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

By

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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.

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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

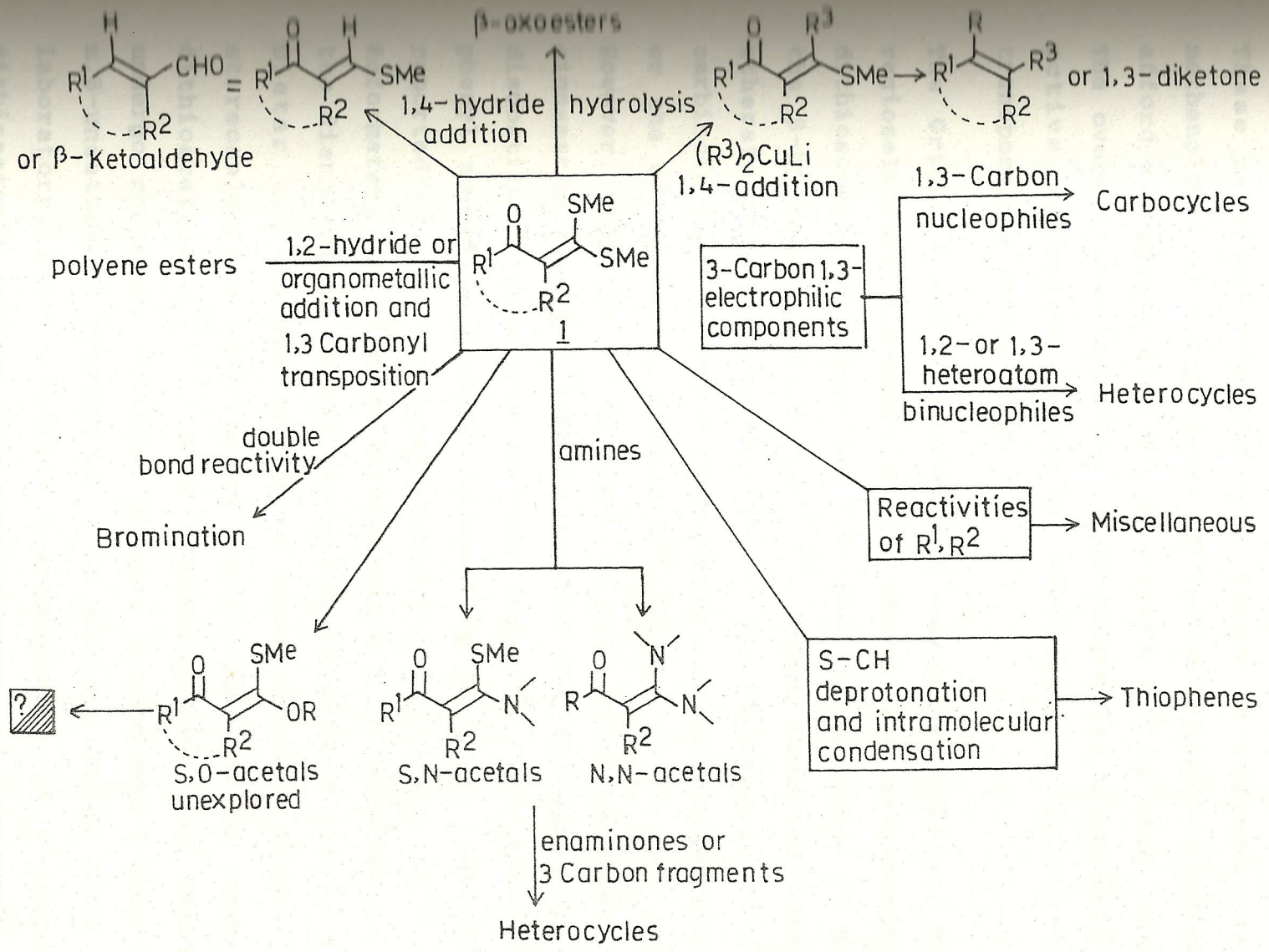
decomposition. However, the corresponding α-oxoketene O,O-acetals are moisture sensitive and undergo hydrolysis under mild conditions. The oxoketene dithioacetal is essentially a masked β-ketoester in which the ester functionality is protected as a ketene dithioacetal. Alternatively it may be viewed 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.

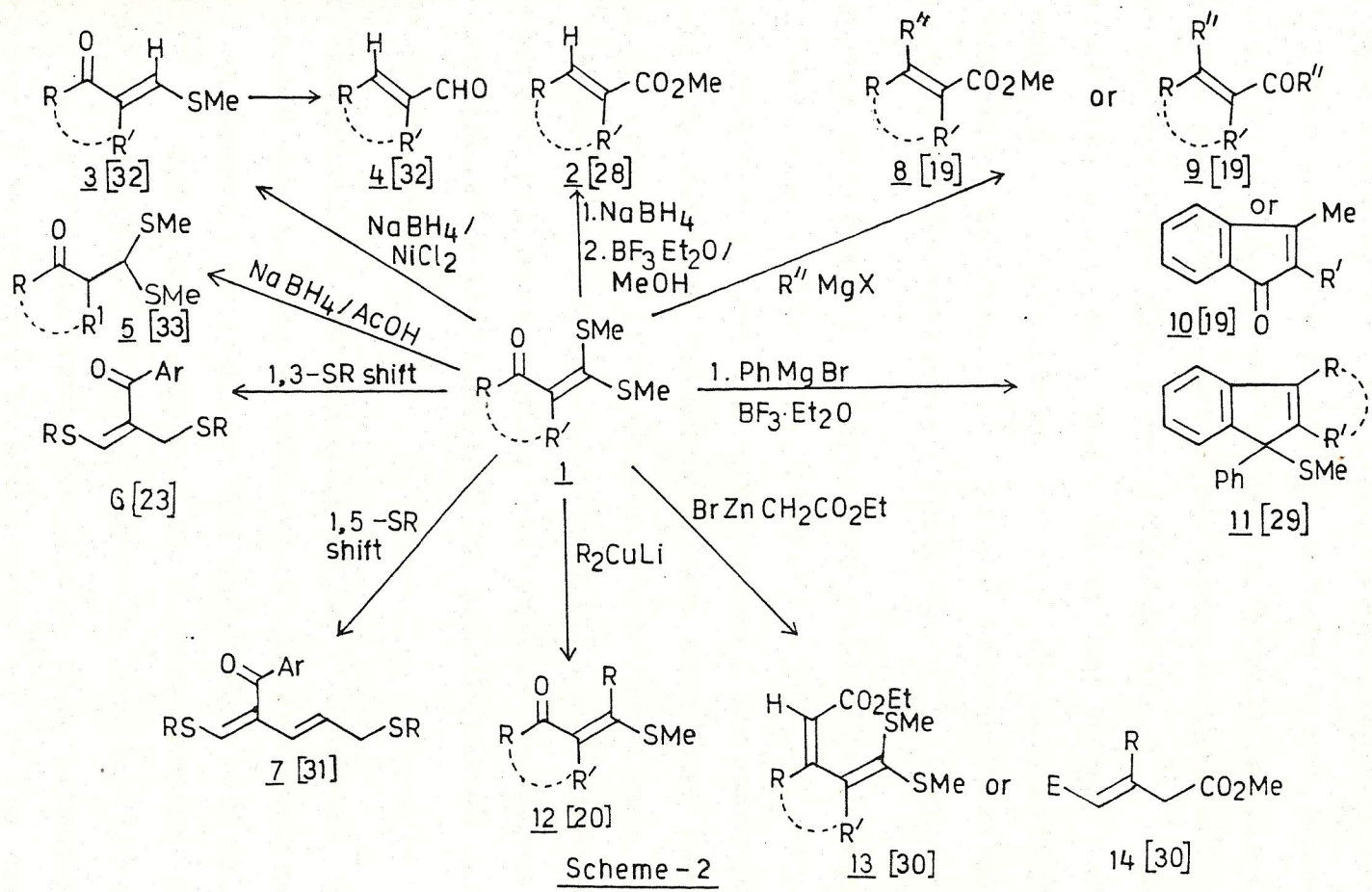
The carbonyl group of α-oxoketene dithioacetals has been reported to undergo sodium borohydride reduction in 1,2-


