic acid (0.9g). Hydrogen sulphide was bubbled through for 5 hours. No product was evident on G.C. analysis.

(c)   . 2-t-Butylfuran (1g) was dissolved in carbon disulphide (20ml) containing P_2S_5 (1g). After 1 hour at 0°C all the furan had been consumed and none of the desired product had been formed (G.C.).

(d)   2-t-Butylfuran (1g) was dissolved in ethanol (20ml) containing 1 drop of conc. hydrochloric acid. Hydrogen sulphide was bubbled through for 2 hours. No starting material remained and none of the desired product had been formed.

2-t-Butylthiophen

To an ice cold mixture of thiophen (57.8g, 0.72M) in carbon disulphide (0.91ℓ) containing t-butylchloride (80g, 0.84M), stannic chloride (226g, 0.86M) was added over 2 hours. The reaction mixture was then treated with 10% HCl (200ml). After separation and drying the mixture was distilled to yield a mixture of mono t-butylthiophens.

144.

Yield 31g b.p. 160-180°C. After distillation through a
1 meter spinning band fractionating column pure 2-t-butyl-
thiophen was obtained. Yield 5g (5.5%) b.p. 165°C
(lit[18] 164°C).

ν_{max} (film) 2950, and 1460 cm^{-1}.

δ(CDCl$_3$) 6.9 (3H,m); and 1.4 (9H,s).

2-Benzyl-5-chlorothiophen

2-Benzylthiophen (10g, 58mM) was treated dropwise
with sulphuryl chloride (7.8g, 58mM) over 30 minutes. Vigorous
evolution of gas resulted. After standing for a further 30
minutes the mixture was taken up in dichloromethane (50ml),
washed with water (2 x 25ml) and then saturated sodium
bicarbonate solution (25ml). The organic solution was dried
over magnesium sulphate, evaporated and the residue dried
over calcium hydride. Distillation yielded 8.5g (71%),
b.p. 94-96°C (0.2mm Hg).

ν_{max} (film) 3060,3010,2900,1600,1540,1490,1450, and 1430 cm^{-1}.

δ(CDCl$_3$) 7.2 (5H,s); 6.6 (1H,d); 6.45 (1H,d); and 4.0 (2H,s).

Found: M$^+$ 208.0101. C$_{11}$H$_9$ClS requires M 208.0113.

2-Benzyl-5-bromothiophen

2-Benzylthiophen (10g, 58mM) was dissolved in dry
DMF (25ml). N-Bromosuccinimide (10.2g, 58mM) in DMF (25ml)
was added and the solution was stirred for 24 hours. It was
then poured into water (500ml) and extracted with diethyl
ether (3 x 100ml). After extraction with water (4 x 100ml)
the solution was dried over magnesium sulphate and the solvent
evaporated. After further drying over calcium hydride the

residue was distilled. Yield 12.6g (86%), b.p. 98-102°C
(0.2mm Hg).

ν_{max} (film) 3010,2900,1600,1500, and 1440 cm^{-1}.

δ(CDCl$_3$) 7.1 (5H,s); 6.7 (1H,d), 6.4 (1H,d); and 3.9 (2H,s).

Found: M$^+$ 251.9602 C$_{11}$H$_9$BrS requires M 251.9609.

2-Benzyl-5-iodothiophen

A mixture of 2-benzylthiophen (10g, 58mM) and
iodine (4.32g, 17mM) was stirred at room temperature. 8M Nitric
acid (1.5ml, 12mM) was added, and after the reaction had
initiated a further 5ml (40mM) of 8M nitric acid was added
over 30 minutes. The mixture was then refluxed for 30 minutes,
the organic layer was separated and 40% sodium hydroxide
solution.was added. After a further ½ hour reflux the organic
layer was separated, washed with water, and dried over calcium
chloride. Chromatography yielded 4.6g (43%).

ν_{max} (film) 3010,2900,1600,1490,1450, and 1430 cm^{-1}.

δ(CDCl$_3$) 7.1 (5H,s); 6.9 (1H,d); 6.35 (1H,d); and 4.0 (2H,s).

