SOME NOVEL ASPECTS

OF

THE CHEMISTRY OF THIOPHENS

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for the

Degree of Doctor of Philosophy

by

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Dedication

To Jenny

for that three year wait

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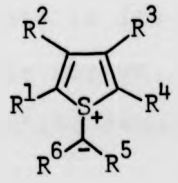
The Science Research Council and Pilot Chemical Co. Ltd. are thanked for a CASE studentship and Johnson, Matthey and Co. Ltd. for the generous loan of rhodium (II) acetate.

ABSTRACT

The research described in this thesis is prefaced by an introductory review on sulfur ylide chemistry.

The initial objective of this project was the development of efficient syntheses of the commercially important compounds 2-thienylacetic acid and 3-thienylmalonic acid and several approaches to these were examined with little success.

Reports that the addition of diazoacetic ester to thiophen gave a cyclopropane derivative which, on treatment under acid conditions, gave a 3-substituted thiophen derivative, prompted us to examine this reaction with a view to the preparation of 3-thienylmalonate. The reactions of diazomalonate with thiophen under traditional cyclopropane-forming conditions gave low yields of 2-thienylmalonate. However when this reaction was carried out at room temperature in the presence of rhodium (II) acetate a quantitative formation of the ylide 57 (R_1,R_2,R_3,R_4 = H; R_5,R_6 = CO_2Me) occurred. An X-ray crystal structure determination helped to confirm the structure of this stable crystalline solid.



57

Several ylides of the type (57) were prepared in high yield using alkyl- or halogenothiophens but thiophens bearing substituents with a -M effect failed to produce ylides. Reactions

with diazo compounds other than diazomalonic esters failed to produce ylides, the products being 2-substituted thiophens, cyclopropanated thiophens, or a mixture of the two.

Thermolyses of the ylides yielded 2-substituted thiophens and other products derived, apparently, from intramolecular nucleophilic rearrangement of the ylides. It is considered likely, in view of these rearrangements, that the reactions of all diazo compounds with thiophens proceed *via* ylides of the type (57) and that all the products are derived from these, often unstable, intermediates.

Thermolyses of the ylides in the presence of transition metal salts proceed by an entirely different mechanism, the intermediacy of bis(methoxycarbonyl)carbene, or a metal-stabilized carbenoid species, being likely. This carbenoid has been trapped by cyclohexene and its formation under the above conditions has proved to be extremely useful from a synthetic viewpoint as illustrated by its use in the cyclopropanation of unactivated olefins, its reaction with activated arenes to form arylmalonates, and its insertion into acidic X-H bonds. A further interesting reaction of this intermediate is its ability to deoxygenate epoxides in a stereospecific manner, a reaction thought to proceed through an intermediate oxonium ylide.

CONTENTS

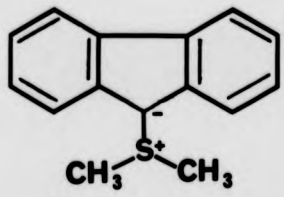
REVIEW

Some New Developments in the Chemistry of Sulfur Ylides

INTRODUCTION

The chemistry of sulfur ylides has been reviewed recently[1] covering developments up to 1974. The present work is not a comprehensive review but discusses some of the more interesting recent developments in this field up to May 1979.

Sulfur ylides, formally zwitterions in which a carbanion achieves stabilization by interaction with an adjacent sulfonium centre, have been known for nearly fifty years since the report of Ingold and Jessop[2] on the isolation of dimethylsulfonium fluorenylide (1).



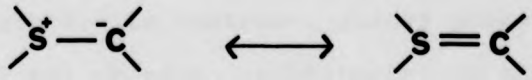
1

Exploitation of the synthetic potential of sulfur ylides did not occur until the late 1960's and a wide variety of sulfur ylides have since been isolated. Many more have been proposed as reactive intermediates and sulfur ylides have generally become extremely important as synthetic intermediates in a variety of transformations.

Structure and Stability of Sulfur Ylides[1]

The ability of sulfur to stabilize an adjacent negative charge remains an interesting phenomenon. Comparison

of sulfur ylides with nitrogen ylides indicates that factors beyond electrostatic stabilization must be involved and the simplest explanation involves delocalization of electron density into low-lying d-orbitals of sulfur. The structure of sulfur ylides appears to depend on the relative importance of structures (2a) and (2b) as resonance contributors.



2a 2b

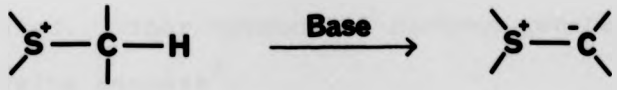
For the double bonded structure (2b) to make a major contribution the carbon and sulfur would tend to become planar for maximum overlap. However X-ray studies[64] have shown that sulfur, in these compounds, is tetrahedral and it has also been shown that the anionic carbon has a tetrahedral configuration as for most simple carbanions. Although the carbon-sulfur bond distance lies between that of a C-S single bond and a C=S double bond this is not necessarily due to a significant double bond contribution. It is clear that charge effects determine these bond lengths to some extent, and hybridization effects must be taken into account. These structural studies combined with the chemical behaviour of ylides fail to support the

existence of significant double bond character between the ylide carbon and sulfur however some double bond character must be invoked to explain the unusual ability of sulfonium centres to stabilize the adjacent negative charge compared with ammonium centres.

Sulfur ylides possessing only alkyl, vinyl or aryl substituents on the anionic centre are unstable and must be generated at low temperature otherwise their lifetime is extremely short. In contrast, ylides possessing carbonyl, cyano, sulfonyl or nitro substituents on the anionic centre have enough stabilization so that they are isolable and storable, some being stable enough for distillation without decomposition.

Synthesis of Sulfur Ylides

Two fundamentally distinct approaches to the generation of sulfonium ylides exist. The most common involves deprotonation of a sulfonium salt (3) which is either preformed or generated *in situ*.



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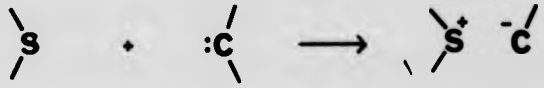
A less common, but increasingly important approach

involves the reaction of a sulfide with a carbene.



In the deprotonation of sulfonium salts the choice of using a preformed salt or an _in situ_ method depends very much on the nature of the sulfonium salt and sulfonium ylide concerned. Similarly the choice of base depends on its likely side reactions with the ylide and with the substrate intended to react with the ylide. Obviously unstable ylides are prepared and used _in situ_ while it is often helpful to isolate a stabilized sulfonium ylide before use.

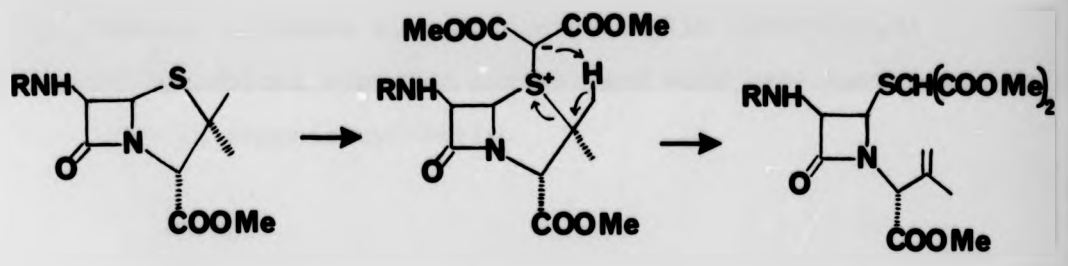
The addition of carbene to a sulfide provides the most direct synthesis of sulfur ylides. Copper- or copper salt-catalysed thermal or photolytic decompositions of diazo compounds in the presence of a sulfide or sulfoxide are the most common synthetic techniques and the sulfur ylides can often be isolated. Other methods of carbene generation have been used with varying success[3].

Ylide Fragmentation and Rearrangement

One of the main synthetic virtues of sulfur ylides is their ability to undergo various fragmentations and rearrangement reactions to attain stability.

One of the most common reactions is known as the β-elimination reaction which occurs in ylides bearing a hydrogen β- to the sulfonium centre and especially in those carrying bulky alkyl groups on sulfur.

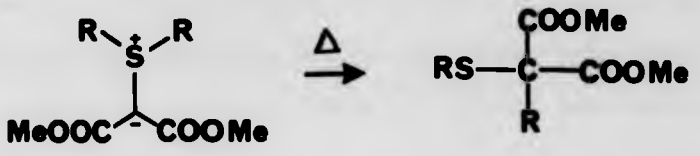
An interesting, illustrative example[4] of this fragmentation is the treatment of the penicillin (4) with dimethyl diazomalonate to form the intermediate sulfur ylide (5) which undergoes β-elimination to give the azetidinone (6).



4 5 6

The eliminative decomposition of sulfur ylides is probably a cis-elimination proceeding through a five-membered cyclic transition state[5].

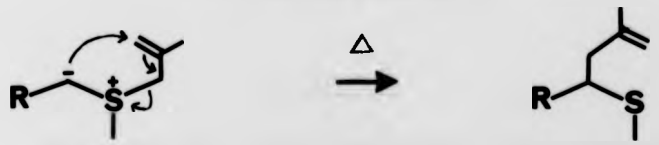
Another common rearrangement in sulfur ylides is the 1,2-shift or Stevens rearrangement. Thermolysis of the sulfonium ylide (7) gives the sulfide (8).



7 8

A concerted [1,2]-sigmatropic rearrangement is thermally disallowed[65] and it is believed that the above reaction proceeds by a homolytic dissociation, to form radicals, followed by recombination. A concerted [1,2]-sigmatropic rearrangement is photochemically allowed and, in many cases, the major reaction in photolysis of sulfur ylides is [1,2]-rearrangement.

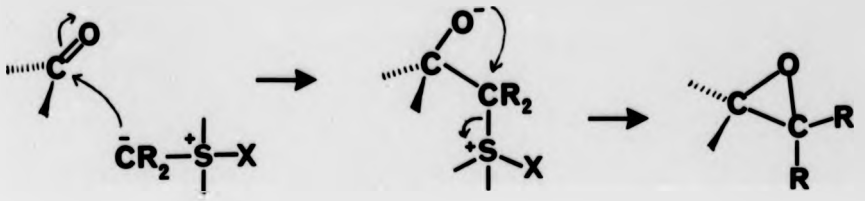
Probably the most common and synthetically useful of the ylide rearrangements is the thermal [2,3]-sigmatropic rearrangement of allylic sulfur ylides. This concerted rearrangement proceeds with complete allylic inversion, as demanded by orbital symmetry control, and many uses have been made of it in organic synthesis.



Reactions of Sulfur Ylides

A comparison between sulfur ylides and diazo compounds is striking in that both condense with carbonyl compounds to form epoxides and both cyclopropanate olefins. However the mechanistic aspect of these reagents is different since virtually all reactions of ylides are nucleophilic in nature.

Although detailed mechanistic studies have not been carried out the epoxidation of carbonyl compounds can most simply be envisaged as nucleophilic addition followed by internal nucleophilic substitution (Scheme 1)



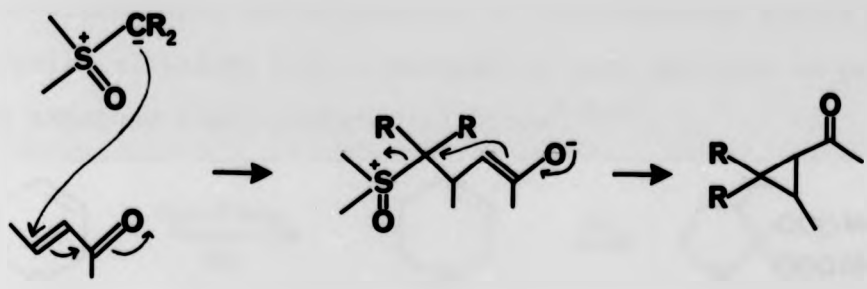
X = Electron Pair or O

Scheme 1

The addition step proceeds with stereochemical retention at the ylide carbon however inversion occurs at this site during the elimination step. The reaction proceeds equally well with sulfonium and sulfoxonium ylides.

Cyclopropanation proceeds well only in systems normally susceptible to Michael addition thus electron-poor double bonds are most susceptible. This is in contrast to the reactions of carbenes where rates are enhanced by electron donating groups on the double bond and retarded by electron withdrawing groups.

The mechanism of cyclopropanation (Scheme 2) involves nucleophilic addition of the ylide to the double bond in a Michael sense, the charge then being stabilized by delocalization on to the carbonyl or other stabilizing substituent. The final step is elimination of the sulfonium group by intramolecular nucleophilic attack of the intermediate enolate.



Scheme 2

The stereochemical integrity of the double bond is lost during the reaction since free rotation occurs in the intermediate.

In α,β-unsaturated aldehydes and ketones dimethylsulfonium methylide favours epoxide formation while dimethylsulfoxonium methylide forms the cyclopropane.

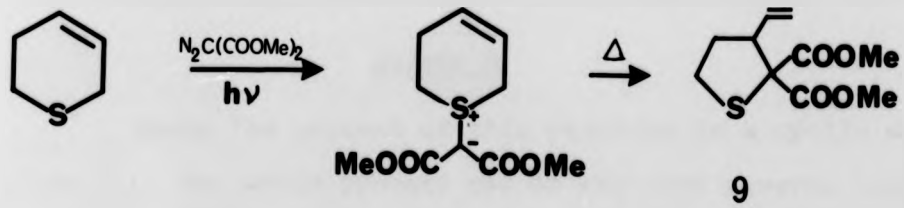
[2,3]-Sigmatropic Rearrangement

The [2,3]-sigmatropic rearrangement of α,β-unsaturated sulfonium ylides is a well documented reaction, however it is

only in recent years that the full synthetic implications of this rearrangement have been realized.

(i) Ring Expansion

Following the earlier reports[6,7] that thermolyses of the stabilized sulfonium ylides of dihydrothiopyran result in a ring contraction reaction to give the 2-substituted-3-vinyltetrahydrothiophen derivatives (9), (10) and (11), the [2,3]-sigmatropic rearrangements of five-membered cyclic α-vinyl sulfonium allylides have subsequently been employed to prepare ring expanded eight-membered sulfides.[8,9,10]



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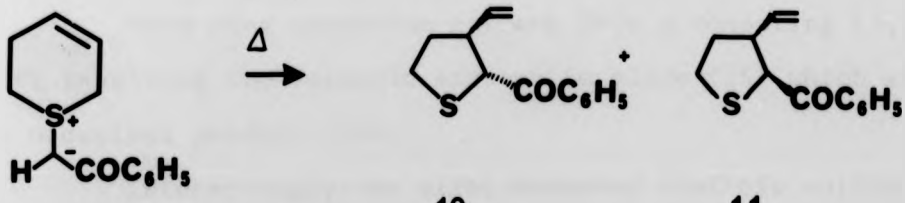
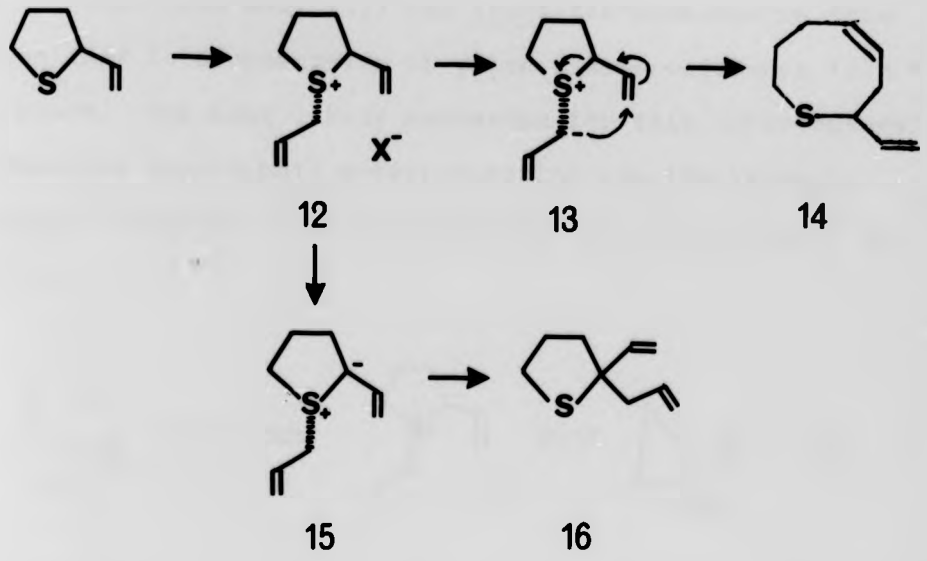


10 11

The ylides (13) were prepared by alkylation of 2-vinyltetrahydrothiophen with allyl triflate followed by treatment of the resulting sulfonium salt (12) with diazabicyclo[5.4.0]undecene (DBU). (Scheme 3).



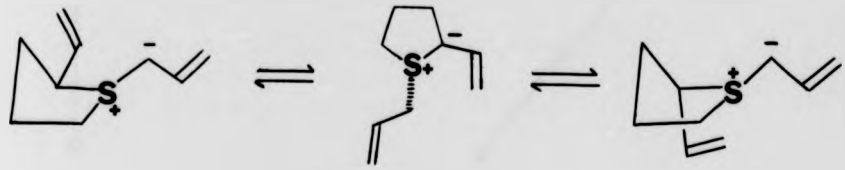
Scheme 3

Since the product of this reaction is a cyclic α-vinyl sulfide (14) the whole process can be repeated several times leading to further ring expansions to eleven-membered rings, fourteen-membered rings, etc.

This ring expansion suffers from a competing [2,3]-shift involving the isomeric endocyclic ylide (15) which affords the undesired product (16).

Interestingly the eight-membered olefinic sulfide (14) produced in this reaction is found exclusively as the cis-$\Delta^{4,5}$ isomer. Examination of the geometry of the cis- and trans-ylides (17a) and (17b) shows that only the cis-diastereoisomer (17a) can attain a reasonable geometry for a [2,3]-shift via a cisoid vinyl rotamer, which would result in the cis-olefin (14).

Since the sulfonium salt (12) has trans-stereochemistry this requires that interconversion of ylide diastereoisomers (17a ⇌ 17b) takes place. The most likely mechanism for this interconversion is reversible deprotonation-reprotonation via the isomeric endocyclic ylide (15) although inversion at sulfur cannot be ruled out.



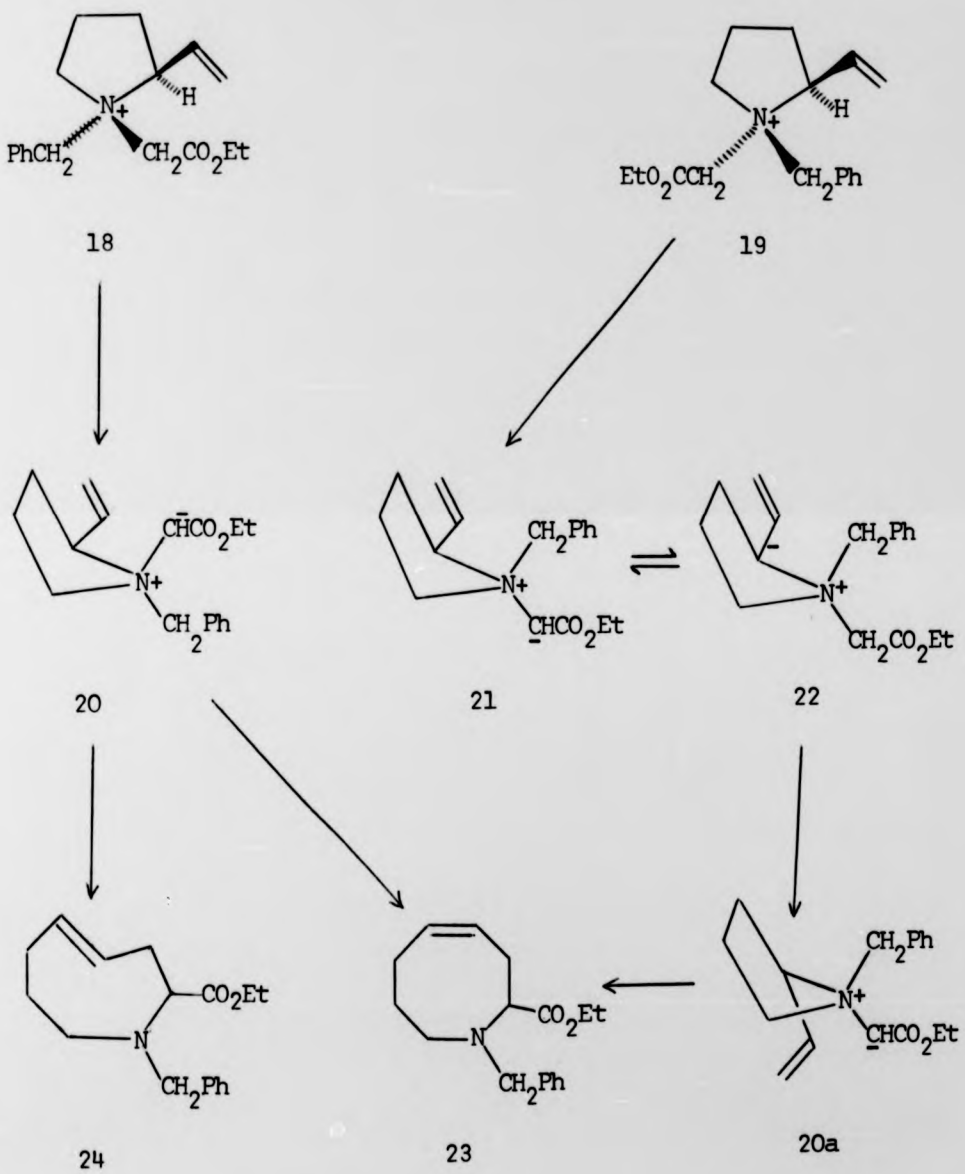
17a 15 17b

In the corresponding nitrogen-containing system[66] treatment of either diastereoisomer (18) or (19) with potassium tert-butoxide gives a mixture of the two possible ring expanded products (23) and (24) (Scheme 4).

Molecular models show that the cis-ylide (20) could conceivably rearrange to either the cis- or the trans-olefin however the trans-ylide (21) cannot give the cis-olefin.

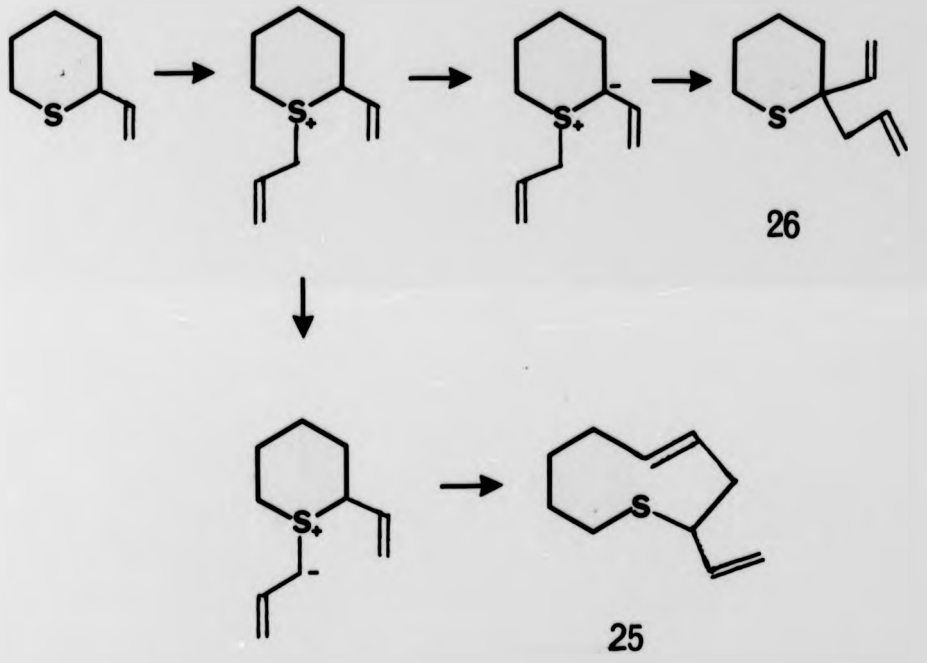
Since both diastereoisomeric ammonium salts give the same two ring-expanded products, it would appear that, similar to the sulfur series, the trans-ylide (21) is interconvertible, via the endocyclic ylide (22), with a cis-ylide (20a), a diastereoisomer of (20) (and not ylide (20) as suggested[66]), which then gives both olefins.

In the six-membered ring series (Scheme 5) the reactions are the same with the predominant product being the


PhCH2
CH2CO2Et
H
18
EtO2CCH2
CH2Ph
19
CHCO2Et
CH2Ph
20
21
22
CO2Et
24
23
20a

Scheme 4

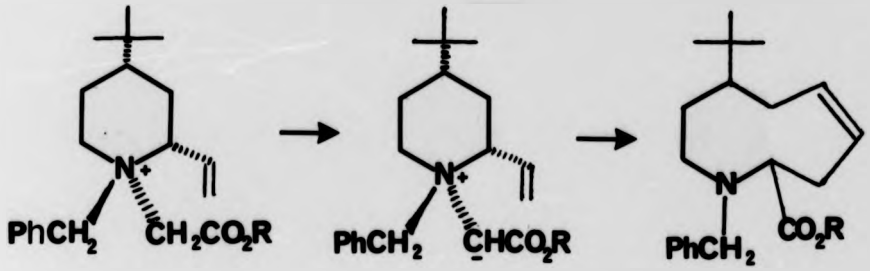
ring-expanded nine-membered sulfide (25), of which only the trans-isomer has been detected, and the minor product, from cyclization of the endocyclic ylide, being the six-membered sulfide (26). Once again this ring-expansion can be repeated giving a twelve-membered ring.



Scheme 5

Although the above ring expanded product is produced exclusively with the trans-olefin geometry the opposite is the case with the six-membered piperidinium salt (27) which, when treated with base[11], gives the ring-expanded nine-membered

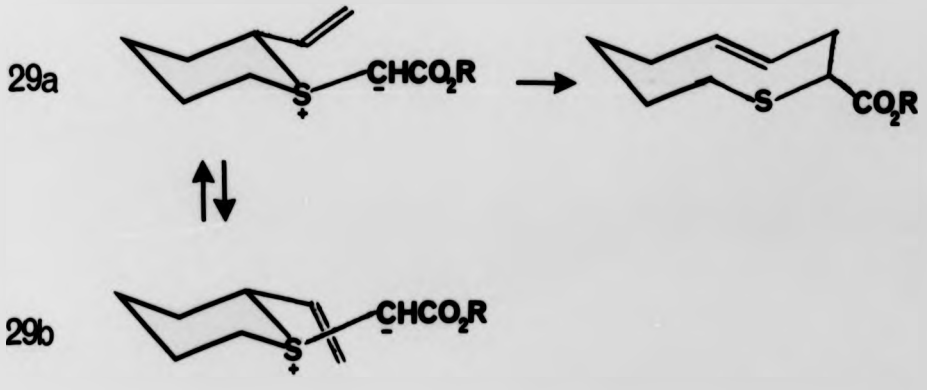
product (28) with exclusively cis-stereochemistry.



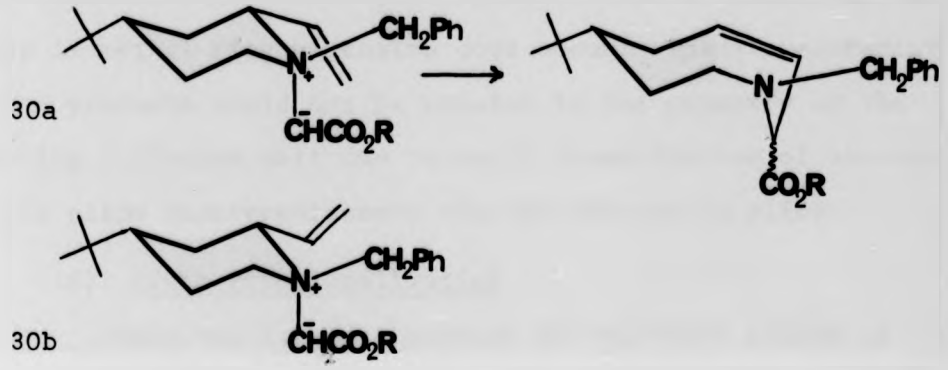
27 28

These stereochemical observations are explained by considering the ylide conformations required for formation of the various olefin geometries.

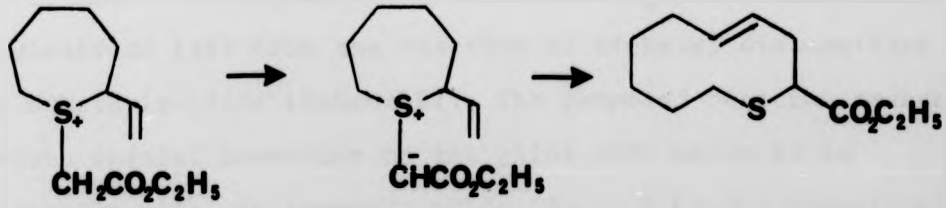
In the all equatorial sulfur system the transoid vinyl rotamer (29a) can achieve the five-centre-overlap required without significant ring distortion whereas the cisoid vinyl rotamer (29b) cannot since the distance between ylide and vinyl carbons is too large.



In the nitrogen system the ylide substituent is axial and, in this case, the cisoid vinyl rotamer (30a) is favoured while the transoid vinyl rotamer (30b) has an unfavourable overlap distance.



A ring expansion from the seven-membered sulfonium salt (31) to the ten-membered trans-olefin (32), by base treatment, has also been reported[12].



31 32

Ring expansion by [2,3]-sigmatropic rearrangements of sulfonium ylides has now been extended to non-stabilized ylides[13,14]. This procedure suffers from disadvantages owing

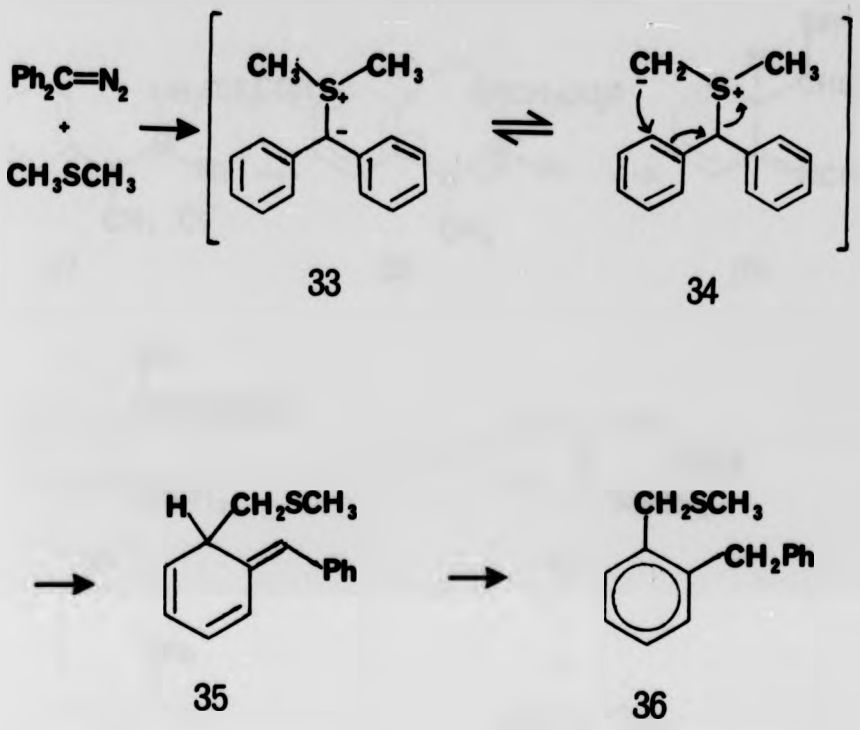
to the fact that the endocyclic ylide is often formed preferentially and many of the products are derived from it. When the exocyclic S-alkyl group contains β-hydrogens the product is often the dealkylated sulfonium salt formed by β-elimination in the endocyclic ylide. However when the S-alkyl group is methyl ring expansion does occur. The stereochemistry of the products could not be related to the geometry of the starting sulfonium salt due to rapid isomerization of the exocyclic ylide diastereoisomers via the endocyclic ylide.

(ii) Ortho Functionalization

When the β,γ-unsaturation of sulfonium ylides is part of an aromatic ring the [2,3]-sigmatropic rearrangement is still a major reaction. The overall result of this reaction is then ortho-substitution of the aromatic compound.

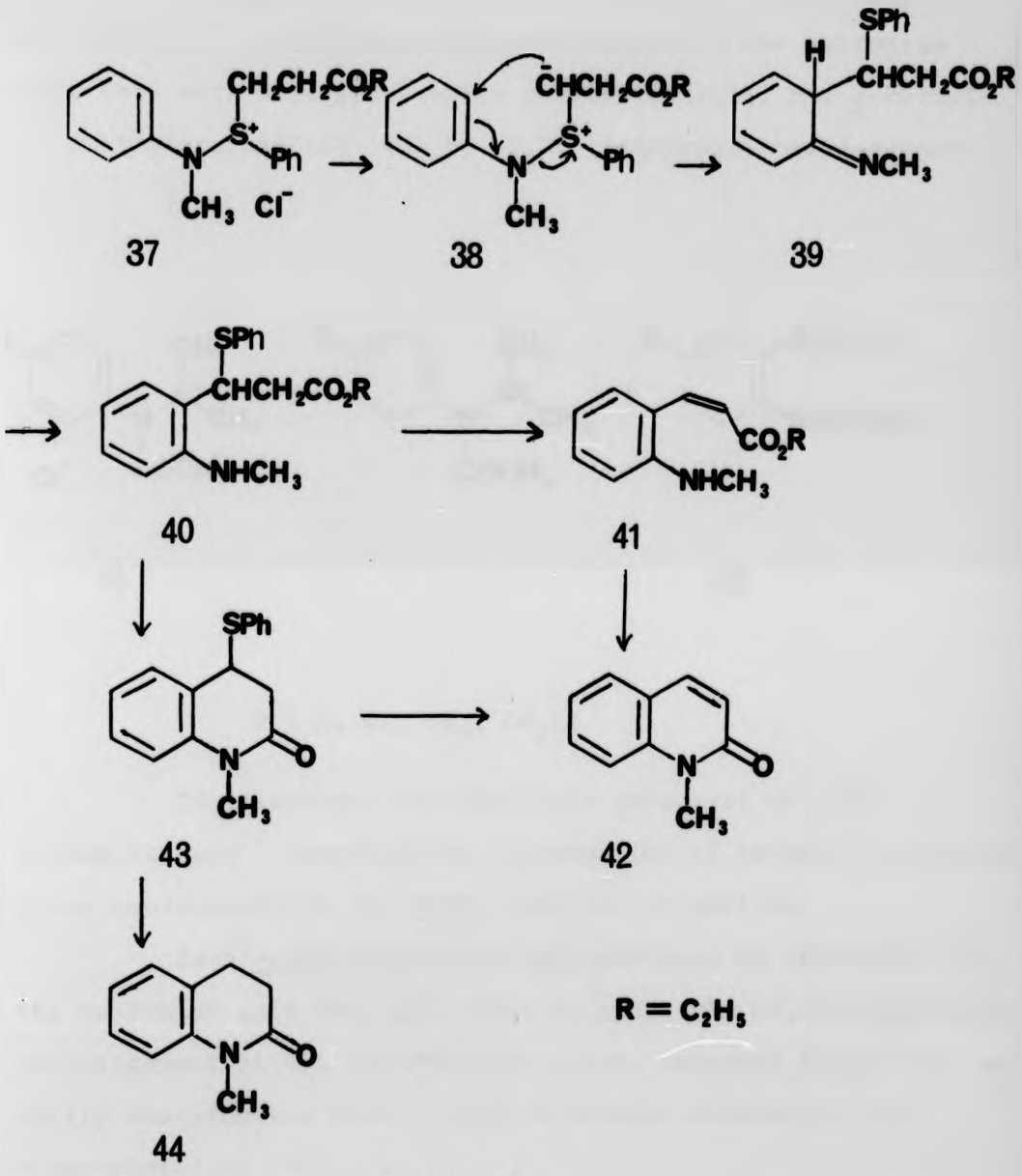
The [2,3]-sigmatropic rearrangement of sulfonium ylides incorporating an aromatic ring was first proposed in 1972 by Ando[15] to explain the formation of o-benzyl benzylmethylsulfide (36) from the reaction of diphenyl diazomethane with dimethylsulfide (Scheme 6). The proposed reaction mechanism involves initial formation of the ylide (33) which is in equilibrium with the isomeric ylide (34). A [2,3]- sigmatropic rearrangement of the latter gave compound (35) which rapidly rearomatized to give the product (36).

