SYNTHETIC STUDIES ON α-OXOKETENE O,S- AND S,S-ACETALS

By

LAXMINARAYAN BHAT

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

A THESIS
SUBMITTED IN FULFILMENT OF THE REQUIREMENT
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

TO

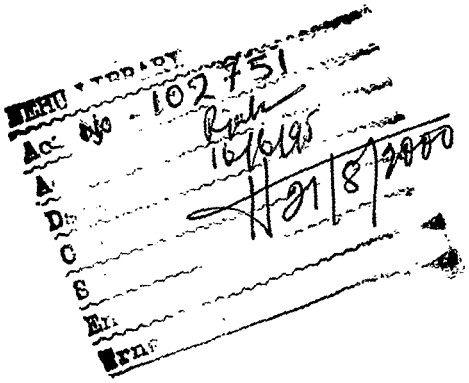
NORTH-EASTERN HILL UNIVERSITY

SHILLONG - 793 008

INDIA

1993

Chem



Phone :
Grams : NEHU

North - Eastern Hill University

Bijni Complex
Bhagyakul, Shillong - 793003 (Meghalaya)

Department of.....,.....

PROFESSOR (MRS.) H. ILA
Department of Chemistry

This is to certify that the work described in this thesis has been carried out by Mr. Laxminarayn Bhat, under my supervision. He has satisfactorily completed the Pre-Ph.D. courses prescribed and the minimum period of two years of investigational work for the award of Ph.D. degree in Chemistry.

The work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other University.

H. Ila

H. ILA
Supervisor

Shillong,

26th August 1993

Phone :
Grams : NEHU

North - Eastern Hill University

Bijni Complex
Bhagyakul, Shillong - 793003 (Meghalaya)

Department of.....

PROFESSOR S.N. BHAT
Head
Department of Chemistry

This is to certify that Mr. Laxminarayan Bhat, a Ph.D. student of the Department of Chemistry has satisfactorily completed the following courses as a part of his Ph.D. programme.

Title

1. Highlights of Organic Chemistry
2. Bioinorganic Chemistry
3. Medicinal Chemistry
4. German Language

Shillong,
26th August 1993.

(S.N. BHAT)

HEAD
Department of Chemistry
North Eastern Hill University
Shillong-793 003

ACKNOWLEDGEMENTS

The research work described in this thesis was carried out under the supervision of Prof.(Mrs.) H. Ila in the Department of Chemistry, North-Eastern Hill University, Shillong. I would like to express my deep sense of gratitude for her excellent guidance and constant encouragement throughout the course of this investigation. I am deeply indebted to Prof. H. Junjappa for his invaluable suggestions and inspiration.

I thank the Directors and Technical staff of RSIC, North-Eastern Hill University and Central Drug Research Institute, Lucknow for providing excellent analytical and spectral facilities. Financial assistance from M/s. Organon Research Centre, Calcutta, India and Council of Scientific and Industrial Research, New Delhi is also thankfully acknowledged.

I also wish to express my gratitude to my colleagues and friends with whom I have been associated during all these years. I am also indebted to all the teachers, library staff and non-teaching staff of the Department of Chemistry for their co-operation and help.

My sincere thanks to Mr. Vijayan, Mrs. Rajamma Johns and Mr. H.R. Choudhury for the help extended by them in processing this thesis. I am also thankful to Mr. M.L. Hirani, Sanjay TV & Electronics, Laitumkhrah for xeroxing this thesis with great care.

Finally I would like to acknowledge the debt I owe to my family members for their support, patience and encouragement.

SHILLONG,

August 1993

LAXMINARAYAN BHAT

C O T E N T S

P R E F A C E

Extensive research has been carried out in this laboratory on the synthetic applications of polarized ketene dithioacetals, which are conveniently prepared from a variety of active methylene compounds in one pot reaction. The work described in this thesis has been carried out as a part of this on going research programme and highlights new transformations of α-oxoketene O,S- and S,S-acetals.

The thesis consists of five chapters. The first chapter gives a general introduction to α-oxoketene O,S- and S,S-acetals and some of the recent transformations reported from this laboratory. In the second chapter the investigation of lead tetraacetate (LTA) oxidation on α-oxoketene dithioacetals has been presented. The α-oxoketene dithioacetals have been shown to undergo LTA oxidation to give α-acetoxy compounds retaining the divalent oxidation state of sulfur. The reaction remains chemoelective when the cinnamoylketene dithioacetals were oxidised under similar reaction conditions and yield the corresponding α-acetoxy cyclopentenone derivatives through an interesting oxidative Nazarov cyclization involving intermediate α-acetoxy dithioacetals accompanied with 1,2-acyl group migration.

In the third chapter, investigation on the reaction of Simmons-Smith reagent to various doubly activated α-carboalkoxyketene dithioacetals and acylketene O,S-acetals is described. The reaction of doubly activated α-carboalkoxyketene dithioacetals with Simmons-Smith reagent

give the corresponding dethiomethylated products. The acylketene O,S-acetals under Simmons-Smith reaction conditions afford the 2-alkoxy/aryloxy thiophenes. This method provides a simple direct route for the synthesis of 2-alkoxy/aryloxy thiophenes in good yields.

Rearrangement studies on acylketene O-propargyl S-methylacetals have been presented in chapter IV. The acylketene O-propargyl S-methylacetals obtained by the displacement reaction of β-oxosulphonium salts by propargyl alcohol are shown to undergo facile rearrangement under neutral and basic conditions to afford diene esters and substituted furans respectively. The probable mechanism for the formation of various products involving initial Claisen rearrangement of acylketene O-propargyl S-methyl acetals has been discussed in detail.

In the last chapter, studies on the nucleophilic addition on α-oxoketene O,S-acetals have been described. A few selected O,S-acetals have been reacted with various metal hydrides to study the mode of reductions of these reducing agents. Subsequent to the metal hydride reduction studies, a preliminary investigation on the addition of carbon nucleophile to the O,S-acetal has also been undertaken. The probable mechanism for the formation of various products is discussed.

Each chapter is divided into Introduction, Results and Discussion, Experimental and Conclusion. Relevant references have been included at the end of each chapter.

CHAPTER I

α-OXOKETENE O,S- AND S,S-ACETALS : GENERAL INTRODUCTION.

The α-oxoketene dithioacetals and the corresponding S,N- N,N- and O,S-acetals are among the simplest synthetic intermediates in organic synthesis. This chapter is devoted to a brief review and discussion on the chemistry of the α-oxoketene S,S- and O,S-acetals in the context of their practical and potential application to organic synthesis. For convenience this chapter is divided into three sections. In the first section a brief survey of α-oxoketene S,S-acetals is described and the second section describes a survey of polarized ketene O,S-acetals. The present work has been described in the third section.

A. *α-Oxoketene S,S-Acetals*

α-Oxoketene dithioacetals have been recognized as useful building blocks in many synthetic operations[1]. These class of compounds can be conveniently prepared[2-10] by reacting any active methylene compound with two equivalents of base and one equivalent of carbon disulphide followed by alkylation. Various bases and reaction conditions have been employed depending on the nature of the active methylene compounds.

The first synthesis of α-oxoketene dithioacetals was reported by Kelber and co-worker[11-13] in 1910. Much of the earlier work on oxoketene dithioacetals was confined to their preparation and properties, while little attention was paid for their synthetic utility. Later Thuillier and Vialle prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with carbon disulphide in the presence of sodium amylate followed by alkylation[2-5]. Subsequently these reaction conditions have been greatly improved using different bases and reaction conditions[6-10]. A large number of α-oxoketene dithioacetals have now been reported and their chemistry has been reviewed by Dieter[1a] in 1986 and by Junjappa and coworkers[1b] in 1990.

The α-oxoketene dithioacetals generally exhibit well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stirred indefinitely without

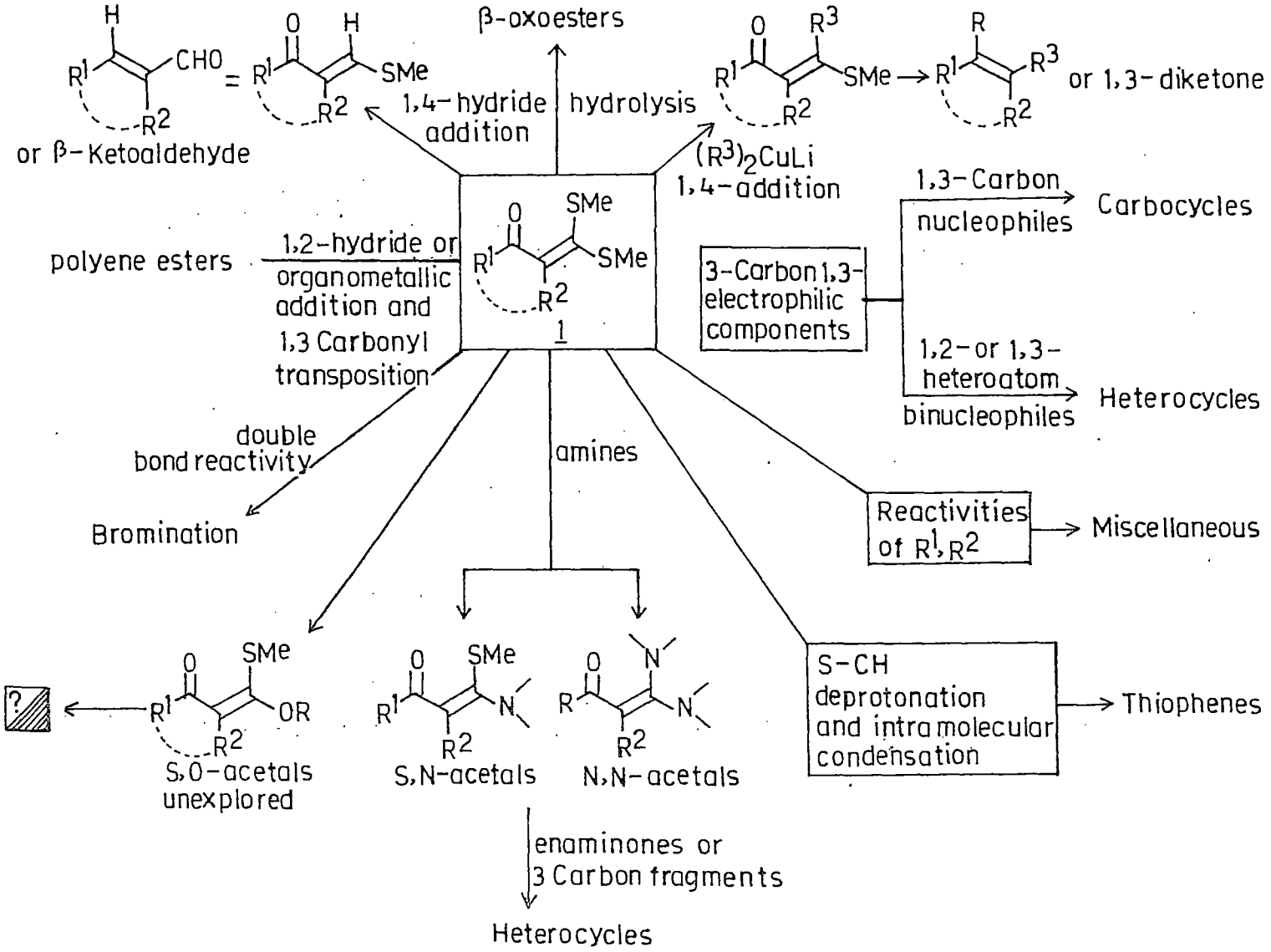
decomposition. However, the corresponding α-oxoketene O,O-acetals are moisture sensitive and undergo hydrolysis under mild conditions. The oxoketene dithioacetal is essentially a masked β-ketoester in which the ester functionality is protected as a ketene dithioacetal. Alternatively it may be viewed as an α,β-unsaturated ketone containing a highly functionalized β-carbon. They are versatile three carbon fragments with 1,3-electrophilic centres of differing electrophilicity. These intermediates possess considerable potential in the stereo- and regio selective construction of new bonds either by a 1,2-nucleophilic addition to carbonyl group or by 1,4-conjugate addition to the β-carbon of the enone system. Also the oxoketene dithioacetals are primary precursors for the corresponding N,N- , N,S- and O,S-acetals. The preparation of O,S-acetals is accomplished through the displacement by oxygen nucleophiles of the sulphonium salts[14] of the corresponding S,S-acetals. The N,S-acetals can be prepared by the displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol[15,16]. Alternatively they can be prepared directly from active methylene ketones by reacting their enolate anions with alkyl and aryl isothiocyanates followed by alkylation[17].

The α-oxoketene N,N-acetals can be prepared in high yields by displacing both the thiomethyl groups by amines in refluxing acetic acid[16,18]. The oxoketene S,S-, N,S- and N,N-acetals have been extensively used in this laboratory for the synthesis of both heterocyclic and carbocyclic compounds[1].

In scheme 1, various reactivity profiles of α-oxoketene S,S-acetals of the general formula 1 have been outlined. Hydrides and organometallic reagents give 1,2-addition products typical of carbonyl function reactivity[19]. These additions can be directed in a 1,4-manner by suitably manipulating the reagent and reaction conditions[19,20]. Further transformations after the initial 1,2- or 1,4-additions are also reported[19]. The enolate ion formed by the deprotonation (when R'=alkyl) can undergo condensation with aldehydes to give α-enoylketene dithioacetals[2,22]. An allylic anion formation has been reported when R^2 is a methyl group, leading to rearranged products[23].

Also deprotonation on the thiomethyl group followed by intramolecular aldol type condensation to thiophene is also reported[24,25]. The reactivity of the mercaptal double bond is also exploited with electrophiles. The dithioacetals 1 (R^2=H) undergo bromination at α-position with N-bromosuccinimide[26]. Thus it is apparent that the oxoketene dithioacetals of general formula 1 constitute an important class of synthons with reactive electrophilic and nucleophilic centres distributed in various centres of its skeleton permitting reactions of great synthetic importance. Some of the selected transformations reported from this laboratory are briefly described in the following section.

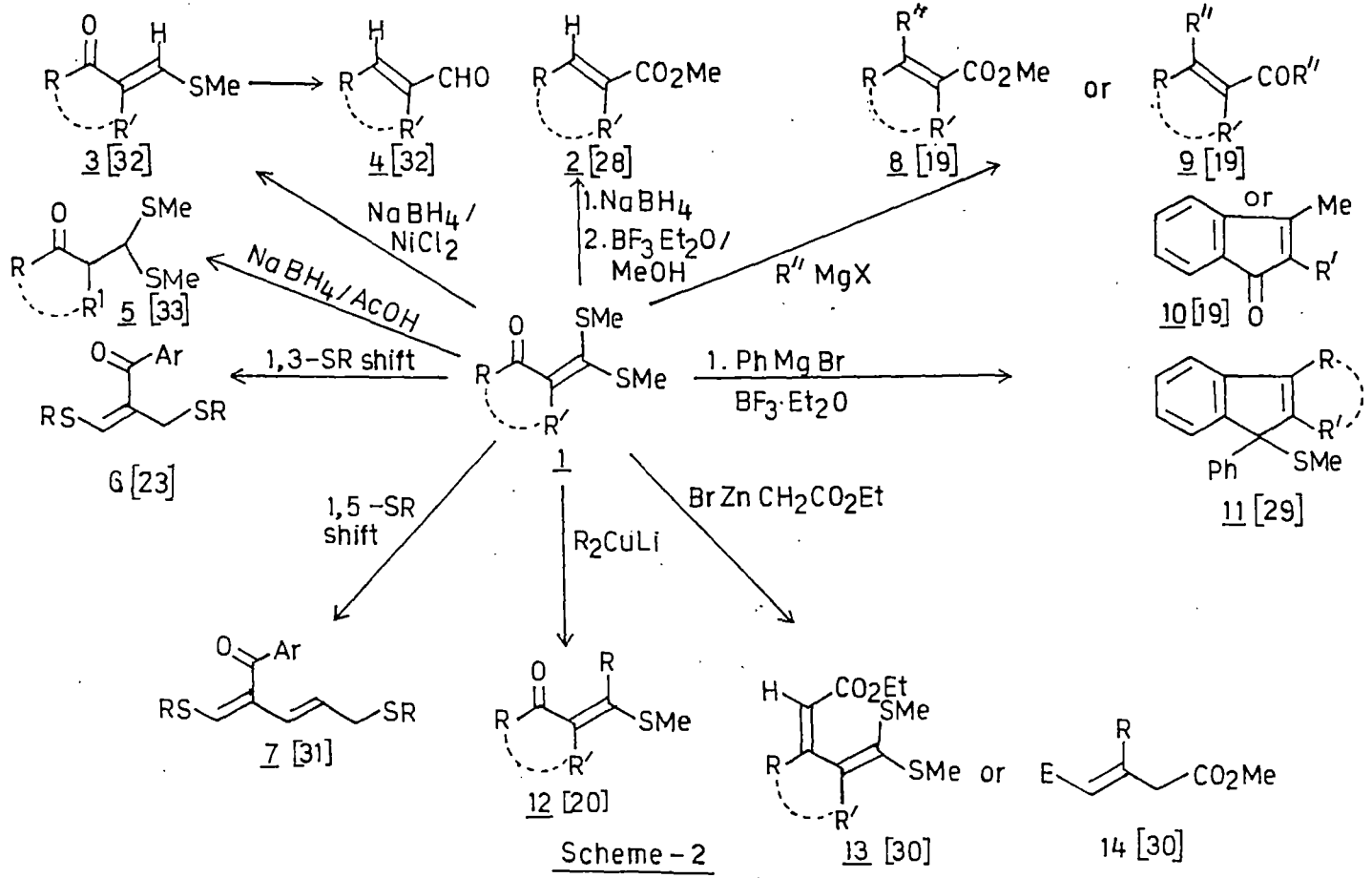
The carbonyl group of α-oxoketene dithioacetals has been reported to undergo sodium borohydride reduction in 1,2-


β-oxoesters
or β-Ketoaldehyde
1,4-hydride addition
hydrolysis
or 1,3-diketone
(R3)2CuLi 1,4-addition
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2-or 1,3-heteroatom binucleophiles
Heterocycles
double bond reactivity
Bromination
amines
Reactivities of R1, R2
Miscellaneous
S-CH deprotonation and intramolecular condensation
Thiophenes
S,O-acetals unexplored
S,N-acetals
N,N-acetals
enaminones or 3 Carbon fragments
Heterocycles

Scheme-1

fashion to give the corresponding carbinol acetals[27,28]. These carbinol acetals were shown to undergo smooth methanolysis in the presence of borontrifluoride-etherate to afford α,β-unsaturated methyl esters 2[28] in high yields. The overall transformation is considered as homologation of active methylene ketones involving a 1,3-carbonyl transposition methodology.

The Grignard and organolithium reagents undergo either regioselective 1,2-addition to afford the α-hydroxyketene dithioacetals or sequential 1,4- and 1,2-additions to afford the β-hydroxyvinylsulfides[19-21]. The borontrifluoride-etherate catalysed solvolysis or the hydrolysis of these carbinols yield either β-substituted α,β-unsaturated esters 8 or the corresponding ketones 9[19] (scheme 2) in good yields. However, when the R' is alkyl or aryl group the open chain cinnamates were not formed, instead the corresponding 2,3-disubstituted indenones 10 were formed[19]. The reaction of phenyl magnesium bromide followed by $BF_3.Et_2O$ treatment is reported to give the 1-methylthio-1-phenylindenes 11[29]. The Reformatsky reaction on dithioacetals 1 is reported to give the diene esters 13 and the α,β-unsaturated esters 14[30]. Dieter and co-workers have reported the chemo- and stereoselective addition of organocuprates to oxoketene dithioacetals 1[20,21]. Thus organocuprates are shown to undergo conjugate addition to give β-alkylthio-β-substitued α,β-unsaturated ketones 12. In another study from this laboratory, base catalysed rearrangement of α-oxoketene dithioacetals derived from propiophenone are reported[23]. The

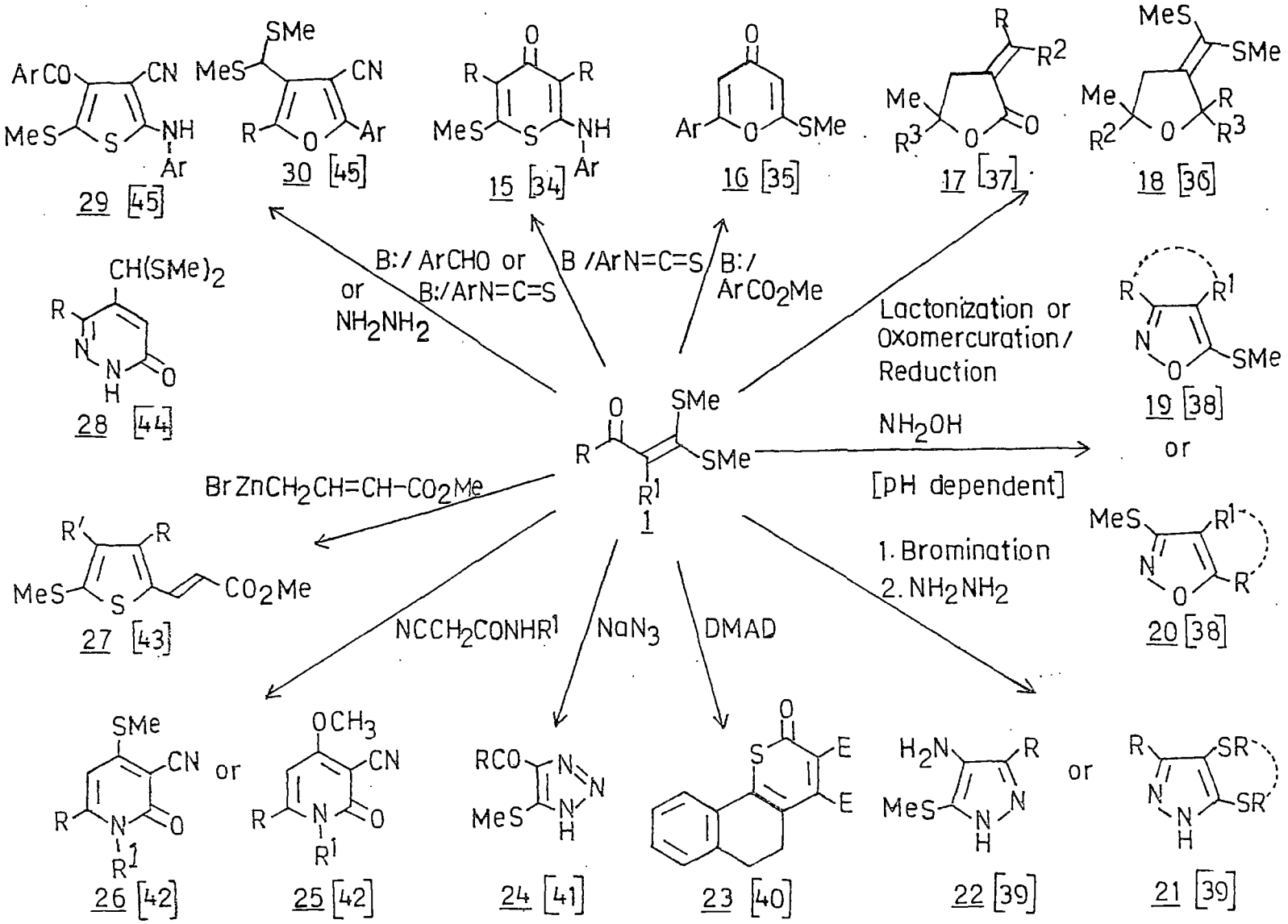

3 [32]
4 [32]
2 [28]
8 [19]
or
9 [19]
5 [33]
NaBH4 / NiCl2
NaBH4/AcOH
1.NaBH4
2.BF3Et2O/ MeOH
R'' MgX
or
10 [19]
1,3-SR shift
1. PhMgBr
BF3·Et2O
6 [23]
1
11 [29]
1,5 -SR shift
R2CuLi
BrZn CH2CO2Et
7 [31]
12 [20]
13 [30]
or
14 [30]

Scheme – 2

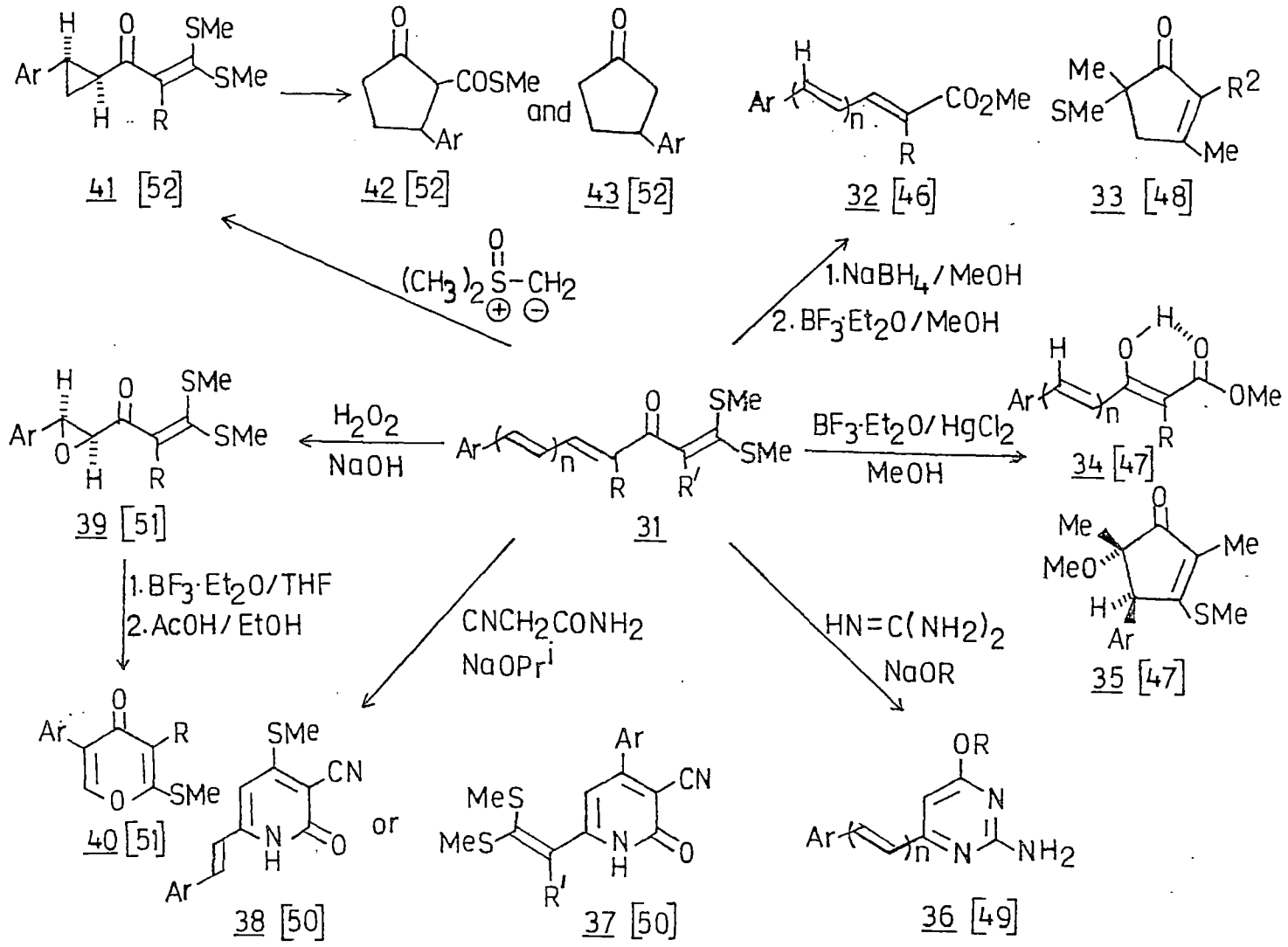
2-alkylthiomethylacrylo- phenones 6 are formed by a 1,3- RS shift. A base assisted 1,5- RS shift to the dienes 7 is also reported[31]. The α-oxoketene dithioacetals 1 are shown to undergo conjugate 1,4-reduction in highly regio- and chemoselective manner with sodium borohydride in acetic acid to afford the corresponding β-oxodithioacetals 5[33]. The α-oxoketene dithioacetals were also shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthioalkenyl ketones 3[32]. These intermediates are hydrolysed to the α,β-unsaturated aldehydes 4[32] (scheme 2).

The α-oxoketne dithioacetals have been extensively explored in this laboratory for the construction of various substituted and fused five and six membered heterocycles[34-45]. Some of the selected transformations developed recently are shown in scheme 3. From these transformations it is apparent that α-oxoketene dithioacetals with wide functional group variation and many easily accessible reagents and reaction intermediates manifest various possibilities leading to diverse product range.

Various transformations developed based on α-cinnamoyl and 5-aryl-2,4-pentadienoylketene dithioacetals 31 are outlined in scheme 4. A general method for the synthesis of polyene esters 32[22,46] has been reported by 1,2-reduction of 31 followed by methanolysis in the presence of borontrifluoride-etherate. In Hg(II) assisted hydrolysis the corresponding τ,δ-unsaturated β-ketoesters 34 are formed[47]. In the case of 2,4-disubstituted (R = R'=CH_3), the corresponding


29 [45]
30 [45]
15 [34]
16 [35]
17 [37]
18 [36]
28 [44]
B:/ ArCHO or B:/ArN=C=S
or NH2NH2
B /ArN=C=S
B:/ ArCO2Me
Lactonization or Oxomercuration/ Reduction
19 [38]
or
NH2OH
[pH dependent]
BrZnCH2CH=CH-CO2Me
1. Bromination
2. NH2NH2
20 [38]
27 [43]
NCCH2CONHR1
NaN3
DMAD
26 [42]
25 [42]
24 [41]
23 [40]
22 [39]
or
21 [39]

Scheme -3


41 [52]
42 [52]
and
43 [52]
32 [46]
33 [48]
(CH3)2S-CH2
1.NaBH4/MeOH
2.BF3·Et2O/MeOH
H2O2
NaOH
BF3·Et2O/HgCl2
MeOH
34 [47]
39 [51]
31
1.BF3·Et2O/THF
2.AcOH/EtOH
CNCH2CONH2
NaOPr^i
HN=C(NH2)2
NaOR
35 [47]
40 [51]
or
38 [50]
37 [50]
36 [49]

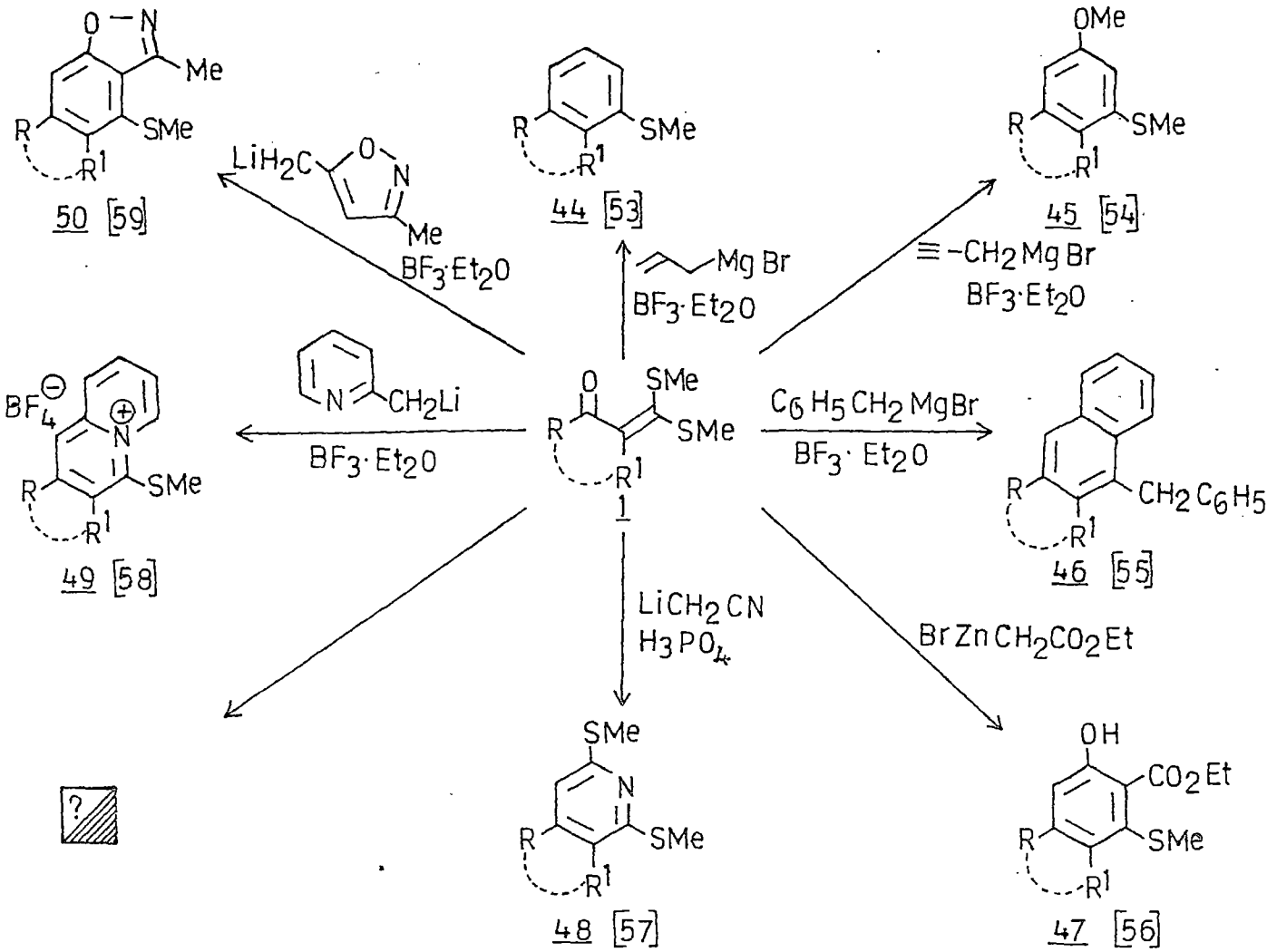
Scheme - 4

cyclopentanones 33 and 35 are formed in both reaction conditions[47,48]. Styryl pyrimidines 36, pyridones 37 and 38 were also synthesized using these intermediates[49,50]. The cinnamoylketene dithioacetals 31 have been reported to undergo regioselective epoxidation 39 and cyclopropanation 41 at the styryl double bond[51,52]. The intermediates 39 and 41 were further exploited for the synthesis of pyrones 40 and cyclopentanones 42 and 43 respectively[51,52].

The synthetic outcome of the aromatic annulation approach via α-oxoketene dithioacetals developed in this laboratory is depicted in scheme 5. Allylmagnesium bromide has been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetals in high yields, which on BF_3. Et_2O assisted cationic cyclization afforded the substituted and fused benzene derivatives **44**[53]. The approach is extended for the synthesis of other benzenoids **45**, **46** and **47**[54-56]. The method is further shown to be extremely versatile and found general application for the synthesis of pyridines **48**[57], quinolizinium salts **49**[58] and 1,2-benzisoxazoles **50**[59].

B. *α-Oxoketene O,S-Acetals*

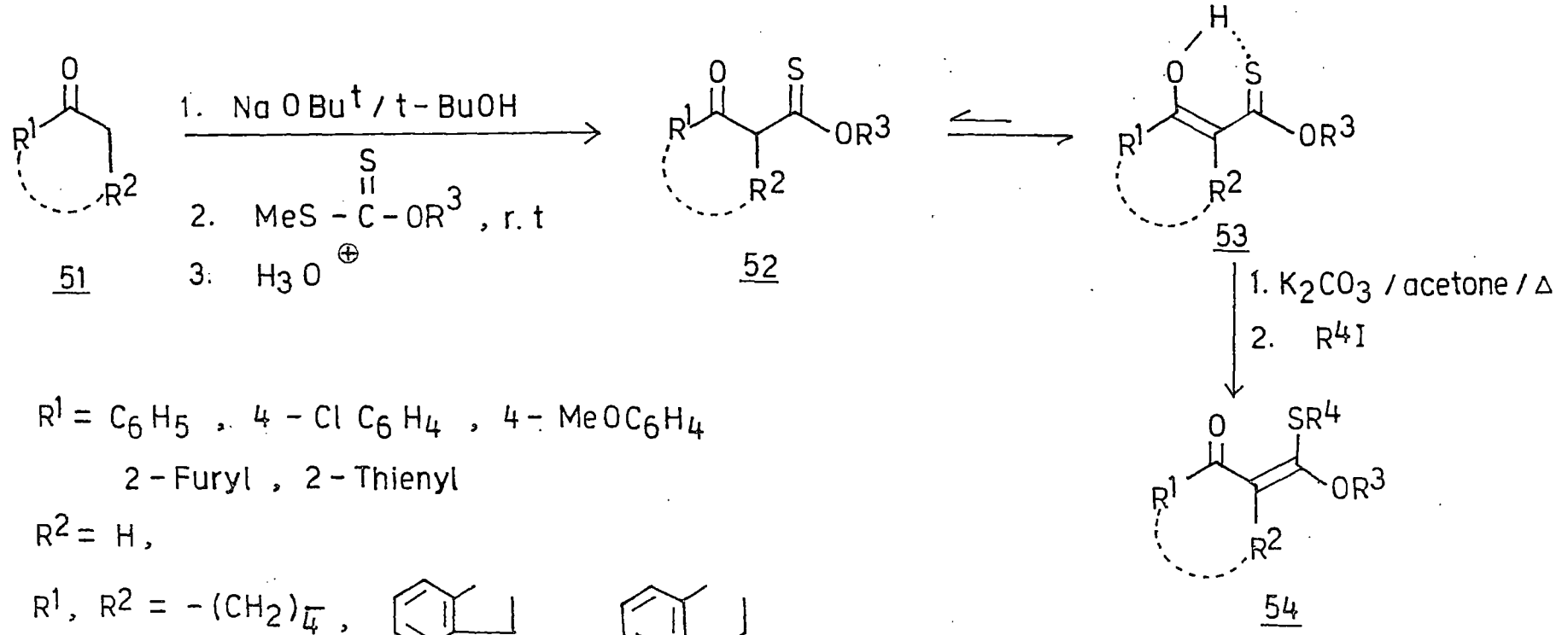
The α-oxoketene dithioacetals of the general formula 1 have been proved to be versatile synthetic intermediates in organic synthesis. As stated in preceding section, they have also served as precursors for the synthesis of the corresponding N,S- and N,N-acetals by direct displacement of SMe group(s) with appropriate primary and secondary amines.


50 [59]
44 [53]
45 [54]
49 [58]
1
46 [55]
48 [57]
47 [56]
?
LiH2C
Me
BF3·Et2O
Mg Br
BF3·Et2O
≡-CH2 Mg Br
BF3·Et2O
CH2Li
BF3·Et2O
C6H5CH2MgBr
BF3·Et2O
LiCH2CN
H3PO4
BrZnCH2CO2Et

Scheme – 5

The displacement of SMe group in 1 is equally facile with carbon nucleophiles particularly enolate anions, yielding stable 1,4-adducts which are further transformed into novel carbocyclic and heterocyclic compounds. Similarly from this laboratory it is reported that 1 undergoes displacement with alkoxide ions to give intermediate O,S-acetals which react *insitu* with either guanidine or hydrazine hydrate to afford the corresponding alkoxy pyrimidines or alkoxy pyrazoles in good yields [9]. However attempts to isolate O,S-acetals by direct displacement reaction in alkanol under varying conditions were not successful.

Schroth and co-workers[14] in an isolated example have reported the synthesis of α-benzoylketene O-methyl S-methylacetal. The benzoylketene dithioacetal was quarternized with dimethylsulphate to give the corresponding activated sulphonium salt which underwent smooth displacement with sodium methoxide in methanol to afford a mixture of benzoylketene O,S-dimethylacetal in 72% yield and the corresponding dithioacetal in 13% yield by demethylation. Despite extensive work on acylketene dithioacetals and the growing interest in acylketene acetals, the chemistry of the corresponding acylketene O,S-acetals has not been investigated and their preparation either directly from the active methylene ketones or through displacement of one SMe group by alkoxide/aryloxide ions form the sulphonium salts of corresponding oxoketene dithioacetals appears to have received little attention. Recently a general method for the preparation of acylketene O,S-acetals[60] has been developed in



R^1 = C_6H_5 , 4-Cl C_6H_4 , 4-MeOC_6H_4

2-Furyl , 2-Thienyl

R^2 = H,

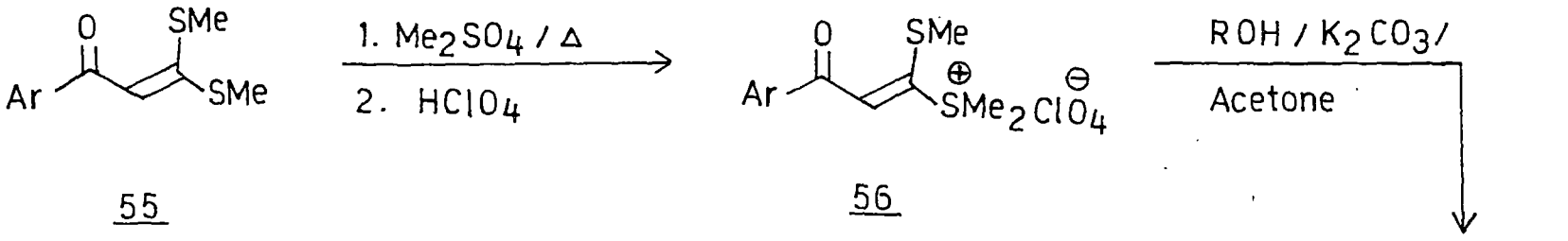
R^1, R^2 = $-(CH_2)_4$,

R^3 = Me, Et, n-Pr, n-Bu ; R^4 = Me

Scheme - 6

our laboratory. The method affords oxoketene O,S-dialkylacetals 54 by base catalysed alkylation of the respective β-oxo thionoesters 52 or 53 prepared by alkoxy thiocarbonylation of active methylene ketones 51 in the presence of sodium *t*-butoxide (scheme 6). The corresponding O-aryl S-alkylacetals 57 were prepared *via* base catalysed displacement of the sulphonium salts 56 of corresponding oxoketene dithioacetals 55 with phenols (scheme 7)

The α-oxoketene O,S-acetals, like S,S-acetals, are well defined compounds which can be preserved without apparent decomposition. The α-oxoketene O,S-acetals might in principle exist either as *E* or *Z* geometrical isomer or as a mixture of both. In all the cases however only one stereoisomer was obtained which was evident further from their sharp melting points and also from their ^{1}H NMR spectra. The stereochemistry of these compounds was established on the basis of difference ^{1}H NMR NOE experiments carried out on O,S-acetals. Thus, the irradiation of vinylic proton (δ = 6.38) in β-benzoyl O-methyl S-methylacetal gave NOE on OCH_3 (δ = 3.98) only, which was further confirmed by reverse experiment by irradiating OCH_3 signal where the NOE enhancement of vinylic proton was observed. The assignment was further confirmed by 2D NOESY spectra of β-benzoyl O-methyl S-methylacetal, which showed a cross peak between vinylic CH and OCH_3 groups while no cross peak was observed between SCH_3 and vinylic protons. Similarly in the case of O-phenyl S-methylacetal irradiation of vinylic



55 56 57

Ar = C_6H_5 , 4-$MeOC_6H_4$

R^1 = $C_{12}H_{25}$, $C_6H_5CH_2$, C_6H_5 , 2-ClC_6H_4

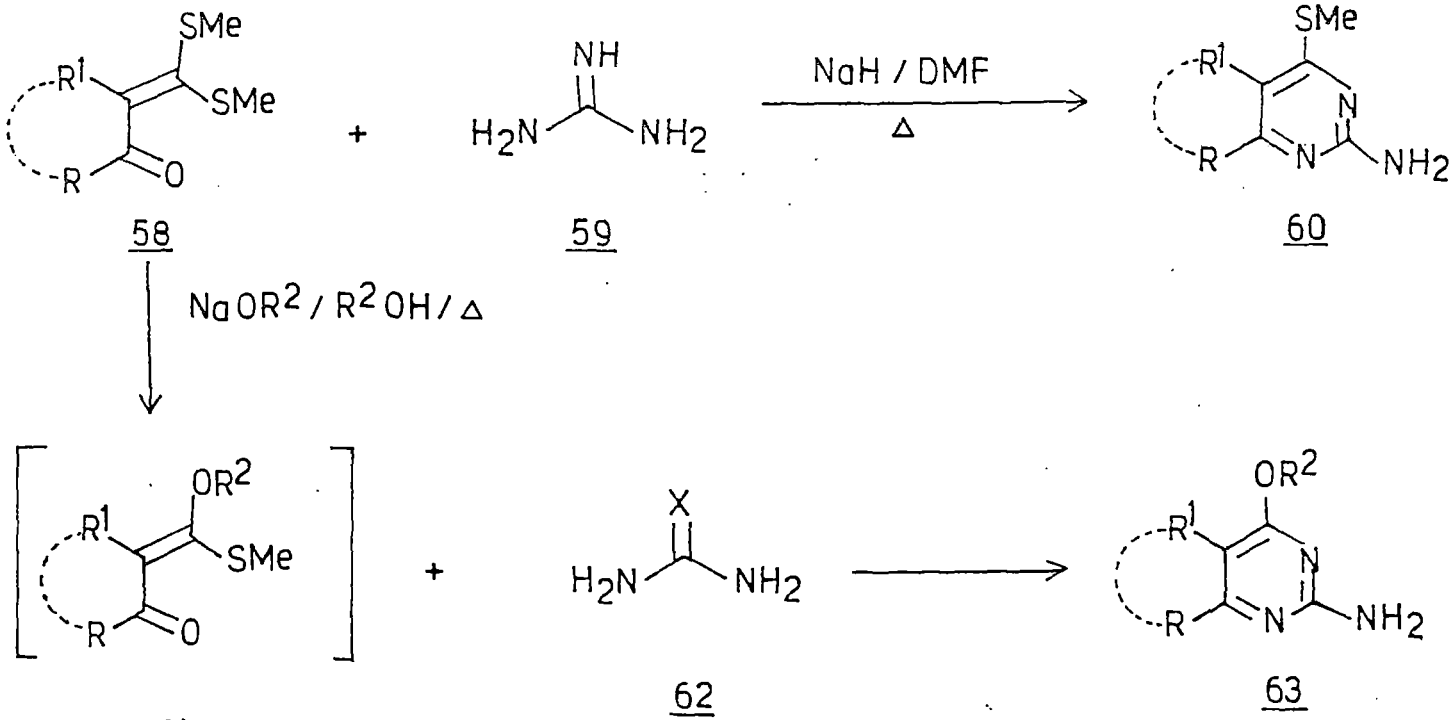
4-ClC_6H_4 , 2-naphthyl , 2-$MeO_2CC_6H_4$

Scheme - 7

CH signal (δ=6.3) gave NOE enhancement on aryl protons while irradiation of SCH_3 (δ=2.37) showed no NOE enhancement on vinylic proton. These observations therefore support Z-stereochemistry for both O-methyl and O-phenyl O,S-acetals. The cyclic O,S-acetals were also assigned 'Z' stereochemistry since chemical shift values for SCH_3 signal *cis* to carbonyl group were found to be very similar to those of acyclic ones.

The chemistry of α-oxoketene dithioacetals has been extensively investigated to construct a variety of carbocycles and heterocycles. In all these cases the final product carries the thioalkyl group as one of the substituents and similarly the corresponding S,N-acetals lead to the product with amino substitution. It was therefore considered of interest to investigate the reactivity of α-oxoketene O,S-acetals with various binucleophiles to afford the corresponding alkoxy substituted end products. Such a synthetic operation will certainly widen the synthetic scope of the α-oxoketene acetals in general. In this context some of the selected transformations on α-oxoketene O,S-acetals reported from this laboratory are briefly described in the following sections.

The α-oxoketene dithioacetals **58** when reacted with guanidine nitrate or thiourea **62** in the presence of sodium alkoxide and the corresponding alcohol, yielded the alkoxy pyrimidines **63** in high yields[9] (scheme 8). In all these reactions the corresponding methylthiopyrimidines **60** were not detected

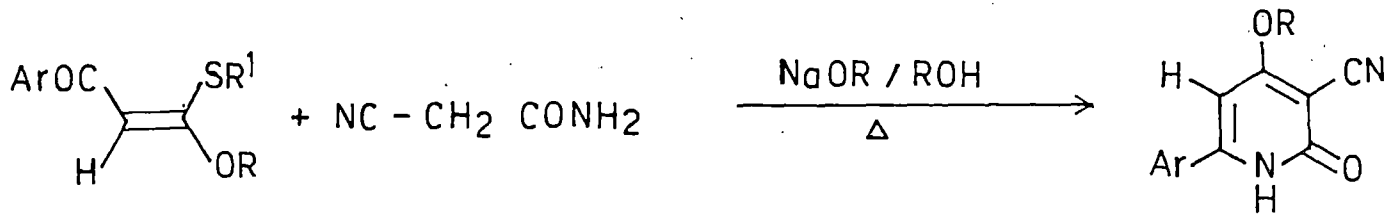


58 59 60

61 62 63

X = NH , S

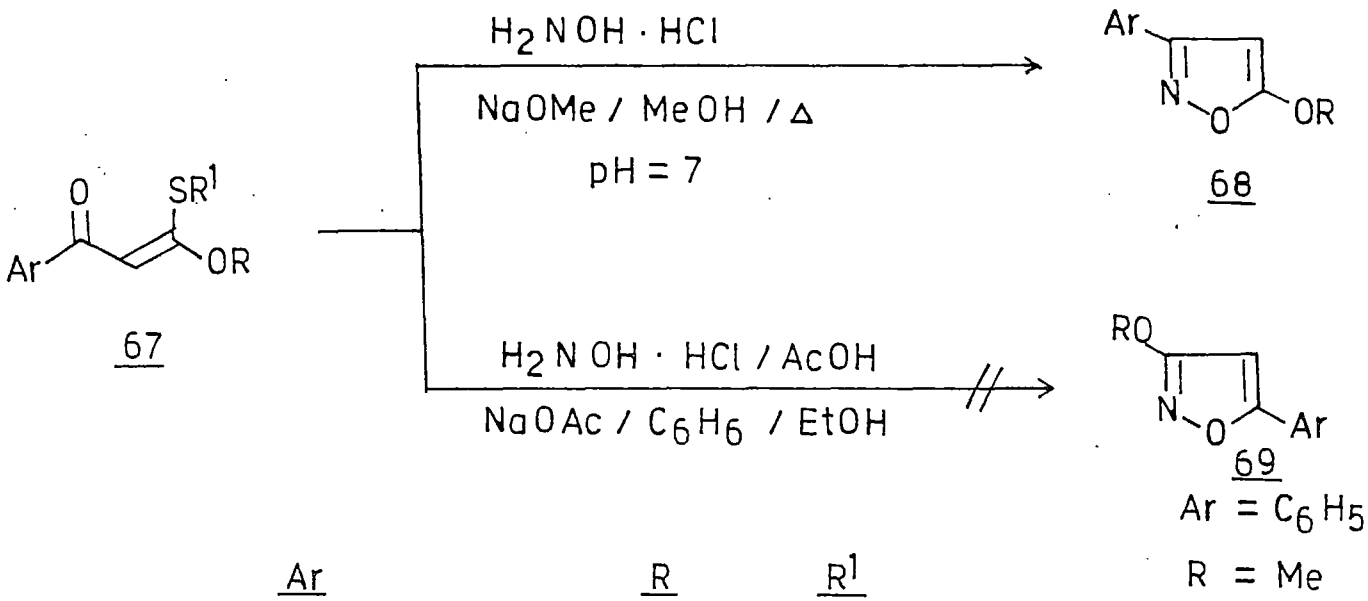
Scheme - 8



64 65 66

	Ar	R	R^1
a,	C_6H_5	Me	Me
b,	C_6H_5	Et	Et
c,	C_6H_5	n - Pr	Me
d,	4-MeO C_6H_4	Me	Me
e,	4-Cl C_6H_4	Me	Me
f,	2,4-Cl_2 C_6H_3	Me	Me

Scheme - 9



	Ar	R	R^1
a,	C_6H_5	Me	Me
b,	C_6H_5	Et	Et
c,	4-MeO C_6H_4	Me	Me
d,	4-MeO C_6H_4	n-Pr	Me
e,	4-Cl C_6H_4	Me	Me

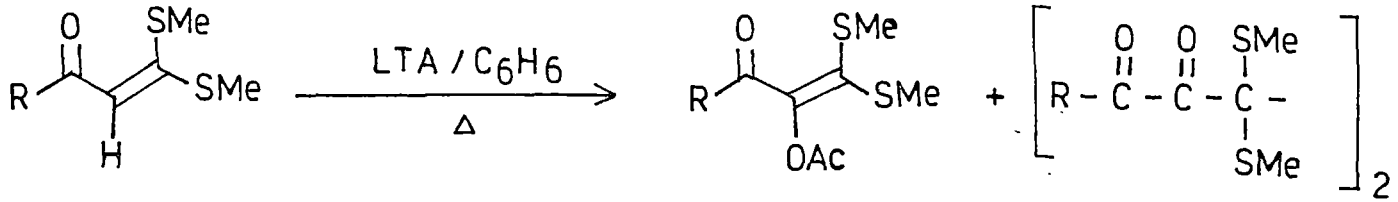
Scheme - 10

although the reaction of 58 with 59 in the presence of aprotic solvent (DMF) and sodium hydride yielded the corresponding 4-methylthio- pyrimidines 60 in comparatively lower yields. The formation of alkoxy pyrimidines thus proved the intermediacy of the O,S-acetals under the described reaction conditions.

The reaction of α-oxoketene O,S-acetals 64 with cyanoacetamide 65 in the presence of sodium methoxide and methanol afforded the corresponding 3-cyano-4-alkoxy-6-substituted pyrimidine-2(1H)-ones 66 in good yields [61] (scheme 9). Similarly when O,S-acetals 67 reacted with hydroxylamine hydrochloride in the presence of sodium methoxide in methanol yielded the corresponding 5-alkoxy-3-substituted isoxazoles 68[61]. However, 67 could not afford the corresponding 3-alkoxy-5-arylisoxazoles 69 on reacting with hydroxylamine hydrochloride in presence of acetic acid/sodium acetate in benzene (scheme 10).

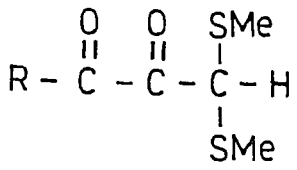
C. *The Work Presented in this Thesis*

From the studies on the synthetic applications of various N,N-, S,N- and S,S-acetals, it is evident that they are versatile synthetic intermediates for the synthesis of various carbocycles and heterocycles. In the present investigation it was proposed to undertake some of the transformations based on α-oxoketene S,S- and O,S-acetals. Although the α-oxoketene S,S-, S,N- and N,N-acetals have been extensively studied, the corresponding O,S-acetals remains less attended.