Found: M$^+$ 299.9473. C$_{11}$H$_9$IS requires M 299.9472.

Preparation of 2-alkyl-5-benzylthiophens (general)

Stannic chloride (65g, 0.25M) was added to a mixture
of the 2-alkylthiophen (0.25M) and benzoyl chloride (35g, 0.25M)
in benzene (250ml) at 0°C over 1 hour. After stirring for
1 hour,1M HCl (100ml) was added and the mixture stirred for
5 minutes. The organic layer was then separated, washed with
water and dried over magnesium sulphate. An attempt was made
to distill the products at this stage but this was abandoned
when the pot temperature reached 160°C. The ketones were

therefore reduced without further purification.

The 2-benzoyl-5-alkylthiophen was dissolved in digol (300ml) containing potassium hydroxide (45g, 0.8M) and 64% hydrazine (45g, 0.9M). After refluxing the mixture for 2 hours the water and excess hydrazine were distilled until the pot temperature had reached 150°C. The mixture was then refluxed for a further ½ hour, cooled, and poured into water (1.5 dm^3). The aqueous mixture was extracted with diethyl ether (3 x 100ml), the ether extracts were combined, washed with water (2 x 100ml) and dried over magnesium sulphate. After evaporation of the solvent the product was dried over calcium hydride for 24 hours and then distilled from fresh calcium hydride.

2-Benzyl-5-methylthiophen

Yield 15.7g (33%), b.p. 74-76°C (0.1mm Hg). m.p. 5°C.

ν_{max} (film) 3060,3020,1495, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.0 (5H,s); 6.4 (2H,s); 3.9 (2H,s); and 2.2 (3H,s).

Found: M$^+$ 188.0655. C$_{12}$H$_{12}$S requires M 188.0659.

2-Benzyl-5-ethylthiophen

Yield 9.3g (19%), b.p. 87-88°C (0.1mm Hg).

ν_{max} (film) 3060,3020,2960,2920,1600,1500, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.5 (5H,s); 6.4 (2H,s); 3.9 (2H,s); 2.6 (sH,q); and 1.1 (3H,t).

Found: M$^+$ 202.0818. C$_{13}$H$_{14}$S requires M 202.0817.

2-Benzyl-5-isopropylthiophen

Yield 13.4g (25%), b.p. 90-91°C (0.1mm Hg).

ν_{max} (film) 3060,3020,2960,2860,1600,1495, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.2 (5H,s); 6.5 (2H,s); 4.0 (2H,s); 3.0 (1H,heptet); and 1.2 (6H,d).

Found: M$^+$ 216 0968. C$_{14}$H$_{16}$S requires M 216.0972.

2-(Phenoxymethyl)thiophen

A mixture of N-bromosuccinimide (49g, 0.27M) and AIBN (0.5g) was added portion-wise to a solution of 2-methylthiophen (29.4g, 0.3M) and AIBN (0.5g) in refluxing benzene. The addition was conducted as rapidly as foaming would permit (30 minutes). The mixture was then cooled and filtered.. The solvent was evaporated and the residue distilled. Yield 15g (28%), b.p. 59°C (0.2mm Hg) (lit.[19] 80-82°C (15mm Hg).

δ(CDCl$_3$) 2.9 (3H,m); and 4.7 (2H,s).

The 2-bromomethylthiophen (15g) was added to an ethanolic solution of sodium phenoxide (9.86g, 85mM). There was an immediate precipitation of sodium bromide and the mixture became warm. After stirring overnight and then refluxing for 30 minutes the ethanol was evaporated and the residue partitioned between diethyl ether (100ml) and water (100ml). The ether layer was separated, washed with water (2 x 50ml), dried over magnesium sulphate and evaporated. After two distillations 2-(phenoxymethyl)thiophen was obtained as a low melting solid. Yield 10.1g (63%), b.p. 102-104°C (0.2mm Hg), m.p. 23°C.

