SYNTHETIC STUDIES ON OXOKETENE S,S- AND S,N-ACETALS : DEVELOPMENT OF NEW METHODS FOR NOVEL HETEROCYCLES

ABSTRACT

By

DINAH.E. POORANCHAND

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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

DOCTOR OF PHILOSOPHY

To

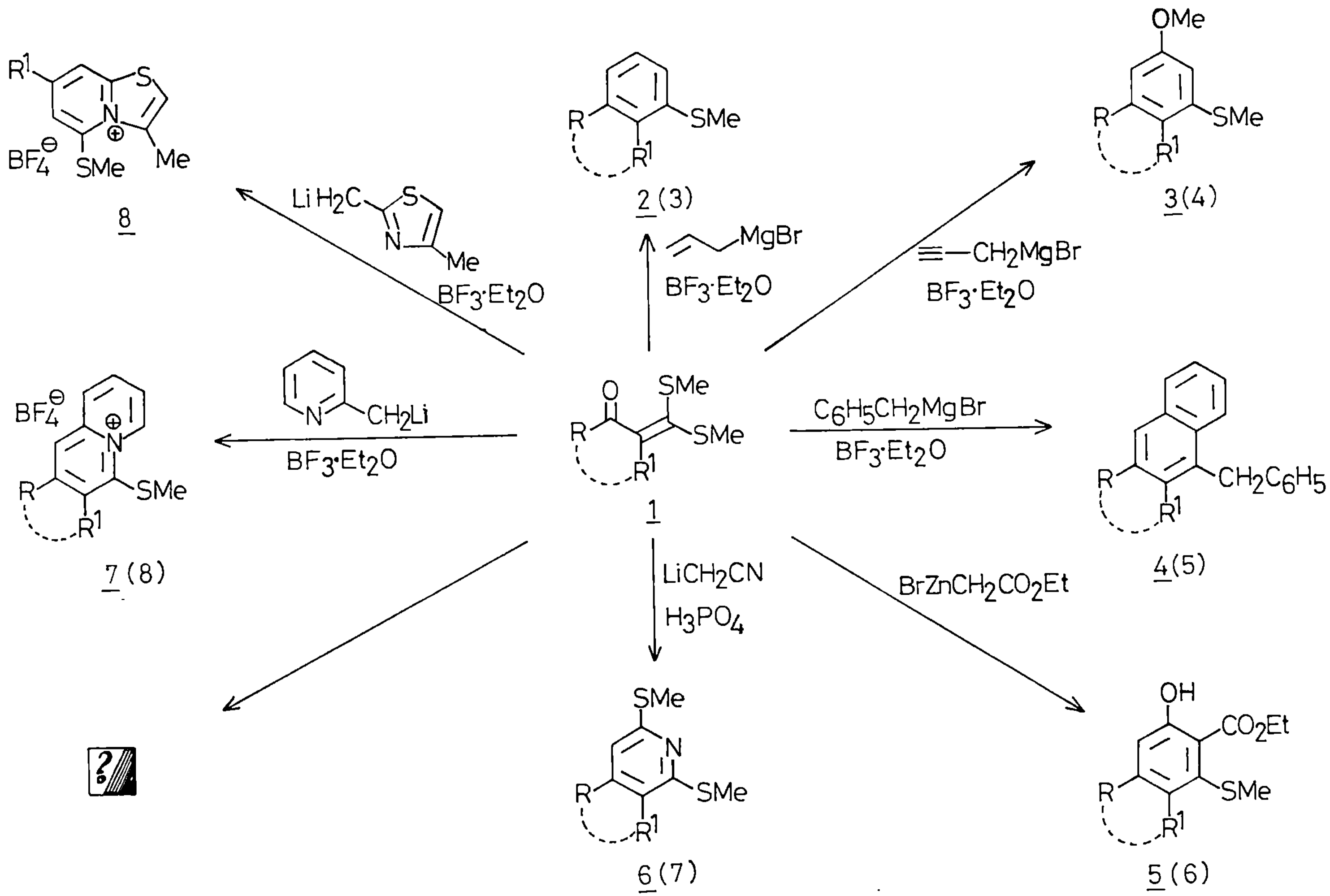
NORTH-EASTERN HILL UNIVERSITY
SHILLONG-793001
MEGHALAYA (INDIA)
1989

chemistry

The α-oxoketene dithioacetals 1 have been known since the first report by Kelber in 1910[1]. This class of compounds can be easily prepared by the reaction of active methylene ketones with carbon disulphide in the presence of a suitable base, followed by alkylation. Many efficient methods, essentially using this procedure, have been developed and these substrates (1) are now available from a large variety of active methylene ketones.

The α-oxoketene dithioacetals have been shown to be an excellent three carbon synthon possessing 1,3-electrophilic centres with differing electrophilicty, which has been extensively exploited for the regioselective construction of new bonds via 1,2- or 1,4-nucleophilic additions leading to a number of organic synthesis[2]. For example, the α-oxoketene dithioacetals 1 (Scheme 1) have been shown to undergo exclusive 1,2-addition with allylmagnesium bromide to yield the corresponding carbinol acetals which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives 2[3]. The approach is extended for the synthesis of other benzenoids 3-5[4-6]. The method is further shown to be extremely versatile and found general application for synthesizing pyridines 6[7], quinolizinium salts 7[8] and thiazolo pyridinium compounds 8.