More recently this reaction has been extended to many different types of aromatic compound and has proved extremely useful in their ortho-functionalization.



Scheme 6

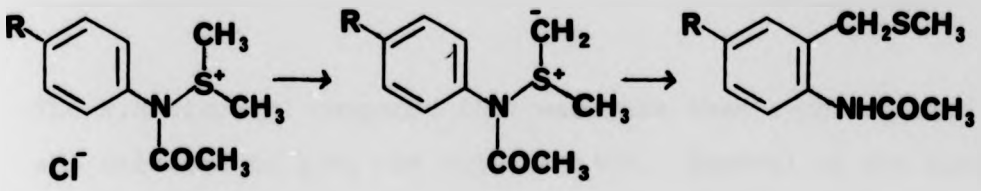
The ortho-substitution of anilines and its synthetic implications have been reported by Gassman[16] (Scheme 7). Treatment of the sulfonium salt (37), formed by reaction of N-chloro-N-methylaniline with ethyl 3-phenylthiopropionate, with base gave the sulfonium ylide (38) which underwent spontaneous [2,3]-sigmatropic rearrangement, via the intermediate (39), to give the unstable ortho-substituted aniline derivative (40) which is isolable at low temperature. Compound (40), on base treatment, gave (41) which was easily cyclized to N-methyl-α-quinolone (42). Acid treatment of (40) gave (43) which was desulfurized to 3,4-dihydro-N-methyl-α-quinolone (44) or subjected to base-catalysed elimination to give (42).



Scheme 7

A major limitation of this synthetic methodology is the tendency for olefin formation to occur in sulfonium salts containing a β-hydrogen, however this can be overcome by working at low temperature.

This methodology has been expanded[17] to the ortho alkylation of acetanilides where treatment of the sulfonium salt (45) with base gave, after rearomatization, the o-methylthiomethylacetanilide (46) by [2,3]-sigmatropic rearrangement.



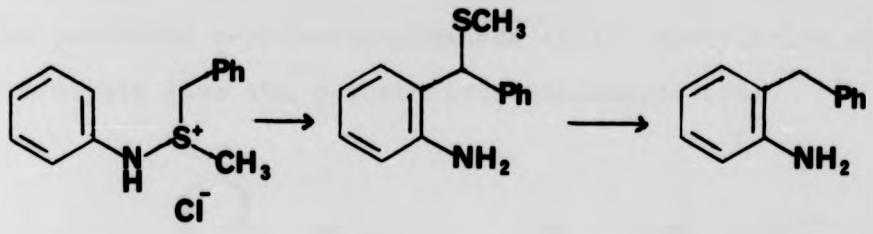
45 46

R = H, Cl, CH_3, CO_2Et

To illustrate the synthetic potential of this method Gassman[17] reported the introduction of several functional group equivalents to the ortho position of aniline.

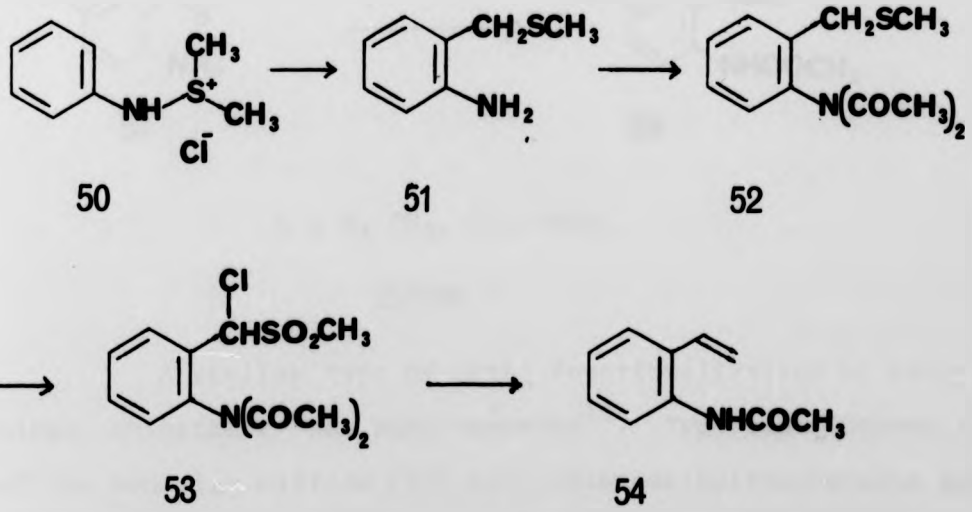
Thus ortho-benzylation was achieved by treatment of the sulfonium salt (47) with base to give, via [2,3]-sigmatropic rearrangement of the intermediate ylide, compound (48) which was easily desulfurized with lithium aluminium hydride to give o-benzylaniline (49).

The ortho-vinylation of aniline was achieved by a similar sequence of reactions starting from aniline (Scheme 8). Base treatment of the sulfonium salt (50) gave (51) as above.



47 48 49

The N,N-diacetyl compound (52) was made then α-chlorinated and oxidized to give the sulfone (53). Removal of one acetyl group followed by treatment with strong base gave o-vinyl-N-acetylaniline (54) via the Ramberg-Backlund reaction[18].

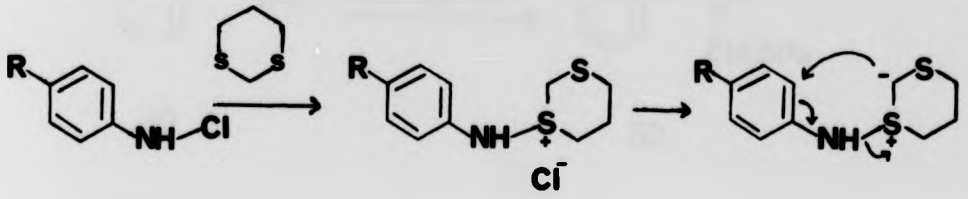


50 51 52 53 54

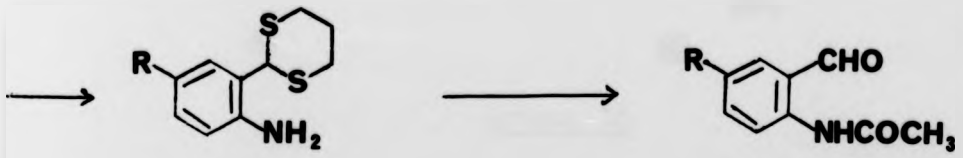
Scheme 8

One of the most useful ortho functionalization reactions is ortho-formylation. Treatment of N-chloroaniline with dithiane (Scheme 9) gave the azasulfonium salt (55) which, on base treatment, underwent [2,3]-sigmatropic rearrangement

via the sulfonium ylide (56) to give, after rearomatization, the protected o-aminobenzaldehyde (57). Acetylation and hydrolysis gave the o-acetamidobenzaldehyde (58).



55 56



57 58

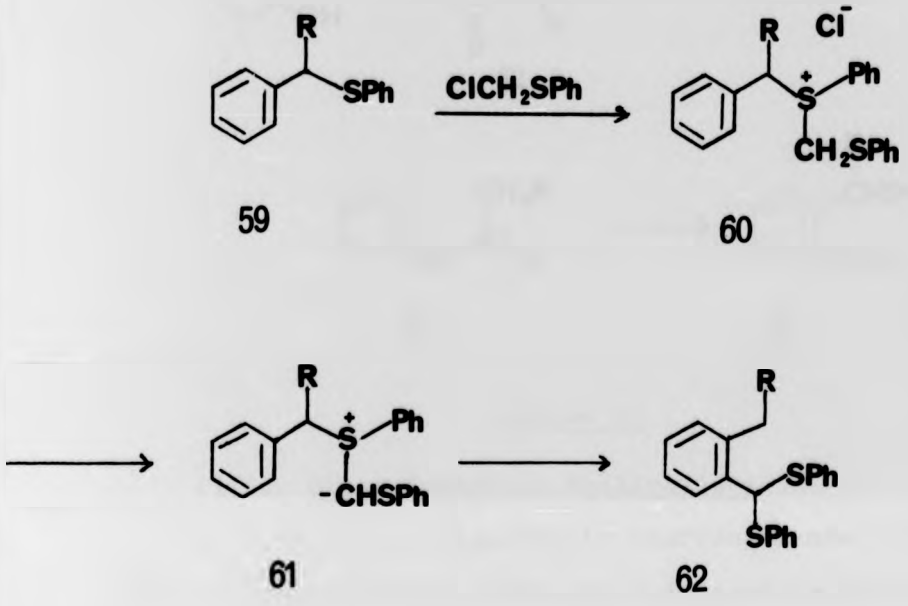
R = H, CH_3, Cl, $COCH_3$

Scheme 9

A similar type of ortho functionalization of benzyl-alkyl thioethers has been reported[19]. Treatment (Scheme 10) of the benzylic sulfide (59) with chloromethylthiobenzene gave the sulfonium salt (60) which, on base treatment, rearranged via the sulfonium ylide (61) to give the o-alkylbenzaldehyde equivalent (62).

The use of migrating aldehyde equivalents can, of course, be applied to aliphatic examples of [2,3]-sigmatropic

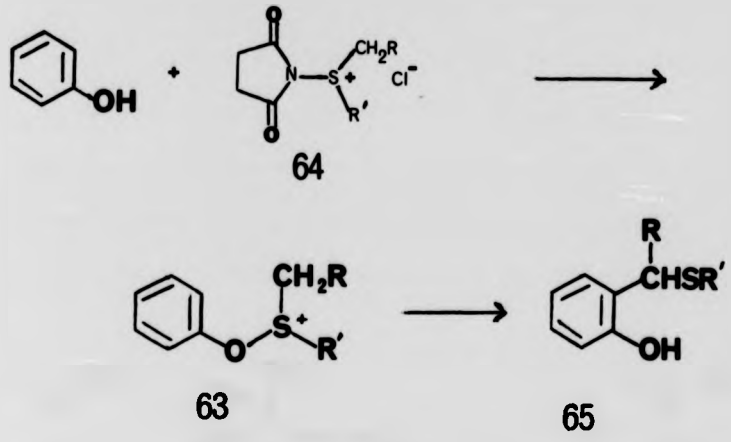
rearrangements of sulfur ylides.



Scheme 10

The above ortho functionalization reactions have now been applied to the ortho formylation and alkylation of phenols[20]. Oxasulfonium salts of the type (63) were prepared (Scheme 11) by treatment of phenol with azasulfonium salts of the type (64). Base treatment gave the o-alkyl or o-formyl phenol (65) after rearrangement and rearomatization.

As a result of the cyclic nature of the rearrangement step these ortho substitutions are relatively insensitive to substituents on the ring thus aromatic compounds bearing substituents ranging from strongly electron-withdrawing to strongly electron-donating can be tolerated.



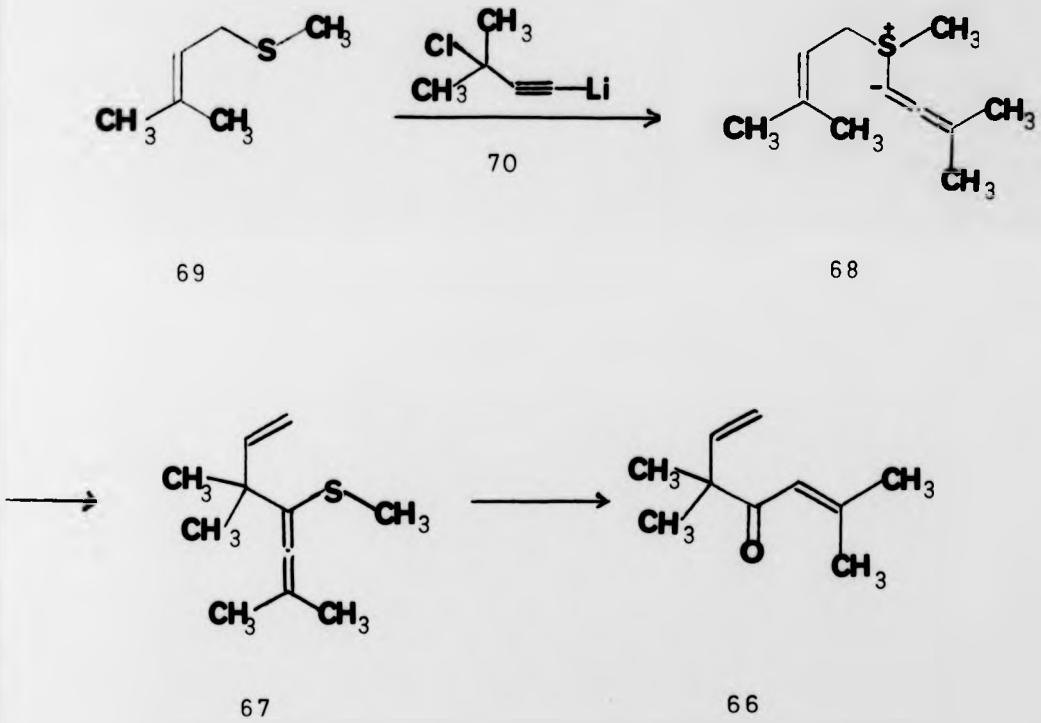
Scheme 11

(iii) Other Synthetic Applications

The [2,3]-sigmatropic rearrangements of allyl substituted sulfonium ylides have frequently been applied to synthetic problems.

A useful synthesis of the artemesia ketone (66) has been reported[21] (Scheme 12) involving preparation of the allenic thioether (67) which can be converted to the artemesia ketone by hydrolysis. The allenic thioether is available from [2,3]-sigmatropic rearrangement of the sulfonium ylide (68) formed by treatment of (69) with the lithio derivative (70).

An approach to the allylic functionalization of olefins with formation of a new carbon-carbon bond, involving the [2,3]-sigmatropic rearrangement of a sulfonium ylide, has been reported by Snider[22] (Scheme 13). The 'ene' reaction of alkenes with hexafluorothioacetone, generated *in situ*, provides

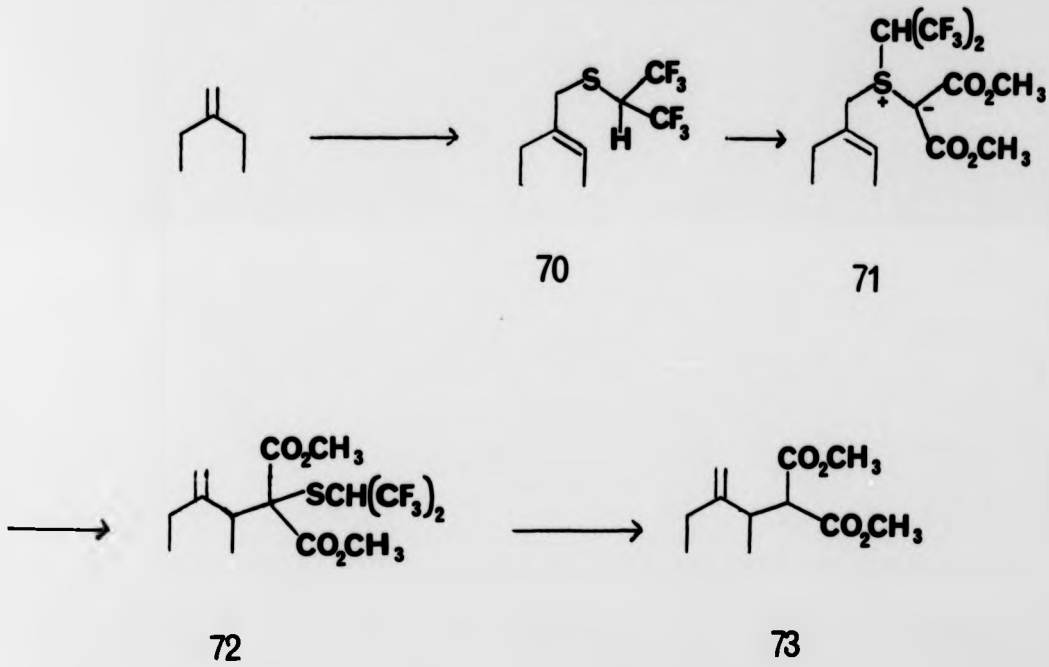


69 68

67 66

Scheme 12

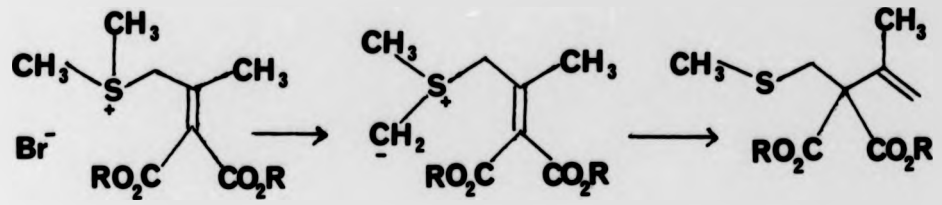
the corresponding allyl hexafluoropropyl sulfides (70) in good yield. Reaction of these sulfides with dimethyl diazomalonate gives sulfonium ylides (71) which undergo [2,3]-sigmatropic rearrangement to allyl(hexafluoropropylthio) malonates (72). Desulfurization leads to allylic malonates (73) which are difficult to prepare from alkenes by other methods.



Scheme 13

The formation of allyl malonates has been reported by Stirling[23] who treated the sulfonium salt (74) with base (Scheme 14) to give the sulfonium ylide (75) which underwent [2,3]-sigmatropic rearrangement to the allyl malonate (76).

Evidence for the participation of a nitrile group in the [2,3]-sigmatropic rearrangement of sulfonium ylides

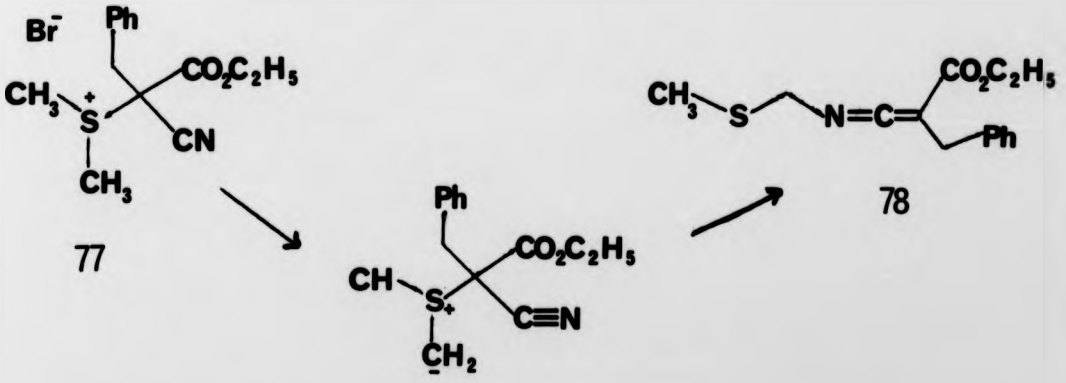


74 75 76

$R = C_2H_5$

Scheme 14

has been presented[24], thus treatment of the sulfonium salt (77) with base (Scheme 15) gave the ketenimine (78) in good yield, presumably via [2,3]-rearrangement of the sulfonium ylide (79).



77 78 79

Scheme 15

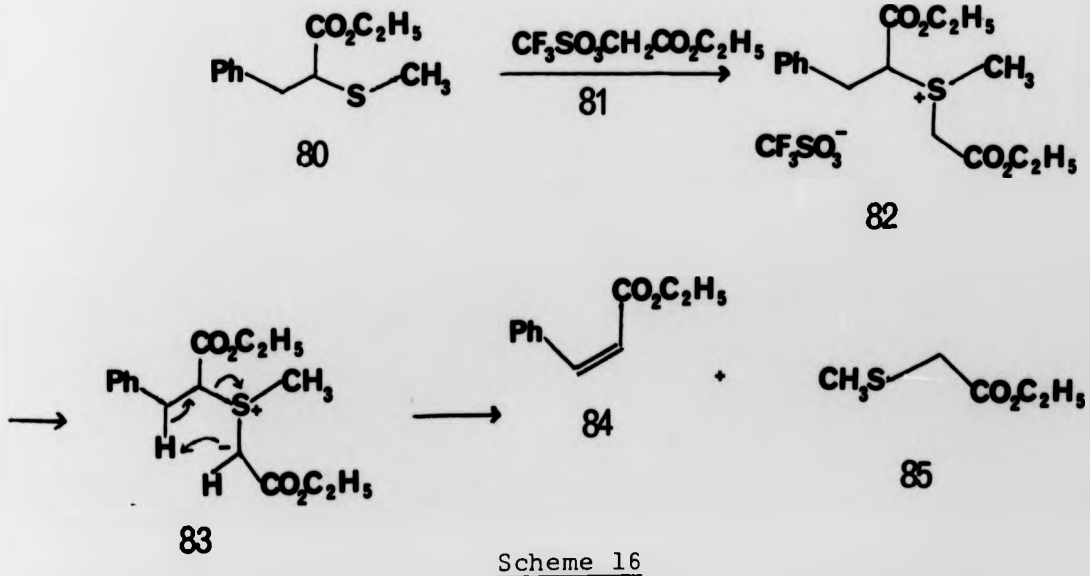
Other Rearrangements of Sulfur Ylides

(i) β-Elimination

The β-elimination of sulfur ylides bearing a β-hydrogen is a well documented reaction and occurs especially in ylides carrying bulky alkyl groups on sulfur[5]. Often the compound derived from this reaction is an undesired by-product, however, in recent years, this elimination has been utilised for synthetic purposes.

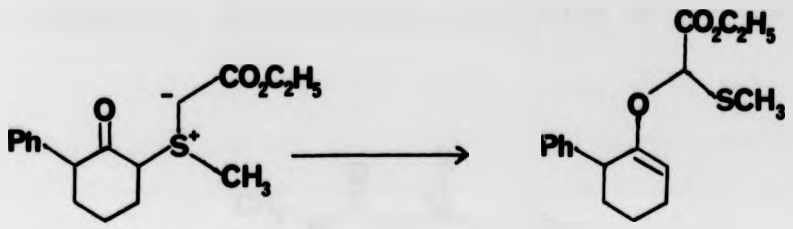
The preparation of synthetically useful alkenes has been achieved by the elimination of simple alkyl sulfide-derived ylides[25] (Scheme 16).

Treatment of the sulfide (80) with the triflate (81) leads to the sulfonium salt (82) which may be deprotonated to give the intermediate sulfonium ylide (83). β-Elimination of this ylide yields the conjugated ester (84) along with the sulfide (85).



Scheme 16

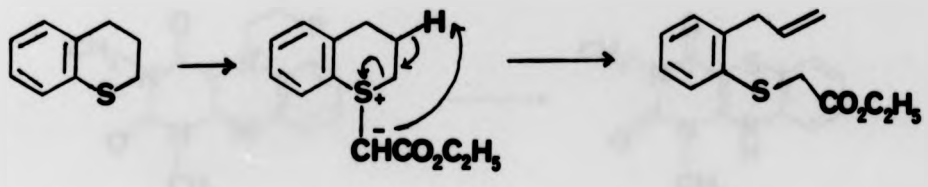
In some cases the reaction suffers from competing [2,3]-sigmatropic rearrangement as in the case (Scheme 17) of the sulfonium ylide (86) which gives an 80% yield of the enol ether (87), a reaction previously observed in analogous systems[26], however, in most cases, the olefin is produced in good yield.



86 87

Scheme 17

The formation of the olefin (88) (Scheme 18) by copper-catalysed thermal reaction of thiochromane (89) with ethyl diazoacetate shows the intermediacy of the sulfonium ylide (90) which underwent β-elimination[27].



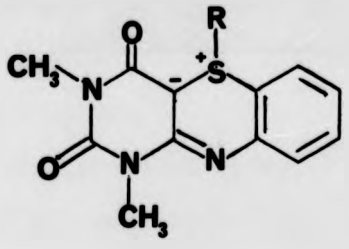
89 90 88

Scheme 18

(ii) 1,2- and 1,4-rearrangement

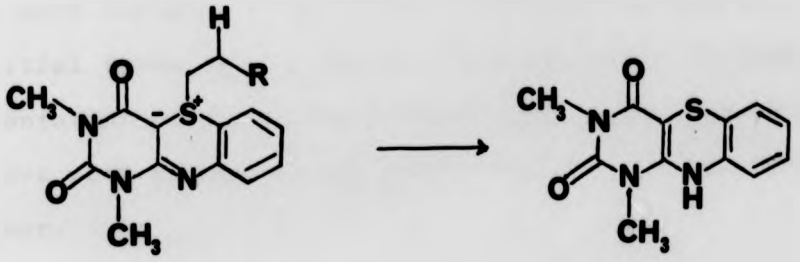
The thermally induced 1,2-rearrangement of sulfonium ylides is well known and evidence has been presented[1] supporting a radical pair mechanism for this rearrangement. Only a few examples of photo-induced [1,2]-rearrangement of sulfonium ylides have been documented[28].

It has been reported[29] that thermal rearrangement of ylides of the type (91) results in competing 1,2- and 1,4-rearrangement or β-elimination, depending on the substituent R.

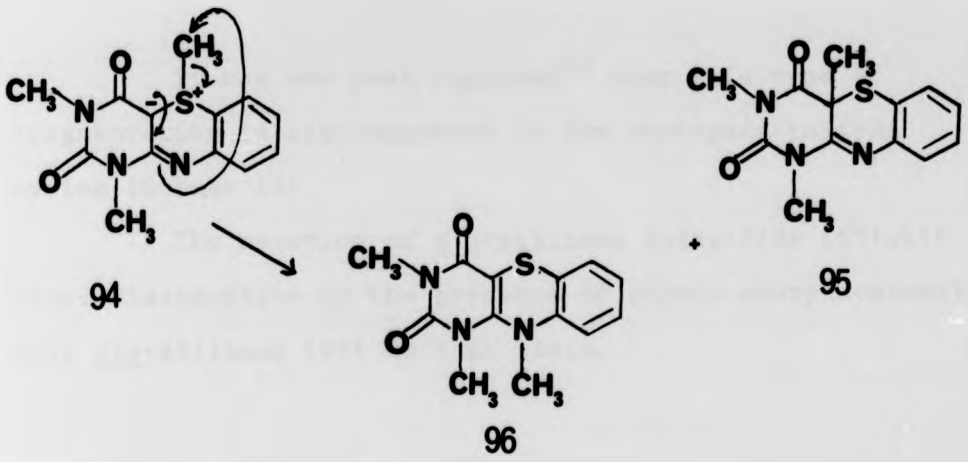


91

When R contains a β-hydrogen (92) β-elimination, to give compound (93), occurs preferentially over rearrangement. However when the substituent R is methyl (94) competing 1,2- and 1,4-rearrangement is observed giving (95) and (96) respectively.



92 93



94 96 95

It has been shown[30] that anionic 1,4-rearrangement of 2-oxyanilinium ylides proceeds principally by a concerted sigmatropic process and the present 1,4-rearrangement, likewise, appears to proceed primarily by a thermal, orbital symmetry allowed, concerted process.

In view of the conclusions[1,30] that have been drawn concerning the radical pair mechanism of thermal 1,2-rearrangements, the 1,2-rearrangement of (94) to (95) appears to involve the radical pair process.

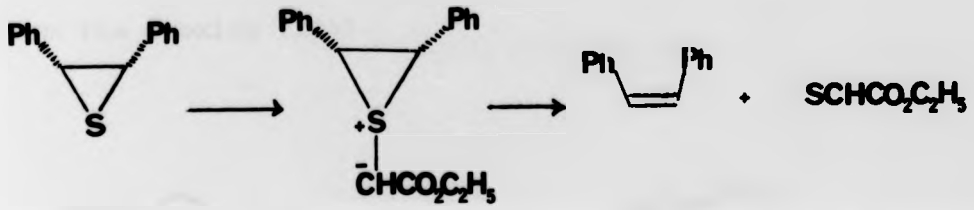
The authors claim that the occurrence of competing 1,2- and 1,4-rearrangement is novel.

(iii) Fragmentation

It has been observed previously[31] that aziridines react with carbenes to give the corresponding olefins, presumably by initial formation of the aziridinium ylides followed by fragmentation of the three-membered ring. The reaction of epoxides with carbenes also gives olefins[33] though the yields are poor.

It has now been reported[32] that this type of fragmentation is also observed in the analogous thiiran system (Scheme 19).

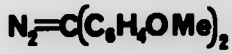
The reaction of cis-stilbene episulfide (97)with ethyl diazoacetate in the presence of cupric acetylacetonate gave cis-stilbene (98) in high yield.



97 99 98 100

Scheme 19

The initial step appears to be formation of the sulfonium ylide (99) which then decomposes, with complete retention of stereochemistry, to the olefin. Attempts to isolate thioglyoxalic ester (100) have failed, however the thioketone (101) was isolated from a similar reaction of bis(p-methoxyphenyl)diazomethane (102).



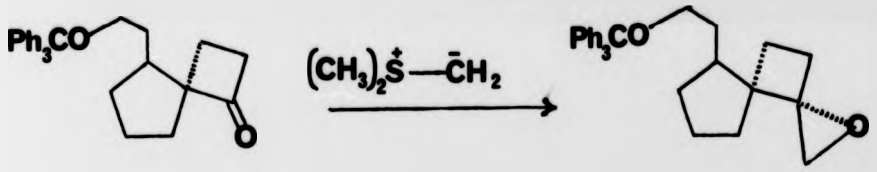
102

101

Cyclopropanation and Epoxidation

The formation of epoxides from ketones or aldehydes and the cyclopropanation of olefins susceptible to Michael addition, by the use of sulfur ylides, are now well documented reactions[1].

A recent example[34] is illustrative where, in a key step in an approach to the total synthesis of the gibberellins, the ketone (103) was treated with dimethylsulfonium methylide to form the epoxide (104).

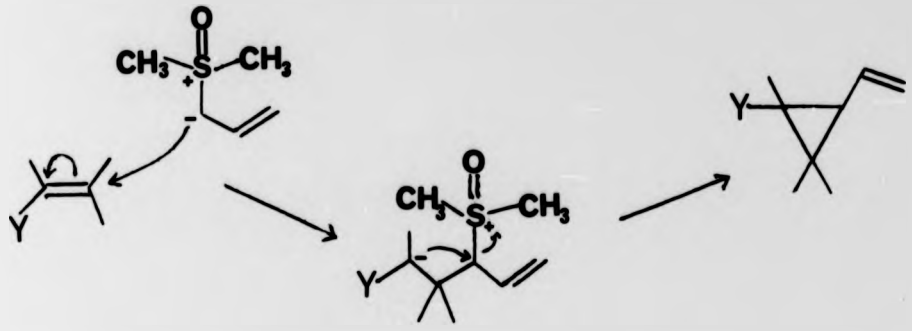


103 104

In recent years several uses of this type of reaction have been developed aiming particularly at the synthesis of functionalized cyclopropane derivatives.

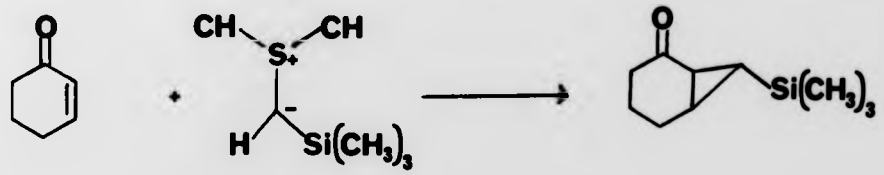
Functionalized vinylcyclopropanes have been obtained (Scheme 20) by reacting a stable allylide with an activated olefin[35].

The conversion of α,β-unsaturated carbonyl compounds into silylcyclopropyl ketones has been achieved by the use of the novel sulfonium ylide, dimethylsulfonium trimethylsilylmethylide (106). Treatment[36] (Scheme 21) of α,β-unsaturated ketones of



Scheme 20

type (105) with (106) gave the cyclopropanated derivative (107). No trace of the corresponding epoxide was observed.



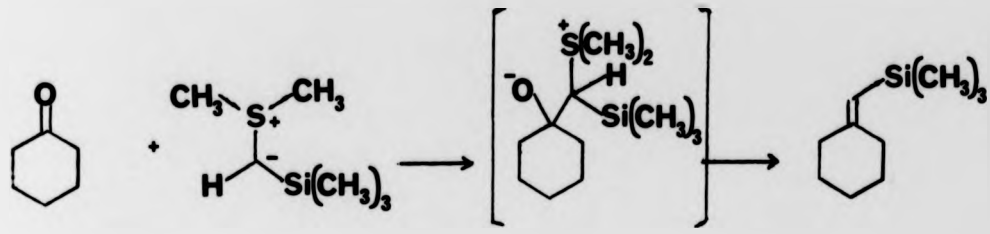
105 106 107

Scheme 21

Whilst a few silylcyclopropanes are known no silylcyclopropyl ketones have previously been prepared.

For saturated aldehydes and ketones the reaction with this sulfur ylide did not give the anticipated epoxides but led to silylalkenes derived from a "Wittig"-type reaction.