β-oxoesters
or β-Ketoaldehyde
1,4-hydride addition
hydrolysis
or 1,3-diketone
(R3)2CuLi
1,4-addition
1,3-Carbon nucleophiles
Carbocycles
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
1
3-Carbon 1,3-electrophilic components
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

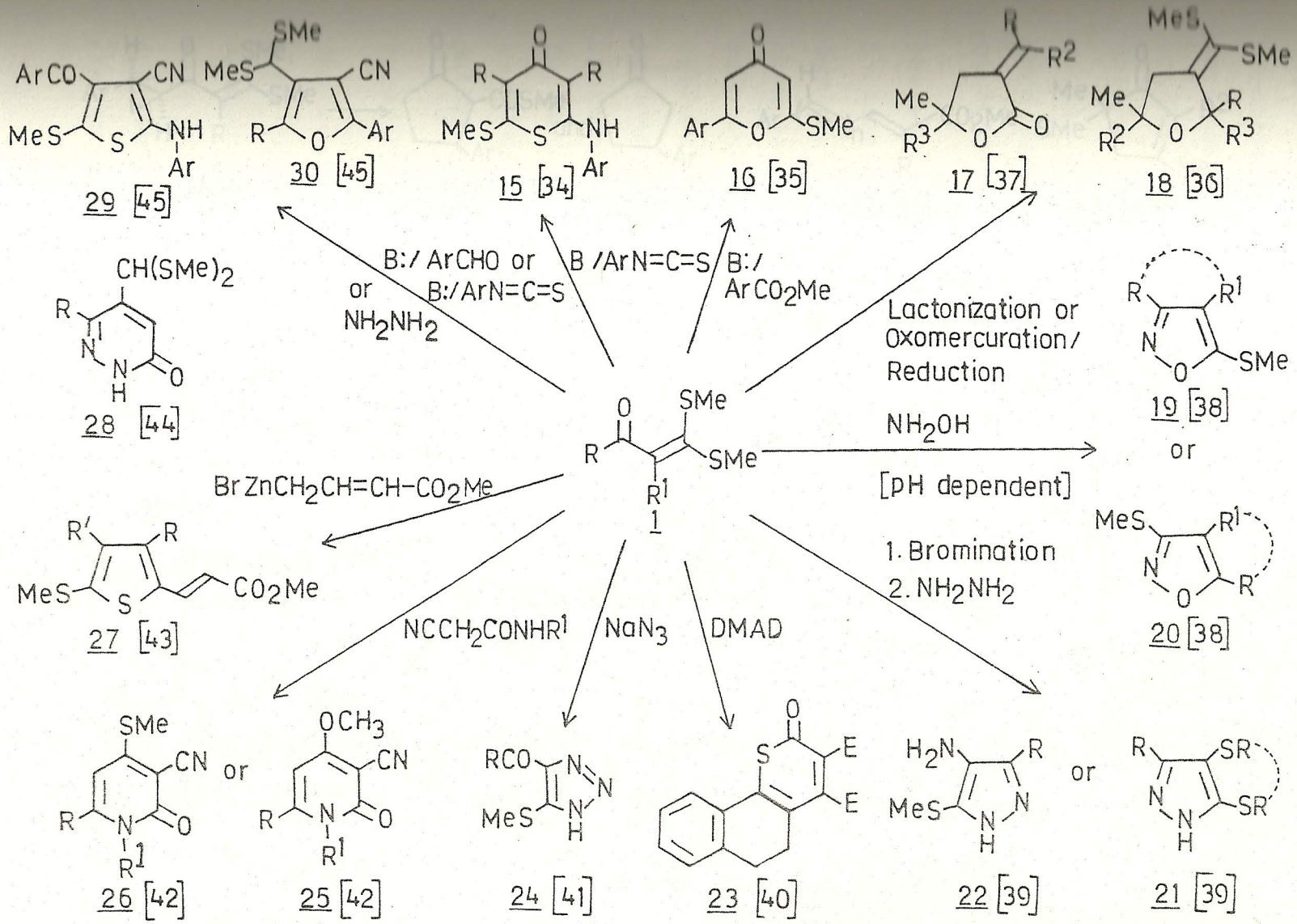

3 [32]
4 [32]
2 [28]
8 [19]
or
9 [19]
NaBH4 / NiCl2
1. NaBH4
2. BF3 Et2O / MeOH
R'' MgX
5 [33]
NaBH4 / AcOH
or
10 [19]
1,3-SR shift
1. Ph Mg Br
BF3·Et2O
6 [23]
1
11 [29]
1,5 -SR shift
R2CuLi
BrZn CH2CO2Et
7 [31]
12 [20]
13 [30]
or
14 [30]