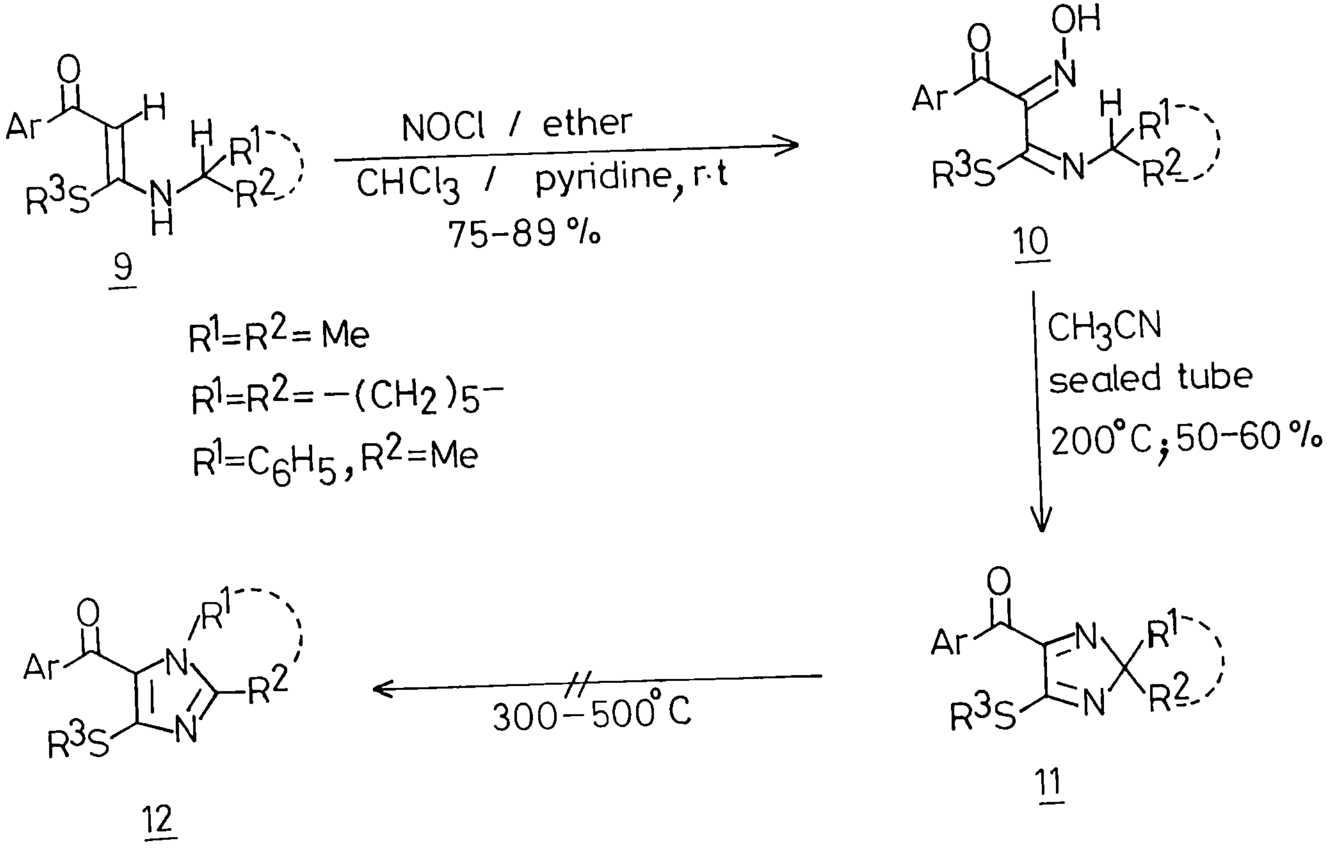
In the light of all these studies and as a part of our ongoing research, it was proposed to study the reaction of α-oxoketene dithioacetals to develop further new methodologies to construct various biologically important heterocycles. It was therefore considered of interest to


8
LiH$_2$C
Me
BF$_3$·Et$_2$O
2 (3)
MgBr
BF$_3$·Et$_2$O
3 (4)
CH$_2$MgBr
BF$_3$·Et$_2$O
7 (8)
CH$_2$Li
BF$_3$·Et$_2$O
1
C$_6$H$_5$CH$_2$MgBr
BF$_3$·Et$_2$O
4 (5)
LiCH$_2$CN
H$_3$PO$_4$
BrZnCH$_2$CO$_2$Et
6 (7)
5 (6)
?