ν_{max} (film) 3010,2920,1580b, and 1480 cm^{-1}.

δ(CDCl$_3$) 7.1 (8H,m); and 5.0 (2H,s).

Found: M$^+$ 190.0439. C$_{11}$H$_{10}$OS requires M 190.0452.

Di-t-butyl diazomalonate

A mixture of di-t-butyl malonate (21.6g, 0.1M), 4-toluenesulphonylazide (19.7g, 0.1M), benzene (600ml), 10M sodium hydroxide solution (20ml), and Aliquot 336 (10mg) was stirred vigorously for 2 days. The mixture was then washed with water (2 x 100ml) and 1M sodium hydroxide solution (100ml). After drying over sodium sulphate the solvent was evaporated and the residue was then distilled to yield 13.2g (58%), b.p. 62-63°C (0.2mm Hg) (lit[20] 45°C (0.02mm Hg).

ν_{max} (film) 2980,2120,1730,1680,1460, and 1410 cm^{-1}.

δ(CDCl$_3$) 1.5 (s).

"Rhodium-(II)-hexanoate"

Rhodium (II)-acetate (100mg) was suspended in hexanoic acid (10ml). The mixture was heated to reflux and the volume was reduced to 5ml by distillation. The remainder of the acid was removed by distillation under vacuum and the residue was dried at 100°C (0.2 torr) for 1 hour.

Preparation of thiophenium bis(t-butoxycarbonyl)-methylides (general)

The thiophen (10mM) was dissolved in methylcyclohexane (10ml) containing rhodium-(II)-acetate (10mg) (method A), or rhodium-(II)-hexanoate (10mg) (method B). Di-t-butyl diazo-malonate (2.42g, 10mM) was added and the mixture was stirred until no diazo band remained (ir). If a solid had precipitated it was filtered off and washed with methylcyclohexane, if not the solvent was evaporated and the residue was chromatographed.

2-Isopropylthiophen bis(t-butoxycarbonyl)methylide

Method A. After 3 days chromatography (silica gel eluted with dichloromethane) yielded 0.86g (26%). m.p. (60-80 petroleum ether) 118-119°C.

ν_{max} (KBr) 3020,2980,1700,1680,1470, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.7 (3H,m); 2.9 (1H,heptet); and 1.3 (24H,m).

Found: C, 63.62%; H, 8.55%; C$_{18}$H$_{28}$O$_4$S requires C, 63.53%; H, 8.24%.

2-Chlorothiophenium bis(t-butoxycarbonyl)methylide

Method A. After 3 days filtration yielded 1.5g (42%).

m.p. (benzene) 166-168°C.

ν_{max} (KBr) 3060,2980,2560,1690,1650,1540,1480, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.9 (3H,m); and 1.4 (18H,s).

Found: C, 54.18%; H, 6.34%; C$_{15}$H$_{21}$ClO$_4$S requires C, 54.20%; H, 6.32%.

2-Bromothiophenium bis(t-butoxycarbonyl)methylide

Method B. After 30 minutes filtration yielded 2.5g (66%).

m.p. (benzene) 140-143°C (dec.).

ν_{max} (KBr) 3060,2900,1690,1640,1570,1490, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.0 (3H,m); and 1.4 (18H,s).

Found: C, 48.03%; H, 5.82%; C$_{15}$H$_{21}$BrO$_4$S requires C, 47.80; H, 5.57%.

2-Iodothiophenium bis(t-butoxycarbonyl)methylide

Method B. After 30 minutes filtration yielded 3.2g (75%).

m.p. (benzene) 134-134.5°C.

ν_{max} (KBr) 3060,2970,1670,1650, and 1460 cm^{-1}.

δ(CDCl$_3$) 7.1 (3H,m); and 1.4 (18H,s).

Found: C, 42.27%; H, 4.76; C$_{15}$H$_{21}$IO$_4$S requires C, 42.45%; H, 4.95%.

2-Benzyl 5-methylthiophenium bis(t-butoxycarbonyl)methylide

Method B. After 16 hours chromatography (silica gel eluted
with dichloromethane) yielded 1.8g (44%). m.p. 78-79°C.