Scheme - 2

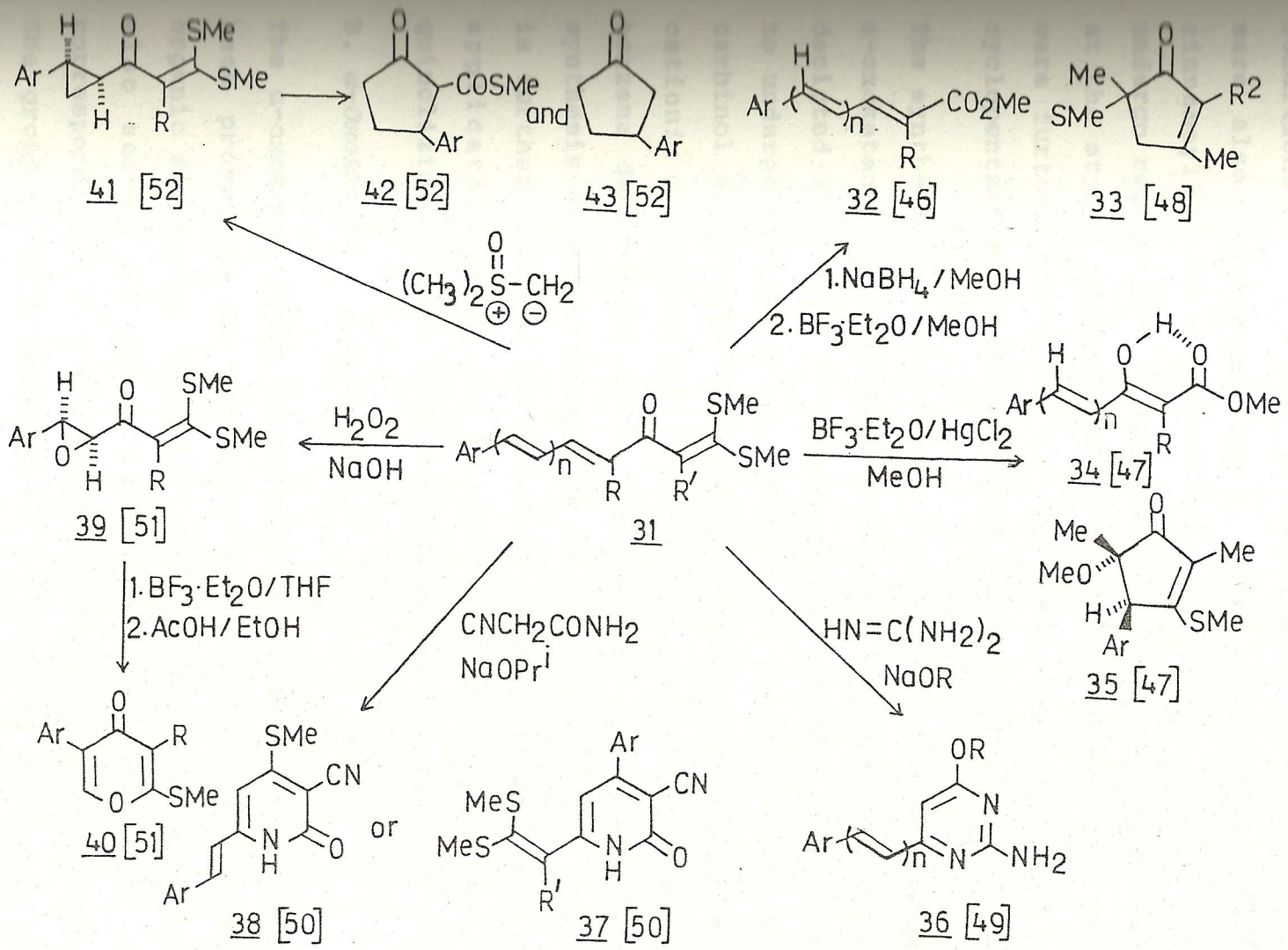
2-alkylthiomethylacrylo- phenones 6 are formed by a 1,3- RS shift. A base assisted 1,5- RS shift to the dienes 7 is also reported[31]. The α-oxoketene dithioacetals 1 are shown to undergo conjugate 1,4-reduction in highly regio- and chemoselective manner with sodium borohydride in acetic acid to afford 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
or B:/ArN=C=S
NH2NH2
B /ArN=C=S
B:/
ArCO2Me
Lactonization or
Oxomercuration/
Reduction
19 [38]
or
NH2OH
[pH dependent]
BrZnCH2CH=CH-CO2Me
1
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]