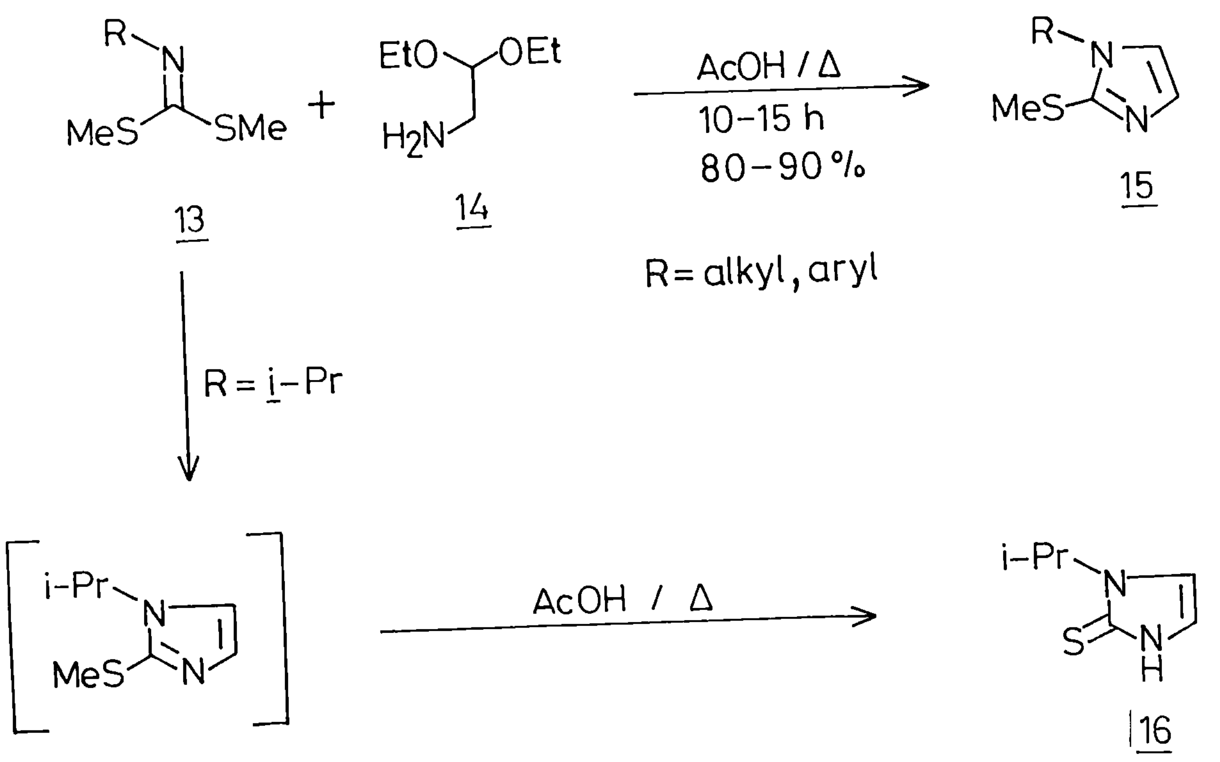
Scheme-1

study the reaction of nitrosyl chloride with corresponding S,N-acetals 9 (Scheme 2) derived from alkylamines and cyclic alkylamines and these S,N-acetals were prepared by our earlier reported procedure[9]. The corresponding hydroxiiminoimines 10 were obtained by reacting S,N-acetals with nitrosyl chloride and these oximino compounds underwent smooth thermal cyclization to yield the 2,2-substituted 2H-imidazoles 11 in quantitative yields[10]. However the attempts to rearrange the disubstituted 2H-imidazoles to yield the corresponding 1H-imidazole 12 were not successful. Our literature retrieval reveals that the preparation and properties of carbonimidodithioates though well explored, their synthetic applications specially for the construction of five membered heterocycles are not much explored. Therefore it was considered of interest to study the reaction of carbonimidodithioates 13 with aminoacetaldehyde diethylacetal 14. Thus when 1-N-aryl/alkyl carbonimidodithioates 13 were reacted with 14 in the presence of refluxing acetic acid the corresponding 1-N-aryl/alkyl imidazoles 15 were obtained in high yields[11]. When R was isopropyl group in 13 the initially formed imidazole undergoes rapid demethylation to yield the corresponding 1-isopropyl imidazole-2(3H)-thione 16 in good yields (Scheme 3). The scope and limitations of these above described transformations along with the analytical and spectral data of the products, leading to the structural assignments, have been discussed in details in Chapter 2 of the thesis.

In continuation of our interest in exploring the reaction of 1 with various allyl and azaallylanions it was considered of interest to extend


9
10
11
12
Ar
O
H
N
R^1
R^2
R^3S
OH
NOCl / ether
CHCl3 / pyridine, r.t
75-89 %
CH3CN
sealed tube
200°C; 50-60 %
300-500°C
R1=R2= Me
R1=R2= -(CH2)5-
R1=C6H5, R2=Me