ν_{max} (film) 3050,2960,2920,1700,1630, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.35 (5H,s); 6.6 (2H,s); 3.85 (2H,s);
2.2 (3H,s); and 1.4 (18H,s).

Found: M$^+$ 301.1285 C$_{18}$H$_{21}$O$_2$S requires M 301.1263.

2-Benzyl 5-ethylthiophenium bis(t-butoxycarbonyl)methylide

Method B. After 24 hours chromatography (silica gel eluted
with 4:1 petroleum ether (40-60)/ethyl acetate) yielded
2.4g (75%) of a gum.

ν_{max} (film) 2600,2200,1705,1640, and 1455 cm^{-1}.

δ(CDCl$_3$) 7.4 (5H,s); 6.65 (2H,s); 3.9 (2H,s);
2.6 (2H,q); 1.4 (18H,s); and 1.2 (3H,t).

Found: M$^+$ 343.1365 C$_{20}$H$_{23}$O$_3$S requires M 343.1368.

2-Benzyl 5-isopropylthiophenium bis(t-butoxycarbonyl)methylide

Method B. After 24 hours chromatography (silica gel eluted
with 4:1 petroleum ether (40-60)/ethyl acetate) yielded
2.4g (56%) of a gum.

ν_{max} (film) 2970,2930,1705,1640, and 1455 cm^{-1}.

δ(CDCl$_3$) 7.35 (5H,s); 6.6 (2H,s); 3.85 (2H,s);
2.9 (1H,heptet); 1.4 (18H,s); and 1.3 (6H,d).

Found: M$^+$ 357.1540 C$_{21}$H$_{25}$O$_3$S requires M 357.1525.

2-Benzyl 5-chlorothiophenium bis(t-butoxycarbonyl)methylide

Method B. After 24 hours filtration yielded 2.2g (51%).
m.p. (benzene/hexane) 125-127°C.

ν_{max} (KBr) 2900,1710,1650,1530,1500,1480,1460, and 1420 cm^{-1}.

δ(CDCl$_3$) 7.3 (5H,m); 6.7 (1H,d); 6.5)1H,m); 3.8 (2H,s);
and 1.4 (18H,s).

Found: C, 62.49%; H, 6.76%; C$_{22}$H$_{27}$ClO$_4$S requires
C, 62.53%; H, 6.39%.

2-Benzyl 5-bromothiophenium bis(t-butoxycarbonyl)methylide

Method B. After 24 hours filtration yielded 2.3g (49%).

m.p. (benzene/hexane) 123-125°C.

ν_{max} (KBr) 2900,1690,1650,1515,1500,1470,1450, and 1425 cm^{-1}.

δ(CDCl$_3$) 7.4 (5H,m); 7.0 (1H,d); 6.55 (1H,m);

3.9 (2H,s); and 1.4 (18H,s).

Found: C, 56.43%; H, 5.97%; C$_{22}$H$_{27}$BrO$_4$S requires

C, 56.57%; H, 5.78%.

2-Benzyl 5-iodothiophenium bis(t-butoxycarbonyl)methylide

Method B. After 24 hours filtration yielded 3.4g (67%).

m.p. (benzene) 159-162°C.

ν_{max} (KBr) 2980,1670,1650,1500,1470,1450, and 1420 cm^{-1}.

δ(CDCl$_3$) 7.4 (5H,m); 7.2 (1H,d); 6.5 (1H,m); 3.9 (2H,s);

and 1.4 (18H,s).

Found: C, 51.14%; H, 5.25%; C$_{22}$H$_{27}$IO$_4$S requires

C, 51.40%; H, 5.25%.

2-(Phenoxymethyl)thiophenium bis(t-butoxycarbonyl)methylide

Method B. After 5 hours filtration yielded 2.6g (64%).

m.p. (toluene, cold crystallization) 102-104°C (dec).

ν_{max} (KBr) 3000,2900,1730,1470, and 1400 cm^{-1}.