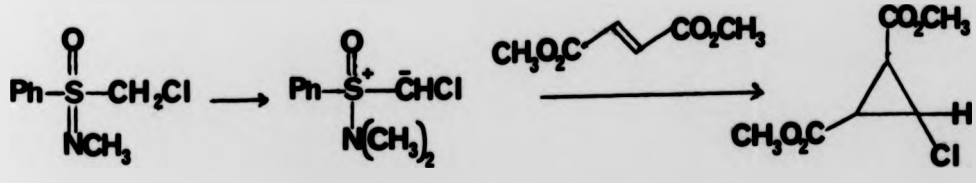
For example the treatment of cyclohexanone (Scheme 22) with the sulfonium ylide led to the olefin (108) in a reaction which is unprecedented in sulfur ylide chemistry.



108

Scheme 22

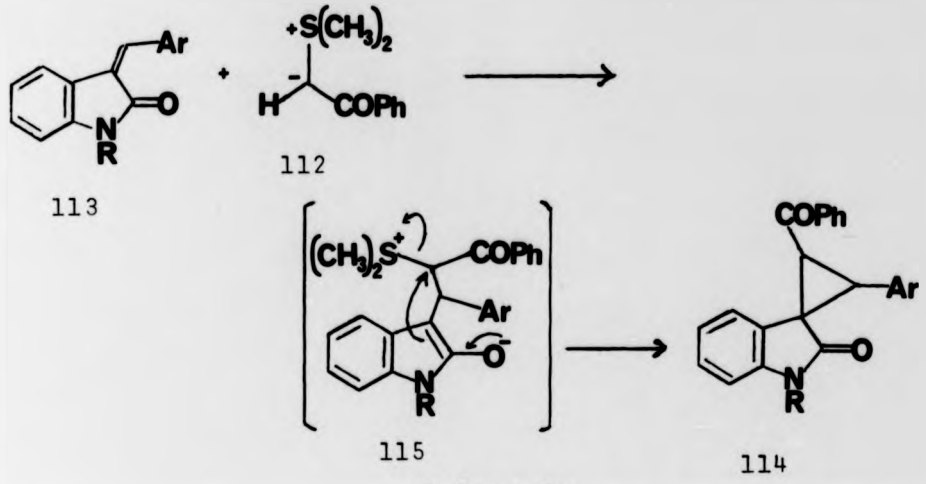
The cyclopropanation of α,β-unsaturated carbonyl compounds by α-chlorosulfoximine-derived sulfoxonium ylides has been reported[37]. N-Methylation (Scheme 23) of the α-chlorosulfoximine (109), a novel class of compounds, with trimethyloxonium fluoroborate followed by base treatment gave the sulfoxonium ylide (110) which reacted, in the usual way, with dimethyl fumarate to give the chlorocyclopropane derivative (111) with mixed stereochemistry.



109 110 111

Scheme 23

Dimethylsulfonium phenacylide (112) has been used[38] (Scheme 24) for the cyclopropanation of 3-arylmethylene-1-methylindoline-2-ones (113).



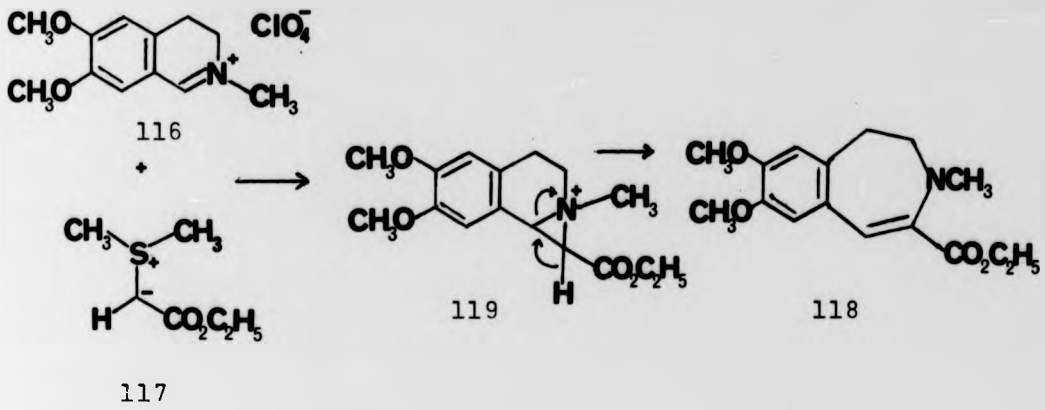
113 112 115 114

Scheme 24

Of the four possible stereoisomers of (114) only two are observed regardless of R. Two of the four possibilities are eliminated because of unfavourable geometry in intermediate (115) and free rotation in this intermediate accounts for the non-stereoselectivity of this reaction.

The cyclopropanation of alkenes by sulfur ylides has now been extended to the formation of aziridines from iminium salts[39] (Scheme 25).

The reaction of the dihydroisoquinolinium salt (116) with dimethylsulfonium ethoxycarbonylmethylide (117) gave the benzazepine (118), as the only stable product, derived from ring expansion of the initially formed aziridinium ion (119).

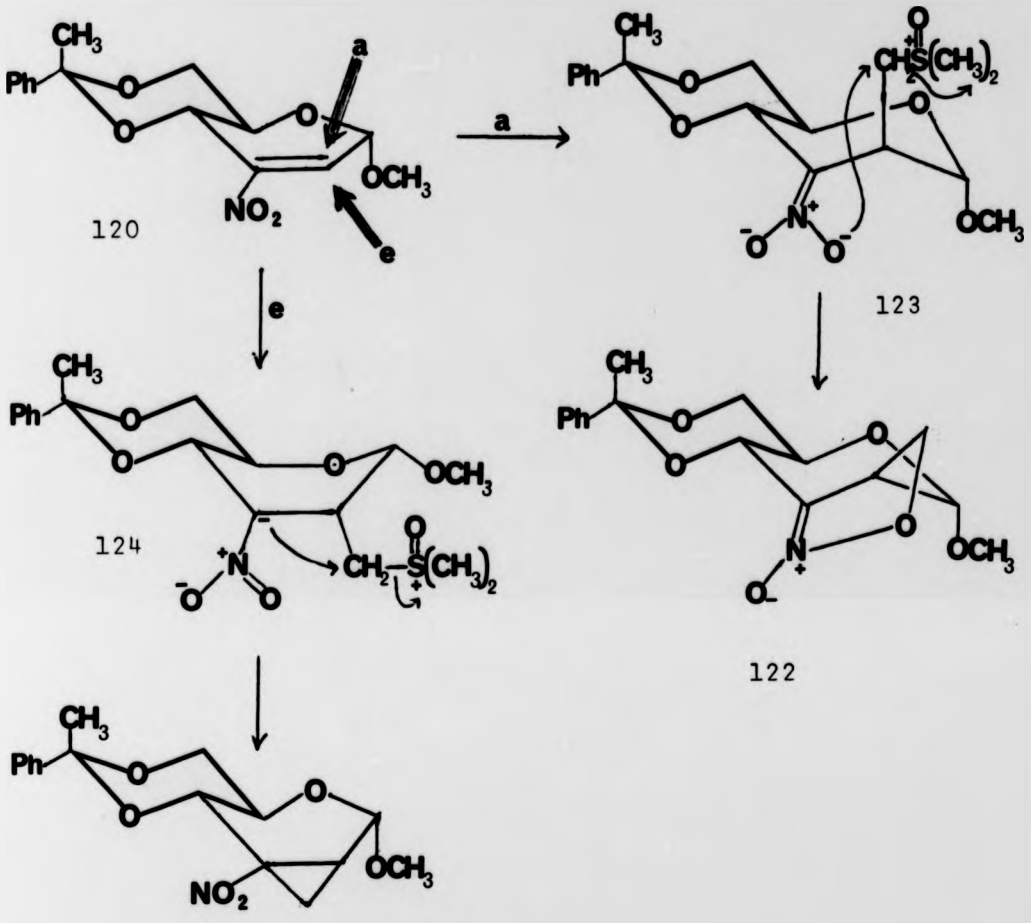


Scheme 25

The reaction of unsaturated nitro sugars with sulfur ylides to form cyclopropanes has been reported[40]. The reaction (Scheme 26) of dimethylsulfoxonium methylide with the nitro sugar (120) gives the cyclopropane (121), in 16% yield, and the isoxazoline-N-oxide (122) in 56% yield.

When the ylide approaches axially 1,4-addition, to form the isoxazoline-N-oxide, occurs specifically because of the unfavourable geometry for 1,2-addition, however when the ylide approaches equatorially 1,2-addition occurs specifically. The mechanistic implications of this reaction are best realised by considering the intermediate ionic species[41] (Scheme 26).

When the ylide approaches from the axial side, the intermediate nitronate (123) should have a chair like transition state in which the carbon bearing sulfur moves up and the carbon bearing nitrogen moves down. Molecular models indicate that, during this movement, interaction between the nitro oxygen and



Scheme 26

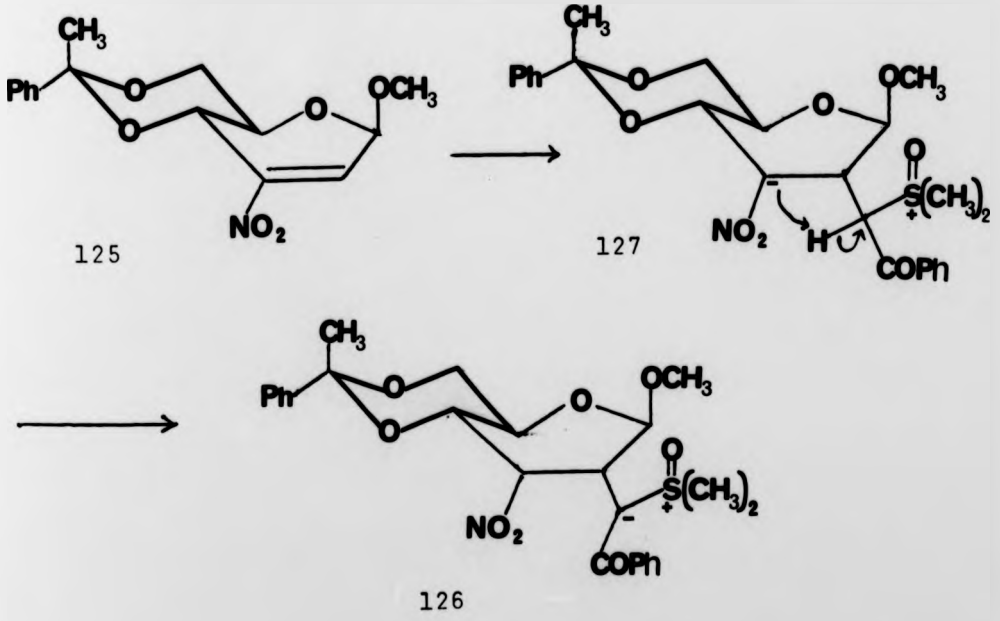
the carbon bearing sulfur is more efficient than that between the two carbon atoms, thus 1,4-addition occurs.

In intermediate (124), derived from equatorial attack, the geometry and internuclear distances are favourable for cyclopropane formation which then occurs specifically.

As might be expected, for steric reasons, axial attack predominates in the series with the α-methoxy group,

giving predominantly isoxazoline-N-oxide. Equatorial attack predominates in the series with the β-methoxy group, giving predominant cyclopropane formation[42]. As the steric bulk of the ylide substituent increases there is the expected increase in the amount of product derived from attack at the less hindered face of the sugar molecule[41].

When the reaction is carried out using sulfur ylides bearing a hydrogen on the anionic carbon, in some cases novel sulfur ylides are formed[42] (Scheme 27). In the reaction of the β-methoxy nitro sugar (125) with dimethylsulfoxonium phenacylide the major product is the novel sulfoxonium ylide (126) derived from intramolecular proton abstraction in the intermediate (127).



Scheme 27

These new ylides appear to be extremely stable compared with normal sulfur ylides having one stabilizing group and this exceptional stability cannot be explained merely in

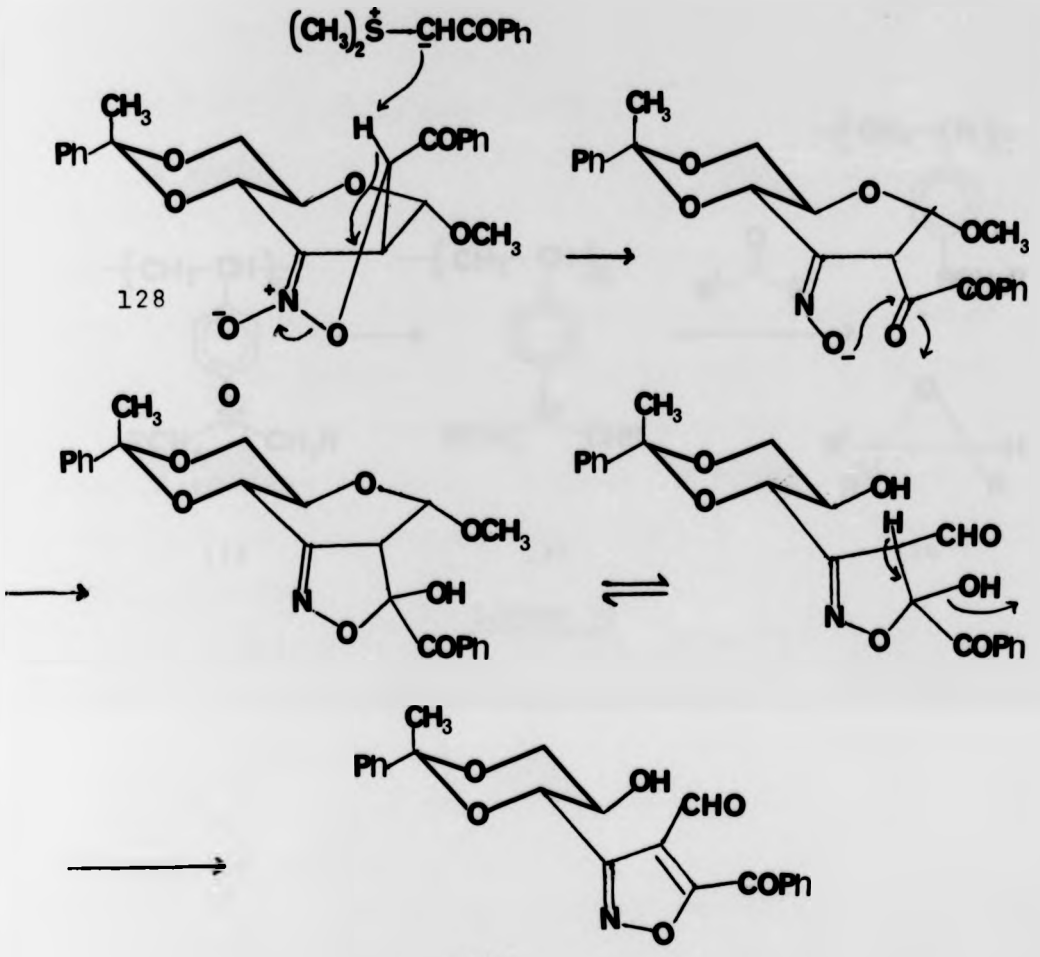
terms of delocalization over the carbonyl group. It seems likely that there is a through-space interaction between the positively charged sulfur atom and the nitro group, in a six-membered ring orientation, resulting in some delocalization of this positive charge over the nitro group.

When the sulfur ylide is fairly basic, as with dimethylsulfonium phenacylide, the isoxazoline-N-oxide (128), formed by axial attack, is susceptible to proton abstraction by unreacted ylide[43] and rearranges to form the isoxazole-derivative (129) presumably by a mechanism similar to that shown in Scheme 28. This reaction does not occur when dimethyl-sulfonium ethoxycarbonylmethylide, or any less basic ylide, is used.

Sulfonium polymers are well known and have been used in many fields such as ion-exchange resins and as the polymer support in Merrifield's peptide synthesis. Recently the first preparation of a polysulfonium ylide has been reported[44] (Scheme 29). The polysulfide (130) was photolysed in the presence of dimethyl diazomalonate to form the poly-sulfonium methylide (131).

This type of polymeric sulfonium ylide has now been used as an insoluble resin in the formation of epoxides from carbonyl compounds[45] (Scheme 30). The ylides (132) are prepared by base treatment of the corresponding sulfonium salts (133) derived from polystyrene.

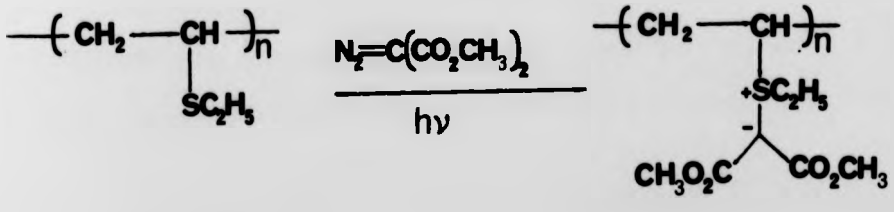
The yields of epoxide (134) obtained by this method are often as high as 95% and the isolation procedure is simple. The sulfonium ylide polymer can be regenerated without loss of activity.



128

129

Scheme 28



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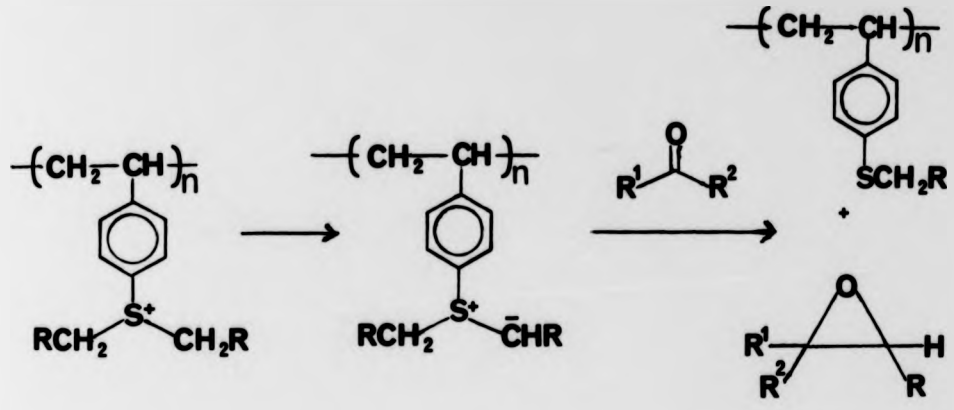
Scheme 29



133 132 134

Scheme 30

Nucleophilicity of Sulfur Ylides

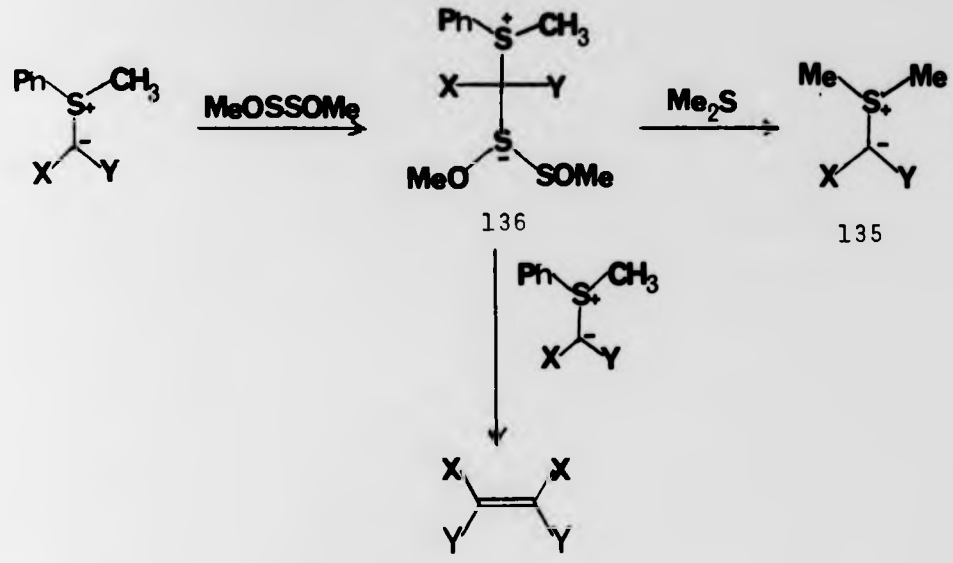
The nucleophilicity of the carbanionic centre of sulfonium ylides is fundamentally important in most of their reactions and depends on the extent of delocalization of the negative charge. Thus sulfur ylides with two stabilizing groups on the anionic carbon would be expected to be less nucleophilic than those with one stabilizing group and those which are non-stabilised. Likewise sulfonium ylides should be more nucleophilic than sulfoxonium ylides due to less charge delocalization.

Matsuyama[46] has attempted to measure the nucleophilicity of sulfonium ylides by observing the ^{13}C chemical shifts of the anionic carbon and by observing the ratio of the two main products of the reaction of the ylides with dimethoxydisulfide.

The two main reactions (Scheme 31) are transylidation to give a new sulfonium ylide (135) and olefin formation. Since olefin formation probably involves nucleophilic attack of the sulfonium ylide on intermediate (136) then an increase in olefin formed over transylidation would indicate increasing nucleophilicity of the original sulfonium ylide.

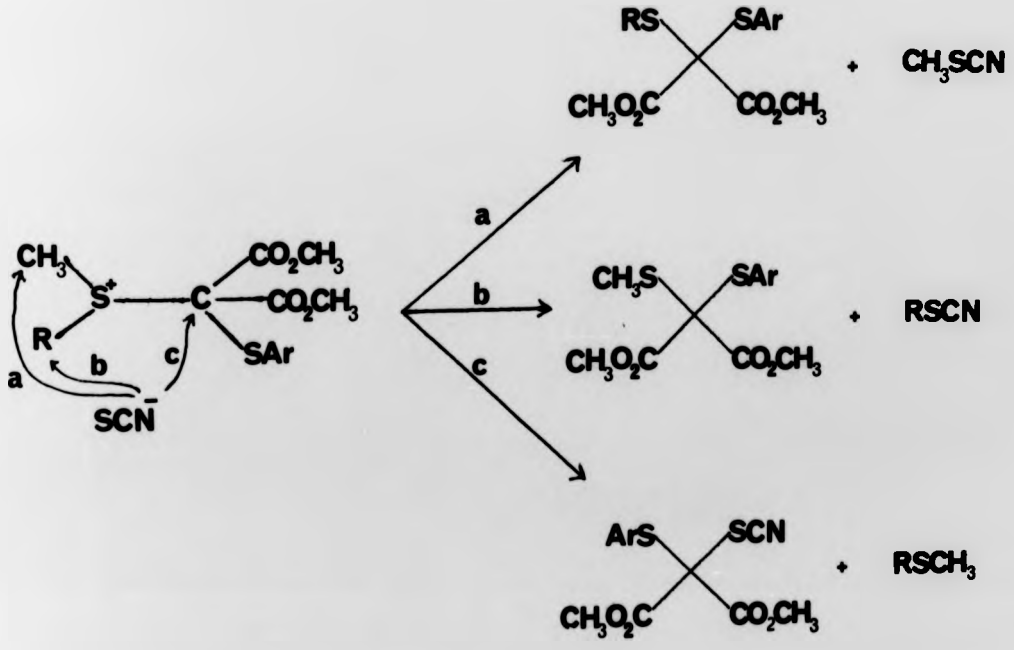
The results were predictable in that when either X or Y = COMe the nucleophilicity was lower than X or Y = CO_2Me. Similarly the presence of two stabilizing substituents lowered the nucleophilicity of the ylide.

The intermediate (136) in Scheme 31 is, of course, susceptible to nucleophilic attack at three different sites. The



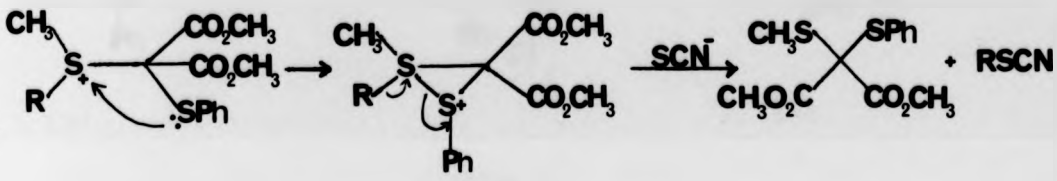
Scheme 31

fate of this type of intermediate has been studied by Matsuyama[47], in the presence of the nucleophilic thiocyanate ion and a non-nucleophilic sulfonium ylide (Scheme 32).



Scheme 32

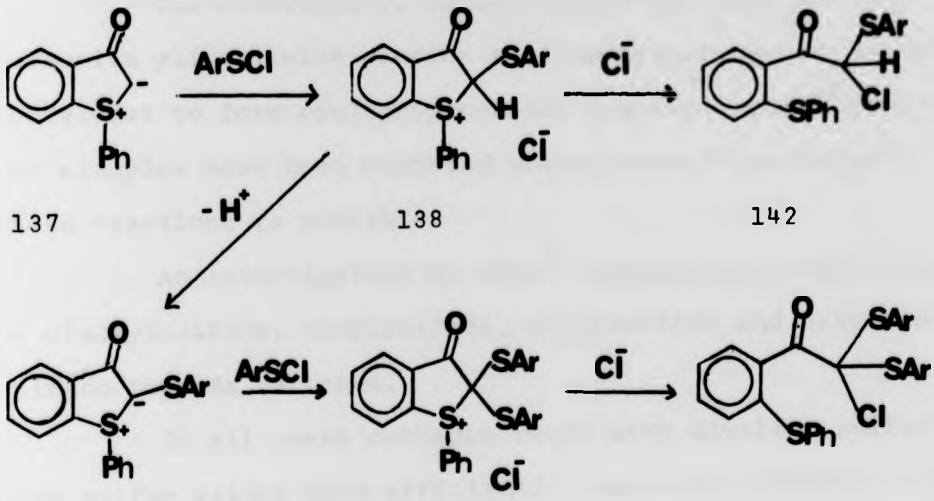
By observation of the products Matsuyama was able to compare the reactivity, towards the nucleophile, of the group R compared with methyl and he found that this decreased in the order $PhCH_2$- > i-Propyl > Me > Et. This order is explained by an S_N1-type mechanism (Scheme 33) involving a unimolecular fragmentation step with the R group leaving and subsequently combining with the nucleophile.



Scheme 33

The reaction of sulfur ylides with dialkyl- and diaryldisulfides has been studied by Field[48] who used ylides of varying nucleophilicity and found that transylidation, to form compounds of type (135) (Scheme 31), was the most common reaction. Products derived from nucleophilic attack of the aryl- or alkylsulfide anion on an intermediate of type (136) (Scheme 31), were also isolated.

The nucleophilicity of sulfonium ylides is fundamental in determining the products of the reaction of cyclic sulfonium ylides of the type (137) with arenesulfenyl chlorides[49] (Scheme 34).



Scheme 34

Reaction of the ylide (137) with arenesulfenyl chloride gave intermediate (138) which could have three different fates depending on the substituents on the aryl group.

If electron-withdrawing groups are present on the aryl group then proton removal is facile to form a stabilized non-nucleophilic sulfonium ylide (139).

If no electron-withdrawing groups are present on the aryl group the ylide (139) formed can act as a nucleophile and react with a further molecule of arenesulfenyl chloride to form a thioacetal (140) which is susceptible to nucleophilic attack by chloride ion to form a comparatively rare chlorothioacetal (141).

The intermediate salt (138) is also susceptible to nucleophilic attack by chloride ion to form the chlorosulfide (142).

Reaction of Divalent Sulfur with Electrophiles

The reactions of carbenes with sulfides to form sulfonium ylides, with olefins to form cyclopropanes and with acetylenes to form cyclopropenes are now well known, however few examples have been reported where competition between these reactions is possible.

An investigation by Ando[50] compares the reactivities of dialkylsulfide, vinylsulfide, allylsulfide and allylvinylsulfide towards carbenes.

In all cases carbenes react with divalent sulfur to form sulfur ylides more efficiently than with unactivated olefins to form cyclopropanes.

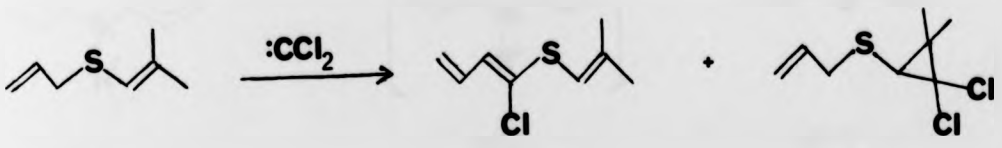
In the thermal reaction of vinyl sulfides with methyl diazoacetate the major product is derived from the sulfonium ylide with only a small amount of cyclopropane formed. Kinetic data reveal that attack on vinylic sulfur is four or five times faster than on the vinylic double bond although this double bond is twice as reactive as that in trimethylethylene. The results of the reactions of vinyl sulfides with dimethyl diazomalonate, phenyl diazomethane and diphenyl diazomethane are in agreement with the above results. In the triplet sensitized photolysis the yield of cyclopropane doubles and the yield of sulfonium ylide is halved.

In the thermolysis of diazocompounds with vinyl sulfides the yield of ylide-derived product is high and the cyclopropane is not observed. This is in agreement with the belief that cyclopropanation is a triplet carbene reaction while ylide formation is through the singlet carbene.

It is well known that carbenes add less easily to acetylenes than to olefins and, as expected, the reactions of acetylenic sulfides with diazocompounds gave only sulfonium ylide-derived products with no cyclopropene being formed.

In the reaction of dichlorocarbene with vinylic sulfides cyclopropane was the major product, however with allylic sulfides the sulfonium ylide-derived products predominated.

In the reaction of allylvinylsulfide (143) with dichlorocarbene the major product (144) is derived from the sulfonium ylide and only a small amount of vinylcyclopropanated product (145) is formed.



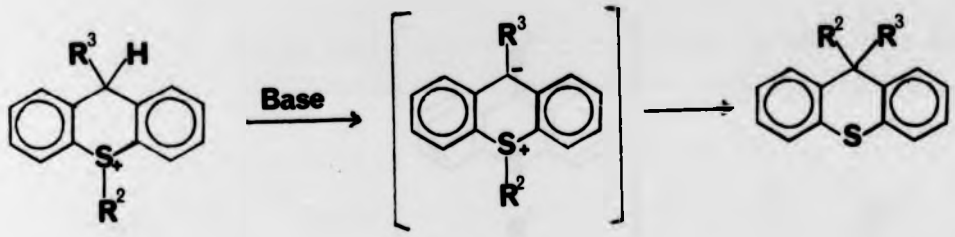
143 144 145

The result of the above reaction emphasises that divalent sulfur is more reactive towards carbene than either activated or unactivated double bonds, and that the vinyl sulfide double bond is more reactive than the allylic sulfide double bond due to activation by vinylic sulfur.

Novel Sulfur Ylides

The chemistry of sulfur ylides is a large and expanding field and novel examples are constantly being reported. Hori[51] has reported the synthesis and properties of the first crystalline 1,4-sulfur ylide (often called a betaine).

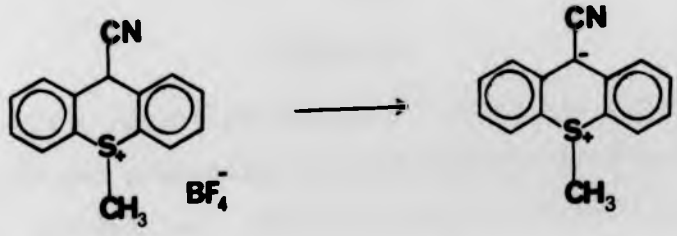
The cyclic sulfur 1,4-ylides (146) derived from 9,10-disubstituted thioxanthenium salts (147) are normally unstable and undergo 1,4-rearrangement to give the corresponding 9,9-disubstituted thioxanthenes (148). However, treatment of



147 146 148

R^2 = alkyl or aryl; R^3 = H or aryl

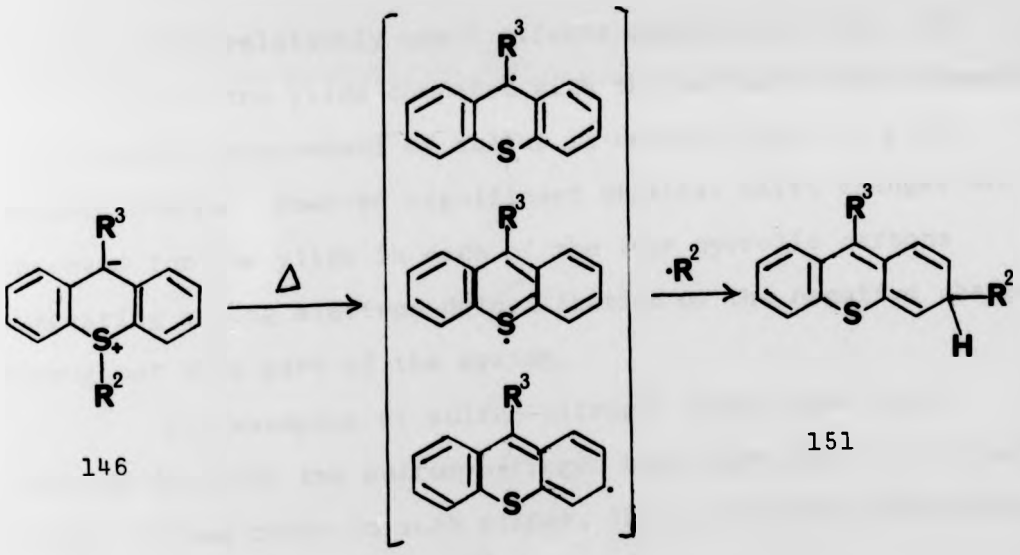
the salt (149) with sodium hydride furnished the stable, crystalline, isolable sulfur 1,4-ylide (150).



149 150

The stable sulfur ylide (150), on heating, undergoes thermal 1,4-rearrangement, as above, giving a compound of the type (148) where R^2 = CN and R^3 = CH_3.

When the substituent R_2 in (146) is sufficiently bulky to prevent the 1,4-rearrangement a new rearrangement occurs[52] giving the 3-alkyl-9-arylthioxanthene (151). Esr. spectra were observed during the rearrangement and their nature suggested the presence of 9-arylthioxanthyl radicals (152). The mechanism proposed on the basis of this evidence is shown in Scheme 35.

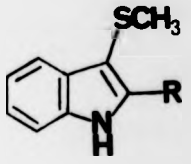


146 152 151

Scheme 35

In a recent publication[53] Daves has reported the preparation and properties of 3-dimethylsulfonioindolide (153), a stable, crystalline, unusually basic sulfonium ylide.

The ^{1}H and ^{13}C chemical shifts of atoms in this series of compounds have been studied[54] and the data analysed in terms of electronic changes in the series thioether (154) → sulfonium salt (155) → sulfonium ylide (153).



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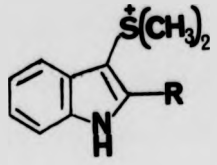

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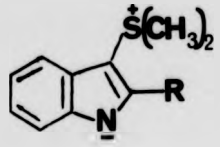


153

The relatively small effects observed for the -SMe resonances in the ylide compared with the sulfonium salt suggest only limited involvement of sulfur in delocalizing the ylide anionic charge. However significant chemical shift changes are observed for the ylide in each of the four pyrrolic carbons suggesting strong electron-delocalization of the negative charge throughout this part of the system.