70 71 72

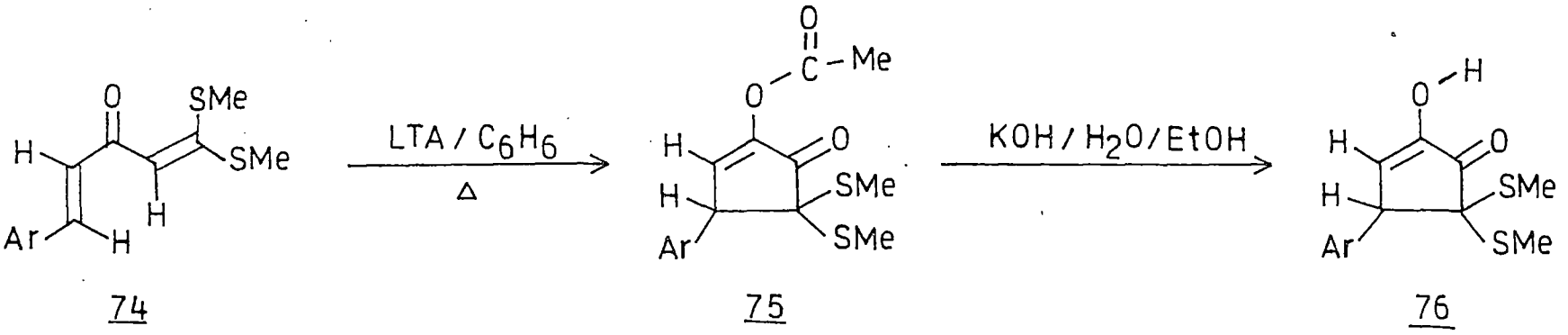
KOH / H_2O / EtOH



73

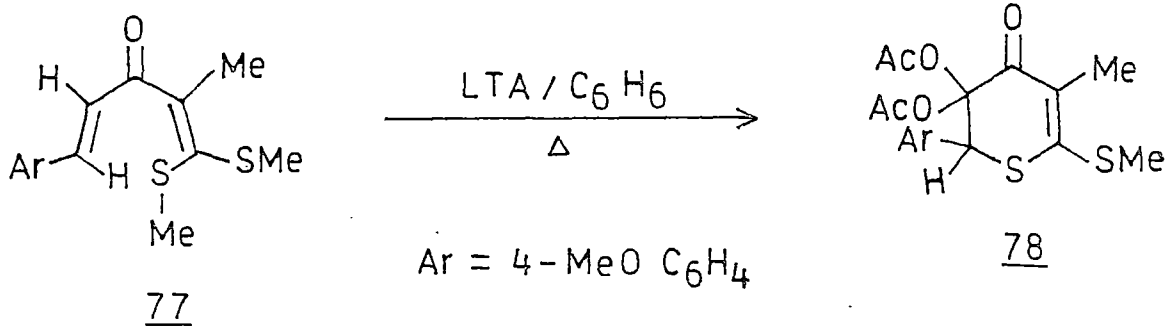
R = C_6H_5 , 4-Cl C_6H_4 ,
4-Me C_6H_4 , 4-MeO C_6H_4 , Me

Scheme - 11



74 75 76

Ar = C_6H_5 , 4-Cl C_6H_4 , 4-MeO C_6H_4 ,
3,4-$(MeO)_2$ C_6H_3 , 3,4-Methylene dioxy C_6H_3



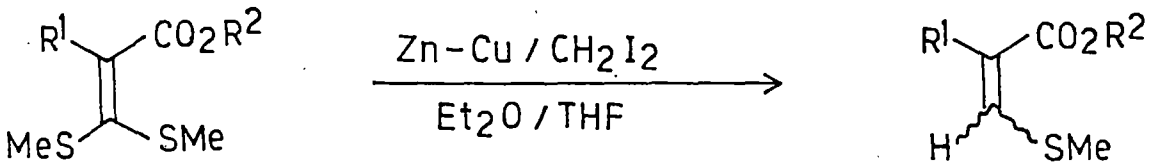
77

Ar = 4-MeO C_6H_4

78

Scheme – 12

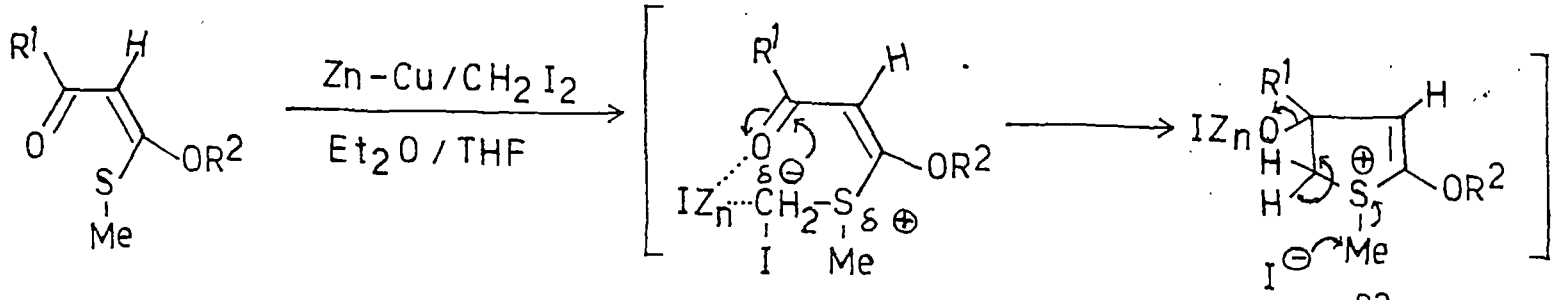
In the second chapter, the results of lead tetraacetate oxidation studies on α-oxoketene dithioacetals 70 and corresponding cinnamoylketene dithioacetals 74 and 77 are described[62]. The oxoketene dithioacetals 70 are shown to give a mixture of corresponding α-acetoxy dithioacetals 71 and diketone dimer 72 in 52-76% and 22-28% overall yields respectively (scheme 11). The α-acetoxy dithioacetals 71 were hydrolysed under mild alkaline conditions to afford the diketone dithioacetals 73 in good yields. The possible pathways for the formation of diketone dimers 72 and α-acetoxy dithioacetals 71 are discussed in detail. The cinnamoylketene dithioacetals 74 were next examined under similar reaction conditions to study the chemoselectivity of the reagent that might react with only the sulfur substituted double bond to yield the corresponding acetoxy products. However, when the cinnamoylketene dithioacetals 74 were oxidized with LTA under the described reaction conditions the products isolated were found to be 2-acetoxy-5,5-bis(methylthio)-4-arylcyclopenten-2-ones 75 in good yields (scheme 12). The α-acetoxycyclopentenones 75 were hydrolysed under mild alkaline conditions to give the corresponding α-diketones 76 in good yields. This overall transformation represents a novel oxidative Nazarov type cyclization and opens a facile entry to substituted cyclopentan-1,2-diones. The probable mechanism for the formation of α-acetoxy cyclopentenones is discussed. Interestingly when α-methyl cinnamoylketene dithioacetal 77 was oxidized with LTA under



79 80

79-80 a, $R^1 = C_6H_5$; $R^2 = Et$
b, $R^1 = CN$; $R^2 = Et$
c, $R^1 = CO_2Et$; $R^2 = Et$
d, $R^1 = COMe$; $R^2 = Me$

Scheme - 13



$R^1 = C_6H_5$; 4-MeO C_6H_4

R^1 = Me, Et, n-Pr, n-Bu, n-$C_{12}H_{25}$,

$-CH_2C_6H_5$, C_6H_5, 2-Cl C_6H_4,

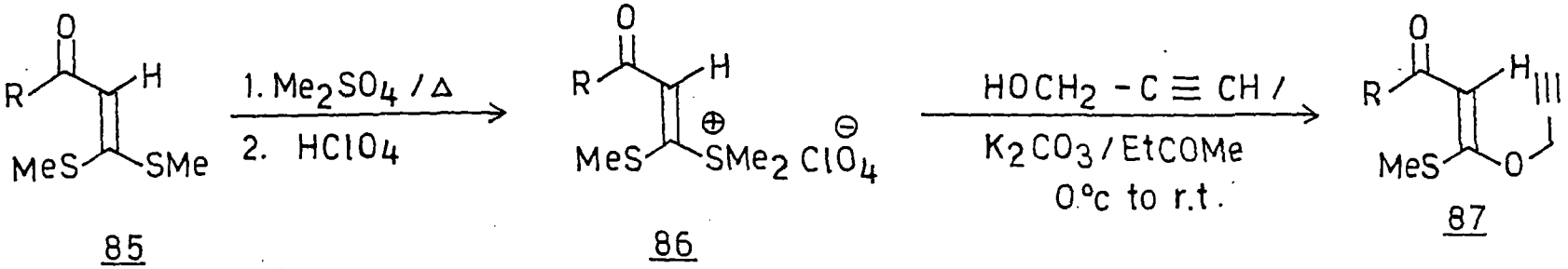
2-naphthyl, 2-methyl salicylate

Scheme -14

the reported conditions, the reaction took entirely a different course and the product isolated was characterized as 3,3-bis(acetoxy)dihydrothio- pyran-4-one 78 (scheme 12). The probable mechanism for this transformation is also described in this chapter.

In chapter 3, the reaction of Simmons-Smith reagent (Zn-Cu/ CH_2I_2) with doubly activated α-carboalkoxyketene dithioacetals and acylketne O,S-acetals is described[63,64]. The doubly activated α-carboalkoxyketene dithioacetals 79 on reaction with Simmons-Smith reagent gave the corresponding dethiomethylated products 80 in overall good yields (scheme 13) rather than the expected 3-hydroxy/amino thiophenes. However, the acylketene O,S-acetals 81 under similar reaction conditions gave the corresponding expected 4-aryl-2-alkoxy/aryloxy thiophenes 84 in overall good yields (scheme 14). The probable mechanism for the formation of 2-alkoxy/aryloxy thiophenes is discussed in this chapter.

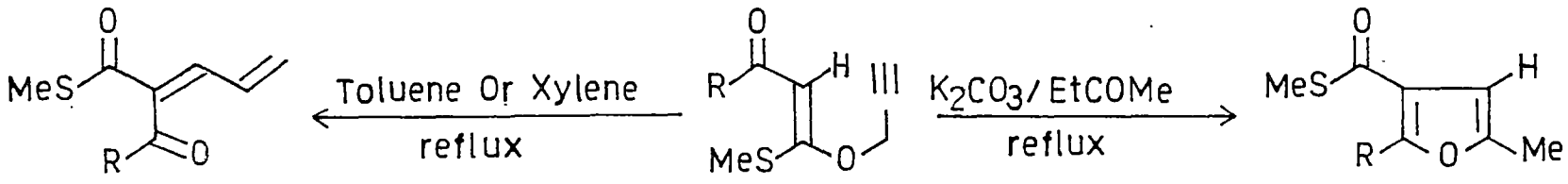
The thermal rearrangement studies on newly synthesized acylketene O-proporgyl S-methylacetals 87 under neutral as wellas basic conditions are described in the chapter 4. Various substituted acylketene O-propargyl S-methylacetals 87 were prepared by treating the perchlorates 86, derived from the corresponding α-oxoketene dithioacetals 85, with propargyl alcohol in ethylmethyl ketone in the presence of potassium carbonate (scheme 15). The O-propargyl S-methylacetals 87 when refluxed in dry benzene or toluene or xylene gave the corresponding diene esters 88 in almost



85 86 87

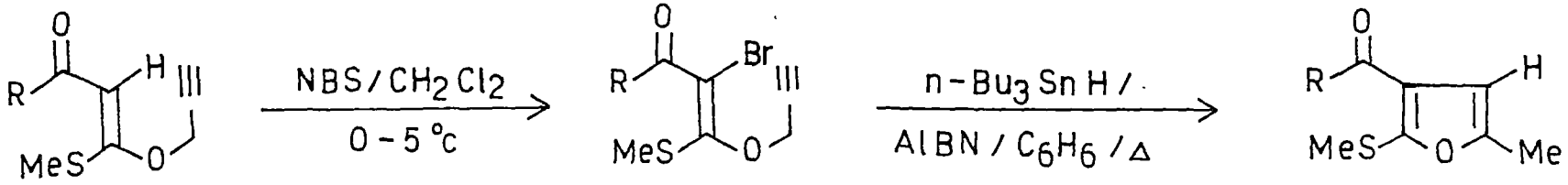
R = C_6H_5 , 4-Cl C_6H_4 , 4-MeO C_6H_4 , 2-Furyl , 2-Thienyl

Scheme - 15



R = C_6H_5 ; 4 - Cl C_6H_4 ; 4 - MeO C_6H_4 ; 2 - Furyl ; 2 - Thienyl.

Scheme - 16



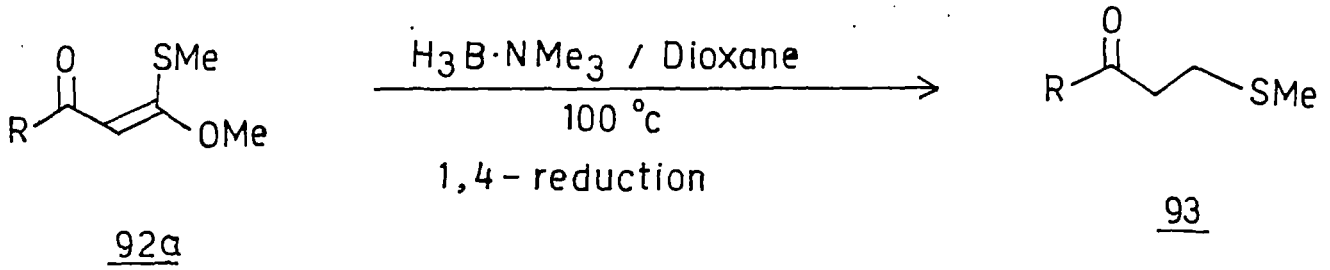
87 90 91

R = C_6H_5 , 4 - MeO C_6H_4

Scheme - 17

quantitative yields. However, the O-propargyl S-methylacetals 87 when refluxed in ethylmethyl ketone in the presence of potassium carbonate, the corresponding 2-aryl/heteroaryl-3-carbomethylthio-5-methyl furans 89 are formed in good yields (scheme 16). The probable mechanism for the formation of diene esters 88 and 5-methylfurans 89 is discussed in detail. The regioisomeric furans 91 were also prepared by initial bromination of the corresponding O-propargyl S-methylacetals followed by cyclization with n-Bu_3SnH/AIBN (scheme 17). The probable mechanism for the formation of furans 91 is also discussed in this chapter.

In the last chapter, the nucleophilic addition (mainly metal hydrides) studies on acylketene O,S-acetals are presented. Reduction of acylketene O-alkyl/phenyl S-methylacetals with trimethylamine borane complex gave the products derived from 1,4-reduction in good yields (scheme 18). The O,S-acetals on reduction with sodium borohydride in ethanol gave the corresponding S-methyl α,β-unsaturated thiocarboxylates in high yields derived from the initial 1,2-reduction followed by hydrolytic cleavage (scheme 19). However, O,S-acetals with sodium borohydride in acetic acid afforded the corresponding methylthiomethlylene ketones in good yields (scheme 20). The reduction studies on O,S-acetals with lithium aluminum hydride and DIBAL (scheme 21 and 22) are also discussed. Subsequent to the metal hydride reduction studies, a preliminary investigation on the addition of a carbon nucleophile to the O,S-acetal is also been undertaken. The results of this study are also presented in this chapter.

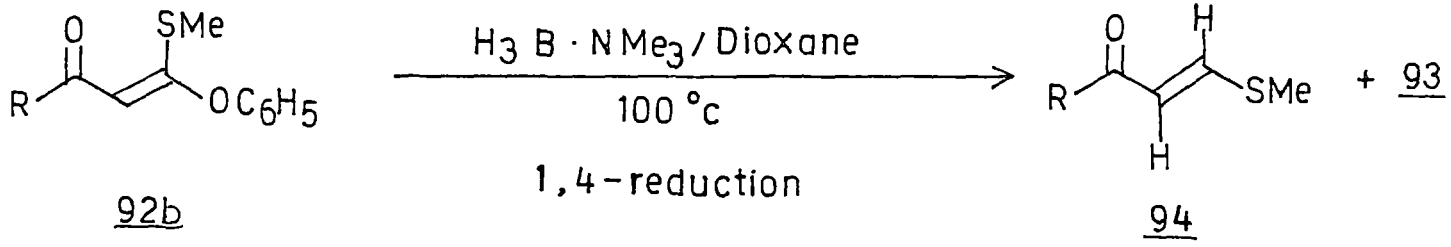


92a

93

92 - 93a , R = C_6H_5

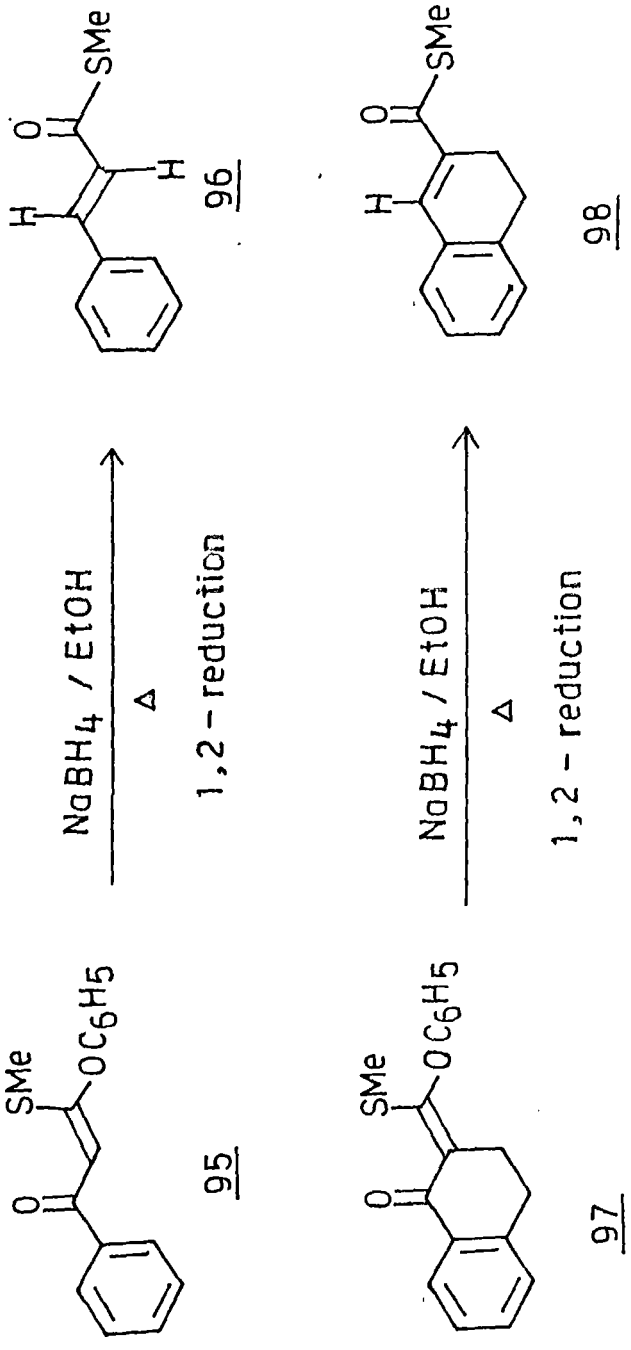
b , R = 2 - Thienyl



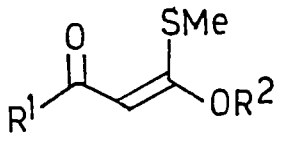
92b

94

Scheme - 18

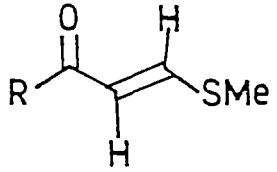

SMe
OC6H5
O
95
NaBH4 / EtOH
Δ
1,2 - reduction
SMe
O
H
H
96
SMe
OC6H5
O
97
NaBH4 / EtOH
Δ
1,2 - reduction
SMe
O
H
98

Scheme - 19



$NaBH_4$ / AcOH

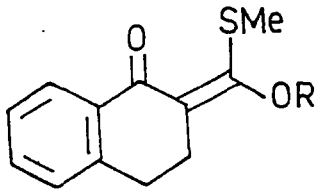
1, 4 - reduction



99 100

$R^1 = C_6H_5$; 2 - Thienyl

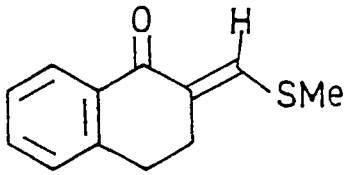
$R^2 =$ Me ; C_6H_5



$NaBH_4$ / AcOH

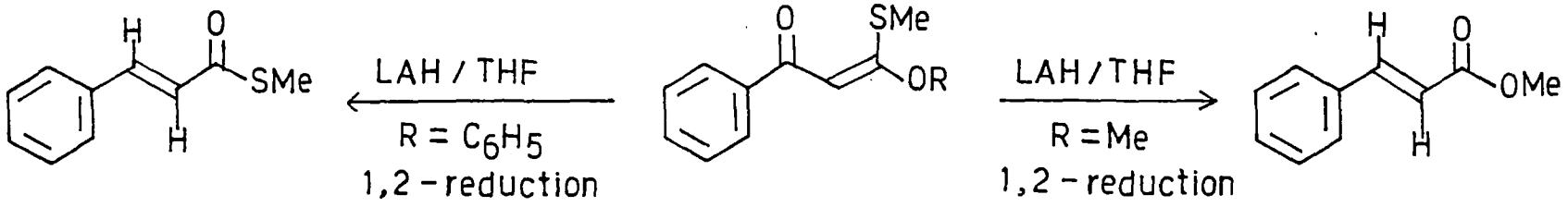
1, 4 - reduction

R = Me , C_6H_5



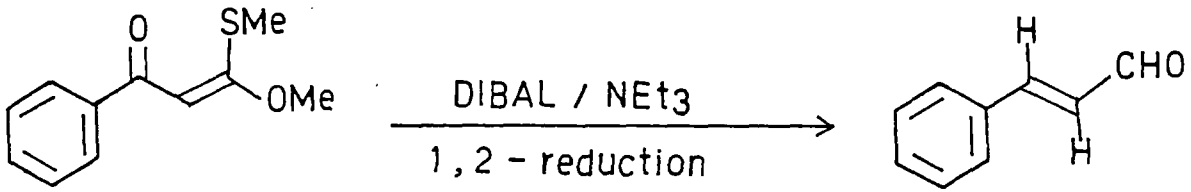
101 102

Scheme - 20



104 103 105

Scheme - 21



106 107

Scheme - 22

REFERENCES

1. For a review see (a) R.K. Dieter, Tetrahedron, *42*, 3029 (1986) (b) H. Junjappa, H. Ila and C.V. Asokan. Tetrahedron, *46*, 5423 (1990).
2. A. Thuillier, J. Vialle. Bull. Soc. Chim. Fr., 2187 (1962).
3. A. Thuillier, J. Vialle. Bull. Soc. Chim. Fr., 2194 (1962).
4. M. Saquet, A. Thuillier. Bull. Soc. Chim. Fr., 1582 (1966).
5. A. Thuillier, J. Vialle. Bull. Soc. Chim. Fr., 1398 (1959).
6. R. Gompper, R.R. Schmidt E. Kutter. Leibig. Ann. Chem., *684*, 37 (1965).
7. E.J. Corey, R.H.K. Chen. Tetrahedron Lett., 3817 (1973).
8. I. Shahat, Y. Sasson. Tetrahedron lett., 4207 (1973).
9. S.M.S. Chauhan, H. Junjappa. Tetrahedron, *32*,1779 (1976).
10. R.K. Dieter, J. Org. Chem., *46*, 5031 (1981).
11. C. Kelber, Chem. Ber., *43*, 1252 (1910).
12. C. Kelber, A. Schwarz, Chem. Ber., *44*, 1693 (1911).
13. C. Kelber, A. Schwarz, Chem. Ber., *45*, 137 (1912).
14. R. Spitzner, M. Menzel, W. Schroth. Synthesis, 206 (1982).
15. R. Gompper, H. Schaefer, Chem. ber., *100*, 591 (1967).
16. D. Borrmann in Houben-Weyl, Methoden der. Organischen. Chemie, 4th Edn., E. Muller, Ed., Vol. VII/4, Georg Thieme Verlag, Stuttgert, 421 (1968).

17. W.D. Rudof, A. Schierhorn, M. Augustin **Tetrahedron**, *35*, 551 (1979).

18. A. Thomas, J. N. Vishwakarma, H. Ila, H. Junjappa. **Tetrahedron**, *44*, 1667 (1988).

19. G. Singh, M.L. Purkayastha, H. Ila, H. Junjappa, **J. Chem. Soc. Perkin Trans. I**, 1289 (1985).

20. R.K. Dieter, L.A. Silks, J.R. Fishpaugh, M.E. Kastner, **J. Am. Chem. Soc.**, *107*, 4679 (1985).

21. R.K. Dieter, J.R. Fishpaugh, L.A. Silks, **Tetrahedron Lett.**, *23*, 3751 (1982)

22. B. Myrboh, C.V. Asokan, H. Ila, H. Junjappa, **Syntheis**, 50 (1984).

23. S. Apparao, A. Rahman, H. Ila, H. Junjappa, **Tetrahedron Lett.**, *23*, 971 (1982).

24. J.P. Marino, J.L. Kostusyk, **Tetrahedron Lett.**, *20*, 2489 (1979).

25. J.P. Marino, J.L. Kostusyk, **Tetrahedron Lett.**, *20*, 2493 (1979).

26. G. Singh, H. Ila, H. Junjappa, **Synthesis**, 165 (1985).

27. M. Saquet, A. Thuillier, **Bull. Soc. Chim. Fr.**, 3969 (1966).

28. B. Myrboh, H. Ila, H. Junjappa, **J. Org. Chem. 48**, 5327 (1983).

29. G. Singh, H. Ila, H. Junjappa, **Synthesis**, 744 (1986).

30. S. Apparao, A. Dutta, H. Ila, H. Junjappa, **Synthesis**, 169 (1985).

31. S. Apparao, S.S. Bhattacharjee, H. Ila, H. Junjappa, **J. Chem. Soc. Perkin Trans. I**, 641 (1985).

32. B. Myrboh, L.W. Singh, H. Ila, H. Junjappa, Synthesis, 307 (1982).

33. Ch. Srinivasa Rao, R.T. Chakrasali, H.Ila, H.Junjappa, Terahedron, *46*, 2195 (1990).

34. L.S. Singh, H. Ila, H. Junjappa, Synthesis, 531 (1985).

35. L.W. Singh, H. Ila, H. Junjappa, Synthesis, 873 (1987).

36. A. Dutta, S. Bhattacharjee, H. Ila, H. Junjappa, Synthesis, 725 (1988).

37. A. Dutta, H. Ila, H. Junjappa, Tetrahedron, *43*, 5367 (1987).

38. M.L. Purkayastha, H. Ila, H. Junjappa, Synthesis, 0000 (1989).

39. G. Singh, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans I, 1945 (1987).

40. J.N. Vishwakarma, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I, 1099 (1983).

41. R.T. Chakrasali, H. Ila, H. Junjappa, Synthesis, 453 (1988).

42. (a) R.R. Rastogi, H. Ila, H. Junjappa, J. Chem. Soc. Chem. Comm., 645 (1975); (b) R.R. Rastogi, A. Kumar, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I, 549 (1978).

43. A. Dutta, H. Ila, H. Junjappa, Synthesis, 556 (1988).

44. L.W. Singh, H. Ila, H. Junjappa, Synthesis, 89 (1988).

45. L.W. Singh, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I, 2365 (1988).

46. C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 163 (1985).

47. C.V. Asokan, S. Bhattacharjee, H. Ila, H. Junjappa. Synthesis, 281 (1988).

48. C.V. Asokan, H. Ila, H. Junjappa, Tetrahedron lett.,*26*, 1087 (1985).

49. L.W. Singh, A.K. Gupta, H. Ila, H. Junjappa, Synthesis, 516 (1984).

50. L.W. Singh, H. Ila, H. Junjappa, Ind. J. Chem., *36B*, 607 (1987).

51. B. Deb, C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 893 (1987).

52. B. Deb, C.V. Asokan, H. Ila, H. Junjappa, Tetrahedron Lett., *29*, 2111 (1988).

53. G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., *25*, 5095 (1984).

54. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett., 1459 (1987).

55. M.P. Balu, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., *27* 117 (1986).

56. A. Dutta, H. Ila, H. Junjappa, Tetrahedron Lett., *29*, 497 (1988).

57. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett., *29*, 6633 (1988).

58. M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett., *28*, 3023 (1987).

59. M.P. Balu, D. Pooranchand, H. Ila, H. Junjappa, Tetrahedron Lett., *29*, 501 (1988).

60. M.L. Purakayasta, M. Chandrasekharam, J.N. Vishwakarma, H. Ila, H. Junjappa, **Synthesis**, 245 (1993).

61. M.L. Purakayasta, H. Ila, H. Junjappa, unpublished results.

62. Laxminarayan Bhat, A. Thomas, H. Ila, H. Junjappa, **Tetrahedron**, *47*, 305 (1991).

63. Laxminarayan Bhat, A. Thomas, H. Ila, H. Junjappa, **Tetrahedron**, *48*, 10377 (1992).

64. Laxminarayan Bhat, H. Ila, H. Junjappa, **Synthesis**, 0000 (1993).

CHAPTER II

STUDIES ON LEAD TETRAACETATE OXIDATION OF α-OXOKETENE DITHIOACETALS*.

II.1 INTRODUCTION

Lead tetracetate (LTA) oxidation of organo nitrogen compounds have been extensively reported in the literature[1-4]. However, similar studies on the oxidation of organosulphur compounds have been few in the literature. The oxidative dimerization of thioles, oxidation of thioethers and disulphides to the corresponding sulphoxides and sulfonate esters which involve oxidation of sulphur atom are among the examples reported

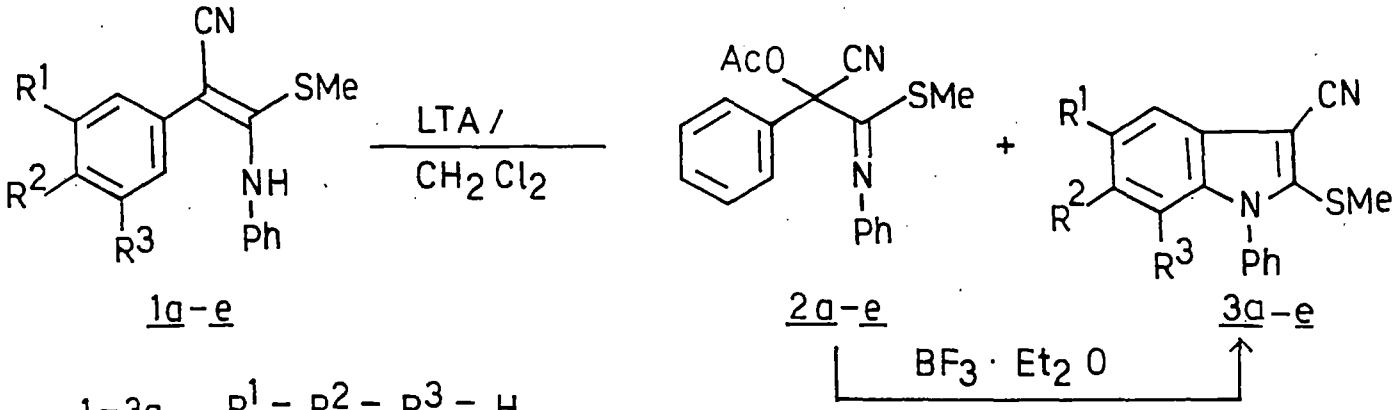
---

* Laxminarayan Bhat, Abraham Thomas, H. Ila, H. Junajappa Tetrahedron, *47*, 305 (1991)

earlier[2]. However, the reactions of greater synthetic utility are sulphur directed oxidative cleavage and acetoxylation of organosulphur compounds with LTA in which sulphur atom remains unaffected. The α-oxoketene dithioacetals therefore appeared to be attractive intermediates for the study of LTA oxidation and the products arising from these reactions. In the present chapter the LTA oxidation has been successfully attempted on the α-oxoketene dithioacetals which afford initially the α-acetoxy oxoketene dithioacetals in fair to good yields. On mild hydrolysis of these acetoxy dithioacetals, the corresponding diketone dithioacetals could be obtained. These studies and other products formed in the course of these oxidations have been presented in the present chapter.

The LTA oxidation of the polarised ketene N,N- and S,N-acetals have been examined in this laboratory with interesting results and useful transformations[5,6] thereof. A few of these examples have been briefly discussed so that the oxidation pathways observed in these transformations could help the present investigation.

The cyanoketene N,S-acetal[5] 1a was oxidised with LTA in dichloromethane at room temperature. After work-up two products were isolated of which the corresponding indole 3a was formed in 30% yield. The other product was characterized as iminoacetoxy compound 2a in 43% yield. The yield of the indole could be improved to 40% when the S,N-acetal 1a was added slowly to the reagent. However, when 2a was treated



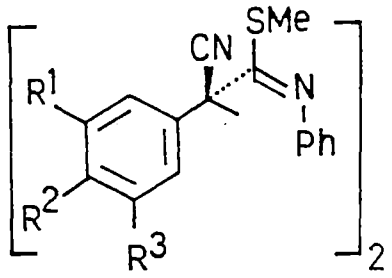
1-3a, $R^1 = R^2 = R^3 = H$

1-4b, $R^1 = R^2 = MeO$; $R^3 = H$

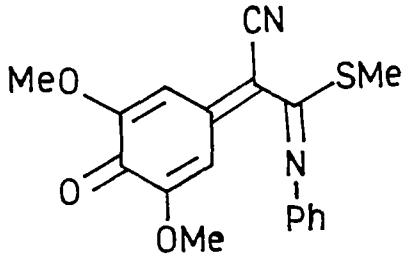
c, $R^1 = R^3 = H$; $R^2 = MeO$

d, $R^1 = R^3 = H$; $R^2 = Cl$

1-5e, $R^1 = R^2 = R^3 = MeO$

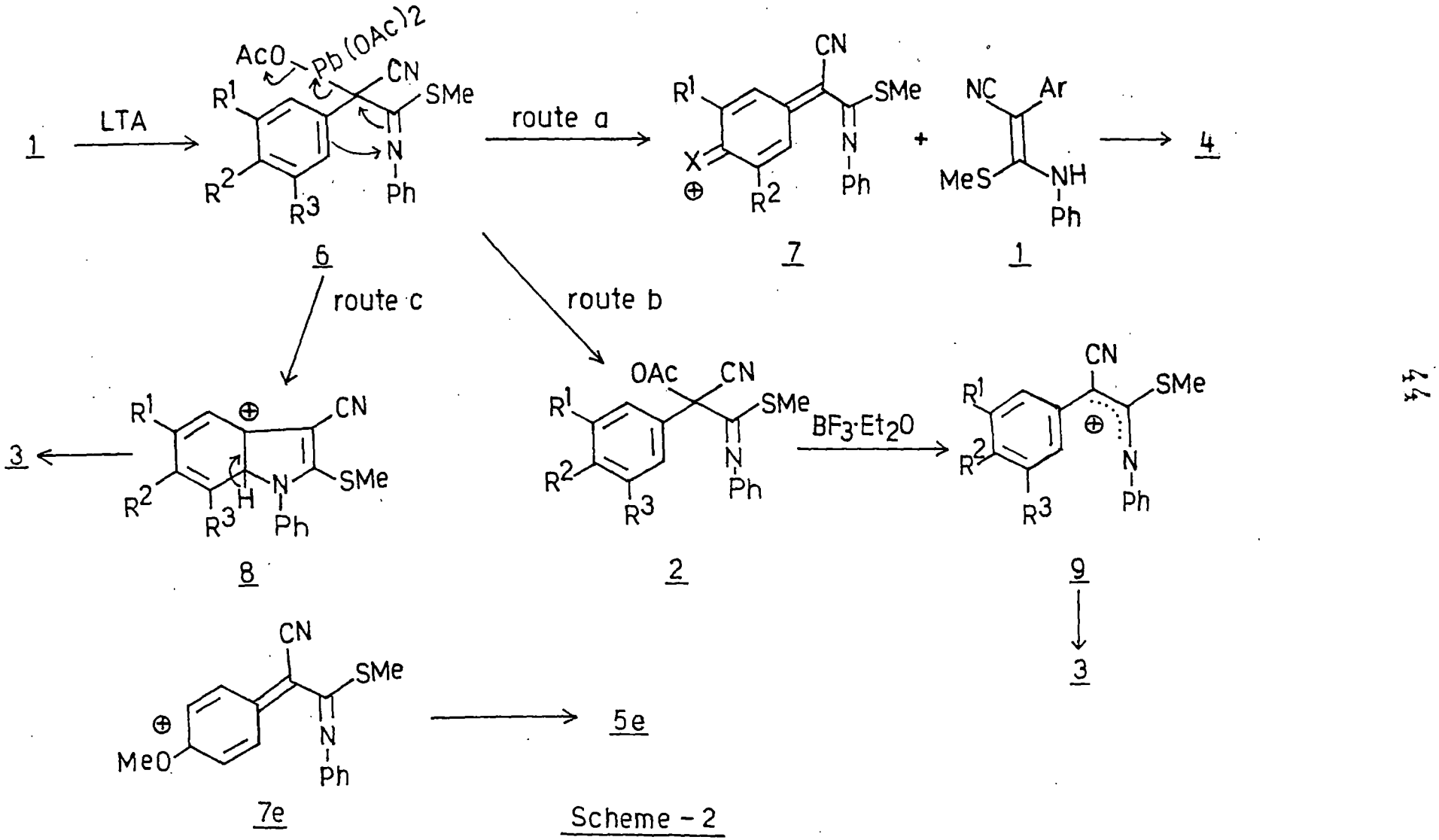


4b-e



5e

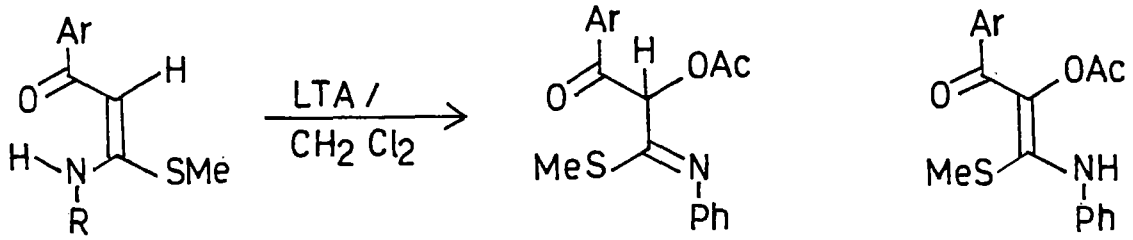
Scheme-1


1
LTA
AcO
Pb(OAc)2
CN
SMe
R1
R2
R3
N
Ph
6
route a
X
7
NC
Ar
MeS
NH
4
route c
route b
3
8
OAc
2
BF3·Et2O
9
MeO
7e
5e
Scheme - 2

with $BF_3.Et_2O$ in refluxing benzene the corresponding indole 3a was obtained in 70% yield. When the S,N-acetal **1b** was similarly oxidized with LTA, the reaction mixture after work up gave an amorphous solid which was characterized as dimer **4b**. The remaining part of the reaction mixture was identified as the corresponding acetate **2b** which on treatment with $BF_3.Et_2O$, afforded the corresponding dimethoxy indole 3b in good yield. Similarly **1c** and **1d** under identical conditions yielded a mixture of the corresponding acetates 2c and 2d and the dimers **4c** and **4d**. The iminoacetates 2c and 2d on treatment with $BF_3.Et_2O$ yielded the corresponding 6-methoxy indole 3c and 6-chloroindole 3d respectively in good yields. However, the S,N-acetal **1e** under similar oxidation conditions yielded quinonemethide **5e** as the main product along with iminoacetate 2e and dimer **4e** in minor quantities (scheme 1).

The mechanism governing these transformations is shown in the scheme 2. The initially formed C-plumbylated adduct 6 is the primary intermediate from which acetates 2, indoles 3, dimers 4 could be derived depending on the nature of the substituents in the *para*-position of the aromatic ring.

Similarly, when the α-oxoketene S,N-acetals[6] **10a-c** were oxidised with LTA in dichloromethane at room temperature. Under the described conditions **10a** gave only **11a** while **10b** and **10c** yielded the corresponding acetates **12b** and **12c** repectively (scheme 3). Further studies on the oxidation of N,N-acetals 13 (scheme-4) with LTA, the course of reaction



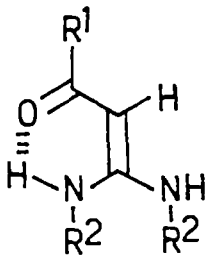
10a-c 11a 12b-c

10 - 11a, Ar = 4 - Me C_6H_4; R = C_6H_5

10, 12b, Ar = 4 - Me C_6H_4; R = $C_6H_5CH_2$

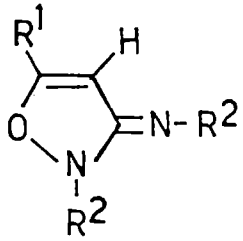
c, Ar = C_6H_5; R = Et

Scheme - 3

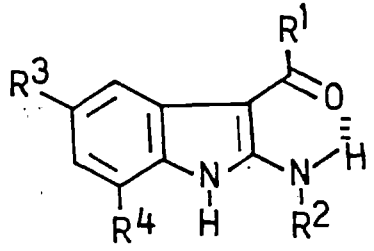


13a-g

LTA / CH_2Cl_2



14a-g



15c-g

13-14a, R^1 = 4-Me C_6H_4 ; R^2 = Ph

b, $R^1 = R^2$ = Ph

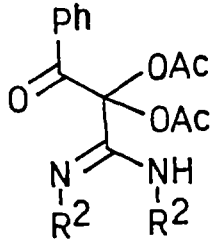
c, R^1 = Ph ; R^2 = 4-Br C_6H_4

d, R^1 = Ph ; R^2 = 3-Me C_6H_4

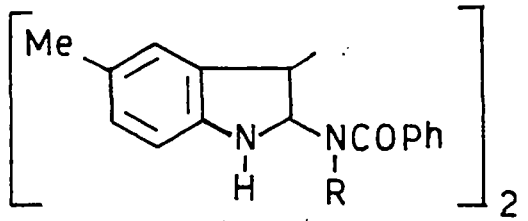
13-17e, R^1 = Ph ; R^2 = 4-Me C_6H_4

13-15f, R^1 = Ph ; R^2 = 2-Me C_6H_4

g, R^1 = 4-Cl C_6H_4; R^2 = 2-Me C_6H_4



16e



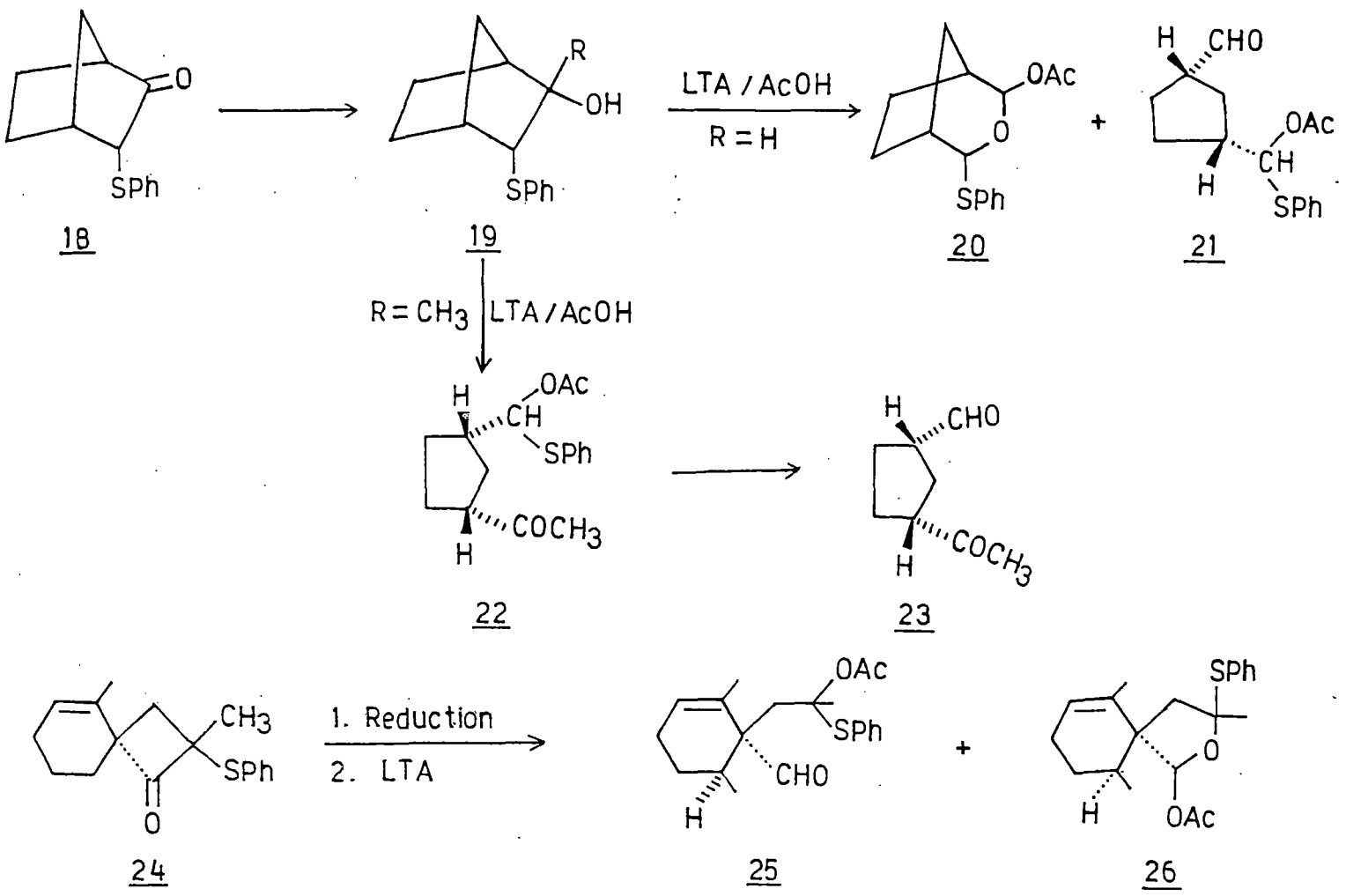
17e

Scheme - 4

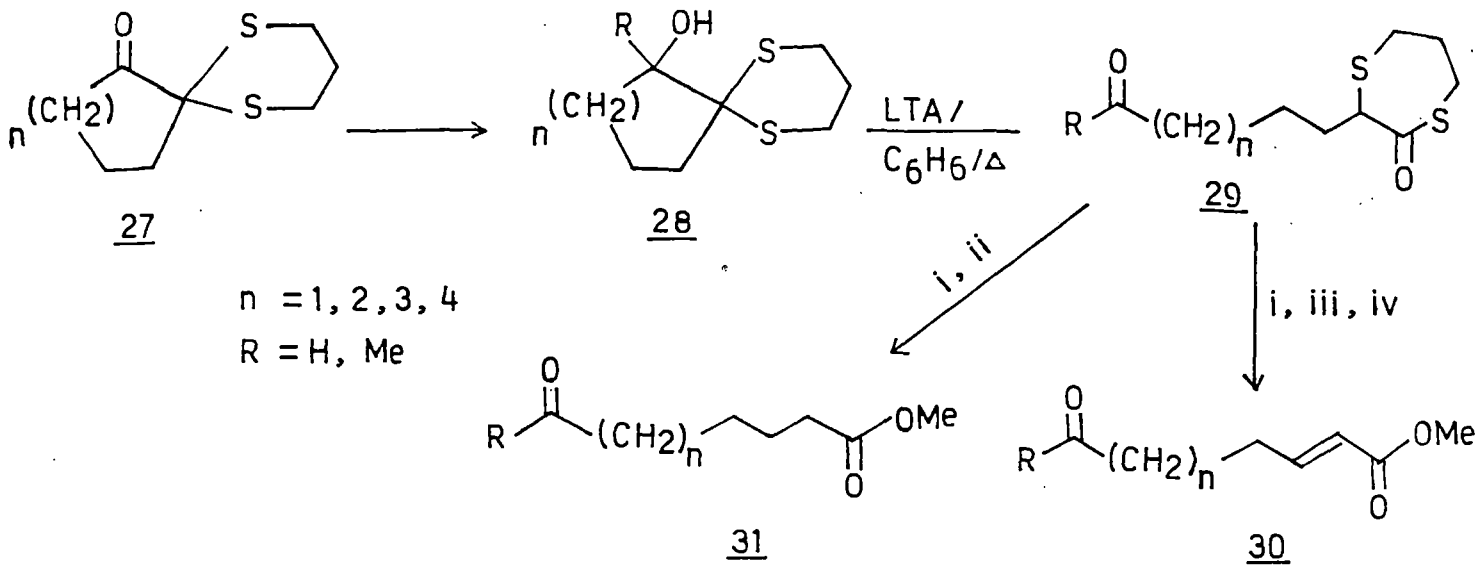
was different. Thus, 13a gave 5-(4'-Methylphenyl)-3-(phenylimino)- 4-isoxozoline **14a** in 57% yield. The reaction path did not follow uniform pattern for all the N,N-acetals examined. Thus 13b-d gave the isoxazoline **14b-d** as the only isolable products. However, the N,N-acetal 13e yielded other products in addition to the corresponding **14e**. The other products were characterized as indole **15e** (10%), diacetate **16e** (8%) and dimeric indole **17e** (13%). The oxidation of 13f and 13g afforded the corresponding isoxazolines **14f** and **14g** along with the corresponding indoles **15f** and **15g** respectively.

The divalent sulfur compounds are generally suceptible for oxidation in the presence of oxidising agents. However, LTA has been successfully used by Trost and Hiroi[7] to oxidise divalent sulfur compounds without altering the oxidation states of sulfur. For example, norborninone on sulfenylation gave generally the *endo* isomer **18** as a major product. The *endo* product after reduction with sodium borohydride gave the corresponding alcohol **19** which on LTA oxidation gave products **20** and **21**. Similarly **19** (R=Me) gave **23** on oxidation through **22**. This approach was extended to cyclobutanone **24** which after reduction and oxidation by LTA gave the products **25** and **26** (scheme 5).

Trost and Hiroi[8] extended LTA oxidation reactions to some novel oxidative *seco*-rearrangements of 2,2-dithiocycloalkan-1-ols **28** to afford the open chain ketoesters **30** and **31** (scheme 6). Lottenbach and Graf[9] have extended this


O
SPh
18
R
OH
SPh
19
LTA / AcOH
R = H
OAc
O
SPh
20
+
H
CHO
OAc
CH
H
SPh
21
R = CH3
LTA / AcOH
H
OAc
CH
SPh
COCH3
H
22
H
CHO
COCH3
H
23
CH3
SPh
O
24
1. Reduction
2. LTA
OAc
SPh
CHO
H
25
+
SPh
O
H
OAc
26

Scheme - 5

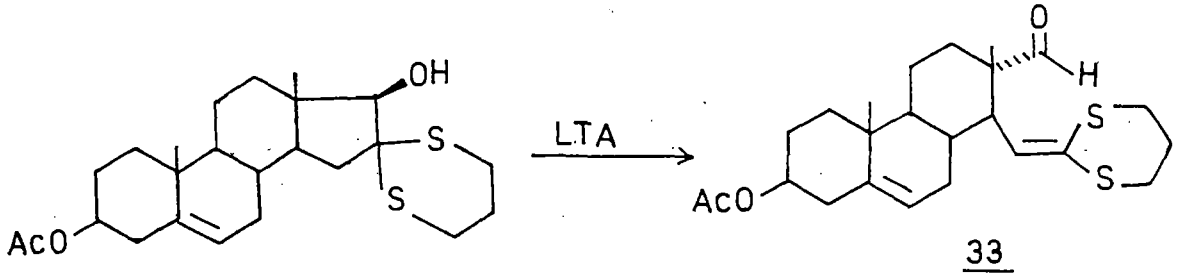


27 28 29 31 30

n = 1, 2, 3, 4

R = H, Me

i, I_2 / MeOH / Δ ; ii, Raney Nickel ; iii, $NaIO_4$ / MeOH ; iv, Δ



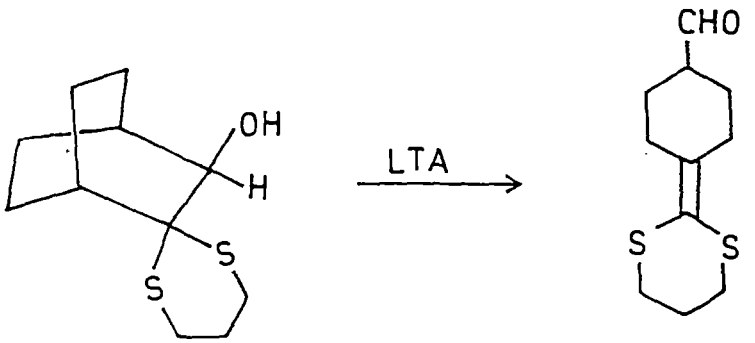
32 33

Scheme – 6

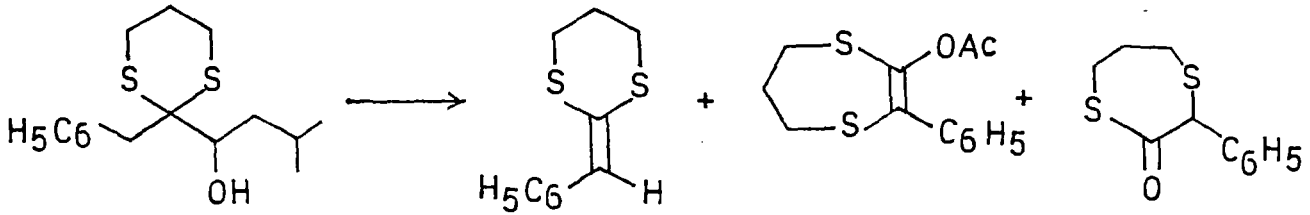
rearrangement to steroidal molecule 32 to obtain the corresponding dithioacetal aldehyde 33 (scheme 6). They also demonstrated that a number of ketene dithioacetals containing unprotected carbonyl groups could be readily obtained by LTA oxidation of the corresponding α-hydroxythioacetals of general formula 34 and 36 (scheme 7). The mechanism governing these transformations is described in scheme 8.

Trost and Tanigawa[10] have accomplished successful allylic alkylation of enol thioethers (scheme 9). The key step involved in the overall sequence of this reaction follows the LTA oxidation of 47 to provide the corresponding diacetate 48 followed by elimination of one of the acetate groups to afford the corresponding allyl acetate 49. It is interesting to note that the sulfide linkage is not oxidized under these oxidation conditions. Using organocuprates the acetate group is easily replaced to give the corresponding alkylated products. This reaction was extended to six membered ring 50 with 4-t-butyl group. The transformation of 50 to 54 has been shown in scheme 9. LTA first complexes with the sulphide sulphur in 50 forming complex 51 which undergoes acetoxylation to give the intermediate 52. The 52 on further acetoxylation gives the intermediate 53, which subsequently undergoes elimination of acetate ion to afford the corresponding acetate 54.