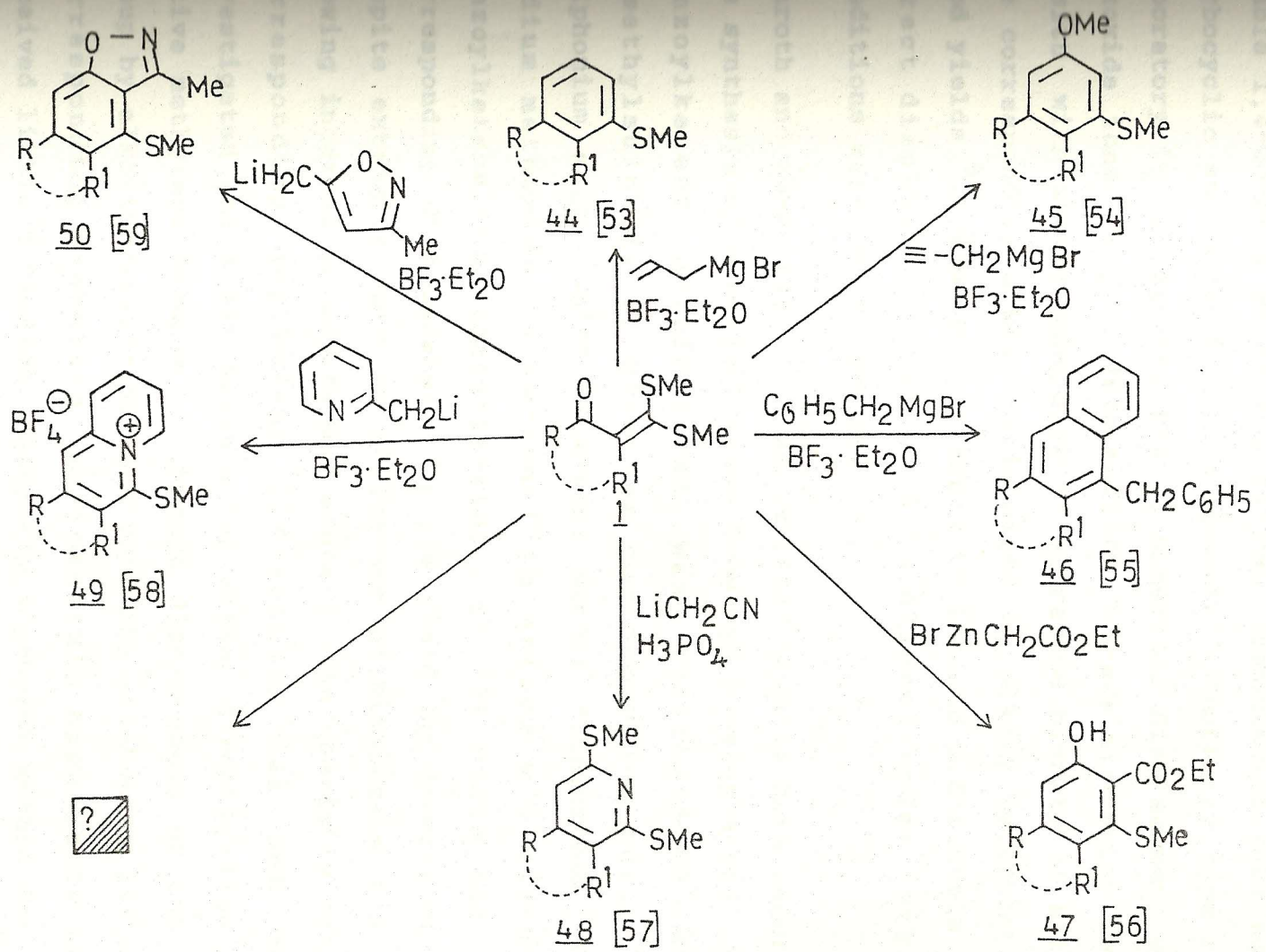
Scheme – 4

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*

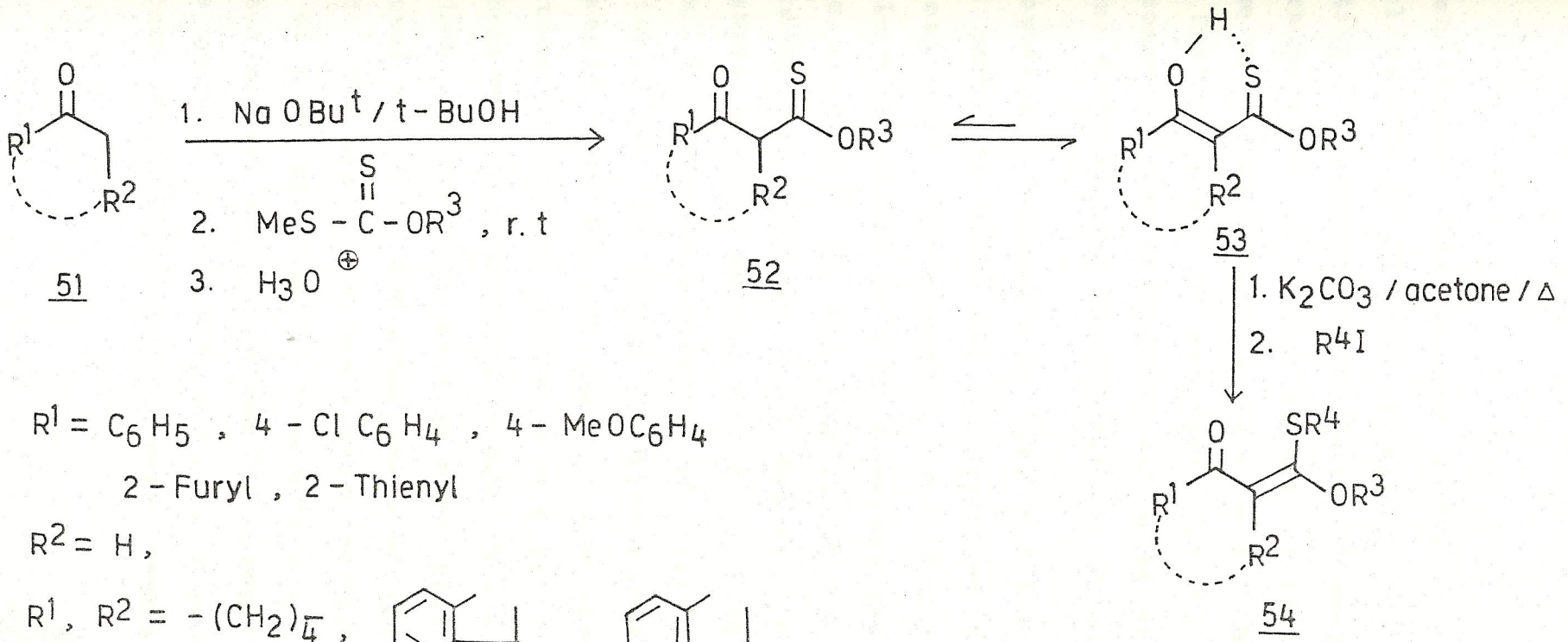
The α-oxoketene dithioacetals of the general formula 1 have been proved to be versatile synthetic intermediates in organic synthesis. As stated in preceding section, they have also served as precursors for the synthesis of the corresponding N,S- and N,N-acetals by direct displacement of SMe group(s)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


50 [59]
LiH2C
Me
BF3·Et2O
44 [53]
Mg Br
BF3·Et2O
45 [54]
OMe
≡-CH2 Mg Br
BF3·Et2O
BF4
CH2Li
BF3·Et2O
1
C6H5CH2MgBr
BF3·Et2O
46 [55]
CH2C6H5
49 [58]
LiCH2CN
H3PO4
BrZnCH2CO2Et
48 [57]
47 [56]
CO2Et
OH

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 ,

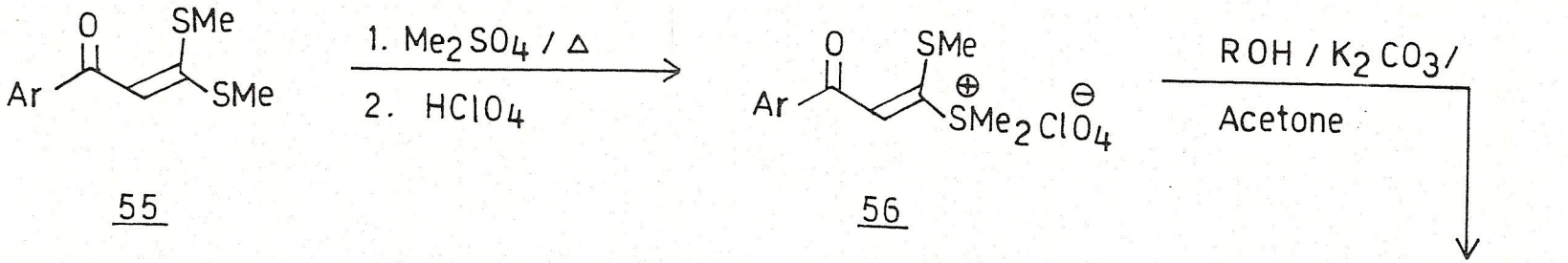
R^1 , R^2 = $-(CH_2)_4$,

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

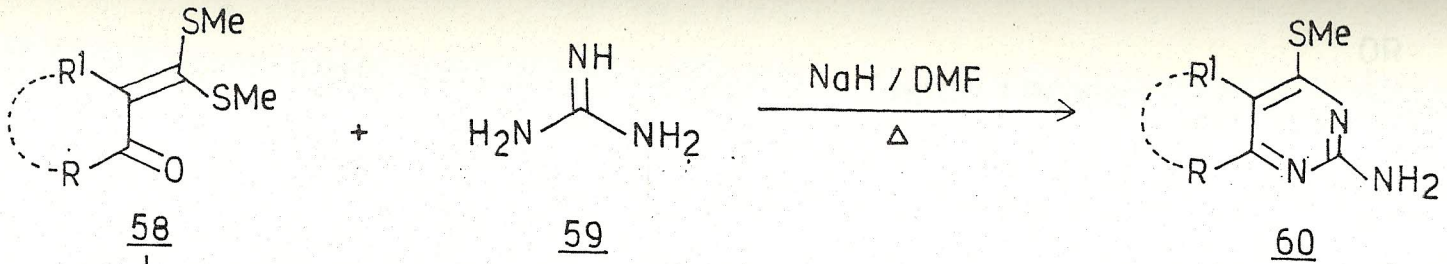
4-ClC_6H_4 , 2-naphthyl , 2-$MeO_2CC_6H_4$