δ(CDCl$_3$) 7.1 (8H,m); 5.0 (2H,s); and 1.45 (18H,s).

Found: C, 65.23%; H, 6.95%; C$_{22}$H$_{28}$O$_5$S requires

C, 65.35%; H, 6.93%.

3-Methylthiophenium bis(t-butoxycarbonyl)methylide

Method B. After 3 hours filtration yielded 2.3g (72%).

m.p. (ethyl acetate) 117-118°C.

ν_{max} (KBr) 3100,2980,1640,1470, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.0 (2H,m); 6.5 (1H,m); 2.2 (2H,d); and 1.3 (18H,s).

Found: C, 61.43%; H, 8.03%; C$_{16}$H$_{24}$O$_4$S requires

C, 61.54%; H, 7.69%.

Thiophenium bis(t-butoxycarbonyl)methylide

Method B. After 8 hours filtration yielded 2.4g (80%).

m.p. (acetonitrile) 140-142°C.

ν_{max} (KBr) 3080,2960,1650,1475, and 1440 cm^{-1}.

δ(CDCl$_3$) 7.05 (4H,m); 1.4 (18H,s).

Found: C, 60.66%; H, 7.50%; C$_{15}$H$_{22}$O$_4$S requires

C, 60.40%; H, 7.38%.

The reaction of dimethyl diazomalonate with thiophen-2-acetamide

Thiophen-2-acetamide[21] (4g) was dissolved in dry DMF (10ml)

containing rhodium-(II)-acetate (10mg). Dimethyl diazomalonate

(1.58g, 10mM) was added and the mixture was stirred. After

14 days the reaction mixture still contained some unreacted

diazo compound. The solvent was evaporated and the residue

chromatographed. The major product was tetra(methoxycarbonyl)

ethylene.

The reaction of dimethyl diazomalonate with 2-methoxythiophen

2-Methoxythiophen[22] (10ml) containing rhodium-(II)-acetate (10mg)

was treated dropwise with dimethyl diazomalonate (1.58g, 10mM)

over 30 minutes. The reaction mixture was stirred until no

diazocompound remained (3 days). Chromatography of the reaction

mixture on silica gel eluted with 1:4 petroleum ether (40-60)/ethyl acetate yielded 1.1g (49%) of a liquid, dimethyl 2-methoxythiophen-2-malonate.

ν_{max} (film) 2940,1760,1550,1500, and 1430 cm^{-1}.

δ(CDCl$_3$) 6.5 (1H,d); 5.9 (1H,d); 4.7 (1H,s); 3.7 (3H,s); and 3.6 (6H,s).

Found: M$^+$ 244.0396 C$_{10}$H$_{12}$O$_5$S requires M 244.0406.

Dithienylmethane.

A mixture of zinc chloride (192g, 1.4M), thiophen (179g, 2.13M), and concentrated hydrochloric acid (146ml 1.46M) was stirred at -10°C with a mechanical stirrer. 37% Form-aldehyde solution (145ml, 1.78M) was added at such a rate that the temperature did not rise above -5°C. After stirring for a further 2 hours water (500ml) was added and the mixture was extracted with diethyl ether (3 x 100ml). The combined extracts were washed with saturated sodium bicarbonate solution, dried, and evaporated. Distillation yielded 96g (53%) of the desired product; b.p. 94°C (1mm Hg). (lit.[23] 131-132°C. 11mm Hg).

δ(CDCl$_3$) 7.0 (6H,m); and 4.25 (2H,s).

2-Thenylthiophenium bis(methoxycarbonyl)methylide

A mixture of dithienylmethane (12g, 66mM), dimethyl diazomalonate (5.2g, 32.9mM), and rhodium-(II)-acetate (20mg) in methylcyclohexane (50ml) was stirred at room temperature for 3 days. After this time an oil had separated from the reaction mixture. The solvent was decanted off and the residue was triturated with a mixture of diethyl ether and methylcyclohexane. The resultant solid was washed with

methylcyclohexane.