Some interesting oxidative ring expansion studies of 2-alkylidine 1,3-dithianes of general formula 55 and 59 have been examined by Hiroi and Sato[11]. Thus the ketene

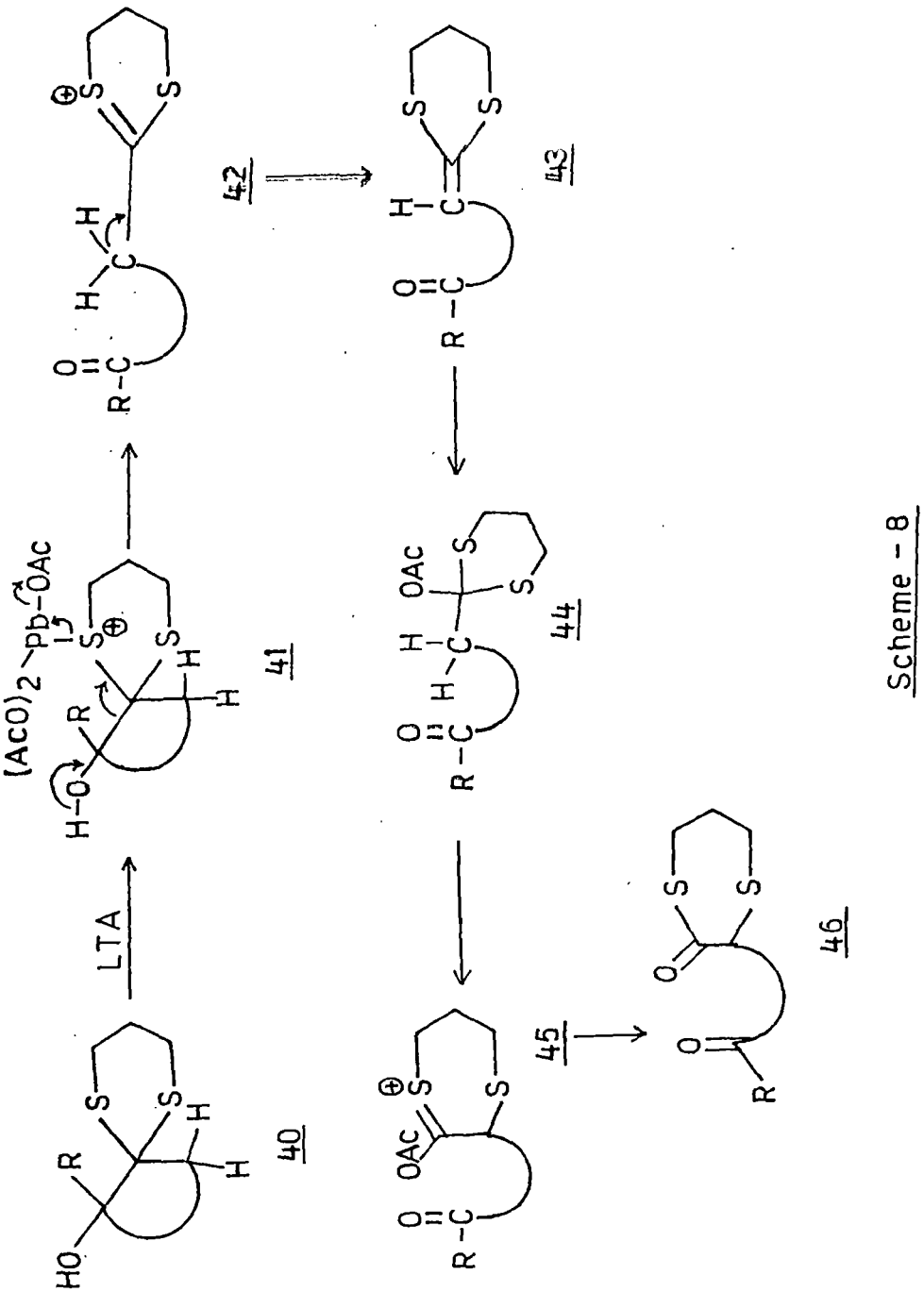


34 35

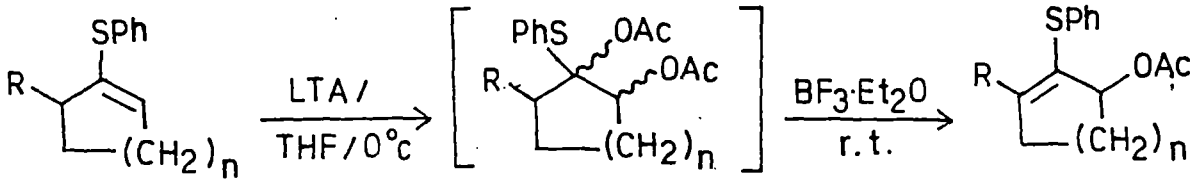


36 37 38 39

Scheme – 7

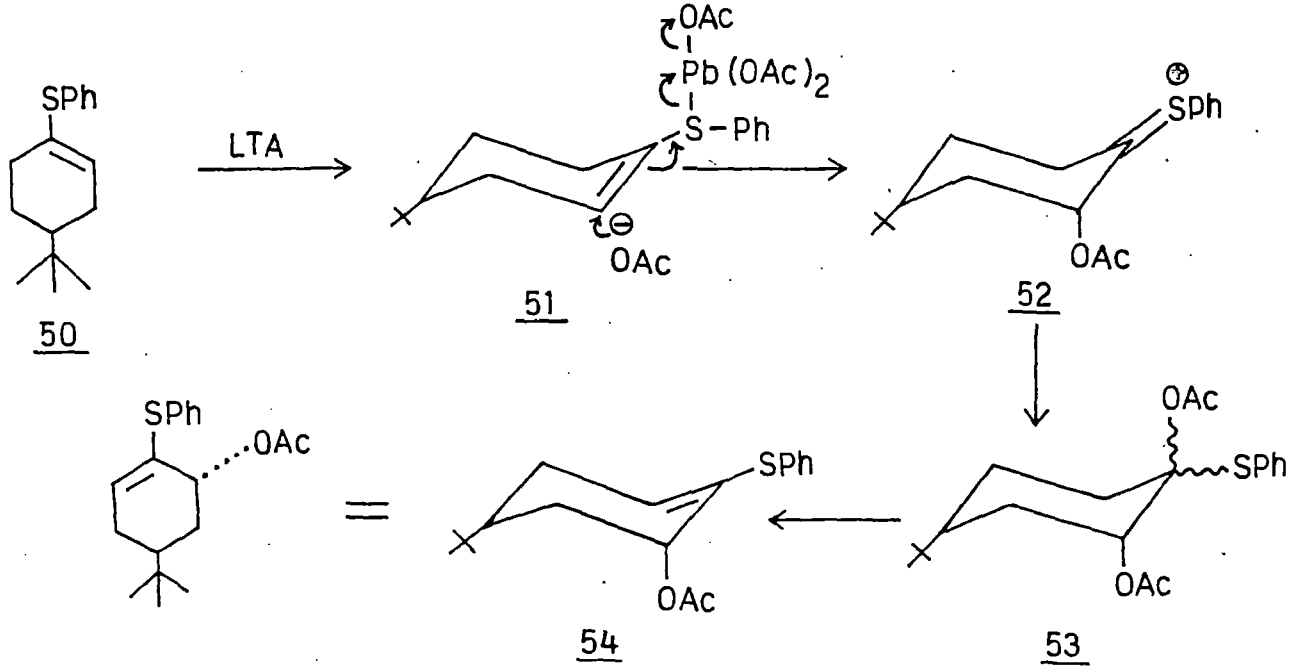


Scheme - 8



47 48 49

R = H, Me ; n = 1, 2



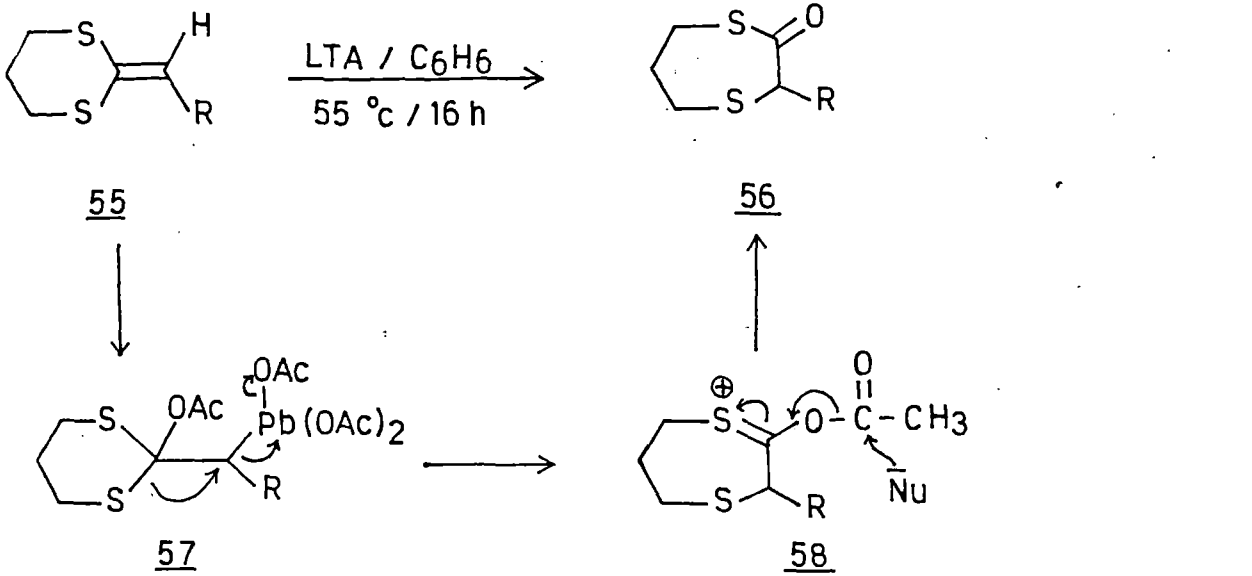
50 51 52 53 54

Scheme - 9

dithioacetal 55 on treatment with LTA in benzene at 55°C afforded 3-alkyl-1,4-dithiepen-2-one 56 in 74% yield. The ring expansion of 55 by LTA was shown through the key intermediates 57 and 58. However when `R' group was phenyl as in 59, the ring expansion did not take place but only the corresponding α-acetoxy acetal 61 was formed (scheme 10).

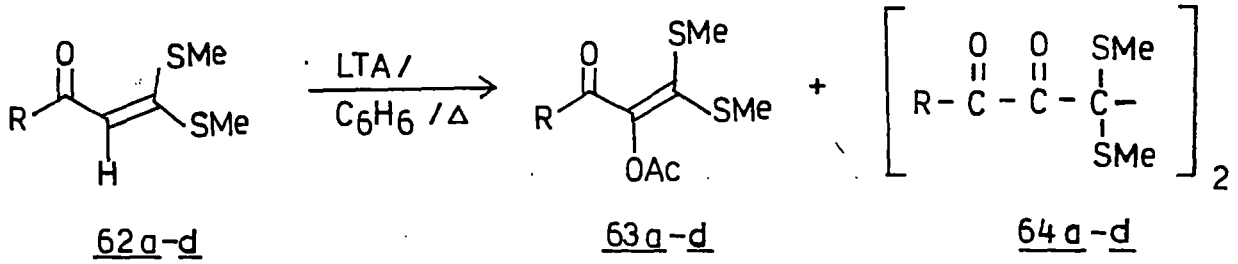
II.2 RESULTS AND DISCUSSION

Organic molecules containing sulfide functional groups have been scantly subjected to LTA oxidation without altering the oxidation state of sulfur. Hence, there is an ample scope that organo sulfur compounds should give more attractive results when subjected to LTA oxidation depending on the structural features. The cyclic dithioacetals have already been examined by some groups as described above where the oxidation led either to ring expansion or to the expected acetoxy substitution. The α-oxoketene dithioacetals are attractive group of organic molecules with ketene dithioacetal structural moiety attached with carbonyl function. These compounds should provide interesting results on subjecting them to LTA oxidation leading to products which are otherwise inaccessible by any other method. In the present investigation it has been observed that the α-oxoketene dithioacetals undergo α-acetoxylation which on mild hydrolysis cleaved to afford the corresponding diketone dithioacetals in good yields.


LTA / C6H6
55 °c / 16 h
55
56
57
58
R = H, CH3 , CH3 CH2 , CH3 CH2 CH2 , C6H5 CH2
LTA /
59
60
61

Scheme -10

In the present chapter, the investigation of lead tetraacetate oxidation of α-oxoketene dithioacetals have been presented. Equimolar quantity of **62a** and LTA were stirred at room temperature in dichloromethane or benzene when the unreacted **62a** was recovered. However, when **62a** was refluxed with two equivalents of LTA in benzene for 28 hr. a mixture of two products was obtained which were characterized as 2-acetoxy-3,3-bis (methylthio)-1-(4'-methylphenyl)-2-propen-1-one **63a** and 1,6-di(4'-methylphenyl)-3,3,4,4-tetra(methylthio) hexan-1,2,5,6-tetraone **64a** in 56% and 25% yields respectively (scheme 11). The structure of **63a** was established on the basis of its analytical and spectral data. It was analysed for $C_{14}H_{16}O_3S_2$. It showed in its mass spectrum a peak at m/z 296 (M^+, 5%). The compound showed strong absorptions in its IR (neat) spectrum at 1761 and 1650 cm^{-1} indicating the presence of two carbonyl functions. The ^1H NMR ($CDCl_3$) of **63a** exhibited a singlet at δ2.19 (3H) and another singlet at δ2.24 (3H), which were assigned to the SMe group protons. The broad singlet at δ2.43 (6H), was assigned to acetate methyl protons and *p*-methyl protons of phenyl group. The doublets at δ7.27 (2H, J=9Hz) and δ7.90 (2H, J=9Hz) were assigned to phenyl protons. The dimer **64a** was analysed for $C_{24}H_{26}O_4S_4$ and exhibited in its mass spectrum peaks at m/z 153 (65%), 107 (19) and 119 (100). In its IR (neat) spectrum, two strong bands at 1691 and 1665 cm^{-1} were observed. The ^1H NMR (CCl_4) spectrum showed a singlet at δ2.10 (12H) for four SMe group protons. The singlet at δ2.39 (6H) was assigned


LTA /
C_6H_6 / Δ
62a-d
63a-d
64a-d
62 - 65a, R = 4 - Me C_6H_4
b, R = 4 - Cl C_6H_4
c, R = 4 - MeO C_6H_4
62 - 64 d, R = Me
KOH / EtOH / H_2O
65 a - c

Scheme - 11

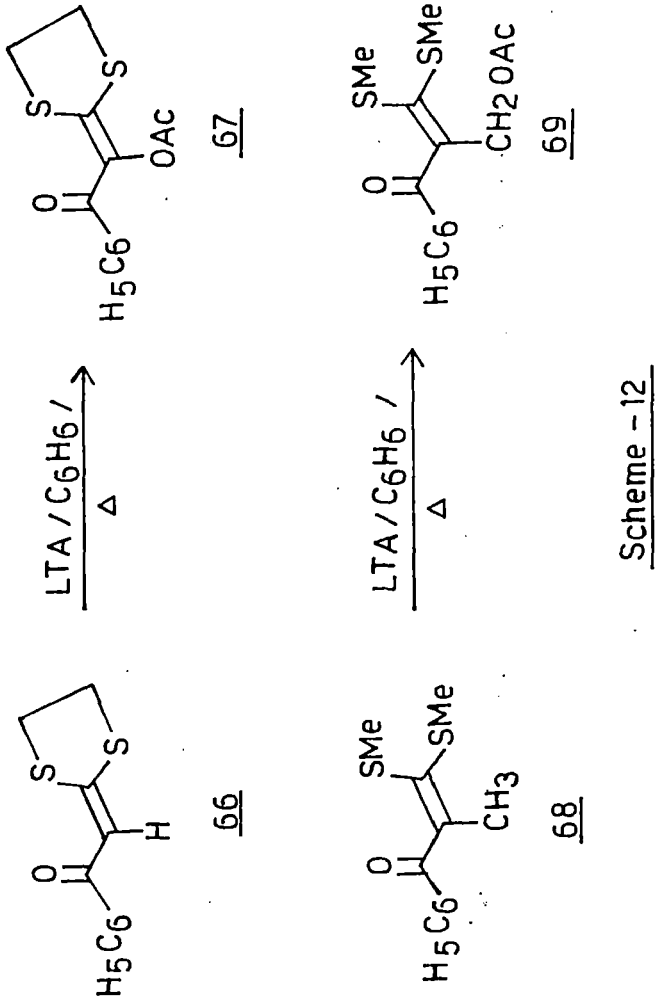
for *p*-methyl protons of two phenyl groups. The doublet appeared at δ7.23 (4H, J=8.5Hz) was attributed to the phenyl protons. Similarly the other doublet at 7.76 (4H, J=8.5Hz) was attributed to other phenyl protons. Similarly the dithioacetal **62b-d** afforded the corresponding acetates **63b-d** in 53-59% overall yields along with corresponding dimers **64b-d** in 28-30% overall yields. All these compounds were characterized by their analytical and spectral data (experimental section). The structure of dimer was also further confirmed by ^{13}C NMR spectrum of **64b** the peak corresponding to the monomer confirmed its symmetrical structure. The chemical shift values of **64b** are listed in the experimental section.

The utility of acetoxy acetal **63** was demonstrated by their facile hydrolysis to the corresponding diketone acetals **65** (scheme 11). Thus when **63a** on treatment with aqueous ethanolic potassium hydroxide, the reaction mixture after work-up, yielded the corresponding diketone acetal **65a** in 90% yield. The structure of 3,3-bis(methylthio)-1-(4'-mehtylphenyl)propan-1,2-dione **65a** was established on the basis of its spectral and analytical data. It was analysed for $C_{12}H_{14}O_2S_2$ and its mass spectrum exhibited peaks at m/z 119 (64%) and 109 (32). The IR (KBr) spectrum showed strong bands at 1700 and 1660 cm^{-1} for two carbonyl groups. The structure was further confirmed by its ^1H NMR ($CDCl_3$) spectrum. The SMe signal appeared as a singlet at δ2.19 (6H) and the singlet at δ2.48 (3H) was attributed to *p*-methyl protons of phenyl group. The proton on bismethylthio carbon

i.e. $-CH(SMe)_2$ appeared as singlet at δ5.47(1H). The characteristic pattern of *p*-substituted phenyl protons appeared as two doublets one at δ7.43(2H, J=9Hz) and other at δ8.09 (2H, J=9Hz). Similarly the α-acetoxy dithioacetals 63b-c underwent hydrolytic cleavage to afford the corresponding diketone acetals 65b-c in 90-94% overall yields. Analytical and spectral data of 65b-c were in accordance with the assigned structures which are described in experimental section. However, 63d under similar hydrolytic conditions with aqueous ethanolic potassium hydroxide did not yield the corresponding diketones instead resulting in complex product mixture.

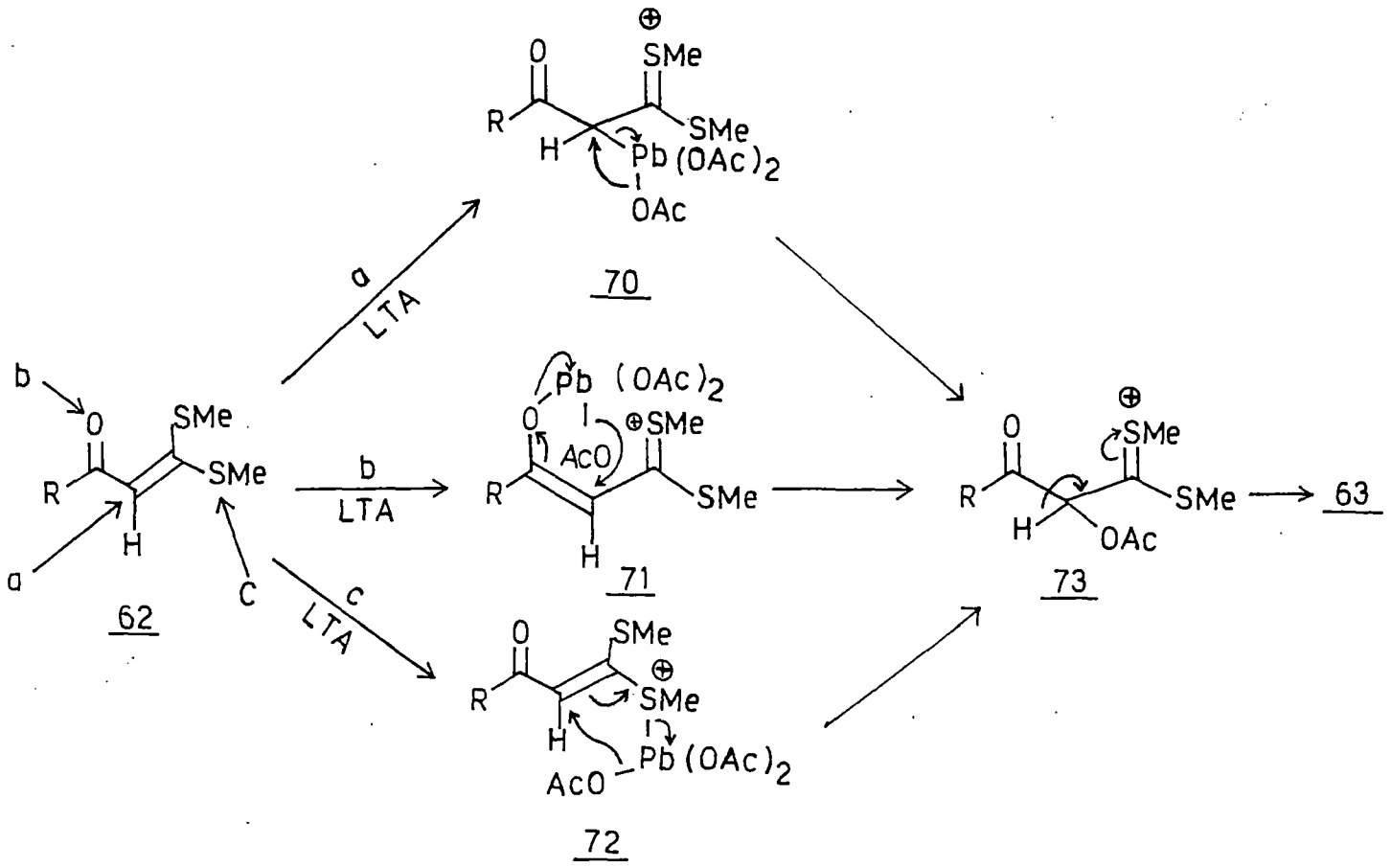
Interestingly, the cyclic dithioacetal 66 underwent LTA oxidation to give exclusively 2-acetoxy-1-phenyl-2-(1,3-thiolan-2-ylidine)ethanone 67 in 62% yield (scheme 12) and it is expected that the corresponding dimer could not have been obtained because of steric reasons. Similarly the α-methyl α-oxoketene dithioacetal 68 was oxidised under the described reaction conditions, when the 2-acetoxymethylene-3,3-bis(methylthio)-1-phenyl-2-propen-1-one 69 was obtained 68% yield (scheme 12). The structures of 67 and 69 were established on the basis of their spectral and analytical data which are described in the experimental section.

The mechanism of acetoxy acetal formation during LTA oxidation of α-oxoketene dithioacetals 62 is depicted in scheme 13. There are many plausible pathways to explain the formation of 63. Path `a' is sulfur assisted C-plubylation

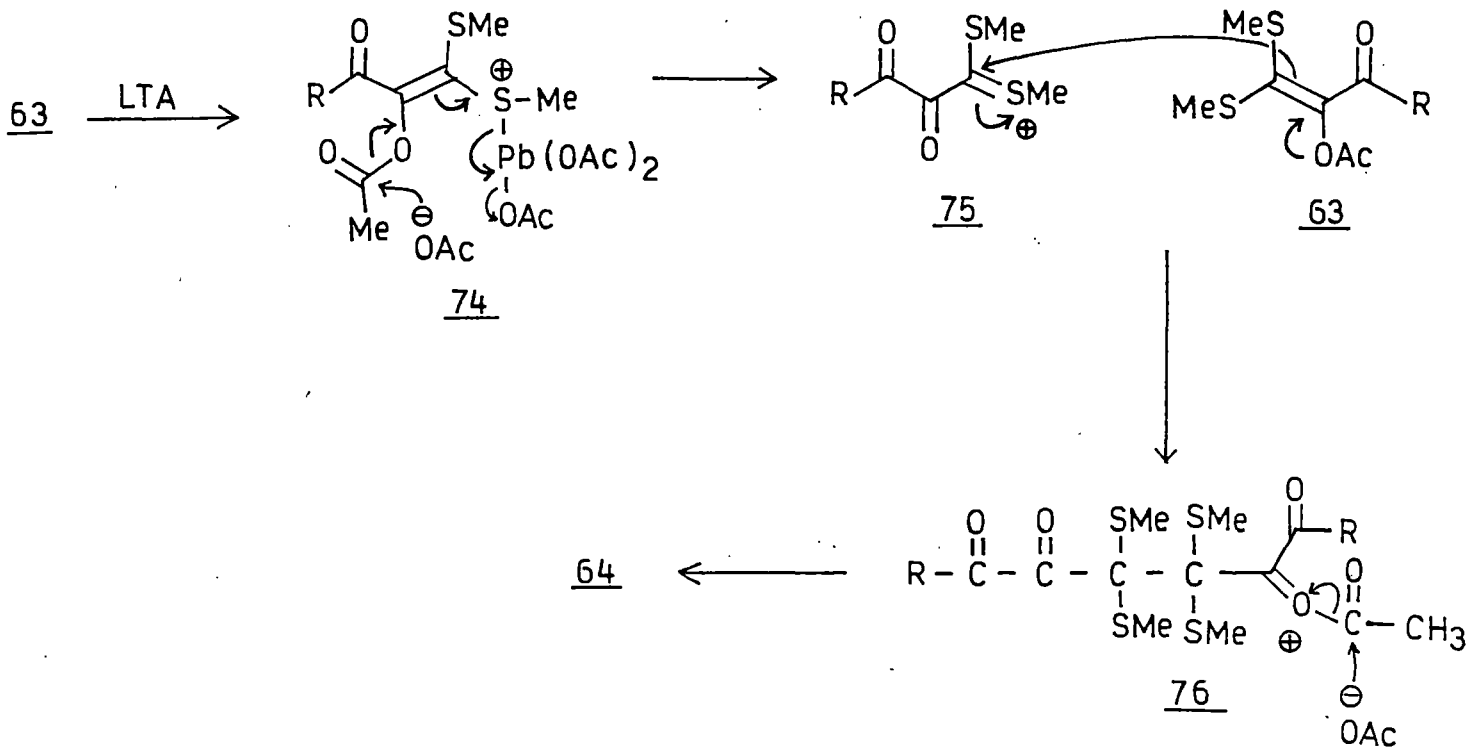


66 67 68 69

Scheme - 12



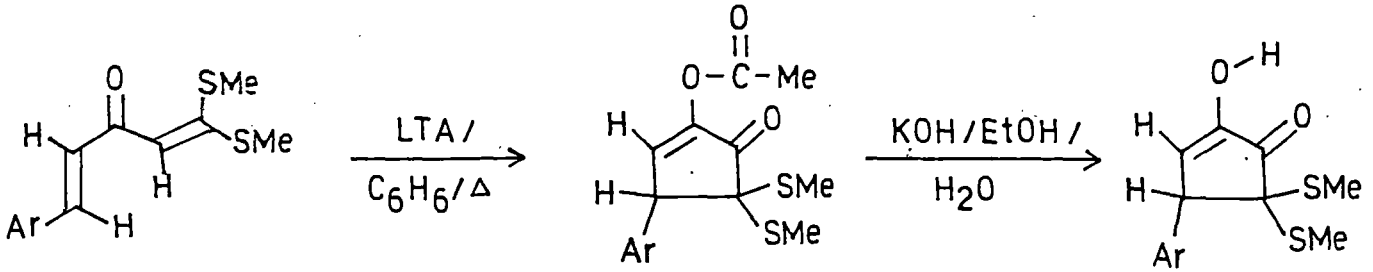
Scheme – 13



Scheme - 14

followed by its cleavage and loss of a proton to afford 63. Similarly 63 could be obtained through O-plumbylated intermediate 71. The third possibility involves the sulphur LTA complex 72 that proceed to 63 *via* 73 (scheme 13). Yet in the final product divalent sulfur has remained unaffected during the overall oxidation process. The formation of dimer 64 has been depicted in scheme 14. The sulfur LTA complex 74 which is formed after the first α-acetoxylation appears to undergo acetoxy cleavage to give an activated diketone 75 which in turn is attacked by 63 leading to the corresponding dimer 64 through 76.

The α-cinnamoylketene dithioacetals 77 were next examined for LTA oxidation with a view to observe the chemoselectivity of LTA between the two double bonds. Interestingly, when 77a was oxidised under the described reaction conditions, the corresponding 2-acetoxy-5,5-bis(methylthio)-4-phenyl-2-cyclo penten-1-one 78a was formed in 74% yield (scheme 15). The structure of 78a was supported by its elemental composition and spectral properties. The structure of 78a was confirmed by its analytical and spectral data. It was analysed for $C_{15}H_{16}O_3S_2$ and molecular weight was confirmed from its mass spectrum with a molecular ion peak at m/z 308 (M^+,44%). The acetoxy cyclopentenone 78a displayed characteristic enolacetate carbonyl frequency at 1770 cm^{-1} in addition to a strong band at 1710 cm^{-1} due to ring carbonyl group. The ^1H NMR ($CDCl_3$; 250MHz) spectrum of 78a showed three singlets each at δ1.80 (3H), δ2.15 (3H) and δ2.30 (3H) for protons of



77a-e 78a-e 79a,b

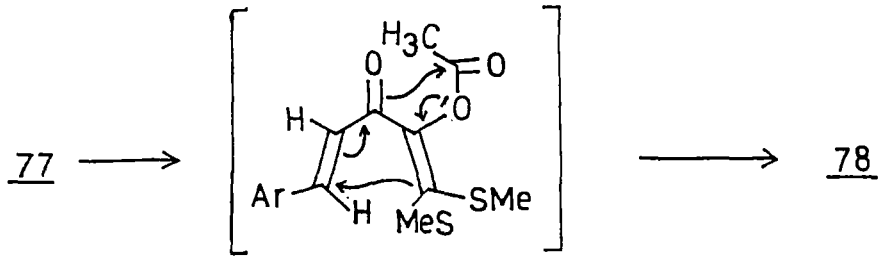
77-79a, Ar = C_6H_5

b, Ar = 4-Cl C_6H_4

77-78c, Ar = 4-MeO C_6H_4

d, Ar = 3,4-$(MeO)_2$ C_6H_3

e, Ar = 3,4-Methylene dioxy C_6H_3



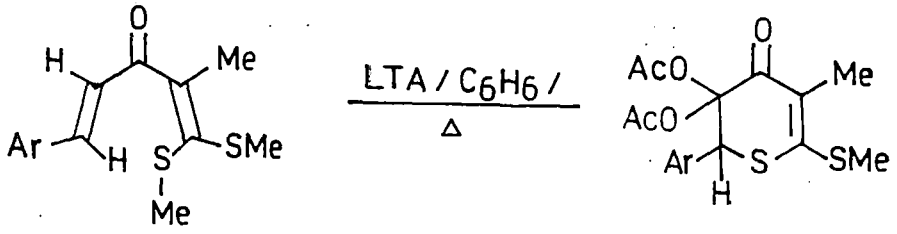
80

Scheme -15

two methylthio and one acetoxy group. The benzylic methyn proton appeared as doublet at δ4.35 (1H, J=3.5Hz), while the signal due to olefinic proton appeared at δ7.20 (1H,J=3.5Hz), partially merged with a broad singlet of phenyl protons at δ7.30 (5H). The structure of **78a** was further confirmed from its ^{13}C NMR spectrum which was in accordance with its assigned structure. The chemical shift values are described in the experimental section. The compound **78a** underwent mild hydrolytic cleavage to afford 5,5-bis(methythio)-2-hydroxy-4-phenyl-2-cyclopenten -1-one **79a** a in 70% yield (scheme 15). The structure of **79a** was established by its analytical and spectral data which are described in the experimental section. Similarly the other cinnamoylketene dithioacetals **77b-e** afforded the corresponding cyclopentene derivatives **78b-e** in 61-78% overall yields. The compound **78b** on hydrolysis gave the corresponding diketone **79b** in 71% yield as described above. The structures of **78b-e** and **79b** were in accordance with their analytical and spectral data which are described in the experimental section. The mechanism governing these transformations involves the formation of dithioacetoxy intermedate **80** through chemoselective acetoxylation of mercapto double bond in preference to the other double bond. Such a selectivity also proves the possible sulfur assisted C-plumbylation leading to the observed acetoxylation of the product. The product further undergoes intramolecular cylcization followed by 1,2- O-alkyl group migration to yield **78**. The overall transformation represents a novel oxidative Nazerov type cyclization which

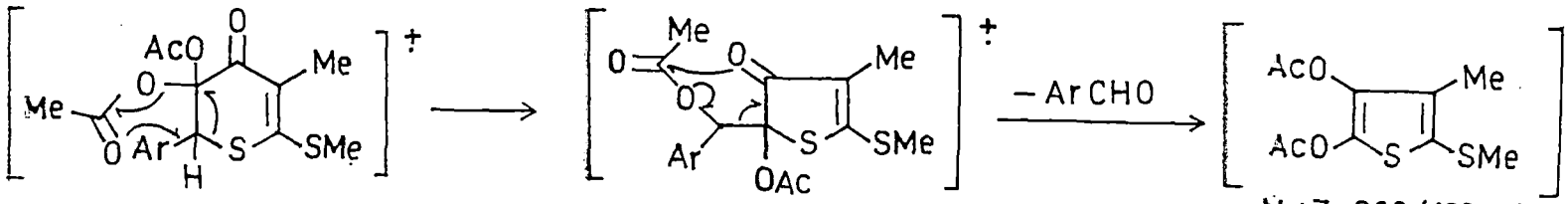
opens a new entry for the synthesis of cylcopentan-1,2-diones.

Interestingly, when acetoxylation point in mercapto double bond was blocked by methyl group the course of LTA oxidation took a different path. When α-methyl α-cinnamoylketene dithioacetal 81 was oxidised with LTA under reported reaction conditions the product isolated in 68% was characterized as 3,3-bis(acetoxy)-2-(4'-methoxyphenyl)-5-methyl-6-(methylthio)-2,3-dihydrothiopyran-4-one 82 (scheme 16) on the basis of its analytical and spectral data. It was analysed for $C_{18}H_{20}O_6S_2$ and its molecular weight was confirmed from its mass spectrum with a peak at m/z 396 (M^+, 12%). The compound 82 exhibited strong absorption bands in its IR (KBr) spectrum at 1747 and 1666 cm^{-1} due to acetoxy carbony and ring carbonyl group respectively. In the ^1H NMR ($CDCl_3$; 250 MHz) spectrum the methylthio protons appeared as singlet at δ1.71 (3H) and the methyl protons appeared as singlet at δ1.91 (3H). The acetate protons appeared as two singlets, one at δ2.01(3H) and the other at δ2.58 (3H). The singlet at δ3.88 (3H), was assigned to *p*-methoxy protons of phenyl group. The benzylic proton appeared as a clean singlet at δ6.26 (1H). The aromatic protons of *p*-methoxyphenyl group appeared as two doublets one at δ6.95 (2H, J=9Hz) and the other at δ7.55 (2H, J=9Hz). The structure of 82 was also confirmed from ^{13}C NMR spectrum. The values which are in confirmity with 82 and are listed in experimental section. The mass fragmentation pattern of 82 was interesting. The base peak at m/z 260 (100%) was assigned to the fragment 85. The molecular ion 83



81 82

Ar = 4-MeO C_6H_4

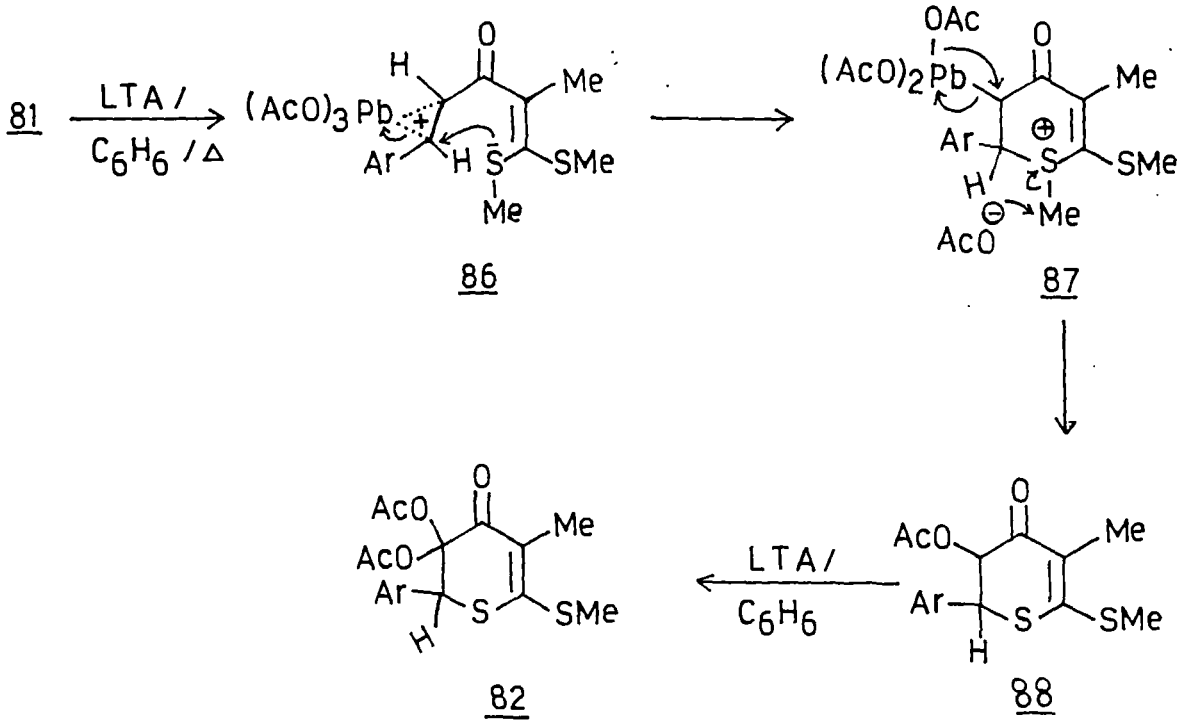


M/Z 396 (M^+, 12%) 84 M/Z 260 (100%)

83 85

Ar = 4-MeO C_6H_4

Scheme - 16


81
LTA /
C6H6 /Δ
(AcO)3Pb
H
O
Me
Ar
H
S
SMe
Me
86
OAc
(AcO)2Pb
O
Me
Ar
S
SMe
H
Me
AcO
87
AcO
AcO
Ar
H
S
SMe
Me
82
LTA /
C6H6
AcO
Ar
H
S
SMe
Me
88

Scheme - 17

under electron impact underwent rearrangement followed by loss of *p*-methoxybenzaldehyde to give the fragment 85. Hydrolysis of 82 under mild alkaline conditions gave only a complex reaction product from which only *p*-methoxybenzaldehyde could be isolated. Inevitably the styryl double bond underwent characteristic attack by LTA since the mercapto double bond was blocked at α-position to give the adduct 86 through intramolecular attack by sulfur. The 86 on subsequent cleavage and demethylation gave the intermediate 88 which underwent further acetoxylation to give 82 (scheme 17).

II.3 CONCLUSION

The α-oxoketene dithioacetal have been shown to undergo LTA oxidation to give α-acetoxy compounds retaining the divalent oxidation state of sulfur. The acetoxy group has been shown to undergo mild hydrolytic cleavage leading to more functionally important diketone acetals. In the case of cyclic acetal the formation of diketone is more useful since it is the only product formed. However, in the case of open-chain acetals the formation of dimers appears distinctly although in low yields. The reaction remains chemoselective when the cinnamoylketene dithioacetals were oxidised under similar reaction conditions. Interestingly when α-methyl group was present in the cinnamoylketene dithioacetal, LTA reacted with styryl double bond selectively to afford different products.

II.4 EXPERIMENTAL

Melting points were determined on a 'Thomas Hoover' capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectro photometer. The ^{1}H NMR spectra were obtained on a Varian EM-390 (90 MHz) and Bruker (250MHz) spectrometer, while ^{13}C NMR spectra were recorded on a Brucker WM-400 spectrometer. Chemical shifts are expressed in δ(ppm) units downfield from TMS mass spectra were obtained on a Jeol JMS D-300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyzer.

Starting Materials

The ketones used for the preparation of α-oxoketene dithioacetals were commercially available and used as supplied without purification. Aromatic aldehydes used for the preparation of cinnamoyl ketene dithioacetals were purified prior to their use. Lead tetraacetate was prepared by the reported procedure and was dried free of acetic acid prior to use. Benzene was purified according to Vogel's procedure and dried over sodium wire.

General Method for the Preparation of α-Oxoketene Dithioacetals

A mixture of ketone (0.2 mol) and caron disulphide (0.2 mol) was added dropwise to an ice-cold and well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (200 ml) and

the reaction mixture was allowed to stirr at room temperature for 5-6 hrs. Acid free dimethyl sulphate (0.2 mol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stirr at room temperature for 6-10 hrs. The reaction mixture was poured over ammonium chloride solution (250 ml) and the layers were seperated. The aqueous layer was extracted with benzene (100 ml) and combined benzene extracts were washed with water (4x250 ml), dried (Na_2SO_4) and evaporated. Trituration of the oily residue with hexane gave the dithioacetals as yellow crystalline solid in good yields. Liquid dithioacetals were purified by passing through silica gel column using hexane/ethylacetate as eluent. The physical and spectral data were compared with that of reported values.

Condensation of α-Acylketene Dithioacetals with Aldehydes : General Procedure for the Preparation of Cinnamoylketene Dithioacetals

To a cooled and stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (0.06 mol) in ethanol (30 ml), a solution of the α-acylketene dithioacetal (0.03 mol) and the aldehyde (0.03 mol) in minimum ethanol was added dropwise over a period of 5 minutes. The reaction mixture was brought to room temperature over a period of 20 minutes and further stirred at room temperature for 4-5 hrs. The mixture was diluted with cold water (100 ml) and dried. Analytical and spectral data were compared with that of reported values.

General Procedure for LTA Oxidation of α-Oxoketene Dithioacetals 62a-d, 66, 68, 77a-e and 81 .

To a solution of oxoketene dithioacetal (10 mmol) in dry benzene (50 ml) LTA (8.80g, 20 mmol) was added and the suspension was heated (60-70°C) with stirring for 18-28 hr (monitored by TLC). The reaction mixture was cooled and the precipitated Lead(II) acetate was removed by filtration. The filtrate was treated with a few drops of ethylene glycol to decompose traces of lead(IV) acetate, washed with water (3x100 ml), dried (Na_2SO_4) and evaporated on water bath. The viscous brown residues thus obtained were purified by column chromatography over silica-gel using EtOAc/hexane (1:20) as eluent to give first dimeric diketones **64** followed by α-acetoxy dithioacetals 63.

2-Acetoxy-3,3-bis(methylthio)-1-(4-methylphenyl)-2-propen-1-one (63a). Yellow viscous liquid ; yield 56% ; IR (neat) 1761, 1650cm^{-1} ; δ_H ($CDCl_3$) 2.19 (3H, s, SCH_3); 2.24 (3H, s, SCH_3); 2.43 (6H, brs, CH_3 and CH_3CO_2); 7.27 (2H, d, J = 9Hz, ArH); 7.90 (2H, d, J = 9Hz, ArH); m/z 296 (M^+, 5%); 253 (7) : 119 (100) (Anal. Calcd. for $C_{14}H_{16}O_3S_2$: C, 56.73 ; H, 5.44. Found : C, 56.96 ; H, 5.62%).

2-Acetoxy-3,3-bis(methylthio)-1-(4-chlorophenyl)-2-propen-1-one (63b). Yellow viscous liquid ; yield 55% ; IR (neat) 1761, 1659cm^{-1} ; δ_H (CCl_4) 2.10 (3H, s, SCH_3) 2.19 (3H, s, SCH_3); 2.31 (3H, s, CH_3CO_2); 7.49 (2H, d, J = 9Hz, ArH); 7.83 (2H, d, J = 9Hz, ArH); m/z 316 (M^+, 2%); 274 (24): 276 (10),

74

107 (100). (Anal.Calcd. for $C_{13}H_{13}ClO_3S_2$: C, 49.28 ; H, 4.14. Found : C, 49.42 ; H, 4.40%).

2-Acetoxy-3,3-bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one (63c). Pale yellow crystals ($CHCl_3$/hexane); yield 59% ; m.p. 68-69°C ; IR (KBr) 1772, 1645, 1600cm^{-1} ; δ_H ($CDCl_3$) 2.08 (3H, s, SCH_3); 2.10 (3H, s, SCH_3); 2.31 (3H, s, CH_3CO_2); 3.76 (3H, s, OCH_3); 6.84 (2H, d, J = 9Hz, ArH); 7.85 (2H, d, J = 9Hz, ArH); m/z 312 (M^+, 2%); 270 (20); 135 (100). (Anal. Calcd. for $C_{14}H_{16}O_4S_2$: C, 53.82 ; H, 5.16. Found : C, 54.03 ; H, 5.01%).

2-Acetoxy-1,1-bis(methylthio)-1-buten-3-one (63d). Yellow viscous liquid ; yield 53% ; IR (neat) 1769, 1689 cm^{-1}; δ_H (CCl_4) 2.17 (3H, s, SCH_3); 2.28 (3H, s, SCH_3); 2.35 (3H, s, $COCH_3$); 2.40 (3H, s, CH_3CO_2); m/z 178 (M^+-42, 12%). (Anal. Calcd. for $C_8H_{12}O_3S_2$: C, 43.61 ; H, 5.49. Found : C, 43.88 ; H, 5.72%).

1,6-Di(4-methylphenyl)-3,3,4,4-tetra(methylthio)hexan-1,2,5,6-tetraone (64a). Yellow viscous semisolid ; yield 25% ; IR (neat) 1691, 1665, 1600cm^{-1}; δ_H (CCl_4) 2.10 (12H, s, SCH_3); 2.39 (6H, s, CH_3); 7.23 (4H, d, J = 8.5Hz, ArH); 7.76 (4H, d, J = 8.5 Hz, ArH); m/z No M^+; 153 (65%): 107 (19); 119(100). (Anal. Calcd. for $C_{24}H_{26}O_4S_4$: C, 56.88 ; H, 5.17. Found : C, 57.11 ; H, 5.36%).

1,6-Di(4-Chlorophenyl)-3,3,4-tetra(methylthio)hexan-1,2,5,6-tetraone (64b). Yellow crystals ($CHCl_3$/hexane); yield 30% ; m.p. 94-95°C ; IR (KBr) 1690, 1680 cm^{-1}; δ_H ($CDCl_3$) 2.16

(12H, s, SCH_3); 7.41 (4H, d, J = 8.5Hz, ArH); 7.82 (4H, d, J = 8.5Hz, ArH); δ_C ($CDCl_3$) 13.66 (SCH_3); 73.95 [$C(SCH_3)_2$]; 129.00, 130.08 (CH, Ar); 132.01, 141.19 (C-1', C-4', Ar); 190.53(CO); 192.17 (CO); m/z 273 ($M^+/2$,2%); 153 (100); 155(13). (Anal. Calcd. for $C_{22}H_{20}Cl_2O_4S_4$: C, 48.25 ; H, 3.68. Found : C, 48.52 ; H, 3.85%).

1,6-Di(4-methoxyphenyl)-3,3,4,4-tetra(methylthio)hexan-1,2,5,6-tetraone (64c). Yellow crystals ($CHCl_3$/hexane); yield 28% ; m.p. 89-90°C ; IR (KBr) 1690, 1660 cm^{-1}; δ_H ($CDCl_3$) 2.23 (12H, s, SCH_3); 3.96 (6H, s, OCH_3); 7.08 (4H, d, J = 9Hz, ArH); 7.98 (4H, d, J = 9Hz, ArH); m/z No M^+; 153 (0%); 135 (100). (Anal. Calcd. for $C_{24}H_{26}O_6S_4$: C, 53.51 ; H, 4.87. Found : C, 53.78 ; H, 5.13%).

4,4,5,5-Tetra(methylthio)-octan-2,3,6,7-tetraone (64d). Yellow viscous liquid ; yield 28% ; IR (neat) 1711, 1690, 1563 cm^{-1}; δ_H (CCl_4) 2.08 (12H, s, SCH_3); 2.46 (6H, s, CH_3); m/z 177 ($^+/2$, 4%); 153 (100). (Anal. Calcd. for $C_{12}H_{18}O_4S_4$: C, 40.65 ; H, 5.12. Found : C, 40.44 ; H, 4.98%).

2-Acetoxy-1-phenyl-2-(1,3-thiolan-2-ylidine)ethanone (67). pale yellow crystals ($CHCl_3$/hexane); yield 62% ; m.p. 88-89°C ; IR (KBr) 1768, 1630, 1500 cm^{-1}; δ_H ($CDCl_3$) 2.02 (3H, s, CH_3CO_2); 3.39 (4H, brs, CH_2); 7.41-7.62 (3H, m, ArH); 7.72-7.93 (2H, m, ArH); m/z 280 (M^+, 3%); 238 (78); 105 (100). (Anal. Calcd. for $C_{13}H_{12}O_3S_2$: C, 55.69 ; H, 4.32. Found : C, 55.77 ; H, 4.53%).

2-Acetoxymethylene-3,3-bis(methylthio)-1-phenyl-2-propen-1-one (69) was obtained by LTA oxidation of 6 under similar conditions. Yellow crystals ($CHCl_3$/hexane); yield 68% ; m.p. 83-84°C ; IR (KBr) 1742, 1698, 1596 cm^{-1}; δ_H (CCl_4)2.12 (6H, s, SCH_3); 2.20 (3H, s, CH_3CO_2); 5.50 (2H, s, CH_2); 7.48-7.71 (3H, m, ArH); 7.89-8.10 (2H, m, ArH). (Anal. Calcd. for $C_{14}H_{16}O_3S_2$: C, 56.73 ; H, 5.44. Found : C, 56.98 ; H, 5.41%).

General Procedure for Alkaline Hydrolysis of 63a-c and 78a-b.

A solution of α-acetoxydithioacetals (63a-d) or 2-acetoxy cyclopentenones (78a-b) (2.5 mmol) in 10 ml of aqueous ethanolic (1:1) KOH (10%) was stirred at 45-50°C for 10-12 hr (monitored by TLC). The reaction mixture was cooled, poured over crushed ice, neutralized with AcOH and extracted with chloroform (2x30 ml). The organic layer was washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give crude products which were further purified by passing through a short length silica gel column using EtOAc/hexane (1:15) as eluent.

3,3-Bis(methylthio)-1-(4-methylphenyl)propan-1,2-dione (65a). Yellow crystals ($CHCl_3$/hexane);yield 90% ; m.p. 116-117°C ; IR(KBr) 1700, 1660, 1600 cm^{-1}; δ_H ($CDCl_3$) 2.19 (6H, s, SCH_3); 2.48 (3H, s, CH_3); 5.47 [1H, s, $HC(SCH_3)_2$]; 7.43 (2H, d, J = 9Hz, ArH); 8.09 (2H, d, J = 9Hz, ArH); δ_C($CDCl_3$) 12.10 (SCH_3); 21.90 (CH_3); 55.72 [$HC(SCH_3)_2$]; 129.57 (CH, Ar); 130.11 (CH, Ar); 130.34, 146.08 (C-1', C-4', Ar); 187.08 (CO); 190.82 (CO); m/z No M^+; 119(64%); 109 (132). (Anal.

Calcd. for $C_{12}H_{14}O_2S_2$: C, 56.66 ; H, 5.55. Found : C, 56.51 ; H, 5.54%).

3,3-Bis(methylthio)-1-(4-chlorophenyl)-propan-1,2-dione (65b). Yellow crystals ($CHCl_3$/hexane): yield 93% ; m.p. 78-79°C ; IR(KBr) 1700, 1670, 1600 cm^{-1}; δ_H ($CDCl_3$) 2.14 (6H, s, SCH_3); 5.40 [1H, s, $CH(SCH_3)_2$]; 7.51 (2H, d, J = 9Hz, ArH); 8.08 (2H, d, J = 9Hz, ArH). (Anal. Calcd. for $C_{11}H_{11}ClO_2S_2$]; 7.51 (2H, d, J = 9Hz, ArH); 8.08 (2H, d, J = 9Hz, ArH). (Anal. Calcd. for $C_{11}H_{11}ClO_2S_2$: C, 48.08 ; H, 4.04. Found : 47.97 ; H, 4.09%).

3,3-Bis(methylthio)-1-(4-methoxyphenyl)propan-1,2-dione (65c). Yellow crystals ($CHCl_3$/hexane); yield 90%; m.p. 58-59°C ; IR (KBr) 1708, 1661, 1605 cm^{-1}; δ_H ($CDCl_3$) 2.10 (6H, s, SCH_3); 3.84 (3H, s, OCH_3); 5.33 [1H, s, $CH(SCH_3)_2$]; 6.90 (2H, d, J = 9Hz, ArH); 8.00 (2H, d, J = 9Hz, ArH); δ_C ($CDCl_3$) 11.88 (SCH_3); 55.29 [$CH(SCH_3)_2$]; 55.47 (OCH_3); 113.91, 132.22 (CH, Ar); 125.60, 164.63 (C-1', C-4', Ar); 187.3 (CO); 190.1 (CO). (Anal. Calcd. for $C_{12}H_{14}O_3S_2$: C, 53.31 ; H, 5.22. Found : C, 53.50 ; H, 5.09%).

2-Acetoxy-5,5-bis(methylthio)-4-phenyl-2-cyclopenten-1-one (78a). Colourless crystals ($CHCl_3$/hexane): yield 74%; m.p. 94-95°C ; IR (KBr) 1770, 1710, 1630 cm^{-1}; ^1H NMR described in text. δ_C ($CDCl_3$) 12.22 (SCH_3); 13.20 (SCH_3); 20.83 (CH_3CO_2); 54.72 (C-4); 62.21 (C-5); 128.14, 128.32, 129.92 (CH, Ar); 135.71 (C-1', Ar)141.61 (=CH); 146.35 (C-2); 167.44 (CH_3CO_2); 192.85 (CO); m/z 308 (M^+, 44%); 266 (29); 218 (55). (Anal.

Calcd. for $C_{15}H_{16}O_3S_2$: C, 58.41 ; H, 5.23. Found : C, 58.48 ; H, 5.29%).

2-Acetoxy-5,5-bis(methylthio)-4-(4'-chlorophenyl)-2-cyclo penten-1-one (78b). Colourless crystals ($CHCl_3$/hexane); yield 78%; m.p. 113-114°C ; IR (KBr) 1756, 1710 cm^{-1}; $\delta_H(CDCl_3)$ 1.91 (3H, s, SCH_3); 2.18 (3H, s, SCH_3); 2.33 (3H, s, CH_3CO_2), 4.31 (1H, d, J = 3.5Hz, H-4); 7.17-7.44 (5H, m, ArH, =CH); $\delta_C(CDCl_3)$ 12.80 (SCH_3); 13.88 (SCH_3); 20.48 (CH_3); 53.83 (C-4); 61.71 (C-5); 128.87, 130.93 (CH, Ar); 134.84 (C-1', Ar); 140.65 (=CH); 146.33 (C-2); 167.89 (CH_3CO_2); 192.20 (CO); m/z 342 (M^+, 46%); 300 (42). (Anal. Calcd. for $C_{15}H_{15}ClO_3S_2$: C, 52.55 ; H, 4.41. Found : C, 52.78 ; H, 4.56%).

2-Acetoxy-5,5-bis(methylthio)-4-(4'-methoxyphenyl)-2-cyclo penten-1-one (78c). Yellow viscous liquid ; yield 69% ; IR (neat) 1776, 1720 cm^{-1}; δ_H ($CDCl_3$) 1.94 (3H, s, SCH_3); 2.20 (3H, s, SCH_3); 2.33 (3H, s, CH_3CO_2); 3.83 (3H, s, OCH_3); 4.35 (1H, d, J = 3.5Hz, H-4); 6.92 (2H, d, J = 9Hz, ArH); 7.24 (2H, d, J = 9Hz, ArH); 7.29 (1H, d, J = 3.5Hz, =CH); m/z 338 (M^+, 44%); 296 (35); 200 (20). (Anal. Calcd. for $C_{16}H_{18}O_4S_2$: C, 56.78 ; H, 5.36. Found : C, 56.61 ; H, 5.22%).

2-Acetoxy-5,5-bis(methylthio)-4-(3,4-dimethoxyphenyl)-2-cyclopenten-1-one (78d). Yellow viscous liquid ; yield 65% ; IR(neat) 1775, 1725 cm^{-1}; $\delta_H(CDCl_3)$ 1.90 (3H, s, SCH_3); 2.14 (3H, s, SCH_3); 2.30 (3H, s, CH_3CO_2); 3.87 (6H, brs, OCH_3); 4.30 (1H, d, J = 3.5Hz, H-4); 6.83 (3H, s, ArH), 7.28 (1H, d, J = 3.5Hz, =CH); m/z 368 (M^+, 25%); 326(25); 278(20);

191(100). (Anal. Calcd. for $C_{17}H_{20}O_5S_2$: C, 55.41 ; H, 5.47. Found : C, 55.69 ; H, 5.23%).

2-Acetoxy-5,5-bis(methylthio)-4-(3,4-methylenedioxyphenyl)-2-cyclopenten-1-one (78e). Yellow viscous liquid ; yield 61% ; IR(neat) 1778, 1722 cm^{-1}; $\delta_H(CDCl_3)$ 1.98 (3H, s, SCH_3); 2.17 (3H, s, SCH_3); 2.32 (3H, s, CH_3CO_2); 4.32 (1H, d, J = 3.5Hz, H-4); 5.98 (2H, s, CH_2); 6.83 (3H, brs, ArH); 7.30 (1H, d, J = 3.5Hz, =CH); m/z 352 (M^+, 32%); 310(12); 264(13); 215(16) (Anal. Calcd. for $C_{16}H_{16}O_5S_2$: C, 54.53 ; H, 4.58. Found : C, 54.61 ; H, 4.66%).

5,5-Bis(methylthio)-2-hydroxy-4-phenyl-2-cyclopentene-1-one (79a). Colourless crystals ($CHCl_3$/hexane); yield 70% ; m.p. 65-66°C ; IR (KBr) 3480, 1690, 1630 cm^{-1}; δ_H ($CDCl_3$) 1.90 (3H, s, SCH_3); 2.20(3H, s, SCH_3); 4.36 (1H, d, J = 3.5Hz, H-4); 6.71 (1H, d, J = 3.5Hz, =CH); 6.82 (1H, brs, OH); 7.03-7.48 (5H, m, ArH). (Anal. Calcd. for $C_{13}H_{14}O_2S_2$: C, 58.62 ; H, 5.30. Found : C, 58.89 ; H, 5.18%).

5,5-Bis(methylthio)-2-hydroxy-4-(4'-chlorophenyl-2-cyclo pentene-1-one (79b). Colurless crystals ($CHCl_3$/hexane); yield 71% ; m.p. 72-73°C ; IR (KBr) 3330, 1691, 1650, 1613 cm^{-1}; δ_H ($CDCl_3$) 1.91 (3H, s, SCH_3); 2.17 (3H, s, SCH_3); 4.30 (1H, d, J = 3.5Hz, H-4); 6.37 (1H, brs, OH); 6.47 (1H, d, J = 3.5Hz, =CH); 7.20-7.48 (4H, m, ArH). (Anal. Calcd. for $C_{13}H_{13}ClO_2S_2$: C, 51.90 ; H, 4.36. Found : C, 52.15 ; H, 4.59%).

3,3-Bis(acetoxy)-2-(4-methoxyphenyl)-5-methyl-6-(methylthio)-2,3-dihydrothiopyran-4-one (82). Colourless crystals

($CHCl_3$/hexane); yield 68% ; m.p. 148-149°C ; IR(KBr) 1747, 1666 cm^{-1}; δ_H ($CDCl_3$) 1.71 (3H, s, SCH_3); 1.91 (3H, s, CH_3); 2.01 (3H, s, CH_3CO_2); 2.58 (3H, s, CH_3CO_2); 3.85 (3H, s, OCH_3); 6.26 (1H, s, ArCH);6.95 (2H, d, J = 9Hz, ArH); 7.55 (2H, d, J = 9 Hz, ArH); δ_C ($CDCl_3$) 10.12 (SCH_3); 14.41 (CH_3); 20.45 (CH_3CO_2); 55.85 (OCH_3); 75.47 (C-2, ArCH); 91.79 (C-3); 113.19, 129.12 (CH, Ar); 122.88 (C-1', Ar); 126.91 (C-5); 159.94 (C-4', Ar); 166.97, 168.33, (CH_3CO_2), 169.44 (C-6), 193.50 (CO) ; m/z 396 (M^+, 12%), 294 (15), 260 (100); 218 (95); 176 (92). (Anal. Calcd. for $C_{18}H_{20}O_6S_2$: C, 54.53 ; H, 5.09. Found : C, 54.20 ; H, 5.29%).