Scheme - 7

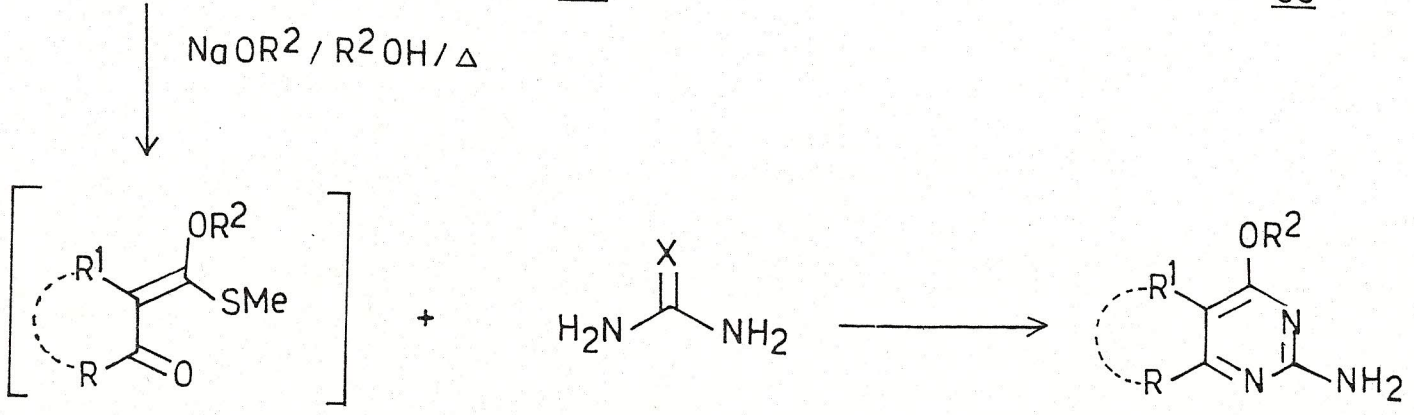
CH signal (δ=6.3) gave NOE enhancement on aryl protons while irradiation of SCH_3 (δ=2.37) showed no NOE enhancement on vinylic proton. These observations therefore support Z-stereochemistry for both O-methyl and O-phenyl O,S-acetals. The cyclic O,S-acetals were also assigned 'Z' stereochemistry since 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



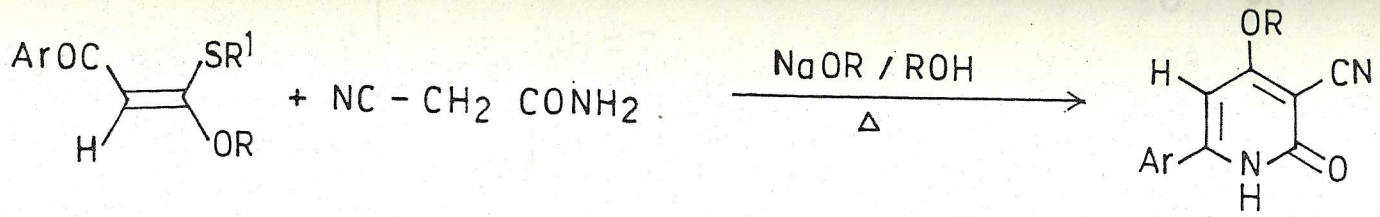
58 59 60



61 62 63

X = NH , S

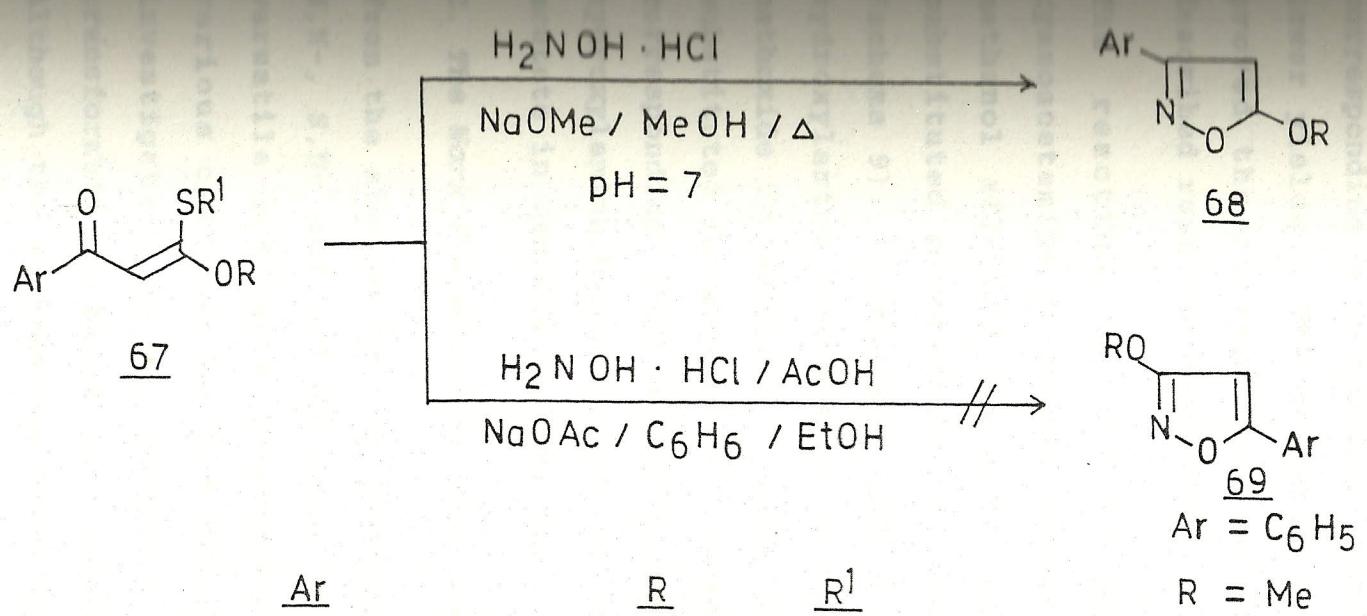
Scheme - 8



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

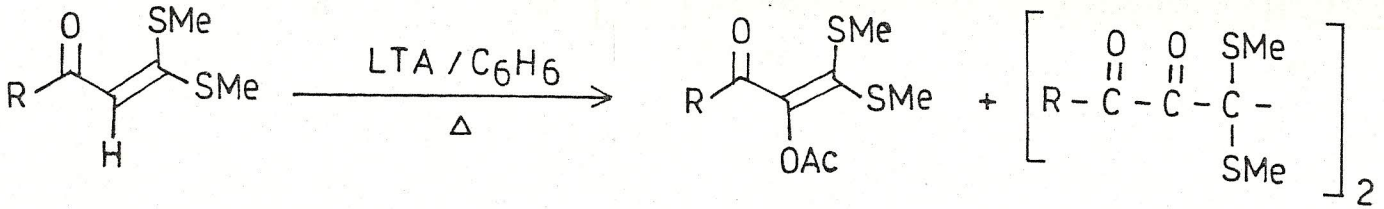
Scheme - 10

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.