Few examples of sulfur-nitrogen ylides have been reported in which the sulfur-nitrogen bond forms part of a ring system. A new route to such ylides, the 1,2,4-benzothiadiazines (156), has now been reported[55].

157

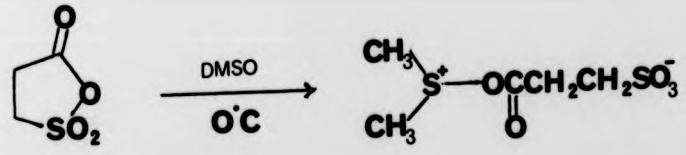
156

N-Arylbenzamidines (157) react with N-chlorosuccinimide and sulfenyl chlorides to form the 1-aryl or 1-alkyl-1,2,4-benzothiadiazines (156). This work could be regarded as a method of ortho-substitution, by electrophilic sulfur, of N-arylamidines. (cf. Page 17).

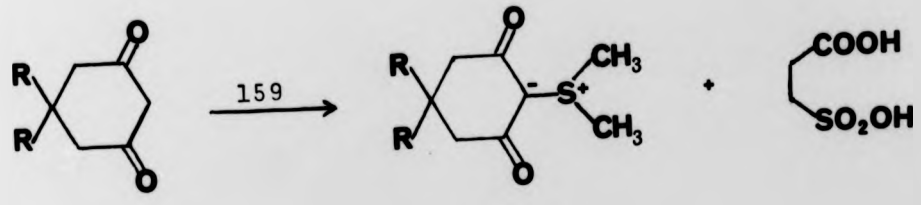
New Methods of Sulfur Ylide Synthesis

Sulfur ylides can be prepared by a variety of methods the most common being the base treatment of sulfonium salts or the reaction of sulfides or sulfoxides with carbenes. Another common method is the condensation of active methylene compounds with dimethyl sulfoxide under a variety of conditions.

A recent publication by Schank[56] reports a modification of the DMSO procedure in which the technically available 3-sulfopropanoic anhydride (158) is used as the condensing reagent (Scheme 36). A mixture of (158) and DMSO stirred in dichloromethane leads to formation of an insoluble zwitterionic complex of assumed structure (159). This complex proved to be an excellent reagent for the transfer of a sulfonium group to activated methylene compounds, such as 1,3-cyclohexane diones, to form sulfonium ylides (160).



158 159



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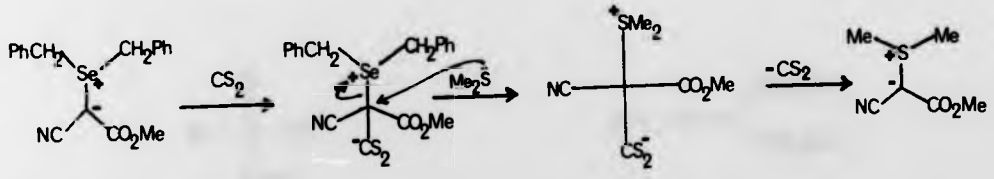
Scheme 36

Sulfonium ylides have been formed[57] by a transylidation reaction of selenonium ylides with sulfides.

Treatment of dibenzylselenonium cyano(methoxycarbonyl)-methylide (161) with excess dimethylsulfide in the presence of carbon disulfide gave a quantitative yield of dimethylsulfonium cyano(methoxycarbonyl)methylide (162). The transylidation reaction did not occur without added CS_2 and this strongly suggests that the reaction proceeds (Scheme 37) by an initial reaction of the selenonium ylide with CS_2 to give intermediate (163), followed by nucleophilic displacement of dibenzylselenide by dimethylsulfide, followed by loss of CS_2. The driving force, apparently, is the formation of a C-S bond which is much stronger than a C-Se bond.

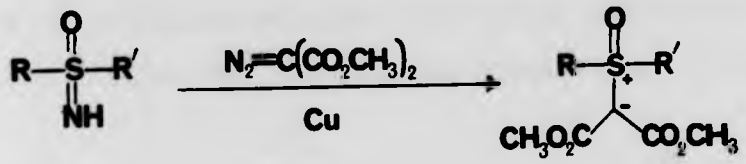


161 163 162

Scheme 37

A recent report by Oae[58] concerning the reaction of sulfoximines with carbenes presents a new synthesis of optically active sulfoxonium ylides.

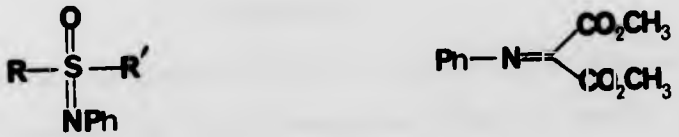
A variety of typical sulfoximines (164) were treated with dimethyl diazomalonate in the presence of a copper catalyst and, in all cases, the major product was the sulfoxonium ylide (165).



164 165

The stereochemistry of the reaction of an optically active sulfoximine was studied and it was found to proceed with complete retention of configuration. The reaction does not proceed photochemically so it would appear that a Cu-carbene complex is a key intermediate.

An intermediate was isolated[59] from the reaction of the N-phenylsulfoximine (166) with diazomalonate and was shown to have the structure (167).

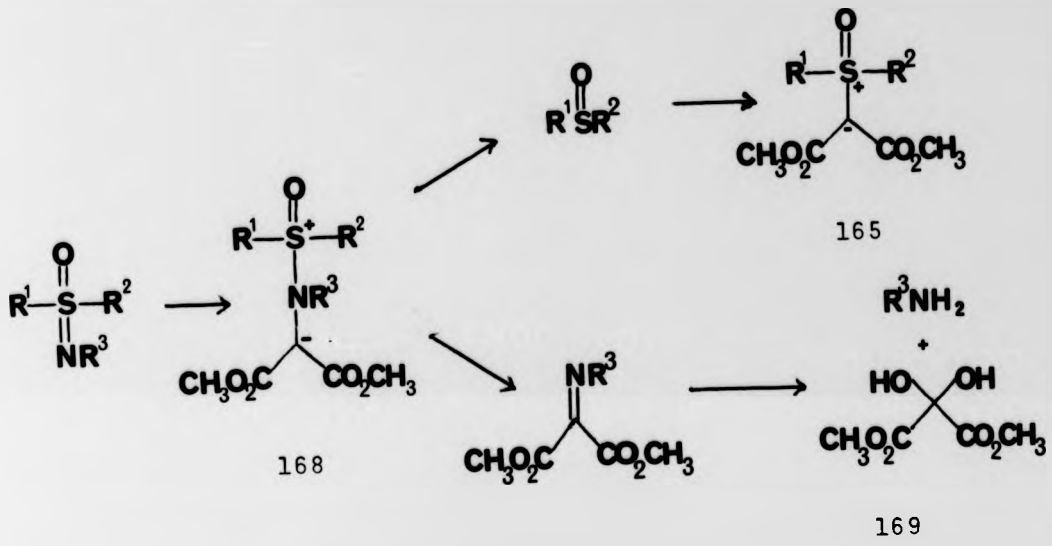


166 167

Aniline and dimethyl dihydroxymalonate (169), which are isolated from the reaction along with the sulfoxonium ylide, appear to be derived from intermediate (167).

It would appear, then, that the initial step (Scheme 38) is attack of the nitrogen atom of the sulfoximine on the carbene

to form the intermediate betaine (168) which readily decomposes to sulfoxide and imine. Subsequent reaction of sulfoxide and carbene gives the sulfoxonium ylide (165) while hydrolysis of the imine gives aniline and dimethyl dihydroxymalonate (169).



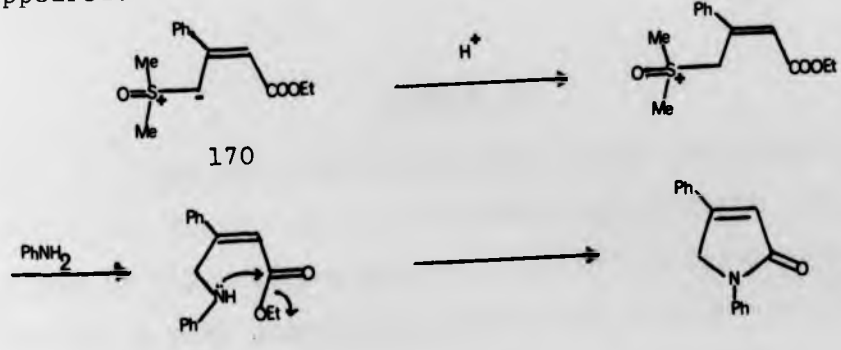
Scheme 38

Since the preparation of optically active sulfoximines is straightforward the above reaction offers a useful approach to the synthesis of optically active sulfoxonium ylides.

Synthetic Uses of Sulfur Ylides

Sulfur ylides have a great variety of uses in organic synthesis especially in epoxide and cyclopropane formations. Many of the other uses depend on the rearrangement of sulfur ylides or their reactions with a variety of reagents. The modern chemical literature regularly contains some new use found for sulfur ylides either as a reagent for a generally applicable synthetic method or as a "one-off" preparation of a desired series of compounds. A publication by Ide[60], in which he reports a convenient method for synthesizing 1-substituted 4-phenyl-3-pyrrolin-2-ones, is an example of the latter.

Treatment of the sulfoxonium ylide (170) with aniline in the presence of HCl afforded 1,4-diphenyl-3-pyrrolin-2-one (171) in high yield. Although a mechanism is not proposed by Ide it seems likely that the first step (Scheme 39) involves protonation of the anionic carbon of the sulfur ylide followed by nucleophilic displacement of the sulfoxonium group by the amine. Intramolecular condensation gives the pyrrolin-2-one. This process is made all the more significant since only a few reports on synthesis of substituted 3-pyrrolin-2-ones have appeared.

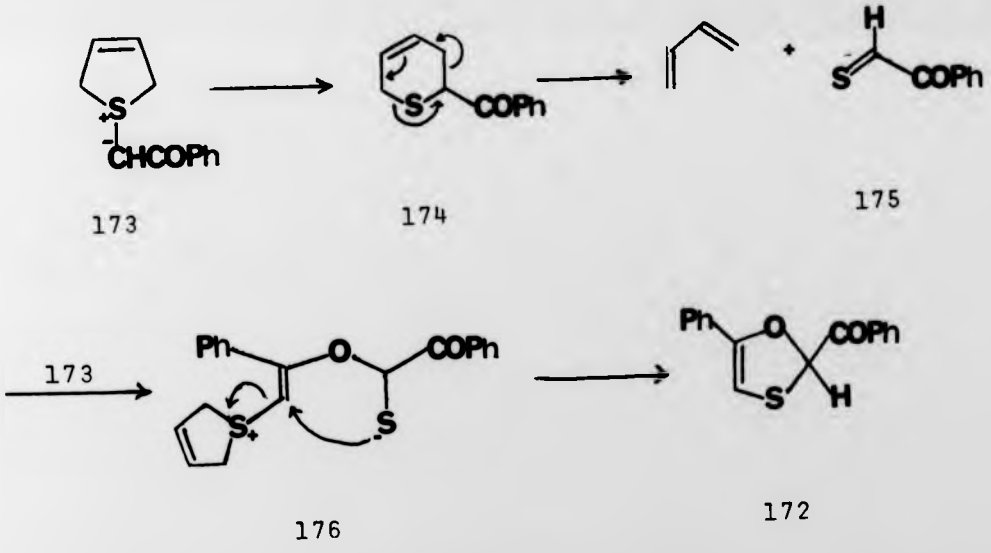


170

171

Scheme 39

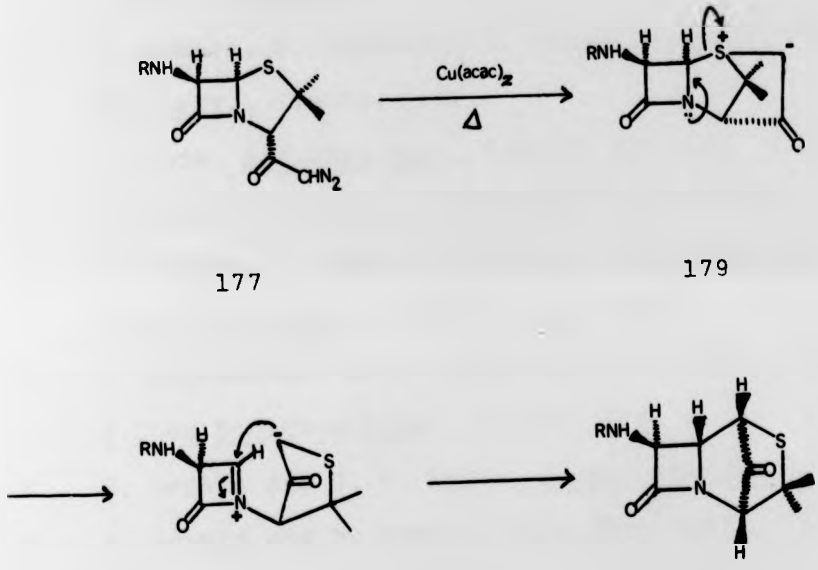
The synthesis and properties of 2-benzoyl-5-phenyl-1,3-oxathiole (172) have been reported by Norin[61]. The key step involves thermal rearrangement of the easily prepared sulfonium ylide (173). It seems likely that the mechanism (Scheme 40) involves initial 1,2-rearrangement (Stevens-type) of the sulfonium ylide (173) to give the intermediate dihydrothiopyran (174), followed by thermal ring opening to give the 2-phenyl thioglyoxal (175) which is susceptible to nucleophilic attack by another molecule of the ylide to form intermediate (176). Simple nucleophilic closure gives the phenacyl oxathiole (172).



Scheme 40

The application of sulfur ylide chemistry in the penicillin field, and in particular the formation of sulfur ylides of the 4-sulfur atom by addition of diazo compounds, has led to some useful and interesting transformations[62,4].

The first intramolecular addition of a carbene to the 4-sulfur atom of a penicillin molecule, to form a cyclic sulfur ylide, has been reported[63] (Scheme 41). Thermolysis of the penicillin-derived diazoketone (177) in the presence of copper(II) acetylacetonate led to formation of the tricyclic ketone (178).



177 179 180 178

Scheme 41

The proposed mechanism involves initial formation of the sulfonium ylide (179) by attack of the sulfur lone pair on the carbenoid species. Intramolecular expulsion of the sulfonium group by the nitrogen lone pair leads to intermediate (180) which recloses, by backside attack of the carbanion, to furnish the final product (178).

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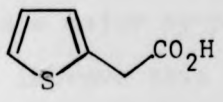
DISCUSSION

Some Novel Aspects of the Chemistry of Thiophens

INTRODUCTION

During the last two decades there has been an increasing interest in the use of thiophen derivatives in medicinal chemistry[1] and in particular 2-thienylacetic acid (1) and 3-thienylmalonic acid (2) have found pharmaceutical importance as side chain intermediates in the production of semi-synthetic β-lactam antibiotics such as cephalothin (3) and ticarcillin (4).



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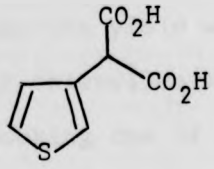

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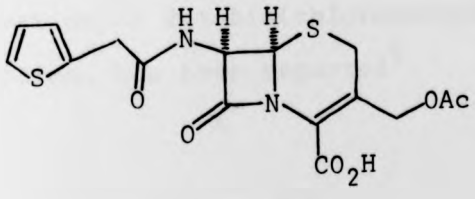

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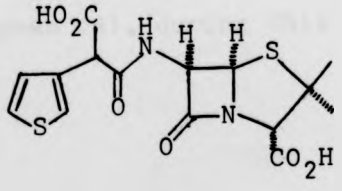
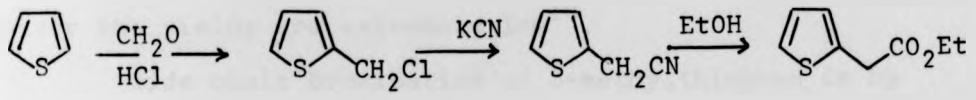


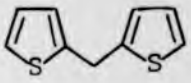
4

A recent publication by Ramage, Taylor and co-workers[2] describes the synthesis of 3-thienylmalonic esters in overall 19% yield by direct cyclization methods, however the most widely used methods for the synthesis of 2- and 3-thienylacetic acids involve the chloromethylation[3] (Scheme 1) or bromomethylation[4] routes and the Willgerodt-Kindler reaction of 2- and 3-acetylthiophen[5]. 3-Thienylmalonic acid is normally made from 3-thienylacetic esters[6].



Scheme 1

Chloromethylation of thiophen was first developed in 1942 by Blicke and Burckhalter[7] however the yield was only 40% and a major by-product was bis(2-thienyl)methane (5). Attempts to improve this synthesis by blocking one of the reactive α-positions of thiophen with a halogen have been successful in the elimination of this major side reaction and in increasing the yield of 2-chloromethylthiophen[8]. The formation of 2,5-bis(chloromethyl)thiophen (6), during this reaction, has been reported[9].



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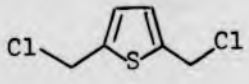

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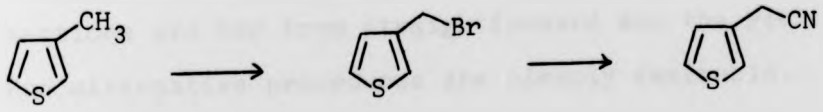
This reaction has other disadvantages in that it is known to result in the formation of dichloromethyl methyl ether as a by-product and recent evidence suggests that this compound is a potent carcinogen. Chloromethylthiophen, once produced, is extremely labile and must be used immediately or excessive decomposition occurs.

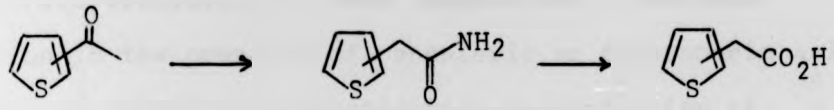
The chloromethylation reaction has been applied to the 3-functionalization of 2,5-disubstituted thiophens however the yields are extremely low[10].

Side chain bromination of 3-methylthiophen is by no means a new method and the procedure has recently been improved by Gronowitz[4]. It is well known that this radical method for side chain bromination using N-bromosuccinnimide is difficult to reproduce and that varying amounts of ring-brominated products are obtained. However, the improved method of Gronowitz renders this reaction more consistent with yields of 3-bromomethylthiophen around 70% and with lower yields of by-products (25%). The crude product is used (Scheme 2) to prepare 3-thenylcyanide in 65% yield (based on 3-methylthiophen) by reaction with sodium cyanide.



Scheme 2

The Willgerodt-Kindler reaction of acetylthiophens (Scheme 3) involves treatment of the thiophen derivatives[5] with sulfur and ammonium hydroxide in a Carius tube heated at 150°C to give the corresponding thienylacetamide derivatives which are hydrolysed, in moderate yields, to the corresponding thienylacetic acids.



Scheme 3

The reaction is particularly difficult to carry out and gives inconsistent and invariably low yields of product. Although some ring-alkylated acetylthiophens give yields of acetamide of over 50% the yields appear to drop with decreasing ring substitution and 3-acetylthiophen gives only 13% yield.

Although the above methods of synthesis of 2- and 3-thienylacetic acid derivatives give the desired products the reactions are far from straightforward and the yields are low thus alternative procedures are clearly desirable.

Synthetic Approaches to 2- and 3-Thienylacetates and Malonates

(i) Transformations of 2- and 3-Acetylthiophens

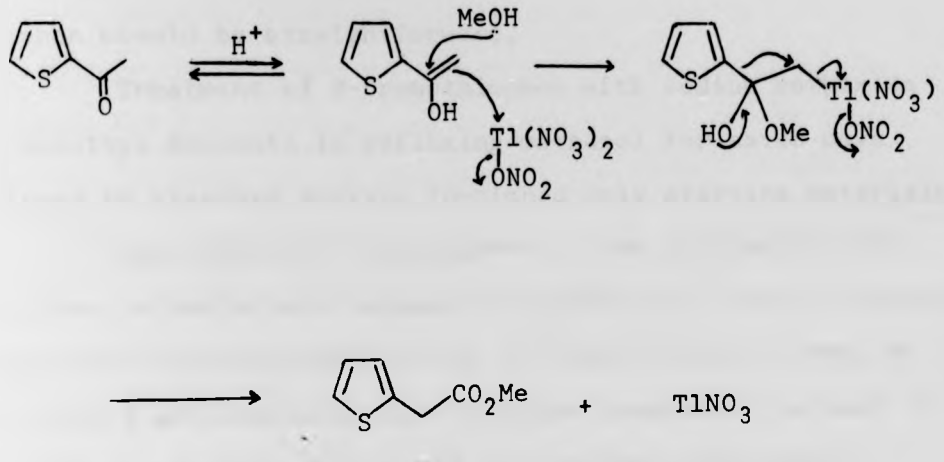
The appearance of thallium trinitrate[11] as a reagent for the conversion of aryl methyl ketones to the corresponding arylacetic acid esters prompted us to examine the possible application of this reaction to the oxidation of 2- and 3-acetylthiophens to 2- and 3-thienylacetic acid esters.

Treatment of 2-acetylthiophen with thallium trinitrate trihydrate at room temperature in methanol solution in the presence of perchloric or fluoroboric acid results in a rapid and quantitative precipitation of thallium (I) nitrate. Filtration of the reaction mixture followed by standard work-up and Kügelrohr distillation gave methyl 2-thienylacetate (7) in 82% yield. Hydrolysis of the ester was effected by refluxing in aqueous sodium hydroxide solution giving 2-thienylacetic acid in 74% overall yield based on 2-acetylthiophen. 3-Thienylacetic acid was prepared in an analogous way in overall 70% yield.

The mechanism of this transformation (Scheme 4) is believed[11] to involve initial acid-catalysed enolization followed by reaction with methanol and thallium trinitrate, as shown, to give the unstable alkylthallium dinitrate. Decomposition of this intermediate proceeds via migration of the aryl substituent, resulting in formation of methyl thienylacetate with simultaneous reduction of thallium (III) to thallium (I).

The value of this method is enhanced by the fact that the thallium (I) salt is recovered quantitatively and can be reoxidized to thallium trinitrate and then recycled.

The reaction has limitations in that amino substituents react preferentially with the thallium electrophile and compounds containing aromatic rings which are highly deactivated by electron-withdrawing substituents are very slow to react and the yields of acetates are low.



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Scheme 4

A further disadvantage is the fact that thallium compounds are highly toxic and great care must be taken during their use.

Although this method provides a fairly facile route to 2- and 3-thienylacetates the starting acetyl compounds are fairly expensive thus it represents only a slight improvement over existing methods.

(ii) Attempted Nucleophilic Displacement of 3-Bromothiophen

A publication by MacDowell[12] reports the treatment of 2,3-dibromothiophen with cupric cyanide in dimethylformamide to form 2,3-dicyanothiophen in 58% yield however the nucleophilic substitution of 3-bromothiophen with simple carbanions is not

reported. If this type of substitution proved to be successful then the formation of 3-thienylmalonate from 3-bromothiophen should be straightforward.

Treatment of 3-bromothiophen with sodium methoxide and dimethyl malonate in refluxing methanol for seven days followed by standard work-up furnished only starting materials.

The effect of crown ethers on the nucleophilicity of anions is now a well documented phenomenon[13] and it has been shown that the nucleophilicities of "naked" anions formed by this method are substantially increased presumably because of weak anion solvation forces and the complete dissociation of the electrolytes[14] by cation complexation.

Treatment of 3-bromothiophen as above but with the addition of one equivalent of 18-crown-6 again failed to effect substitution. Generation of the malonate anion by sodium hydride and by potassium hydroxide was also attempted in the presence of 18-crown-6 but again only starting 3-bromothiophen was recovered.

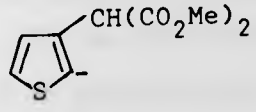
The result of this investigation is not altogether unexpected since nucleophilic displacements on π-excessive heterocycles normally require strong activation by substituents[15].

(iii) Attempted Preparation and Reaction of Thiophyne

Bromobenzene, on treatment with sodium in liquid ammonia in the presence of the malonate anion, is known to form phenylmalonates derived from nucleophilic addition of malonate to the intermediate benzyne species[16].

It has been discussed as a possibility[17] that thiophyne is formed as an intermediate in the treatment of 2-bromothiophen under typical benzyne-producing conditions, where the products are 3-aminothiophen and 3-bromothiophen. Thiophyne has been proposed as an intermediate in the flash vacuum thermolysis of the anhydride of thiophen-2,3-dicarboxylic acid[18] where the products are considered to be derived from an adduct of thiophyne and the trapping reagent.

It would be expected that the generation of thiophyne in the presence of the malonate anion might furnish a mixture of 2- and 3-thienylmalonates as thiophyne trapping products. The intermediates in such a reaction would be anions (8) and (9) and if the thermodynamic product prevails then (8) should be formed exclusively due to the stability of this anion[19]. It seems possible that this method could lead to a practicable synthesis of 3-thienylmalonates.



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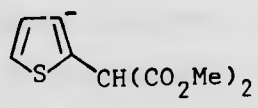

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Treatment of 2-bromothiophen with excess sodium in liquid ammonia[16] in the presence of one equivalent of dimethyl malonate followed by the standard work-up procedure failed to produce either 2- or 3-thienylmalonate, the only recovered products being starting 2-bromothiophen and dimethyl malonate.

Since thiophen is well known to "lithiate" preferentially in the 2-position[19] it may be more likely that thiophyne would be more easily formed from 3-bromothiophen, the initial step being removal of a proton α- to the halogenated carbon.

Treatment of 3-bromothiophen with excess sodium in liquid ammonia in the presence of one equivalent of dimethyl malonate, followed by standard work-up, again failed to produce either of the desired substitution products, the only recovered products being 3-bromothiophen and dimethyl malonate.

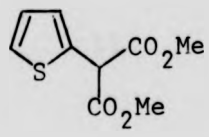
Since there appeared to be no scrambling of the position of bromide in 2- and 3-bromothiophen during the course of the above reactions and since no amino- or malonate-substituted thiophens were detected it must be assumed that the intermediate thiophyne species was not formed under the reaction conditions.

(iv) Photolysis of 2-Substituted Thiophens

It has been reported[20] that 2-arylthiophens, upon prolonged uv irradiation, isomerize to 3-arylthiophens, often in high yield. The postulated mechanism involves valence shell expansion of the sulfur atom, in the excited state, involving the 3d orbitals. It has been proved[21] that the aryl-carbon bond is not severed during this rearrangement nor is there any rearrangement in the aryl group.

It was considered that a similar rearrangement of 2-thienylmalonates to 3-thienylmalonates might serve as a useful synthesis of the latter since this compound is difficult to make by alternative methods.

A methanolic solution of dimethyl 2-thienylmalonate (10) was irradiated using a high pressure mercury lamp however tlc. analysis of the reaction mixture and nmr. analysis of the product indicated that the only compound present after seventeen hours was 2-thienylmalonate, and that no rearrangement had occurred.



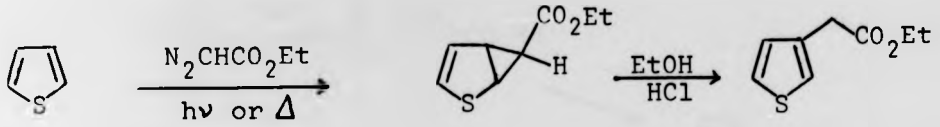
10

Reaction of Thiophens with Diazo Compounds

The reactions of thiophen with diazo compounds under thermal, transition metal-catalysed thermal[22], and photochemical conditions are now well established and, in particular, the reaction of thiophen with ethyl diazoacetate is of interest. The cyclopropanation of thiophen by thermal reaction with ethyl diazoacetate was first reported in 1922 by Steinkopf and Augestad-Jensen[23] and, in 1963, Müller and co-workers[22] cyclopropanated thiophen (22%) and furan using diazomethane in the presence of cuprous bromide. Schenck and Steinmetz[24] reported cyclopropanation of thiophen (23%) and furan by photolysis with ethyl diazoacetate.

Treatment of 6-ethoxycarbonyl-2-thiabicyclo[3.1.0]-

hex-3-ene (11), the product of the latter reaction, with ethanolic hydrogen chloride solution is reported[24] to give ethyl 3-thienylacetate (12) which was not isolated as such, but was converted to the corresponding amide for characterization.



11 12

It was considered that a development of this low-yield reaction sequence might lead to an efficient synthesis of 3-thienylacetates.

An important application of this reaction might be found in the addition of diazomalonic ester to thiophen. If addition occurs by a similar mechanism to give the corresponding cyclopropane (Scheme 5) then this compound might be expected to yield 3-thienylmalonate on acid-catalysed rearrangement or possibly 2-thienylmalonate by a slight manipulation of the rearrangement conditions.

This route would offer considerable advantages over all existing methods since both 2- and 3-thienylmalonates would be available from a single intermediate. Decarboxylation of the thienylmalonates would then furnish the 2- and 3-thienylacetates thus providing a single route to four desirable compounds.

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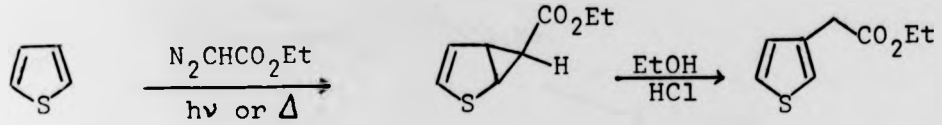

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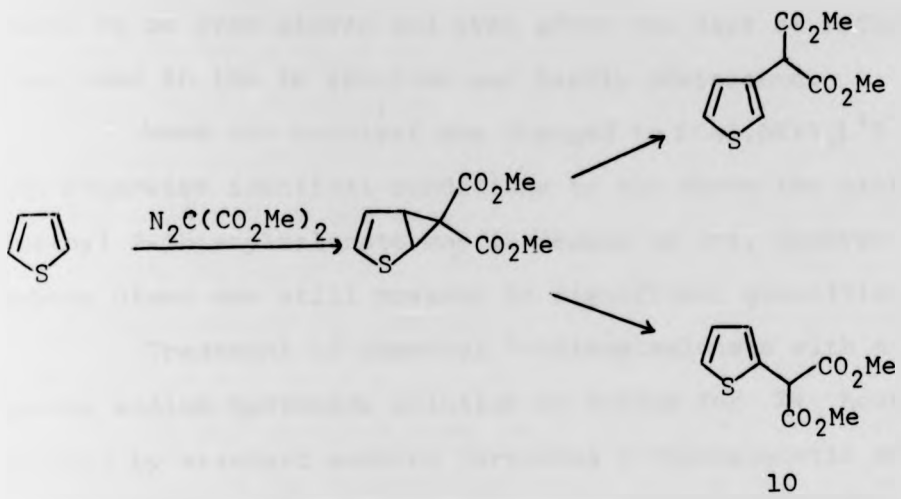

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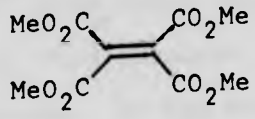
Scheme 5

Treatment of thiophen with dimethyl diazomalonate in the presence of anhydrous cupric sulfate, with the exclusion of moisture, produced no reaction. On refluxing the mixture the diazo band in the ir spectrum was slowly diminished in intensity and, after eight days, was almost negligible. The major reaction product was found to be dimethyl 2-thienylmalonate (10) formed in low yield, with significant quantities of the malonate carbene dimer, tetra(methoxycarbonyl)-ethylene (13) also being present. No sign of the desired cyclopropane was observed and the remainder of the reaction mixture appeared to be polymeric in nature.



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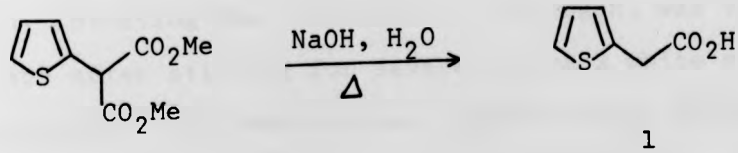
The same reaction, using silver nitrate as catalyst, proved to be even slower and even after ten days at reflux the diazo band in the ir spectrum was hardly diminished.

When the catalyst was changed to $[CuP(OEt)_3]^+I^-$ with otherwise identical conditions to the above the yield of dimethyl 2-thienylmalonate was increased to 36%, however the carbene dimer was still present in significant quantities.

Treatment of dimethyl 2-thienylmalonate with a 10% aqueous sodium hydroxide solution at reflux for 24 hours followed by standard work-up furnishes 2-thienylacetic acid (1) in 83 % yield. However when the yield of the thiophen-substitution step is taken into account the overall yield of this sequence, based on starting diazo compound, is very low, thus some improvement is required before this reaction betters existing methods for the synthesis of 2-thienylacetic acid.



1

Recent reports by Hubert and co-workers on the use of rhodium (II) acetate as catalyst in the insertion of carbenes into activated H-bonds[25] and, more especially, in the cyclopropanation of alkenes[26] with alkyl diazoacetates prompted us to examine the use of this catalyst in the reaction of thiophen with diazomalonate. It has since been reported[27] that this compound is an efficient catalyst in the cyclopropenation of alkynes with diazo compounds.

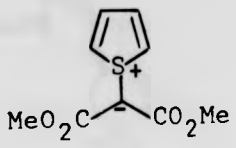
Treatment of thiophen with dimethyl diazomalonate in the presence of $Rh_2(OAc)_4$ and subsequent reflux of the mixture effected a rapid reaction involving expulsion of nitrogen, and ir examination after only fifteen minutes showed that no diazo compound remained. Evaporation of the excess thiophen followed by tlc examination revealed that the major product was the dimer (13), formed in high yield, and that only a small amount of dimethyl 2-thienylmalonate had been formed.

It was believed that the high yield of the carbene dimer was due to the high concentration of the diazo compound during the reaction. Dropwise addition of dimethyl diazomalonate, over a two hour period, to a refluxing solution of the rhodium catalyst in thiophen effected a rapid, but controlled, reaction and dimethyl 2-thienylmalonate was isolated in 66% yield.

When dimethyl diazomalonate was added to a solution of the rhodium catalyst in thiophen at room temperature a slow reaction, involving the liberation of nitrogen, was seen to occur, and after stirring for several hours a white solid began to precipitate. The reaction was complete after stirring at room temperature for two days and the white solid was filtered, recrystallized and characterized.

The nmr spectrum of this compound showed a characteristic four proton AA'BB' multiplet centred at τ 2.9 along with a six proton singlet at τ 6.35 characteristic of a dimethyl malonic ester group. Microanalysis and mass spectral data supported a molecular formula of $C_9H_{10}SO_4$ and this, along

with the absence of a malonate methine proton signal around τ 5.0 in the nmr spectrum, and the apparent symmetry of the thiophen ring protons, suggested that the compound was thiophenium bis(methoxycarbonyl)methylide (14) formed in almost quantitative yield.