REFERENCES

1. R. Criege, in `Oxidation in Organic Chemistry', K.B. Wilberg Ed., Academic Press, New York, Part A, p.277 (1965).
2. R.N. Butler, in Synthetic Reagents-3, p.277 (1977).
3. G.M. Rubotton, in `Oxidation in Organic Chemistry', W.S. Trahanovsky, Ed., Academic Press, new York, Part D, p.1 (1982)
4. R.S. Atkinson, in `Azides and Nitrenes',E.F.U.Series, Acedemic Press, Orlando, Florida, ch.5 (1984).
5. J.N. Vishwakarma, A. Thomas, S. Apparao, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans I, 169 (1988).
6. A. Thomas, J.N. Vishwakarma, S. Apparao, H. Ila, H. Junjappa, Tetrahedron, *44*, 1667 (1988).
7. B.M. Trost, K. Hiroi, J. Am. Chem. Soc., *97*, 6911 (1975).
8. B.M. Trost, K. Hiroi, J. Am. Chem. Soc., *98*, 4313 (1976).
9. W. Lottenbach, W. Graf, Helv. Chem. Acta, *61*, 3087 (1978).
10. B.M. Trost, Y. Tanigawa, J. Am. Chem. Soc., *101*, 4413 (1979).
11. K. Hiroi, S. Sato, Chemistry Lett., 923 (1979).
12. Laxminarayan Bhat, A. Thomas, H. Ila, H. Junjappa, Tetrahedron, *47*, 305 (1991).

CHAPTER III

A NEW GENERAL METHOD FOR THE SYNTHESIS OF 2-ALKOXY/ARYLOXY THIOPHENES *VIA* SIMMONS-SMITH REACTION ON ACYLKETENE O,S-ACETALS.*

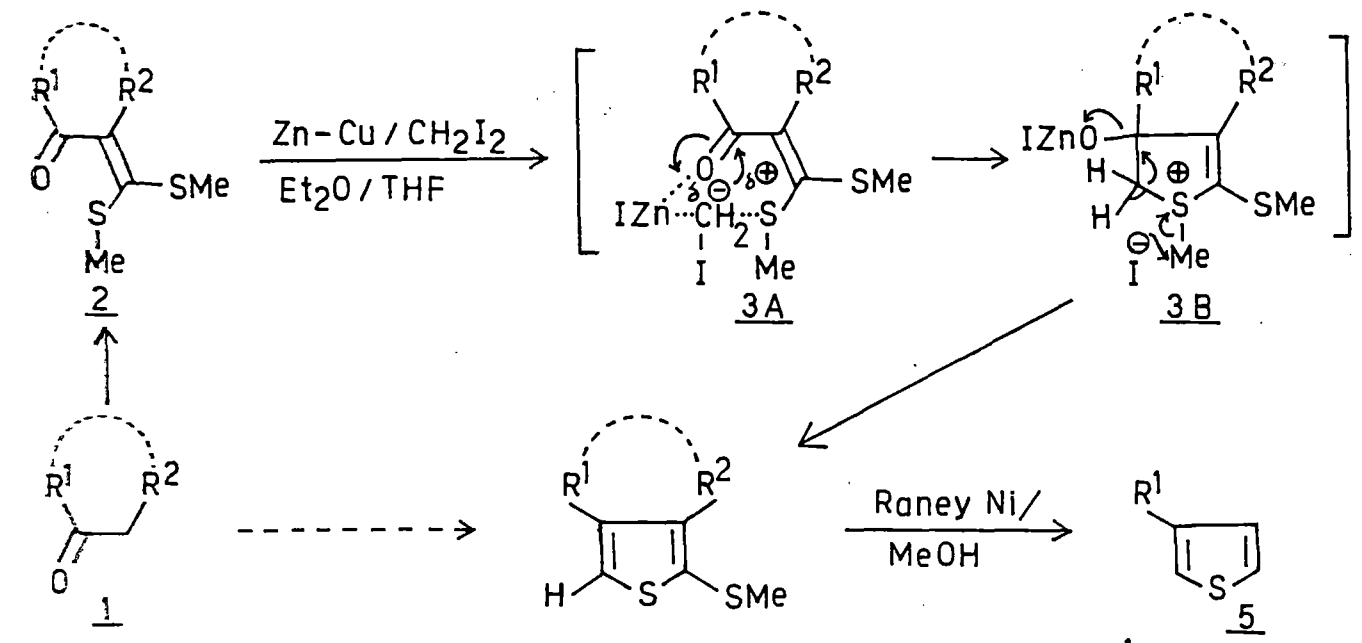
III.1 INTRODUCTION

While attempting cyclopropanation of the α-oxoketene dithioacetals 2 under the Simmons-Smith reaction conditions it was accidentally discovered that the course of reaction led to the development of a new method for the synthesis of corresponding thiophenes 4 in excellent yields[1,2] (scheme 1).

---

* 1. Laxminarayan Bhat, A. Thomas, H. Ila, H. Junjappa Tetrahedron, *48*, 10377 (1992).

2. Laxminarayan Bhat, H. Ila, H. Junjappa Synthesis, 0000 (1993).



1 - 4, R^1 = C_6H_5 ; 4 - Cl C_6H_4; 4 - Me C_6H_4 ;
2 - Furyl ; 2 - Thienyl ; Me ; Et ;

R^1 = H ; Me ; Et ; n - Pr ; n - Bu ;

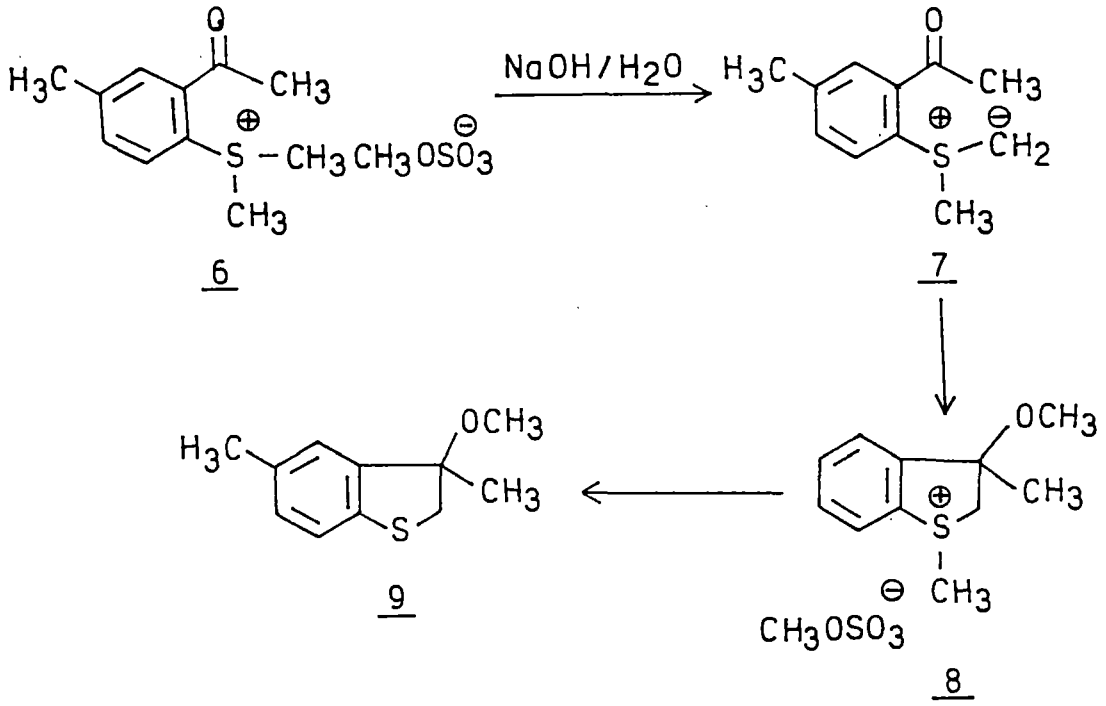
 ; $C_6H_5CH_2$; C_6H_5

a, R^1 = C_6H_5,
b, R^1 = 4 - Me C_6H_4
c, R^1 = 4 - Cl C_6H_4

Scheme - 1

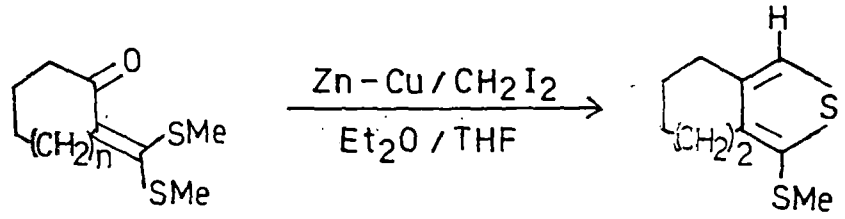
The course of reaction followed the interaction of the divalent sulphur with an electrophilic carbenoid species to give the intermediate ylids 3A which on intramolecular aldol type of addition-elimination sequence followed by demethylation of the quarternary sulphoniun salts 3B yield the product thiophenes 4. The interaction of divalent sulfur with carbenoid species to give the ylid was not very unusual since there were many examples reported in the literature that the divalent sulphur compounds attack the electrophilic carbene species to give the corresponding sulphonium ylids[3]. However, the intermediate ylid participating in an intramolecular aldol type condensation to provide thiophene was not known. The first and the only example reported in the literature[4] is the intramolecular aldol type condensation of the ylid 7 generated from the corresponding dimethyl (*o*-aceto-*p*-tolyl) sulfonium methylsulphonate 6 to give the corresponding sulphonium salt 8 which on demethylation yielded the corresponding dihydrobenzthiophene 9 (scheme 2). This example was reported in 1949 when the sulphur ylids were not discovered.

The new thiophene synthesis discovered in our laboratory by reacting α-oxoketene dithioacetals with Simmons-Smith reagent was a novel and versatile method since it was applicable to a large majority of the structural variants of α-oxoketene dithioacetals which could be derived from various active methylene ketones. In nut-shell, the method is the conversion of active methylene ketones to thiophenes in two

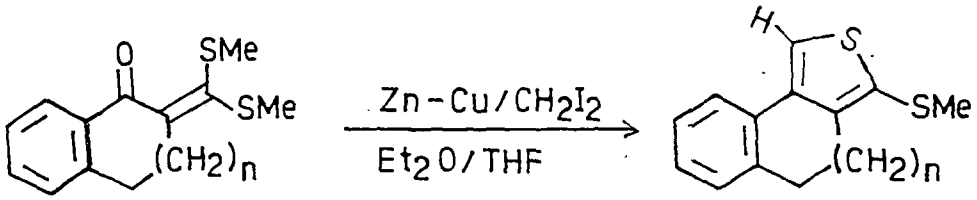


Scheme - 2

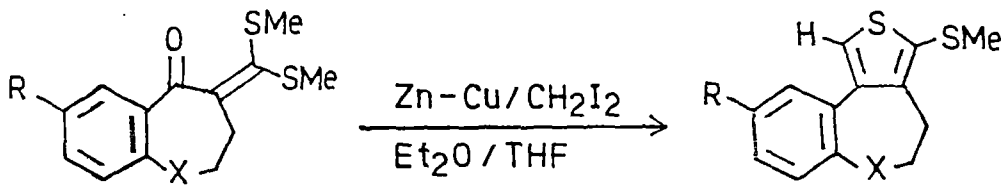
steps *via* corresponding α-oxoketene dithioacetals. The thiophene synthesis using Simmons-Smith reagent was the first of its kind and there were no hitherto reported examples of thiophene synthesis involving Simmons-Smith reaction. The method was of general application which was demonstrated by selecting cyclic oxoketene dithioacetals 10, 12 and 14 (scheme 3) which yielded the corresponding annelated thiophenes 11, 13 and 15 respectively in high yields. The method was also extended to the cinnamoylketene dithioacetals 16 where the corresponding 4-vinylthiophenes 17 were formed in high yields. It was noted that in the presence of divalent sulphur the interaction of double bond with Simmons-Smith reagent was not observed. Also when dienyl and trienyl oxoketene dithioacetals 18 were reacted under Simmons-Smith reaction conditions yielded the corresponding 4-dienyl and trienyl thiophenes 19 in high yields. Here again the extended double bonds remain unaffected by Simmons-Smith reagent. The cyclopropyl oxoketene dithioacetals 20 also underwent smooth condensaton to give the corresponding thiophenes 21 in high yields under similar reaction conditions. It may be noted again that the double bonds insulated by cyclopropane ring [R^1=C_6H_5, C_6H_5-CH=CH, also C_6H_5-$(CH=CH)_2$-] remained unaffected in the overall thiophene synthesis. Therefore, the method was extremely useful for the synthesis of various thiophenes from α-oxoketene dithioacetals with diverse functional groups which were otherwise sensitive to Simmons-Smith reagent in the absence of divalent sulphur group.



10 n = 1, 2, 3, 7 11



12 n = 1, 2 13

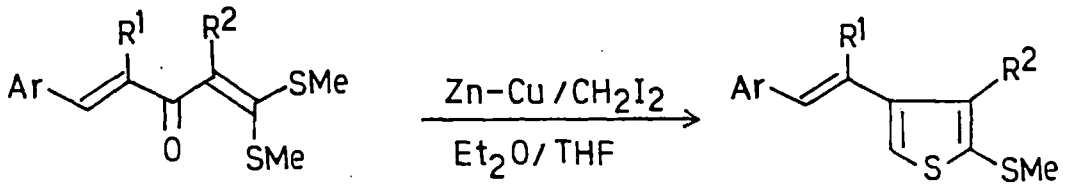


14 15

14-15 a, R = H ; X = O

b, R = Me ; X = S

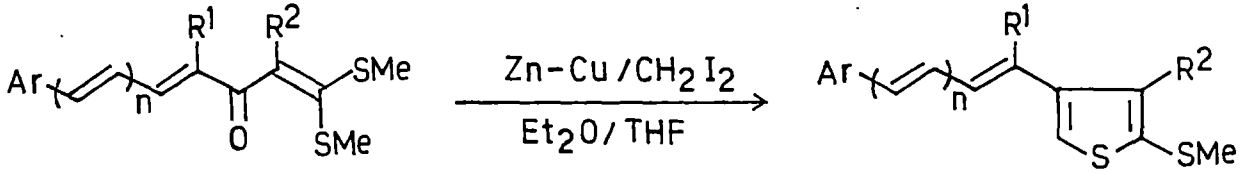
Scheme - 3



16 17

$Ar = C_6H_5$; 4-Cl C_6H_4 ; 2-Cl C_6H_4 ; 4-MeO C_6H_4 ; 3,4-$(MeO)_2$ C_6H_3

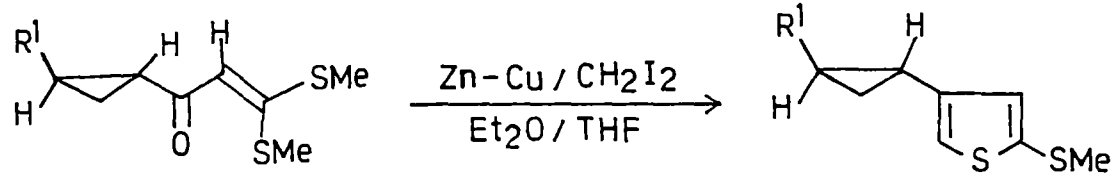
$R^1 = R^2 = H$, Me



18 19

a n = 1 ; Ar = C_6H_5 ; 4-MeO C_6H_4 ; R^1 = H, Me ; R^2 = H, Me, n-Bu

b n = 2 ; Ar = C_6H_5 ; 3,4- Methylene dioxy C_6H_3 ; R^1 = H ; R^2 = H, Me.



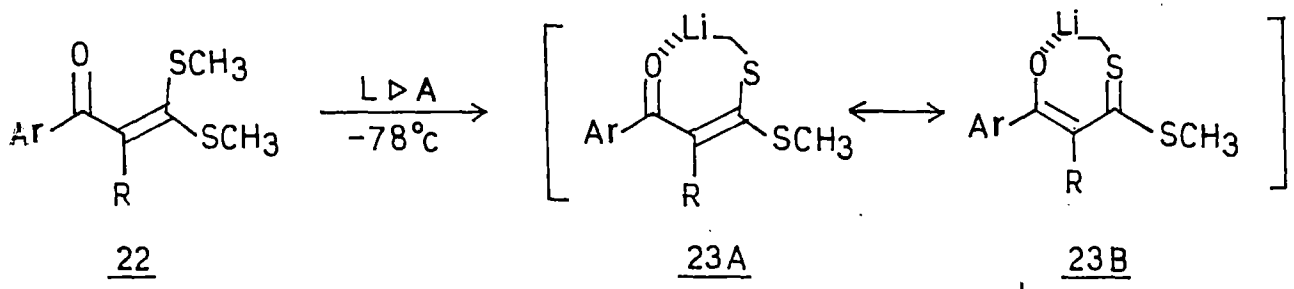
20 21

$R^1 = C_6H_5$; C_6H_5 CH = CH ; C_6H_5-(CH = CH)$_2$-

Scheme-4

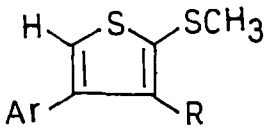
When this reaction was discovered in our laboratory, the α-oxoketene dithioacetals were indeed already used for the synthesis of thiophenes by Marino and Kostusyk[5]. The reaction involved deprotonation of the thiomethyl group *cis* to carbonyl group to give the corresponding sulphur stabilized carbanions 23 which underwent intramolecular cyclization to give thiophenes 24 in moderate yields (scheme 5). However the method suffered serious drawbacks in terms of yields of thiophenes. The overall yields were found to be low except that only in one case 55% of thiophene formation was observed. Also the method failed to give thiophenes when acylketene dithioacetals were used as substrates. The reason for the failure with acylketene dithioacetals was due to their competative deprotonation of the acyl group to form the corresponding enolate anions in preference to methylthio group deprotonation (scheme 6). Thus the method was not suitable for the synthesis of 3-alkyl and 3,4-dialkyl thiophenes. Similarly it is doubtful whether the method could be used for the synthesis of 4-enylthiophenes due to competative deprotonation of vinylic proton. Also the α-position cannot carry the alkyl group which readily gives allyl anion although higher alkyl chains are tolerated to some extent.

The α-oxoketene dithioacetals have been shown to be an alternate precursors for the synthesis of thiophenes which carry methylthio group at 2- or 5- position. The attempted selective desulphurization of methylthio group in the



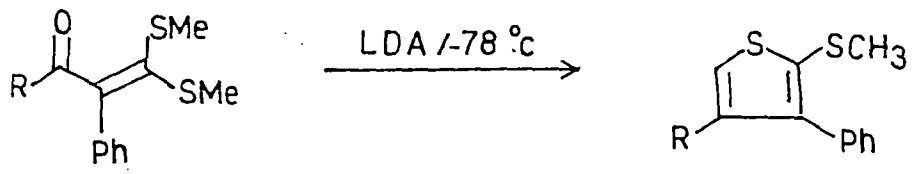
22 23A 23B

Ar	R	Yield %
C_6H_5	H	30
4-MeO C_6H_4	H	30
C_6H_5	Et	55
C_6H_5	MeO	42



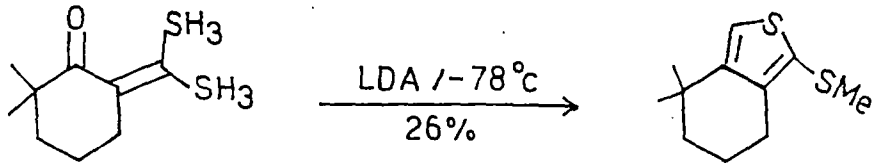
24

Scheme - 5

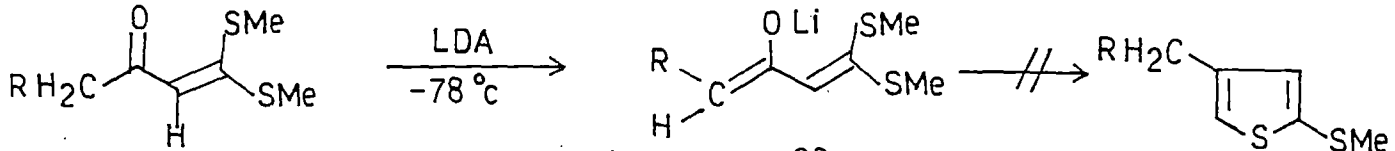


25 26

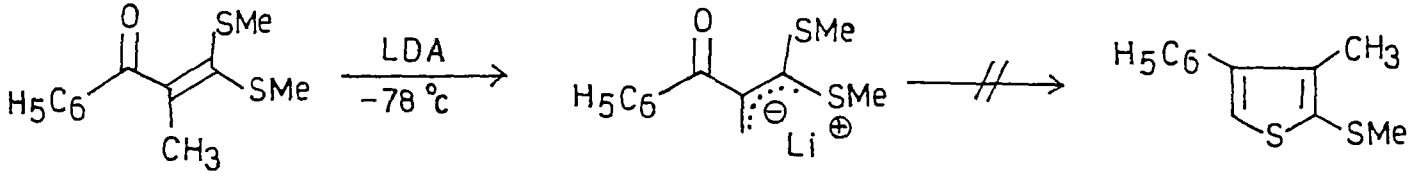
a , R = H 22 %
b , R = OMe 38 %



27 28



29 30 31

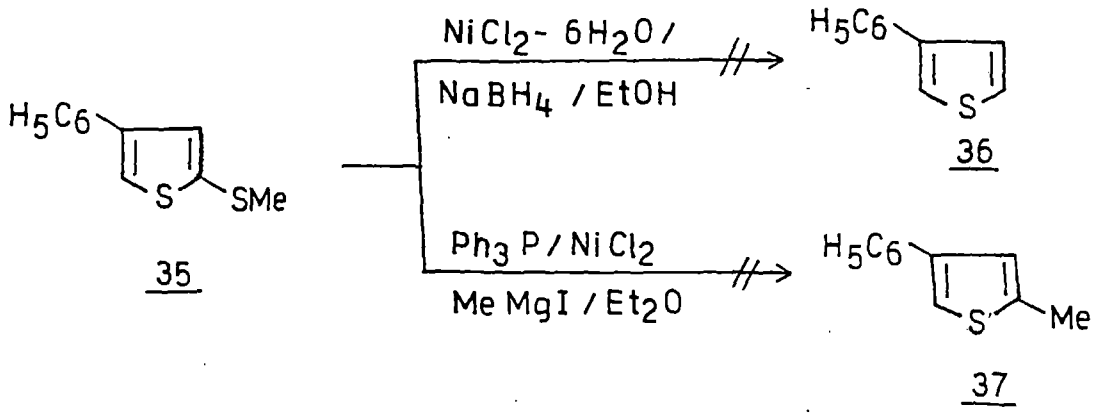


32 33 34

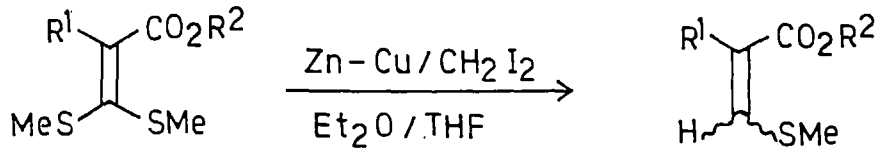
Scheme - 6

presence of Raney Nickel was not very satisfactory since desulphurized thiophenes were accompanied by open chain products. Also our attempts to desulphurise in the presence of nickel boride ($NaBH_4/NiCl_2$) failed as the unreacted methylthiothiophene 35 (scheme 7) was recovered. The reaction of Grignard reagent in the presence of triphenylphosphine nickel chloride complex also failed to give the corresponding thiophene 37 (scheme 7). Therefore one major limitation of this thiophene synthesis is retaining of the SMe group in the product thiophenes which could neither be removed nor be replaced.

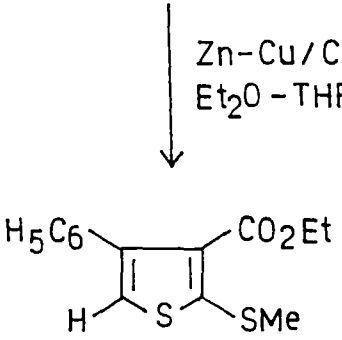
In the present study doubly activated α-carboalkoxyketene dithioacetals 38a-e were ivestigated with a view to observe the effect of the carbonyl moiety and also whether the reaction could be extended for the synthesis of 3-hydroxy/aminothiophenes. When 38a was examined under the Simmons-Smith reaction conditions, the corresponding dethiomethylated product ethyl 3-methylthio-2-phenyl propenoate 39a was obtained in 79% yield (scheme 8). The structure of 39a was established on the basis of its analytical and spectral data. It was analysed for $C_{12}H_{14}O_2S$ and the molecular weight was confirmed by its mass spectrum with a peak at m/z 222 (M^+, 100%). The compound showed a strong absorption in its IR (neat) spectrum at 1710 cm^{-1} indicating the presence of carbonyl function and other important peaks which are listed in the experimental section. The ^1H NMR (CCl_4) of 39a exhibited a triplet at δ1.10(3H, J=6Hz) was assigned to ester CH_3 group. The singlet at


H_5C_6
S
SMe
35
$NiCl_2 \cdot 6H_2O$ / $NaBH_4$ / EtOH
Ph_3P / $NiCl_2$
Me MgI / Et_2O
H_5C_6
S
36
H_5C_6
S
Me
37

Scheme - 7



38 39



40

38-39 a , $R^1 = C_6H_5$; R^2 = Et

b , R^1 = CN ; R^2 = Et

c , $R^1 = CO_2Et$; R^2 = Et

d , R^1 = COMe ; R^2 = Me

38 e , $R^1 = COC_6H_5$; R^2 = Et

Scheme - 8

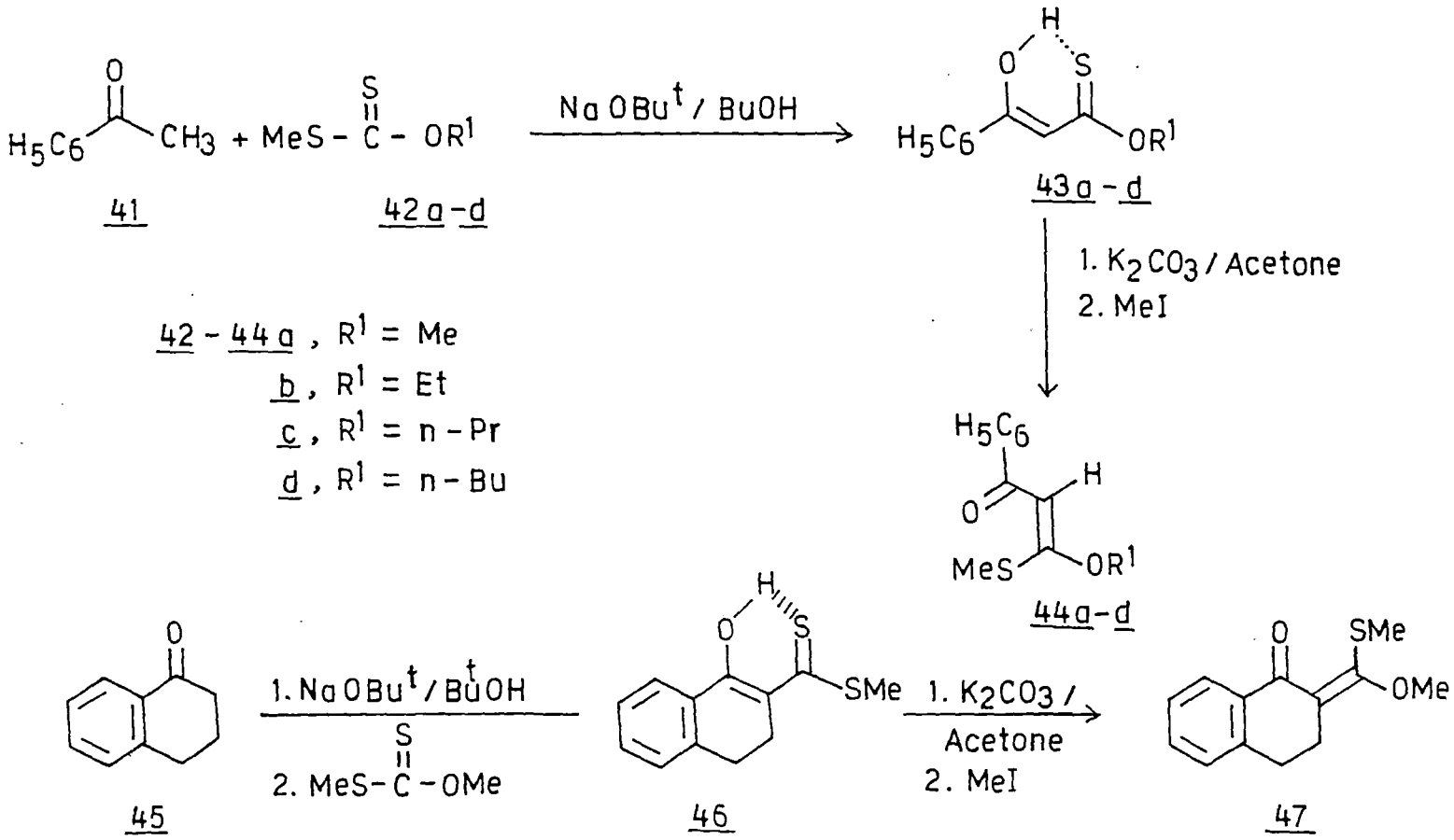
δ2.27(3H) was assigned for SMe protons. The ester CH_2 group was appeared as quartet at δ4.30(2H, J=6Hz). The broad singlet at δ7.27(5H), was assigned to phenyl protons. Similarly the dithioacetals **38b-d** afforded the corresponding dethiomethylated products **39b-d** in 56-82% overall yields. All these compounds were characterised by their analytical and spectral data (experimental section).

Interestingly, when dithioacetal **38e** was treated with Simmons-Smith reagent, expected thiophene **40** was formed in 51% yield (scheme 8). The structure **40** was supported by its analytical and spectral data. It was analysed for $C_{14}H_{14}O_2S$ and the molecular weight was confirmed from its mass spectrum with molecular ion peak at m/z 278 (M^+, 100%). The compound had strong absorption in its IR (neat) region at 1710 cm^{-1}. The ^1H NMR (CCl_4) signal for ester CH_3 protons appeared at δ1.03(3H, J=6Hz) as triplet and the SMe protons appeared as singlet at δ2.57(3H). The quartet at δ4.08(2H, J=6Hz) was assigned to ester CH_2 protons. The thiophene ring proton appeared as singlet at δ6.97(1H). The phenyl protons appeared as singlet at δ7.28(5H).

The mechanism of formation of dethiomethylated products **39a-d** from doubly activated α-carboalkoxyketene dithioacetals **38a-d** under Simmons-Smith reaction conditions appears to be not very clear. The combination of Zn-Cu couple and diiodomethane was necessary for this transfomation, since the starting material was recovered unchanged when **38a** was refluxed with Zn-Cu couple alone in tetrahydrofuran under identical

conditions. Reductive dsulphurisation of α-phenylthioketones with zinc in the presence of trimethyl silyl chloride is reported in the literature[6]. The methylthio group in these doubly activated ketene dithioacetals is more labile and less nucleophilic. Therefore the reaction appears to take different course under Simmons-Smith reaction conditions causing reductive dethiomethylation of the substrates.

Thus it was considered of interest to explore further the possibilties to alter the functonal groups in the substrate molecules so that the desired substituents could be carried to the product thiophenes. However, such substitution should be highly configurationally favourable so that the lone SMe group should remain *cis* to the oxo group in the acetals. Thus for the displacement of SMe group, the oxoketene dithioacetals should necessarily be possessing *'Z'* configuraton so that the SMe group remains *cis* to the carbonyl group as desired. This has been successfully achieved by developing a methodology[7] in this laboratory by condensing active methylene ketones **41** and **45** with alkylxanthates **39** (scheme 9) in presence of sodium *t*-butoxide to give corresponding thionoesters **43** and **46** in overall good yields. The thionoesters **43** and **46** were subsequently alkylated in the presence of potassium carbonate/acetone and methyliodide to give the corresponding α-oxoketene O-alkyl S-methylacetals **44a-d** and **47** respectively in high yields. These O,S-acetals possess exclusive *'Z'* geometry as confirmed by their NOE studies which is an



41 42a-d 43a-d

42 - 44a , R^1 = Me
b , R^1 = Et
c , R^1 = n-Pr
d , R^1 = n-Bu

44a-d

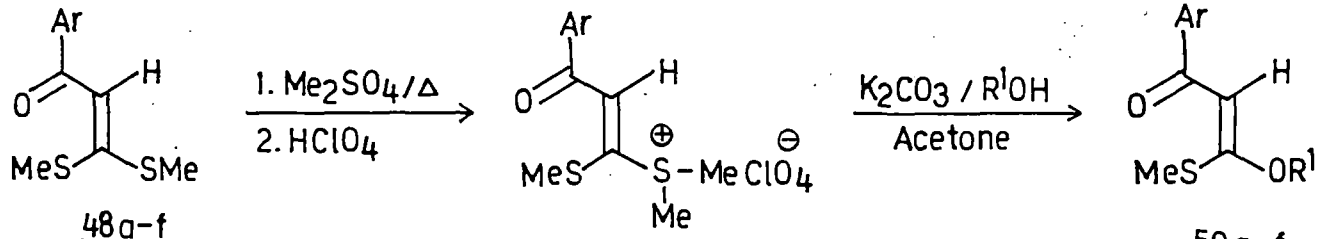
45 46 47

Scheme - 9

essential requirement for our efforts to develop suitable precursors for alkoxythiophenes.

However, the above described method of O,S-acetals could not be used for the synthesis of α-oxoketene O-aryl S-methyl acetals that were needed as starting materials in the present investigation. For this the best alternative method adopted has been formulated in scheme 10. The α-oxoketene dithioacetals **48** and **51** were conveniently quarternized by reacting with dimethyl sulphate followed by perchloric acid to the corresponding sulphonium salts **49** and **52** which are stable crystalline products as perchlorates. The sulphonium salts **49** and **52** underwent facile displacement with various phenols and alcohols to give the corresponding O,S-acetals **50a-f** and **53**. The configuration of all these O,S-acetals was assigned *'Z'* geometry where the desired SMe group was cis to the carbonyl group.

The preliminary reaction of O,S-acetals under Simmons-Smith reaction conditions yielded the corresponding thiophenes in excellent yields[8]. The synthesis of alkoxy and aryloxy thiophenes from the corresponding O,S-acetals described is the subject of this chapter. The development of an efficient method for the synthesis of alkoxy and aryloxy thiophenes was necessitated in view of the lack of good methods in the literature. There have been few attempts in the literature for the synthesis of alkoxy and aryloxy thiophenes which are briefly illustrated in the following section before the present new method is discussed.



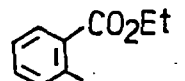
48a-f 49a-f 50a-f

a, Ar = C_6H_5 ; $R^1 = C_6H_5CH_2$

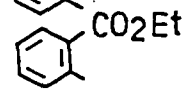
b, Ar = C_6H_5 ; R^1 = n – $C_{12}H_{25}$

c, Ar = 4 – MeO C_6H_4 ; $R^1 = C_6H_5$

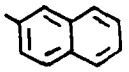
d, Ar = C_6H_5 ; R^1 =

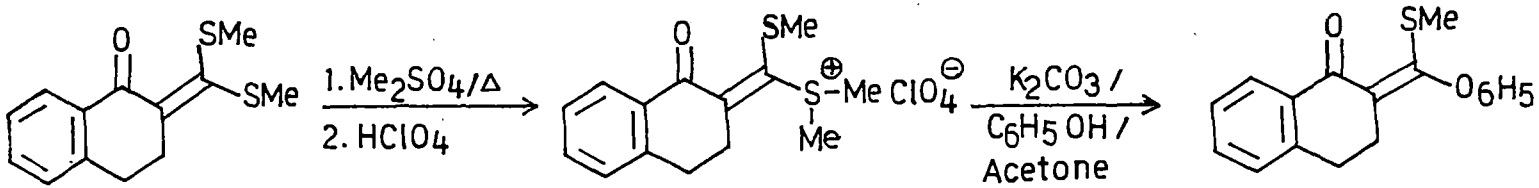


e, Ar = 4 – MeO C_6H_4 ; R^1 =



f, Ar = 4-MeO C_6H_4 ; R^1 =





51 52 53

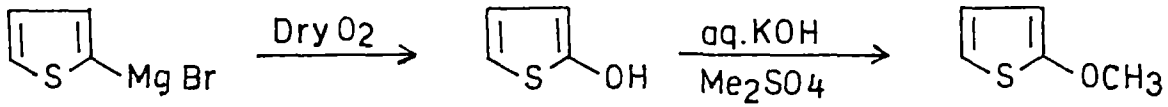
Scheme – 10

III.2 ALKOXY AND ARYLOXYTHIOPHENES : A BRIEF SURVEY

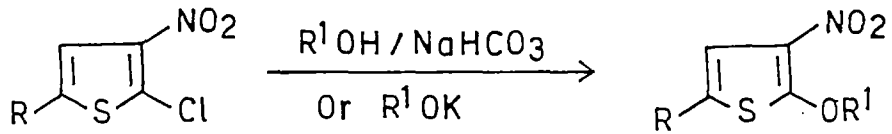
The earliest synthesis of 2-methoxythiophene 56 (scheme 11) appears to be reported by Hurd and Krenz[8] in 1950. The thiophene magnesium bromide 54 was reacted with dry oxygen to give the corresponding 2-hydroxythiophene 55 which was alkylated with dimethyl sulphate in the presence of aqueous potassium hydroxide. Similarly 2-chloro-3-nitrothiophenes 57 were also shown to undergo facile displacement in the presence of potassium alkoxides to afford the corresponding 2-alkoxy-3-nitrothiophenes 58[9] (scheme 11).

Subsequently, Sice[10] and Proft[11] employed the 2-halothiophenes 59 under the conditions of Williamsons synthesis to obtain the corresponding 2-alkoxythiophenes 60 (scheme 12). They observed that the iodothiophenes gave better yields than the corresponding bromothiophenes while the corresponding chlorothiophenes failed to undergo this reaction. Improved yields of alkoxy thiophenes were obtained when the reaction was carried out in the presence of copper(II) salts rather than copper(I) salts (scheme 12).

Lawesson and co-worker[12] attempted to prepare the methoxy thiophenes 66 from the corresponding thiolene-2-ones 64 using the corresponding thallium salts 65 (scheme 13). However, the thallium salts on alkylation gave a mixture of products including O-and C-alkylated products. The required thiolene-2-ones 64 were prepared from metallation of thiophenes 61 followed by treatment of anion 62 with *t*-butylperoxy ester to



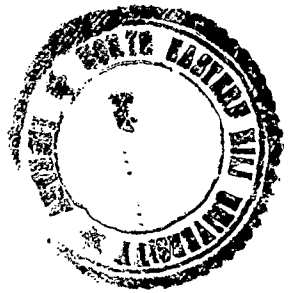
54 55 56

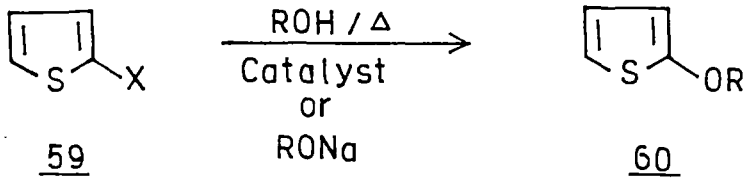


57 58

R = H, NO_2 ; R^1 = Me, Et, C_6H_5

Scheme - 11



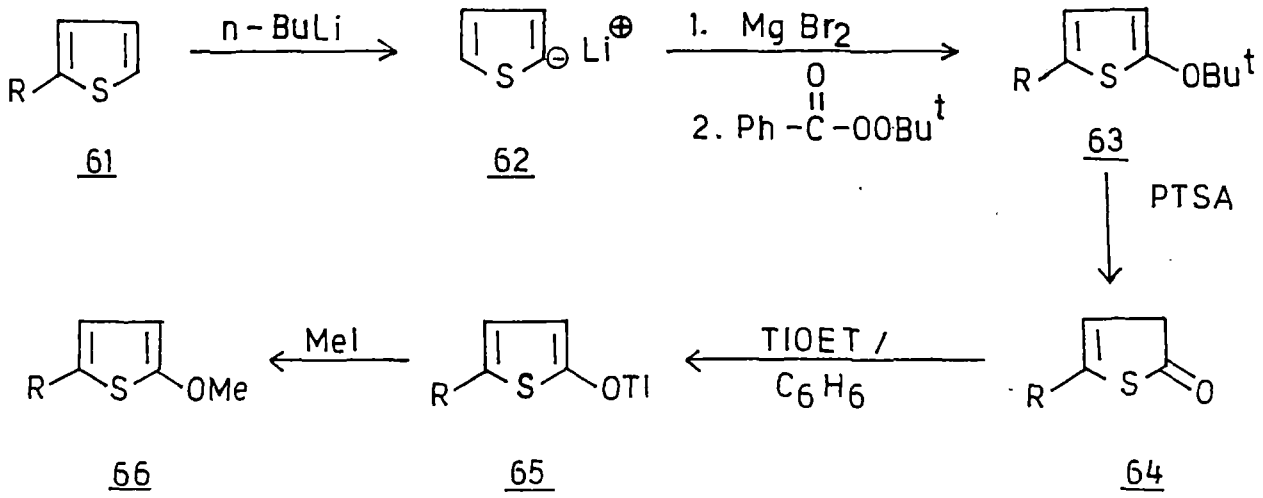


59 60

X = Cl, Br, I,

; R = Me, Et , C_6H_5

Scheme - 12



61 62 63 64 65 66

R = H, Me.

Scheme -13

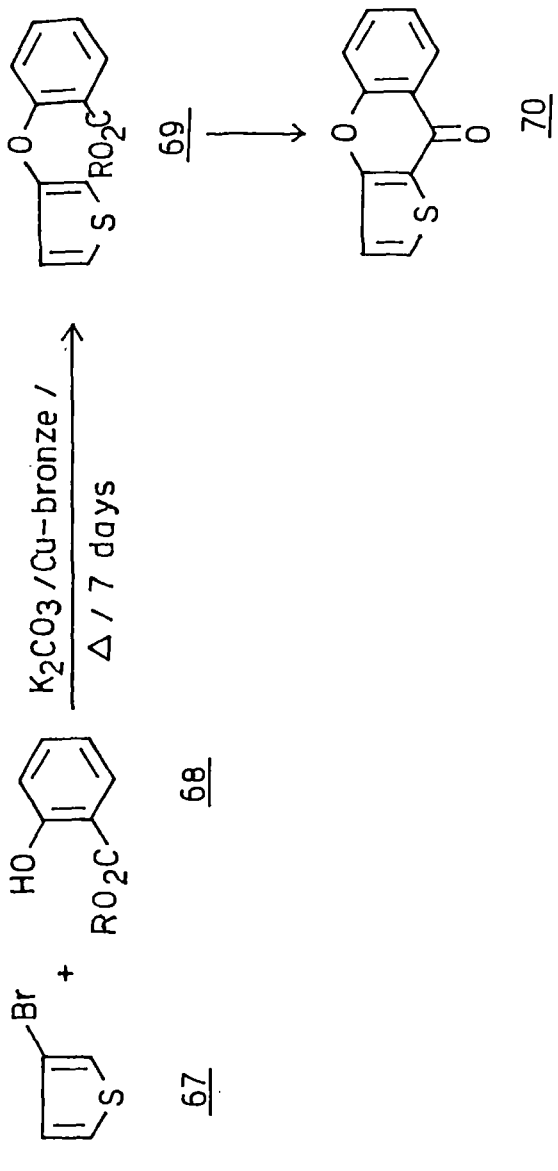
afford the corresponding *t*-butoxy thiophenes 63 which were hydrolysed with *p*-toluene sulphonic acid to afford 64. The thallium salts 65 were obtained by treatment of thiolene-2-ones 64 with thallium ethoxide which on alkylation with methyl iodide afforded 2-methoxythophenes 66.

Ashby and co-workers[13] reacted 3-bromothiophene 67 with salicylate 68 in the presence of potassium carbonate and copper bronze to afford the corresponding ether 69 which was subsequently cyclized to give the corresponding xanthone 70 (scheme 14).

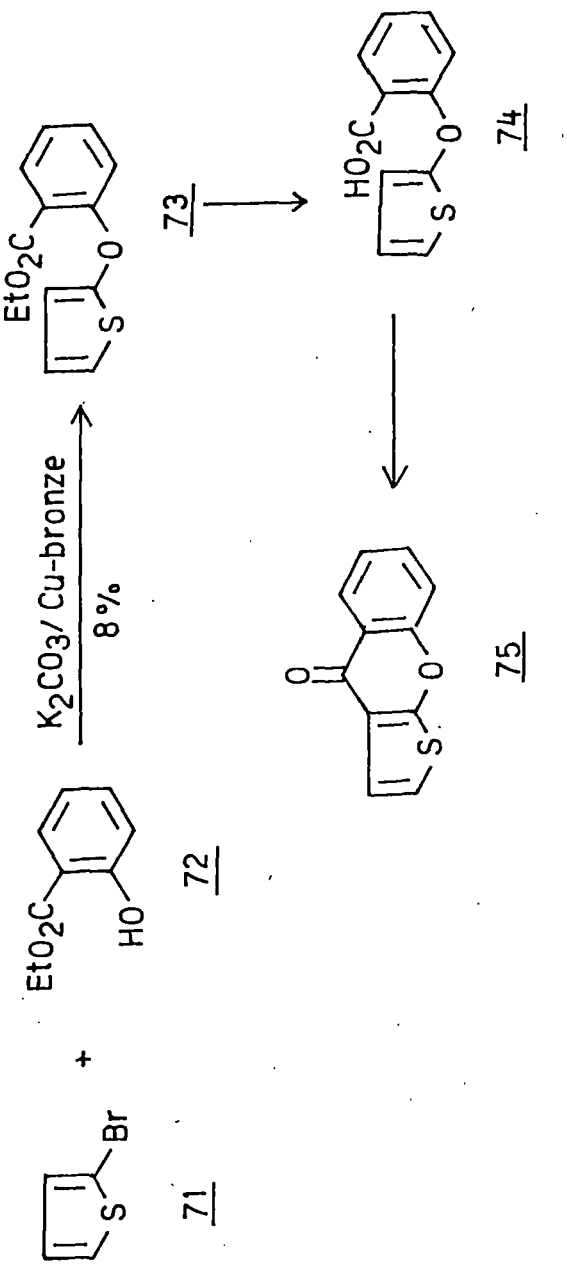
Subsequently, Watthey and Desai[14] reacted 2-bromothiophene 71 with ethylsalicylate 72 essentially under similar reaction conditions reported by Ashby and co-workers [13] to get the ether 73 but only in 8% yield (scheme 15). The corresponding ether after hydrolysis of the ester group was cyclized to the corresponding xanthone 75 in the presence of polyphosphoric ester.

Brunet and Paquer[15] prepared the ethoxy thiophenes 77 by treating the β-ketoesters 76 with hydrogen sulphide in the presence of hydrochloric acid (scheme 16).

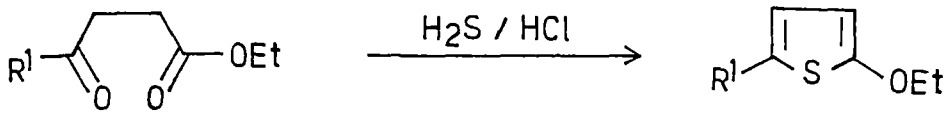
Recently, Brandsma and co-workers[16] have investigated copper (I) halide catalysed synthesis of alkyl, aryl and alkyl heteroaryl ethers and found that 2-bromothiophene tended to undergo reduction rather than displacement with alkoxy group. However, they found that the displacement reaction is favoured when the alkoxide concentration in the reaction



Scheme – 14


EtO2C
HO
72
+
Br
S
71
K2CO3/ Cu-bronze
8%
EtO2C
O
S
73
HO2C
O
S
74
O
O
S
75

Scheme - 15



76 77

R = C_6H_5 ; 4 - Cl C_6H_4 ; 4 - Me C_6H_4

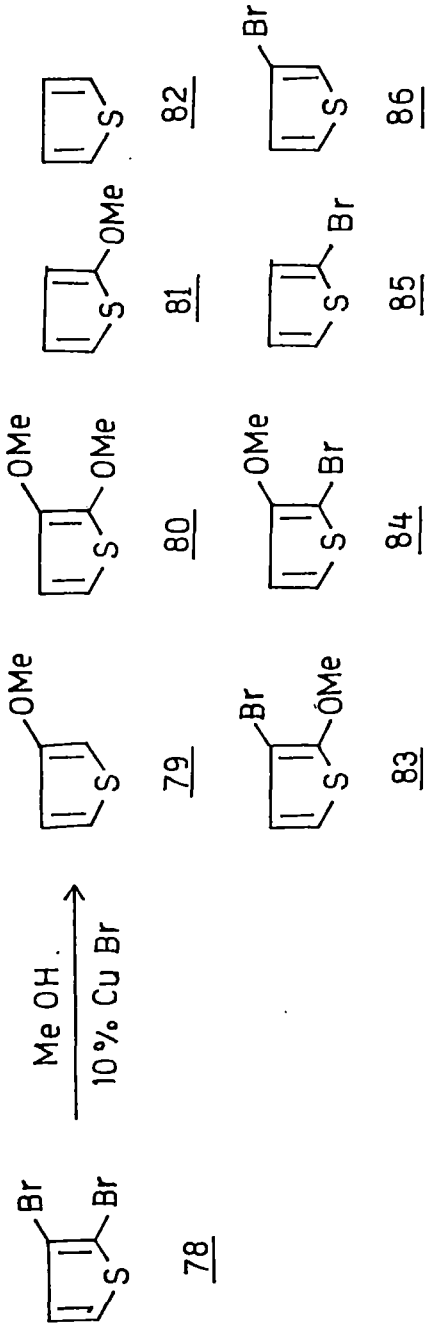
Scheme - 16

mixture is high. They also observed that 2,3-dibromothiophene undergoes both displacement and reductive transformation in varying degrees as shown in scheme 17. Maximum yield of 3-methoxy thiophene **79** (60%) was obtained by the reduction of the 2-bromo group along with 3% of completely reduced thiophene **82** and the complete conversion required prolonged heating under reflux.

From these examples described above, it is apparent that the methods available in the literature for the synthesis of alkoxy thiophenes are not many and most of them suffer from serious limitations. Besides all the methods have employed halothiophenes which are to be prepared from the corresponding thiophenes. Therefore, a direct method for the synthesis of alkoxy and aryloxy thiophenes will be of great synthetic importance. In the present investigation it has been successfully demonstrated that the easily accessible O,S-acetals as described earlier have the requisite geometrical (*Z*) configuraton suitable for the alkoxy thiophene synthesis under Simmons-Smith reaction conditions. These results are described as follows.

III.3 RESULTS AND DISCUSSION

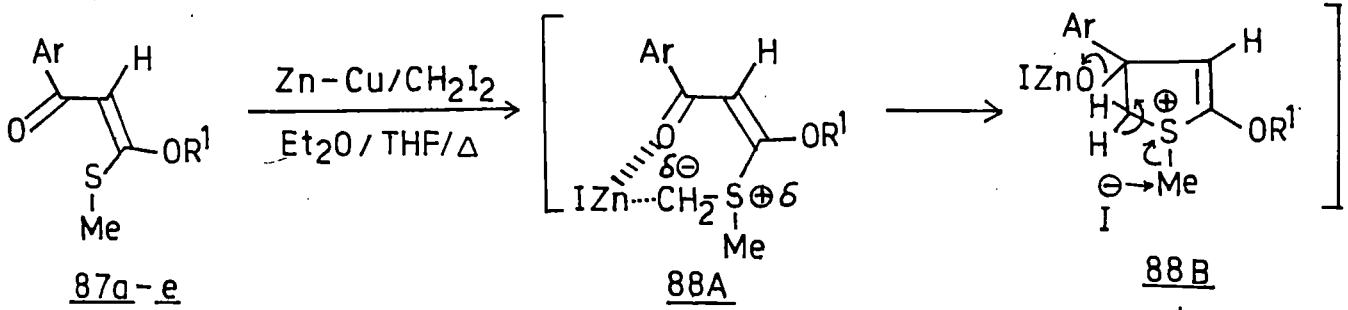
The O,S-acetal **87a** (scheme 18) when treated with Zn-Cu/ methylene iodide in the presence of ether and tetrahydrofuran the reaction mixture after work-up yielded the corresponding 2-methoxy-4-phenylthiophene **89a** in 66% yield. The methoxythiophene was not reported earlier and had melting point 40-41°C. It was analysed for $C_{11}H_{10}OS$ and its molecular


Br
Br
S
78
Me OH
10% Cu Br
OMe
S
79
OMe
OMe
S
80
OMe
S
81
82
Br
OMe
S
83
OMe
Br
S
84
Br
S
85
Br
S
86

Scheme – 17

weight was confirmed by its mass spectram with a peak at m/z 190 (M^+, 19%). In its IR(KBr) spectrum it showed strong bands at 1620, 1600, 1507, 1465 and 1218 cm^{-1}. Its structure was further confirmed from its ^1H NMR ($CDCl_3$) spectrum. The singlet at δ3.84(3H) was assigned to methoxy protons. The doublet at δ6.55(1H, J=1.5Hz) was assigned to H-3 ring proton which showed 1,3-coupling with the H-5 proton. The H-5 proton was found at δ6.88(1H), as a doublet with coupling constant J=1.5Hz. The phenyl protons appeared as multiplet between δ7.22-7.29 (5H). The other alkoxy thiophenes 87b-e were similarly obtained under the described reaction conditions in 32-72% overall yields. The structure of 87b-e were established by their analytical and spectral data (experimental section). Similarly the oxoketene O-dodecyl S-methylacetal 87f also underwent thiophene ring formation to give the 2-dodecyloxy-4-phenylthiophene 89f in 59% yield (scheme 18). The structure of 89f was confirmed by its spectral and analytical data (experimental section).

The O-aryl S-methyl acetals were next examined for thiophene synthesis. Thus O,S-acetal 87g (scheme 19) on treatment under the Simmons-Smith reaction conditions yielded the corresponding 4(4'-methoxyphenyl)-2-phenoxythiophene 89g in 66% yield. It was analysed for $C_{17}H_{14}O_2S$ and the molecular weight was confirmed from its mass spectrum with a peak at m/z 283 (M^+, 100%). It showed in its IR(KBr) spectrum bands at 1619, 1608, 1583, 1486, 1252, and 1214 cm^{-1}. The structure was further confirmed from its ^1H NMR ($CDCl_3$)



87a-e

88A

88B

87 - 89a , Ar = C_6H_5 ; R^1 = Me

b , Ar = C_6H_5 ; R^1 = Et

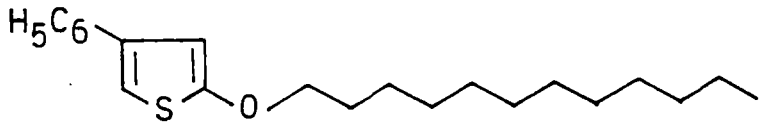
c , Ar = C_6H_5 ; R^1 = n-Pr

d , Ar = C_6H_5 ; R^1 = n-Bu

e , Ar = C_6H_5 ; R^1 = $C_6H_5CH_2$

89a-e

87f, $\xrightarrow[Et_2O/THF/\Delta]{Zn-Cu/CH_2I_2}$



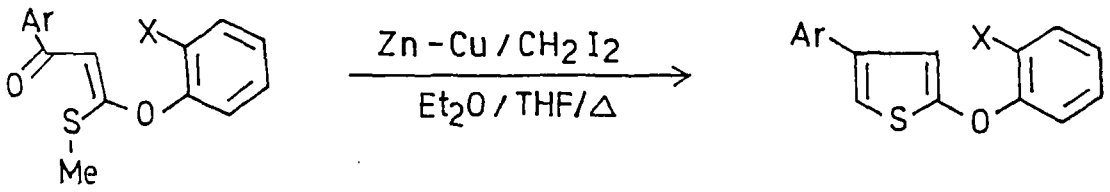
89f

Scheme-18

spectrum. The singlet at δ3.78(3H), was assigned to *p*-methoxy protons of phenyl group. The thiophene ring protons at 3 and 5 positions (H-3 and H-5) were submerged with aromatic two protons in a multiplet at δ6.76-7.00(4H). The other aromatic protons appeared as multiplet between δ7.03-7.57 (7H). Similarly the O,S-acetal 87h prepared by reacting the dimethylsulphonium perchlorate salt of the corresponding oxoketene S,S-acetal with *ortho*-chlorophenol under the Simmons-Smith reaction conditions afforded the corresponding thiophene 89h in 62% yield (scheme 19). The structure of 89h was in accordance with its analytcal and spectral data (expermental section).