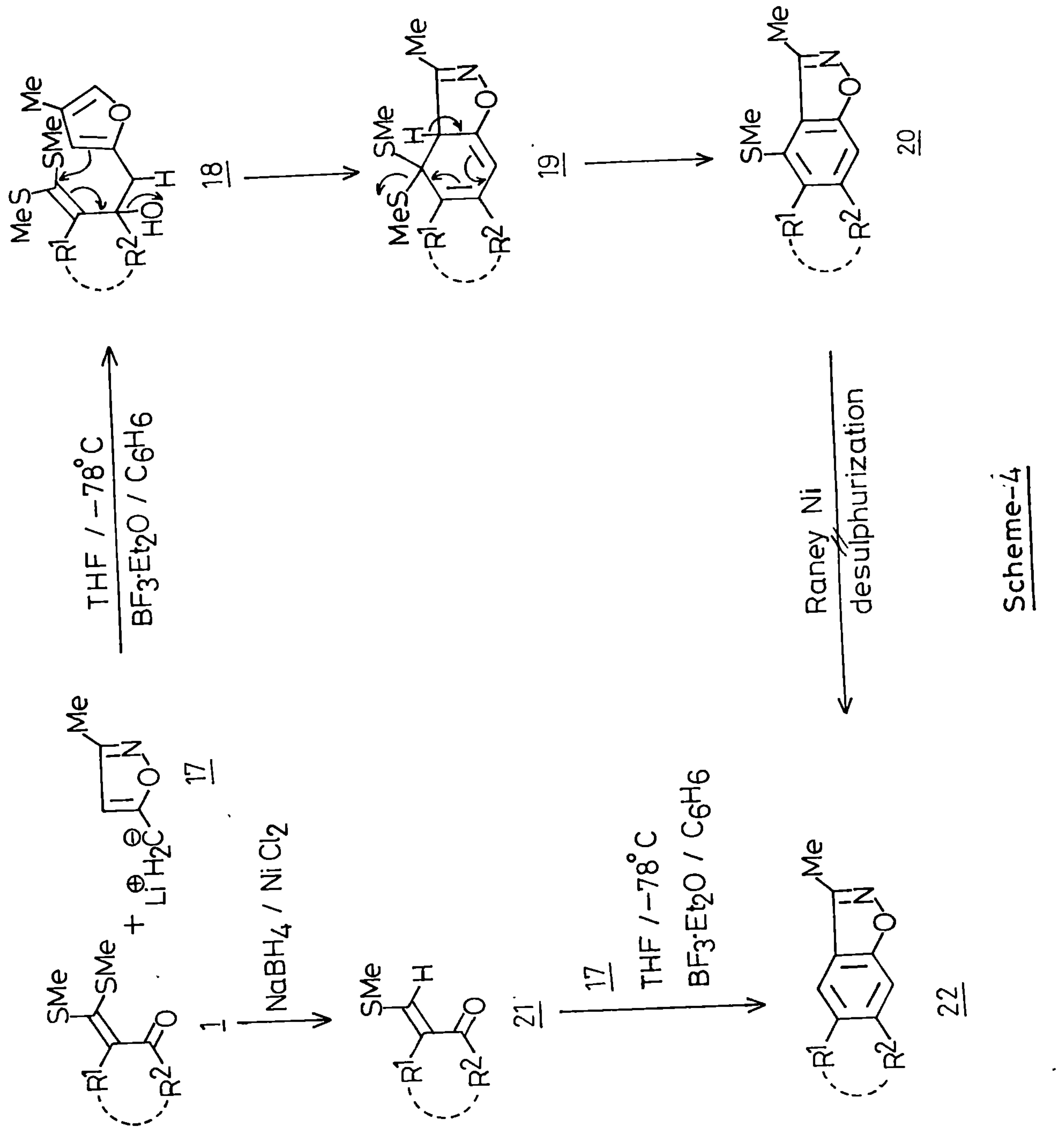
Scheme-2


R
MeS
SMe
+
EtO
OEt
H₂N
13
14
AcOH / Δ
10–15 h
80–90 %
R
MeS
15
R = alkyl, aryl
R = i–Pr
i-Pr
MeS
AcOH / Δ
i-Pr
S
H
16

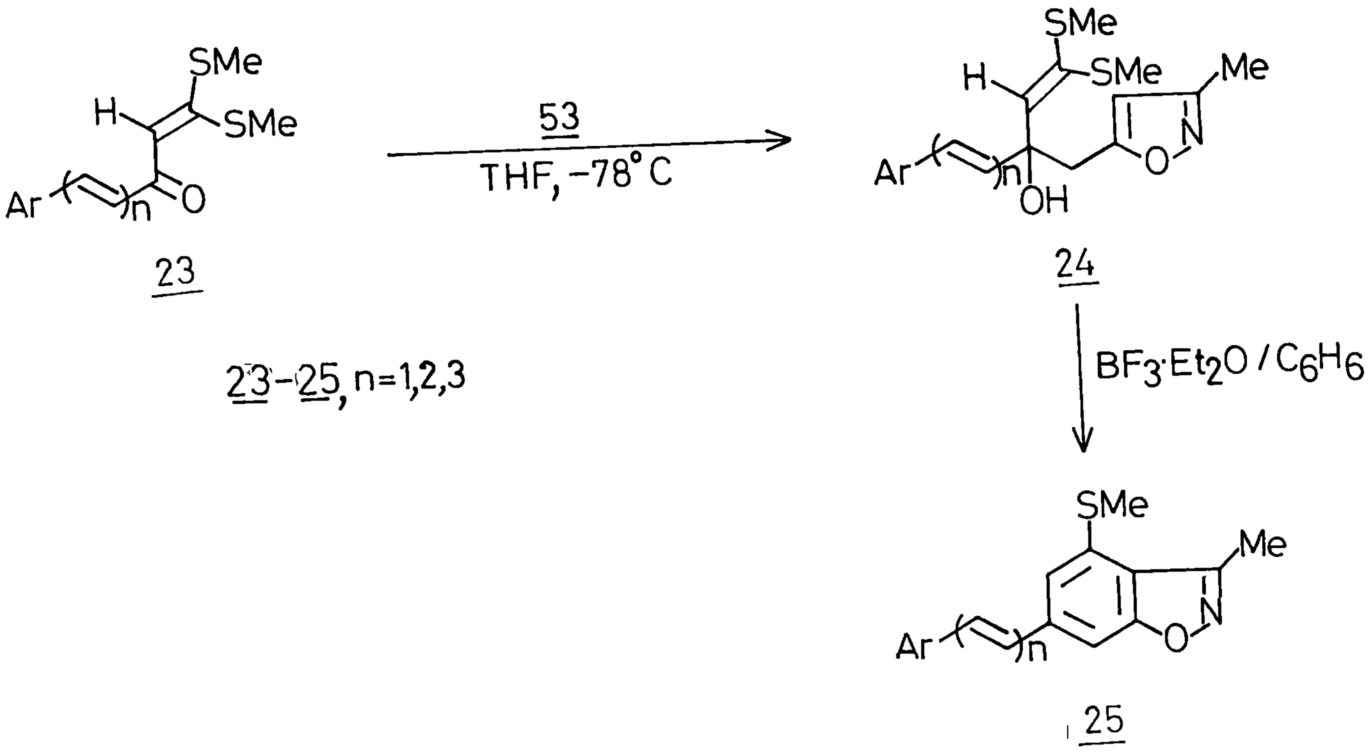
Scheme–3

the aromatic annelation approach for the synthesis of heteroaromatics. Therefore in the present investigation 3-methyl-5-lithiomethyl isoxazole 17 was selected as an allylanion system to extend the aromatic annelation approach for the synthesis of benzisoxazoles 20. Thus the 3-methyl-5-lithiomethyl isoxazole 17 underwent exclusive 1,2-addition with 1 at -78°C to yield quantitatively the carbinol acetal 18 which on $BF_3.Et_2O$ assisted cyclization afford the corresponding benzisoxazoles 20 in high yields (Scheme 4). The β-methylthio-α-β-enones 21 prepared from our earlier reported method[12] from 1 also reacted with 17 to yield the corresponding sulfur free benzisoxazoles 22 in identical yields.
In order to generalize the reaction it has been extended to cinnamoylketene dithioacetals. Thus cinnamoylketene dithioacetals 23 under similar reaction conditions yielded benz isoxazoles 25 in good yields (Scheme 5)[13]. Scope and limitations of these synthetic methods and the analytical and spectral data of the products formed have been described in Chapter 3 of the thesis.