14

An X-ray crystal structure determination was undertaken[28] to confirm this structure (Fig.1).

The crystals are monoclinic, space group C2/c, a = 19.56(2), b = 9.28(1), c = 14.08(1) Å, β = 51.70(1)°, U = 2004.3 Å^3, Z = 8, F(000) = 1328, μ(Mo-K_α) = 2.6 cm^{-1}. The structure was solved by direct methods from data collected to $2\theta_{max}$ = 55° on a Stoe 2-circle diffractometer. All atoms except hydrogen were refined anisotropically and for 1427 independent reflections with I > 3σ(I), R = 5.6%.

The molecule has an approximate mirror plane with the sulfur atom pyramidal as expected, and the ylide bond (S - C(6)) is significantly shorter (by 0.035 Å) than the C-S bond in the thiophen ring. There is greater localization of double bonds in the ring than in thiophen itself[29] and this probably reflects the shift in electron density from the ring

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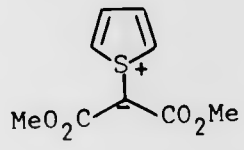

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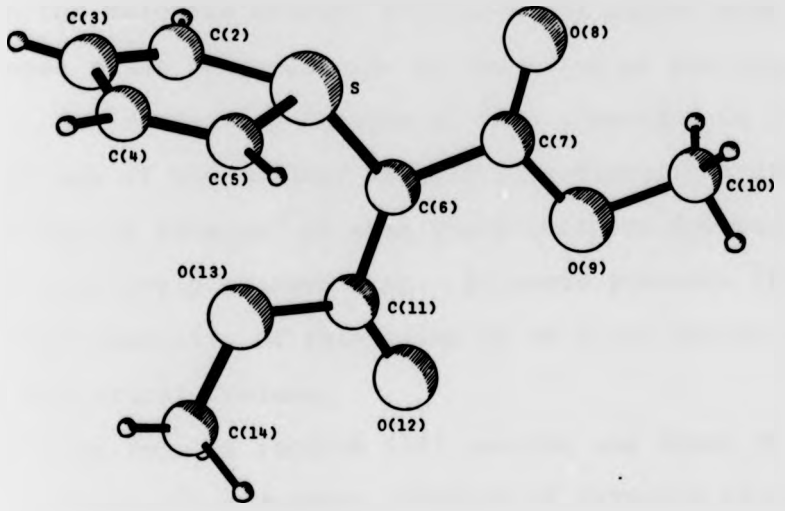


Fig.1

Bond Lengths (Å)	Ylide		Thiophen	
	S - C(2)	1.745 (7)		
	S - C(5)	1.743 (4)	C - S	1.718
	S - C(6)	1.711 (4)		
	C(2) - C(3)	1.326 (6)	C_α-C_β	1.369
	C(3) - C(4)	1.439 (10)	C_β-$C_{\beta'}$	1.443
	C(4) - C(5)	1.320 (8)		
	C(6) - C(7)	1.441 (6)		
	C(6) - C(11)	1.431 (6)		

Bond Angles (degrees)	
C(2)-S-C(5)	92.3 (3)
C(2)-S-C(6)	116.8 (2)
C(5)-S-C(6)	114.7 (2)

to the malonate group. The ring is planar and all the atoms in the malonate moiety, including the sulfur atom, lie in the same plane perpendicular to the plane of the ring.

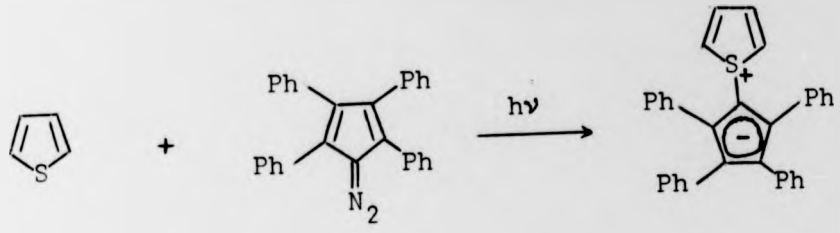
An interesting feature of this structure is the fact that one of the methoxy oxygens lies directly under the ring and may be involved in some donor-acceptor interaction with the positively charged ring. It seems possible that the exceptional stability of this ylide is at least partly related to this structural feature.

The role of rhodium (II) acetate was shown to be truly catalytic since further addition of dimethyl diazomalonate to the reaction filtrate followed by stirring at room temperature effected further precipitation of the ylide in virtually quantitative yield. On five successive additions to the same catalyst solution the yield of ylide was not diminished and the catalytic activity remained.

Only three reports in the literature indicate the previous possible existence of sulfur ylides which have the sulfur atom as part of a thiophen ring.

A report by Durr and co-workers[30] in 1972 indicates that thiophenium tetraphenylcyclopentadienylide (15) was formed, along with other products, during photolysis of tetraphenyl diazocyclopentadiene in thiophen, although no yields were quoted.

Evidence for the existence of 2,3,4,5-tetramethylthiophenium methylide (16) in solution was presented by Heldeweg and Hogeveen[31] in 1974. Nmr signals corresponding to the ylide were observed during the treatment of 1,2,3,4,5-pentamethylthiophenium hexafluorophosphate (17) with base, and the



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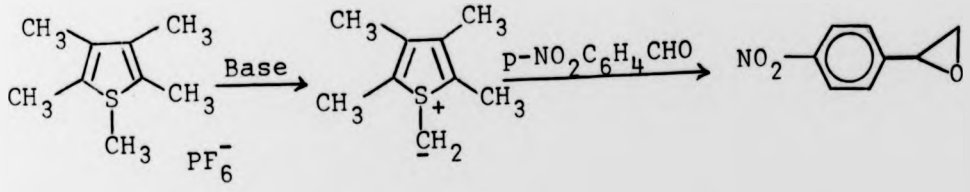
ylide was trapped, albeit in low yield, by p-nitrobenzaldehyde to give the epoxide (18) in a well known reaction.



17 16 18

In a recent publication[32] Ando has reported the formation of thiophenium bis(methoxycarbonyl)methylide (14), in 8% yield, during the photolysis of dimethyl diazomalonate in thiophen and his physical and spectral data for this compound are in close agreement with those reported in this work.

Due to the efficiency and ease with which the

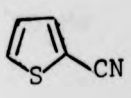
thiophenium ylide was formed it was decided to investigate the generality of this reaction by the use of substituted thiophen derivatives and a variety of diazo compounds.

The reaction was extended over a wide range of thiophen derivatives and the ylides produced in this way are summarized in Table 1.

In all cases the ylides were isolated as white crystalline solids and all exhibited satisfactory physical and spectroscopic properties.

It should be noted that in the reaction of 2-hydroxymethylthiophen with dimethyl diazomalonate the only isolated product was the ylide and that no sign of the product derived from carbene insertion into the O-H bond was observed.

In the case of 2-cyanothiophen (28) and thiophen-2-carboxaldehyde (29) the above reaction was carried out under normal conditions however in neither case was the expected thiophenium ylide formed. With the former the diazo compound was still present after a two week period and in the latter case the diazo compound reacted to give a complex mixture of products which proved impossible to separate.



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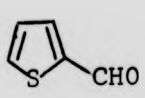
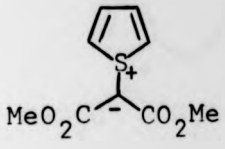
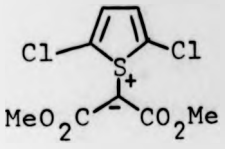
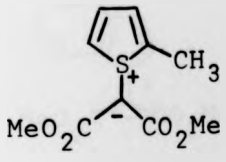
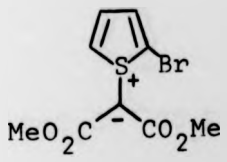
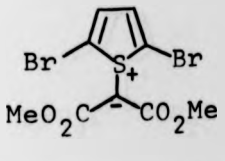


29

The report by Durr and co-workers[30] on the isolation of thiophenium tetraphenylcyclopentadienylide prompted us to investigate the possible preparation of the unsubstituted cyclo-

TABLE 1

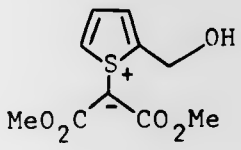
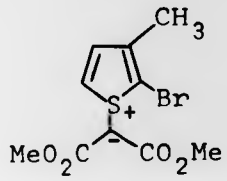
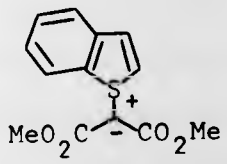
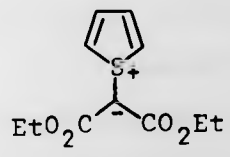
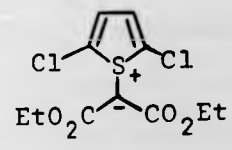
Thiophenium Ylides

Ylide	Compound Number	Yield(%)	m.p.(°C)
	14	93	145 -146
	19	90	174 -174.5
	20	92	146 -146.5
	21	73	138 -140
	22	55	190 -190.5

Continued

TABLE 1 (continued)

Thiophenium Ylides

Ylide	Compound Number	Yield(%)	m.p.(°C)
	23	54	133 -133.5
	24	86	128.5-129
	25	97	177 -177.5
	26	90	111 -111.5
	27	60	82.5- 83

pentadienylide (30) by the rhodium-catalysed reaction. However difficulties were experienced during the preparation of diazocyclopentadiene[33] and a violent explosion occurred on isolation of this compound at room temperature so this aspect of the work was not investigated further.

30

In general it would appear that simple alkyl-substituted thiophens react readily under the above conditions to give high yields of thiophenium ylides. Similarly halogeno-thiophens and aromatic fused thiophens appear to give high yields of the corresponding ylides. However the reaction with 2-cyano and 2-formyl substituted thiophens failed to give any of the desired ylides.

It appears likely that the ylide-forming reaction requires the availability of the sulfur lone pair to perform nucleophilic attack on a metal stabilized carbenoid species derived from the interaction of diazomalonates with the rhodium catalyst. In thiophens containing substituents with electron donating properties the electronic situation is then favourable however when substituents with electron withdrawing effects, such as cyano and formyl, are present the availability of the

sulfur lone-pair is substantially reduced rendering the sulfur atom much less nucleophilic than its unsubstituted analogue and the ylide-forming reaction does not occur.

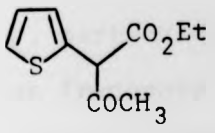
The success of the ylide-forming reaction with thiophens and diazomalonic esters prompted us to examine the reaction of thiophens with a variety of stabilized diazo compounds in order to test the generality of the reaction.

The synthesis of ethyl diazoacetoacetate was readily accomplished by the standard diazo-transfer reaction using tosyl azide[34].

The reaction of thiophen with ethyl diazoacetoacetate was carried out, as before, at room temperature in the presence of rhodium (II) acetate and was complete after twenty hours. No precipitation occurred and, on removal of the excess solvent, an oily residue remained which was shown by tlc to be a mixture of two products. The separation of these products was readily accomplished by column chromatography and they were both shown, by mass spectrometry and microanalysis, to be 1:1 adducts of the carbene and thiophen.

The major product (60%), a colourless oil, had an ir spectrum which showed absorptions at 1720 and 1640 cm^{-1}, typical of a β-keto ester. The nmr spectrum showed thiophen ring protons at τ 2.9 (1H) and 3.2 (2H) in a pattern typical of 2-substituted thiophen derivatives. The spectrum also included a D_2O-exchangeable malonate-methine singlet at τ 5.2 and a D_2O-exchangeable enol signal at τ -3.3, in a ratio of about 1:3, integrating for a total of one proton. Also present were two singlets at τ 7.9

and 8.1, in a ratio of about 1:3, integrating for a total of three protons, which can be assigned to the keto and enol forms of the 2-substitution product ethyl 3-oxo-2-(2'-thienyl)butanoate (31 and 32). The spectrum also contains typical ethyl ester signals.



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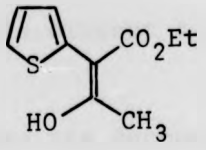
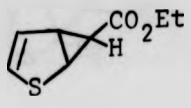


32

The minor product (5%), a colourless oil, again showed typical β-keto ester absorptions in the ir spectrum. The nmr spectrum was similar to that previously recorded for 6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (11) and showed one proton multiplets at τ 3.45, 4.03, 4.4, and 4.7 corresponding to the four thiophen ring protons. The spectrum also showed two overlapping methylene quartets (2H), two overlapping ethyl triplets and two sharp acetyl signals at τ 7.7 and 7.71 integrating for a total of three protons. The presence of two ethyl signals and two acetyl signals indicates that, although the product is chromatographically homogeneous, it is a 1:1 mixture of two compounds; the <u>exo</u>- and <u>endo</u>-isomers of 6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (33).

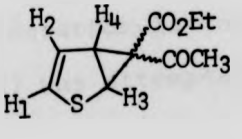


11

Decoupling experiments were attempted in order to measure the ring coupling constants however this proved to be more difficult than anticipated. The very small chemical shift differences between equivalent protons in the exo- and endo- isomers would be expected to result in broadening of the spectral lines. Since all the ring protons appear in a relatively narrow range of the nmr spectrum a significant line-broadening occurs due to the application of a second radiofrequency during decoupling, particularly in those signals closest to the irradiation frequency.

Both the above effects rendered the decoupling experiments less than satisfactory however it was possible, by direct measurement from scale-expanded spectra and with the aid of a limited number of decoupling experiments, to make proton assignments and obtain approximate coupling constants (Table 2) confirming that the product is a mixture of the two cyclopropanes (33).

The reaction of thiophen with ethyl diazoacetoacetate was repeated using dropwise addition of the diazo compound to a refluxing solution of $Rh_2(OAc)_4$ in thiophen. The reaction was complete almost immediately and the products isolated were identical to those described although the yields were slightly higher. Compound (31), the 2-substitution product, was formed in 67% yield while the mixture of cyclopropanes (33) was obtained in 13% yield.



33

TABLE 2

Nmr data for compound 33

Chemical Shift (τ)[a]	Assignment	Coupling Constants (J/Hz)[b,c]
3.45	1-H	$J_{1,2}$ 6; $J_{1,4}$ 1
4.03	4-H	$J_{4,3}$ 10; $J_{4,2}$ 3; $J_{4,1}$ 1
4.4	2-H	$J_{2,1}$ 6; $J_{2,4}$ 3
4.7	3-H	$J_{3,4}$ 10
5.83	$\underline{CH_2}$-CH_3	J 7
7.70 & 7.71	$COCH_3$	
8.85	$CH_2\underline{CH_3}$	J 7

(a) Spectra were run on 10% w/v solutions in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard.

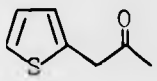
(b) All couplings are approximate to the nearest whole number.

(c) Other small couplings are present in some cases but measurement of these is ruled out for reasons discussed in the text.

In order to determine the utility of the above reaction in the synthesis of 2- and 3-substituted thiophens the hydrolysis and decarboxylation of the 2-substitution product (31) and the acid catalysed rearrangement of the cyclopropanes (33) were attempted.

Hydrolysis and decarboxylation of ethyl 3-oxo-2-(2'-thienyl)butanoate (31) was attempted by the standard aqueous

sodium hydroxide method however the product, rather than the expected 2- alkylthiophen (34) proved to be 2-thienylacetic acid (1) formed, in 94% yield, by ketonic cleavage of the acetoacetate moiety.



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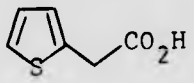
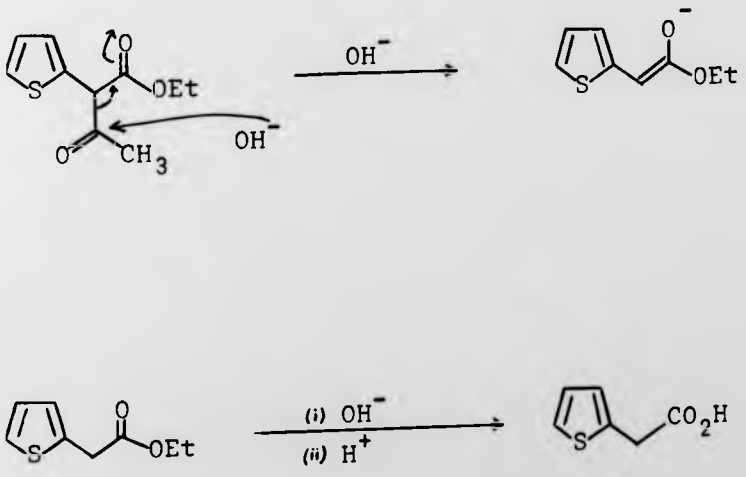


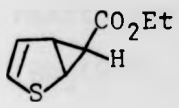
1

This type of cleavage is not unusual and the probable mechanism (Scheme 6) may involve nucleophilic attack of hydroxide at the ketone carbonyl followed by acetyl cleavage then standard ester hydrolysis to give the acid.



Scheme 6

The treatment of 6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (33) with an ethanolic HCl solution might be expected to follow a path analogous to the rearrangement of 6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (11) described by Schenck and Steinmetz[24]. The expected product would then be ethyl 3-oxo-2-(3'-thienyl)butanoate (35).



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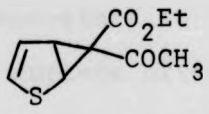
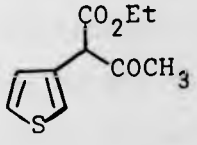


33

The reaction produced a thiophen derivative which showed an nmr spectrum identical to that recorded for the 2-substitution product (31).



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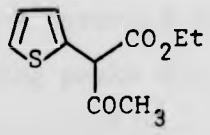


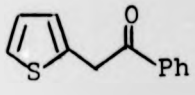
31

Treatment of the product from this reaction with an aqueous sodium hydroxide solution as described above gave 2-thienylacetic acid (1) in overall 81% yield based on the cyclopropane (33) thus proving that the product of acid-catalysed rearrangement of this cyclopropane is indeed the 2-substituted

thiophen derivative (31) and not the expected 3-substitution product. The result helps to substantiate the earlier claim that it may be possible to find conditions by which rearrangement of thiophen cyclopropanes of this type could be directed to give either 2- or 3-substituted thiophen derivatives.

Diazoacetophenone (N_2= CHCOPh) was prepared[35] and allowed to react with thiophen at room temperature in the presence of $Rh_2(OAc)_4$. The reaction was complete after three hours and several products were observed by tlc. Separation by column chromatography showed that the major product (23%) was phenyl 2-thenyl ketone (36), the 2-substitution product, and this compound exhibited the expected physical and spectral properties.

The nmr spectrum of another fraction from the column showed it to be a mixture of products, however evidence for the presence of the cyclopropane (37), in low yield, was observed. One proton multiplets at τ 3.8, 4.1, 6.3, 6.75 and 7.9, corresponding to all the ring protons, were observed and were remarkably similar to the corresponding peaks for 6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (11). Unfortunately further attempts to isolate this compound proved unsuccessful and no further characterization was possible.



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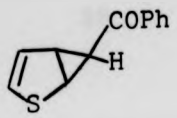

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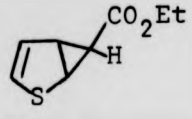
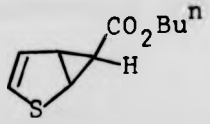


11

A logical extension to the study of the reaction of diazo compounds with thiophen derivatives is the examination of the use of diazoacetic esters. It was decided that the relatively stable n-butyl diazoacetate, which is more easily prepared than the ethyl ester, should be used in preference.

The treatment of thiophen with n-butyl diazoacetate at room temperature in the presence of $Rh_2(OAc)_4$ failed to produce any of the anticipated thiophenium ylide. However 6-butoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (38) was produced in over 50% yield. This compound showed physical and spectral characteristics which were very similar to those observed for the ethyl ester (11) and the yield was significantly greater than that obtained by repeating the conditions of Schenck and Steinmetz[24] using the ethyl ester. For this reason, and because the feasibility of this reaction being used as part of a synthetic route to 3-thienylacetates depends on the yield of the cyclopropanation step, it was decided to carry out a detailed investigation into the effect of temperature and catalyst on this reaction.



38

Reactions were carried out using purified thiophen and n-butyl diazoacetate in the presence of copper or rhodium catalysts at various temperatures and, in most cases, the major product was the cyclopropane (38). The results are shown

in Table 3.

TABLE 3

The Reaction of n-Butyl Diazoacetate with Thiophen

Catalyst	Temp. (^{o}C)	Reaction Time[a]	Yield of 38 (%)
d_{Cu}^{I}	25	4h	0
d_{Cu}^{I}	85	15 min.	0
CuCl	85	15 min.	17.2[b]
No Catalyst	25	No Reaction	0
No Catalyst	85	120h	10.6[b]
Rh^{II}	32	73h	60[c]
Rh^{II}	42	3h	58[c]
Rh^{II}	52	2.5h	62[c]
Rh^{II}	62	30 min.	62[c]
Rh^{II}	84	15 min.	71[c]

(a) Monitored by the disappearance of the diazo band in the ir spectrum

(b) Isolated by prep.tlc

(c) Isolated by distillation

(d) $[CuP(OEt)_3]^{+}I^{-}$ [34]

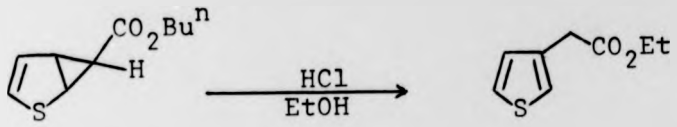
The most obvious conclusion is that rhodium(II) acetate catalysis is vastly superior to the use of conventional copper catalysts where most of the diazo ester appears to be converted to the carbene dimer, di-n-butyl fumarate.

The results are quite reproducible on a small scale however low yields of distilled products were obtained from scaled-up reactions although reaction times were similar and tlc analysis of product mixtures appeared similar. In the larger scale reactions the distillation residues were much larger so it would appear that the reaction is equally efficient on small and large scale but prolonged heating during distillation causes decomposition of the product. The conclusion then is that 2-thiabicyclo[3.1.0] hex-3-ene carboxylates are thermally labile.

The synthesis of 3-thienylacetate derivatives seems much more attractive now that the yield of the initial cyclopropanation has been raised to over 70%. It might be expected that the conditions used for acid-catalysed rearrangement of this type of cyclopropane would also induce ester exchange such that the product would depend on the solvent used for the isomerization.

Treatment of 6-butoxycarbonyl-2-thiabicyclo[3.1.0] - hex-3-ene with a solution of HCl in ethanol, followed by the normal work-up, gave ethyl 3-thienylacetate (12) in 76% yield.

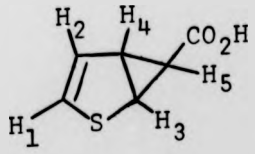
The overall yield of ethyl 3-thienylacetate based on starting butyl diazoacetate is then 54% so this method probably constitutes the most efficient synthesis, to date, of this compound.



12

Although the formation of 2-thiabicyclo[3.1.0]hex-3-ene carboxylates is by no means a new reaction there is no evidence in the literature, nor in this work, to indicate whether this type of compound is formed as a mixture of exo- and endo- isomers or whether there is any preference for the formation of a single product.

Detailed analysis of either the ethyl ester (11) or the n-butyl ester (38) proved impossible due to the overlap of one of the ring protons with the alkyl ester signals in the τ 9 region of the nmr spectrum. To overcome this difficulty the ethyl ester was hydrolysed to the corresponding acid (39).



39

The nmr spectrum of the acid (39) was virtually identical to that of the ethyl ester (11) with the exception that the ethyl quartet and triplet were no longer present and

a one proton triplet was observed, at τ 8.9, which had previously been obscured by the ethyl ester triplet. The other four ring protons appeared as distinct multiplets.

The spectrum was first order and decoupling experiments allowed assignment of all the ring protons and determination of the coupling constants (Table 4).

The two low-field multiplets centred at τ 3.8 and 4.1 constitute the two halves of an AB quartet (δ_{AB} 27Hz) in which each half is further split due to further couplings. The two multiplets centred at τ 6.4 and 6.87 constitute the two halves of another AB quartet (δ_{AB} 41Hz) in which each half is again further split due to smaller couplings. The large (1.7Hz) four-bond coupling between 1-H and 3-H almost certainly arises from the W (molecular models) arrangement of the two protons. The appearance of 5-H as a triplet rather than the expected doublet of doublets is due to the fact that the coupling constants $J_{4,5}$ and $J_{3,5}$ are identical.

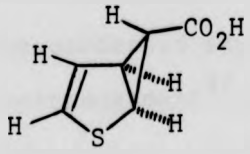
TABLE 4

Nmr data for compound 39

Chemical Shift (τ)[a]	Assignment	Coupling Constants (J/Hz)
3.8	1-H	$J_{1,2}$ 5.8; $J_{1,3}$ 1.7; $J_{1,4}$ 0
4.1	2-H	$J_{1,2}$ 5.8; $J_{2,4}$ 2.8
6.4	3-H	$J_{3,4}$ 7.5; $J_{3,5}$ 3.2; $J_{1,3}$ 1.7
6.87	4-H	$J_{4,3}$ 7.5; $J_{4,5}$ 3.2; $J_{4,2}$ 2.8; $J_{4,1}$ 0
8.9	5-H	$J_{5,4}$ 3.2; $J_{5,3}$ 3.2

(a) Spectra were run on 10% w/v solutions in $CDCl_3$ using TMS as an internal standard, and recorded on a Perkin-Elmer R32 at 90 MHz.

The small coupling constants (3.2Hz) for $J_{4,5}$ and $J_{3,5}$ are consistent[36] with a trans-arrangement for these protons in the cyclopropane ring confirming that the product has the exo-stereochemistry (40). The fact that the spectrum is so clean and the ease with which these particular coupling constants were measured confirm that this is the sole product and that none of the endo-isomer is present.



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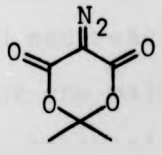
Meldrum's diazo compound (41) might be expected to react in a very similar manner to diazomalonic esters and it was expected that its reaction with thiophen under ylide-forming conditions would give the thiophenium ylide (42).



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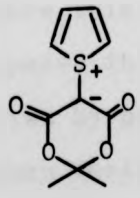


42

Meldrum's diazo compound was prepared from Meldrum's acid[37] however its reaction with thiophen at room temperature in the presence of $Rh_2(OAc)_4$ proved to be exceptionally slow,

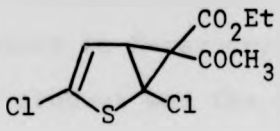
the diazo band in the ir spectrum still being intense after three days. The mixture was heated at 50°C with no effect and higher temperatures, although increasing the rate of decomposition of the diazo compound, did not induce a clean reaction, giving only dark brown polymeric products which proved impossible to isolate and characterize.

It can only be assumed that the failure of this reaction must reflect the reduced reactivity of Meldrum's diazo with the rhodium salt to give a carbenoid intermediate. At higher temperatures the carbenoid may be formed but may prefer to undergo Wolff rearrangement[37], dimerization and other decompositions to by-products rather than undergo ylide formation which appears to be favourable only at ambient temperature.

In continuation of the study of the reactions of diazo compounds with thiophens the reactions of some substituted thiophens with ethyl diazoacetoacetate were examined.

The reaction of 2,5-dichlorothiophen with ethyl diazoacetoacetate at room temperature in the presence of $Rh_2(OAc)_4$ was complete after 24h. Once more this diazo compound did not react to give the anticipated thiophenium ylide however one major product was isolated by preparative tlc and shown to be a 1:1 adduct of the thiophen derivative and the carbene. Nmr and ir analyses showed that the compound was the cyclopropane (43), 1,3-dichloro-6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene, formed in 61% yield.

The nmr spectrum showed an AB quartet centred at τ 3.75 (δ_{AB} 48Hz; J_{AB} 5Hz) corresponding to the two ring



43

protons. The normal ethyl ester and acetyl peaks were also present.

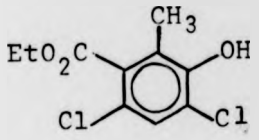
Like 6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (11) this compound appears to be thermally labile and, during vacuum distillation at 94°C, some decomposition was seen to occur. Tlc analysis of the distillate showed it to be mainly starting cyclopropane however two new products appeared to have formed.

One of the products, though soluble in $CDCl_3$, showed no nmr signals and was shown to be elemental sulfur. The other product, a crystalline solid, was then assumed to be a product of sulfur extrusion from the original cyclopropane, and mass spectrometry confirmed this suspicion.

The nmr spectrum of this compound showed singlets at τ 2.90 (1H), 4.00 (1H), and 7.85 (3H) along with the characteristic two proton quartet (τ 5.65) and three proton triplet (τ 8.70) of an ethyl ester. The ir spectrum showed significant absorptions at 3540, 1725, and 1595 cm^{-1}.

Mechanistic considerations did not immediately bring to mind any particular compound, simply derived from (43) by sulfur extrusion, which would exhibit the above physical and

spectral characteristics. This data did not conclusively distinguish between any of the possibilities considered and it was necessary to resort to X-ray crystallography to prove that the rearrangement product was the simple benzoic acid derivative ethyl 2,4-dichloro-5-hydroxy-6-methylbenzoate (44).



44

The structure (Fig.2) was shown[28] unambiguously to be that of compound (44), and all bond lengths and angles were similar to those expected from previous measurements on similar compounds.

Thermolysis of the cyclopropane (43) in refluxing toluene for 38h followed by column chromatography of the crude product gave the benzoic acid derivative (44) in 86% yield.

The relationship between this structure and the compound from which it was derived is not apparently obvious and this transformation must involve several complex migrations and rearrangements. Any mechanism proposed at this stage would be exceedingly speculative and extensive mechanistic work requires to be carried out before any clue to the true mechanism is revealed.

The reaction of 2-acetylthiophen with ethyl diazoacetoacetate in the presence of $Rh_2(OAc)_4$ at room

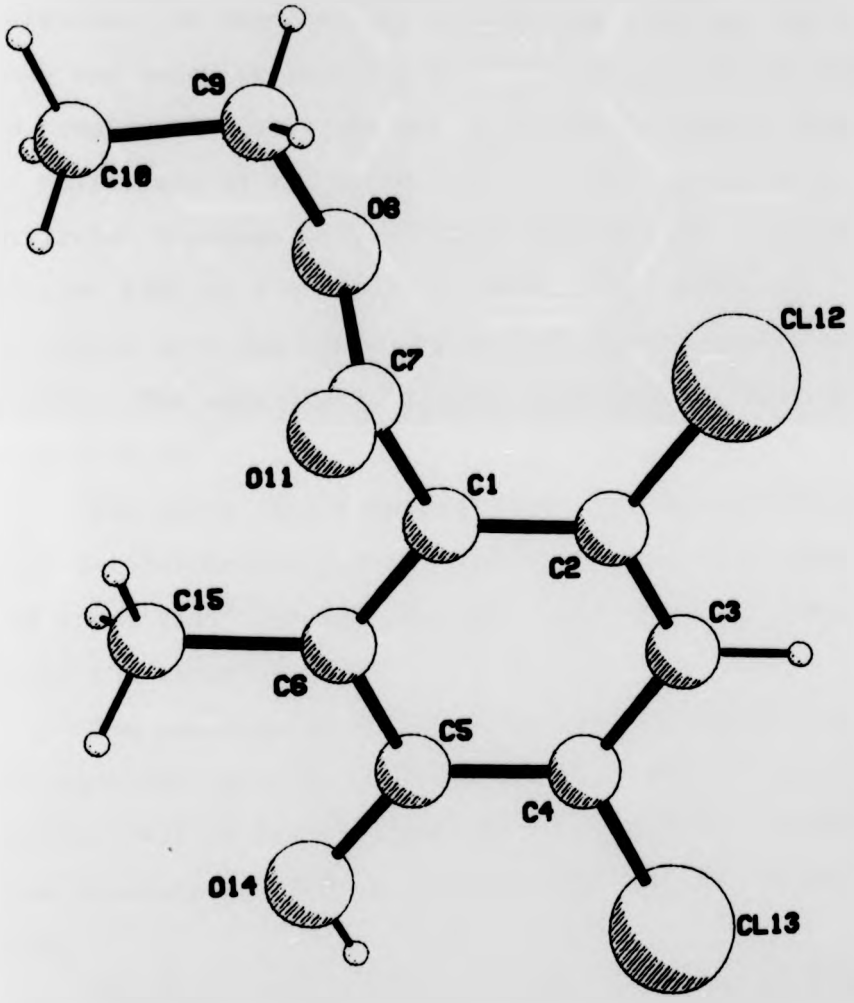


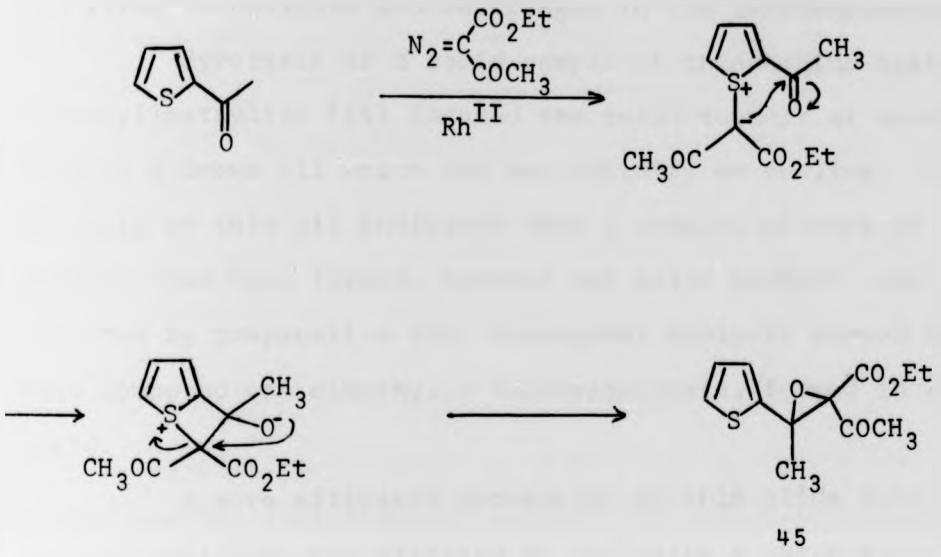
Fig.2

temperature was studied. The formation of a thiophenium ylide from this reaction was not expected since the acetyl group is strongly electron withdrawing and since ylides had not previously been formed during reactions of ethyl diazoacetoacetate. As expected the thiophenium ylide was not formed and only one major product was isolated, by preparative tlc, from a complex mixture. The nmr of the major product (18%) showed multiplets at τ 3.0 (2H) and 3.3 (1H) typical of a 2-substituted thiophen derivative, a quartet (2H) at τ 5.95 and triplet (3H) at τ 8.9 typical of an ethyl ester, an acetyl signal at τ 8.0 (3H), and another methyl singlet at τ 8.2 (3H). The only distinctive ir absorption is that of the ester at 1675 cm^{-1}.