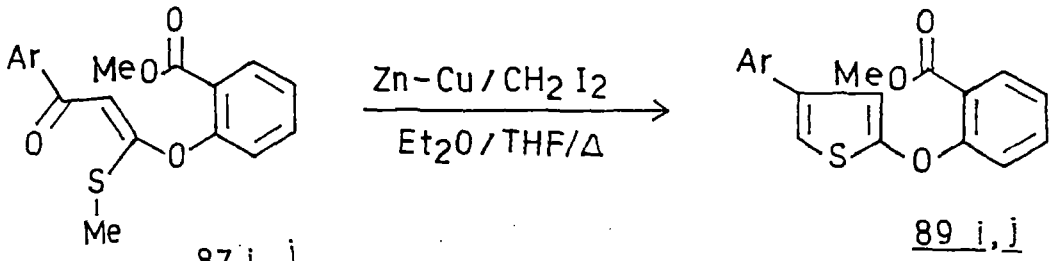
The O,S-acetals 87i and 87j obtained by the reaction of dimethylsulphonium salts of the corresponding S,S-acetals with methylsalicylate were also found to undergo thiophene ring closure to afford the corresponding thiophenes 89i and 89j under Simmons-Smith reaction conditions in 78% and 84% yields respectively (scheme 19). The structure of thiophenes 89i and 89j were in accord with their analytical and spectral data (experimental section).

It may be noted here that these aryloxy thiophenes with orthocarbomethoxy group in aryl group are important starting materials for the corresponding xanthone synthesis[14]. The present method therefore is of practical importance for the synthesis of a number of xanthones by appropriately carrying the substituents in the substrate O,S-acetals.



87 g,h 87- 89g, Ar = 4 - MeO C_6H_4 ; X = H
h, Ar = C_6H_5 ; X = Cl

89 g, h



87 i, j

89 i, j

87- 89 i, Ar = C_6H_5
j, Ar = 4 - MeO C_6H_4

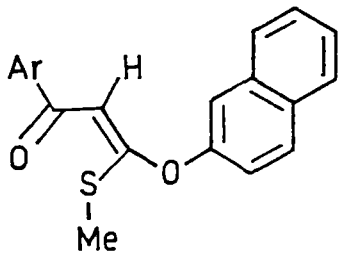
Scheme - 19

The O,S-acetal 87k obtained from the sulphonium salt of corresponding S,S-acetals and β-naphthol also underwent thiophene ring closure under Simmons-Smith reaction conditions to afford the corresponding 2-(β-naphthyloxy)-4-(4'-methoxyphenyl) thiophene 89k in 76% yield. Similarly O,S-acetal 87l from tetralone gave the corresponding condensed thiophene 89l under similar reaction conditions in 34% yield (scheme 20). The structure of 89k and 89l were established by their analytical and spectral data (experimental section).

Apparently, the O,S-acetals which can be easily prepared by either one of the methods described are shown to be excellent precursors for the synthesis of 2-alkoxy and 2-aryloxy thiophenes in attaractive yields. However, when the method was extended to N,S-acetal 90 under similar reaction conditions the corresponding aminothiophene 91 could not be obtained and the reaction mixture resulted in intractable tar.

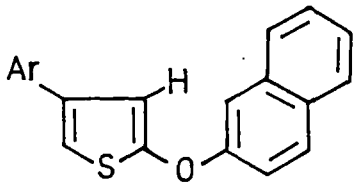
III.4 CONCLUSION

In conclusion, it may be inferred that the O,S-acetals including alkoxy and aryloxy groups are excellent precursors for the synthesis of the corresponding 2-alkoxy and 2-aryloxythiophenes. The aryloxythiophenes could be of further importance to synthesize the condensed thiophene derivatives with appropriate functional groups placed in the *ortho* position of the aryl group. The method certainly suffers a



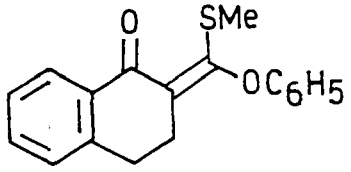
87k

$\xrightarrow[Et_2O/THF/\Delta]{Zn-Cu/CH_2I_2}$



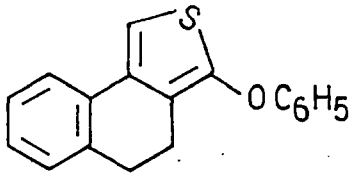
89k

Ar = 4 - Me O C_6H_4



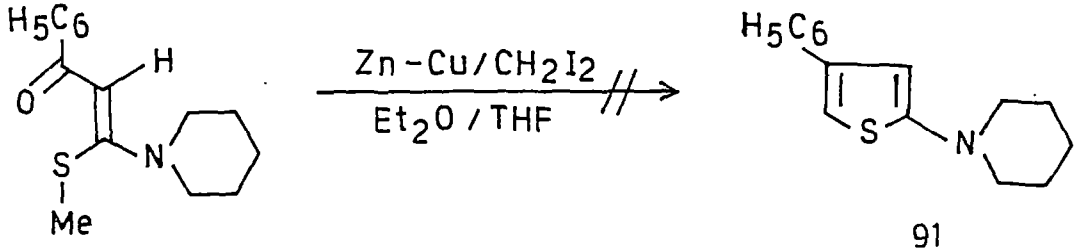
87l

$\xrightarrow[Et_2O/THF/\Delta]{Zn-Cu/CH_2I_2}$



89l

Scheme - 20



90 91

Scheme - 21

limitation that it failed to undergo thiophene ring closure with S,N-acetals to afford the corresponding aminothiophenes.

III.5 EXPERIMENTAL

Melting points were determined on a 'Thomas Hoover' capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in $CDCl_3$ or CCl_4 using TMS as internal standard. While ^{13}C NMR spectra were recorded on a Bruker WM-400 spectrometer and chemical shifts are expressed in δ(ppm) units downfield from TMS. Mass spectra were obtained on a Jeol JMS-D 300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyzer.

Starting Materials

Commercially available ketones and esters were purchased and were used as supplied without further purification. Zinc-Copper couple was purchased (ventron) and was dried at 120°C for 24 hr prior to use. Methylene iodide was distilled before use. Diethylether and tetrahydrofuran were dried over sodium wire and distilled prior to use.

General Procedure for the Preparation of Acylketene O,S-Dialkylacetals (87a-d).

(a) Preparation of β-Oxothionoesters.

To an ice cold stirring suspension of sodium *t*-butoxide (38.4 g, 0.4 mol, prepared from 9.2g, 0.4 atom of sodium) in *t*-

butylalcohol (150 ml), a mixture of dialkyl xanthate (0.2 mol) and respective ketones (0.2mol) was added dropwise and the resulting mixture was stirred at room temperature for 8-10hr. (monitored by tlc). It was then poured on to crushed ice(200g), acidified with 50% HCl(50 ml), extracted with benzene (3x100 ml) and the combined extracts were washed with water (3x150 ml), dried (Na_2SO_4) and concentrated to give the crude thionoesters, which were purified by column chromatography over silica gel using hexane as eluent.

(b) Preparation of Acylketene O,S-Dialkylacetals (87a-d).

A suspension of β-oxothiono esters (0.2 mol) and anhydrous K_2CO_3 (52.59g, 0.4mol) in dry acetone (100 ml) was refluxed with stirring for 3hr. and then cooled to room temperature. Appropriate alkyl halide (0.25 mol) was added dropwise with stirring at 0-5°C and the resulting reaction mixture was further stirred at room temperature for 8-10 hr. (monitored by tlc). It was then filtered, washed the precipitate with acetone (2x25ml) and the combined filtrate was concentrated on a water bath. The residue was cooled to room temperature and poured onto crushed ice (200g), extracted with $CHCl_3$ (2x100ml). The combined extracts were washed with water (3x100ml), dried (Na_2SO_4) and evaporated to give the crude O,S-acetals 87 which were purified by column chromatography over silica gel using EtOAc/hexane (1:99) as eluent.

General Procedure for the Preparation of Acylketene O-Alkyl/Aryl S-Methylacetals (87e-l).

A suspension of the appropriate alcohols or phenols (0.03mol) and anhydrous K_2CO_3 (12.50g,0.09mol) in anhdrous acetone (100ml) was refluxed with stirring for 2-3hr. The resulting mixture was cooled to 0-5°C and the dimethyl sulphonium perchlorate salt (0.01mol) was added in small portions with stirring. The reaction mixture was further stirred for 7-8hr. and filtered. Washed the precipitate with acetone (2x25ml) and the combined filtrate was concentrated on water bath. The residue was cooled to room temperature and poured onto crushed ice (200g), extracted with $CHCl_3$ (2x100ml). The organic layer was washed with 10% NaOH solution (3x50 ml) and then with water (3x100 ml), dried Na_2SO_4 and evaporated to give crude O,S-acetals, which were purified by column chromatography over silica gel using EtOAc/hexane (1:99) as eluent.

General Procedure for Simmons-Smith Reaction : Synthesis of β-Methylthio-α,β-unsaturated esters (39a-d) and 2-Alkoxy/ Aryloxythiophenes (89a-l).

To a well stirred suspension of Zinc-Copper couple (4.0g, 0.03 mol) in dry ether (25ml), under nitrogen atmosphere, a small crystal of iodine and methylene iodide (6.70g, 0.025mol) were added and the reaction mixture was refluxed for 45 minutes. A solution of the respective α-oxoketene O,S- or S,S-acetal (0.01mol) in dry THF (25ml) was added in one lot into the reaction mixture, which was further refluxed with stirring for 8-12 hr (monitored by tlc). The solvent was removed under reduced pressure and the residue was

diluted with chloroform (150 ml) and water (200 ml). The extract was filtered and the residue was washed with chloroform (2x25 ml). The chloroform layer was separated and washed with saturated NH_4Cl solution (2x25ml), water (2x100ml), dried over sodium sulphate and concentrated to give the crude esters (39a-d) and thiophenes (89a-l) which were purified by column chromatography over silica gel using hexane as eluent.

Ethyl 3-methylthio-2-phenylpropenoate (39a). Yellow viscous liquid ; yield 79% ; IR (neat) 1710, 1570, 1230 cm^{-1} ; δ_H (CCl_4) 1.10 (3H, t, J = 6Hz, OCH_2CH_3), 2.27 (3H, s, SCH_3), 4.30 (2H, q, J = 6Hz, OCH_2CH_3), 7.27 (5H, brs, arom), 7.61 (1H, s, = CH) ; m/z 222 (M^+, 100%), 175 (60) (Anal. Calcd. for $C_{12}H_{14}O_2S$: C, 64.83 ; H, 6.35. Found : C, 65.11 ; H, 6.61%).

Ethyl-2-cyano-3-methylthiopropenoate (39b). Yellow crystals ($CHCl_3$/hexane) ; yield 82% ; m.p. 51-52°C ; IR (KBr) 2218, 1712, 1540, 1300, 1245 cm^{-1} ; δ_H ($CDCl_3$) 1.34 (3H, t, J = 6Hz, OCH_2CH_3), 2.68 (3H, s, SCH_3), 4.28 (2H, q, J = 6Hz, OCH_2CH_3), 8.50 (1H, s, =CH) ; m/z 171 (M^+, 100%) (Anal. Calcd. for $C_7H_9NO_2S$: C, 49.10 ; H, 5.30. Found : C, 49.37 ; H, 5.56%).

Ethyl 2-carboethoxy-3-methylthiopropenoate (39c). Yellow viscous liquid ; yield 56% ; IR (neat) 1710, 1554, 1242 cm^{-1} ; δ_H (CCl_4) 1.08-1.43 (6H, m, OCH_2CH_3), 2.40 (3H, s, SCH_3), 3.89-4.32 (4H, m, OCH_2CH_3), 7.90 (1H, s, =CH) ; m/z 218 (M^+,

100%) (Anal. Calcd. for $C_9H_{14}O_4S$: C, 49.52 ; H, 6.46. Found : C, 49.81 ; H, 6.73%).

Methyl 2-acetyl-3-methylthiopropenoate (39d). Pale yellow crystals ($CHCl_3$/hexane) ; yield 69% ; m.p. 57°C ; IR (KBr) 1711, 1644, 1493, 1343, 1201 cm^{-1} ; δ_H ($CDCl_3$) 2.48 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 8.50 (1H, s, =CH) ; m/z 174 (M^+, 100) (Anal. Calcd. for $C_7H_{10}O_3S$: C, 48.26 ; H, 5.79. Found : C, 48.51 ; H, 6.02%).

Ethyl 2-methylthio-4-phenylthiophene-3-carboxylate (40) was obtained by Simmons-Smith reaction on 38e under similar reaction conditions as described in the general procedure. Yellow viscous liquid ; yield 51% ; IR (neat) 1710, 1600, 1482, 1420, 1310, 1245 cm^{-1} ; δ_H 1.03 (3H, t, J = 6Hz, OCH_2CH_3), 2.57 (3H, s, SCH_3), 4.08 (2H, q, J = 6Hz, OCH_2CH_3), 6.97 (1H, s, H-5), 7.28 (5H, s, arom) ; m/z 278 (M^+, 100%) (Anal. Calcd. for $C_{14}H_{14}O_2S_2$: C, 60.40 ; H, 5.07. Found : C, 60.67 ; H, 5.35%).

2-Methoxy-4-phenylthiophene (89a). Colourless solid (hexane) : yield 66% ; m.p. 40-41°C ; IR (KBr) 1620, 1600, 1507, 1465, 1218 cm^{-1} ; δ_H (CCl_4) 3.84 (3H, s, OCH_3), 6.55 (1H, d, H-3, J = 1.5Hz), 6.68 (1H, d, H-5, J = 1.5 Hz), 7.22-7.69 (5H, m, ArH) ; m/z 190 (M^+, 19%) (Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.44 ; H, 5.30. Found : C, 69.67 ; H, 5.49%).

2-Ethoxy-4-phenylthiophene (89b). Viscous liquid ; yield 72%; IR (neat) 1600, 1580, 1549, 1502, 1465, 1388 cm^{-1} ; δ_H (CCl_4) 1.37 (3H, t, J = 6Hz, OCH_2CH_3), 4.09 (2H, q, J = 6Hz,

OCH_2CH_3), 6.45 (1H, d, J = 1.5Hz, H-3), 6.63 (1H, d, J = 1.5 Hz, H-5), 7.12-7.64 (5H, m, ArH) ; m/z 204 (M^+, 62%), 176 (100) (Anal. Calcd. for $C_{12}H_{12}OS$: C, 70.55 ; H, 5.92. Found : C, 70.36 ; H, 5.70%).

2-Propyloxy-4-plhenylthiophene (89c). Colourless solid (hexane) : yield 58% ; m.p. 35-36°C ; IR (KBr) 1562, 1520, 1481, 1203 cm^{-1} ; δ_H (CCl_4) 1.07 (3H, t, J = 6Hz, $OCH_2CH_2CH_3$), 1.75 (2H, sext, J = 6Hz, $OCH_2CH_2CH_3$), 3.98 (2H, t, J = 6Hz, $OCH_2CH_2CH_3$), 6.54 (1H, d, J = 1.5Hz, H-3), 6.67 (1H, d, J = 1.5Hz, H-5), 7.23-7.67 (5H, m, ArH) ; m/z 218 (M^+, 39%), 176 (100) (Anal. Calcd. for $C_{13}H_{14}OS$: C, 71.52 ; H, 6.46. Found : C, 71.35 ; H, 6.27%).

2-Butyloxy-4-phenylthiophene (89d). Colourless solid (hexane) ; yield 72% ; m.p. 43-44°C : IR (KBr) 1622, 1602, 1570, 1522, 1481, 1396 cm^{-1} ; δ_H (CCl_4) 0.88 [3H, t, J = 7Hz, $OCH_2(CH_2)_2CH_3$], 1.17-1.88 [4H, m, $OCH_2(CH_2)_2CH_3$], 4.02 [2H, t, J = 7Hz, $OCH_2(CH_2)_2CH_3$], 6.58 (1H, d, J = 1.5Hz, H-3) 6.69 (1H, d, J = 1.5 Hz, H-5), 7.27-7.79 (5H, m, ArH) ; m/z 232 (M^+, 24%), 176 (100) (Anal. Calcd. for $C_{14}H_{16}OS$: C, 72.37 ; H, 6.94. Found : C, 72.64 ; H, 7.12%).

2-Benzyloxy-4-phenylthiophene (89e). Colourless crystals (hexane/ether) ; yield 32% ; m.p. 82-83°C ; IR (KBr) 1562, 1518, 1472, 1400, 1201 cm^{-1} ; δ_H ($CDCl_3$) 5.08 (2H, s, $CH_2C_6H_5$), 6.62 (1H, d, J = 1.5Hz, H-3), 6.70 (1H, d, J = 1.5Hz, H-5), 7.19-7.73 (10H, m, ArH) ; m/z 266 (M^+, 14%), 175

(15), 91 (100) (Anal. Calcd. for $C_{17}H_{14}OS$: C, 76.66 : H, 5.30. Found : C, 76.92 ; H, 5.45%).

2-Dodecyloxy-4-phenylthiophene (89f). Colourless solid (hexane) ; yield 59% ; m.p. 34-35°C ; IR (KBr) 1559, 1518, 1478, 1196 cm^{-1} ; δ_H (CCl_4) 0.89 [3H, brt, J = 6Hz, $OCH_2(CH_2)_{10}CH_3$], 1.13-1.41 [20H, m, $OCH_2(CH_2)_{10}CH_3$], 4.10 [2H, t, J = 6Hz, $OCH_2(CH_2)_{10}CH_3$], 6.62 (1H, d, J = 1.5Hz, H-3), 7.76 (1H, d, J = 1.5Hz, H-5), 7.31-7.75 (5H, m, ArH) ; m/z 344 (M^+, 43%), 176 (100) (Anal. Cacd. for $C_{22}H_{32}OS$: C, 76.69 ; H, 9.36. Found : C, 76.97 ; H, 9.58%).

2-Phenoxy-4-(4'methoxyphenyl)thiophene (89g). Colourless crystals (hexane/ether) ; yield 66% ; m.p. 97-98°C ; IR (KBr) 1619, 1608, 1583, 1486, 1255, 1214 cm^{-1} ; δ_H ($CDCl_3$) 3.78 (3H, s, OCH_3), 6.76-7.0 (4H, m, H-3, H-5 and ArH), 7.03-7.57 (7H, m, ArH) ; m/z 283 (M^+, 100%), 206 (46) (Anal. Calcd. for $C_{17}H_{14}O_2S$: C, 72.31 ; H, 5.00. Found : C, 72.49 ; H, 5.13%).

2-(2'-Chlorophenoxy)-4-phenylthiophene (89h). Colourless crystals (hexane) : yield 62% ; m.p. 46-47°C ; IR (KBr) 1598, 1562, 1484, 1238 cm^{-1} ; δ_H (CCl_4) 6.80-6.93 (2H, m, H-3 and H-5), 7.07-7.63 (9H, m, ArH) ; m/z 286, 288 (M^+, 100, 30%), 252 (51) (Anal. Calcd. for $C_{16}H_{11}ClOS$: C, 67.01 ; H, 3.87. Found : C, 67.28 ; H, 4.09%).

2-(2'-Carbomethoxyphenyl)-4-phenylthiophene (89i). Colourless crystals (ether/hexane) ; yield 78% ; m.p. 59.60°C ; IR (KBr) 1748, 1626, 1508, 1472, 1320, 1240 cm^{-1} ; δ_H ($CDCl_3$) 3.88 (3H, s, OCH_3), 6.82-6.97 (2H, m, H-3 and H-5), 7.10-7.63 (8H,

m, ArH), 7.96 (1H, d, J = 9Hz, ArH) ; m/z 310 (M^+, 100%) 279 (9), 190 (55) (Anal. Calcd. for $C_{18}H_{14}O_3S$: C, 69.66 ; H, 4.55. Found : C, 69.90 ; H, 4.76%).

2-(2'-Carbomethoxyphenyl)-4-(4'-methoxyphenyl)thiophene (89j). Colourless crystals (ether/hexane) ; yield 84% ; m.p. 69°C ; IR (KBr) 1721, 1602, 1500, 1482, 1442, 1298, 1217 cm^{-1} ; δ_H ($CDCl_3$) 3.78 (3H, s, OCH_3), 3.82 (3H, s, CH_3OCO), 6.62-6.98 (4H, m, H-3, H-5 and ArH), 7.02-7.24 (2H, m, ArH), 7.26-7.53 (3H, m, ArH), 7.73-7.96 (1H, s, ArH) ; m/z 340 (M^+, 17%), 399 (100), 205 (20), 135 (13) (Anal. Calcd. for $C_{19}H_{16}O_4S$: C, 67.04 ; H, 4.74. Found : C, 67.16 ; H, 4.83%).

2-(2'-Naphthyloxy)-4-(4'methoxyphenyl)thiophene (89k). Colourless crystals (ether/hexane) ; yield 76% ; m.p. 149°C ; IR (KBr) 1621, 1530, 1478, 1310, 1276 cm^{-1} ; δ_H ($CDCl_3$) 3.80 (3H, s, OCH_3), 6.73-7.0 (4H, m, H-3, H-5 and ArH), 7.33-7.59 (6H, m, ArH), 7.64-7.83 (3H, m, ArH) ; m/z 332 (M^+, 100%) (Anal. Calcd. for $C_{21}H_{16}O_2S$: C, 75.88 ; H, 4.85. Found : C, 76.03 ; H, 4.96%).

2-Phenoxy-3,4-dihydronephtho[2-1-c]thiophene (89l). Colourless viscous liquid ; yield 34% ; IR (neat) 1620, 1510, 1238 cm^{-1} ; δ_H ($CDCl_3$) 2.51-2.98 (4H, m, CH_2), 6.97-7.19 (3H, m, H-5 and ArH), 7.20-7.49 (6H, m, ArH), 7.68 (1H, d, J = 4.5Hz, ArH) ; m/z 278 (M^+, 50%), 201 (4), 185(14) (Anal. Calcd. for $C_{18}H_{14}OS$: C, 77.66 ; H, 5.07. Found : C, 77.95 ; H, 5.30%).

REFERENCES

1. A. Thomas, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., *30*, 3093 (1989).
2. Laxminarayan Bhat, A. Thomas, H. Ila, H. Junjappa, Tetrahedron, *48*, 10377 (1992).
3. B.M. Trost, L..Jr. Melvin, Sulphur Ylids, Emerging Synthetic Intermediates ; Acedemic press ; 1975, (a) Chapt. 1, pp. 2 (b) Chapt. 2, pp. 21.
4. F. Krolipfeife, H. Hartmann, F. Schimdt, Justus Liebig Ann. Chem., 563, 15 (1949).
5. J.P. Marino, J.L. Kostosyk, Terahedron Lett., 2493 (1979).
6. S. Kurozumi, T. Toru, M. Kobayashi, S. Ishimoto, Synthetic Commun., 7, 427 (1977).
7. M.L. Purakayasta, M. Chandrasekharam, J.N. Vishwakarma, H. Ila, H. Junjappa, Synthesis, 245 (1993).
8. Laxminarayan Bhat, H. Ila, H. Junjappa, Synthesis, 0000(1993).
9. C.D. Hurd, K.L. Krenz, J. Am. Chem. Soc., *74*, 2965 (1952.
10. J, Sice, J. Am. Chem. Soc., *75*, 3698 (1953).
11. E.Proft, Liebig. Ann. Chem., *622*, 196 (1959).
12. E.B.Pedersen, S.O.Lawesson, Tetrahedron, *28*, 3861 (1971).
13. J. Ashby, M. Ayad, O. Meth-Cohn, J. Chem. Soc. Perkin Trans 1, 404 (1973).
14. J.W.H. Watthey, M. Desai, J. Org. Chem., *47*, 1755 (1982).
15. J. Brunet, D. Paquer, Phosphorous Sulphur, 3 (1977).
16. M.A.Keegstra, T.H.A.Peters, L.Brandsma Tetrahedron, *48*, 3633(1992).

CHAPTER IV

REARRANGEMENT STUDIES ON ACYLKETENE O-PROPARGYL S-METHYL ACETALS.

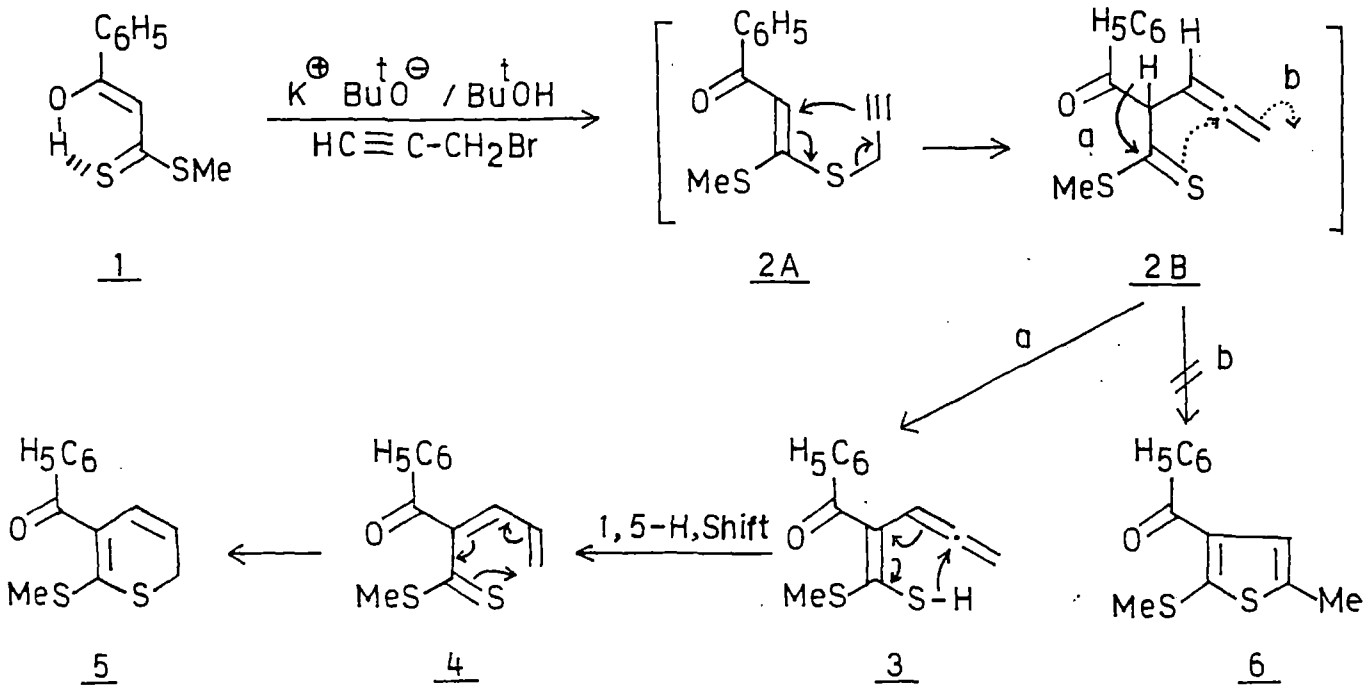
IV.1 INTRODUCTION

The synthesis of unsymmetrical α-oxoketene dithioacetals were first reported by Lawesson and co-workers[1] in 1972. Although a number of symmetrical substituted α-oxoketene dithioacetals were known earlier, no attempts were made to prepare the corresponding unsymmetrical α-oxoketene dithioacetals. One of the primary reasons for this was the difficulty associated with the preparation of the monosalt of the dithioate as it underwent alkylation on both sulfur atoms invariably since the intermediate alkyldithioate underwent alkylation faster

than the disodium salt. However, Lawesson and co-worker resolved this problem by successfully isolating the mono tetrabutylammonium salts using ion pair extraction techniques. They prepared the dithioester 1 by this method which was then treated with propargyl bromide to get the correspondng S-propargyl S-methyl dithioacetal 2A. The dithioacetal 2A *insitu* underwent 3,3-sigmatropic rearrangement to allene 2B which subsequently rearranged to thiopyran 5 as depicted in scheme 1. However, the expected thiophene 6 was not formed.

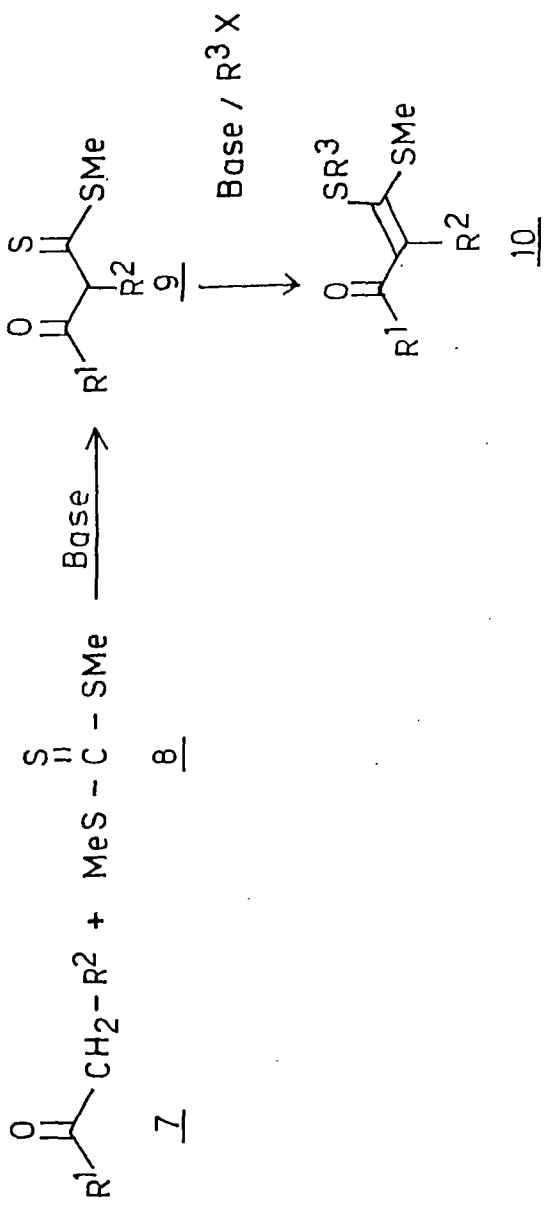
Subsequently, a new method for the synthesis of dithioesters directly from active methylene ketones 7 in one pot reaction was developed in this laboratory[2]. Thus the enolate anions on treatment with dimethyl trithiocarbonate 8 in the presence of base after work up yielded the corresponding methyl dithioesters 9 in high yields. These dithioesters were then used for the sythesis of unsymmetrical α-oxoketene dithioacetals 10 (scheme 2).

Prior to this, Brandsma and co-workers[3,4] had studied the rearrangements of propargyl thiovinyl compounds 11 and 14 (scheme 3) which underwent thio-Claisen or 3,3-sigmatropic rearrangement to give the corresponding allenes 12 and 15 respectively. When these allenes 12 and 15 were heated in the presence of triethylamine afforded the corresponding thiopyrans 13 and 17 respectively. However, when 15 were heated in the presence of acid the corresponding thiophenes 16 were obtained.



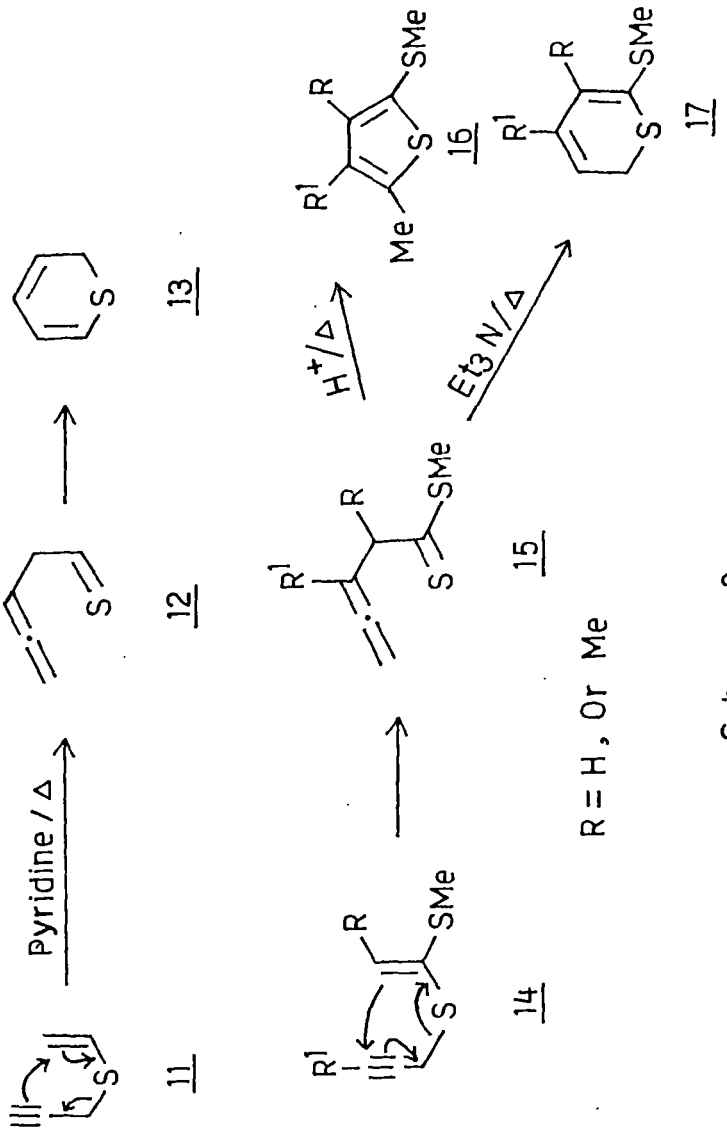
1 2A 2B 5 4 3 6

Scheme - 1



7 8 9 10

Scheme - 2

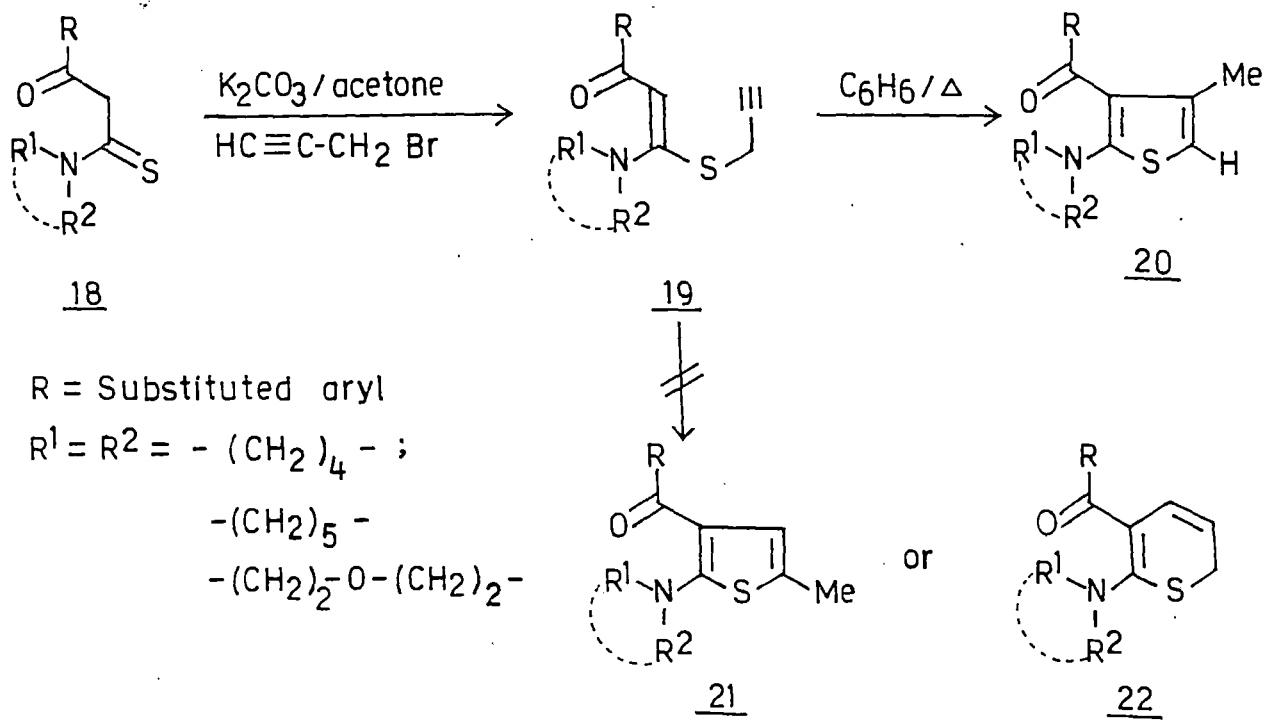


Scheme - 3

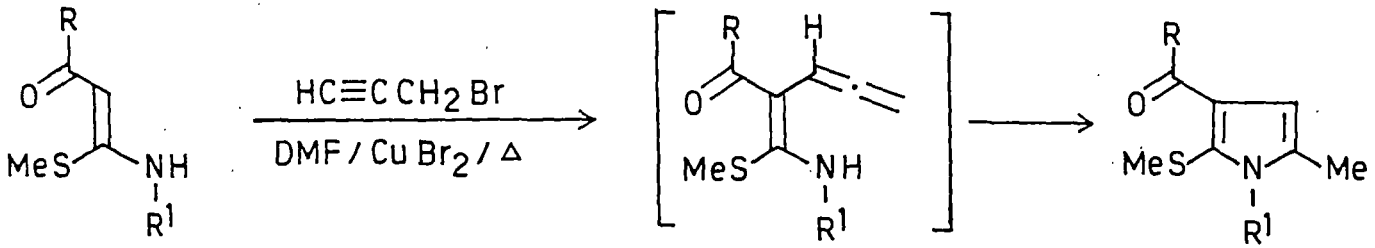
Junjappa and co-workers[5] prepared the S-propargyl N-acetals in high yields by converting the dithioesters to the corresponding thioamides 18 followed by their alkylation with propargyl bromide (scheme 4). These S,N-acetals 19 on refluxing in benzene yielded the corresponding 2-amino-3-benzoyl-4-methyl thiophenes 20. Thus 19 did not undergo expeted 3,3-sigmatropic rearrangement under these reaction conditions but simply underwent intramolecular cyclization to give 20. Hence neither the corresponding regioisomeric thiophenes 21 nor the corresponding thiopyrans 22 were detected in the reaction mixture.

Subsequently, in our laboratory when the S,N-acetals 23, 26 and 28 (scheme 5) were reacted with propargyl bromide in the presence of copper (I) bromide in hot DMF, the corresponding 5-methylpyrroles 25, 27 and 29 were formed respectively in good yields[6]. In this reaction the formation of intermediate allene of the type 24 appears to be the first step which on intramolecular ring closure yielded the observed 5-methylpyrroles.

In the preceeding chapter we have described the preparation of α-oxoketene O,S-acetals[7] which were subsequently used as precursors for the synthesis of alkoxy substituted thiophenes[8]. In the present study the method used for the preparation of O-aryl S-alkyl acetals[7] was extended to prepare the α-oxoketene O-propargyl S-methylacetals with a view to examine the sigmatropic rearrangement of these acetals and the products thus formed. We have subsequently

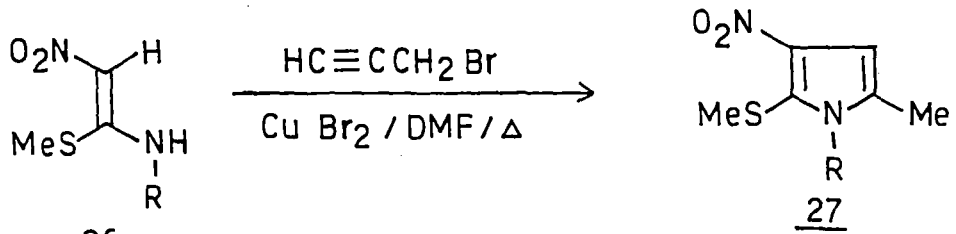

R
O
R1
N
S
R2
K2CO3 / acetone
HC≡C-CH2 Br
III
C6H6 / Δ
Me
H
18
19
20
R = Substituted aryl
R1 = R2 = - (CH2)4 - ;
-(CH2)5 -
-(CH2)2-O-(CH2)2-
or
21
22

Scheme - 4



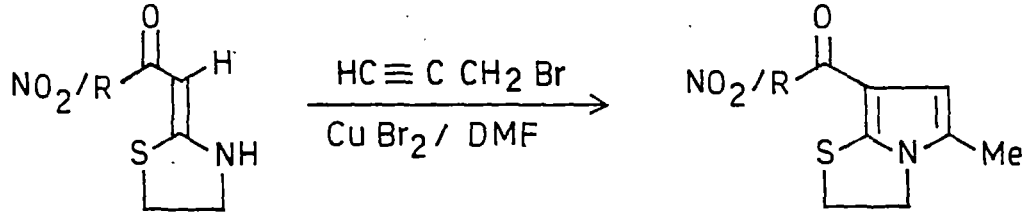
23 24 25

R = Me, Substituted aryl ; R = Me, Et, $C_6H_5CH_2$, C_6H_5



26 27

R = Me, Et, C_6H_5 etc.



28 29

Scheme - 5

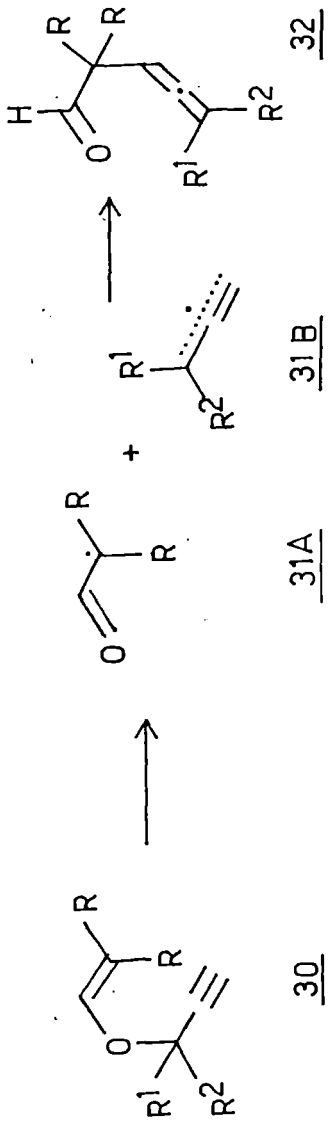
prepared a number of hitherto unknown α-oxoketene O-propargyl S-methylacetals and subjected them to thermal rearrangement both under neutral and basic conditions to afford the products thereof.

Extensive studies have been made on the rearrangement of propargyl O-arylethers[9] which are related to the present study and their references are briefly reviewed in the following section.

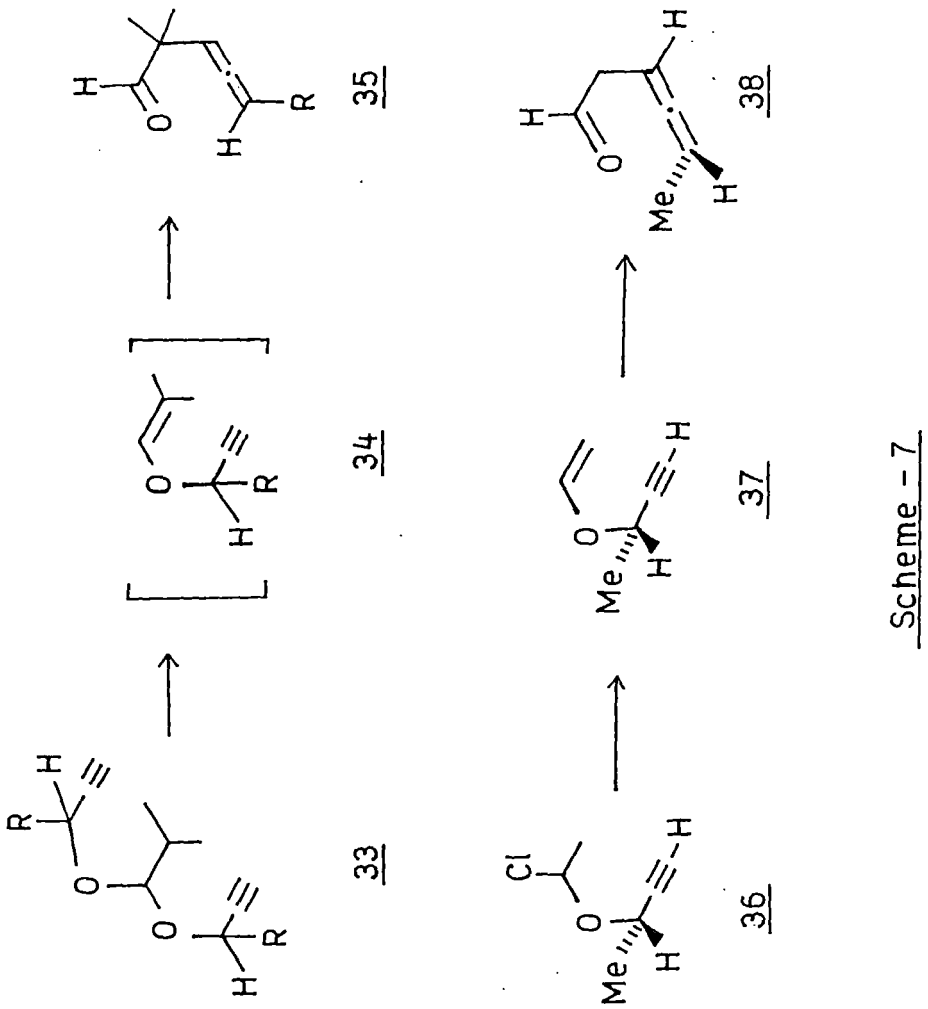
Black and Landor[10] studied the Claisen rearrangement of propargyl vinyl ethers **30** and observed their thermal rearrangement to provide the corresponding allenic aldehydes **32** (scheme 6).

Jones and co-workers[11] prepared the propargyl vinyl ethers **34** which *insitu* underwent 3,3-sigmatropic rearrangement to the corresponding allenic intermediates **35**. Similarly Landor and co-workers[12] prepared the propargyl vinyl ether **37** which on rearrangement gave the corresponding allenic intermediate **38** (scheme 7).

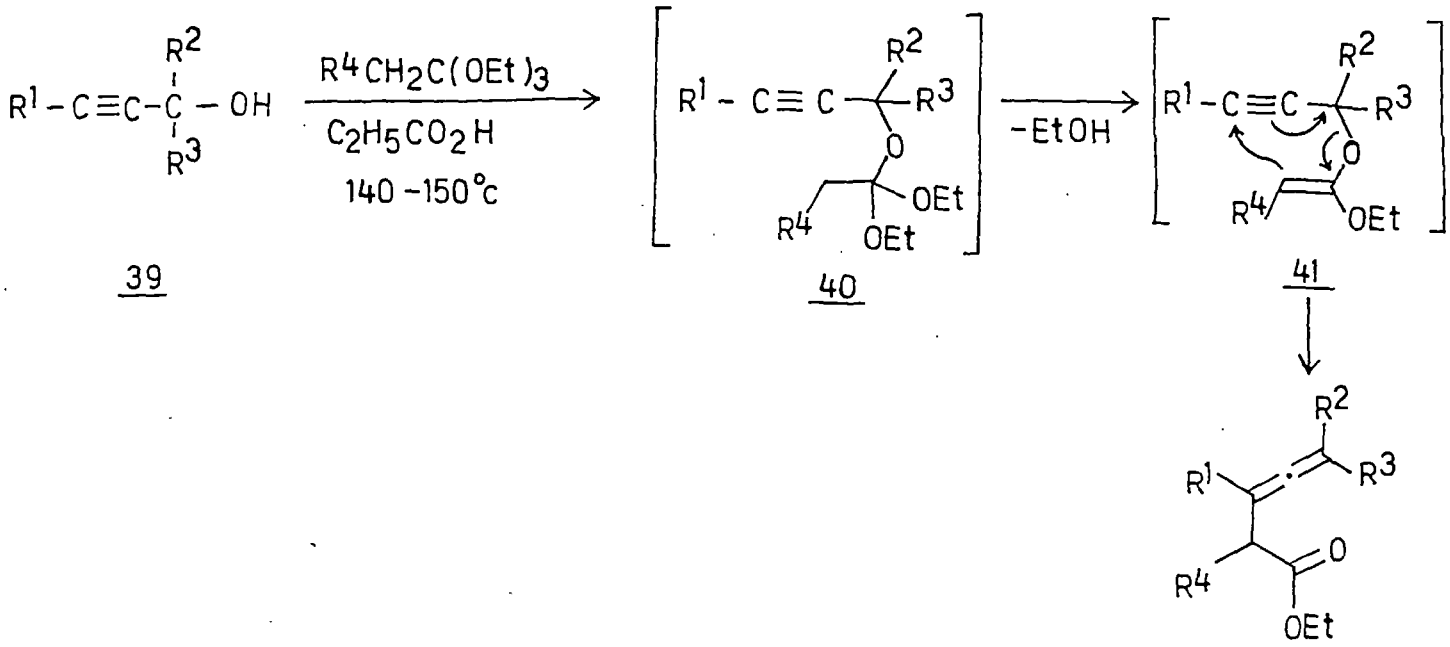
Tindell and co-workers[13] similarly prepared allenic esters **42** as depicted in scheme 8. The reaction of propargyl alcohols **39** with triethyl orthoalkanoates followed the addition elimination sequence when reacted with to provide the required propargyl vinyl ethers **41** which *insitu* underwent 3,3-sigmatropic rearrangement to give the allenic esters **42**.



Scheme - 6



Scheme - 7

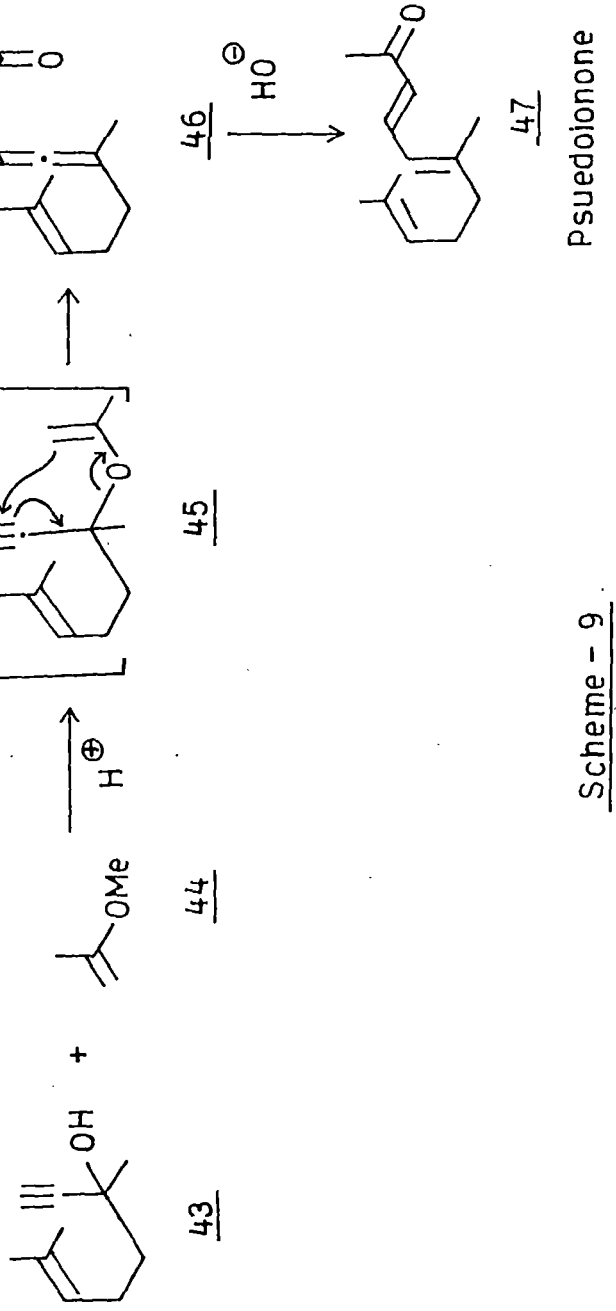

R1 - C≡C - C(R2)(R3) - OH
R4CH2C(OEt)3
C2H5CO2H
140 -150°c
39
R1 - C≡C - C(R2)(R3) - O - C(R4)(OEt)(OEt)
40
-EtOH
41
42

Scheme – 8

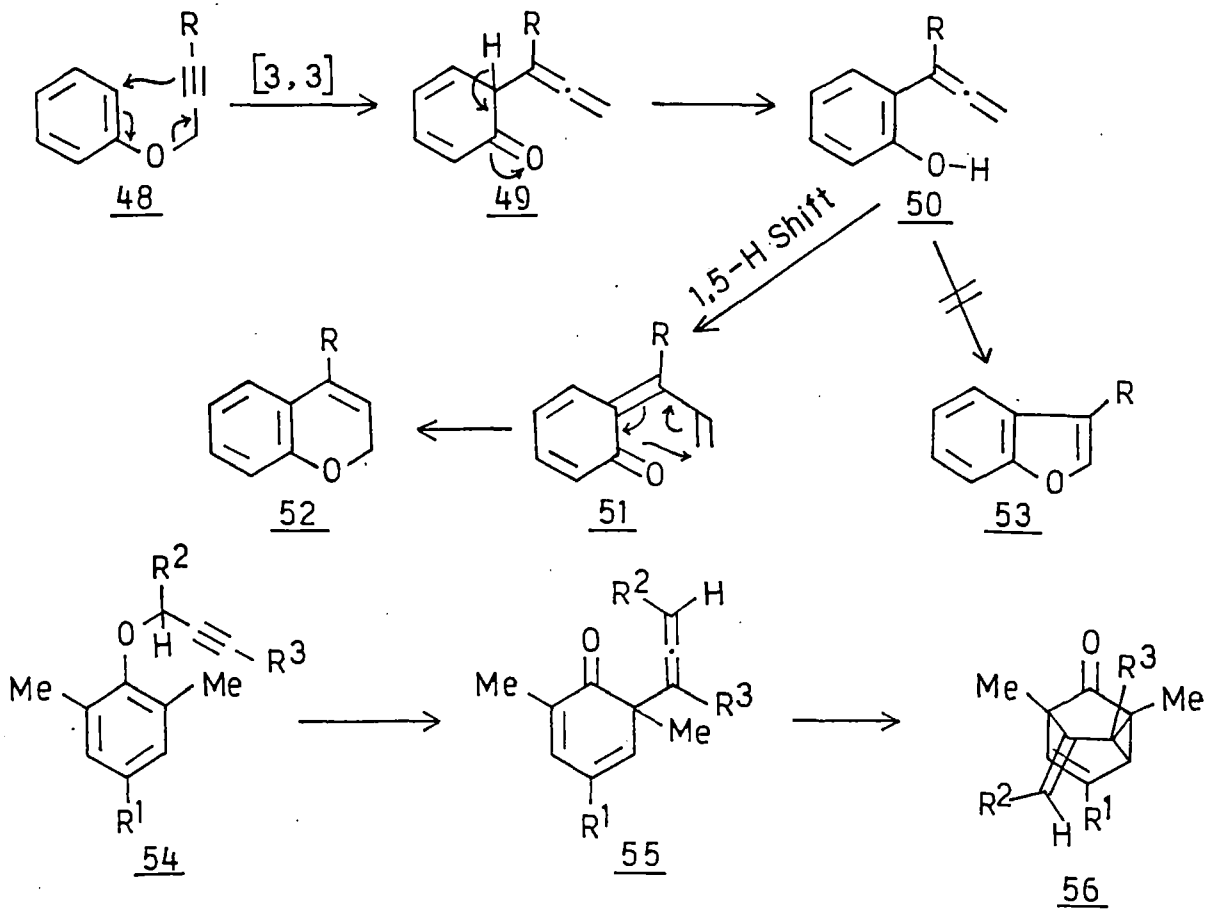
An interestng example of preparation of psuedoionone 47[14] is formulated as in scheme 9, involving 3,3-sigmatropic shift of propargyl vinyl ether 45. The propargyl alcohol 43 on condensation with methoxy propene 44 yielded *insitu* the corresponding propargyl vinyl ether 45 which underwent thermal rearrangement to give the corresponding allenic ketone 46 followed by base assisted 1,3-proton shift to afford pseudoionone 47.

Sindely and Schmid[15] reported the rearrangement of ortho allenic phenol 50 to the corresponding pyran 52 through 1,5-hydride shift followed by cyclization. However, the corresponding benzofuran 53 was not detected in the reaction mixture. The same authors also studied the rearrangement of propargyl ethers of formula 54 where the adjacent positions in the phenyl ring were substituted by methyl groups. The initial 3,3-sigmatropic shift yielded the allenic intermediate 55 which underwent intramolecular [4+2] cycloaddition to give the corresponding adduct 56 (scheme 10).