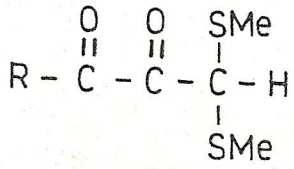


70

71

72

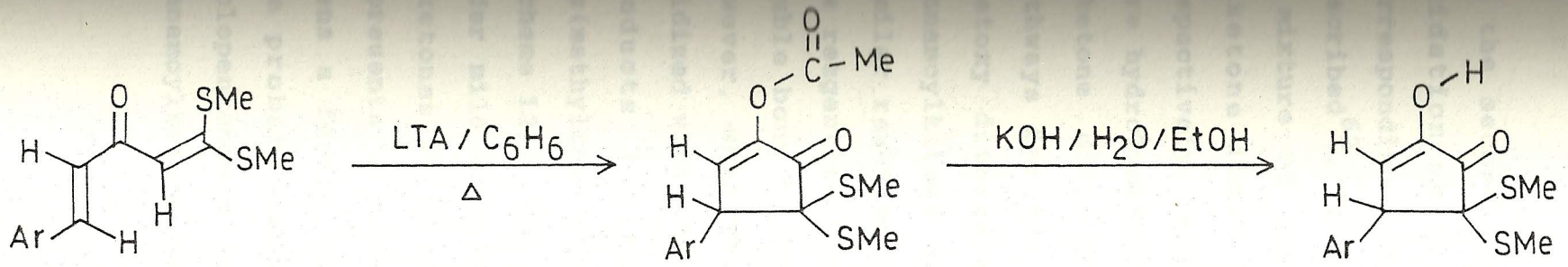
KOH / H_2O / EtOH



73

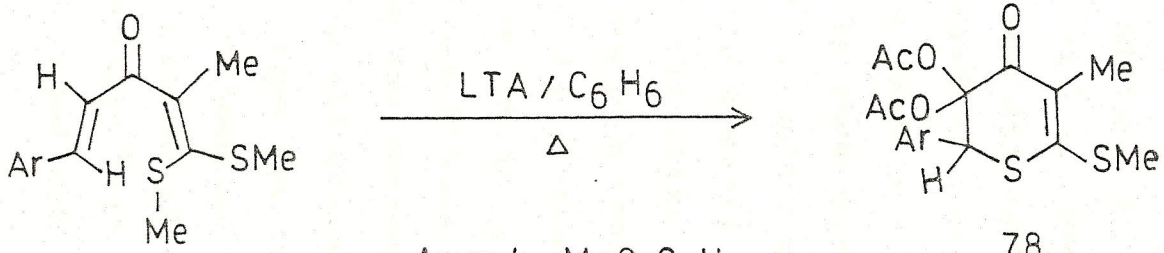
R = C_6H_5 , 4-Cl C_6H_4 ,
4-Me C_6H_4 , 4-MeO C_6H_4 , Me

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



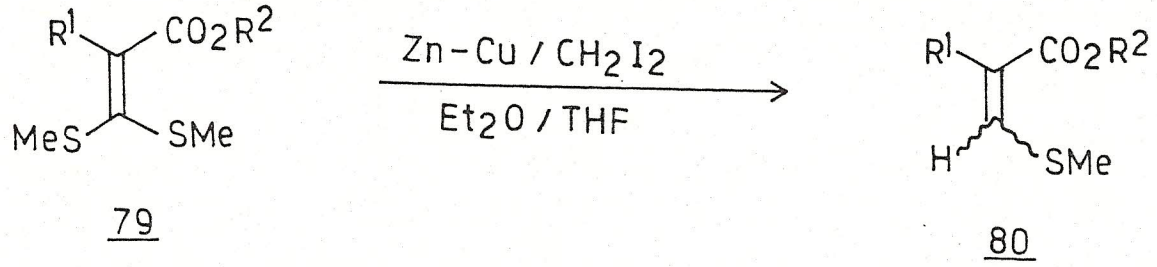
77

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

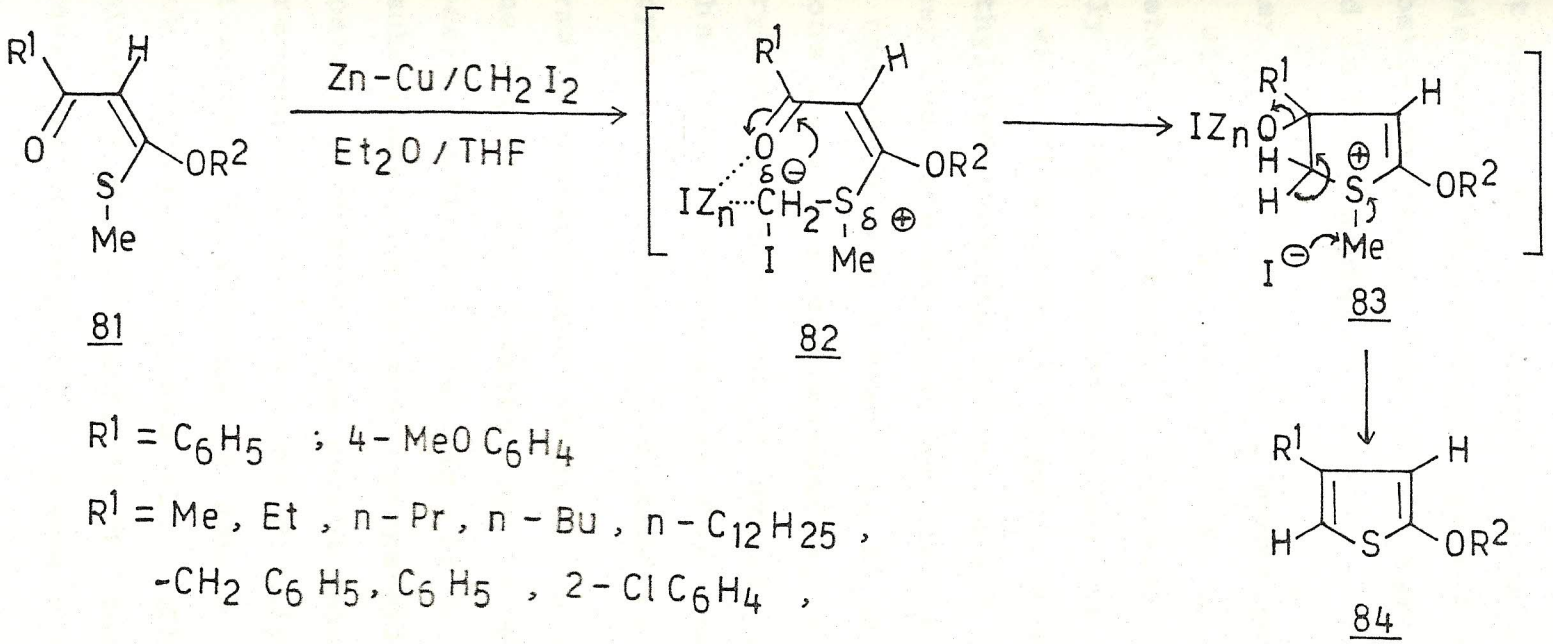
79-80 a, $R^1 = C_6H_5$; $R^2 = Et$

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_2 C_6H_5, C_6H_5, 2-Cl C_6H_4,