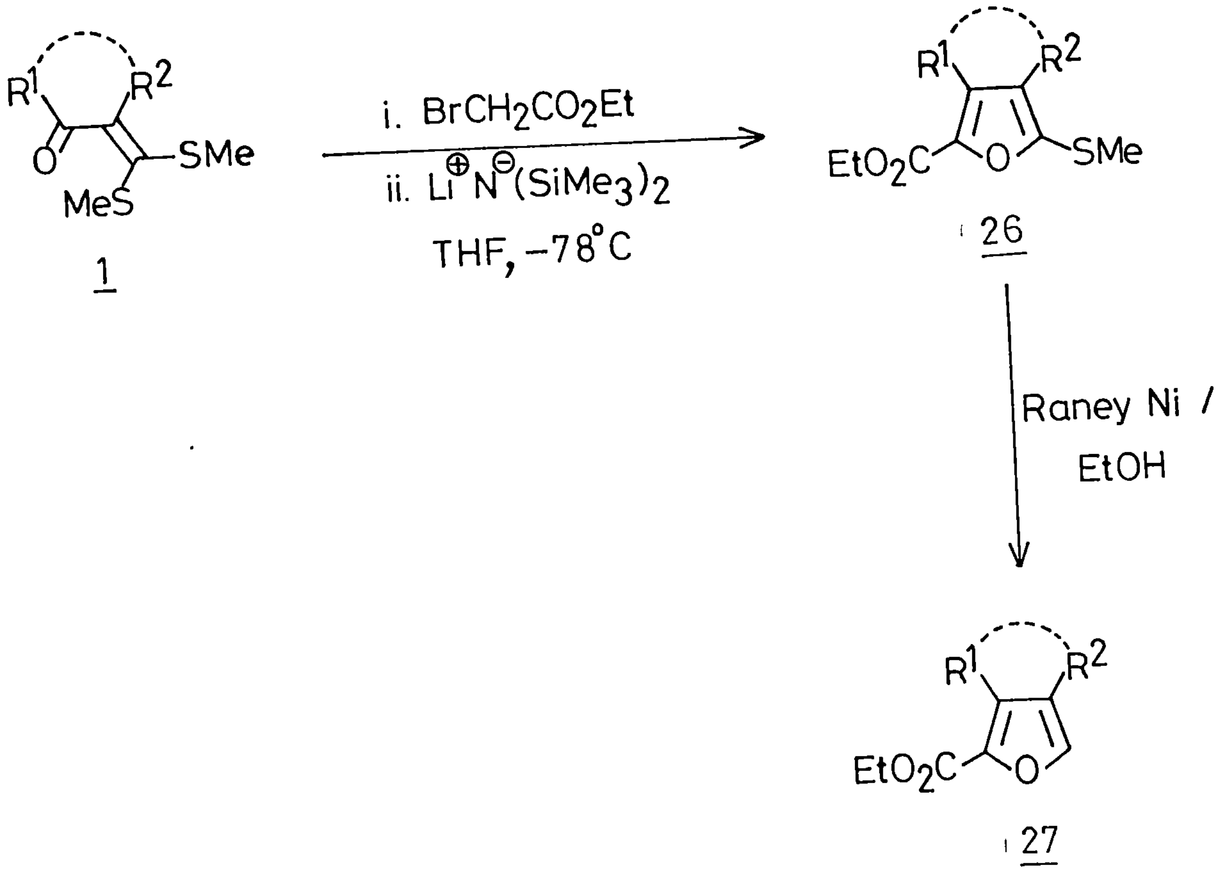
The α-oxoketene dithioacetals 1 were then reacted with ethylbromoacetate under Darzen's reaction conditions. Thus when the bromoacetate anion which was generated by reacting ethylbromoacetate with hexamethyldisilazane at -78°C in presence of n-butyllithium, was reacted with 1 at -78°C in tetrahydrofuran the furan carboxylates 26 were obtained in quantitative yields. The structures of 26 were established by spectral data as well as by subjecting them to Raney Nickel desulfurization to the known furan derivatives 27 in some cases (Scheme 6)[14]. Interestingly when the reaction was extended to cinnamoylketenedithioacetals 23 the products 28 and 29 were obtained (Scheme 7). The results of these reactions and the analytical and spectral data of the compounds are discussed in details in Chapter 4 of the thesis.


1
17
18
19
20
21
22
NaBH$_4$ / NiCl$_2$
THF / −78°C
BF$_3$·Et$_2$O / C$_6$H$_6$
Raney Ni
desulphurization
SMe
MeS
Me
R1
R2
Li⊕ H$_2$C⊖
H
HO