The sigmatropic rearrangement has also been observed in heterocyclic molecules[16]. Thus 5-hydroxy uracil 57 (scheme 11) was converted first into corresponding O-propargyl ether 58, which underwent rearrangement depending on the solvent used to provide either furan 59 or pyran 60. In DMF at 140°C 59 was the major product with 60 in minor quantities. In DMSO 58 yielded the corresponding pyran 60 as major product which on prolonged heating converted into the corresponding

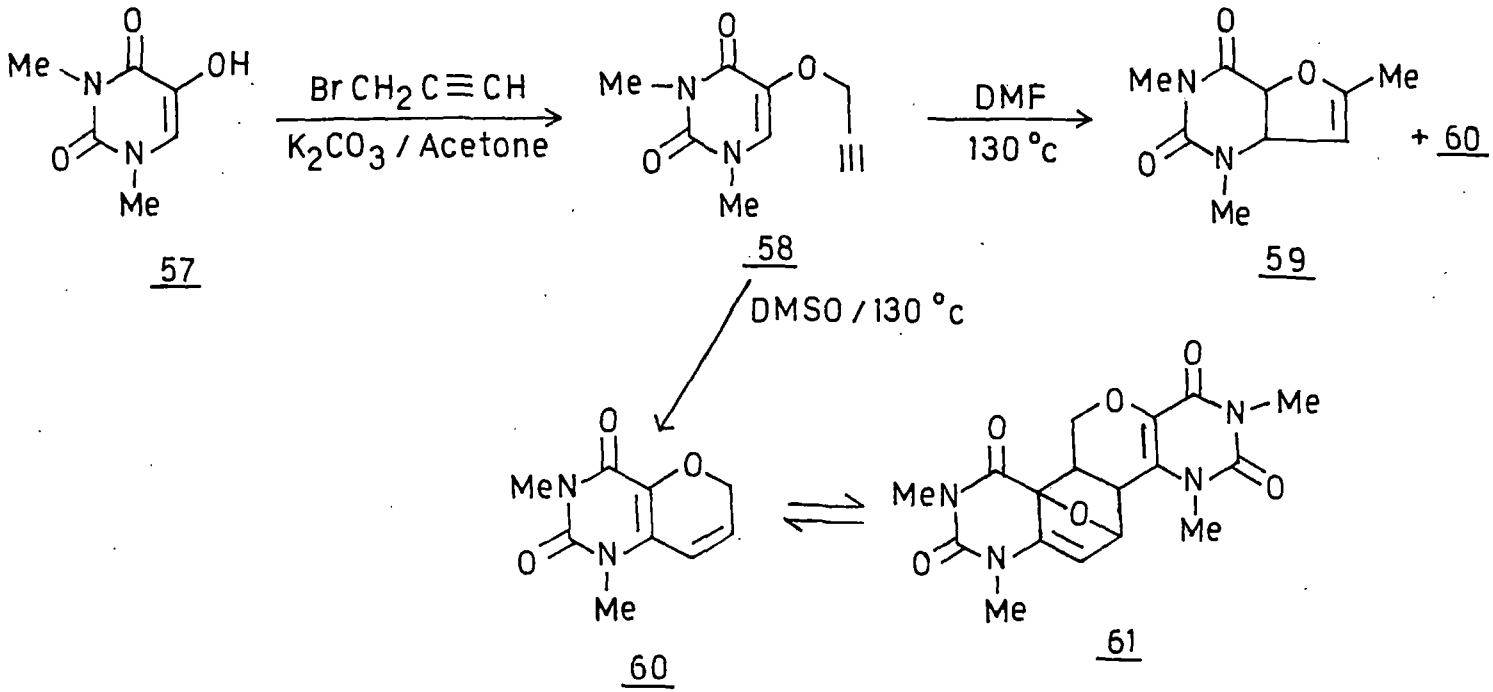


Scheme - 9



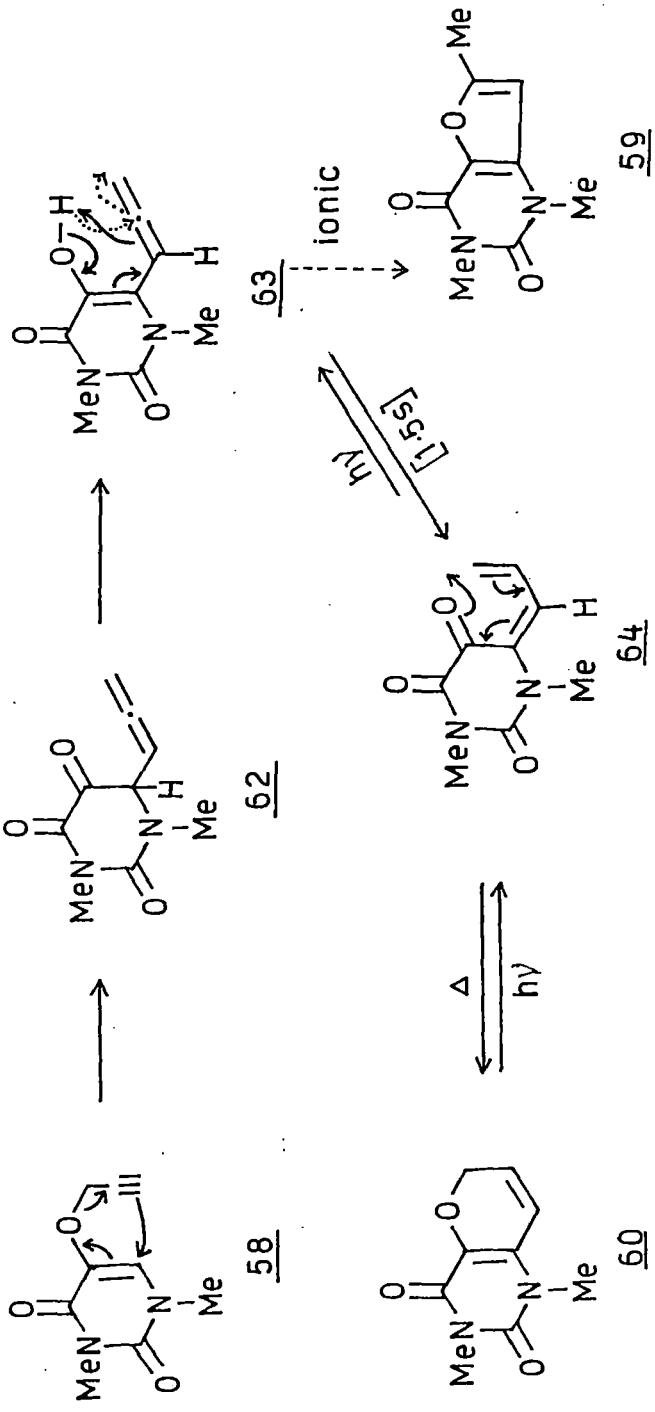
$R^1 = R^2 = R^3 = H, D, Me.$

Scheme – 10



57 58 59 60 61

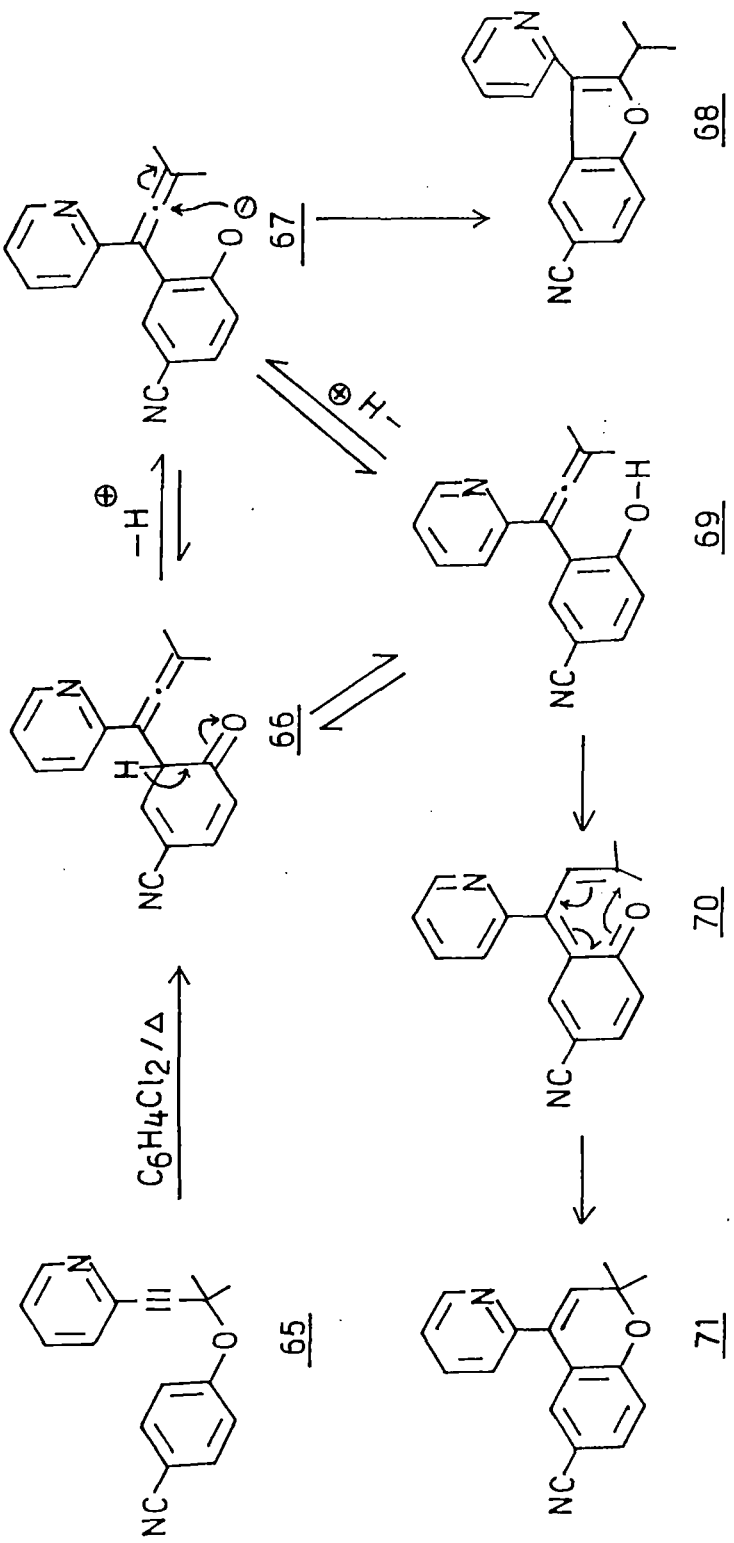
Scheme - 11



Scheme - 12

Diels-Alder adduct 61. The mechanism governing these rearrangements is though apparent but significant since the formation of furan 59 is observed under some reaction conditions besides the formation of pyran 60 as generally observed in the proceeding examples. Thus allenic intermediate 63 in DMF underwent intramolecular ring closure to give 59 while in DMSO 63 preferred to follow 1,5 hydride shift to give 64 followed by its electrocyclic ring closure to give 60 (scheme 12).

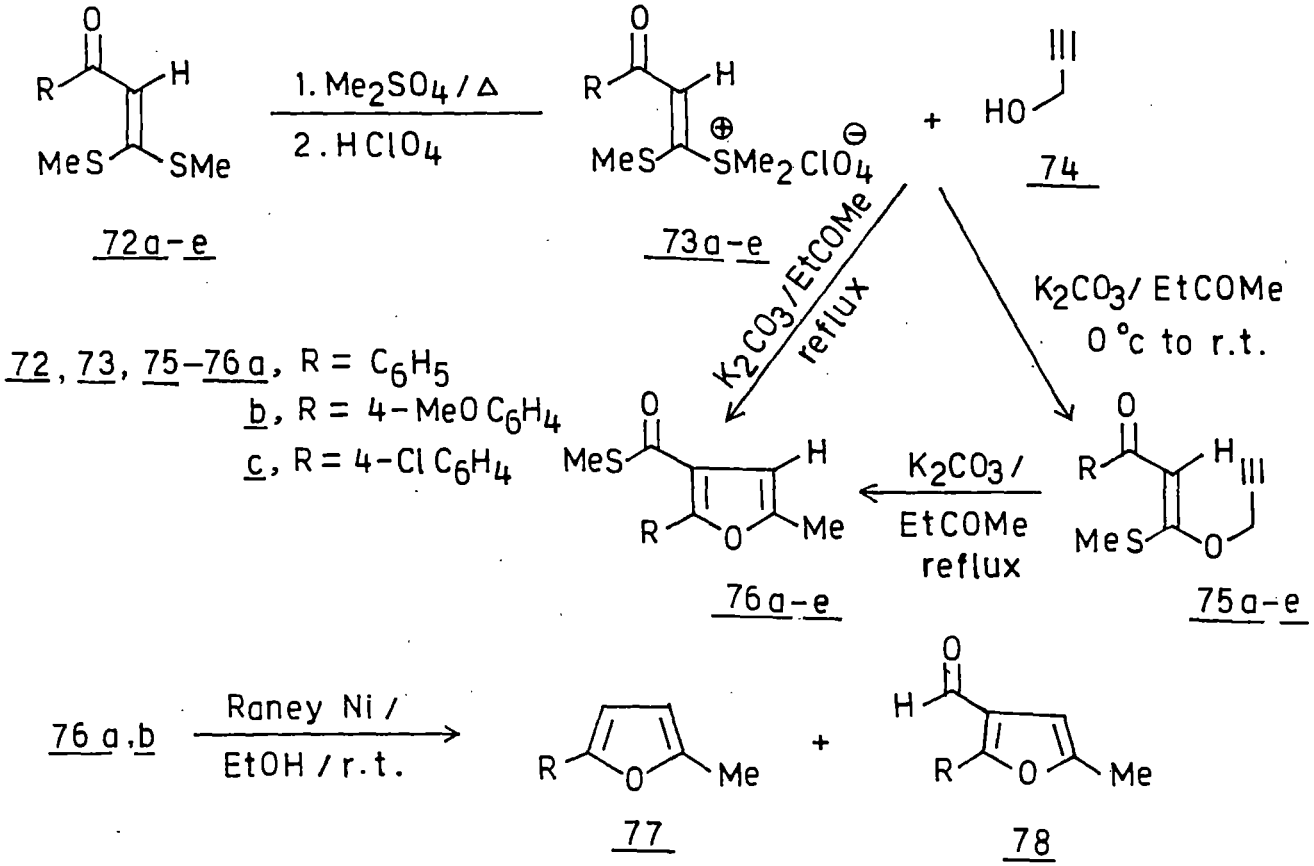
Attwood and co-workers[17] have reported the Claisen rearrangement of phenyl propargyl ether 65 to the corresponding benzopyran 71 and benzofuran 68 under neutral conditions (scheme 13). The benzofuran products have not been reported from Claisen rearrangements of phenyl propargyl ethers before, although a similar route has been observed for pyrimidyl propargyl ethers[16]. The conversion of O-allenylphenol to 2-methylbenzofuran has been observed under strongly basic conditions although under milder conditions (triethylamine or thermal) only conversion to the benzopyran was observed[15]. In this case the authors rationalised that the deprotonation in 66 is favoured by the presence of electron withdrawing group on the aryl ring and also the intermediate 67 thus formed will be fovourably disposed to benzofuran cyclisation due to the stabilisation afforded to the resultant anion by the pyridyl group.



Scheme – 13

IV.2 RESULTS AND DISCUSSION

It has been shown that the α-oxoketene dithioacetals 72 undergo facile displacement with various alcohols and phenols through their dimethyl sulphonium perchlorates 73 to give the corresponding O,S-acetals in good yields[7]. Thus it is possible to extend this method for the preparation of propargyl vinyl ethers of general formula 75 which are of interest for subsequent transformations. In the present investigation therefore the propargyl alcohol 74 was reacted with 73a in ethylmethyl ketone in the presence of potassium carbonate at 0°C to afford a pale yellow solid, m.p. 99-100°C which was characterized as 3-methylthio-1-phenyl-3-propargyloxy-2-propenone 75a in 76% yield (scheme 14). The structure of O,S-acetal 75a was established on the basis of its analytical and spectral data. It was analysed for $C_{13}H_{12}O_2S$ and its molecular weight 232 was confirmed by its mass spectrum with a peak at m/z 232 (M^+, 23%). In its IR(KBr) spectrum a weak band at 2130 cm^{-1} was assigned to the acetylenic triple bond whereas the benzoyl carbonyl absorbed at 1629 cm^{-1}. The structure was further confirmed by its ^1H NMR ($CDCl_3$) spectrum. The singlet at δ2.30(3H) was assigned to SMe protons and the triplet at δ2.60(1H, J=1.5Hz) was assigned to the acetylenic proton. The doublet at δ4.83(2H, J=1.5Hz) was assigned to the methylene protons. The vinylc proton appeared at δ6.55(1H) as singlet. The phenyl protons appeared as two multiplets one at δ7.30-7.58(3H) and the other at δ7.82-8.02(2H). The other O,S-acetals 75b and 75c



72, 73, 75–76 a, R = C_6H_5
b, R = 4-MeO C_6H_4
c, R = 4-Cl C_6H_4

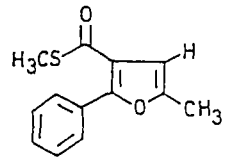
Scheme - 14

were similarly prepared in identical yields. Their structures were established on the basis of their analytical and spectral data (experimental section).

The O,S-acetal **75a** on subsequent heating in ethylmethyl ketone in the presence of anhydrous potassium carbonate after work up the reaction mixture yielded the product which was characterized as 3-carbomethylthio-5-methyl-2-phenylfuran **76a** in 84% yield (scheme 14). Its structure was established on the basis of its analytical and spectral data. It was analysed for $C_{13}H_{12}O_2S$ and its molecular weight 232 was confirmed from its mass spectrum with a peak at m/z 232 (M^+, 20%). The IR (neat) showed a strong band at 1695 cm^{-1}, which was due to methylthio carbonyl group. The other bands observed are listed in experimental section. The structure was further confirmed from its ^1H NMR (250MHz, $CDCl_3$) spectrum. The doublet at δ2.29(3H, J=1.5Hz) was assigned to methyl protons. The SMe three protons appeared as singlet at δ2.36(3H) and the ring H-4 proton appeared as doublet at δ6.64(1H, J=1.5Hz). The phenyl protons appeared as two multiplets one at δ7.33-7.42(3H) and the other at δ7.72-7.96(2H). The furan **76a** was also obtained directly by reacting propargyl alcohol with **73a** in boiling ethylmethyl ketone in the presence of anhydrous potassium carbonate in 56% yield. The product was identical (superimposable ir and nmr) with that obtained from **75a**. The other furans **76b-c** were similarly obtained from both the routes and their structures were confirmed from their analytical and spectral

data (experimental section). The ^{1}H and ^{13}C NMR spectra of 76a are shown in figure 1 and 2 respectively.

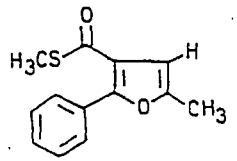
When 76a was subjected to Raney Nickel desulphurization in ethanol at room temperature, a mixture of furan 77a and 78a was formed in 34% and 46% yield respectively (scheme 14). The structure of 5-methyl-2-phenylfuran 77a was confirmed by its analytical and spectral data which are described in the experimental section. The structure of 5-methyl-2-phenylfuran-3-aldehyde 78a was confirmed from its analytical and spectral data. It was analysed for molecular formula $C_{12}H_{10}O_2$ and the molecular weight 186. The mass spectrum confirmed its molecular weight with a peak at m/z 186 (M^+, 100%). The IR (neat) specturm showed strong band at 1683 cm^{-1} which was assigned to aldehyde carbonyl function. The other important IR bands are listed in the experimental section. The structure was further confirmed by its ^{1}H NMR ($CDCl_3$) spectrum. The singlet δ2.44(3H) was assigned to the methyl protons. The singlet at δ6.50(1H) was assigned to H-4 proton or ring proton. The phenyl protons appeared as two multiplets one at δ7.48-7.69(3H) and the other at δ7.86-7.96(2H). The low field signal singlet at δ10.23(1H) was assigned to the aldehyde proton. The other furan 76b similarly gave a mixture of the corresponding furan 77b and furan aldehyde 78b in identical yields. The structures of both 77b and 78b were in accord with their analytical and spectral data (expermental section).



^{1}H NMR ($CDCl_3$; 250MHz) spectrum of

3-Carbomethylthio-5-methyl-2-phenylfuran (76a).

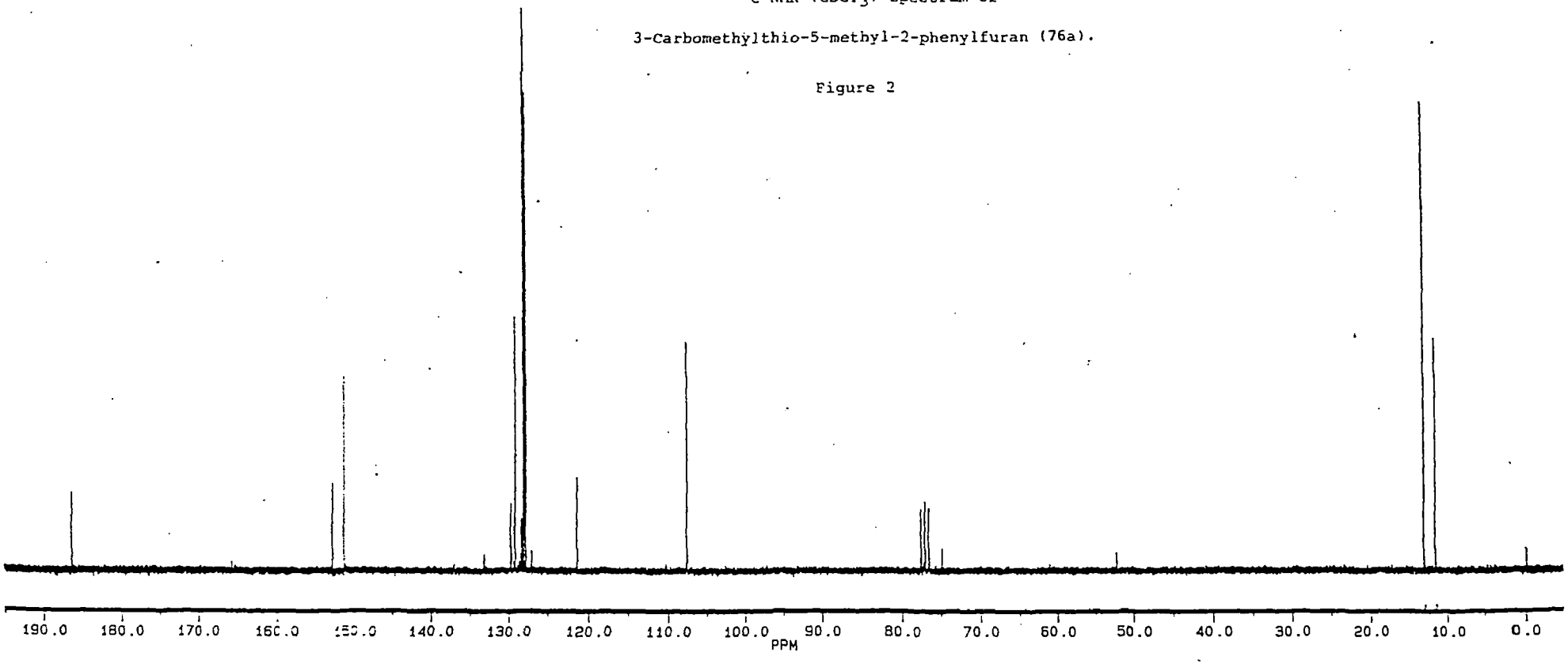
Figure 1



^{13}C NMR ($CDCl_3$) spectrum of

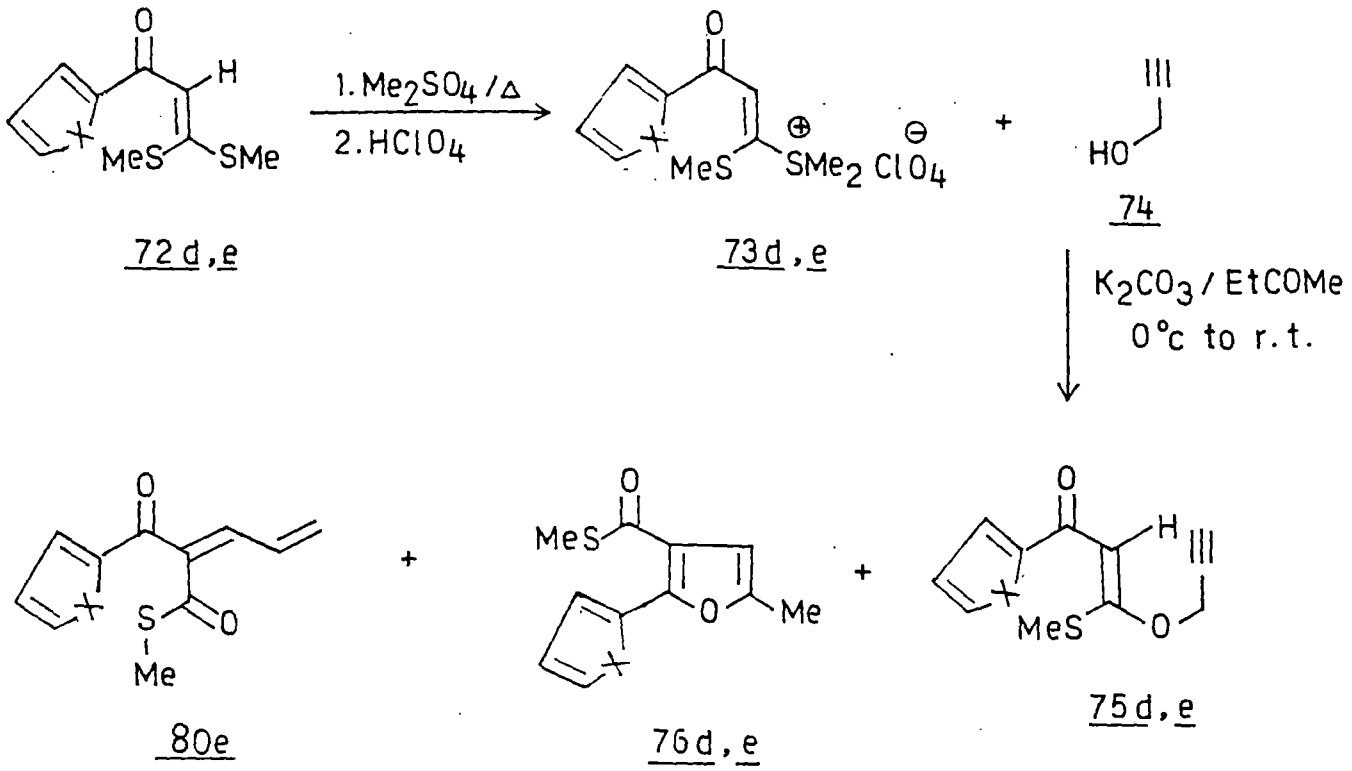
3-Carbomethylthio-5-methyl-2-phenylfuran (76a).

Figure 2



The probable mechanism for the formation of furans 76 is depicted in scheme 16. The first step appears to involve the Claisen rearrengement of the O,S-acetals 75 to the corresponding allene intermediates 81. Under basic conditions (K_2CO_3/EtCOMe) the 81 underwent proton abstraction to give the enolate anions 82 which on intramolecular ring closure through nucleophilic attack on activated allene moiety afforded the 5-methylfurans 76.

When this reaction was extended to 2-furyloxoketene dithioacetal 72d and 2-thienyloxoketene dithioacetal 72e, there was a slight deviation in the product distribution. Thus, when corresponding sulphonium perchlorate 73d was reacted with propargyl alcohol at 0°C a mixture of the corresponding O,S-acetal 75d and furan 76d was formed in 68% and 22% yields respectively (scheme 15). However, at elevated temperature only 76d was formed as observed in the earlier experiments. Apparently the formation of 76d requires milder reaction conditions than the corresponding aroylketene dithioacetals as described earlier. The structures of 75d and 76d were confirmed by their analytical and spectral data (experimental section). Interestingly when 2-thienyloxoketene dithioacetal 72e reacted with 74 through its dimethylsulphonium perchlorate 73e in ethylmethyl ketone in the presence of potassium carbonate at 0°C, as described earlier, yielded a mixture of three products. In addition to the corresponding O,S-acetal 75e (11%), furan 76e (58%) and diene ester 80e (22%) were also formed (scheme 15). The



72 d, e

73 d, e

74

80e

76 d, e

75 d, e

72, 73, 75, 76 d, X,= O

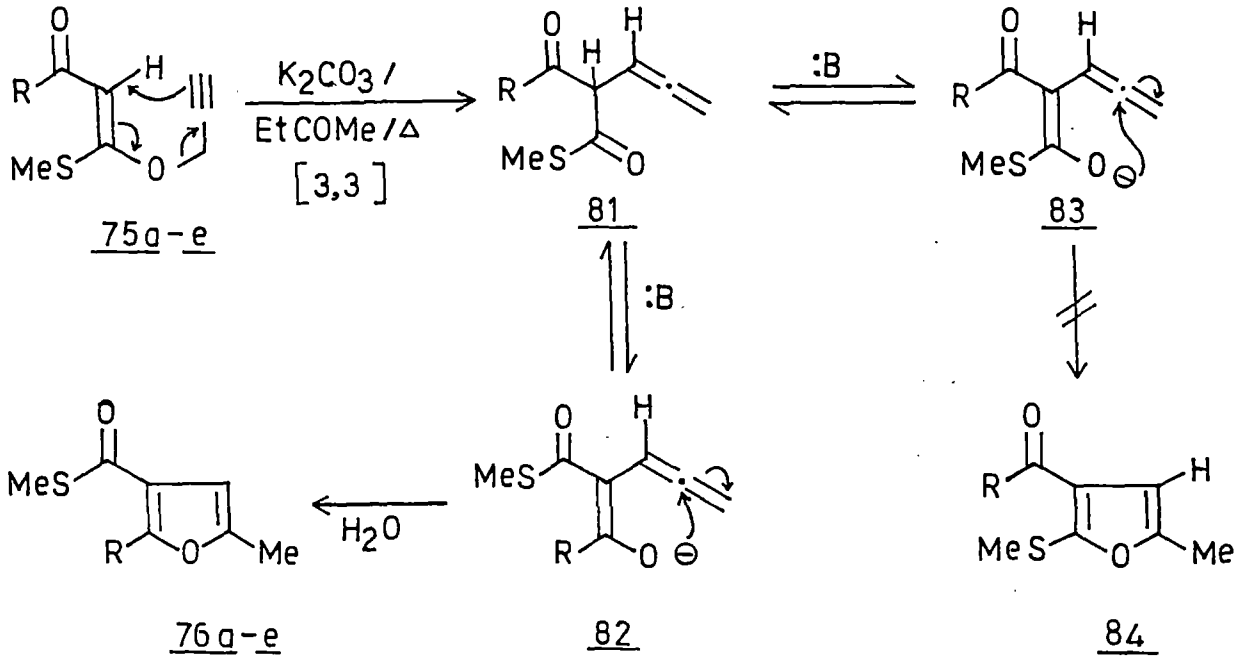
76, 80 e, X,= S

Scheme - 15

structures of O,S-acetal 75e, furan 76e and diene ester 80e were confirmed from their analytical and spectral data which are described in experimental section.

Formation of furan 76e and diene ester 80e are apparently formed after the 3.3-sigmatropic rearrangement of 76e to the corresponding allene ester (scheme 16). It appears that the allene ester rearranged by dual pathways of which one is leading to the formation of 76e and the other to the formation of 80e. This is apparent since the formation of 76e is irreversibly stable and not convertable to 80e. The formation of diene ester 80e appears to compete through the 1,5 hydride shift with the intramolecular ring closure that leads to the formation of 76e.

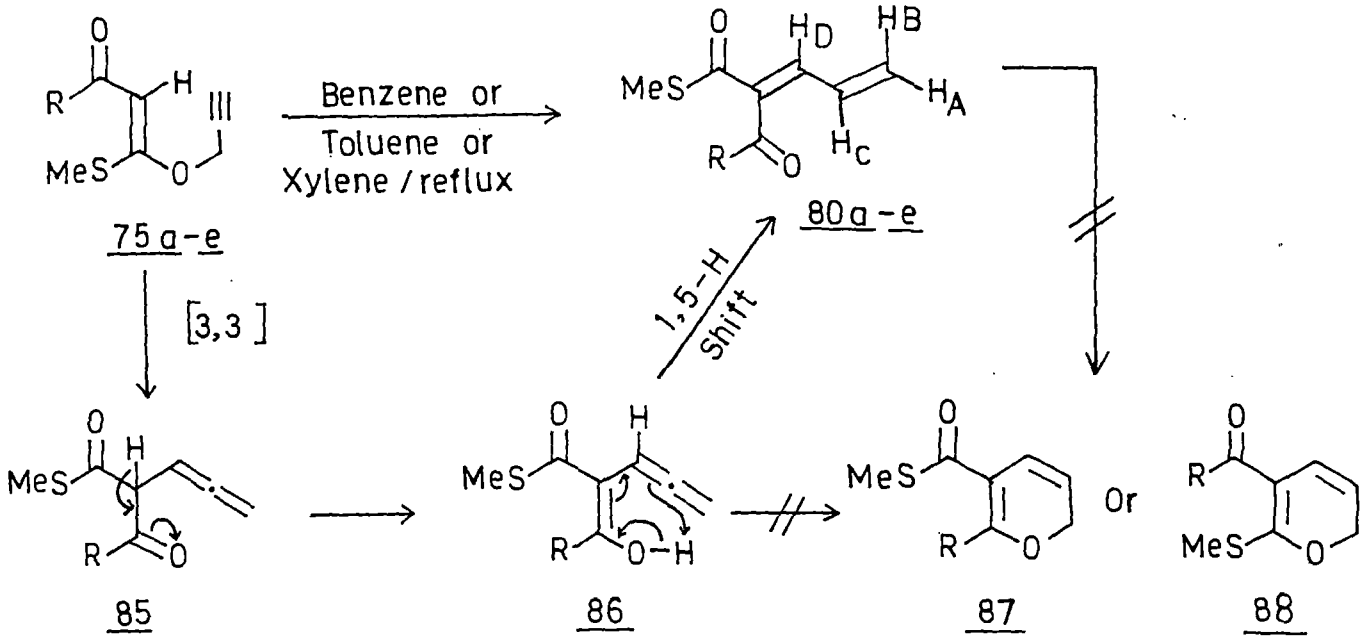
The α-oxoketene O-propargyl S-methylacetals 75a-e were examined under purely thermal conditions without using any base in the reaction mixture (scheme 17). Thus, when 75a was refluxed in benzene for 3hr, only corresponding diene ester 80a was formed in 94% yield and no other product was detected in the reaction mixture. However, when the reaction time for the conversion of 75a to 80a was reduced to 1 hr. by refluxing in toluene and for 15 min. in xylene, the yields were found to be identical. The structure of 2-carbomethylthio-1-phenyl-2,4-pentadienone 80a was assigned on the basis of its analytical and spectral data which confined to the *E* configuration. Its IR (neat) spectrum showed characteristic bands at 1686 and 1671 cm^{-1} due to two different carbonyl groups. In its ^1H NMR (CCl_4) the signal



Scheme - 16

due to the SCH_3 group appeared as a singlet at δ2.32(3H). The vinylic proton H_A appeared as double duoblet at δ5.56(1H, J_{AC}=10Hz and J_{AB}=2Hz) and proton H_B also appeared as double doublet at δ5.78(1H, J_{BC}=17Hz and J_{AB}=2Hz). The doublets at δ6.49(1H, J_{BC}=17Hz, J_{CD}=12Hz and J_{AC}=10Hz) were assigned for H_C proton and H_D proton appeared as doublet at δ7.42(1H, J_{CD}=10Hz). The phenyl protons appeared as two multiplets one at δ7.48-7.62(3H) and other at δ7.79-8.08(2H). The structure of this compound was also confirmed by its mass spectrum which exhibited molecular ion peak at m/z 232 (M^+, 4%) and the peak at 185 (70%) was assigned for the fragment ion formed by the loss of SMe group. The base peak appeared at m/z 105 (100%) due to C_6H_5CO fragment.

The thermal rearrangement of 75 in hydrocarbon solvents appears to proceed through initial 3,3- sigmatropic shift to give the intermediate allenes 85 which under neutral conditions rearranged to diene esters 80 through enolization and subsequent 1,5-hydride shift in the intermediate 86. The other possible product 2*H* pyrans 87 and 88 were not formed since they are unstable and rearranges to the corresponding diene esters 80. The other O,S-acetals **75b-e** also underwent the described rearrangement to afford the corresponding diene esters **80b-e** in 90-93% overall yields. The structures of **80b-e** were established on the basis of their analytical and spectral data which are described in experimental section.



75a-e 80a-e 85 86 87 88

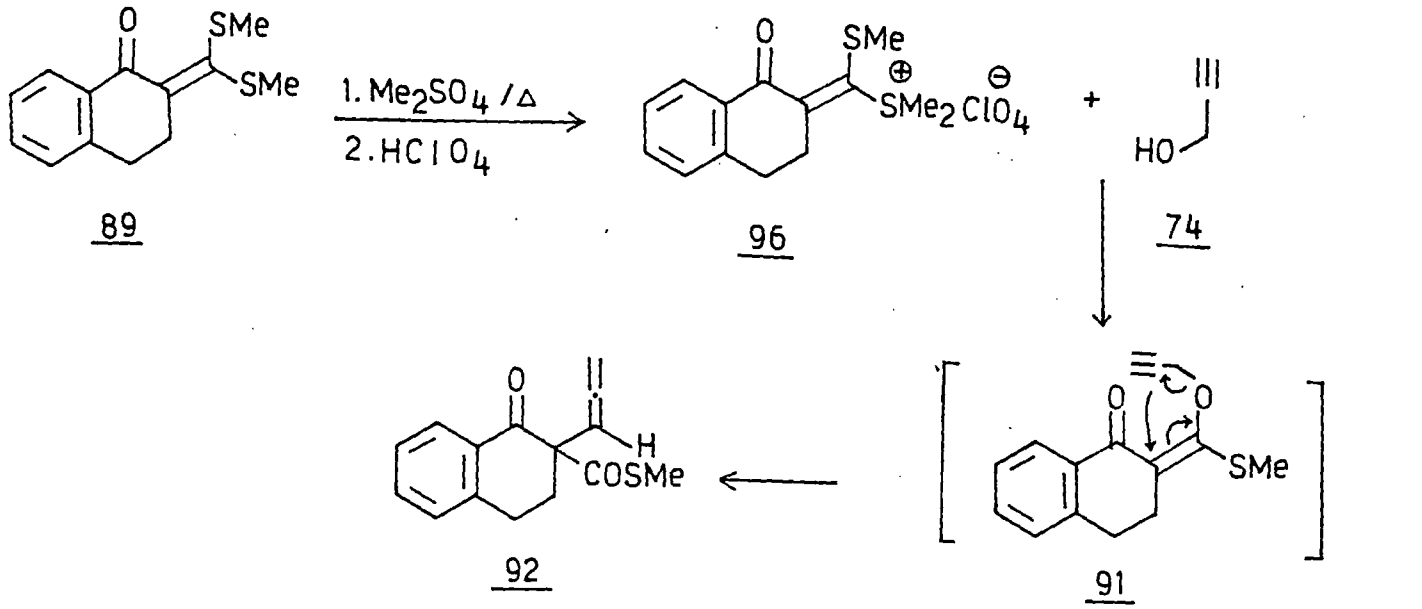
75-80a, R = C_6H_5
b, R = 4-MeO C_6H_4
c, R = 4-Cl C_6H_4
d, R = 2-Furyl
e, R = 2-Thienyl

Scheme-17

Dimethylsulphonium perchlorate 90 derived from tetralone mercaptal also underwent smooth displacement with propargyl alcohol under the described reaction conditions, to afford directly the corresponding allenic esters 92 (scheme 18). The structure of 2-allenyl-2-carbomethylthio-1-tetralone 92 was established on the basis of its analytical and spectral data (experimental section).

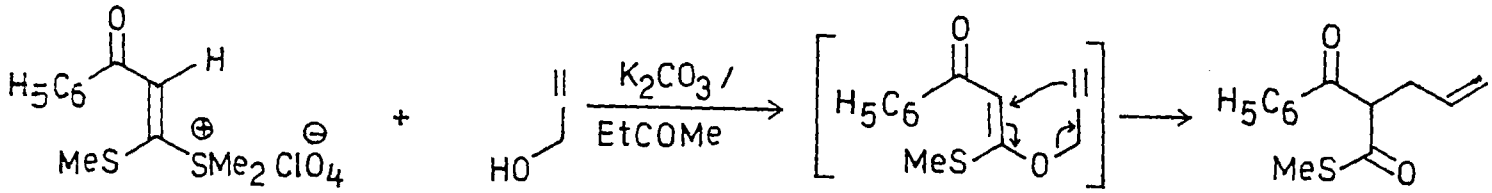
Similarly dimethylsulphonium perchlorate 73a when reacted with allyl alcohol under the described reaction conditions afforded the corresponding rearranged product 95 (scheme 19). The structure of 2-carbomethylthio-1-phenyl-4-penten-1-one 95 was in accord with its analytical and spectral data (experimental section).

It was considered of interest to examine the corresponding O,S-acetals 75a and 75b as typical examples to introduce bromine at α-position and subject them to radical assisted cyclization. Thus 75a was conveniently brominated with N-bromosuccinimide in dichloromethane to give the corresponding α-bromo O,S-acetal 96a in 90% yield which was then directly treated with tri-n-butyltinhydride in the presence of AIBN in refluxing benzene, the corresponding 3-benzoyl-5-methyl-2-methylthiofuran 97a was obtained in 54% yield. The structure 97a was established by its analytical and spectral data. It was analysed for $C_{13}H_{12}O_2S$ and its molecular weight 232 confirmed by the mass spectrum with a peak at m/z 232 (M^+, 41%). Its IR(neat) spectrum showed stretching carbonyl absorption at 1660 $(C_6H_5CO)cm^{-1}$ [the corresponding furan 76a



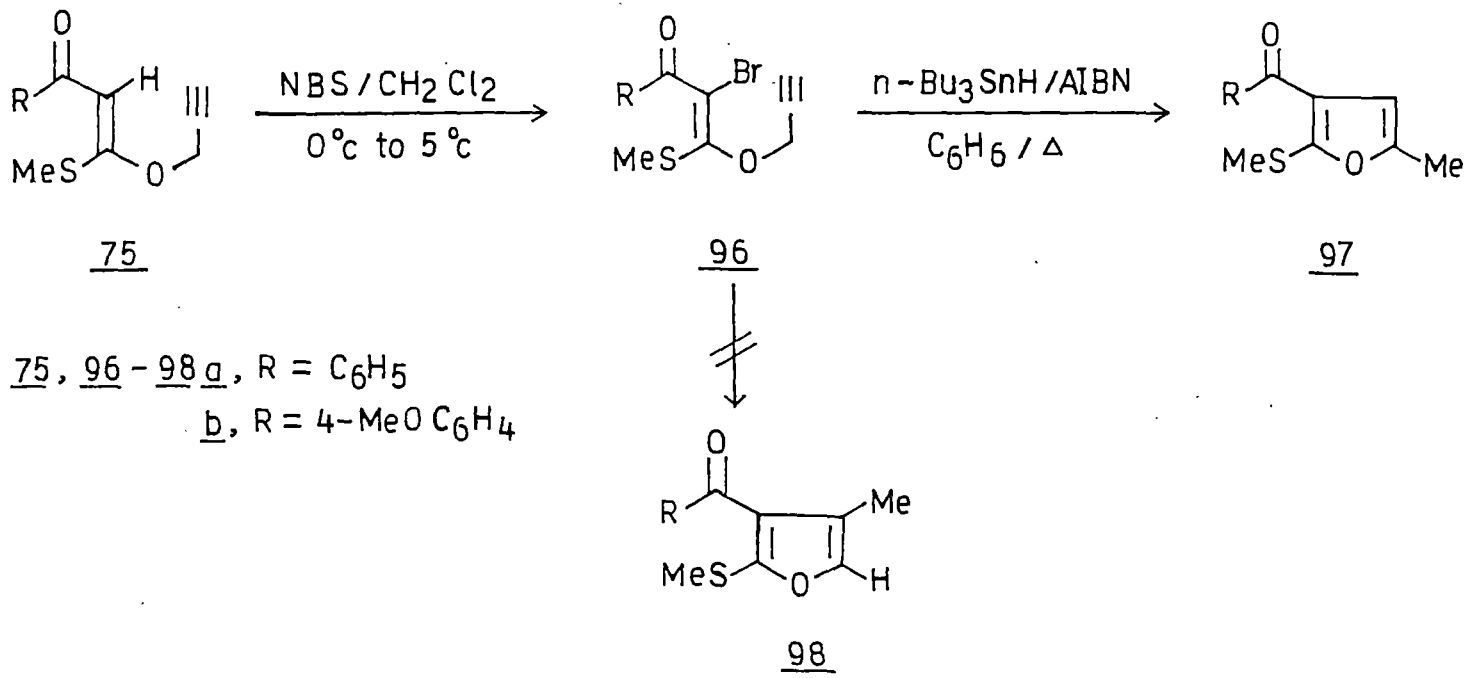
89 96 74 92 91

Scheme - 18



73a 93 94 95

Scheme - 19



75

96

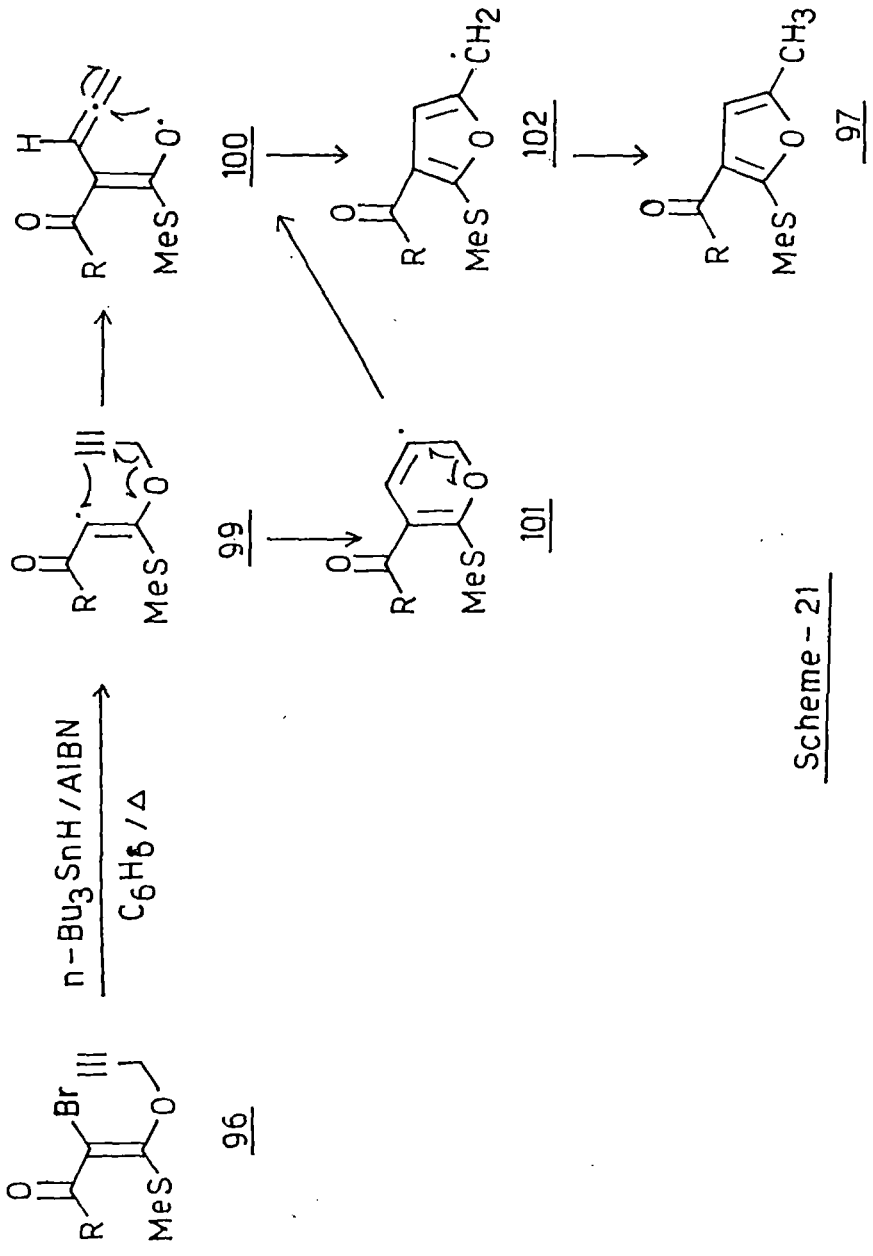
97

75, 96 - 98 a, R = C_6H_5

b, R = 4-MeO C_6H_4

98

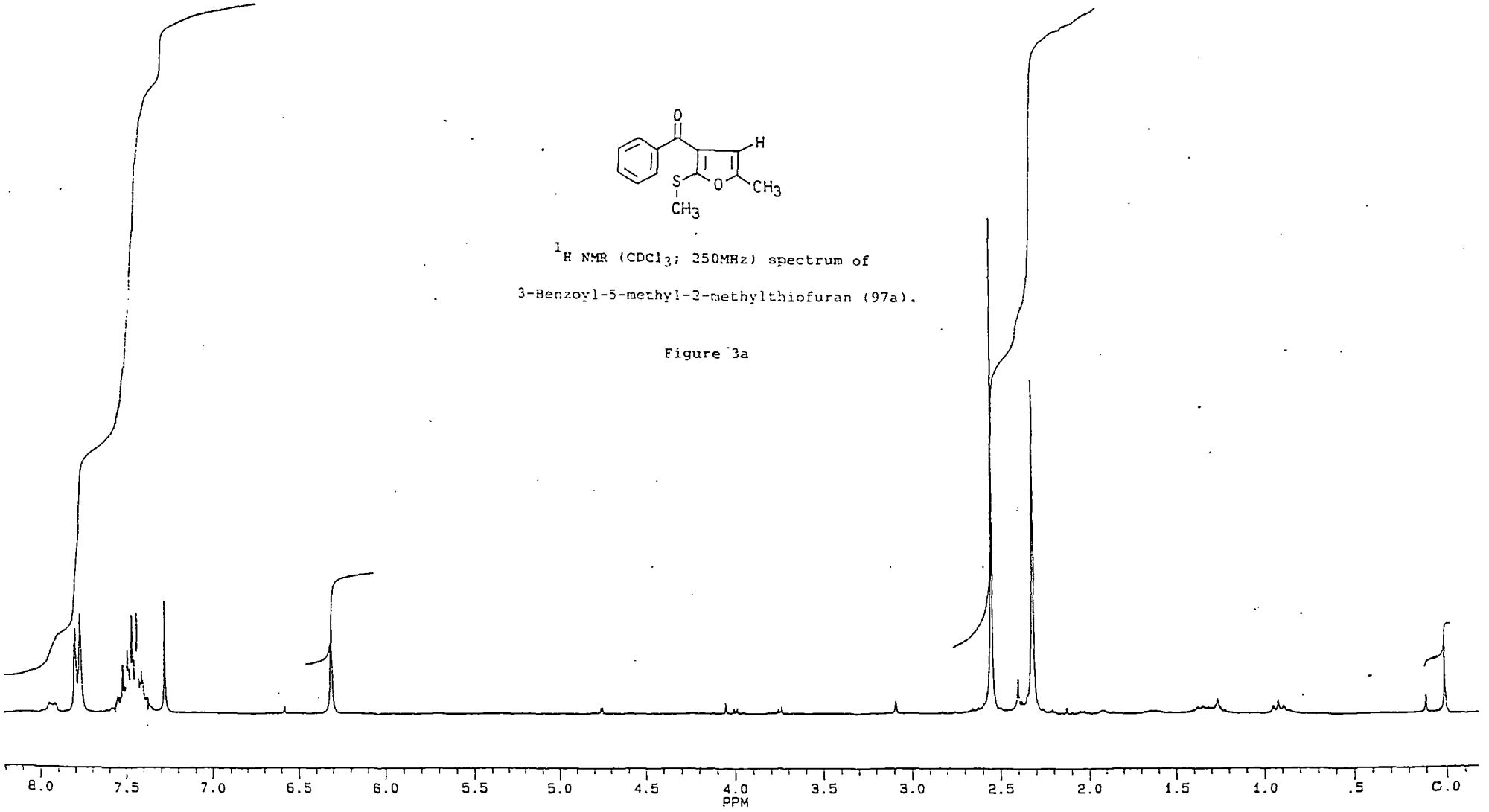
Scheme - 20



Scheme - 21

obtained from the base catalysed cyclization had absorption at 1675 (CH_3SCO) cm^{-1}]. Its ^1H NMR ($CDCl_3$; 250 MHz) spectrum (Figure 3a, b and c) showed a signal singlet at δ2.31(3H) for methyl protons. The singlet at δ6.31(1H) was assigned to H-4 or furan ring proton. The phenyl protons appeared as two multiplets one at δ7.43-7.52(3H) and other at δ7.76-7.79(2H). The structure was further confirmed from its ^{13}C NMR spectrum (Figure 4). The important signal for phenyl C-1' carbon which is characteristic of its position next to carbonyl group appeared at δ138.9 while the corresponding C-1' in 2-phenyl furan 76a (Figure 2) appeared at δ129.64. The other signals are reported in the experimental section. Thus the structure of 97a was confirmed to have the benzoyl group which is absent in the other furan 76a. Similarly 75b gave the corresponding furan 97b in 52% yield. The structure of 97b was identical with that of 97a and the values are reported in the experimental section.

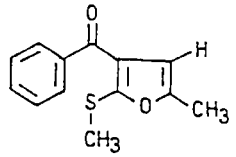
The typical mode of cyclization of α-bromo O,S-acetals 96 in the presence of tri-*n*-butyltinhydride and AIBN involved the formation of radical intermediates 99 followed by their cyclization through 6-*endo trig* process to give the cyclic radical intermediates 101. 101 on subsequent ring cleavage afforded the corresponding radical allene 100 which could also be derived from 97 through radical Claisen rearrangement. Subsequent intramolecular cyclization of 100 to radical intermediates 102 followed by reduction afforded the corresponding furans 97 (scheme 21).



^{1}H NMR ($CDCl_3$; 250MHz) spectrum of

3-Benzoyl-5-methyl-2-methylthiofuran (97a).

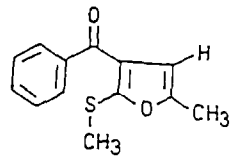
Figure 3a



^{1}H NMR ($CDCl_3$; 250MHz) spectrum of (97a).

(peak at δ2.3 irradiated)

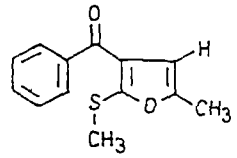
Figure 3b



^{1}H NMR ($CDCl_3$; 250MHz) spectrum of (97a).

(peak at δ6.3 irradiated)

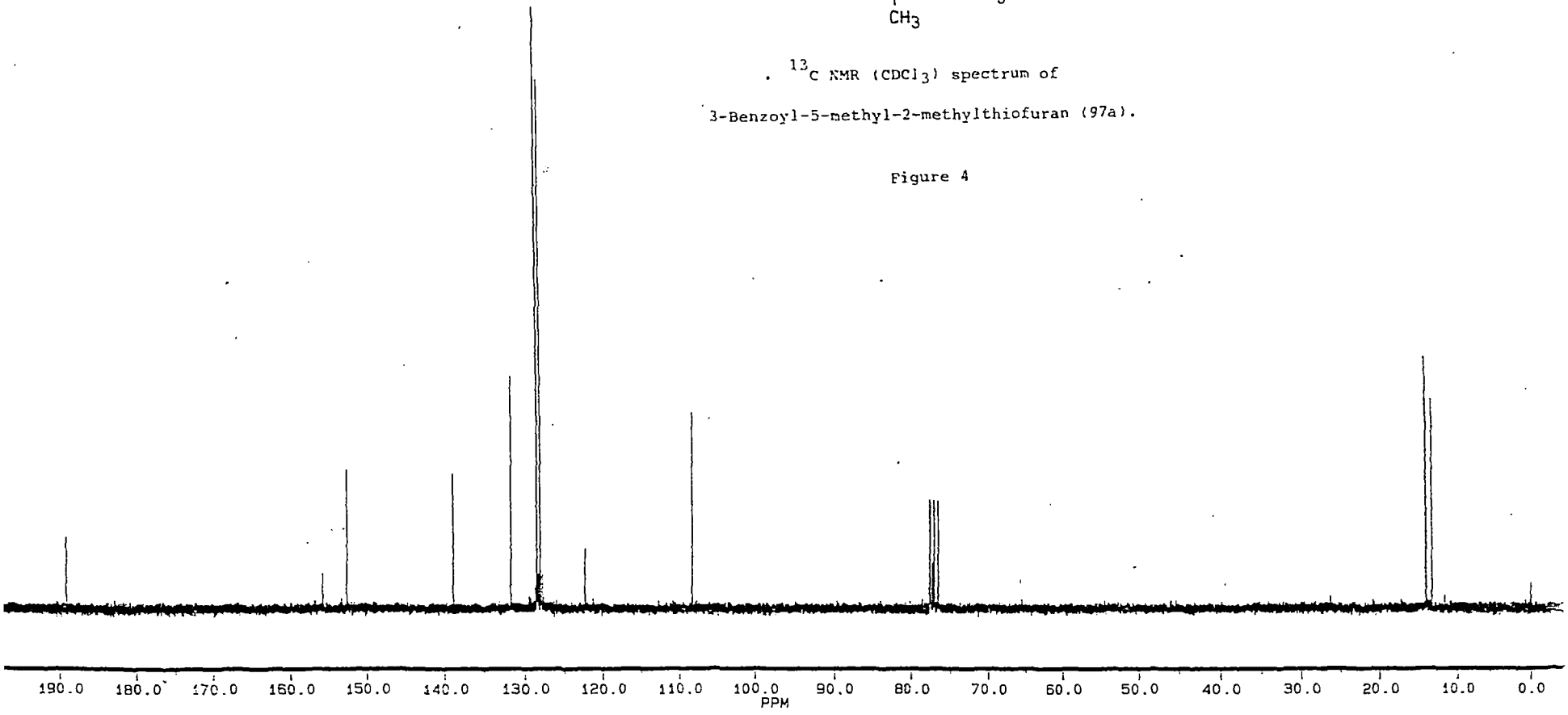
Figure 3c



. ^{13}C NMR ($CDCl_3$) spectrum of

3-Benzoyl-5-methyl-2-methylthiofuran (97a).