The above data suggested that the compound was ethyl 2-acetyl-3-(2'-thienyl)-2,3-epoxybutanoate (45) and a specific epoxide spray test[38] proved positive. Mass spectral data supported the structure (45).

The reaction of sulfur ylides with carbonyl compounds to form epoxides is well documented[39] and it must be assumed that the epoxide (45) is formed either by the analogous intramolecular reaction presented in Scheme 7 or by a similar intermolecular reaction.

The first step in the reaction would then be ylide formation followed by nucleophilic attack of the ylide anionic carbon on the ketone. Expulsion of the thiophenium ion would then furnish the epoxide (45).



Scheme 7

Rearrangements of Thiophenium Ylides

It appears that the thiophenium ylide may have been formed in the reaction of 2-acetylthiophen with ethyl diazoacetoacetate thus it seems possible that in some, or all of the other reactions of diazo compounds with thiophens, the first step is ylide formation and that the observed products are, in some way, derived from this ylide.

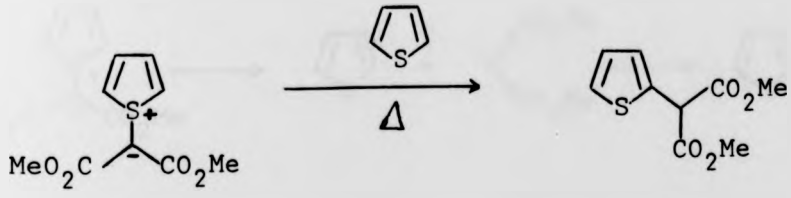
The reaction of dimethyl diazomalonate with thiophen immediately lends itself to a study of this problem since, in the presence of $Rh_2(OAc)_4$, the reaction gives the thiophenium ylide (14) at room temperature and 2-thienylmalonate (10) at higher temperatures.

The most obvious postulate is that the first step in

both cases is ylide formation but at the higher temperature the ylide is unstable and rearranges to the 2-thienylmalonate.

Pyrolysis of a solid sample of thiophenium bis(methoxycarbonyl)methylide (14) induced the solid to melt at around 145°C to give a brown oil which did not solidify on cooling. Tlc analysis of this oil indicated that a complex mixture of products had been formed, however one major product was isolated by preparative tlc. Subsequent analysis showed that this compound was dimethyl 2-thienylmalonate, formed in 33% yield.

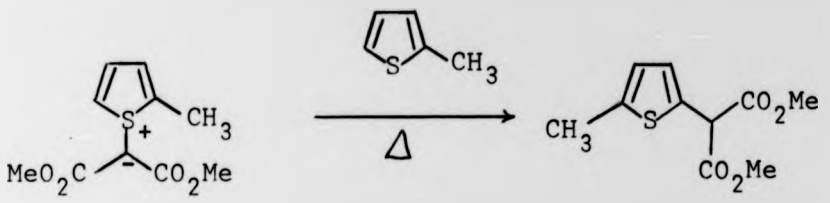
A more efficient conversion of this ylide into 2-thienylmalonate was effected by refluxing a suspension of the ylide in thiophen where the isolated yield of 2-thienylmalonate was 60%.



14 10

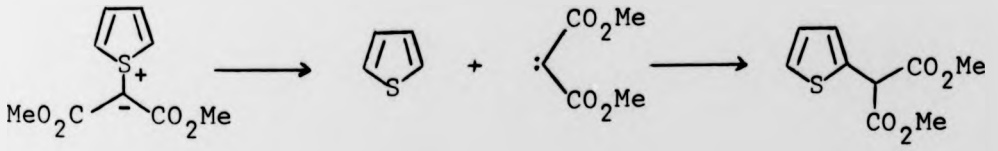
Similarly, thermolysis of 2-methylthiophenium bis(methoxycarbonyl)methylide (20) in 2-methylthiophen produced dimethyl 2-(5-methylthienyl)malonate (46) in 94% yield.

It appears, then, that the pyrolysis of thiophenium ylides leads to rearrangement to 2-substituted thiophen derivatives, however there is no indication as to whether this



20 46

is an intramolecular reaction or an intermolecular reaction involving cleavage of the ylide bond to give the thiophen moiety and the free malonate carbene (47) which is subsequently trapped by solvent or other substrate (Scheme 8). Several experiments were carried out in order to clarify this point.

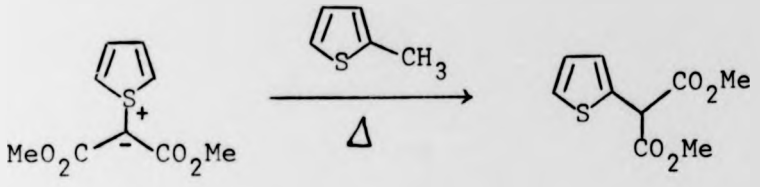


47

Scheme 8

If the rearrangement is truly intramolecular then the presence of other substrates should not affect the yield or the nature of the product. Likewise if the reaction is intermolecular the presence of other reactive substrates or solvents would affect both the yield and nature of the products.

Thermolysis of thiophenium bis(methoxycarbonyl)-methylide (14) in 2-methylthiophen gave only dimethyl 2-thienyl-malonate (10) in 82% yield.



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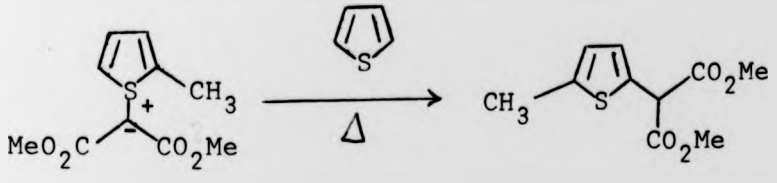
Similarly thermolysis of 2-methylthiophenium bis(methoxycarbonyl)methylide (20) in thiophen gave only dimethyl 2-(5-methylthienyl)malonate (46) in 88% yield.



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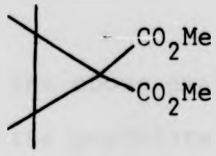
The results of the above experiments present strong evidence in favour of the rearrangement being truly intramolecular since none of the "cross-over" product was observed in either case.

The reaction of carbenes with olefins to form cyclo-propanes is well known and it is common for the presence or non-presence of a carbene to be confirmed by the addition of

an olefin to the reaction mixture and observation of the cyclopropanated products. In the case of the above thiophenium ylides it would be expected, if the free malonate carbene was formed in any quantity, that formation of 1,1-bis(methoxycarbonyl)-cyclopropanes (48) would be observed.



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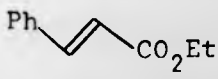
Thiophenium bis(methoxycarbonyl)methylide (14) was subjected to thermolysis in ethyl cinnamate (49), dimethyl acetylenedicarboxylate (50), vinyl acetate (51), and cyclohexene, each at 60°C for two days. In all cases the only product was dimethyl 2-thienylmalonate and in all cases the anticipated cyclopropane derivative was not observed.



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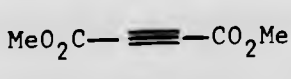

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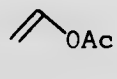
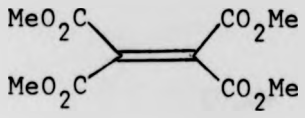


51

Formation of the malonate carbene dimer, tetra(methoxycarbonyl)ethylene (13) in any of the above reactions would be expected if the free malonate carbene was formed at any time. In all of the experiments mentioned above

there was no indication of the formation of this compound.



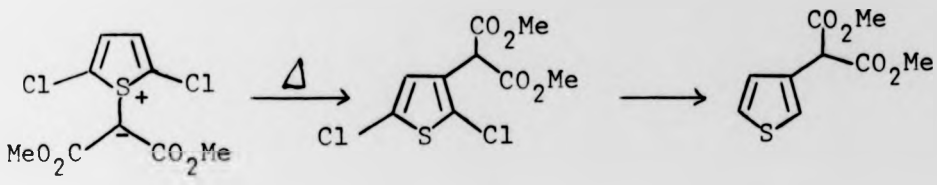
13

The results of the above experiments provide overwhelming support for the postulate that the thermal rearrangement of thiophenium ylides to 2-substituted thiophen derivatives is truly intramolecular.

Since the rearrangement of the thiophenium ylides tested appears to be facile attention was turned to 2,5-disubstituted thiophenium ylides. It was considered that, while substitution of thiophens occurs almost exclusively at the α-position, the presence of substituents in these α-positions may well leave the appropriate ylide no alternative but to rearrange to give a 3-substituted thiophen derivative. This transformation would be particularly useful in the case of 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (19) which would rearrange to give dimethyl 2-(2',5'-dichloro-3'-thienyl)malonate (52). This compound could easily be converted to dimethyl 3-thienylmalonate (53) by simple hydrogenolysis of the chlorine substituents. If these reactions were successful the result would be a convenient synthesis of the elusive dimethyl 3-thienylmalonate.

2,5-Dichlorothiophenium bis(methoxycarbonyl)-methylide (19) was allowed to reflux in 2,5-dichlorothiophen until reaction was complete (40 min). Tlc analysis showed

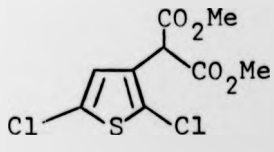
that a complex mixture of products had been formed however it was undertaken to isolate and characterize as many of these



19 52 53

products as possible. Due to the numerous purification techniques employed during the isolation of each compound the yields diminished in size and for this reason it is meaningless to quote accurate yields.

Four products have been isolated, purified, and characterized as far as the minute amounts of purified material allowed and these have been assigned the structures (52), (54), (55), and (56).



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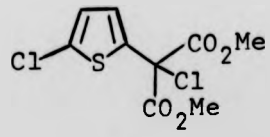

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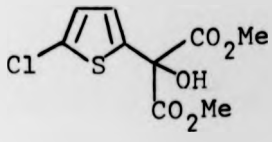

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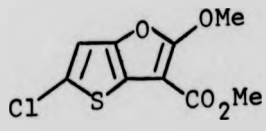

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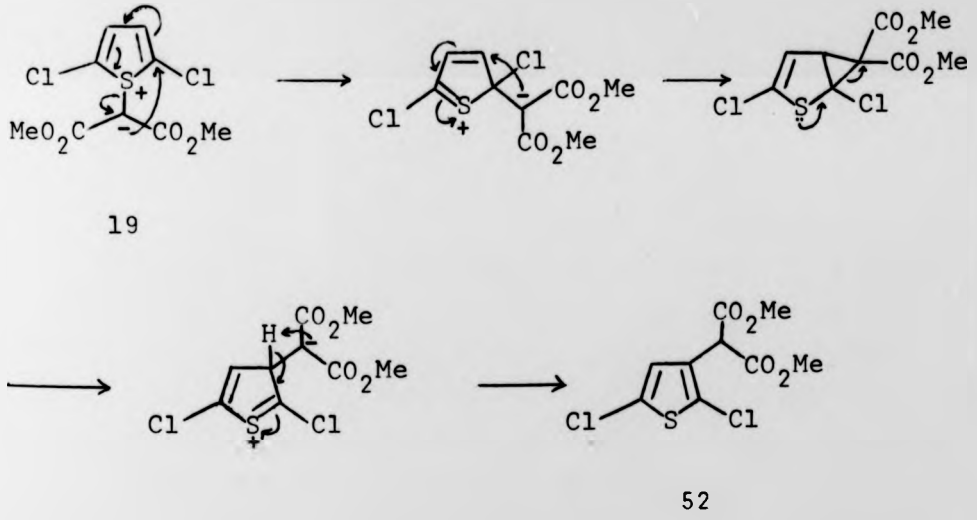
Dimethyl 2-(2',5'-dichloro-3'-thienyl)malonate (52) shows an nmr spectrum comprising of a one proton singlet at τ 3.25 (thiophen proton), a one proton singlet at τ 4.90 (malonate methine) and a six proton singlet at τ 6.20 (malonic ester). Mass spectrometry confirms that the molecular formula is $C_9H_8SO_4Cl_2$ and the characteristic pattern for the two chlorine atoms is observed in the fragmentation pattern.

Compound (52) can be considered to be derived from the ylide (19) by the mechanism in Scheme 9.



19

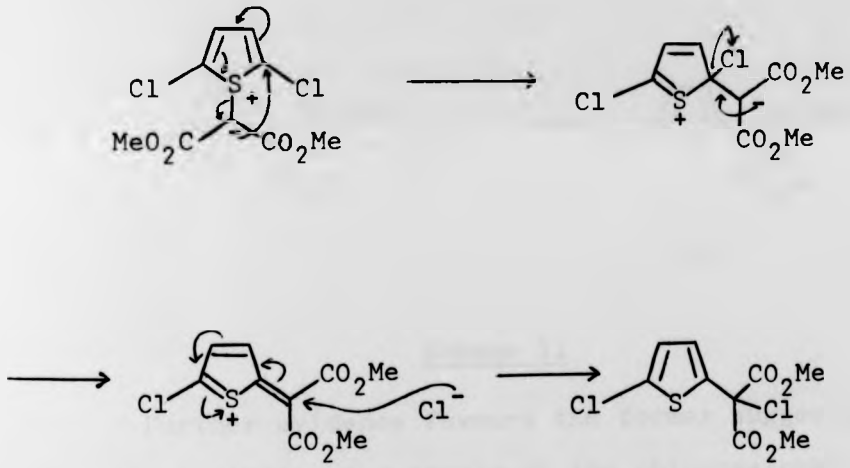
52

Scheme 9

Although this compound has been formed as predicted it was one of the minor products and the yield was only in the region of a few per cent. Unless this yield can be increased by a substantial amount this reaction does not provide a useful route to 3-thienylmalonates.

Dimethyl 2-(5'-chloro-2'-thienyl)chloromalonate (54), produced in low yield, shows an nmr spectrum comprising of an AB quartet centred at τ 3.17 (thiophen protons) and a six proton singlet at τ 6.20 (malonic esters). Mass spectrometry confirms a molecular formula of $C_9H_8SO_4Cl_2$ and the characteristic pattern for two chlorine atoms is observed in the fragmentation pattern.

Compound (54) can be considered to be derived from the dichloroylide by a mechanism such as that shown in Scheme 10.



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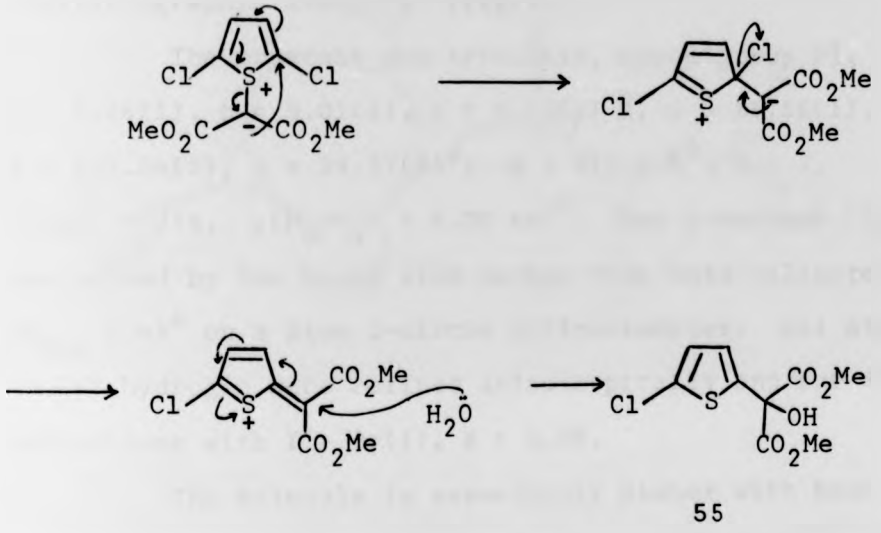
Scheme 10

Dimethyl 2-(5'-chloro-2'-thienyl)hydroxymalonate (55), produced in low yield, shows an nmr spectrum similar to that of compound (54), comprising of an AB quartet centred at τ 3.08 (thiophen protons), a singlet at τ 6.75 (hydroxyl), and a six proton singlet at τ 6.25 (malonic ester). Mass spectrometry confirms a molecular formula of $C_9H_9SO_5Cl$ and the characteristic pattern due to one chlorine atom is observed.

Compound (55) can be considered to be derived, either by simple hydrolysis of the chloromalonate (54), or from the dichloroylide by the mechanism in Scheme 11.



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Scheme 11

Further evidence favours the former suggestion since a tlc analysis of a sample of the chloromalonate (54) just after purification by preparative tlc always shows the presence of some of the hydroxymalonate (55). It would appear that hydrolysis of the chloromalonate (54) occurs during preparative tlc due to the water present in the silica.

Methyl 5-chloro-2-methoxythieno[3,2-b] furan-3-carboxylate (56) is the major product, formed in about 35% yield. Microanalysis and mass spectral data indicate a molecular formula of $C_9H_7SO_4Cl$ corresponding to loss of HCl from the dichloroylide (19). The nmr spectrum shows singlets at τ 3.15 (thienyl), 5.80 (methoxy), and 6.15 (methoxycarbonyl),

and the presence of only one chlorine atom is confirmed by the fragmentation pattern in the mass spectrum.

Due to the uncertainty and unusual nature of this product confirmation of its structure was sought from an X-ray crystallographic study[28]. (Fig.3)

The crystals are triclinic, space group $P\bar{1}$, $a = 7.28(1)$, $b = 9.01(1)$, $c = 8.62(1)$ Å, $\alpha = 85.56(1)$, $\beta = 113.54(3)$, $\gamma = 99.57(3)^{\circ}$; $U = 511.9$ Å^3, $Z = 2$, $F(000) = 252$, $\mu(M_o\text{-}K_\alpha) = 5.00$ cm^{-1}. The structure (Fig.3) was solved by the heavy atom method from data collected to $2\theta_{max} = 45^{\circ}$ on a Stoe 2-circle diffractometer. All atoms except hydrogen were refined anisotropically and for 883 reflections with $I > 3\sigma(I)$, $R = 5.0\%$.

The molecule is essentially planar with bond lengths in the thiophen ring being comparable with those in thiophen itself[29].

Compound (56) can be considered to be derived from the dichloroylide by the mechanism in Scheme 12.

It must be brought to notice that the mechanisms proposed for the rearrangements of the dichloroylide (19) involve, as a first step, the intramolecular nucleophilic rearrangement of the ylide, and that a dissociative mechanism, such as that considered earlier for the rearrangement of thiophenium bis(methoxycarbonyl)methylide, has been ruled out. The reasons for this assumption are two-fold. Firstly, in all thermolysis reactions of the dichloroylide, in the absence of catalyst, no indication of the presence of the carbene dimer, tetra(methoxycarbonyl)ethylene (13), was observed. Secondly,

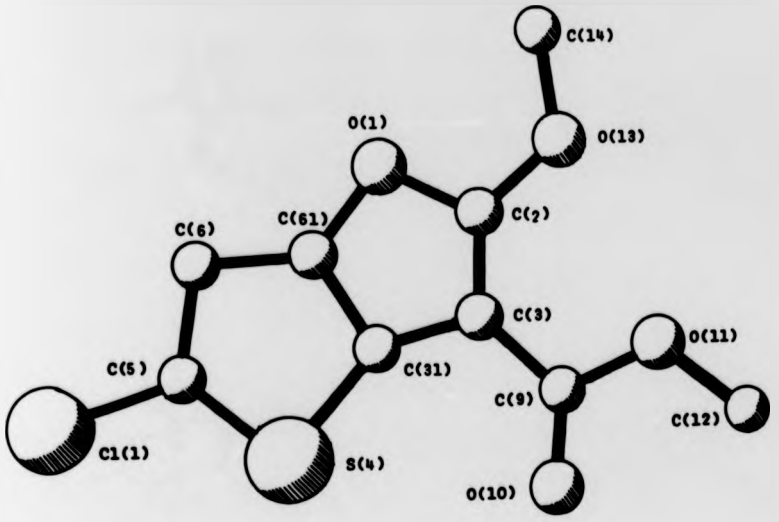
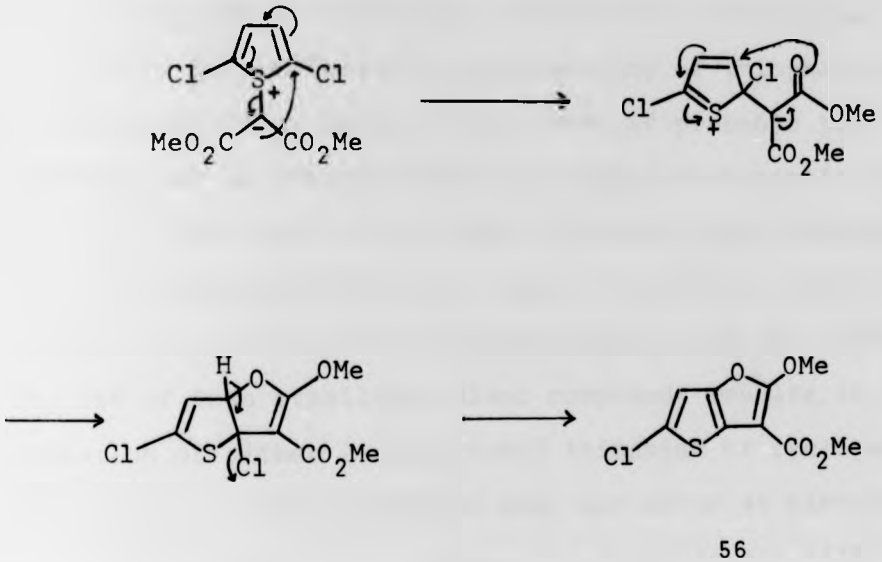


Fig.3

Bond Lengths (Å) (e.s.d's ca. 0.007 Å)

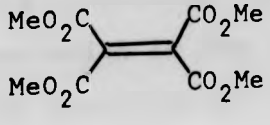
S(4) - C(5)	1.738
S(4) - C(31)	1.728
C(3) - C(31)	1.443
C(2) - C(3)	1.361
O(1) - C(2)	1.367
O(1) - C(61)	1.388
C(6) - C(61)	1.430
C(5) - C(6)	1.430
C(31) - C(61)	1.352



56

Scheme 12

the dichloroylide was allowed to reflux in cyclohexene, a known carbene trap, for nine days without any sign of reaction to form the cyclopropane. Similarly, thermolysis of the dichloroylide in the presence of ethyl cinnamate provided no evidence of a cyclopropanation reaction having occurred. These observations provide strong evidence that the thermal rearrangement of the dichloroylide, in the absence of catalysts, is truly intramolecular.



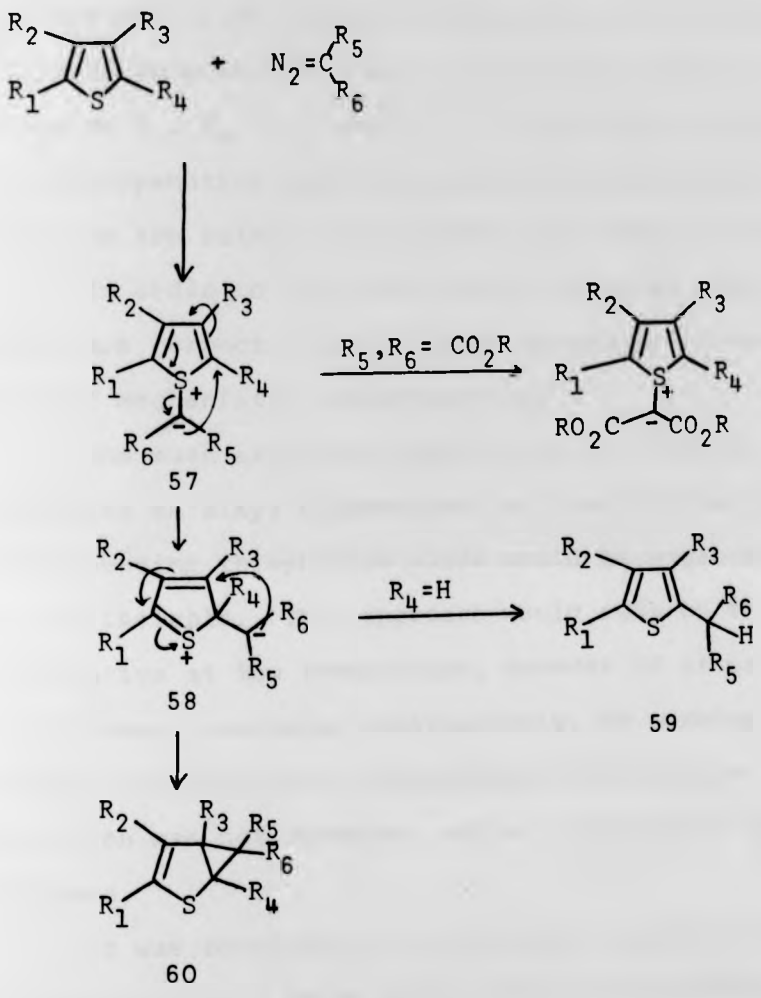
13

Consideration of all the above reactions of diazo compounds with thiophen derivatives, and of the apparently intramolecular rearrangements of thiophenium bis(methoxycarbonyl)methylides, makes it probable that the products can be rationalized by a single mechanistic scheme.

The reactions of diazo compounds with thiophens can give rise to three different types of product. In the case of diazomalonic esters stable thiophenium ylides are isolated. The use of less stabilized diazo compounds results in the formation of either 2-substituted thiophens or cyclopropanated derivatives. Ylide formation does not occur at elevated temperatures and, in all cases, the products are either 2-substituted thiophens or cyclopropanes, or a mixture of both.

The above results suggest that, in all cases, the substituted thiophen derivatives are directly derived from the corresponding thiophenium ylides and a mechanistic scheme is proposed (Scheme 13).

In all cases the first step is formation of the thiophenium ylide (57). When both R_5 and R_6 are CO_2R the ylide (57) is stable at room temperature and can be isolated as a crystalline solid (unless R_1, R_2, R_3, or R_4 is strongly electron withdrawing). However when either R_5 or R_6 is anything other than CO_2R it appears that the ylide is unstable at room temperature and undergoes spontaneous rearrangement. In cases where R_5 or R_6 is a group which is less stabilizing than CO_2R, not only does this render the ylide (57) less stable, but it also makes the anionic carbon more nucleophilic and therefore more likely to undergo the proposed rearrangement.



Scheme 13

The first step in the rearrangement leads to intermediate (58) and, in general, this has two options for stabilization. The first is a simple proton transfer from the adjacent ring carbon to the anionic centre to give the 2-substituted thiophen derivative (59). The second is nucleophilic attack of the anionic centre on the carbon bearing R_3 to give the cyclopropane derivative (60).

The reasons for selectivity between these two options are not clear but may involve factors such as the stability of intermediate (58) or the steric bulk of substituents R_3, R_4, R_5, and R_6. If the latter is operative then cyclopropanation might be disfavoured when these substituents are bulky, and favoured when they are small groups.

In order to be certain that the above mechanistic proposals are correct it was thought necessary to carry out a number of mechanistic investigations.

One such experiment might involve reaction of thiophen with an alkyl diazoacetate at low temperature where the corresponding thiophenium ylide would be expected to be stable and isolable. This approach would rely on the reaction being operative at low temperature, however if it was successful the ylide should rearrange spontaneously, on warming to room temperature, to give the corresponding cyclopropane. This investigation was not attempted and an alternative approach was followed.

It was considered that the most practical approach to this problem would be to prepare the corresponding thiophenium salt, to remove the acidic proton, and to observe the ylide rearrangement.

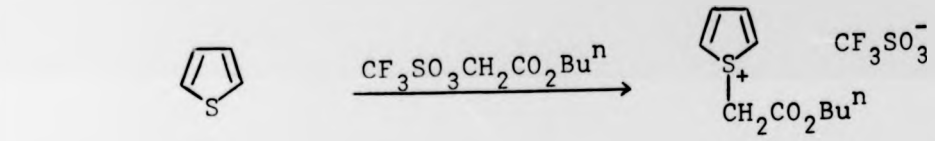
The triflate (61) is reported[40] to alkylate a variety of sulfides in high yield, at room temperature, to give sulfonium salts. The n-butyl derivative of this compound was easily prepared from n-butyl diazoacetate and trifluoromethane sulfonic acid.

The intention (Scheme 14) was to react the triflate

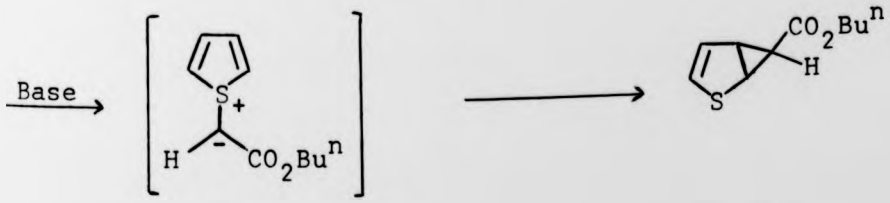
$CF_3SO_3CH_2CO_2Et$

61

with thiophen to form the thiophenium salt (62) which, on deprotonation, should form the unstable thiophenium ylide (63) and, hopefully, the rearranged cyclopropane (38)



62



63 38

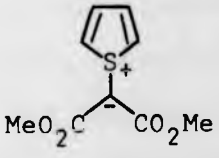
Scheme 14

Unfortunately the reaction of thiophen with the triflate proved to be unsuccessful at room temperature and, when the mixture was allowed to reflux, an evil-smelling reaction produced a polymeric product.

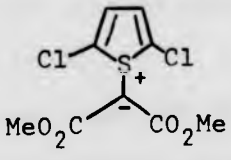
Generation and Reactions of Bis(methoxycarbonyl)carbene

The thermolysis of thiophenium ylides and, in particular thiophenium bis(methoxycarbonyl)methylide (14) and 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (19), has been shown to proceed, in the absence of a catalyst, by an intramolecular mechanistic pathway not involving the intermediacy of a carbene.

The thermal reactions of the dichloroylide (19) in the presence of rhodium (II) acetate or copper (II) acetylacetonate[41] proceed by an entirely different mechanism to give different products.



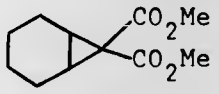
14



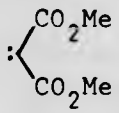
19

(i) Cyclopropanation

It has already been mentioned that thermolysis of the dichloroylide (19) in the presence of cyclohexene, but in the absence of a catalyst, produces none of the cyclopropane derived from carbene reaction. When this reaction is carried out in the presence of a transition metal catalyst a high yield of the cyclopropane 7,7-bis(methoxycarbonyl)bicyclo[4.1.0]-heptane (64) is formed during a comparatively short reaction period.



64



47

The formation of the cyclopropane (64) is strongly suggestive of the intermediacy of bis(methoxycarbonyl)carbene (47) or, more likely, a metal-stabilized carbenoid species.

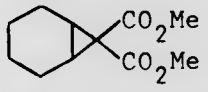
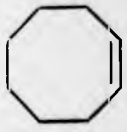
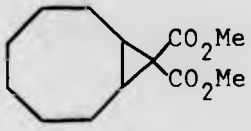
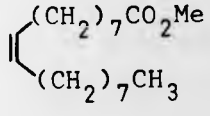
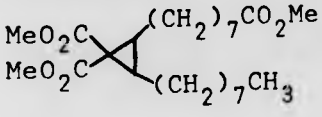
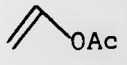
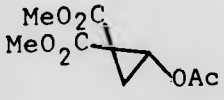
In view of the current interest in the applications of the chemistry of bis(methoxycarbonyl)carbene in synthetic methodology[42,43] it was decided to carry out an investigation into the use of 2,5-dichlorothiophenium bis(methoxycarbonyl)-methylide as a source of the carbene (47).

The initial investigation was aimed at the cyclopropanation of olefins to form 1,1-bis(methoxycarbonyl)cyclopropanes, a reaction normally carried out[41] by the treatment of the olefin with dimethyl diazomalonate in the presence of a transition metal catalyst.

The reactions were normally carried out using the olefinic substrate as solvent and by stirring a mixture of the ylide and $Cu(acac)_2$ in the solvent at the required temperature. Once the reaction was complete (tlc) the excess solvent was evaporated and the cyclopropane isolated by passage through a short silica column. The results of this investigation are presented in Table 5.

TABLE 5

Cyclopropanation of Olefins

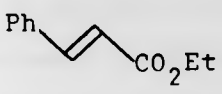
Reactant	Product	Product Number	Yield (%)[a]	Temp. (°C)	Time (h)
		64	66	Reflux	16
		65	86	120	0.5
		66	83[b]	120	1.5
		67	60	110	0.5
		68	81	75	11

(a) In all cases the yields are of isolated products

(b) A small yield (2%) of the dicyclopropanated product was also formed in this reaction.

In addition to the results in Table 5 a number of attempted cyclopropanations were unsuccessful.

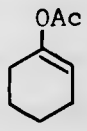
With ethyl cinnamate (49) a complex mixture of products was formed, none of which could be isolated. With trans-stilbene (69) a complex mixture was formed during a two hour reaction.



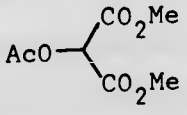
49

69

With cyclohexenylacetate (70) a mixture of at least ten products was formed none of which appeared to be the desired cyclopropane. The only product isolated and purified was dimethyl acetoxymalonate (71) apparently formed by insertion of the malonate carbene into the ester bond of cyclohexenyl-acetate.

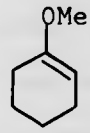


70



71

With both 1-methoxycyclohexene (72) and dihydro-pyran (73) complex mixtures of products were formed and no indication of cyclopropane formation was observed.



72

73

In general it was found that higher temperatures, and hence shorter reaction times, provided higher yields of cyclopropanes and lower yields of the malonate carbene dimer, a compound formed, in low yield, in most of the above reactions.

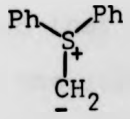
It would appear that with unactivated and simple olefins the cyclopropanation reaction is straightforward, however when oxygen functions are present the reaction, in most cases, is complicated by countless side-reactions. In some cases this may be due to deactivation of the olefin by the oxygen-containing substituent, and in some cases the oxygen-substituted cyclopropanes and other products may be unstable under the reaction or work-up conditions.

The reaction of carbenes with oxygen-containing compounds has been studied by Ando and co-workers[44] and many of the products appear to be derived from intermediate oxonium ylides. It seems likely that such ylides could be formed in some of the above reactions leading to numerous products of complex rearrangements.

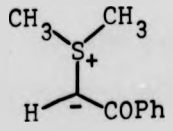
Although this method of cyclopropanation clearly has its limitations it offers many distinct advantages over existing methods. The ylide is a stable crystalline solid

and has been stored, without precautions, at ambient temperature for over a year. In the examples quoted the yields are comparable with, and in some cases superior to, the use of dimethyl diazomalonate as a carbene source, and the reaction times are invariably shorter. The main advantage is the ease with which the reaction may be carried out, especially on a small scale. When diazomalonic esters are used the reaction conditions, and in particular catalyst concentration and rate of addition of diazo compound[34], appear to be critical in determining yields of products.