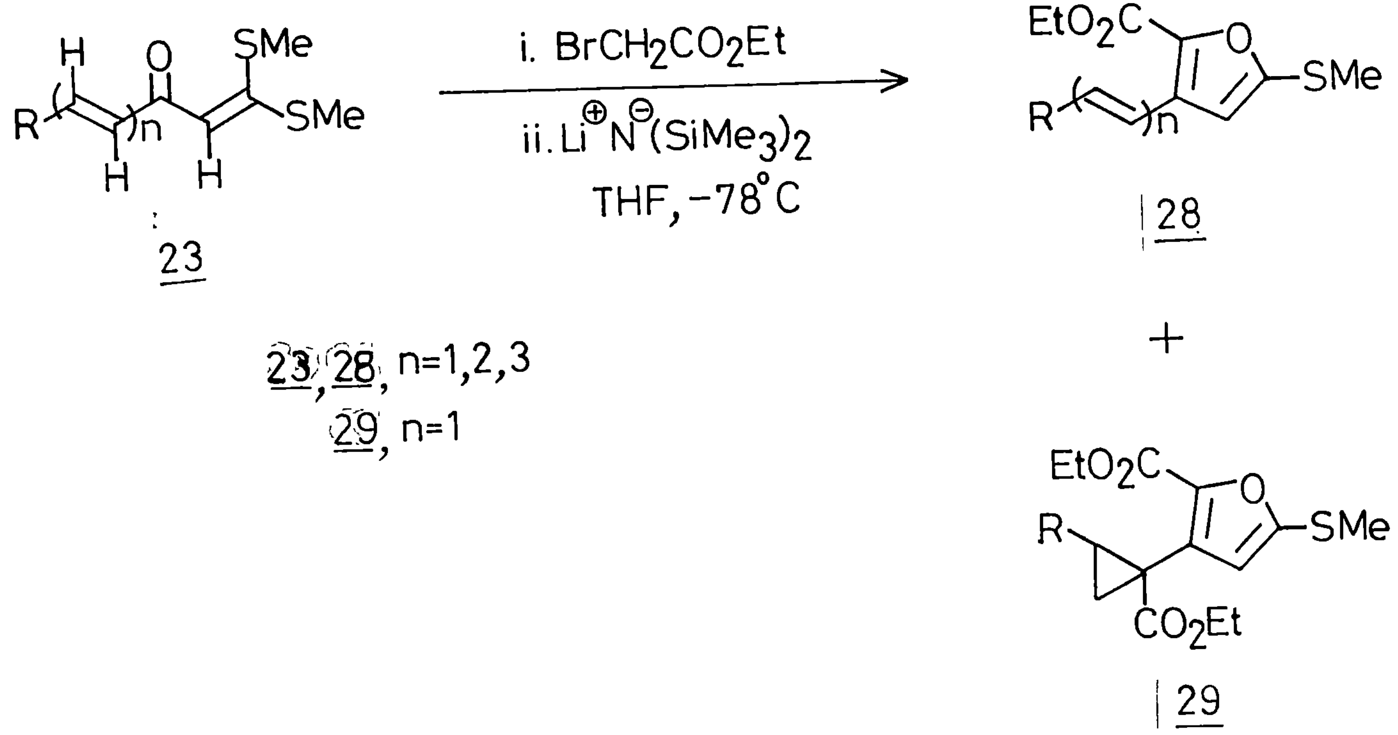
Scheme-4


SMe
SMe
H
Ar
n
O
23
53
THF, −78° C
SMe
SMe
H
Me
N
O
Ar
n
OH
24
BF$_3$·Et$_2$O / C$_6$H$_6$
SMe
Me
N
O
Ar
n
25
23–25, n=1,2,3

Scheme–5



Scheme–6



23, 28, n=1,2,3
29, n=1

Scheme–7

REFERENCES

1. C. Kelber, Chem. Ber., 43, 1252 (1910).
2. For a review see: R.K. Dieter, Tetrahedron, 42, 3029 (1986).
3. G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., 25, 5095 (1984).
4. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett., 1459 (1987).
5. M.P. Balu, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., 27, 117 (1986).
6. A. Datta, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 497 (1988).
7. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 6633 (1988).
8. M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett., 28, 3023 (1987).
9. A. Kumar, V. Aggarwal, H. Ila, H. Junjappa, Synthesis, 748 (1980).
10. D. PooranChand, H. Ila, H. Junjappa, Synthesis, 547 (1987).
11. D. PooranChand, H. Ila, H. Junjappa, Synthesis, 1136 (1987).
12. B. Myrboh, L.W. Singh, H. Ila and H. Junjappa, Synthesis, 307 (1982).
13. D. PooranChand, M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 501 (1988).
14. J.D. Prugh, A.C. Huitric, W.G. McCarthy, J. Org. Chem., 29, 1991 (1964).

SYNTHETIC STUDIES ON OXOKETENE S,S- AND S,N-ACETALS DEVELOPMENT OF NEW METHODS FOR NOVEL HETEROCYCLES

By

DINAH.E. POORANCHAND

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-793001
MEGHALAYA (INDIA)

1989

chemistry

CORAL AND JASPER ARE NOT
WORTHY OF MENTION;
THE PRICE OF WISDOM IS
BEYOND RUBIES.

JOB 28:18

Phone :
Grams : NEHU

North-Eastern Hill University
Bijni Complex
Bhagyakul, Shillong - 793003 (Meghalaya)

Department of Chemistry

This is to certify that the work described in this thesis has been carried out by Miss Dinah E. PooranChand. She has satisfactorily completed 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. JUNJAPPA)
SUPERVISOR

ACKNOWLEDGEMENT

The research work described in this thesis was carried out in the Department of Chemistry, North-Eastern Hill University, Shillong, under the supervision of Professor H. Junjappa of the Department of Chemistry. I sincerely thank him for his valuable guidance, timely suggestions and constructive criticism which has been a steady source of inspiration resulting in the presentation of this investigation. I am also thankful to Professor (Mrs.) H. Ila, Head, Department of Chemistry for her supervision and encouragement.

I extend my thanks to the Directors and Technicians of the Regional Sophisticated Instrumentation Centres at Central Drug Research Institute, Lucknow and North-Eastern Hill University, Shillong for providing the spectral and analytical data of the compounds described in the thesis. Financial assistance from the Council of Scientific and Industrial Research and Department of Science and Technology is also acknowledged.