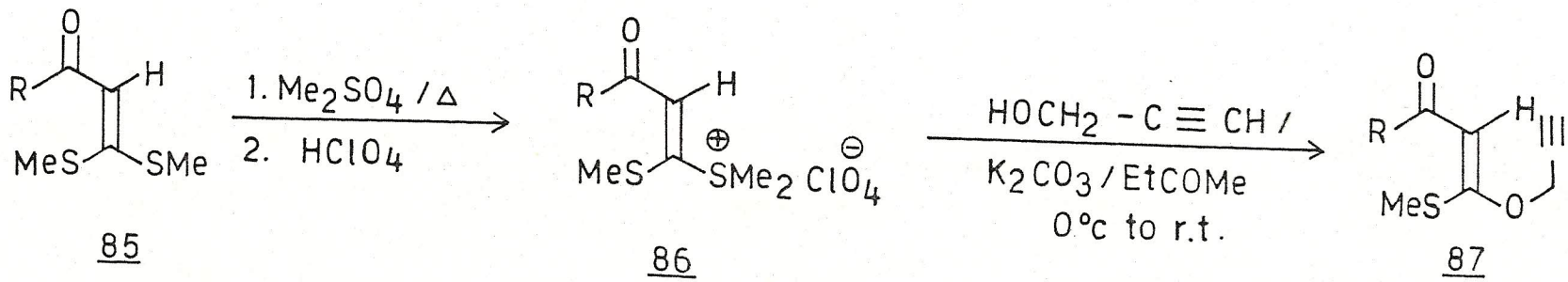
2-naphthyl, 2-methyl salicylate

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.

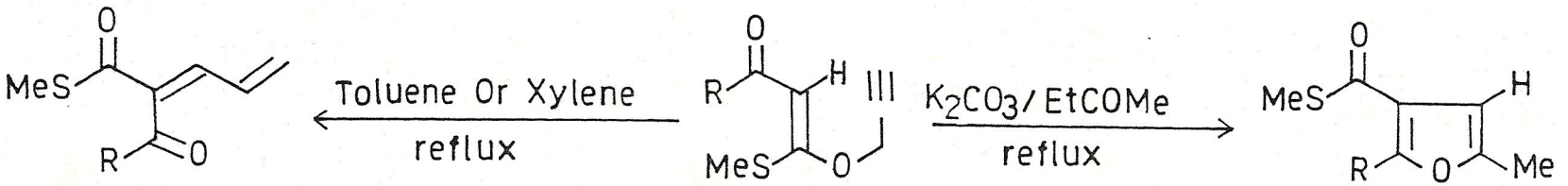
The thermal rearrangement studies on newly synthesized acylketene O-proporgyl S-methylacetals 87 under neutral as wellas basic conditions are described in the chapter 4. Various substituted acylketene O-propargyl S-methylacetals 87 were prepared by treating the perchlorates 86, derived from the corresponding 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

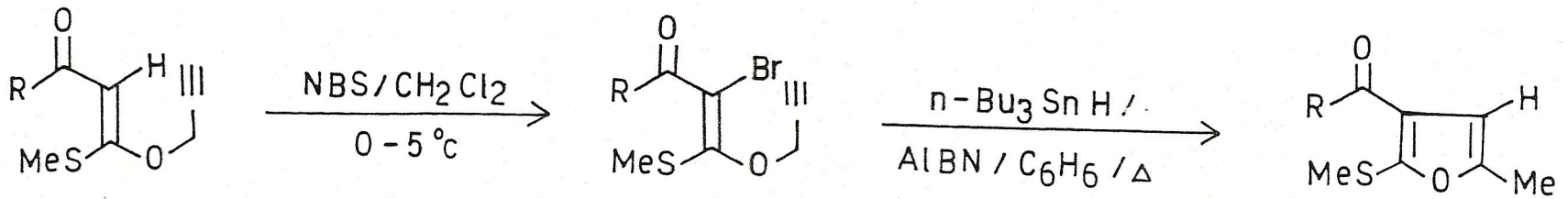
R = C_6H_5 , 4- Cl C_6H_4 , 4- MeO C_6H_4 , 2 - Furyl , 2 - Thienyl

Scheme - 15



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

Scheme - 16



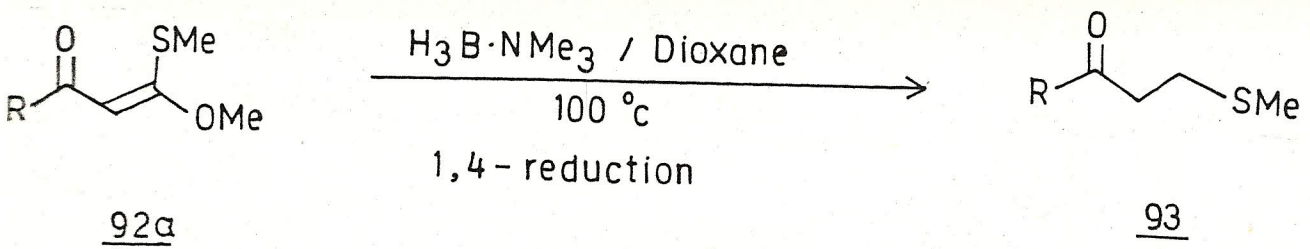
87 90 91

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.