The cyclopropanation of olefins by sulfonium ylides in the presence of copper salts appears in the chemical literature. Cohen and co-workers[45], in an attempt to substantiate a proposal that cyclopropanation of unactivated olefins in nature may involve sulfonium ylides, have demonstrated the cyclopropanation of several simple olefins, in low yield, by diphenylsulfonium methylide (74) in the presence of $Cu(acac)_2$. Trost[64] reported the cyclopropanation of cyclohexene, in low yield, by dimethylsulfonium phenacylide (101) in the presence of cupric sulfate.



74

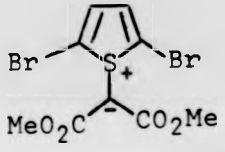


101

This method of cyclopropanation is interesting in that it appears to be the only method of generation of copper-stabilized carbenoid species other than thermolysis of diazo

compounds.

In an attempt to broaden the scope of this reaction the substrates in Table 5 were tested using 2,5-dibromothiophenium bis(methoxycarbonyl)methylide (22) in place of the dichloroylide but with all other conditions identical. The reactions were complete (tlc) within two days however in no case was there any indication of cyclopropanation having occurred, and a complex mixture of products was produced.



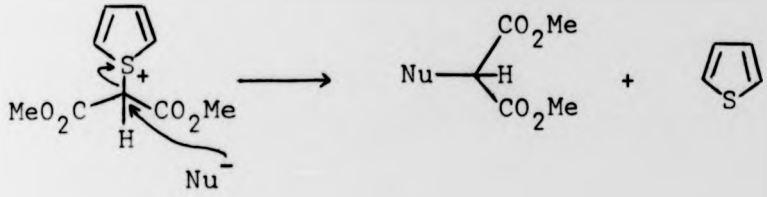
22

(ii) Reaction with Aromatic Nucleii and Acidic Hydrogens

Only a few reports have appeared in the literature on the reactions of sulfonium ylides in the presence of acid[46] and protonation normally occurs at the carbanionic site. It was considered that the sulfonium salt (75), derived from acid treatment of the ylide, might serve as a useful source of "electrophilic malonate", the desired nucleophile attacking in the manner indicated in Scheme 15, with thiophen serving as a good leaving group.

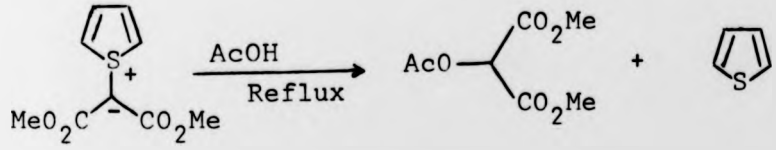
The thermolysis of thiophenium bis(methoxycarbonyl)-methylide (14) in glacial acetic acid in the absence of a catalyst gave dimethyl acetoxymalonate (71) in 96% yield after

a three hour reaction.



75

Scheme 15



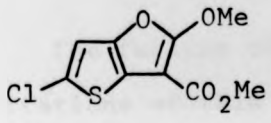
14 71

In order to ensure that competition from intramolecular rearrangement did not interfere with this type of reaction the dichloroylide (19) was used for all further investigations.

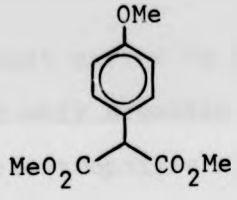
One of the most useful reactions which this reagent might be expected to undergo is the electrophilic substitution of aromatic substrates. In these reactions a catalytic amount of acid should be sufficient along with the ylide since

substitution at "active" hydrogen sites liberates a proton.

Treatment of the dichloroylide (19) with refluxing anisole in the presence of a catalytic quantity of p-toluene sulfonic acid failed to produce the desired substituted anisole derivative, the only isolated product being methyl 5-chloro-2-methoxythieno[3,2-b]furan-3-carboxylate (56), a compound previously described as being derived from intramolecular thermal rearrangement of the dichloroylide, formed in 36% yield.



56



76

The use of boron trifluoride etherate as the acidic catalyst gave the same product in 21% yield however the desired product, dimethyl anisole-4-malonate (76), was also isolated in 10% yield.

Carbenes and carbenoids are known to react with aromatic substrates[47] although the products are notoriously variable. Since the thermolysis of 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide, in the presence of $Cu(acac)_2$, is known to produce an intermediate carbenoid species it might be expected that reaction with aromatic substrates could be induced under similar conditions.

Reaction of the dichloroylide (19) in anisole in the presence of $Cu(acac)_2$ at reflux gave, after a 1.5h reaction followed by column chromatography, dimethyl anisole-4-malonate (76) in 48% yield.

Due to the success of this reaction with a fairly nucleophilic aromatic compound, anisole, it was decided to examine the scope of the reaction using a wide range of aromatic species ranging from the poorly nucleophilic to the highly nucleophilic substrates. The results are presented in Table 6.

The failure of toluene to react serves to indicate the limitations of this method in that only aromatic systems which are strongly activated towards electrophilic substitution give reasonable yields of products. In the toluene reaction most of the carbene was recovered as the dimer (13) and polymers thus it appears that, although the carbene was generated, the substrate was not sufficiently nucleophilic to react with it.

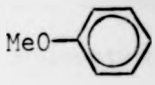
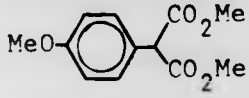
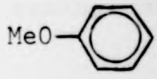
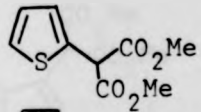
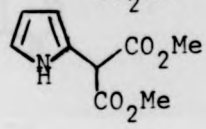
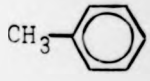
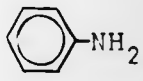
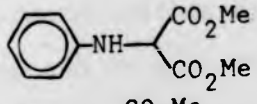
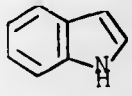
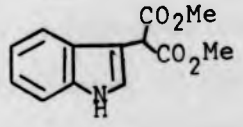
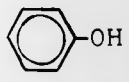
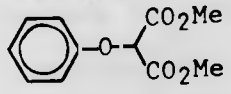
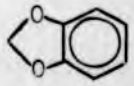
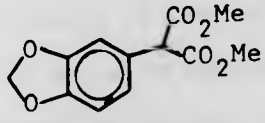
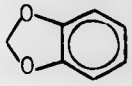
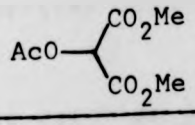
Fortunately toluene serves as a useful solvent for these reactions especially in the case of indole where the best recrystallization solvent for indole-3-malonate is toluene.

Another limitation of this method is seen in the reaction with substrates containing an acidic hydrogen. Thus with phenol and aniline the main reaction is insertion of the carbene into the OH and NH bonds respectively.

Indole is well known to undergo electrophilic substitution in the 3-position and it is no surprise that its reaction with the dichloroylide gives a high yield of dimethyl indole-3-malonate (79) in a rapid reaction.

TABLE 6

The Substitution of Aromatic Compounds

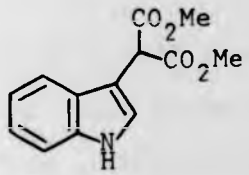
Substrate	Major Product	Compound Number	Yield (%)[a]	Method	Reaction Time
		76	48	A	1.5h
	—		0	B	2.5h
		10	98	A	24h
		77	73	A	2.5h
	—		0	A	2.5h
		78	93	B	15 min
		79	84	B	2 min
		80	40	B	1h
		81	20	A	1 min
	—		0	B	6h
AcOH		71	98.5	A	4h

(a) Yields are of isolated products

Method A The substrate was used as solvent and the mixture refluxed

Method B The ylide and substrate, in equimolar proportions, were stirred in toluene at 110°C

It was undertaken to prove the structure of dimethyl indole-3-malonate by its conversion to the known indole-3-acetic acid (82). It was expected that simple aqueous base hydrolysis and thermal decarboxylation would furnish the desired product however the product isolated from this procedure did not exhibit the expected spectral and physical properties.



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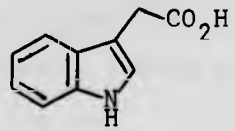


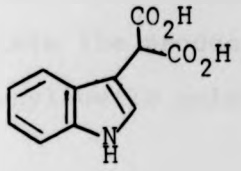
82

Characterization by mass spectrometry and microanalysis as well as nmr and ir spectroscopy showed that the compound isolated was indole-3-malonic acid (83) in 76% yield.

The report of Markgraf[48] on the decarbalkoxylation of geminal diesters to give the mono-esters prompted us to examine this reaction with respect to indole-3-malonate.

Treatment of dimethyl indole-3-malonate, in wet dimethylsulfoxide, with sodium chloride, under reflux for one hour followed by column chromatography gave the known methyl indole-3-acetate (84) in 92% yield with all spectroscopic and physical properties identical to those of the authentic material.

This reaction is particularly useful since indole-3-



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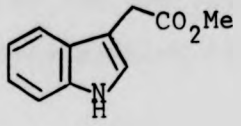
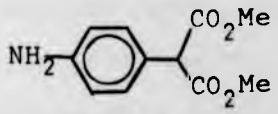


84

acetic acid is a well known plant growth regulator, and the above method could prove to be an extremely useful synthetic route to this commercially important compound.

The reaction of aniline with the dichloroylide served to examine the limitations of this reaction since there are two alternative sites for electrophilic attack of the carbenoid; the aromatic nucleus and the acidic NH bond.

The reaction produced a compound in 93% yield which was shown by mass spectrometry and microanalysis to be a 1:1 adduct of aniline and the malonate carbene. As expected, however, the spectroscopic evidence did not distinguish conclusively between the two possible products, dimethyl aniline-4-malonate (85) and 2-methoxycarbonyl-N-phenylglycine methyl ester (78).



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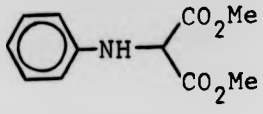
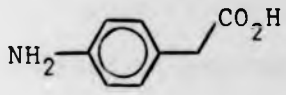


78

The most satisfactory method of distinguishing between these two possibilities would be to hydrolyse and decarboxylate the product to give one of the two known acids, p-aminophenylacetic acid (86) and N-phenylglycine (87).



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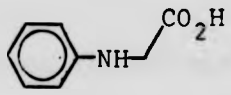


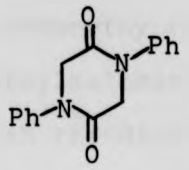
87

The product was allowed to reflux in aqueous sodium hydroxide solution however, after standard work-up, the product isolated was a white solid melting in excess of 300°C. Clearly this solid was neither of the two expected acids which both melt at a much lower temperature.

It was decided that a better preparation of the desired acid might be to employ the method of Markgraf[48] to form the methyl ester which should easily hydrolyse to the acid.

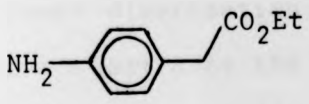
Decarbalkoxylation by Markgraf's method gave a product which showed spectral properties similar to those expected for N-phenylglycine methyl ester, however hydrolysis of the crude product in aqueous base gave only the high melting white solid. It was thought likely that the strongly basic conditions may have induced dimerization to give the diketo-piperazine (88) however no further attempts were made to characterize this product.

Since the ethyl esters of both possible decarboxylation products are known and have distinctly different melting points



88

it was decided to perform ester exchange on the original malonic ester produced by the reaction of aniline with the dichloroylide, then to subject this product to decarbalkoxylation by the method of Markgraf to give one of the ethyl esters (89) or (90).



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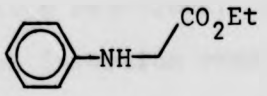


90

Treatment of the original product (85) or (78) with an ethanolic HCl solution followed by standard work up gave a product whose nmr confirmed that ester exchange had occurred. Decarbalkoxylation of this crude product by the method of Markgraf, followed by column chromatography, gave white platelets whose melting point, nmr and ir spectra were identical to those of an authentic sample of N-phenylglycine ethyl ester (90).

This result gives conclusive evidence that the reaction of aniline with the dichloroylide gives the NH insertion

product 2-methoxycarbonyl-N-phenylglycine methyl ester (78).

One of the most noteworthy reactions is the formation of dimethyl 2-thienylmalonate (10) in 98% yield by the reaction of thiophen with the dichloroylide. This is by far the most efficient synthesis of this compound to date and could prove to be important commercially.

It would appear that the malonate carbenoid species is generated fairly easily at moderate temperatures however the reaction temperature and reactivity of the substrate then determine the fate of the carbenoid.

With highly reactive substrates the substitution or insertion reaction takes place rapidly and takes preference over the slower dimerization or polymerization reactions. With less reactive substrates the substitution or insertion reactions are much slower and the dimerization or polymerization reactions can then compete. In this case raising the temperature appears to favour reaction with the substrate and increased yields are obtained at the expense of dimer or polymer.

All reactions of the carbenoid species with acidic hydrogens, such as those in phenol, aniline and acetic acid, are fairly rapid and specific processes even at moderate temperatures.

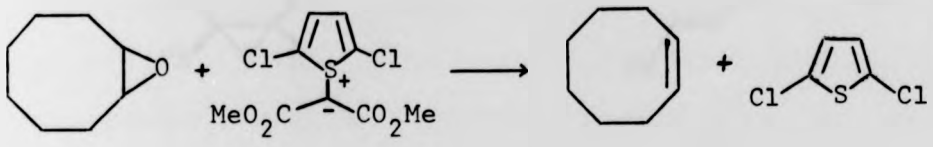
In all cases examined, substitution of the aromatic nucleus occurs at the site predicted on the basis of known substituent activating effects. In the case of anisole and benzo-1,3-dioxole substitution at the available <u>para</u>-position is favoured and no products of <u>ortho</u>-substitution are observed. Presumably this is a consequence of steric interactions between the carbenoid and the substrate.

(iii) Deoxygenation of Epoxides

The reaction of carbenes with three-membered heterocyclic rings has been studied by various workers. A publication by Hata and Watanabe[49] in 1972 reports that the reaction of aziridines with dichlorocarbene leads to olefin formation via fragmentation of an intermediate aziridinium ylide. The reaction of episulfides with ethyl diazoacetate has been shown[50] to produce the corresponding olefin by fragmentation of an intermediate sulfonium ylide. More recently the reaction of epoxides with dichlorocarbene has been reported[51,52] to lead to olefin formation resulting from a stereospecific fragmentation reaction of an intermediate oxonium ylide. The resulting olefin was isolated in very low yield since most of it went on to react with the excess of dichlorocarbene to give cyclopropanes.

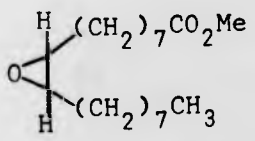
Since the thermolysis of 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (19), in the presence of $Cu(acac)_2$, in solution leads to the formation of a copper-stabilized carbenoid species it was considered likely that reaction of epoxides under these conditions would lead to deoxygenation and olefin formation.

Cyclooctene epoxide (91) was prepared and allowed to stir at 100°C in toluene in the presence of one equivalent of the dichloroylide (19) and a catalytic quantity of $Cu(acac)_2$. The reaction was complete after 40 min. and the products analysed by gas chromatography. The major product was cyclooctene and the use of an internal standard (C_{11}) allowed calculation of the yield, which was 82%. As expected 2,5-dichlorothiophen was detected in the product mixture.



91 19

cis-Methyl oleate epoxide (92) was prepared and subjected to the same conditions as above. The major product after a three hour reaction, was cis-methyl oleate (93) in 77% yield (isolated) resulting from deoxygenation of the epoxide. Nmr analysis indicated that the reaction had proceeded with retention of stereochemistry.



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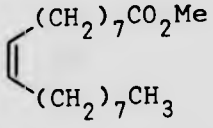
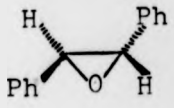


93

trans-Stilbene epoxide (94) was prepared and allowed to react with the dichloroylide as above. The reaction was complete after 1.5h and the mixture of products separated and isolated by column chromatography. trans-Stilbene (69) was isolated in 10% yield and was shown to have identical spectral properties, melting point and chromatographic properties to an authentic sample. The major product was unchanged trans-stilbene epoxide in 88% yield.



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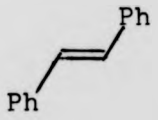
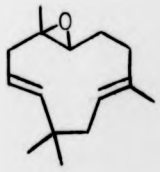


69

Deoxygenation of the epoxides of humulene is of interest[53] and the use of the dichloroylide in this field was examined briefly[54]. Treatment of humulene-1,2-epoxide (95) with the dichloroylide as above gave humulene (96) in 20% yield, the reaction having proceeded with retention of configuration.



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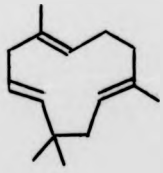
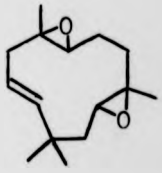


96

Treatment of humulene-1,2-8,9-bisepoxide (97) with the dichloroylide as above gave a 1:1 mixture of the two mono-epoxides (98) and (95) in total 5% yield. Once again the reaction proceeded with complete retention of stereochemistry.



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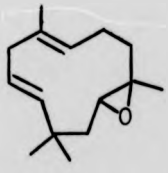
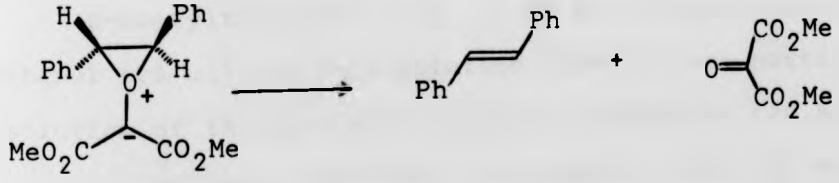


98

The results of the above reactions are in accord with those published in the literature and, likewise, the deoxygenation reaction appears to be stereospecific with trans-stilbene epoxide giving only trans-stilbene and cis-methyl oleate epoxide giving only cis-methyl oleate. The reactions with the humulene derivatives, likewise, are stereospecific.

These stereochemical consequences help to substantiate the idea that the mechanism of this reaction involves initial formation of an oxonium ylide (99) by reaction of the carbenoid with the epoxide. Concerted stereospecific fragmentation of this oxonium ylide then gives the olefin and dimethyl oxomalonate (100). The latter compound was not detected in the reaction mixtures.



99 100

The above deoxygenation reaction was attempted with cyclooctene epoxide using thiophenium bis(methoxycarbonyl)-methylide (14) in place of the dichloroylide, however none of the expected olefin was detected and the major product was dimethyl 2-thienylmalonate, derived from intramolecular rearrangement of the thiophenium ylide, along with recovered cyclooctene epoxide.

EXPERIMENTAL

General

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. Infrared spectra were recorded on a Perkin-Elmer 577 Grating Infrared Spectrophotometer. Melting points were recorded on a Kofler block and are uncorrected. Analytical tlc was carried out using glass plates coated with Merck Kieselgel 60F-254, preparative tlc was carried out using glass plates coated with Merck Kieselgel GF_{254} (Type 60), and column chromatography was carried out using Merck Kieselgel HF_{254} in an adaption of the pressure method of Still[55].

2-Thienylacetic Acid

2-Acetylthiophen (6.3g; 0.05 mol.) was dissolved in methanol (25 ml) and this solution added in one portion to a solution of thallium (III) nitrate trihydrate (24.5g; 0.05 mol.) in methanol (100 ml). Fluoroboric acid (25 ml, 40%) was added and the resultant pale yellow solution stirred at room temperature. Almost immediately a precipitate of thallium (I) nitrate began to appear and tlc (light petroleum - ethyl acetate, 5:1) indicated that the reaction was complete after 3h.

The solid thallium (I) nitrate (quantitative recovery) was removed by filtration, the filtrate added to water (800 ml), and the aqueous solution extracted with chloroform (3 x 100 ml). The combined chloroform extracts were evaporated to give a pale

yellow oil which was purified by passage through a short alumina column as a benzene solution. Kügelrohr distillation (oven temp. 104-108°C at 0.15 Torr) gave methyl 2-thienylacetate (7) (6.32g; 82%) as a pale yellow oil, ν_{max} ($CHCl_3$) 1730 cm^{-1}; τ($CDCl_3$) 7.1 (3H,m), 6.3 (2H,s), and 6.4 (3H,s); spectral and physical properties identical to those of the authentic material.

The ester was suspended in an aqueous sodium hydroxide solution (100 ml; 10%), refluxed for 4h, cooled and extracted with chloroform (2 x 25 ml). The aqueous phase was acidified (pH = 1), extracted with chloroform (3 x 25 ml) and the combined chloroform extracts dried ($MgSO_4$), filtered and evaporated to give 2-thienylacetic acid (1) (5.27g; 74% based on 2-acetylthiophen) as an off-white solid, m.p. 62°C (lit.[56] 63-64°C); ν_{max} ($CHCl_3$) 3500-2500 br, 1710 cm^{-1}; τ($CDCl_3$) 2.3 (3H,m), 6.3 (2H,s), and -0.7 (1H,s, exchanges with D_2O); physical and spectral properties identical to those of the authentic material.

3-Thienylacetic Acid

The procedure above was repeated exactly, thus 3-acetylthiophen (6.3g; 0.05 mol.) was used to produce methyl 3-thienylacetate (6.48g; 84%) as a pale yellow oil which was Kügelrohr distilled (oven temp. 96-106°C at 0.15 Torr); ν_{max} ($CHCl_3$) 1735 cm^{-1}; τ($CDCl_3$) 2.95 (3H,m), 6.4 (5H,s, overlapping signals of $C\underline{H}_2$ and $CO_2\underline{Me}$); physical and spectral properties identical to those of the authentic material.

Hydrolysis of the ester by the above procedure gave 3-thienylacetic acid (5.03g; 70% based on 3-acetylthiophen) as

an off-white solid, m.p. 77°C (lit.[56] 79-80°C); ν_{max} ($CHCl_3$) 3400-2600 br, and 1700 cm^{-1}; τ($CDCl_3$) 2.3 (3H,m), 6.3 (2H,s), and -1.0 (1H,s, exchanges with D_2O); physical and spectral properties identical to those of the authentic material.

Attempted Nucleophilic Substitution of 3-Bromothiophen

(i) To a suspension of commercial sodium methoxide (0.43g; 8 mmol.) in methanol (25 ml) was added dimethyl diazomalonate (1.06g; 8 mmol.) and the mixture refluxed to effect dissolution. To the cooled solution was added 3-bromothiophen (1.22g; 7.5 mmol.) in methanol (10 ml) and the mixture stirred for 2h without any apparent change. The mixture was heated under reflux but after 7 days the starting 3-bromothiophen still remained. The mixture was poured into water, extracted with chloroform and the combined chloroform extracts dried ($MgSO_4$), filtered and evaporated to give 3-bromothiophen.

(ii) The above procedure was repeated with the addition of 18-crown-6 (2.11g; 8 mmol.) however, after refluxing for 7 days the starting 3-bromothiophen still remained.

(iii) The above procedure was repeated this time using freshly cut sodium (0.184g; 8 mmol.) and 18-crown-6 (2.11g; 8 mmol.) in dry methanol. No reaction took place.

(iv) The above procedure was repeated using potassium hydroxide pellets (0.448g; 8 mmol.) in place of sodium methoxide, and with the inclusion of 18-crown-6. No reaction took place.

(v) To a solution of dimethyl malonate (1.056g; 8 mmol.) in dimethyl sulfoxide (25 ml) was added sodium hydride (9 mmol.).

Once the evolution of hydrogen stopped 3-bromothiophen (1.22g; 7.5 mmol.) was added and the mixture heated at 120°C. No reaction occurred after 3 days and starting 3-bromothiophen was isolated.

Attempted Formation and Alkylation of "Thiophyne".[17]

To liquid ammonia (800 ml) was added clean sodium (23.0g; 1.0 mol.) in small pieces. Once the blue colour appeared $FeCl_3$ (catalytic quantity) was added to facilitate the formation of sodamide. Once addition was complete and all the sodium had dissolved dimethyl malonate (66.0g; 0.50 mol.) was added dropwise over a period of 30 mins, then stirring was continued for 30 mins. To the mixture was added slowly solid ammonium chloride (59.0g; 1.1 mol.) then ether (200 ml.). The cooling was removed and the mixture left overnight to allow the ammonia to evaporate. The mixture was refluxed to ensure complete removal of ammonia then dilute hydrochloric acid was added to dissolve any amines which had formed. The organic layer was washed with sodium bicarbonate solution, then with water, then dried ($MgSO_4$), filtered and evaporated to leave a brown oil. Nmr indicated the presence of dimethyl malonate and 2-bromothiophen and distillation at reduced pressure gave 2-bromothiophen.

The above procedure was repeated exactly using 3-bromothiophen however the only products isolated were 3-bromothiophen and dimethyl malonate.

Dimethyl 2-Thienylmalonate

To a solution of $[CuP(OEt)_3]^+I^-$ (25 mg) in thiophen (100 ml.) was added a solution of dimethyl diazomalonate[34] (12.72g; 0.08 mol.) in thiophen (10 ml) and the mixture was heated under reflux for 8 days. Filtration followed by evaporation of the excess thiophen gave a brown oil which was distilled to yield dimethyl 2-thienylmalonate (10) (6.2g; 36.4%) as a pale yellow oil, b.p. 89-94°C at 0.06 Torr; ν_{max} (film) 2955, 1735, 1432, and 1240 cm^{-1}; $\tau(CDCl_3)$ 2.9 (3H,m), 5.0 (1H,s), and 6.3 (6H,s); Found: C, 50.2; H, 4.7; S, 15.05. Calc. for $C_9H_{10}O_4S$: C, 50.45; H, 4.7; S, 14.95%; Found: M^+, 214.0281. Calc. for $C_9H_{10}O_4S$: M, 214.0300.

Photolysis of Dimethyl 2-Thienylmalonate

A solution of freshly distilled dimethyl 2-thienylmalonate (10.0g; 0.047 mol.) in methanol (400 ml) was irradiated using a high pressure mercury lamp. After 17h the colourless solution had gone slightly yellow however tlc ($CHCl_3$) showed that only dimethyl 2-thienylmalonate was present. Evaporation of the solvent gave a brown oil which was shown to be dimethyl 2-thienylmalonate.

Hydrolysis and Decarboxylation of Dimethyl 2-Thienylmalonate

Dimethyl 2-thienylmalonate (0.407g; 1.9 mmol.) was added to an aqueous solution of sodium hydroxide (10 ml, 10%) and the mixture refluxed overnight. The mixture was cooled, acidified (pH = 1), extracted with chloroform (3 x 10 ml), and the combined chloroform extracts dried ($MgSO_4$), filtered and evaporated to give 2-thienylacetic acid (1) (0.224g; 83.0%) as a pale brown solid, m.p. 61-62°C (lit.[56] 63-64°C); physical and spectral properties identical to those reported above.

Rhodium (II) Acetate-catalysed Addition of Diazomalonic Esters to Thiophen Derivatives.

General Conditions

The diazo compound (10 mmol.) was added dropwise over a period of 1h to a solution of $Rh_2(OAc)_4$ (5 mg) in the thiophen derivative (10 ml). Stirring at room temperature was continued until the diazo band (2100 cm^{-1}) was no longer present in the ir spectrum. In most cases filtration of the mixture gave the ylide as a white solid which was purified by recrystallization. Thus prepared were (Table 1);

Thiophenium bis(methoxycarbonyl)methylide (14), (93%), m.p. (acetonitrile) 145-146°C; ν_{max} ($CHCl_3$), 1650, 1435, 1330, 1230, and 1090 cm^{-1}; $\tau(CDCl_3)$ 2.9 (4H,m), and 6.35 (6H,s); Found: C, 50.5; H, 4.5. $C_9H_{10}O_4S$ requires C, 50.45; H, 4.7%.

2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide (19), (90%), m.p. (acetonitrile) 174-174.5°C; ν_{max} ($CHCl_3$) 1690, 1660, 1440, 1330, and 1095 cm^{-1}; $\tau(CDCl_3)$ 3.10 (2H,s), and 6.30 (6H,s); Found: C, 38.2; H, 2.8; S, 11.9; Cl, 25.3. $C_9H_8Cl_2O_4S$ requires C, 38. 2; H, 2.85; S, 11.65; Cl, 25.05%.

2-Methylthiophenium bis(methoxycarbonyl)methylide (20), (92%), m.p. (ethyl acetate) 146-146.5°C; ν_{max} ($CHCl_3$) 1680, 1650, 1435, 1330, 1210-1240 br, and 1090 cm^{-1}; $\tau(CDCl_3)$ 2.90 (1H,m), 3.15 (2H,m), 6.33 (6H,s), and 7.75 (3H,s); Found: C, 52.3; H, 5.3; S, 14.4. $C_{10}H_{12}O_4S$ requires C, 52.65; H, 5.3; S, 14.05%.

2-Bromothiophenium bis(methoxycarbonyl)methylide (21), (73%) isolated by evaporation of the reaction mixture, m.p. (acetonitrile) 138-140°C; ν_{max} ($CHCl_3$) 1680, 1660, 1435, 1330, 1245 br, and 1090 cm^{-1}; τ($CDCl_3$) 2.80 (1H,m), 2.95 (2H,m), and 6.30 (6H,s); Found: C, 37.0; H, 3.2; S, 11.1; Br, 27.6. $C_9H_9BrO_4S$ requires C, 36.85; H, 3.1; S, 10.95; Br, 27.3%.

2,5-Dibromothiophenium bis(methoxycarbonyl)methylide (22), (55%), m.p. (acetonitrile) 190-190.5°C; ν_{max} ($CHCl_3$) 1690, 1660, 1440, 1330, 1250, and 1095 cm^{-1}; τ($CDCl_3$) 2.90 (2H,s), and 6.25 (6H,s); Found: C, 29.05; H, 2.15; S, 8.4; Br, 43.05. $C_9H_8Br_2O_4S$ requires C, 29.05; H, 2.15; S, 8.6; Br, 42.95%.

2-Hydroxymethylthiophenium bis(methoxycarbonyl)methylide (23), (54%) isolated by evaporation of the reaction mixture, m.p. (chloroform) 133-133.5°C; ν_{max} ($CHCl_3$) 3400 br, 1675, 1630, 1435, 1330, 1245, and 1090 cm^{-1}; τ($CDCl_3$) 3.00 (2H,m), 3.15 (1H,m), 5.45 (2H,d, J 6Hz), 6.35 (6H,s), and 6.55 (1H,t, J 6Hz, exchanges with D_2O); Found: C, 48.9; H, 5.0; S, 13.4. $C_{10}H_{12}O_5S$ requires C, 49.15; H, 4.95; S, 13.15%.

2-Bromo-3-methylthiophenium bis(methoxycarbonyl)methylide (24), (86%), m.p. (acetonitrile) 128.5-129°C; ν_{max} ($CHCl_3$) 1680, 1645, 1440, 1330, 1225 br, and 1090 cm^{-1}; τ($CDCl_3$) 3.05 (2H,s), 6.35 (6H,s), and 7.80 (3H,s); Found: C, 39.1; H, 3.7; S, 10.0; Br, 26.2. $C_{10}H_{11}BrO_4S$ requires C, 39.1; H, 3.6; S, 10.45; Br, 26.0%.

Benzo[b] thiophenium bis(methoxycarbonyl)methylide (25), (97%), m.p. (acetonitrile) 177-177.5°C; ν_{max} ($CHCl_3$) 1680, 1650, 1435, 1330, 1245 br, and 1090 cm^{-1}; τ($CDCl_3$) 2.45 (5H,m), 3.25 (1H,d), and 6.40 (6H,s); Found: C, 59.1; H, 4.7; S, 12.1. $C_9H_{12}O_4S$ requires C, 59.05; H, 4.6; S, 12.15%.

Thiophenium bis(ethoxycarbonyl)methylide (26), (90%), m.p. (acetonitrile) 111-111.5°C; ν_{max} ($CHCl_3$) 1675, 1640, 1370, 1310, 1205-1240 br, and 1085 cm^{-1}; τ($CDCl_3$) 2.90 (4H,m), 5.95 (4H,q), and 8.80 (6H,t); Found: C, 54.8; H, 5.8; S, 13.4. $C_{11}H_{14}O_4S$ requires C, 54.55; H, 5.8; S, 13.25%.

2,5-Dichlorothiophenium bis(ethoxycarbonyl)methylide (27), (60%), isolated by column chromatography ($CHCl_3$-methanol, 97.5:2.5), m.p. (acetonitrile) 82.5-83°C; ν_{max} ($CHCl_3$) 1690, 1650, 1370, 1310, 1205-1240 br, and 1085 cm^{-1}; τ($CDCl_3$) 3.10 (2H,s), 5.85 (4H,q), and 8.75 (6H,t); Found: C, 42.4; H, 3.9; S, 10.5; Cl, 22.9. $C_{11}H_{12}Cl_2O_4S$ requires C, 42.45; H, 3.9; S, 10.3; Cl, 22.8%.

Reaction of Thiophen with Ethyl Diazoacetoacetate

To a solution of $Rh_2(OAc)_4$ (5 mg) in thiophen (10 ml) was added dropwise, over a period of 30 mins, a solution of ethyl diazoacetoacetate[34] (1.56g; 10 mmol.) in thiophen (5 ml) and the mixture stirred at room temperature for 20h until the diazo band was no longer present in the ir spectrum. The excess solvent was removed and the residual oil examined by tlc (light petroleum-ether, 4:1) which indicated that two products were present. The mixture was separated by column chromatography (light petroleum-ether, 85:15) to give the two main products,

ethyl 3-oxo-2-(2'-thienyl)butanoate (31) (1.28g; 60.5%), ν_{max} ($CHCl_3$) 3000, 2990, 1720, 1640, 1340, 1260, 1060, 920, 850, and 695 cm^{-1}; τ($CDCl_3$) 2.9 (1H,d), 3.2 (2H,m), 5.2 (s, exchanges with D_2O) and -3.3 (s, exchanges with D_2O) (total 1H), 5.95 (2H,q), 7.9 (s) and 8.1 (s) (total 3H), and 8.9 (3H,dt, Ethyl in keto and enol forms), Found: C, 56.8; H, 5.8; S, 15.0. $C_{10}H_{12}O_3S$ requires C, 56.6; H, 5.7; S, 15.1%, and 6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (33), (0.11g; 5.2%), ν_{max} (CCl_4) 2940-2900 br, 1705, 1640, 1210, 1085, 970, and 715 cm^{-1}; τ($CDCl_3$) 3.45 (1H,m), 4.03 (1H,m), 4.7 (1H,m),4.4(1H,m), 5.83 (2H, overlapping q), 7.70 and 7.71 (3H, overlapping s), and 8.85 (3H, overlapping t)(see Table 2); Found: M^+, 212.0524. $C_{10}H_{12}O_3S$ requires M, 212.0508.