Figure 4



IV.3 CONCLUSION

The proprgyl vinyl ethers of wide structural variation which are otherwise called the α-oxoketene O-propargyl S-methylacetals were prepared by displacement reaction of the dimethylsulphonium perchlorate salts of the corresponding α-oxoketene dithioacetals. These O,S-acetals have been shown to undergo expected 3,3-sigmatropic rearrngement followed by their base assisted ring closure to the corresponding furans involving the carbonyl oxygen as a part of the furan ring. The corresponding dihydro 2H pyrans which are known to be unstable and therefore reverse to the corresponding dienes, which are obtained when the reaction was carried out under neatral thermal conditions. The O,S-acetals in the absence of enolizable proton rearranged to the corresponding allenic ketoester which was isolated and characterized. Similarly the allyl alcohol also underwent the expected rearrangement to afford the corresponding rearranged product. Two O-propargyl S-methylacetals were studied for bromination and the corresponding bromo compounds were subjected to radical assisted ring closure in the presence of tributyltin hydride and AIBN afforded the corresponding regioisomeric furans where the methylthio carbonyl oxygen was part of the furan ring.

IV.4 EXPPERIMENTAL

Melting points were determined on a `Thomas Hoover' melting point (capillary method) apparatus and are uncorrected. The

IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer and the IR frequencies have been reported in cm^{-1}. The ^1H NMR spectra were recorded on a Varian EM-390, 90 MHz and Bruker 250 MHz spectrometer and are reported in δ units down field from TMS. The Mass spectra were recorded on a Jeol JMS-D 300 mass spectrometer respectively. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyzer.

Starting Materials

All α-oxoketene dithioacetals used for the preparation of dimethylsulphonium perchlorates were prepared according to the general procedure described in experimental section of chapter II. The ketones required for the preparation of α-oxoketene dithioacetals are commercially available and used as such without further purification. The propargyl alcohol, ethylmethyl ketone were distilled prior to use. The benzene, toluene and xylene were dried dried over sodium wire. Commercially available tri *n*-butyltinhydride (Fluka) and AIBN were used as such without further purification.

General Procedure for Preparation of Acylketene O-Propargyl S-Methylacetals (75a-e).

A suspension of the propargyl alcohol (1.7g, 0.03, mol) and anhydrous K_2CO_3 (12.5g, 0.09, mol) in anhydrous acetone (or ethylmethyl ketone) (100 ml) was refluxed with stirring for 3hr. The resulting mixture was cooled to 0-5°C and the dimethylsulphonium perchlorate salt 73 (0.01 mol) was added

in small portions with stirring. The mixture was further stirred in the same temperature for 2 hr. and another 5-6 hrs. at room temperature, filtered, washed with acetone (ethylmethylketone) (2x25 ml) and the filtrate was concentrated under reduced pressure. The residue was then cooled to room temperature , poured onto crushed ice (200g), extracted with $CHCl_3$ (2x100 ml), washed with water (3x100 ml), dried (Na_2SO_4) and evaporated to give crude products which were purified by crystalisation ($CHCl_3$/hexane).

3-Methylthio-1-phenyl-3-propargyloxy-2-propen-1-one (75a). Pale yellow crystals ($CHCl_3$/hexane) ; yield 76% ; m.p. 99-100°C ; IR (KBr) 3326, 2130, 1629, 1609, 1503, 1261 cm^{-1} ; δ_H($CDCl_3$) 2.30 (3H, s, SCH_3), 2.60 (1H, t, J=1.5Hz, ≡CH), 4.83 (2H, d, J=1.5Hz, CH_2), 6.55 (1H, s, =CH), 7.30-7.58 (3H, m, ArH), 7.82-8.02 (2H, m, ArH); m/z 232 (M^+, 23%) (Anal. Calcd. for $C_{13}H_{12}O_2S$: C,67.21 ; H, 5.21. Found : C, 67.44 ; H, 5.35%).

1-(4'-Methoxyphenyl)-3-methylthio-3-propargyloxy-2-propen-1-one (75b). Yellow crystals ($CHCl_3$/hexane) ; yield 78% ; m.p. 113°C ; IR (KBr) 3255, 2150, 1620, 1510, 1268, 1174 cm^{-1} ; δ_H ($CDCl_3$) 2.30 (3H, s, SCH_3), 2.65 (1H, t, J=1.5Hz, ≡CH), 3.82 (3H, s, OCH_3), 4.82 (2H, d, J=1.5Hz, CH_2), 6.59 (1H, s, =CH), 6.99 (2H, d, J=9Hz, ArH), 7.99 (2H, d, J=9Hz, ArH); m/z 263 (M^+, 17%) 216 (72), 135 (100) (Anal. Calcd. for $C_{14}H_{14}O_3S$: C, 64.10 ; H, 5.38. Found : C, 64.38 ; H, 5.65%).

1-(4'-Chlorophenyl)-3-methylthio-3-propargyloxy-2-propen-1-one (75c). Pale yellow crystals ($CHCl_3$/hexane) ; yield 75% ;

m.p. 95-96°C ; IR (KBr) 3225, 2129, 1625, 1602, 1480, 1242 cm^{-1} ; $\delta_H(CDCl_3)$ 2.32 (3H, s, SCH_3), 2.73(1H, t, J=1.5Hz, ≡CH), 4.88 (2H, d, J=1.5Hz, CH_2), 6.59 (1H, s, =CH), 7.49 (2H, d, J=9Hz, ArH), 7.93 (2H, d, J=9Hz, ArH); m/z 267 and 266 (M^+, 4 and 2%), 219 (78), 139 (100) (Anal. Calcd. for $C_{13}H_{11}ClO_2S$: C, 58.53 ; H, 4.16. Found : C, 58.79 ; H, 4.41%).

1-(2'-Furyl)-3-methylthio-3-propargyloxy-2-propen-1-one(75d). Yellow crystals ($CHCl_3$/hexane) ; yield 68% ; m.p. 101-102°C ; IR (KBr) 3225, 2125, 1622, 1594, 1538, 1280, 1210 cm^{-1} ; δ_H ($CDCl_3$) 2.32 (3H, s, SCH_3), 2.72 (1H, t, J=1.5Hz, ≡CH), 4.85 (2H, d, J=1.5Hz, CH_2), 6.48-6.63 (2H, m, =CH and H-furyl), 7.19 (1H, d, J=1.5Hz, H-furyl), 7.58 (2H, brs, H-furyl) ; m/z NO M^+ ; 197 (17%), 175 (17%), 95 (100) (Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44 ; H, 4.54. Found : C, 59.68 ; H, 4.59%).

3-Methylthio-3-propargyloxy-1-(2'-thienyl)-2-propen-1-one (75e). Yellow crystals ($CHCl_3$/hexane) ; yield 11% ; m.p. 85-86°C ; IR (KBr) 3250, 2128, 1620, 1500, 1410, 1358, 1262, 1160 cm^{-1} ; δ_H ($CDCl_3$) 2.28 (3H, s, SCH_3), 2.71 (1H, t, J=1.5Hz, ≡CH), 4.81 (2H, d, J=1.5Hz, CH_2), 6.46 (1H, s, =CH), 7.13 (1H, t, J=1.5Hz, H-thienyl), 7.50-7.78 (2H, m, H-thienyl) ; m/z No M^+, 193 (2%), 191 (11), 111 (100) (Anal. Calcd. for $C_{11}H_{10}O_2S_2$: C, 55.44 ; H, 4.23. Found : C, 55.72; H, 4.51%).

General Procedure for the Preparation of 2-Aryl-3-Carbomethylthio-5-Methylfurans (76a-e).

To a stirred solution of acylketene O-propargyl S-methylacetals 75 (0.01mol) in ethylmethyl ketone (25ml) was added potassium carbonate (4g. 0.03mol) and refluxed for 3-6hr. (monitored by tlc). Filtered the reaction mixture , washed the residue with ethylmethyl ketone (2x25ml) and distilled off the combined filtrate on water bath. Diluted the crude reaction mixture with 50ml of chloroform and washed the organic layer with water (3x100ml), dried (Na_2SO_4) and evaporated. The crude products **76** thus obtained were purified by passing through a short length silica gel column using hexane as eluent.

3-Carbomethylthio-5-methyl-2-phenylfuran (76a). Colorless viscous liquid ; yield 84% ; IR (neat) 1695, 1558, 1550, 1380, 1228, 1166 cm^{-1} ; δ_H ($CDCl_3$, 250 MHz) 2.29 (3H, d, J=1.5Hz, CH_3), 2.36 (3H, s, SCH_3), 6.64 (1H, d, J=1.5Hz, furyl H-4), 7.33-7.42 (3H, m, ArH), 7.72-7.96 (2H, m, ArH) ; δ_C ($CDCl_3$) 11.57 (SCH_3), 13.09 (CH_3), 107.52 (furyl C-4), 121.32 (furyl C-3), 127.66, 127.96, 129.08, 129.59 (phenyl CH), 129.645 (phenyl C-1'), 151.24 (furyl C-2), 152.84 (furyl C-5), 186.46 (CO) ; m/z 232 (M^+, 20%), 185 (100), 105 (57) (Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.21 ; H,12.10. Found: C, 67.39 ; H, 12.25%).

3-Carbomethylthio-2-(4'-methoxyphenyl)-5-methylfuran (76b). Colorless viscous lquid ; yield 88% ; IR (neat) 1679, 1620, 1505, 1268 cm^{-1} ; δ_H ($CDCl_3$), 2.29 (3H, s, CH_3), 2.33 (3H, s, SCH_3), 3.76 (3H, s, OCH_3), 6.47 (1H, s, furyl H-4), 6.95 (2H, d, J=9Hz, ArH), 8.02 (2H, d, J=9Hz, ArH) ; m/z 262 (M^+, 42%),

237 (100) (Anal. Calcd. for $C_{14}H_{14}O_3S$: C, 64.10 ; H, 5.38. Found : C, 64.32 ; H, 5.67%).

3-Carbomethylthio-3(4'-chlorophenyl)-5-methylfuran (76c). Colorless crystals ($CHCl_3$/hexane) ; yield 86% ; m.p. 60-61°C ; IR (neat) 1678, 1562, 1495, 1383, 1280, 1175 cm^{-1} ; δ_H ($CDCl_3$) 2.32 (3H, d, J=1.5Hz, CH_3), 2.39 (3H, s, SCH_3), 6.47 (1H, d, J=1.5Hz, furyl H-4), 7.50 (2H, d, J=9Hz, ArH), 7.91 (2H, d, J=9Hz, ArH) ; m/z 266 (M^+, 11%), 219 (100), 139 (37) (Anal. Calcd. for $C_{13}H_{11}ClO_2S$: C, 58.53 ; H, 4.16. Found : C, 58.64 ; H, 4.27%).

3-Carbomethylthio-2(2'-furyl)-5-methylthiofuran (76d). Colorless viscous liquid : yield 89% ; IR (neat) 1663, 1610, 1535, 1374, 1265, 1174 cm^{-1} ; δ_H ($CDCl_3$) 2.29 (3H, s, CH_3), 2.37 (3H, s, SCH_3), 6.33-6.56 (2H, m, furyl H-4 and furyl H), 7.51 (1H, brs, furyl H), 7.63 (2H, d, J=1.5Hz, furyl H) ; m/z 222 (M^+, 57%), 174 (100), 94 (48) (Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44 ; H, 4.54. Found : C, 59.71 ; H, 4.77%).

3-Carbomethylthio-5-methyl-2(2'-thienyl)furan (76e). Yellow viscous liquid ; yield 91% ; IR (neat) 1662, 1620, 1569, 1508, 1425, 1392, 1260, 1219, 1173 cm^{-1} ; δ_H ($CDCl_3$: 250MHz), 2.35 (3H, d, J=1.5Hz, CH_3), 2.45 (3H, s, SCH_3), 6.46 (1H, d, J=1.5Hz, furyl H-4), 7.08-7.12 (1H, m, thienyl H), 7.40 (1H, d, J=1.5Hz, thienyl H), 8.04 (1H, d, J=1.5Hz, thienyl H) ; m/z 238 (M^+, 34%), 191 (100), 111 (33) (Anal. Calcd. for $C_{11}H_{10}O_2S_2$: C, 55.44 ; H, 4.23. Found: C, 55.66 ; H, 4.44%).

General procedure for dethiomethylation of 2-Aryl-3-Carbomethylthio-5-Methylfurans (76a-b).

To a stirred solution of furan 76 (0.005mol) in ethanol (30ml) was added Ranely Nickel (W-4, ~5 times by weight) and the mixture was stirred at room temperature for 8-10hr. (monitered by tlc). The reaction mixture was filtered and the residue was washed with hot ethanol (2x20ml). The bulk of the ethanol was distilled off on water bath and chloroform (50ml) was added. This solution was washed with water (2x100ml), dried over sodium sulphate and evaporated. Analyticaly pure compounds 77 and 78 were obtained by passing through a short length silica gel column using hexane as eluent.

5-Methyl-2-phenylfuran (77a). Colorless liquid ; yield 34% ; IR (neat) 1623, 1571, 1475 cm^{-1} ; ^1H NMR (CCl_4) 2.36 (3H, s, CH_3), 5.95 (1H, d, J=3Hz, furyl H-4), 6.46 (1H, d, J=3Hz, furyl H-3), 7.10-7.42 (3H, m, ArH), 7.46-7.69 (2H, m, ArH) (Anal. Calcd. for $C_{11}H_{10}O$: C, 83.51 ; H,6.37. Found : C, 83.69 ; H, 6.57%).

2-(4'-Methoxyphenyl)-5-methylfuran (77b). Colorless crystals (hex) ; yield 36% ; m.p. 38°C ; IR (KBr) 1627, 1542, 1491, 1453, 1244 cm^{-1} ; ^1H NMR ($CDCl_3$) 2.37 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 6.10 (1H, d, J=3Hz, furyl H-4), 6.48 (1H, d, J=3Hz, furyl H-3), 6.99 (2H, d, J=9Hz, ArH), 7.71 (2H, d, J=9Hz, ArH) (Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57 ; H, 6.43. Found : C, 76.81 ; H, 6.68%).

*5-Methyl-2-phenylfuran-3-aldehyde (78a).*colorless liquid ;

yield 46% ; IR (neat) 1683, 1635, 1579, 1510, 1462, 1409, 1237 cm^{-1} ; ^1H NMR (CCl_4) 2.44 (3H, s, CH_3), 6.50 (1H, s, furyl H-4), 7.48- 7.69 (3H, m, ArH), 7.86-8.96 (2H, m, ArH), 10.28 (1H, s, CHO) ; m/z 186 (M^+, 100%), 157 (14), 115 (42), 105 (65) (Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40 ; H, 5.41. Found : C, 77.66 ; H,5.69%).

2-(4'-Methoxyphenyl)-5-methylfuran-3-aldehyde (78b). Light yellow crystals (ether/hexane) ; yield 48% ; m.p. 52°C ; IR (KBr) 1656, 1611, 1499, 1443, 1380, 1304, 1247 cm^{-1} ; ^1H NMR ($CDCl_3$) 2.32 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 6.50 (1H, s, furyl H-4), 7.02 (2H, d, J=9Hz, ArH), 7.73 (2H, d, J=9Hz, ArH), 10.15 (1H, s, CHO) (Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98 ; H, 6.04. Found : C, 78.15 ; H,6.19%).

General Procedure for Preparation of 1-Aryl-2-carbomethylthio -2,4-pentadien-1-ne (80a-e).

A solution of acylketene O-propargyl S-methylacetal 75 (0.01mol) in dry toluene (25ml) was refluxed for 1-2hr. (when the solvent was benzene refluxed for 3-4hr., xylene for 15-30 min. monitored by tlc.). Removed the solvent under reduced pressure and the residue was chromatographed over silicagel using hexane as eluent.

2-Carbomethylthio-1-phenyl-2,4-pentadien-1-one (80a). Yellow viscous liquid ;yield 94% ; IR (neat) 1686, 1671, 1620, 1478, 1232 cm^{-1} ; δ_H (CCl_4) 2.32 (3H, s,SCH_3), 5.56 (1H, dd, J_{AC} = 10Hz, J_{AB}=2Hz, H_A), 5.78 (1H, J_{BC}=17Hz, J_{AB}=2Hz, H_B), 6.49 (1H, ddd, J_{BC}=17Hz, J_{CD}= 12Hz, J_{AC}=10Hz, H_C), 7.42(1H, d,

J_{CD}=12Hz, H_D), 7.44-7.62 (2H, m, ArH) 7.79-8.08 (2H, m, ArH); m/z 232 (M^+, 4%), 185 (70) 105 (100) (Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.21 ; H, 12.10. Found : C, 67.42 ; H, 12.29%).

2-Carbomethylthio-1(4'-methoxyphenyl)-2,4-pentadien-1-one *(80b)*. *Yellow viscous liquid ; yield 93% ;* IR (neat) 1681, 1666, 1618, 1238 cm^{-1}; δ_H ($CDCl_3$) 2.34 (3H, s, SCH_3), 3.86 (3H, s, OCH_3), 5.58 (1H, dd, J_{AC}=10Hz, J_{AB}=2Hz, H_A), 5.84 (1H, dd, J_{BC}=16Hz, J_{AB}=2Hz, H_B), 6.27 (1H, ddd, J_{BC}=16Hz, J_{CD}=12Hz, J_{AC}=10Hz, H_C), 7.03 (2H, d, J=9Hz, ArH), 7.42 (1H, d, J_{CD}=12Hz, H_D), 7.84 (2H, d, J=9Hz, ArH); δ_C ($CDCl_3$) 12.01 (SCH_3), 56.43 (OCH_3), 115.2 (phenyl CH), 118.08 (C-4), 130.01 (C-2), 130.05 (phenyl C-1'), 132.4 (C-3), 132.6 (phenyl CH), 140.01 (C-5), 165.57 (phenyl C-4'), 190.68 (phenyl CO), 193.3 ($COSCH_3$) ; m/z 262 (M^+, 4%), 215 (19), 187 (8), 135 (100). (Anal. Calcd. for $C_{14}H_{14}O_3S$: C, 64.10 ; H, 5.38. Found : C, 64.33 ; H, 5.64%).

2-Carbomethylthio-1(4'-chlorophenyl)-2,4-pentadien-1-one **(80c)**. Yellow viscous liquid ; yield 91% ; IR (neat) 1676, 1600, 1498, 1410, 1222 cm^{-1}; δ_H(CCl_4) 2.33 (3H, s, SCH_3), 5.58 (1H, dd, J_{AC}=10 Hz, J_{AB}=2Hz, H_A), 5.77 (1H, dd, J_{BC}=17Hz, J_{AB}=2Hz, H_B), 6.53 (1H, ddd, J_{BC}=17Hz, J_{CD}=12Hz, J_{AC}= 10Hz, H_C), 7.45 (1H, d, J_{CD}=12Hz, H_D), 7.77 (2H, d, J=9Hz, ArH), 7.91 (2H, d, J=9Hz, ArH); m/z 265 and 267 (M^+, 25 and 11%), 219 (22), 141 (71). (Anal. Calcd. for $C_{13}H_{11}ClO_2S$: C, 58.53 ; H, 4.16. Found: C, 58.79 ; H, 4.43%).

2-Carbomethylthio-1(2'-furyl)-2,4-pentadien-1-one (80d). Yellow viscous liquid ; yield 89% ; IR (neat) 1678, 1656, 1582, 1479, 1403, 1224 cm^{-1}; δ_H (CCl_4) 2.38 (3H, s, SCH_3), 5.73 (1H, dd, J_{AC}=10Hz, J_{AB}=2Hz, H_A), 5.91 (1H, dd, J_{BC}=18Hz, J_{AB} =2Hz, H_B), 6.31-6.82 (2H, m, H_C and furyl H), 7.30 (1H, d, J=1.5Hz, furyl H), 7.49 (1H, d, J_{CD}=12Hz, H_D), 7.81 (1H, brs, furyl H) ; m/z 222 (M^+, 3%), 175 (66), 147(17), 95(100). (Anal. Calcd. for $C_{11}H_{10}H_{10}O_3S$: C, 59.44 ; H, 4.54. Found : C, 59.71 ; H, 4.87%).

2-Carbomethylthio-1(2'-thienyl)-2,4-pentadien-1-one (80e). Yellow viscous liquid ; yield 86% ; IR (neat) 1666, 1653, 1538, 1424, 1375, 1258, 1237 cm^{-1}; δ_H ($CDCl_3$) 2.38 (3H, s, SCH_3), 5.68 (1H, d, J_{AC}=10Hz, J_{AB}=2Hz, H_A), 5.82 (1H, d, J_{AC}=10Hz, J_{AB}=2Hz, H_B), 6.23-6.63 (1H, m, H_C), 7.10-7.28 (1H, m, thienyl H), 7.43 (1H, d, J_{CD}=11Hz, H_D), 7.72 (1H, d, J=3Hz, thienyl H), 7.83 (1H, d, J=3Hz, thienyl H); m/z 237 (M^+-1, 3%), 190 (86), 163 (19), 111 (100). (Anal. Calcd. for $C_{11}H_{10}O_2S_2$: C, 55.44 ; H, 4.23. Found : C, 55.67 ; H, 4.49%).

2-Allenyl-2-carbomethylthio-1-tetralone (92) was obtained by the reaction of dimethylsulphonium perchlorate 90 devrived from teralone mercaptal and propargyl alcohol according to the general procedure described for 75a-e. It was isolated as yellow viscous liquid ; yield 68% ; IR (neat) 2950, 1962, 1690, 1618, 1305, 1238 cm^{-1}; δ_H(CCl_4) 2.22 (3H, s, SCH_3), 2.52-2.81 (2H, m, CH_2), 2.82-3.15 (2H, m, CH_2), 4.98 (2H, d, J=6Hz, $=C=CH_2$), 5.92 (1H, t, J=6Hz, $HC=C=CH_2$), 7.18-7.64 (3H, m, ArH), 8.14-8.20 (1H, m, ArH); m/z 258 (M^+, 8%), 183 (100),

115 (24). (Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74 ; H, 5.46. Found: C, 69.99 ; H, 5.75%).

1-Phenyl-2-carbomethylthio-4-penten-1-one (95) was obtained by the reaction of dimethylsulphonium perchlorate salt 73a and allyl alcohol under similar reaction conditions as described in the general procedure for the preparation of 75a-e. Isolated as yellow viscous liquid ; yield 70% ; IR (neat) 3050, 1210, 1620, 1600, 1460, 1238 cm^{-1} ; $\delta_H(CDCl_3)$ 2.28 (3H, s, SCH_3), 7.73 ((2H, t, J=6Hz, CH_2), 4.62 (1H, t, J=6Hz, CH), 5.18 (2H, dd, J=9Hz, J=10Hz, $=CH_2$), 5.53-6.10 (1H, m, =CH), 7.30-7.74 (3H, m, ArH), 7.90-8.20 (2H, m, ArH) ; m/z 234 (M^+, 4%), 186 (36), 158 (24), 105 (100) (Anal. Calcd. for $C_{13}H_{14}O_2S$: C, 66.64 ; H, 6.02. Found : C, 66.48 ; H, 6.14%)

General Procedure for the Preparation of 3-Aroyl-5-methyl-2-methylthiofurans (97a-b).

To a stirred solution of O-propargyl S-methylacetals 75 (0.01mol) in dichloromethane (25ml) at 0°C was added N-bromosuccinimide (2.13g, 0.012mol) and stirred the reaction mixture for 20-30min. (monitored by tlc). Filtered the reaction mixture, washed the precipitate with dichloromethane (2x25ml) and the combined filterate concentrated under reduced pressure. The crude bromocompounds (in dry benzene 50ml) were taken in a dry three neck 250ml round bottom flask, placed on a oil bath of temperature 80°C, fitted with a condensor, nitrogen gas inlet and a septum . Flushed the nitrogen gas and added AIBN (100mg) followed by *n*-Bu_3SnH

(3.5g, 0.012mol) through syringe. Refluxed the reaction mixture with stirring for 1hr. (monitored by tlc) and evaporated. The crude products 97 were directly chromatographed over silicagel using hexane as eluent to get the analytically pure furans 97a an 97b.

3-Benzoyl-5-methyl-2-methylthiofuran (97a). Colorless viscous liquid ; yield 58% ; IR (neat) 1660, 1620, 1510, 1462, 12195 cm^{-1}; δ_H ($CDCl_3$) 2.31 (3H, s, CH_3), 2.55 (3H, s, SCH_3), 6.31 (1H, s, furyl H-4), 7.43-7.52 (3H, m, ArH), 7.76-7.79 (2H, m, ArH); δ_C($CDCl_3$) 13.34 (SCH_3), 14.09 (CH_3), 108.27 (furyl C-4), 122.24 (furyl C-3), 128.35, 128.67, 131.69 (phenyl CH), 138.92 (phenyl C-1'), 152.63 (furyl C-5), 155.85 (furyl C-2), 189.04 (CO); m/z 232 (M^+, 41%), 217(3), 105 (100) (Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.21 ; H, 5.21. Found : C, 67.49 ; H, 5.48%).

3-(p-Anisoyl)-5-methyl-2-methylthiofuran (97b). Colorless viscous liquid ; yield 56% ; IR (neat) 1678, 1620 cm^{-1} ; δ_H ($CDCl_3$) 2.33 (6H, brs, SCH_3 and CH_3), 3.79 (3H, s, OCH_3), 6.46 (1H, s, furyl H-4), 6.88 (2H, d, J=9Hz, ArH), 7.96(2H, d, J=9Hz, ArH) (Anal. Calcd. for $C_{14}H_{14}O_3S$: C, 64.10 ; H, 5.38. Found : C, 64.38 ; H, 5.59%).

REFERENCES

1. F.C.V. Larsson, S.O. Lawesson, Tetrahedron, *28*, 5341 (1972).
2. G. Singh, S,S. Bhattacharjee, H. Ila, H. Junjappa, Synyhesis, 693 (1982).
3. L. Brandsma, P.J.W. Schuijl, Rec. Trav. Chim. Pays-Bas, *88*, 30 (1969).
4. P.J.W. Schuijl, H.J.T. Bos, L. Brandsma, Rec. Trav. Chim. Pays-Bas, *88*, 597 (1969).
5. S.S. Bhattacharjee, H. Ila, H. Junjappa, Synthesis, 410 (1983).
6. A.K. Gupta, H. Ila, H. Junjappa, un published results.
7. M.L. Purakayasta, M. Chandrasekharam, J.N. vishwakarma, H.Ila, H.Junjappa, Synthesis, 245 (1993).
8. Laxminarayan Bhat, H. Ila, H. Junjappa, Synthesis, 0000 (1993)
9. A. Viola, J.J. Collins, N. Fillip, Tetrahedron, *37*, 3765 (1981).
10. D.K. Black, S.R. Landor, J. Chem. Soc., 6784 (1965).
11. E.R.H. Jones, J.D. Landor, M.C. Wittig, Proc. Chem. Soc., 180 (1960).
12. J.D. Evans, S.R. Landor, J.P. Regon, Chem. Comm., 397 (1965).
13. J.K. Crandall, G.L. Tindell, Chem. Commun., 1411 (1970)
14. G. Saney, R. Market, HelV. Chem. Acta, *50*, 1158 (1967).

15. J.Z. Sindely, H. Schmid, **Helv. Chem. Acta**, *51*, 1510 (1968).

16. B.A. Otter, S.S. Saluja, J.J. Fox, **J. Org. Chem.**, *37*, 2858 (1972).

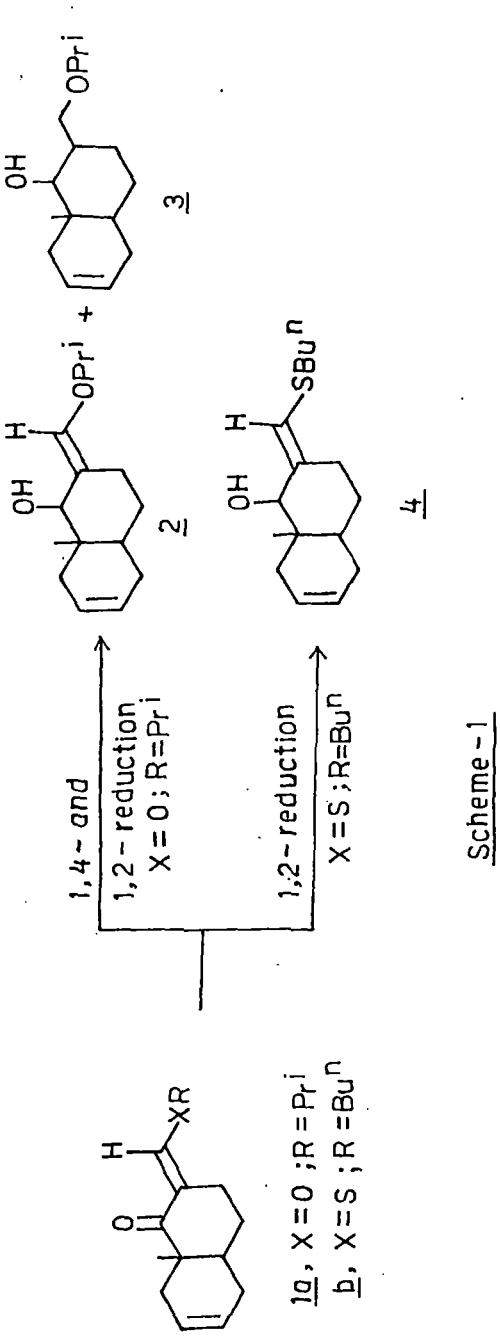
17. M.R. Attwood, I. Churcher, R.M. Dunsdon, D.N. Hurst, R.S. Jones, **Tetrahedron Lett.**, *32*, 811 (1991).

CHAPTER V

NUCLEOPHILIC ADDITION STUDIES ON α-OXOKETENE O,S-ACETALS.

V.1 INTRODUCTION

The reduction of α,β-unsaturated enones have been extensively carried out by using metal hydride complexes to afford the corresponding allyl alcohols. The substrate enones particularly *i*-propoxymethylene ketones of general formula 1a (scheme 1) have been known to undergo sodium borohydride reduction to give a mixture of products 2 and 3 in 68% and 21% yields respectively[1]. The formation of 3 involves sequential 1,4-followed by 1,2-reduction. Thus the regioselective reduction of ketone alone could not be satisfactorily achieved when the alkoxy group was present in

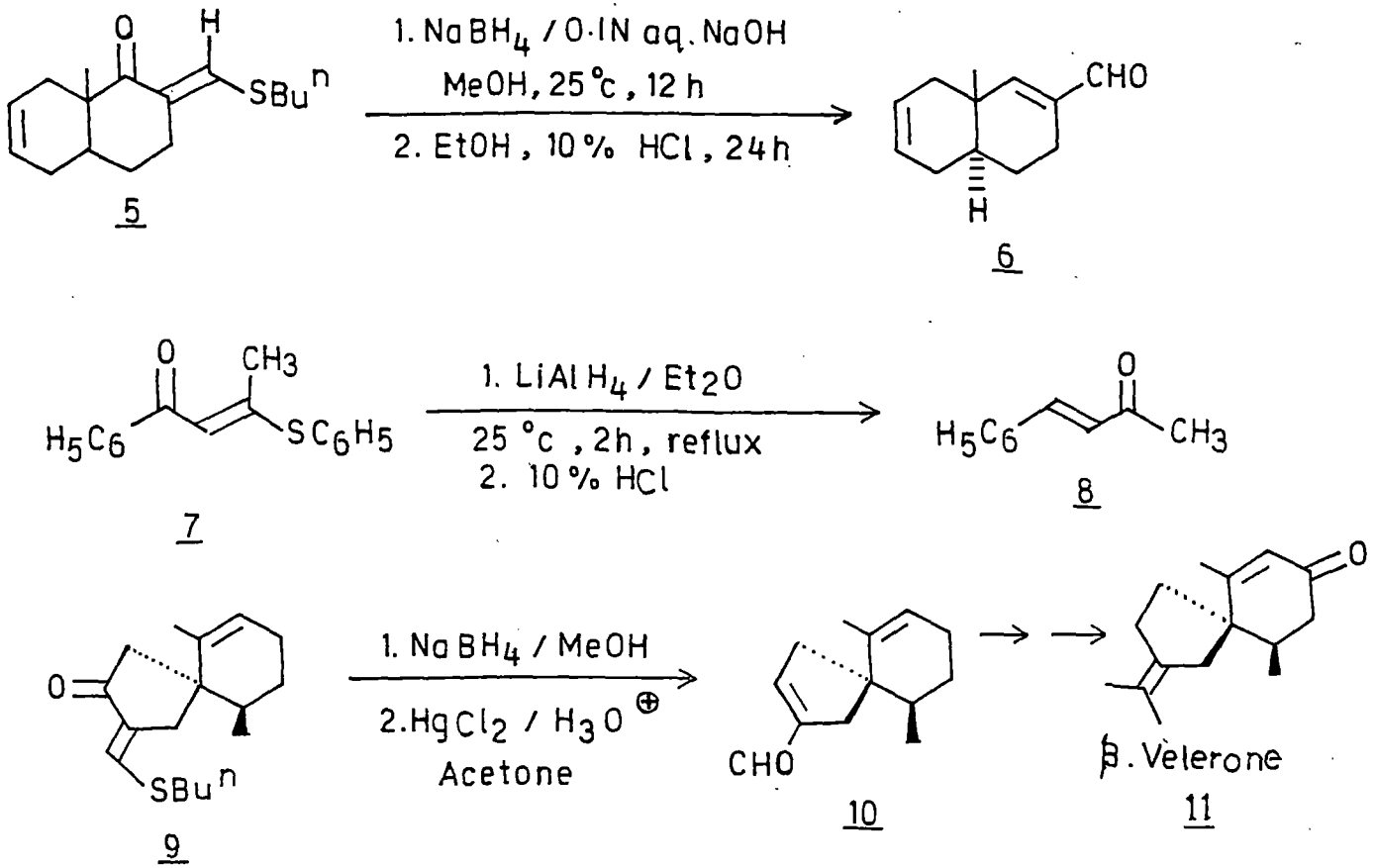

1,4- and
1,2- reduction
X = O ; R = Pr^i
1,2- reduction
X = S ; R = Bu^n
1a, X = O ; R = Pr^i
b, X = S ; R = Bu^n
2
3
4

Scheme - 1

the enone system. However, Marshall and co-workers[2,3] were the first to observe that the regioselective reduction could be achieved if the alkoxy group replaced by *n*-butylmercapto group **1b** by reacting the corresponding hydroxy derivative with *n*-butylmercaptan in the presence of *p*-toluenesulphonic acid with continuous removal of water. The *n*-butylthio methylene ketone **1b** thus obtained underwent exclusive 1,2-reduction with sodium borohydride in alcohol to afford the corresponding allyl alcohol **4** in 81% yield. The allyl alcohol was then hydrolysed to afford the corresponding enealdehyde which is an important intermediate in natural product synthesis.

Thus Marshall and co-workers[4] successfully extended this reaction to prepare the aldehyde **6** from the corresponding *n*-butylthiomethylene ketone **5**. Similarly the phenylthio methylene ketone **7** on reaction with lithium aluminium hydride in ether underwent 1,2-reduction followed by hydrolytic cleavage to give α,β-unsaturated ketone **8** in good yield[4] (scheme 2).

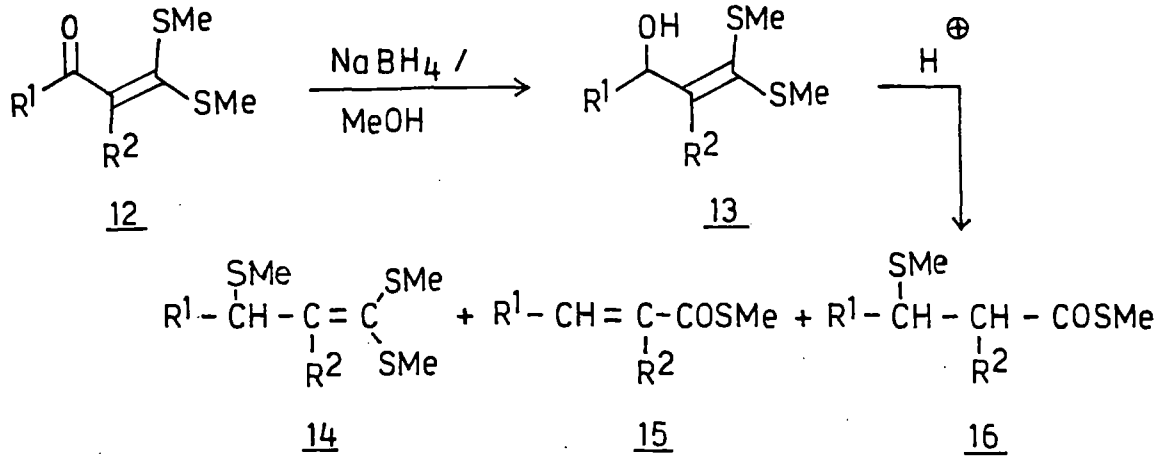
Similarly Marshall and co-workers[5] successfully applied this new transformation in the synthesis of natural product β-valerone **11**. The mercaptomethylene ketone **9** after exclusive 1,2-reduction with sodium borohydride to the corresponding allyl alcohol which was subjected to mercuric chloride assisted hydrolysis to give the corresponding ene aldehyde **10** in high yield. This was then converted into β-velerone **11** through several steps (scheme 2).


1. NaBH4 / 0·1N aq. NaOH
MeOH, 25 °c, 12 h
2. EtOH, 10 % HCl, 24 h
SBu n
CHO
H
5
6
CH3
H5C6
SC6H5
1. LiAlH4 / Et2O
25 °c, 2h, reflux
2. 10 % HCl
CH3
7
8
1. NaBH4 / MeOH
2. HgCl2 / H3O ⊕
Acetone
SBu n
CHO
β. Velerone
9
10
11

Scheme - 2

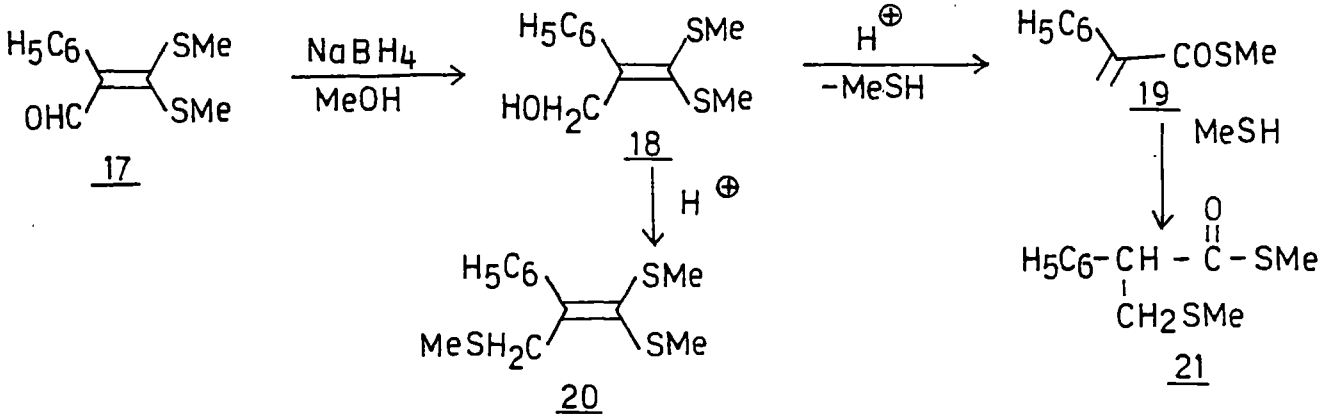
The α-oxoketene dithioacetals 12 (scheme 3) were first reduced with sodium borohydride in methanol by Thuillier and co-workers[6] to afford the corresponding allyl alcohols 13 in high yields. The allyl alcohols thus obtained when subjected to acid assisted hydrolytic cleavage a mixture of products 14, 15 and 16 were formed. Thuillier and co-workers also observed some interesting rearrangements when they reduced α-phenyloxoketene dithioacetal 17 to the corresponding alcohol 18 (scheme 3). The allyl alcohol 18 in the presence of acid underwent rearrangement involving hydrolytic cleavage either to give 21 or the sulfur stabilized carbonium ion 23 which acted as Micheal acceptor to give the adduct 20. The mechanism proposed for the formation of products 20 and 21 from 17 is depicted in scheme 4.

Myrboh, lla and Junjappa[7] in this laboratory repeated the reduction studies on α-oxoketene dithioacetals reported by Thuillier and co-workers[6] using sodium borohydride in methanol to get identically high yields of the corresponding alcohols 26 (scheme 5). These alcohols were shown to undergo a facile borontrifluoride-etherate assisted methanolysis to give the corresponding eneesters 27 exclusively in high yields. Also the allyl alcohols in the presence of borontrifluoride-etherate and water underwent hydrolytic cleavage to afford the thiolesters 28 exclusively. It may be noted here that the Thuillier's group employed acids such as *p*-toluene sulphonic acid and aqueous sulphuric acid and thus could not get a single product of which the ene ester 27 was

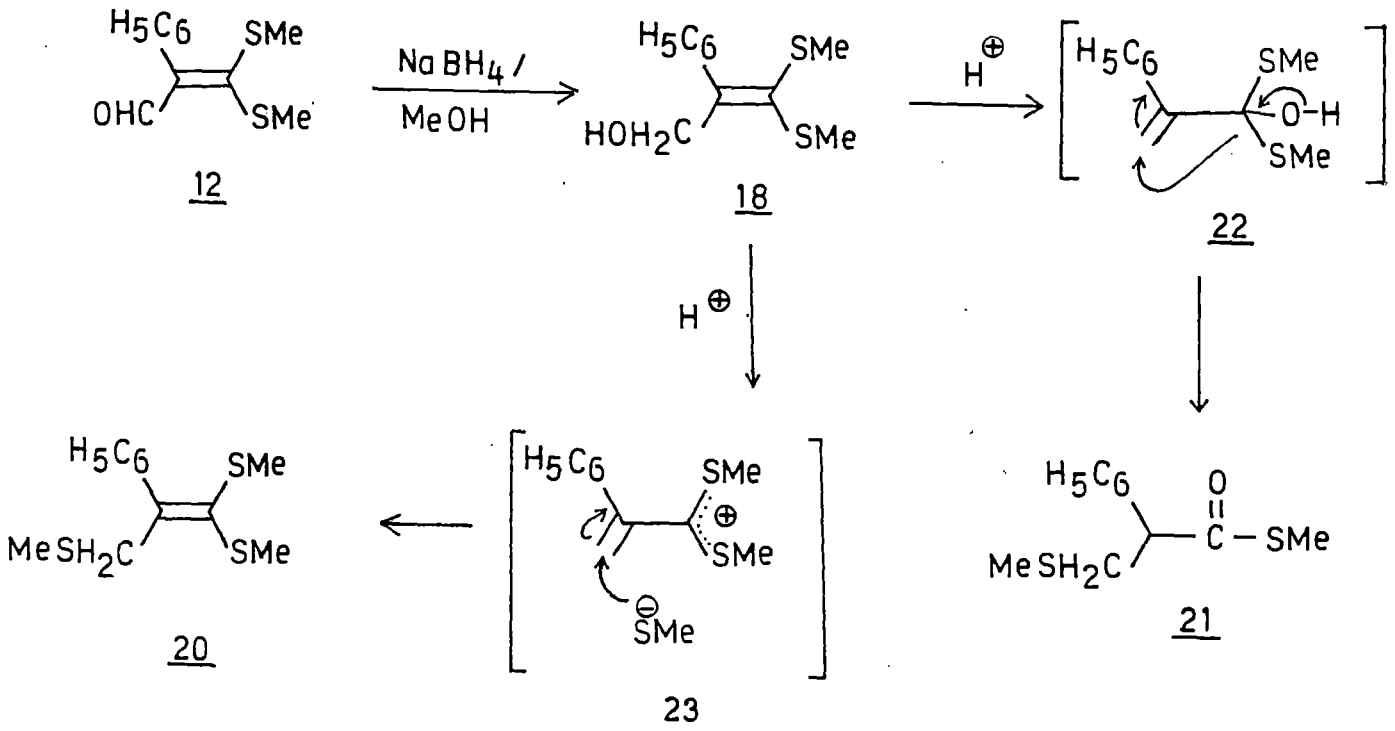


R^1 = Me, C_6H_5; R^2 = H; R^1 = C_6H_5, $C_6H_5CH_2$, Me; R^2 = C_6H_5, CH_3;

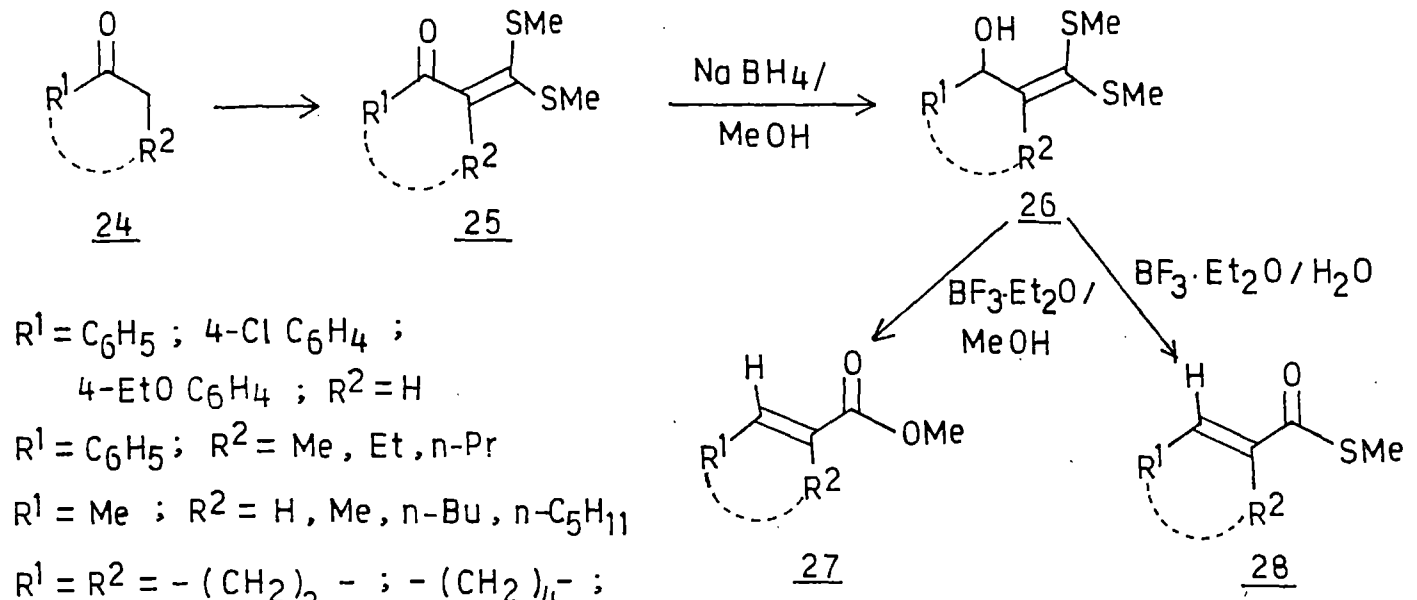
$R^1 = R^2 = -(CH_2)_4-$



Scheme – 3


H5C6
SMe
OHC
SMe
12
NaBH4 /
MeOH
H5C6
SMe
HOH2C
SMe
18
H⊕
H5C6
SMe
O-H
SMe
22
H⊕
H5C6
O
C – SMe
MeSH2C
21
H5C6
SMe
MeSH2C
SMe
20
H5C6
SMe
⊕
SMe
⊖
SMe
23

Scheme – 4

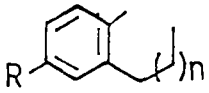


$R^1 = C_6H_5$; 4-Cl C_6H_4 ;
4-EtO C_6H_4 ; $R^2 = H$

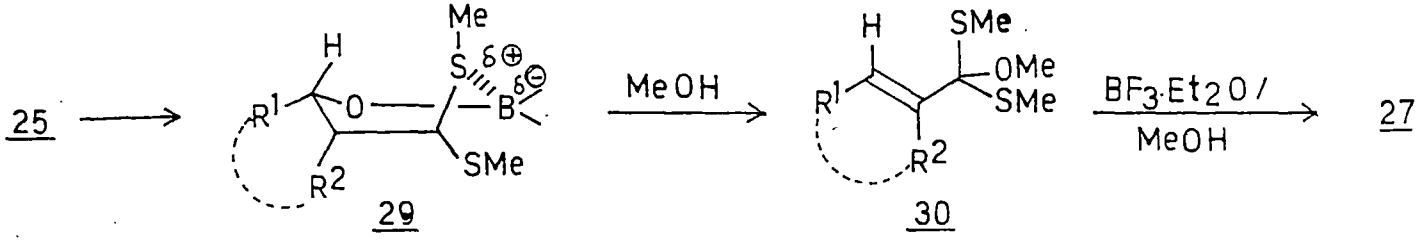
$R^1 = C_6H_5$; R^2 = Me, Et, n-Pr

R^1 = Me ; R^2 = H, Me, n-Bu, n-C_5H_{11}

$R^1 = R^2 = -(CH_2)_3-$; $-(CH_2)_4-$;



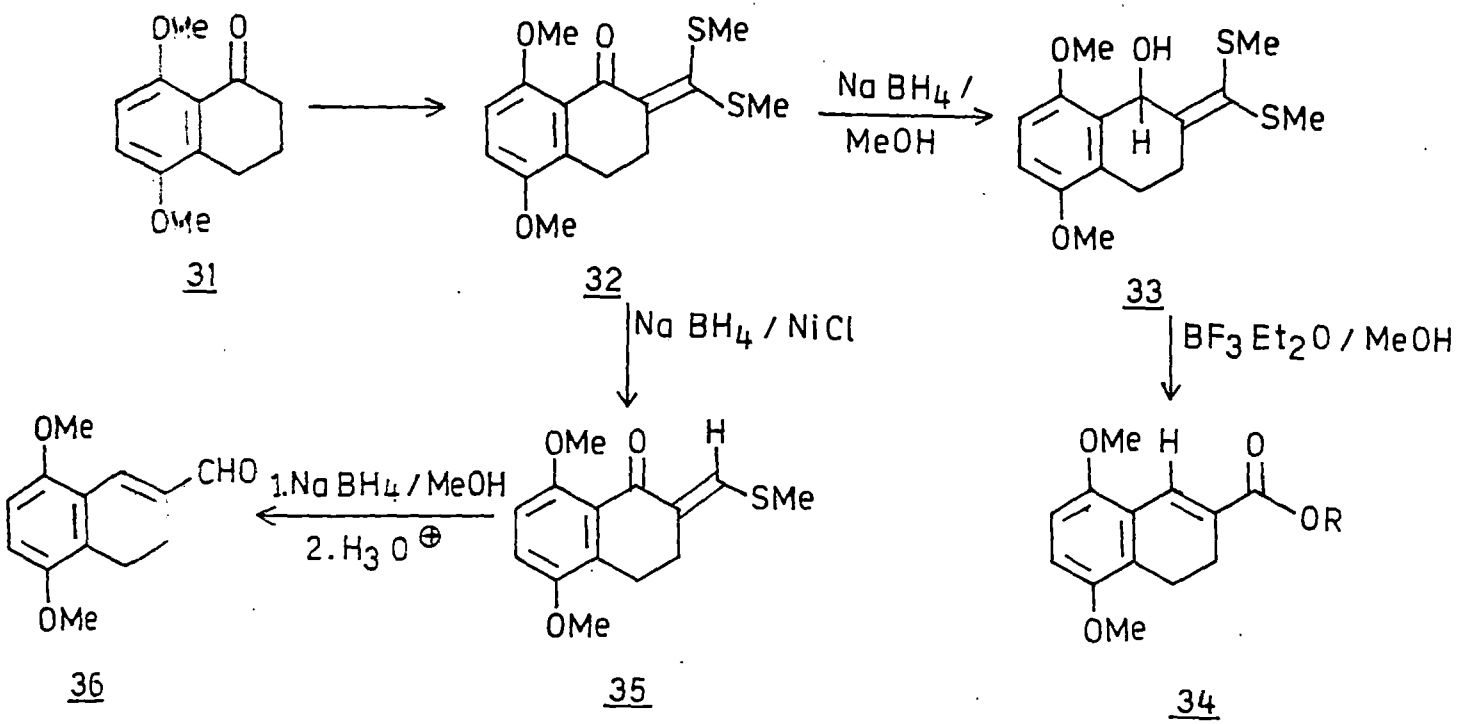
R = H, MeO ; n = 1,2



Scheme – 5

not the only product. They obtained only the thiolesters 28 as one of the mixtures along with other rearranged products. The solvolytic clean reaction to afford the eneesters 27 in exclusive *trans* geometry was explained through the cyclic transition state 29 which led to the stereoselective methanolysis of the mercapto group to afford 27. The reaction was found to be of general application for the synthesis of a variety of eneesters in high yields. Thus a new method was developed for the conversion of active methylene ketones to the correspondng eneesters through α-oxoketene dithioacetals. The acetophenones and higher homologs of acetophenones were conveniently converted in to corresponding *trans* cinnamates and β-substituted cinnamates in good yields respectively. This method was extended to the preparation of enealdehydes also. Thus the oxoketene dithioacetal 32 derived from dimethoxytetralone 31 could not only be transformed in to the corresponding ene esters 34 but also to enealdehyde 36 (scheme 6). The oxoketene dithioacetal 32 was first partially dethiomethylated with sodium borohydride in the presence of nickel chloride to afford the corresponding methylthiomethylene ketone 35 . This on reduction with sodium borohydride in methanol and subsequent hydrolysis gave the correspondng enealdehyde 36 which is used in the total synthesis of antibiotic anthracyclinones[8].

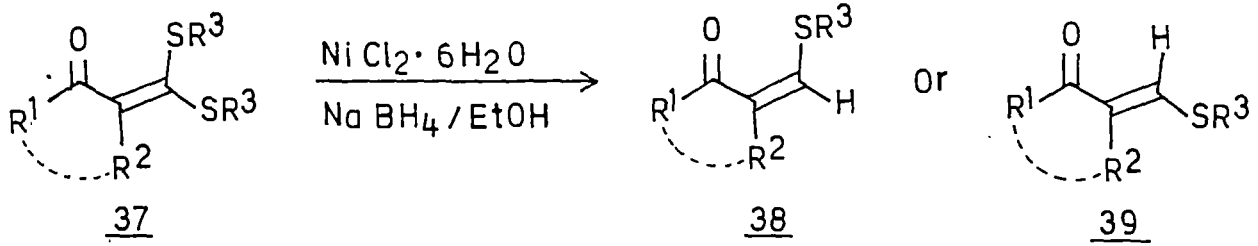
The partial dethiomethylation of α-oxoketene dithioacetals 37 was developed in our laboratory using sodium borohydride in


OMe O
OMe
31
OMe O SMe
SMe
OMe
32
Na BH4 / MeOH
OMe OH SMe
H
SMe
OMe
33
Na BH4 / NiCl
BF3 Et2O / MeOH
OMe O H
SMe
OMe
35
OMe H O
OR
OMe
34
1.Na BH4 / MeOH
2. H3 O ⊕
OMe
CHO
OMe
36

Scheme – 6

the presence of nickel chloride to give the corresponding methylthiomethylene ketones[9] as a mixture of *cis* and *trans* isomers 38 and 39 in moderate to good yields (scheme 7). The reducing agent in this reaction was proposed to be nickel boride derived from the reaction of sodium borohydride and nickel chloride. The reduction was though selective but afforded the dethiomethylated products in moderate yields. In the case of α-oxoketene dithioacetals derived from aliphatc ketones yields were not satisfactory.