Yield 4.9g (49%). m.p. (ethyl acetate) 118-119°C.

ν_{max} (KBr) 3080,2940,1690,1650, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.2-6.6 (6H,m); 4.0 (2H,s); and 3.6 (6H,s).

Found: M$^+$ 310.0323 C$_{14}$H$_{14}$O$_4$S requires M 310.0334.

The reaction of di-t-butyl diazomalonate with 2-t-butylthiophen

Di-t-butyl diazomalonate (1.21g, 5mM) was added to a solution of 2-t-butylthiophen (0.7g, 5mM) in methylcyclohexane (5ml) containing rhodium-(II)-hexanoate (5mg). The solution was then stirred for 24 hours after which time the diazo-band (ir) had disappeared. The solvent was then evaporated and the residue was chromatographed on silica gel eluted with 4:1 petroleum ether (40-60)/ethyl acetate. The fractions containing the major product were combined, the solvent evaporated, and the residue was recrystallized from methylcyclohexane.

Yield 0.44g (28%) m.p. (methylcyclohexane) 175-178°C.

ν_{max} (CCl$_4$) 2970,2920,1730,1690,1630,1480, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.1 (1H,q,J=0.7 and 3 Hz); 3.45 (2H,m,J=0.7, 3 and 7 Hz); 1.4-1.55 (36H,4s); and 1.1 (9H,s).

Found: C, 63.64%; H, 9.06%; C$_{30}$H$_{48}$O$_8$S requires

C, 63.35%; H, 8.51%.

Found: M$^+$ 495.2403; C$_{26}$H$_{39}$O$_5$S requires M 495.2417.

Di-t-butyl 6-iodo — 2(H)-thiopyran-2,2-dicarboxylate

2-Iodothiophenium bis(t-butoxycarbonyl)methylide (100mg) was heated for 20 minutes in refluxing toluene (5ml). After evaporation of the solvent the residue was chromatographed

on silica gel eluted with 9:1 petroleum ether (40-60)/ethyl

acetate.

Yield 60mg (60%) of a yellow oil.

ν_{max} (film) 2800,2100,1720,1520, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.7 (1H,m); 5.9 (2H,d); and 1.45 (18H,s).

Found: M$^+$ 424.0235 C$_{15}$H$_{21}$IO$_4$S requires M 424.0208.

Di-t-butyl 6-(phenoxymethyl) — 2(H)-thiopyran-2,2-dicarboxylate

2-(Phenoxymethyl)thiophenium bis(<u>t</u>-butoxycarbonyl)methylide

(0.5g) was heated for 1 minute in refluxing methylcyclohexane

(10ml). After evaporation of the solvent the residue was

chromatographed on silica gel eluted with 9:1 petroleum ether

(40-60)/ethyl acetate.

Yield 0.47g (97%) of a yellow oil.

ν_{max} (film) 2960,2920,1730,1590,1490, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.4-6.7 (5H,m); 6.3-5.5 (3H,m); 4.5 (2H,s);

and 1.4 (18H,s).

Found: M$^+$ 404.1617; C$_{22}$H$_{28}$O$_5$S requires M 404.1658.

Di-t-butyl 4/5-methyl — 2(H)-thiopyran-2,2-dicarboxylate

3-Methylthiophenium bis(<u>t</u>-butoxycarbonyl)methylide (0.5g)

was heated in refluxing toluene for 20 minutes. After

evaporation and chromatography on silica gel eluted with

9:1 petroleum ether (40-60)/ethyl acetate.

Yield 0.49g (98%) of a yellow oil.

ν_{max} (film) 2980,2910,1710, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.3-5.6 (3H,m); 1.85 (3H,s); and 1.5 (18H,s).

Found: M$^+$ 312.1420; C$_{16}$H$_{24}$O$_4$S requires M 312.1396.