Reaction of Thiophen with Ethyl Diazoacetoacetate at Reflux

To a refluxing solution of $Rh_2(OAc)_4$ (5 mg) in thiophen (10 ml) was added dropwise, over a period of 30 mins, ethyl diazoacetoacetate (1.56g; 10 mmol.). A vigorous reaction occurred with evolution of nitrogen being clearly visible. The reaction was complete almost immediately giving a red solution which was evaporated to dryness to yield a red oil. The mixture was separated by column chromatography (light petroleum-ether, 85:15) to yield the same compounds as above; ethyl 3-oxo-2-(2'-thienyl)butanoate (31) (1.42g; 67%) and 6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (33) (0.28g; 13%) with identical physical and spectral properties to those described above.

Hydrolysis Decarboxylation of Ethyl 3-Oxo-2-(2'-thienyl)butanoate

Ethyl 3-oxo-2-(2'-thienyl)butanoate (0.85g; 4.01 mmol.) was added to an aqueous sodium hydroxide solution (10 ml, 10%) and the mixture refluxed overnight. The solution was cooled, acidified (pH = 1), extracted with chloroform (3 x 10 ml) and the combined chloroform extracts dried ($MgSO_4$), filtered and evaporated to give 2-thienylacetic acid (1) (0.53g; 94%) as a pale brown solid with physical, spectral and chromatographic properties identical to those described above.

Acid-catalysed Isomerization of 6-Acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene.[24]

6-Acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]-hex-3-ene (0.11g; 0.52 mmol.) was added to a solution of hydrogen chloride in ethanol (5 ml, 5%) and the solution stirred at 45°C overnight until tlc ($CHCl_3$) showed that no starting material remained. Excess solvent was removed under vacuum and the remaining pale brown liquid had identical spectroscopic properties to ethyl 3-oxo-2-(2'-thienyl)butanoate (31) above. The product was treated with sodium hydroxide as above to give 2-thienylacetic acid (1) (0.06g; 81% based on starting cyclopropane) with physical, spectral and chromatographic properties identical to those described above.

Reaction of Thiophen with Diazoacetophenone

To a stirred solution of $Rh_2(OAc)_4$ (5 mg) in thiophen (5 ml) at room temperature was added dropwise, under nitrogen, a solution of diazoacetophenone[35] (0.438g; 3 mmol.) in thiophen (5 ml). Nitrogen evolution occurred and the

initially green solution became brown. The reaction was complete after 3h when the ir no longer showed a diazo absorption. The excess thiophen was evaporated and the resultant brown oil subjected to preparative tlc ($CHCl_3$) to yield phenyl 2-thenyl ketone (36) (0.12g; 22.6%) as a yellow oil, ν_{max} (film) 3015, 1680, 1595, 1580, 1440, 1320, and 1280 cm^{-1}; $\tau(CDCl_3)$ 2.15 (2H,m), 2.65 (3H,m), 2.97 (1H,m), 3.22 (2H,m), and 5.73 (2H,s); Found: M^+, 202.0466. $C_{12}H_{10}OS$ requires M, 202.0453.

General Conditions for the Catalysed Addition of n-Butyl Diazoacetate to Thiophen (Table 3)

To a solution of the catalyst (5 mg) in thiophen (10 ml) at the required temperature was added dropwise, over 1.5h, a solution of n-butyl diazoacetate[57] (1.42g; 10 mmol.) in thiophen (5 ml). Evolution of nitrogen was normally observed. When ir indicated that the reaction was complete the excess thiophen was removed under reduced pressure and the resultant brown liquid distilled to yield 6-n-butoxycarbonyl-2-thiabicyclo-[3.1.0]hex-3-ene (38) as a pale yellow oil, b.p. 85-95°C at 0.1 Torr; ν_{max} ($CHCl_3$) 2850, 1710, 1460, 1400, 1365, 1280, 1170, 1070, 1030, 945, and 695 cm^{-1}; $\tau(CDCl_3)$ 3.9 (1H,m), 4.2 (1H,m), 5.95 (2H,m), 6.55 (1H,m), 7.05 (1H,m), 8.50 (4H,m), and 9.05 (4H,m); Found M^+, 198.0704. $C_{10}H_{14}O_2S$ requires M, 198.0714.

Acid-catalysed Rearrangement of 6-n-Butoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene[24]

6-n-butoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (7.92g; 40 mmol.) was added to a solution of hydrogen chloride

in ethanol (100 ml, 5%) and stirred at 40°C for 3 days until tlc ($CHCl_3$) indicated that no starting material remained. The solution was evaporated to dryness to yield an orange oil which was distilled to give ethyl 3-thienylacetate (12) (5.18g; 76.2%) as a pale yellow oil, b.p. 87°C at 0.15 Torr (lit.[56] 107-115°C at 6 Torr); τ($CDCl_3$) 2.95 (1H,m), 3.05 (2H,m), 5.95 (2H,q), 4.30 (2H,s), and 8.85 (3H,t); physical and spectroscopic properties identical to those of the authentic material.

2-Thiabicyclo[3.1.0]hex-3-ene-6-carboxylic Acid

Thiophen (10 ml) and ethyl diazoacetate[57] (1.14g; 10 mmol.) were stirred together in the presence of $[CuP(OEt)_3]^+I^-$ (10 mg) at room temperature for 2h until the diazo band was no longer present in the ir spectrum. Excess thiophen was evaporated and the crude product subjected to preparative tlc ($CHCl_3$). The major product (0.34g; 20%) was 6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (11) isolated as a pale yellow oil, ν_{max} ($CHCl_3$) 2850, 1710, 1460, 1365, and 1280: τ($CDCl_3$) 8.9 (4H,m), 6.87 (1H,m), 6.42 (1H,m), 6.10 (2H,q), 4.8 (1H,m), and 3.1 (1H,m).

The ester was dissolved in aqueous methanol (10 ml, 20%) and sodium (0.1g) was added. When the sodium had dissolved the mixture was refluxed for 2 days, cooled then reduced in volume. The residue was dissolved in water (20 ml) and the aqueous solution extracted with ether. The remaining aqueous phase was acidified and extracted with chloroform (2 x 10 ml) and the combined chloroform extracts dried ($MgSO_4$), filtered and evaporated to yield a brown solid. The product was purified by

column chromatography ($CHCl_3$-methanol, 9:1) to give 2-thiabicyclo[3.1.0]hex-3-ene-6-carboxylic acid (39) (68%) as a colourless crystalline solid, m.p. 110-111.5°C; ν_{max} ($CHCl_3$) 3300-2500br, 3010, 1690, 1555, 1440, 1325, 1287, and 1230-1205 br cm^{-1}; τ($CDCl_3$) 8.9 (1H,t), 6.87 (1H,m), 6.4 (1H,m), 4.1 (1H,m), 3.8 (1H,m), and -2.0 (1H,br s, exchanges with D_2O) (Table 4); Found: C, 50.7; H, 4.4; S, 22.55. $C_6H_6O_2S$ requires C, 50.7; H, 4.25; S, 22.55%.

Reaction of 2,5-Dichlorothiophen with Ethyl Diazoacetoacetate

To a solution of $Rh_2(OAc)_4$ (5 mg) in 2,5-dichlorothiophen (10 ml) was added dropwise ethyl diazoacetoacetate (1.56g; 10 mmol.) and the mixture stirred at room temperature for 20h until the diazo band was no longer present in the ir spectrum. The excess 2,5-dichlorothiophen was removed under reduced pressure and the crude product subjected to preparative tlc (light petroleum-ether, 4:1) to give 1,3-dichloro-6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (43) (1.88g; 67%) as a pale yellow oil, b.p. 94°C at 1 Torr; ν_{max} ($CHCl_3$) 2960, 1710, 1625, 1600, 1370, 1300, 1245 br, 1080, 1060, 940, and 895 cm^{-1}; τ($CDCl_3$) 3.35 (1H,d), 4.15 (1H,d), 5.80 (2H,q), 7.65 (3H,s), and 8.70 (3H,t); Found: M^+, 279.9755. $C_{10}H_{10}Cl_2O_3S$ requires M, 279.9728.

Thermal Rearrangement of 1,3-Dichloro-6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene

Distillation of 1,3-dichloro-6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (43) gave mainly the desired compound however some decomposition occurred and the distillation mixture was separated by preparative tlc (light petroleum-ether, 4:1) to give ethyl 2,4-dichloro-5-hydroxy-6-methylbenzoate (44)

(0.44g) as a white crystalline solid, m.p. (toluene) 92.5-93°C; ν_{max} ($CHCl_3$) 3540, 2990, 1725, 1595, 1440, 1290, 1235br, 1145, 1055, and 865 cm^{-1}, τ($CDCl_3$) 2.85 (1H,s), 4.25 (1H,s, exchanges with D_2O), 5.65 (2H,q), 7.80 (3H,s), and 8.60 (3H,t); Found: M^+, 248.0005. $C_{10}H_{10}Cl_2O_3$ requires 248.0007.

Thermolysis of 1,3-dichloro-6-acetyl-6-ethoxycarbonyl-2-thiabicyclo[3.1.0]hex-3-ene (0.505g; 1.80 mmol.) by refluxing in toluene (10 ml) was complete after 38h. The solvent was removed and the crude brown material subjected to column chromatography (light petroleum-ethyl acetate, 9:1) to give ethyl 2,4-dichloro-5-hydroxy-6-methylbenzoate (44), (0.39g; 86.4%) as a white solid with physical and spectroscopic properties identical to those reported above.

Reaction of 2-Acetylthiophen with Ethyl Diazoacetoacetate

To a solution of $Rh_2(OAc)_4$ (5 mg) in 2-acetylthiophen (10 ml) was added dropwise ethyl diazoacetoacetate (1.56g; 10 mmol.) and the mixture stirred at room temperature for 21h until the diazo band was no longer present in the ir spectrum. The excess 2-acetylthiophen was removed by distillation and the remaining brown oil subjected to preparative tlc (light petroleum-ether, 4:1) to give a compound which appeared to be ethyl 2-acetyl-3-(2'-thienyl)-2,3-epoxybutanoate (45) (0.41g; 18%) as a yellow oil, ν_{max} (film) 2985, 1710, 1675, 1375, 1332, 1270 br, 1165, 1110 br, 960, 850 br, 790, 760, and 710 cm^{-1}; τ($CDCl_3$) 3.0 (2H,m), 3.3 (1H,m), 5.95 (2H,q), 8.0 (3H,s), 8.2 (3H,s), and 8.9 (3H,t); no molecular ion was observed in the mass spectrum.

Thermolysis of Thiophenium bis(methoxycarbonyl)methylide

(i) Solid

Thiophenium bis(methoxycarbonyl)methylide (14), (0.227g; 1.06 mmol.) was placed in a tube and heated in an oil bath at 140-150°C. The solid melted to form a brown oil which was purified by preparative tlc (light petroleum-ethyl acetate, 85:15) to give dimethyl 2-thienylmalonate (10) (0.071g; 33%) as a yellow oil with identical physical and spectroscopic properties to those reported above.

(ii) In Thiophen

Thiophenium bis(methoxycarbonyl)methylide (0.209g, 0.98 mmol.) was added to thiophen (5 ml) and the mixture refluxed overnight until tlc ($CHCl_3$) indicated that reaction was complete. The excess thiophen was evaporated and the crude brown oil purified by preparative tlc ($CHCl_3$) to give dimethyl 2-thienylmalonate (10) (0.121g; 60%) as a yellow oil with identical physical and spectral properties to those described above.

(iii) In 2-Methylthiophen

Thiophenium bis(methoxycarbonyl)methylide (0.50g; 2.34 mmol.) was added to 2-methylthiophen (10 ml) and the mixture refluxed for 3h until no starting ylide remained on tlc ($CHCl_3$-methanol, 96:4). The excess 2-methylthiophen was removed under reduced pressure and the crude material purified by column chromatography ($CHCl_3$) to give dimethyl 2-thienylmalonate (10) (0.41g; 82%) as a pale yellow oil with physical and spectroscopic properties identical to those described above.

Thermolysis of 2-Methylthiophenium bis(methoxycarbonyl)methylide

(i) In 2-Methylthiophen

2-Methylthiophenium bis(methoxycarbonyl)methylide (20) (1.00g; 4.39 mmol.) was added to 2-methylthiophen (10 ml) and the mixture refluxed for 2.5h until no starting ylide remained on tlc ($CHCl_3$-methanol, 96:4). The excess 2-methylthiophen was removed and the crude material Kügelrohr distilled to give dimethyl 2-(5'-methyl-2'-thienyl)malonate (46) (0.94g; 94%) as a pale yellow oil, b.p. 100-115°C at 0.1 Torr; ν_{max} (film) 3000, 2955, 1740, 1435, 1360, 1305, 1235, 1150, 1050, 1020, 930, 910, 805, 750, and 665 cm^{-1}; $\tau(CDCl_3)$ 3.20 (1H,d), 3.45 (1H,m), 5.20 (1H,s), 6.32 (6H,s), and 7.60 (3H,s); Found: C, 52.55; H, 5.31; S, 13.90. $C_{10}H_{12}O_4S$ requires C, 52.61; H, 5.30; S, 14.05%.

(ii) In Thiophen

The above reaction was repeated using the ylide (20) (0.50g; 2.19 mmol.) in thiophen (10 ml) at reflux for 36h until no starting ylide remained on tlc ($CHCl_3$-methanol, 96:4). The excess thiophen was evaporated and the crude product purified by column chromatography ($CHCl_3$) to give dimethyl 2-(5'-methyl-2'-thienyl)malonate (46) (0.44g; 88%) as a pale yellow oil which had physical and spectroscopic properties identical to those reported above.

Thermolysis of Thiophenium bis(methoxycarbonyl)methylide in the Presence of Olefins

In general a solution of the ylide (14) (0.214g; 1 mmol.) in acetonitrile (10 ml) was added to a solution of the olefinic substrate (1 mmol.) in acetonitrile (5 ml) and the

mixture stirred at 60°C. The reaction was followed by tlc ($CHCl_3$) until the ylide was no longer present then the solvent was removed to leave the crude product which was purified by preparative tlc ($CHCl_3$) to give, in all cases, dimethyl 2-thienylmalonate (10). Olefins used in this way were ethyl cinnamate, dimethyl acetylenedicarboxylate, vinyl acetate and cyclohexene.

Thermolysis of 2,5-Dichlorothiophenium bis(methoxycarbonyl)-methylide

2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide (19) (0.505g; 1.78 mmol.) was added to 2,5-dichlorothiophen (10 ml) and the mixture refluxed for 40 min. until tlc ($CHCl_3$-methanol, 96:4) indicated that no ylide remained. The solvent was removed under reduced pressure to leave a brown oil which was subjected to preparative tlc (light petroleum-ethyl acetate, 9:1) to give three main products. One of these products was shown to be a mixture and further preparative tlc (light petroleum-ether, 9:1, multiple elution) allowed separation of four different compounds. Although at least six products were detected two of these appeared to be mixtures and characterization was possible for only four of these compounds.

Dimethyl 2-(2',5'-dichloro-3'-thienyl)malonate (52), pale yellow oil, ν_{max} ($CHCl_3$) 3020, 2960, 1743, 1530, 1455, 1440, 1340, 1310, 1265, 1155, 1100, 1025, 940, 860, and 820 cm^{-1}; τ($CDCl_3$) 3.25 (1H,s), 4.90 (1H,s), and 6.20 (6H,s); Found: M^+, 281.9527; M+2, 284; M+4, 286. $C_9H_8Cl_2O_4S$ requires M^+, 281.9521., Dimethyl 2-(5'-chloro-2'-thienyl)chloromalonate (54), pale yellow oil, ν_{max} ($CHCl_3$) 3020, 2960, 2930, 1750, 1440,

1265, 1180, 1105, 1015, 940, and 805 cm^{-1}; $\tau(CDCl_3)$ 3.05 and 3.30 (2H total, two halves of ABq), and 6.20 (6H,s); Found: M^+, 281.9524; M+2, 284; M+4, 286. $C_9H_8Cl_2O_4S$ requires M, 281.9521., Dimethyl 2-(5'-chloro-2'-thienyl)hydroxymalonate (55), pale yellow oil, ν_{max} ($CHCl_3$) 2960, 2930, 1745, 1440, 1265, 1135, 1105, 1010, and 810-720 br cm^{-1}; $\tau(CDCl_3)$ 2.95 and 3.20 (2H total, two halves of ABq), 5.55 (1H,s), and 6.15 (6H,s); Found: M^+, 264, M+2, 266. $C_9H_9ClO_5S$ requires M, 264., Methyl 5-chloro-2-methoxythieno[3,2-b]furan-3-carboxylate (56), pale brown crystalline solid, m.p. (methylcyclohexane) 131-131.5°C; ν_{max} ($CHCl_3$) 3010, 2960, 1720, 1595, 1450, 1410, 1320, 1210, 1095, 1015, 975, 935, 855, 790-770 br, and 670 cm^{-1}; $\tau(CDCl_3)$ 3.15 (1H,s), 5.80 (3H,s), and 6.15 (3H,s); Found: C, 44.01; H, 2.93; S, 13.05; Cl, 14.33. $C_9H_7ClO_4S$ requires C, 43.82; H, 2.86; S, 13.00; Cl, 14.37%; X-ray crystal structure determination is reported in the main text.

Reaction of Thiophen with n-Butyl Triflate

n-Butyl triflate was prepared by the method of Vedejs[40] and showed the anticipated physical and spectral characteristics; ν_{max} (film) 2970, 2880, 1750, 1415, 1375, 1295, 1215, 1150, 1035, 920, 815, 765, 740, and 620 cm^{-1}; $\tau(CDCl_3)$ 5.25 (2H,s), 5.95(2H,m), 8.60 (4H,m), and 9.20 (3H,m). The triflate (5g) was added to dry thiophen (100 ml) and the solution stirred overnight. No change was apparent on tlc ($CHCl_3$) and the mixture was refluxed for 2.5h until an unpleasant gas was produced. The cooled mixture was dark and viscous and trituration with methanol followed by filtration produced a polymeric solid (107g) which obviously contained most of the solvent (thiophen) in its composition.

General Procedure for Cyclopropanation of Olefins using 2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide

2,5-Dichlorothiophenium bis(methoxycarbonyl)-methylide (1.00g; 3.53 mmol.) was added to a solution of $Cu(acac)_2$ [58] (10 mg) in the olefin (10 ml) and the mixture stirred at the appropriate temperature (Table 5). The reactions were followed by tlc ($CHCl_3$-methanol, 97:3) and, once the ylide had completely reacted, the excess solvent was removed and the crude product purified by column chromatography ($CHCl_3$). Thus prepared were:

7,7-Bis(methoxycarbonyl)bicyclo[4.1.0]heptane (64), (66%) as a white crystalline solid, m.p. 86-87.5°C (lit.[41] 88.5-89°C); $\tau(CDCl_3)$ 6.24 (3H,s), 6.34 (3H,s), 8.15 (6H,m), and 8.85 (4H,m).

9,9-Bis(methoxycarbonyl)bicyclo[6.1.0]nonane (65), (86)%) as white needle crystals, m.p. (methanol) 69-70°C (lit.[41] 68-69°C); $\tau(CDCl_3)$ 6.30 (6H,s), and 2.5 (14H, br.m).

1,1-Bis(methoxycarbonyl)-2-(hex-5-enyl)cyclopropane (66), (83%) as a pale yellow oil, ν_{max} ($CHCl_3$) 3020, 2955, 2935, 2860, 1725, 1640, 1440, 1335, 1290, 1265, 1200-1230 br, 1040, 995, and 915 cm^{-1}; $\tau(CDCl_3)$ 4.3 (1H,m), 5.0 (2H,m), 6.29 (3H,s), 6.30 (3H,s), and 7.7-8.7 (11H,m); Found: M^+, 240.1336. $C_{13}H_{20}O_4$ requires M, 240.1362.

1,1-Bis(methoxycarbonyl)-2-(7-methoxycarbonylheptyl)-3-n-octylcyclopropane (67), (60%) as a colourless, viscous oil, ν_{max} ($CHCl_3$) 3020, 2955, 2930, 2860, 1725, 1460, 1435, 1325, 1260, 1200-1230 br, 1145, 1100, and 1020 cm^{-1}; $\tau(CDCl_3)$ 6.38 (3H,s), 6.39 (3H,s), 6.42 (3H,s), and 7.7-9.3 (33H,m); Found: M^+, 426.2998. $C_{24}H_{42}O_6$ requires M, 426.2982.

1,1-Bis(methoxycarbonyl)-2-acetoxycyclopropane (68), (82%) as a colourless oil, ν_{max} (film) 3010, 2960, 1725-1765 br, 1440, 1365, 1330, 1290, 1235, 1210, 1130, 1085, 1040, 930, 825, 790, and 710 cm^{-1}; $\tau(CDCl_3)$ 5.30 (1H,m), 6.25 (6H,s), 8.00 (3H,s), and 8.20 (2H,m); Found: M^+, 216.0648. $C_9H_{12}O_6$ requires M, 216.0635.

Reaction of Thiophenium bis(methoxycarbonyl)methylide with Acetic Acid

Thiophenium bis(methoxycarbonyl)methylide (14) (0.199g; 0.93 mmol.) was added to glacial acetic acid (5 ml) and the solution refluxed for 3h until tlc ($CHCl_3$) indicated that the ylide was no longer present. The mixture was cooled and evaporated to dryness to yield dimethyl acetoxymalonate (71), (0.17g; 96%) as a pale yellow oil, b.p. 100-115°C at 0.25 Torr; ν_{max} (film) 2960, 1740, 1440, 1210 br, 1100, 1030, 885, and 755 cm^{-1}; $\tau(CDCl_3)$ 4.55 (1H,s), 6.25 (6H,s), and 7.85 (3H,s); Found: M^+, 190.0459. $C_7H_{10}O_6$ requires M, 190.0478.

Reaction of 2,5-Dichlorothiophenium bis(methoxycarbonyl)-methylide with Anisole

A mixture of 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (19) (1.00g; 3.53 mmol.) and p-toluenesulfonic acid (10 mg) in anisole (10 ml) was refluxed for 2.5h until tlc ($CHCl_3$-methanol, 97:3) indicated that no ylide remained. The excess anisole was removed under vacuum and the remaining brown residue purified by column chromatography (light petroleum-ethyl acetate, 9:1) to give methyl 5-chloro-2-methoxythieno[3,2-b]furan-3-carboxylate (56) (0.31g; 36%) as a pale brown solid with physical and spectral

properties identical to those reported above.

The above reaction was repeated with borontrifluoride etherate (3 drops) in place of the acid catalyst. The reaction was complete after 1h and column chromatography allowed separation of two major products; methyl 5-chloro-2-methoxy-thieno[3,2-b]furan-3-carboxylate (56) (21%) and dimethyl 4-methoxyphenylmalonate (76) (0.08g; 10%) as a pale yellow viscous oil, ν_{max} ($CHCl_3$) 3010, 2910, 2840, 1735, 1610, 1585, 1510, 1460, 1435, 1305, 1210-1250 br, 1380, 1350, 1030, and 830 cm^{-1}; τ($CDCl_3$) 3.25 (4H, ABq), 5.68 (1H,s), and 6.70 (9H, overlapping s); Found: M^+, 238.0856. $C_{12}H_{14}O_5$ requires M, 238.0842.

Reaction of 2,5-Dichlorothiophenium bis(methoxycarbonyl)-methylide with Arenes. (Table 6).

Method A

A mixture of 2,5-dichlorothiophenium bis(methoxycarbonyl)-methylide (1.00g; 3.53 mmol.) and $Cu(acac)_2$ (10 mg) in the substrate (10 ml) was refluxed until tlc ($CHCl_3$-methanol, 97:3) indicated that reaction was complete. The excess substrate was removed by distillation and the product purified by column chromatography ($CHCl_3$).

Method B

A mixture of 2,5-dichlorothiophenium bis(methoxycarbonyl)-methylide (1.00g; 3.53 mmol.), $Cu(acac)_2$ (10 mg) and the substrate (3.53 mmol.) in toluene (10 ml) was stirred at 110°C until tlc ($CHCl_3$-methanol, 97:3) indicated that the reaction was complete. Toluene was removed under reduced pressure and the crude product purified by column chromatography ($CHCl_3$).

Thus prepared were:

Dimethyl 4-methoxyphenylmalonate (76), (Method A, 48%) as a pale yellow viscous oil with physical and spectral properties identical to those reported above.

Dimethyl 2-thienylmalonate (10), (Method A, 98%) as a pale yellow oil with physical and spectral characteristics identical to those reported above.

Dimethyl pyrrole-2-malonate (77), (Method A, 73%). (Thanks are due to J. Cuffe who carried out this experiment). Pale yellow oil, b.p. 105-115°C at 0.5 Torr; ν_{max} (film) 3400, 2960, 1735, 1440, 1245, 1150, 1095, 1030, 960, 800, 760, and 730 cm^{-1}; $\tau(CDCl_3)$ 0.85 (1H, br s, NH), 3.40 (1H,m), 3.95 (2H,m), 5.25 (1H,s), and 6.40 (6H,s); Found: C, 54.61; H, 5.67; N, 6.94. $C_9H_{11}NO_4$ requires C, 54.82; H, 5.62; N, 7.10%.

Methyl 2-methoxycarbonyl-N-phenylglycinate (78), (Method B, 93%) as a pale yellow oil, ν_{max} ($CHCl_3$) 3415, 3010, 2960, 1764, 1744, 1606, 1505, 1435, 1300, 1205-1230 br, 1160, 1080, and 1016 cm^{-1}; $\tau(CDCl_3)$ 3.15 (5H,m), 5.25 (2H, br s, NH and methine CH), and 6.30 (6H,s); Found: M^+, 223.0855. $C_{11}H_{13}NO_4$ requires M, 223.0845.

Dimethyl indole-3-malonate (79), (Method B, 84%) as a white crystalline solid, m.p. (toluene) 129-130°C; ν_{max} ($CHCl_3$) 3480, 3010, 2955, 1755, 1738, 1455, 1435, 1365, 1310, 1280, 1230, 1195, 1150, 1100, 1025, 1015, 930, and 810 cm^{-1}; $\tau(CDCl_3)$ 1.70 (1H, br m, slowly exchanges with D_2O, NH), 2.40 (1H,m), 2.80 (4H,m), 5.05 (1H,s), and 6.25 (6H,s); Found: C, 63.11; H, 5.32; N, 5.59. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.67%.

Dimethyl phenoxymalonate (80), (Method B, 40%) as a pale yellow crystalline solid, m.p. 70-72°C; ν_{max} ($CHCl_3$) 3020, 2960, 1760 br, 1600, 1593, 1495, 1440, 1290, 1205-1230 br, 1175, 1095, 1025, 930, 815, 720-790 br, 665, and 625 cm^{-1}; τ($CDCl_3$) 3.10 (5H,m), 4.85 (1H,s), and 6.30 (6H,s); Found: C, 58.66; H, 5.51. $C_{11}H_{12}O_5$ requires C, 58.92; H, 5.40%.

Dimethyl 2-(3',4'-methylenedioxyphenyl)malonate (81), (Method A, 20%) as a yellow oil, ν_{max} ($CHCl_3$) 3015, 2950, 1735, 1505, 1490, 1445, 1435, 1210-1250 br, 1155, 1045, 940, and 910 cm^{-1}; τ($CDCl_3$) 3.25 (1H,s), 3.42 (2H,s), 4.25 (2H,s), 5.60 (1H,s), and 6.41 (6H,s); Found: M^+, 252.0660. $C_{12}H_{12}O_6$ requires M, 252.0635.

Dimethyl acetoxymalonate (71), (Method A, 98.5%) as a pale yellow oil with physical and spectroscopic properties identical to those reported above.

Indole-3-malonic Acid

Dimethyl indole-3-malonate (79), (0.45g; 1.82 mmol.) was added to an aqueous sodium hydroxide solution (10 ml, 10%) and the mixture refluxed for 24h. The homogeneous solution was cooled, acidified (pH = 2), extracted with ether, and the combined ether extracts dried ($MgSO_4$), filtered and evaporated to give indole-3-malonic acid (83) (0.30g; 76%) as a pale brown solid, m.p. 142-144°C; ν_{max} (methanol) 3500-2500 br, and 1720 cm^{-1}; τ(dmso-d_6) 2.4-3.2 (m), 5.25 (s), and -1.0 (s, OH); τ(acetone) 0.4 (br s, NH), 2.7-3.6 (m), and 5.5 (s); Found: C, 60.13; H, 4.27; N, 6.46. $C_{11}H_9NO_4$ requires C, 60.27; H, 4.14; N, 6.39%.

Methyl Indole-3-acetate

Dimethyl indole-3-malonate (79) (0.364g; 1.47 mmol.) was treated with sodium chloride in wet dimethyl sulfoxide according to Markgraf[48]. Column chromatography (light petroleum-ethyl acetate, 70:30) of the crude product gave methyl indole-3-acetate (84) (0.255g; 92%) as a pale brown oil, ν_{max} (film) 3400, 3050, 3000, 2950, 2840, 1720, 1620, 1450, 1430, 1350, 1340, 1300, 1270, 1250, 1200, 1160, 1130, 1090, 1060, 1010, 930, 850, 780, 740, 710, and 625 cm^{-1}; $\tau(CDCl_3)$ 1.85 (1H, br s, NH), 2.45 (1H,m), 2.90 (3H,m), 3.25 (1H,m), 6.25 (2H,s), and 6.35 (3H,s); physical and spectroscopic properties identical to those reported in the literature[59].

Ethyl N-Phenylglycinate

Methyl 2-methoxycarbonyl-N-phenyl glycinate (78) was added to a solution of hydrogen chloride in ethanol (24 ml, saturated) and refluxed for 24h. The mixture was cooled and neutralized (pH = 8) with aqueous ammonia solution and the solvent was removed. The crude brown residue was dissolved in water and extracted with chloroform (X3) and the combined chloroform extracts dried ($MgSO_4$), filtered and evaporated to give a brown oil which showed ethyl ester signals in the nmr spectrum.

The above crude product was treated with sodium chloride in wet dimethyl sulfoxide according to Markgraf[48] and the resultant brown oil subjected to column chromatography ($CHCl_3$) to give ethyl N-phenylglycinate (89) as white plates, m.p. (methylcyclohexane) 55-57°C (lit.[60] 58°C); ν_{max} ($CHCl_3$) 3415,

3010, 1740, 1605, 1508, 1450, 1375, 1350, 1318, 1230, 1195, 1145, 1023, and 927 cm^{-1}; $\tau(CDCl_3)$ 2.9 (2H,m), 3.45 (3H,m), 5.85 (2H,q), 6.18 (2H,s), and 8.72 (3H,t).

Cyclooctene Epoxide

To a stirred solution of cyclooctene (4.40g; 0.04 mol) in dichloromethane (dried P_2O_5, 40 ml) was added excess m-chloroperbenzoic acid (0.045 mol) in dichloromethane (dried P_2O_5, 100 ml) over a period of 30 min, using an ice-bath to keep the temperature below 30°C. The mixture was stirred and solid m-chlorobenzoic acid precipitated out. After 2 days the solid was filtered and the filtrate extracted (X2) with aqueous sodium sulfite (10%), with saturated sodium bicarbonate solution (X4), washed with water (X2) and finally with saturated sodium chloride solution. The remaining organic solution was dried ($MgSO_4$), filtered and evaporated to give an oil which was distilled under vacuum to give cyclooctene epoxide (91) (3.1g; 61%) as a colourless solid, m.p. 58-58.5°C (lit.[61] 53-56°C); b.p. 64°C at aspirator pressure (lit.[61] 55°C at 5 Torr); $\tau(CDCl_3)$ 7.2 (2H,m), and 8.2-9.1 (12H, br m).

Methyl Oleate Epoxide

cis-Methyl oleate (93) (5.92g; 0.02 mol) was treated as above to give a colourless liquid which was distilled under vacuum to give cis-methyl oleate epoxide (92) as a colourless oil, b.p. 170-174°C at 0.8 Torr; ν_{max} ($CHCl_3$) 2930, 2860, 1730, 1465, 1437, 1360, 1195-1230 br, 1170, 1110, and 1012 cm^{-1}; $\tau(CDCl_3)$ 6.40 (3H,s), 7.20 (2H, br m), and 7.60-9.30 (31H,m); Found: M^+, 312.2688. $C_{19}H_{36}O_3$ requires M, 312.2665.

trans-Stilbene Epoxide

trans-Stilbene (3.00g; 0.017 mol) was treated as above to give trans-stilbene epoxide (94), (3.01g; 90%) as white needles, m.p. (ethanol) 63-67°C (lit.[56] 69-70°C); τ($CDCl_3$) 3.00 (10H, s), and 6.40 (2H, s); physical and spectroscopic properties comparable with reported data[59].

Deoxygenation of Epoxides with 2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide

In general a mixture of 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (1 equivalent), $Cu(acac)_2$ (10 mg) and the epoxide (1 equivalent) in toluene (10 ml) was stirred at 95-105° until tlc ($CHCl_3$-methanol, 97:3) showed that no starting ylide remained.

Deoxygenation of Cyclooctene Epoxide

The reaction mixture contained an internal standard (C_{11}, estimated[63] molar response factor 0.751) and the yield of cyclooctene produced (82%) was estimated by gas chromatography, using a Perkin-Elmer, F30 Gas Chromatograph, from peak areas obtained from a computing integrator. The column was Scot Degs. (50 ft), carrier gas pressure 5 kNm^{-2}, injection temperature 100°C, detection temperature 100°C, oven temperature initially 50°C raised to 90°C after 3.2 min; retention times were; cyclooctene, 2.8 min; toluene, 3.1 min; internal standard, 5.6 min; 2,5-dichlorothiophen, 6.5 min; all checked by co-injection.

Deoxygenation of Methyl Oleate Epoxide

The solvent was evaporated to leave a brown oil which was subjected to column chromatography ($CHCl_3$) to give cis-methyl oleate (93) (0.804g; 77%) as a colourless oil showing physical and spectroscopic properties identical to those of the authentic

material.

Deoxygenation of trans-Stilbene Epoxide

In a reaction using one equivalent of the ylide the solvent was evaporated to leave a brown oil. Column chromatography (light petroleum-ethyl acetate, 98:2) gave two major products; trans-stilbene (0.05g; 8.2%) as a white solid, m.p. 118-121°C (lit.[56] 124°C) and trans-stilbene epoxide (94), (0.63g; 91%), both compounds showing physical and spectroscopic properties identical to those of the authentic material.

In a reaction using two equivalents of the ylide the yield of trans-stilbene was 10% with trans-stilbene epoxide recovered in 88% yield.

Deoxygenation of Humulene Epoxides[54]

Treatment of humulene-1,2-epoxide (95) with 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (1 equivalent) as above, followed by column chromatography using silver nitrate-impregnated silica (60-200 mesh) (light petroleum-ethyl acetate) gave humulene (96) (20%) as a colourless oil which exhibited physical and spectroscopic properties identical to those of the authentic material.

Treatment of humulene-1,2-8,9-bisepoxide (97) as above followed by column chromatography as above gave humulene-1,2-epoxide (95) (2.5%) and humulene-8,9-epoxide (98) (2.5%) as colourless oils which showed physical and spectroscopic properties identical to those reported[62].

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