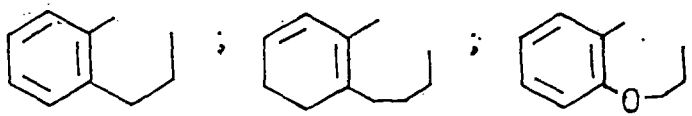
However, subsequently some important modifications were made in the reduction of α-oxoketene dithioacetals of general formula **40** which underwent sodium borohydride reduction in the presence of acetic acid to afford the corresponding β-oxodithioacetals **41** in high yields [10] and no 1,2-reduction products were detected in the reaction mixture. The sodium borohydride in acetic acid reduction was originally thought of going through the formation of the corresponding borane intermediate which by regioselective 1,4-reduction to afford **41** was ruled out. However, it was demonstrated that the borane was not the intermediate reducing agent under these reaction conditions since the borane complex itself yielded only poor yield of **41** when it was used for reduction of **40**. However, the mechanism of this regioselective reduction was explained on the basis of hard soft affinity inversion. Thus the protonated **40** in the presence of acetic acid underwent initial protonation on oxygen which was stabilized by mercapto double bond with a cation residing on the carbon atom adjacent to two thiomethyl groups. The cation which is



37 38 39

$R^1 = C_6H_5$, 4-Me C_6H_4 , 4-Cl C_6H_4 , 4-MeO C_6H_4 , Me ; $R^2 = H$; $R^3 = Me$, Et

$R^1 = C_6H_5$, Me ; $R^2 = Me$, Et , n-C_3H_7 , $R^3 = Me$

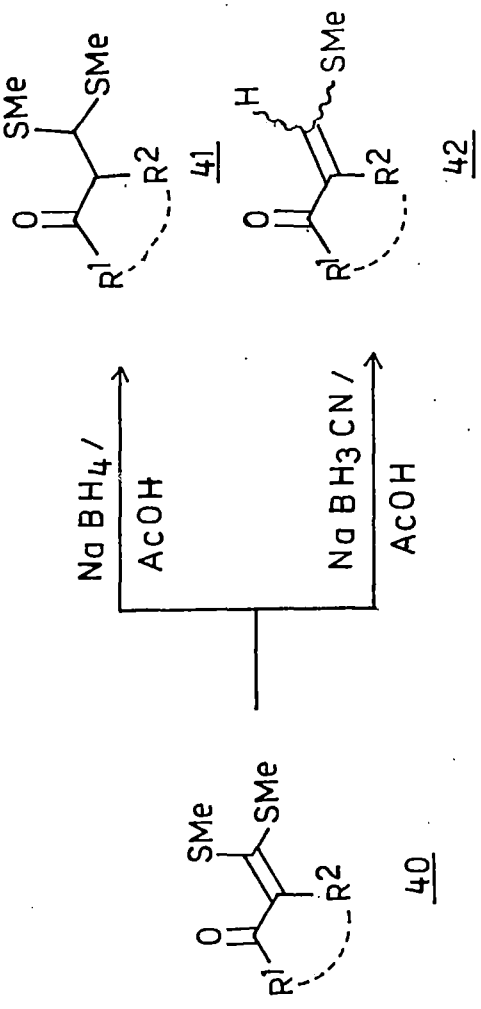
$R^1 = R^2 = -(CH_2)_3-$, $-(CH_2)_4-$;  ; ;

Scheme - 7

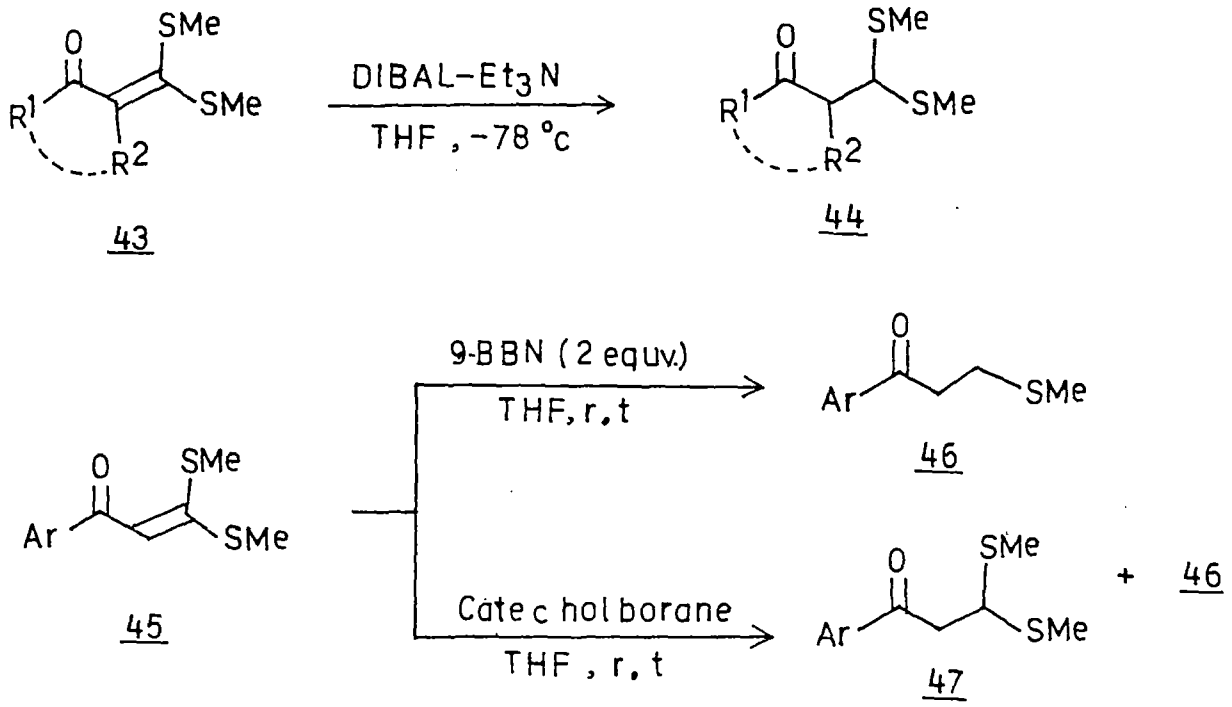
a hard electrophilic centre was then proposed to be attacked by the hard hydride directly from sodium borohydride. The electrophilic hydride from sodium cyanoborohydride in acetic acid also reduces **40** in the 1,4-fashion gave the probable intermediate β-oxodithioacetals which invariably underwent elimination to afford the corresponding methylthiomethylene ketones **42** in good yields (scheme 8).

Gammill and co-workers[11] had similarly used diisobutyl aluminium hydride in the presence of triethylamine to reduce the α-oxoketene dithioacetals **43** to afford the corresponding β-oxodithoacetals **44**. However, they also found that when oxoketene dithioacetal **45** treated with 2 equivalent of 9-BBN over reduced product **46** was formed in 83% yield (scheme 9). The same dithioacetal **45** in catechol borane gave a mixture of β-oxodithioacetal **47** in 56% yield and the over reduction product **46** in 10% yield (scheme 9).

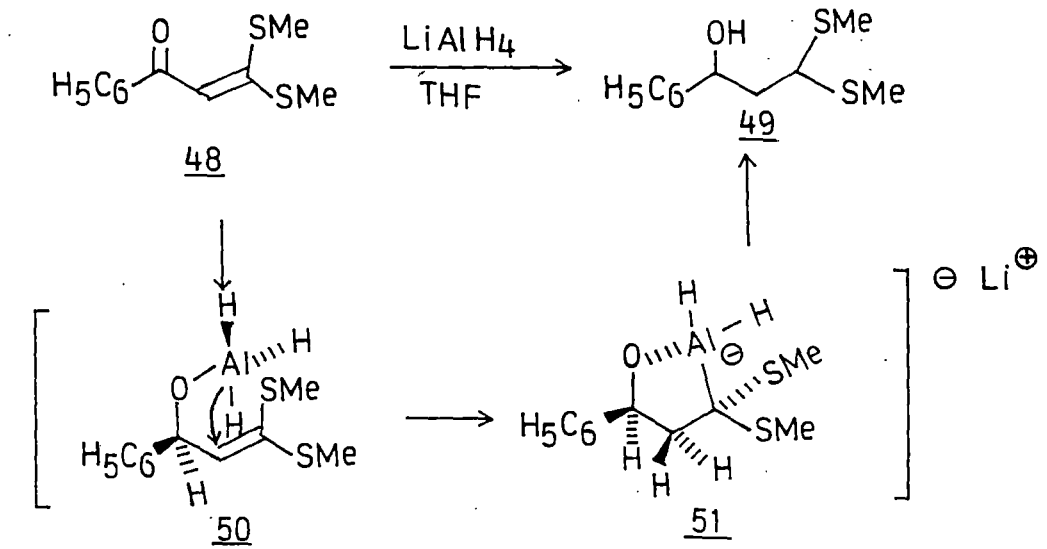
Gammill and co-workers[12] further reported that the α-oxoketene dithioacetals undergo facile lithium aluminium hydride reduction to afford the corresponding highly diastereoselective β-hydroxy dithioacetals **49**. The mechanism governing these reduction is depicted in Scheme 10. The initial 1,2-adduct **50** undergoes the formation of organo aluminium complex **51** which on subsequent intramolecular hydroalumination diastereoselectively to afford the corresponding β-hydroxy dithioacetal **49**. This was the first example of open chain enones to have undergone diastereoselective reduction with lithium aluminium hydride.

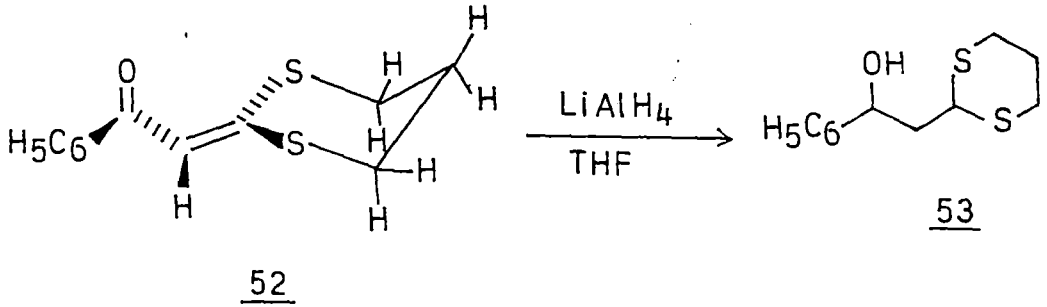

SMe
SMe
O
R2
R1
41
H
SMe
O
R2
R1
42
NaBH4 /
AcOH
NaBH3CN /
AcOH
SMe
SMe
O
R2
R1
40

Scheme - 8


SMe
O
SMe
R1
R2
DIBAL–Et3N
THF , –78 °C
43
44
9-BBN (2 equv.)
THF, r.t
Ar
46
Catecholborane
THF , r.t
47
+ 46

Scheme – 9


O
SMe
H5C6
SMe
LiAlH4
THF
OH
SMe
H5C6
SMe
48
49
H
Al
H
O
SMe
H
H5C6
SMe
H
50
H
Al
H
O
SMe
H5C6
SMe
H
H
H
51
⊖ Li⊕


O
S
H
H
H5C6
S
H
H
H
H
LiAlH4
THF
OH
S
H5C6
S
52
53

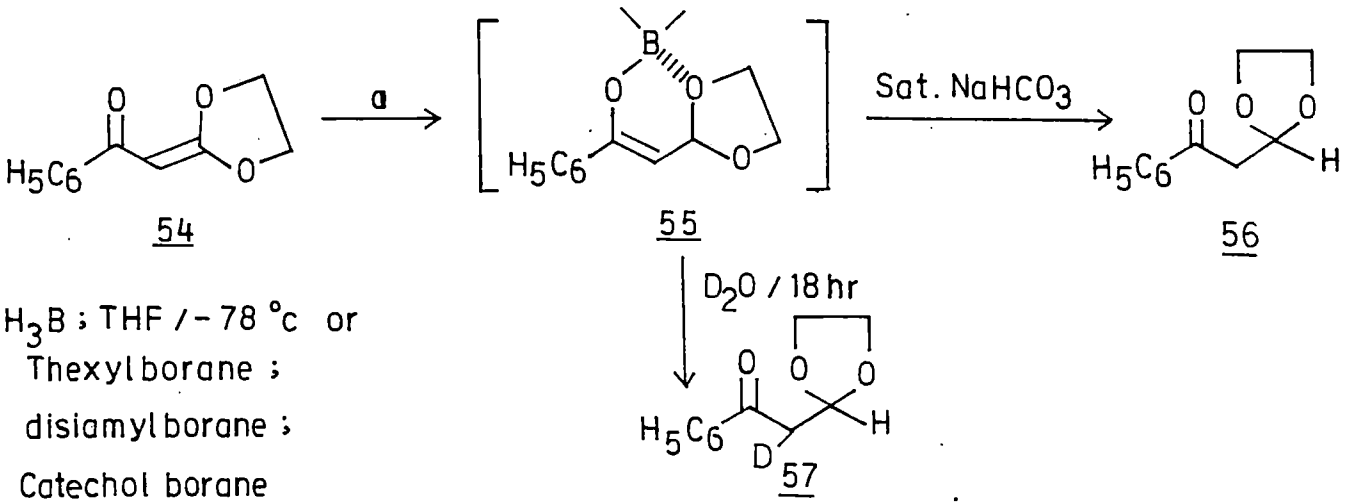
Scheme – 10

Similarly the cyclic oxoketene dithoacetal 52 also gave the corresponding β-hydroxy dithioacetal 53 which followed the same mechanism as described above (scheme 10).

Recently the α-oxoketene O,O-acetals are reduced by borane to afford the corresponding 1,4-reduction product 56 [13,14]. The reduction was established when carried out in presence of D_2O yielding the corresponding α-deuterated β-oxoacetal 57. The cyclicketene acetal 58 was also reduced in the presence of disiamylborane to the corresponding dihydroketone 59 in 50% yield. The β-oxodithioacetals 60 and 62 however gave β-hydroxyacetals 61 and 63 in 89% and 37% yield respectively when reduced with sodium borohydride in methanol (scheme 11).

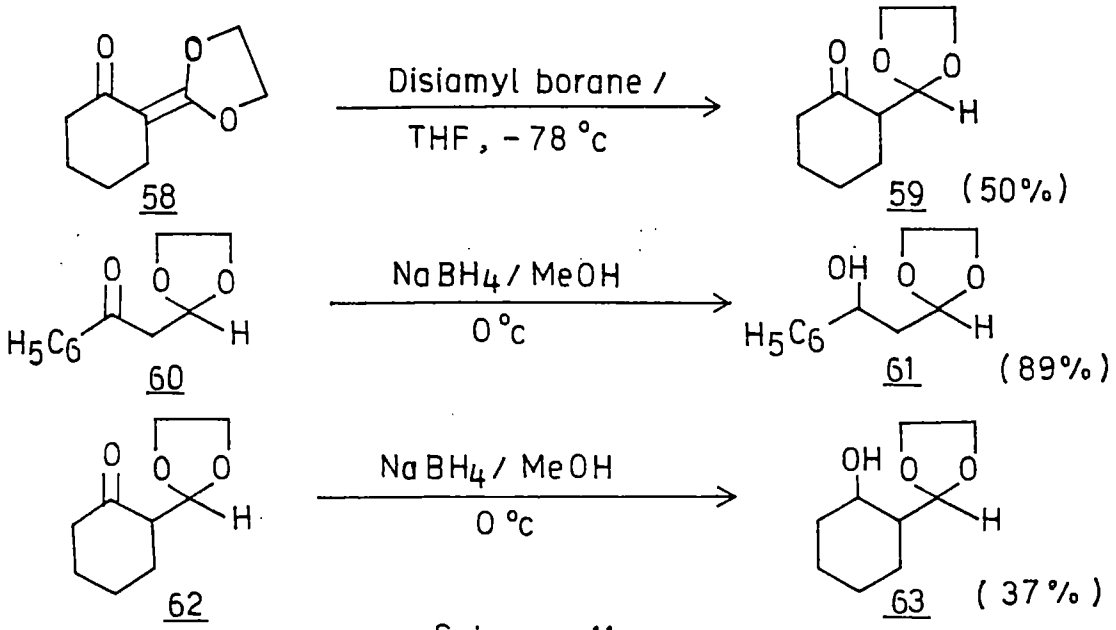
V.2 RESULTS AND DISCUSSION

As illustrated in the preceding brief review, the alkoxymethylene ketones show lack of regioselectivity in the sodium borohydride reduction, since both 1,4- and 1,2-reduction products were formed. However, when the corresponding *n*-butylmercaptomethylene ketones were reduced with sodium borohydride, the correspondng 1,2-adduct allyl alcohols were found to be the sole products. Similar was the situation when the S,S-acetals were reduced with sodium borohydride. However, the α-oxoketene dithioacetals yielded 1,4-reduction products in the presence of electrophilic reducing agents like sodium cyanoborohydride, DIBAL, 9-BBN, and catechol borane or with sodium borohydride in acetic acid. The oxoketene cyclic O,O-acetals were known to be



54 55 56 57

a, H_3B ; THF / - 78 °c or
Thexyl borane ;
disiamyl borane ;
Catechol borane



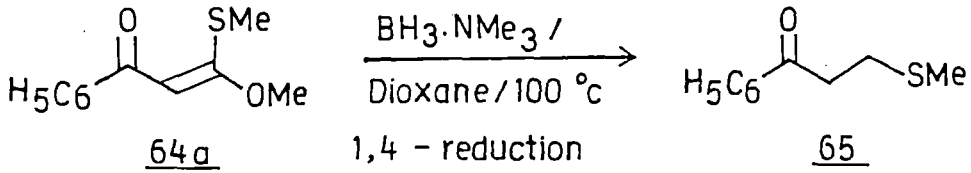
58 59 (50%) 60 61 (89%) 62 63 (37 %)

Scheme - 11

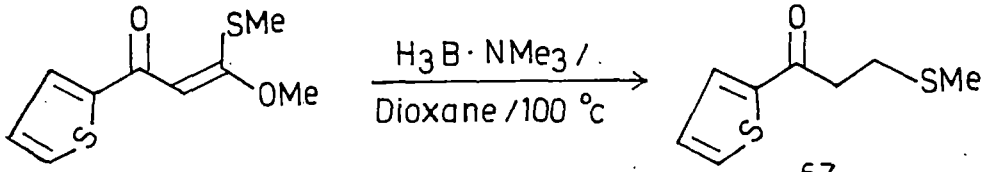
reduced regioselectively with borane which are known to yield the 1,4-addition products. It was therefore, considered of interest to examine the reduction pattern of the various α-oxoketene O,S-acetals which are available easily as described elsewhere in the thesis.

In the present investigaton, few selected O,S-acetals have been examined with various reducing agents to study the mode of reduction of these reducing agents. Thus the α-oxoketene O,S-acetal **64a** when subjected to reduction with sodium borohydride in methanol yielded a mixture of several products and the reduction therefore found to be not as clean as it was in the case of corresponding S,S-acetals. Evidently replacement of sulfur by oxygen dramatically alters the electrophilic centres in **64a** towards sodium borohydride leading to a mixuture of several products.

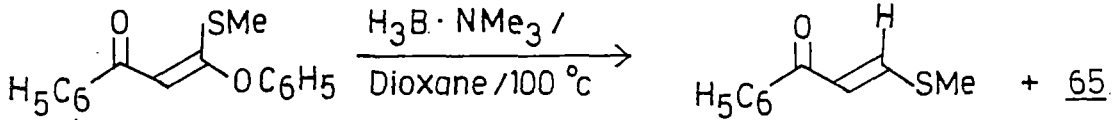
When α-oxoketene O-methyl S-methylacetal **64a** was reduced using borane trimethylamine complex in dioxane the corresponding over reduced product 3-methylthio-1-phenylpropan-1-one **65** was formed in 81% yield through exclusive 1,4-reduction fashion (scheme 12). The compound **65** was found to show identical physical and chemical properties with that reported in the literature[11]. The O,S-acetal **66** was similarly reduced under the described reaction conditions to give 3-methylthio -1(2'-thienyl)propan-1-one **67** in 80% yield. The structure of **67** was established from its analytical and spectral data which are described in the experimental section. However, when oxoketene O-phenyl S-methylacetal **64b**



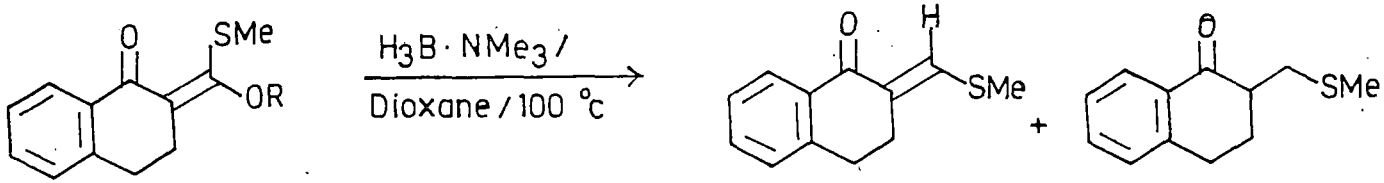
64a — 1,4 - reduction — 65



66 — 67



64b — 68



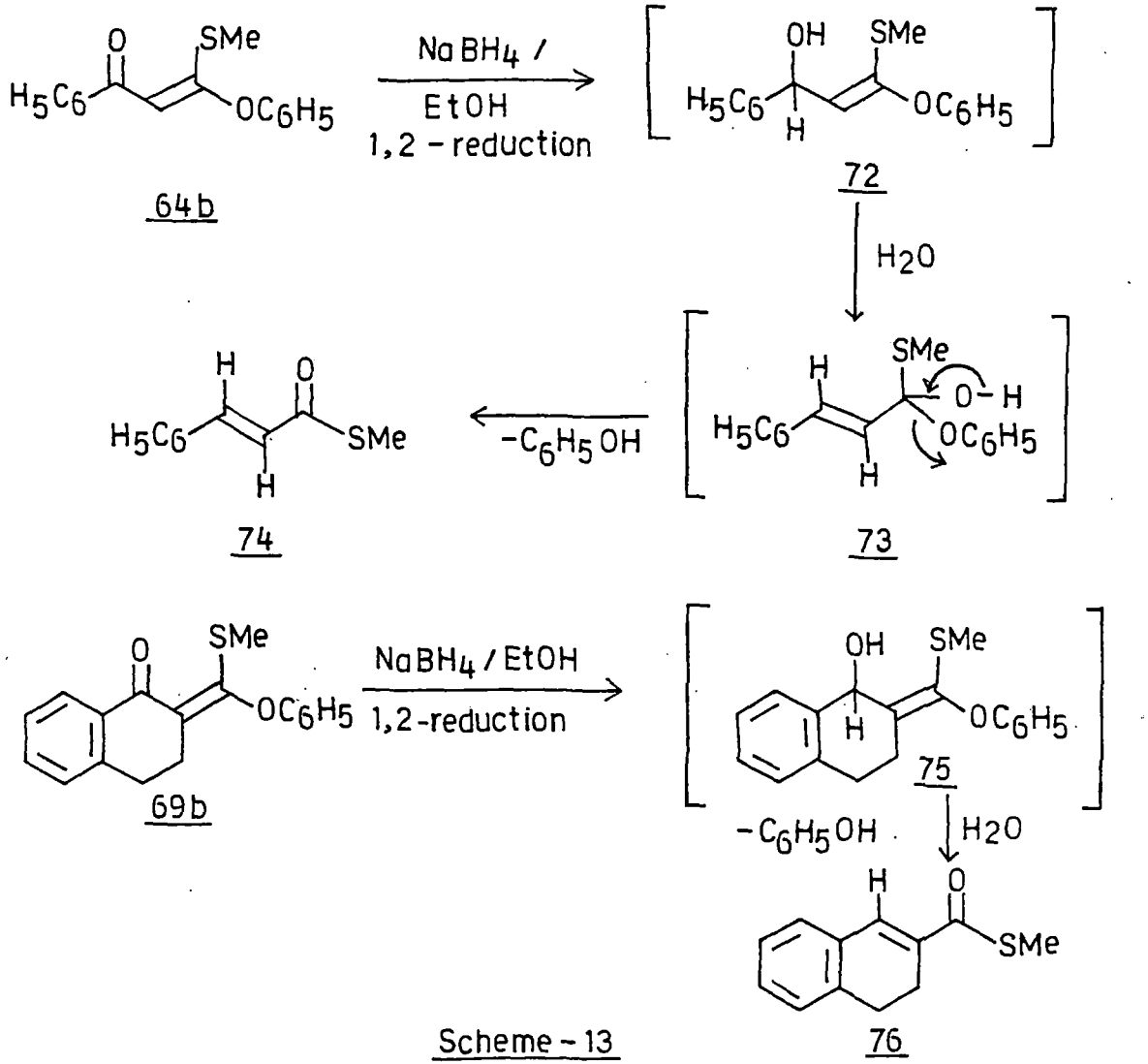
69 — 70 + 71

69a, R = Me
b, R = C_6H_5

Scheme - 12

was reduced under similar reaction conditions, it gave 3-methylthio-1-phenyl-2-propen-1-one **68** in 76% yield along with minor amount of **65** in 9% yield (scheme 12). It may be noted here that the phenoxy group has behaved like a leaving group in preference to the elimination of methylmercaptan. This behaviour was further evident when both O-methyl S-methyl and O-phenyl S-methylacetals were reduced under similar reaction conditions. Thus when O-methyl S-methylacetal **69a** derived from tetralone was reduced under similar reaction conditions only 5% of methylthiomethylene ketone **70** was formed along with 68% of over reduction product **71**. . On the other hand the O-phenyl S-methylacetal **69b** on reduction with borane trimethylamine complex yielded **70** in 76% yield while **71** was obtained in only 9% yield (scheme 12). Apparently the O-phenyl group has proved to be a good leaving group in these transformations. The structure of **70** and **71** were confirmed by their analytical and spectral data which were identical with those reported in the literature[9].

The reduction of α-oxoketene O-methyl/phenyl S-methylacetals were next examined employing sodium borohydride in ethanol. The α-oxoketene O-methyl S-methylacetal **64a** gave a mixture of products after reduction with sodium borohydride in ethanol. On the other hand the oxoketene O-phenyl S-methylacetals **64b** and **69b** when reduced with sodium borohydride in ethanol after work-up, the corresponding S-methyl α,β-unsaturated thiocarboxylates **74** and **76** were formed in 78% and 82% yields respectively (scheme 13). Apparently, the reaction proceeded initially with 1,2-reduction followed

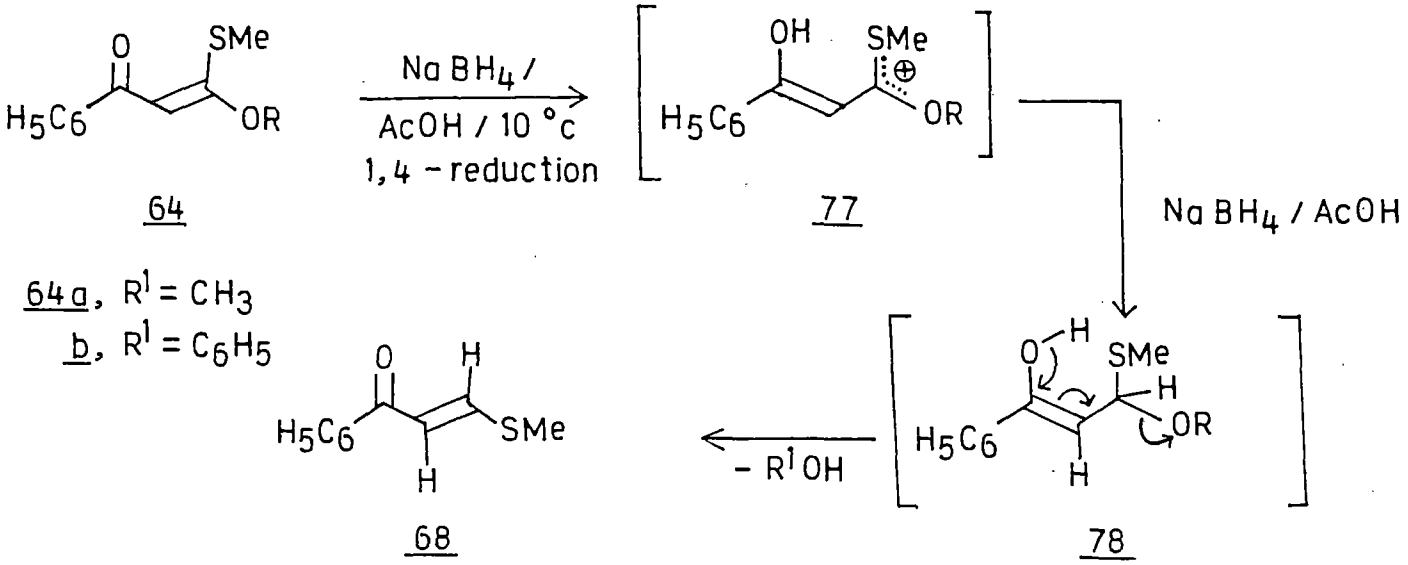

O
SMe
H_5C_6
OC_6H_5
64b
$NaBH_4$ /
EtOH
1,2 - reduction
OH
SMe
H_5C_6
H
OC_6H_5
72
H_2O
H
O
SMe
H_5C_6
H
$-C_6H_5OH$
SMe
H
O - H
H_5C_6
OC_6H_5
H
74
73
O
SMe
OC_6H_5
69b
$NaBH_4$ / EtOH
1,2-reduction
OH
SMe
H
OC_6H_5
75
$-C_6H_5OH$
H_2O
H
O
SMe
76

Scheme - 13

by hydrolytic cleavage and elimination of phenol to afford the 74 and 76 in high yields. The analytical and spectral data of S-methylthiocinnamate 74 and S-methyl 3,4-dihydronaphthalene-2-thiocarboxylate 76 were in accordance with the values reported in literature[7].

Interestingly, when O-methyl S-methylacetal 64a was reduced with sodium borohydride in acetic acid, the corresponding 3-methylthio-1-phenyl-2-propen-1-one 68 was formed in 88% yield. The analytical and spectral data (superimposable ir and nmr) of 68 was identical with that of reported in literature[9]. Similarly O-phenyl S-methylacetal 64b also underwent reduction under the similar reaction conditions to afford the corresponding methylthiomethylene ketone 68 in 82% yield. It is interesting to note that this reduction in the presence of acetic acid provides the protons, a hard acid which preferentially protonates oxygen in preference to sulphur that contributes for their preferential elimination in both the cases to give 68. Similar was the situation when 66 and 69 were reduced under the described reaction conditions, the corresponding 79 was obtained in 76% yield and 70 in 81% (from 69a)and in 79% (from 69b) yield (scheme 14). The analytical and spectral data of 70 and 79 were in agreement with those of reported in the literature [9].

When the O,S-acetal 64a was reduced with lithium aluminium hydride, the corresponding methylcinnamate 80 (scheme 15) was formed in 76% yield through initial 1,2-reduction of 64a followed by hydrolytic cleavage. The observed hydro



64

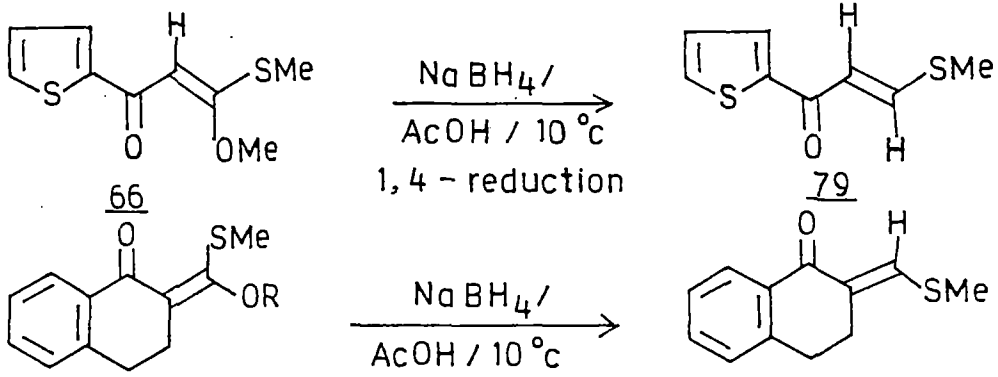
64a, $R^1 = CH_3$

b, $R^1 = C_6H_5$

77

78

68



66

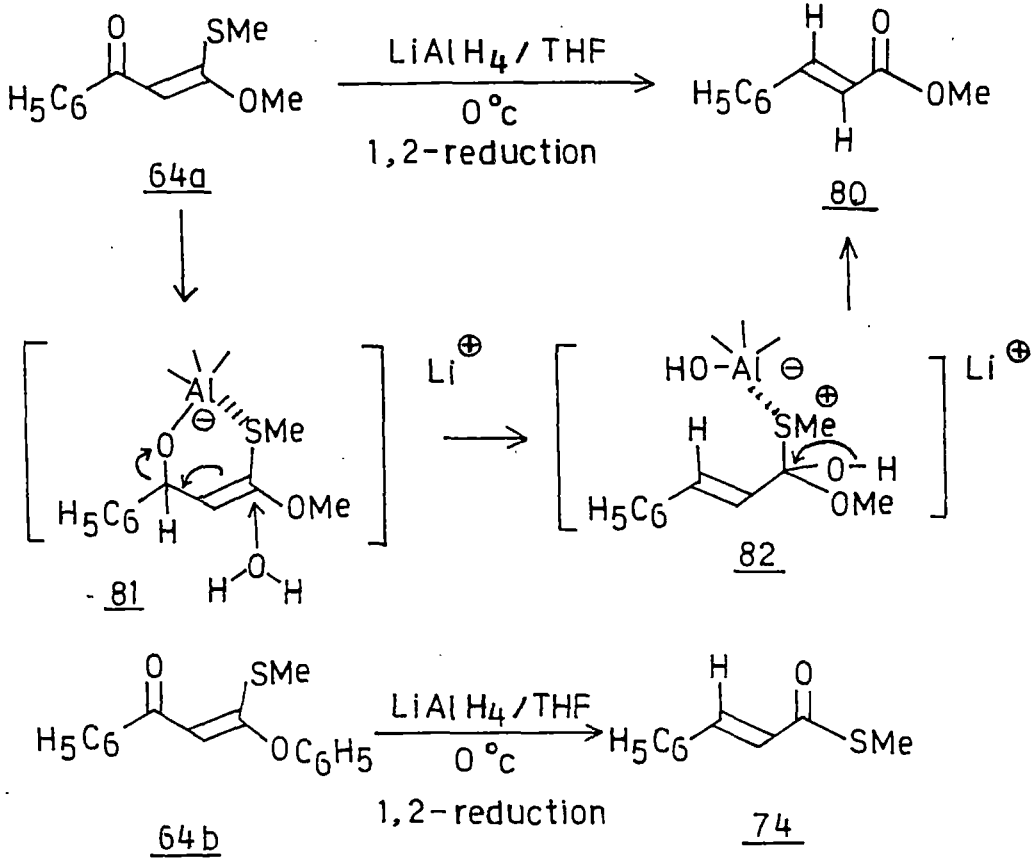
79

69 a, R = Me

b, R = C_6H_5

70

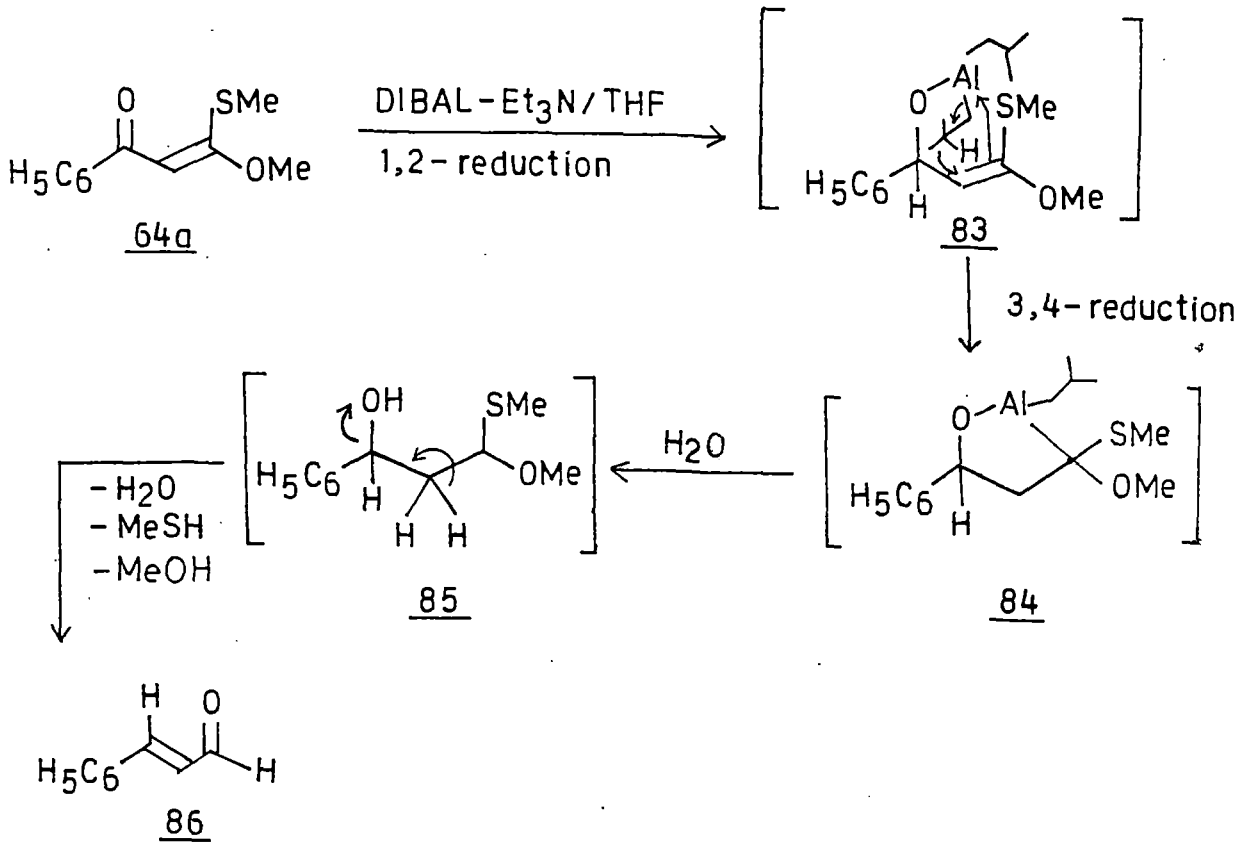
Scheme - 14


LiAlH4 / THF
0 °c
1,2-reduction
64a
80
81
82
LiAlH4 / THF
0 °c
1,2-reduction
64b
74

Scheme - 15

alumination in the case of dithioacetals did not follow in the case of O,S-acetals. Evidently the methylthio group in **64a** is *cis* to the carbonyl group resulting in organometallic complex **81** co-ordinating with sulfur rather than preferred oxygen (hard-hard) because of geometrical reasons. The elimination of methyl mercaptan appears to prefer over the elimination of methanol because of the favourable equilibrium created by escaping methyl mercaptan gas. On the other hand when **64b** was reduced with lithium aluminium hydride the corresponding S-methylthiocinnamate **74** was formed in 78% yield. Here the elimination of phenol is observed preferentially over the elimination methyl mercaptan. The structures **80** and **74** were established by their analytical and spectral data which were in agreement with the values reported in the literature [7].

When α-benzoylketene O-methyl S-methylacetal **64a** was reduced with diisobutyl aluminium hydride in presence of triethylamine (DIBAL-NEt_3), the corresponding cinnamaldehyde **86** was formed in 58% yield (scheme 16). It appears that the unstable β-hydroxy O,S-acetal **85** was the reduction product, probably obtained through the collapse of the organo aluminium complex **84** formed through 1,2-reduction followed by hydroalumination. The hydrolytic cleavage of β-hydroxy acetal **85** afforded the cinnamaldehyde **86**. The spectral data (ir and nmr) of **86** are identical with the authentic sample of cinnamaldehyde.

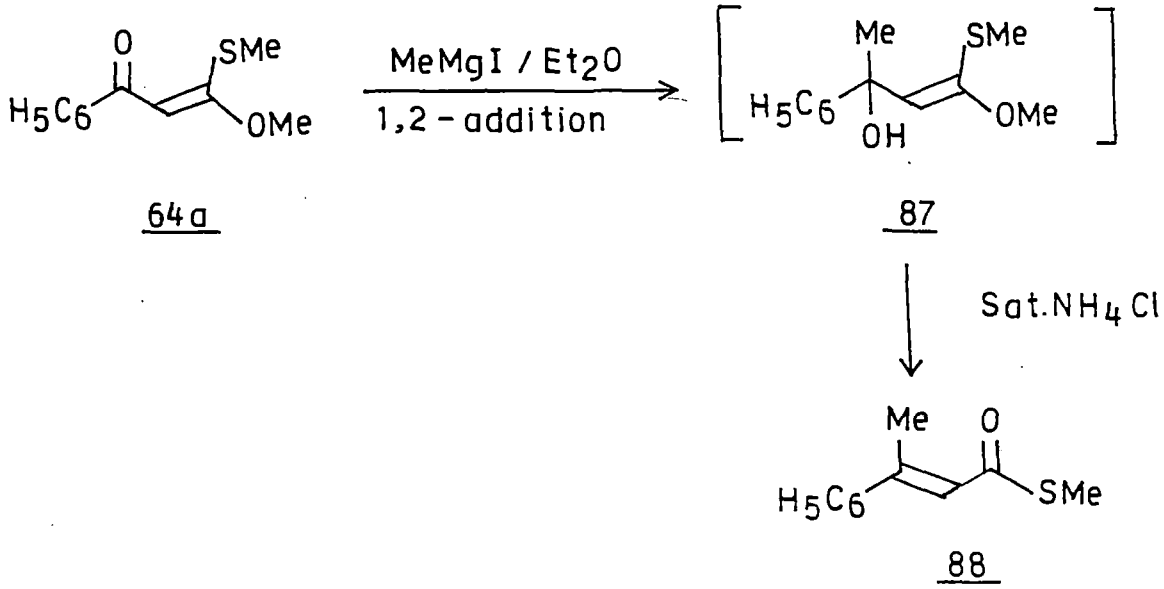

O
SMe
H5C6
OMe
64a
DIBAL-Et3N/THF
1,2-reduction
Al
O
SMe
H
H5C6
H
OMe
83
3,4-reduction
O
Al
SMe
H5C6
H
OMe
84
H2O
OH
SMe
H5C6
H
OMe
H H
85
-H2O
-MeSH
-MeOH
H
O
H5C6
H
86

Scheme - 16

Subsequent to the metal hydride reduction studies, a preliminary ivestigation on the addition of carbon nucleophile to the O,S-acetal is also been undertaken. Thus the α-benzoylketene O-methyl S-methylacetal **64a** when treated with methylmagnesium iodide the S-methyl β-methylthio cinnamate **88** obtained in 62% yield (scheme 17). The known product **88**[16] was having the analytical and spectral data in accord with the assigned structure. Apparently, the reaction followed 1,2-addition to give the corresponding carbinol **87** which during work-up underwent hydrolytic cleavage to afford the cinnamate **88**. No product derived from 1,4-addition was detected in the reaction mixture.

V.3 CONCLUSION

The behaviour of various O,S-acetals towards different reducing agents varies from those of the corresponding S,S-acetals. The reduction of O,S-acetals in the presence of sodium borohydride in ethanol was totally unsatisfactory while those reductions in the case of S,S-acetals were highly rewarding. The O,S-acetals however followed some definite pattern when they were reduced with sodium borohydride in acetic acid. The observed 1,4-reduction and elimination of OCH_3 or OC_6H_5 group in preference to SCH_3 group was noted. The lithium aluminium hydride reduction did not follow hydroalumination and underwent only 1,2-reducton followed by hydrolysis to give the corresponding ene esters. Similarly reduction of O,S-acetal by DIBAL appears to follow 1,2-



64a

87

88

Scheme - 17

reduction followed by hydroalumination to afford the corresponding aldehyde.

V.4 EXPERIMENTAL

Melting points were determined on a 'Thomas Hoover' capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin Elmer 297 spectrophotometer, ^{1}H NMR spectra on a Varian EM-390 (90MHz)spectrometer. Mass spectra were recorded on a Jeol D-300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyzer.

Starting materials and Reagents

All the α-oxoketene O,S-acetals used for the present investigation were prepared according to the earlier reported procedures[15] and are described in the experimental section of chapter 3. The borane-trimethylamine complex (Ventron), sodium borohydride (Aldrich), lithium aluminium hydride (Aldrich) and diisobutyl aluminium hydride (Fluka) were purchased and used as supplied. Triethylamine was dried over KOH and distilled prior to the reaction. Diethyl ether, tetrahydrofuran and dioxane were dried over sodium wire and distilled prior to use.

General Procedures :

(A) Reduction of α-Oxoketene O,S-Acetals 64a-b, 66 and 69 with Borane-Trimethylamine Complex.

To a stirred solution of α-oxoketene O,S-acetals (0.01mol) in dry dioxane (15ml) was added borane-trimethylamine complex (0.9g, 0.012mol) and heated at 100°C with stirring for 2-3hr.(monitored by tlc). It was then cooled to room temperature, poured on to crushed ice (100g) and extracted with chloroform (2x50ml). The organic layer was washed with saturated sodium bicarbonate solution (1x50ml), water (3x100ml), dried over sodium sulphate and evaporated to give crude products which were purified by column chromatography over silica gel using hexane as eluent.

(B) Reduction of α-Oxoketene O,S-Acetals 64b and 69b with Sodium Borohydride in Ethanol.

To a solution of α-oxoketene O,S-acetals (0.01mol) in absolute ethanol (20ml) was added sodium borohydride (0.75g, 0.02mol) in one lot and refluxed on oil bath with stirring for 2-3hr.(monitored by tlc). It was then cooled to room temperature, poured on to crushed ice (100g) and extracted with chloroform (3x50ml). The organic layer was washed with saturated sodium bicarbonate solution (1x50ml), water (3x100ml),dried over sodium sulphate and evaporated to give crude products which were purified by column chromatography over silica gel using ethylacetate /hexane (2:98) as eluent.

(C) Reduction of α-Oxoketene O,S-Acetals 64a-b, 66 and 69a-b with Sodium Borohydride in Acetic acid.

To a well stirred solution of α-oxoketene O,S-acetals (0.01mol) in glacial acetic acid (25ml), sodium borohydride

(1.20g, 0.03mol) was added slowly (portion wise) (30min) at 5-10°C. The reaction mixture was further stirred at room temperature for 3hr.(monitored by tlc). The reaction mixture was poured into ice cold water (100ml), extracted with chloroform (3x100ml), dried over sodium sulphate and concentrated to give the viscous residue which on column chromatography over silica gel (hexane eluent) gave the pure methylthiomethylene ketones.

(D) Reduction of O,S-Acetals 64a and 64b with Lithium Aluminium Hydride.

To a stirred solution of lithium aluminium hydride (0.4g, 0.01mol) in THF (25ml) at 0°C under nitrogen atmosphere, O,S-acetal (0.01mol) in THF (15ml) was added dropwise. Continued the stirring at the same temperature for 1-2hr (monitored by tlc) and poured on to crushed ice (100g). It was then neutralised with 2N HCl and extracted with chloroform (2x50ml). The chloroform extract was washed with saturated sodium bicarbonate solution (1x50ml), water (2x100ml), dried (Na_2SO_4) and evaporated to give crude product. The crude product eneesters thus obtained were purified by passing through a short length silica gel column using hexane as eluent.

(E) Reduction of α-Oxoketene O-Methyl S-Methylacetal 64a with Diisobutyl Aluminium Hydride.

To a stirred solution of O,S-acetal **64a** (2.20g, 0.01mol) in dry THF (25ml) at -78°C under nitrogen atmosphere, was added

DIBAL-TEA complex [prepared by the addition of DIBAL (1.7g, 0.012mol) to a stirred solution of triethylamine (1.2g, 0.012mol) in THF (15ml), at -78°C, under nitrogen atmosphere and stirred the mixture for 30min. at the same temperature] through a syringe and continued the stirring at -78°C for 30min. Allowed the reaction mixture to come to 0°C and poured on to crushed ice (100g), drenched with 5ml Conc. HCl. It was then extracted with chloroform (2x50ml), washed with water (3x100ml), dried over sodium sulphate and evaporated. The residue was chromatographed over silica gel using hexane as eluent. The pure cinnamaldehyde 86 thus obtained in 58% yield exhibited ir and ^{1}H nmr spectra identical with the authantic sample of cinnamaldehyde.

The yields of all the products obtained by the reduction of O,S-acetals on subjecting to various reducing agents following the general procedures as described above are given in the Table.

3-Methylthio-1-phenylpropan-1-one (65). Colorless viscous liquid (Table entry 1 and 4) ; IR (neat) 1695, 1612, 1598, 1440, 1360 cm^{-1} ; ^{1}H NMR (CCl_4) 2.16 (3H, s, SCH_3), 2.82 (2H, t, J=6Hz, CH_2), 3.21 (2H, t, J=6HZ, CH_2), 7.44-7.68 (3H, m, ArH), 7.91-8.06 (2H, m, ArH) (Anal. Calcd. for $C_{10}H_{12}OS$: C, 66.62 ; H,6.71. Found : C, 66.49 ; H, 6.57%).

3-Methylthio-1-(2'-thienyl)propan-1-one (67). Colorless liquid (Table entry 2) ; IR (neat) 1678, 1537, 1432, 1379 cm^{-1} ; ^{1}H NMR (CCl_4) 2.01 (3H, s, SCH_3), 2.78 (2H,t, J=6Hz, CH_2), 3.01 (2H, t, J=6Hz, CH_2), 7.03-7.21 (2H, m, thienyl H),

7.54-7.75 (2H, m, thienyl H) (Anal. Calcd. for $C_8H_{10}OS_2$: C, 51.58 ; H, 5.41. Found : C, 51.81 ; H, 5.66%).

3-Methylthio-1-phenyl-2-propen-1-one (68). Colorless viscous liquid (Table entry 3,11 and 12); IR (neat) 1660, 1619, 1562, 1443, 1227 cm^{-1} ; ^1H NMR (CCl_4) 2.49 (3H, s, SCH_3), 6.82 (1H, d, J=18Hz, =CH), 7.42-7.71 (3H, m, ArH), 7.82-8.16 (3H, m, ArH and =CH) (Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.38 ; H,5.66. Found : C, 67.63 ; H, 5.89%).

2-(Methylthiomethylene)-1-tetralone (70). Yellow crystals (Table entry 5, 7, 14 and 15) ($CHCl_3$/hex) ; m.p. 67-68°C (lit.[9] 68°C) ;IR (KBr) 1653, 1590, 1547 cm^{-1} ; ^1H NMR ($CDCl_3$) 2.46 (3H, s, SCH_3), 2.64-2.79 (2H, m, CH_2), 2.80-3.03 (2H, m, CH_2), 7.20-7.65 (3H, m, ArH), 7.85 (1H, s, =CH), 8.10-8.29 (1H, s, ArH) (Anal. Calcd. for $C_{12}H_{12}OS$: C, 70.55 ; H,5.92. Found : C, 70.78 ; H, 6.19%).

2-(Methylthiomethyl)-1-tetralone (71). Colorless liquid (Table entry 6 and 8) ; IR (neat) 1703, 1620, 1468 cm^{-1} ; ^1H NMR (CCl_4) 2.18 (3H, s, SCH_3), 2.31-2.64 (4H, m, CH_2), 2.80-3.19 (3H, m, CH and CH_2), 7.01-7.47 (3H, m, ArH), 7.85-8.02 (1H, m, ArH) (Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.86 ; H, 6.84. Found : C, 70.15 ; H, 7.01%).

S-Mehtylthiocinnamate (74). Colorless solid (Table entry 9 and 17) (ether/hex) ; m.p. 46-47°C (lit 48-49°C) ; IR (CCl_4) 1679, 1636, 1598, 1509, 1461 cm^{-1} ; ^1H NMR (CCl_4) 2.40 (3H, s, SCH_3), 6.69 (1H, d, J=16Hz, =CH), 7.31-7.78 (6H, m, =CH and ArH) (Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.38 ; H, 5.66. Found : C, 67.59 ; H, 5.91%).

S-Methyl 3,4-dihydronaphthalene-2-thiocarboxylate (76). Colorless thick liquid (Table entry 10); IR (CCl_4) 1742, 1676, 1585, 1510, 1282 cm^{-1} ; ^1H NMR (CCl_4) 2.36 (3H, s, SCH_3), 2.52-2.93 (4H, m, CH_2), 7.30 (4H, brs, ArH), 7.58 (1H, s, =CH) (Anal. Calcd. for $C_{12}H_{12}OS$: C, 70.55 ; H, 5.92. Found : C, 70.74 ; H, 6.09%)

3-Methylthio-1-thienyl-2-propen-1-one (79). Yellow viscous liquid (Table entry 13) ; IR (neat) 1652, 1575, 1439,1286, cm^{-1} ; ^1H NMR (CCl_4) 2.40 (3H, s, SCH_3), 6.73(1H, d, J=16Hz, =CH), 7.02 (1H, t, J=3Hz, thienyl H), 7.63- 7.88 (2H, m, thienyl H), 7.91 (1H, d, J=16Hz, =CH) (Anal. Calcd. for $C_8H_8OS_2$: C, 63,12 ; H, 5.30. Found : C, 63.35 ; H, 5.57%).

S-Methy β-methylthiocinnamate (88). To astirred solution of methylmagnesium iodide (prepared by reacting magnesium 0.5g, 0.02mol and methyl iodide 1.7g, 0.012mol) in THF was added O,S-acetal **64a** (2.2g, 0.01mol) at 0°C. Stirred the reaction mixture between 0-5 °C for another 2hr. It was then poured in to saturated ammonium chloride solution (100ml) and extracted with chloroform (2x50ml). Washed the organic layer with water (3x100ml), dried over sodium sulphate and evaporated . The residue was chromatographed over silica gel using hexane as eluent. It was isolated as yellow viscous liquid ; yield 62% ; IR (CCl_4) 1709, 1620, 1457, 1372 cm^{-1} ; ^1H NMR (CCL_4) 2.20 (3H, s, SCH_3), 2.49 (3H, s, CH_3), 6.48 (1H, s, =CH), 7.24-7.61 (5H, m, ArH) (Anal. Calcd. for $C_{11}H_{12}OS$: C, 68.71 ; H, 6.29. Found : C, 68.98 ; H, 6.55%).

TABLE

Entry	Reducing agent	substrate	Product	Yield (%)
1	A	64a	65	81
2	A	66	67	80
3	A	64b	68	76
4	A	64b	65	9
5	A	69a	70	5
6	A	69a	71	68
7	A	69b	70	76
8	A	69b	71	9
9	B	64b	74	78
10	B	69b	76	82
11	C	64a	68	88
12	C	64b	68	82
13	C	66	79	76
14	C	69a	70	81
15	C	69b	70	79
16	D	64a	80	76
17	D	64b	74	78
18	E	64a	86	58

A. H_3B-NMe_3/Dioxane ; B. $NaBH_4$/EtOH ; C. $NaBH_4$/AcOH ;
D. $LiAlH_4$/THF ; E. DIBAL-TEA/THF

REFERENCES

1. R.F. Church, R.E. Ireland, J.M. Marshall, J. Org. Chem., *27*, 1118 (1962).
2. R.E. Ireland, J.A. Marshall, J. Org. Chem., *27*, 1615 (1962).
3. R.E. Ireland, J.A. Marshall, J. Org. Chem., *27*, 1620, 1622 (1962).
4. J.A. Marshall, P.C. Johanson, J. Org. Chem., *35*, 192 (1970).
5. R.F. Church, R.E. Ireland, J.A. Marshall, J. Org. Chem., *27*, 1118 (1962).
6. M. Saquet, A. Thuillier, Bull.Soc.Chem.Fr., *1582*, 3969 (1966).
7. B. Myrboh, H. Ila, H. Junjappa, J. Org. Chem., *48*, 5327 (1983).
8. (a) S. Terashima, S. Subjew, K. Koga, Terahedron Lett., 4397 (1978) (b) S. Subjew, S. Terashima, K. Koga Chem. Pharm. Bull., *27*, 2351 (1979) (c) M.P. Reddy, G.S. Krishna Rao, U.N. Deshpande, ibid, 1116 (1982).
9. B. Myrboh, L.W. Singh, H. Ila, H. Junjappa, Synthesis, 307 (1982).
10. Ch. Srinivasa Rao, R.T. Chakrasali, H. Ila, H. Junjappa, Terahedron, *46*, 2195 (1990)
11. R.B. Gammill, D.M. Sobieray, P.M. Gold, J. Org. Chem., *46*, 3555 (1981).
12. R.B. Gammill, P.M. Gold, S.A. Mizsak, J. Am. Chem. Soc., *102*, 3096 (1980).

13. C.N. Eid, J.P. Konopelski, **Tetrahedron Lett.**, 305 (1990).

14. C.N. Eid, J.P. Konopelski, **Tetrahedron**, 975 (1991).

15. M.L. Purakayasta, M. Chandrasekharam, J.N. Vishwakarma, H. Ila, H, Junjappa, **Synthesis**, 245 (1993).

16. Gurdeep Singh, M.L. Purakayasta, H. Ila, H. Junjappa, J. **Chem. Soc. Perkin Trans I**, 1289 (1985).