My deep sense of gratitude is due to all my colleagues specially to Dr. Apurba Dutta, Dr. Chakrasali and Dr. Asokan for their help and cooperation throughout this investigation. I wish to express my thanks to Miss Sasmita Acharya, Miss Sarita Misra and Miss Joymati Saikia for their help and encouragement.

I am indebted to Mrs. R. Johns for meticulous typing of the manuscript, Mrs. Florency Jose for efficient photocopying and to Mr. Prabeer Mazumdar for drawing the schemes.

Finally, I acknowledge the debt I owe to my parents and family members for their prayers and encouragement without which it would have been impossible for me to complete this investigation.

Dinah Eleanor PooranChand.
DINAH E. POORANCHAND

CONTENTS

PREFACE

Polarized ketene dithioacetals, which are easily available from wide structural variants of active methylene compounds have been extensively explored in this laboratory for the development of several new synthetic methods for a variety of heterocyclic and carbocyclic compounds. The work described in this thesis has also been carried out as a part of this continuing research programme and highlights new transformations of oxoketene S,S- and S,N-acetals.

The thesis consists of four chapters. The first chapter gives a general introduction of polarized ketene dithioacetals and some of the recent transformations reported from this laboratory. The second chapter is divided into two parts. Part one deals with the reaction of S,N-acetals with nitrosyl chloride and the thermal cyclization of the resulting hydroxiiminoimines for the synthesis of novel 2,2-disubstituted 2*H*-imidazoles. In part two reaction of 1-N-aryl/alkyl carbonimidodithioates for the synthesis of 1-N-substituted imidazoles is described.

In the third chapter, a novel heteroaromatic annelation approach for the synthesis of 1,2-benzisoxazoles is discussed. Darzen's condensation on α-oxoketene dithioacetals for versatile synthesis of substituted and annelated furoates has been described in the last chapter.

All the compounds synthesized have been characterized with the help of their spectral data. The entire documentation in the thesis is supported by appropriate references; The references of the published work of the present investigation are cited in the respective chapter.

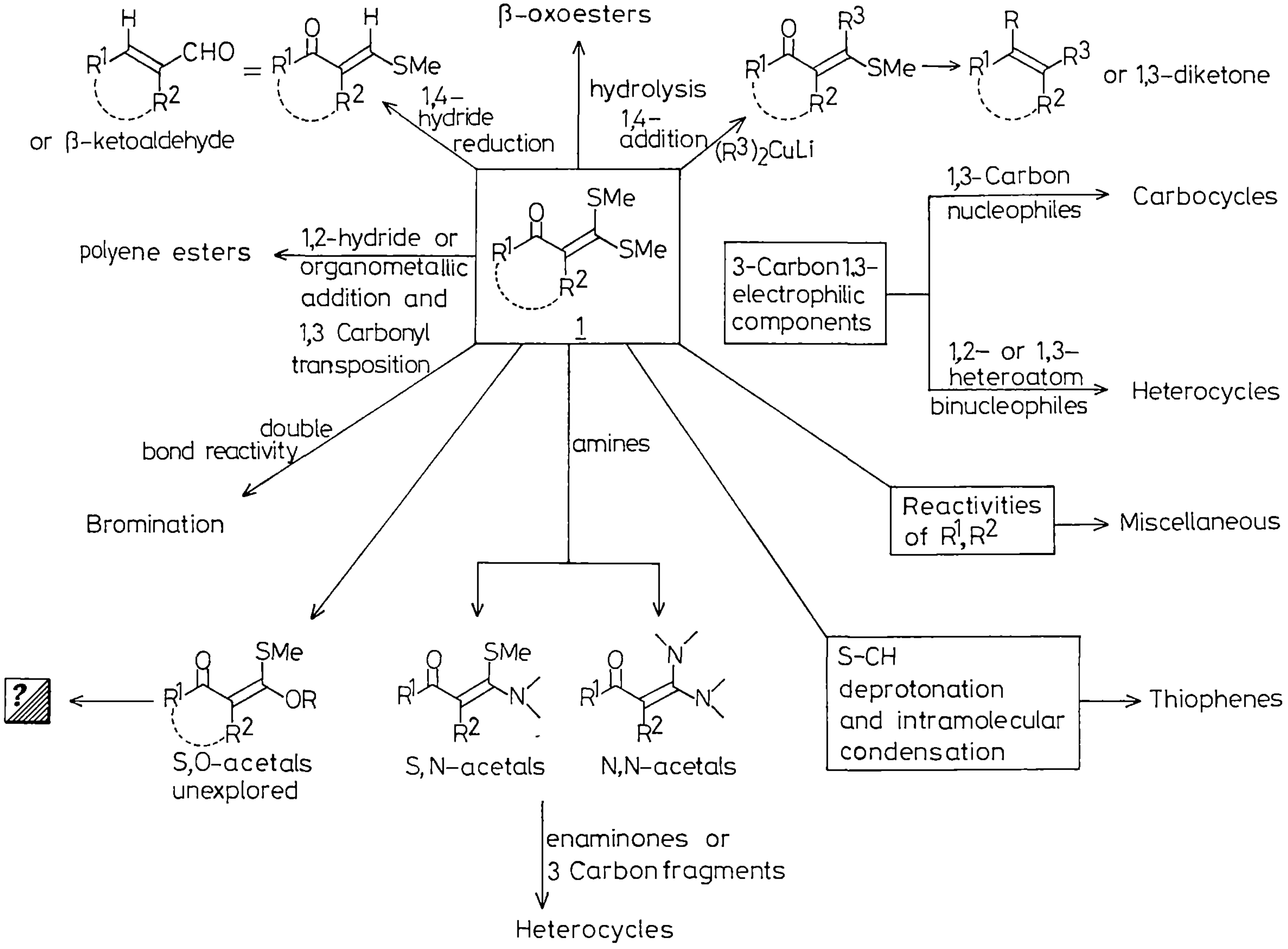
CHAPTER I

INTRODUCTION

The α-oxoketene dithioacetals were first reported by Kelber and coworkers in 1910[1-3]. The earlier work on oxoketene dithioacetals was confined to their preparation and properties and little attention was paid for their synthetic utility. The chemistry of these compounds remained unexplored till Thuillier and coworkers in the early sixties reinvestigated the preparation of oxoketene dithioacetals and obtained them in high yields by reacting the active methylene ketones with carbondisulfide in the presence of sodium amylate followed by alkylation[4-7]. Subsequently these reaction conditions have been greatly improved by using different bases and reaction conditions[8-12].