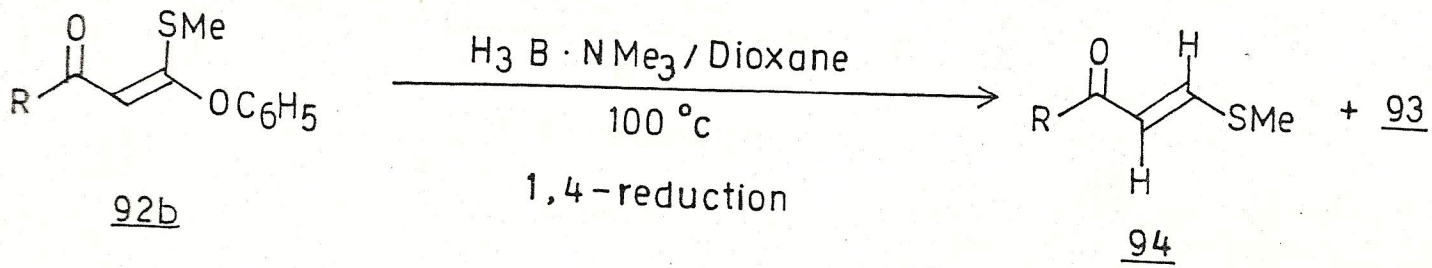


92a

93

92 - 93a , R = C_6H_5

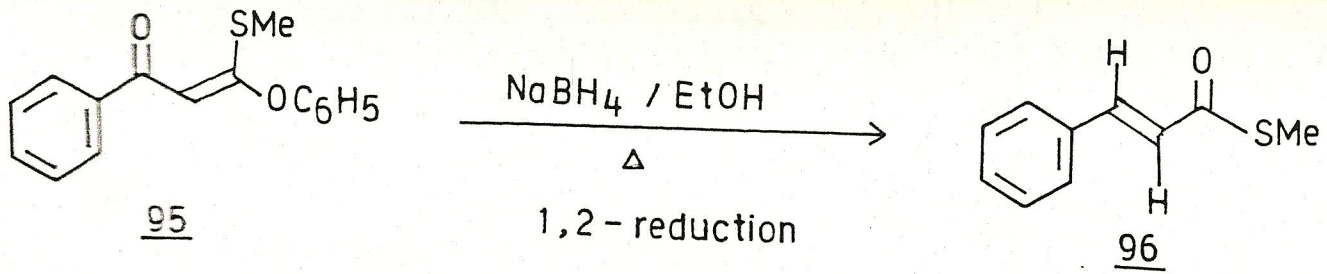
b , R = 2 - Thienyl



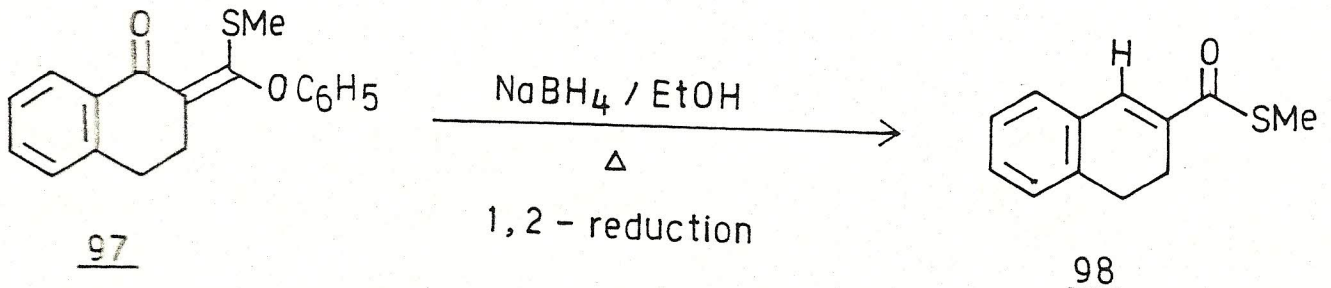
92b

94

Scheme - 18

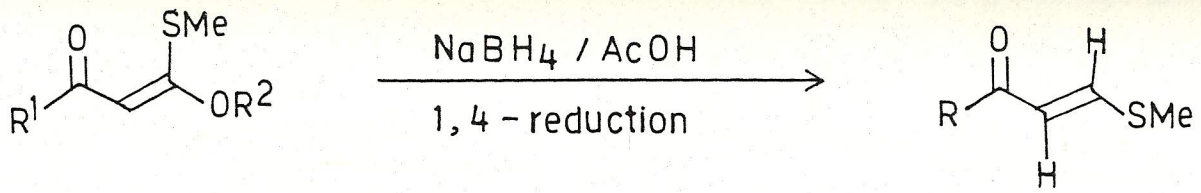


95 96



97 98

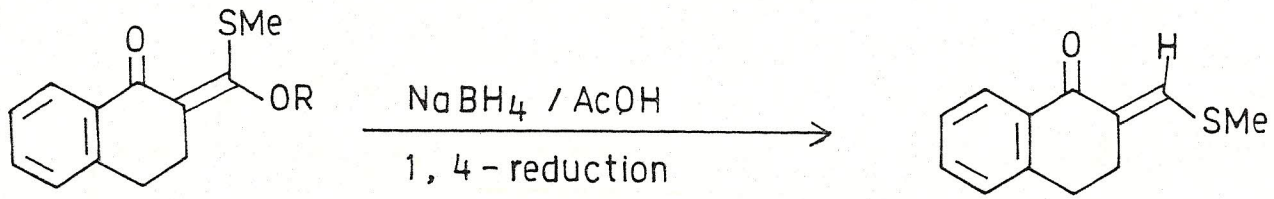
Scheme - 19



99 100

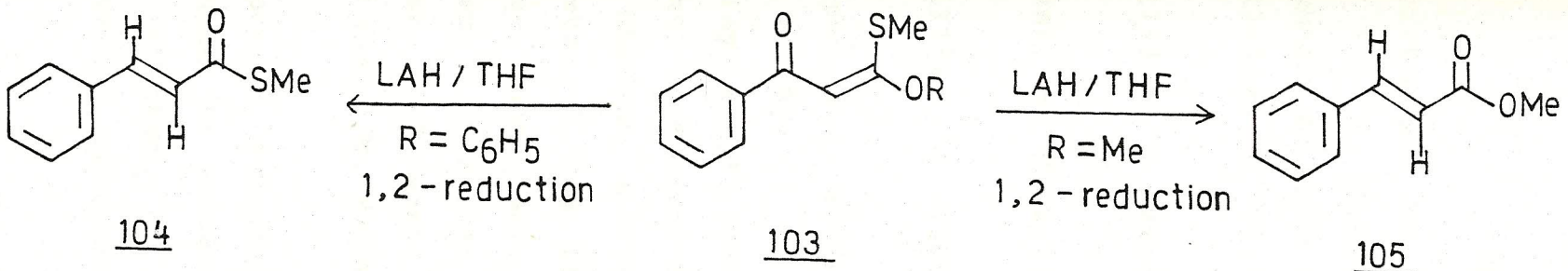
$R^1 = C_6H_5$; 2 - Thienyl

$R^2 =$ Me ; C_6H_5



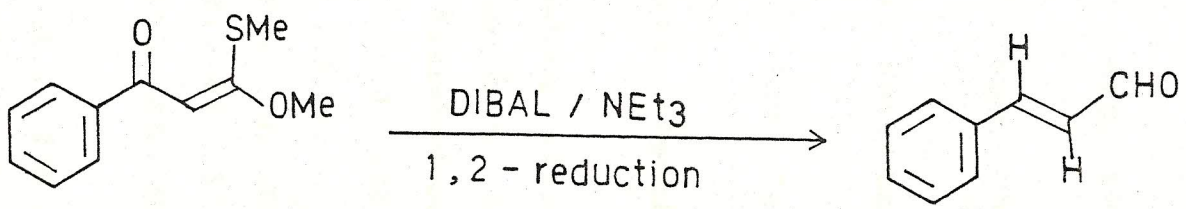
101 102

Scheme - 20



104 103 105

Scheme - 21



106 107

Scheme - 22

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