Dimethyl 2(H)-thiopyran-2,2-dicarboxylate

Thiophenium bis(methoxycarbonyl)methylide (0.5g) was
heated in refluxing toluene for 10 minutes. The cooled
solution was then filtered and the solvent was evaporated.
Chromatography of the residue on silica gel eluted with
dichloromethane yielded 0.15g (30%) of a yellow oil.
ν_{max} (film) 3000,2940,1730, and 1430 cm^{-1}.
δ(CDCl$_3$) 6.4-5.6 (4H,m); and 3.8 (6H,s).
Found: M$^+$ 214.0292; C$_9$H$_{10}$O$_4$S requires M 214.0300.

Di-t-butyl 2(H)-thiopyran-2,2-dicarboxylate

Thiophenium bis(t-butoxycarbonyl)methylide (0.5g) was
heated in refluxing xylene (10ml) for 5 minutes. After
evaporation of the solvent the residue was chromatographed on
silica gel eluted with 4:1 petroleum ether (40-60)/ethyl
acetate.
Yield 0.42g (84%). m.p. (methanol) 93-96°C.
ν_{max} (KBr) 2980,1725,1550,1450, and 1390 cm^{-1}.
δ(CDCl$_3$) 6.4-5.6 (4H,m); and 1.4 (18H,s).
Found: C, 60.13%; H, 7.45%; C$_{15}$H$_{22}$O$_4$S requires
C, 60.40%; H, 7.38%.

The reaction of dimethyl 2(H)-thiopyran with iodotrimethyl-silane

A mixture of dimethyl 2(H)-thiopyran-2,2-dicarboxylate
(107mg, 0.5mM), sodium iodide (75mg, 1.5mM), and chloro-
trimethylsilane (52mg, 1.5mM) in acetonitrile (20ml) was
stirred at room temperature under an atmosphere of dry
nitrogen for 2 days. The dark solution was then treated
with water (50ml), extracted with diethyl ether (2 x 50ml)

and the ether extracts were washed with sodium thiosulphate solution. After washing with water, drying and evaporation, the ether solution yielded only unchanged starting material and a small amount of dimethyl thiophen-2-malonate.

The reaction of dichlorothiophenium bis(methoxycarbonyl)-methylide with substituted thiophens

A mixture of dichlorothiophenium bis(methoxycarbonyl)methylide (2.83g, 10mM), the substituted thiophene (10mM), and copper-(II)-acetylacetonate (20mg) in toluene (10ml) was heated at reflux until no more ylid remained (2-3 hours). In all cases 5-10 products were formed with no obvious major product (tlc). The reactions were repeated with the reactants being stirred at 90°C in an oil bath. Times for completion extended to ca. 24 hours but similar numbers of products were obtained.

Attempted hydrogenolysis of thiophenium methoxycarbonyl-(benzyloxycarbonyl)methylide

A solution of thiophenium methoxycarbonyl(benzyloxycarbonyl)-methylide (100mg) in methanol (10ml) containing 10% palladium on charcoal (50mg) was hydrogenated at atmospheric pressure for 8 hours. The solution was then filtered through celite and the filtrate evaporated to yield only unchanged starting material.

Attempted de-esterification of thiophenium methoxycarbonyl-(4-nitrobenzyloxycarbonyl)methylide

A solution of thiophenium methoxycarbonyl(4-nitrobenzyloxy-carbonyl)methylide (335mg, 1mM) in THF (12ml) and water (6ml) was treated with a solution of $Na_2S.9H_2O$ (480mg, 2mM) in 5ml

of water. After 48 hours no change in starting material was apparent (tlc). The mixture was extracted with dichloromethane (2 x 10ml), the extracts were then washed with and dried over sodium sulphate. Evaporation of the solvent yielded only unchanged starting material.

The reaction of 2-(methylmagnesium bromide),5-methylthiophen with methyl 3-(5-formyl 2-furyl)prop-trans-2-enoate

A mixture of 2,5-dimethylthiophen (5.6g, 50mM), azo bis(iso-butyronitrile) (100mg), and carbontetrachloride (25ml) was heated at 60°C in an oil bath. A mixture of N-bromosuccinimide (8.4g, 50mM) and azo bis(isobutyronitrile) (100mg) was added portion-wise as rapidly as foaming would permit. When the foaming had subsided the mixture was filtered and the solvent evaporated. The residue was then distilled under vacuum. Yield 1.68g (18%). b.p. 48-52°C (0.5mm Hg). (lit.[19] 90°C 13mm Hg).

$\delta(CDCl_3)$ 6.85 (1H,d); 6.5 (1H,d); 4.65 (2H,s); and 2.4 (3H,s).

2-Bromomethyl-5-methylthiophen (1.59g, 8.4mM) was added to magnesium turnings (0.22g, 9.2mM) under diethyl ether (4ml), when the reaction had initiated a further 5ml of diethyl ether were added and the mixture was stirred until the magnesium had dissolved. The purple solution was then added to a suspension of methyl 3-(5-formyl 2-furyl) prop-trans-2-enoate (1.5g, 8.3mM) in diethyl ether (10ml) and the mixture was stirred for 16 hours at room temperature. The reaction was quenched with saturated ammonium chloride solution and then extracted with dichloromethane (2 x 20ml).

The combined extracts were dried over magnesium sulphate and the solvent was evaporated to yield only impure starting aldehyde.

The reaction of dimethylsulphonium methylide with methyl 3-(5-formyl-2-furyl)prop-trans-2-enoate

A solution of methyl 3-(5-formyl-2-furyl)prop-trans-2-enoate (180mg, 1mM) in dry tetrahydrofuran (1ml) was added dropwise to a stirred solution of dimethylsulphonium methylide[24] (1mM) in an ice/salt bath at -10°C. After 15 minutes the reaction mixture was allowed to warm to room temperature and it was then stirred for a further 60 minutes. Water (5ml) was then added and the mixture was extracted with diethyl ether. After drying and evaporation a mixture of starting aldehyde and a dark tarry material was obtained.

2-Methylthiophenium bis(t-butoxycarbonyl)methylide

Method A. After 3 days filtration yielded 0.58g (37%).

m.p. (methylcyclohexane) 133-135°C.

ν_{max} (KBr) 2980,1710,1640,1480, and 1450 cm^{-1}.

δ(CDCl$_3$) 7.0 (3H,m); 2.5 (3H,s); and 1.7 (18,s).

Found: C, 61.22%; H, 7.98%; C$_{16}$H$_{24}$O$_4$S requires
C, 61.37%; H, 7.69%.

Method B. After 16 hours filtration yielded 2.9g (92%).
Characteristics as above.

2-Ethylthiophenium bis(t-butoxycarbonyl)methylide

Method A. After 6 hours filtration yielded 1.24g (38%).

m.p. (methylcyclohexane) 108-109°C.

ν_{max} (KBr) 3060,2960,1675,1650,1460, and 1450 cm^{-1}.

δ(CDCl$_3$) 6.8 (3H,m); 2.6 (2H,q); and 1.4 (21H,s and t superimposed).

Found: C, 62.68%; H, 8.33%; C$_{17}$H$_{26}$O$_4$S requires
C, 62.64%; H, 7.98%.

## 3-Bromothiophenium bis(methoxycarbonyl)methylide

Dimethyl diazomalonate[2] (1.58g, 10mMole) was added to a solution of rhodium-(II)-acetate (5mg) in 3-bromothiophen (10 ml). After 21 days at 0°C the bulk of the excess 3-bromothiophen was evaporated under vacuum at ambient temperature. The residue was chromatographed on 55g of silica eluted with 5% ethanol/dichloromethane. The appropriate fractions were evaporated to yield a yellow oil. The oil was stored at 0°C under ethanol (5 ml) for 3 days, after which the crystalline product was filtered off and dried under vacuum. Yield 0.31g (10%), m.p. (ethanol) 105-109°C.

ν_{max} (KBr) 3180,1670, and 1430, cm^{-1}.

$\delta(CDCl_3)$ 7.5-6.9 (3H,m); and 3.65 (6H,s).

Found: M^+, 291.9407. $C_9H_9BrO_4S$ requires M.291.9406.

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