A large number of α-oxoketene dithioacetals have been reported and their chemistry has been reviewed[13] by Dieter.

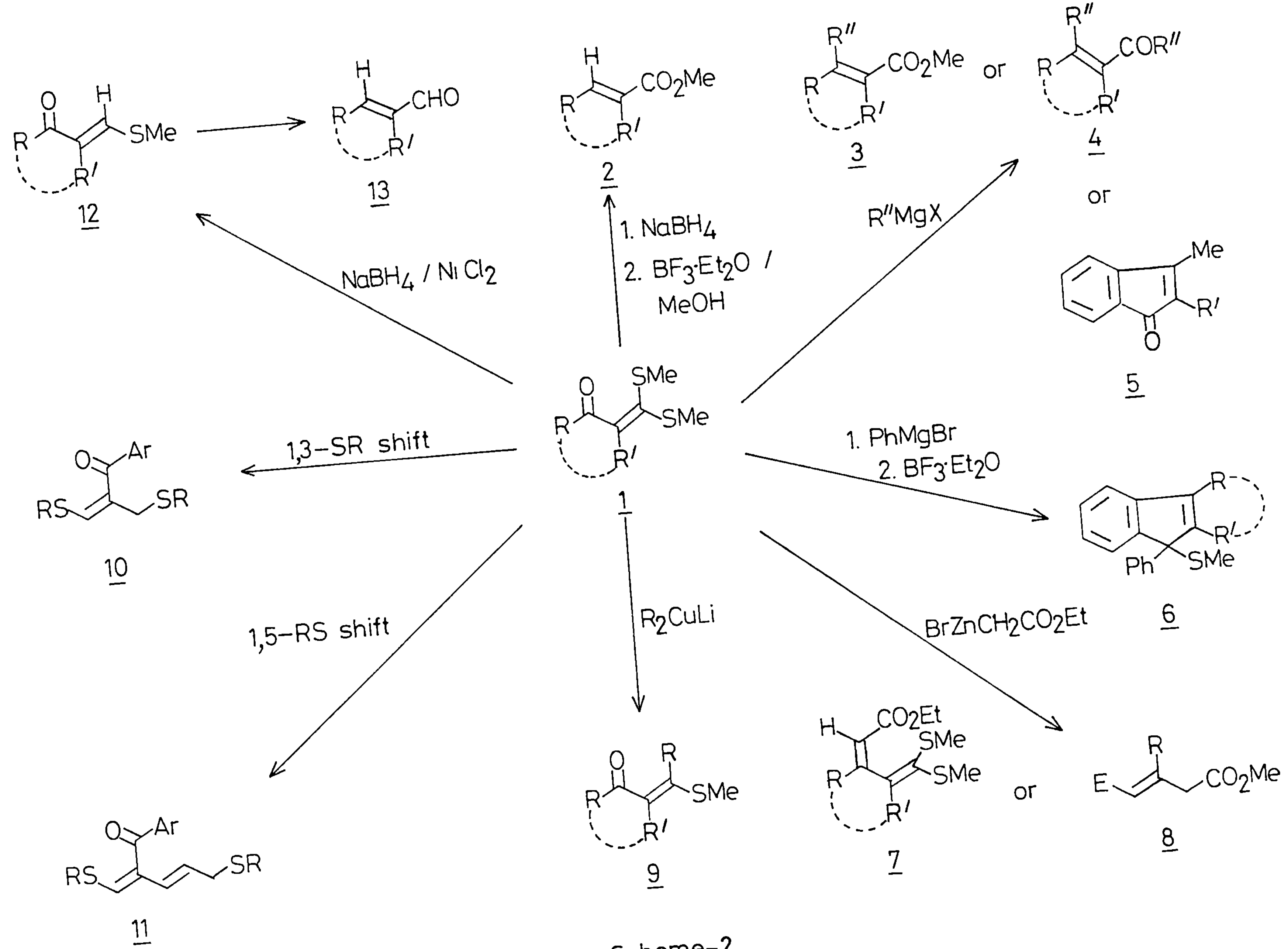
These α-oxoketene dithioacetals 1 exhibit well defined physical properties either as crystalline solids or distillable liquids, and can be purified by conventional purification methods. They are stable at room temperature and can withstand mild acidic and alkaline conditions and can be stored indefinitely without apparent decomposition. The oxoketene dithioacetal is essentially a masked β-keto ester 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 regioselective construction of new bonds either by 1,2-nucleophilic addition to carbonyl group or by 1,4-conjugate addition to the β-carbon of the enone system. Some of these transformations are described in (Scheme 1). The oxoketene dithioacetals are primary precursors for the corresponding O,S-, N,S- and N,N-acetals. The preparation of O,S-acetal is accomplished through the displacement by an oxygen nucleophile of the sulfonium salt[14]. The N,S-acetal can be prepared by the displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol[15,16] or directly from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates followed by alkylation[17]. The oxoketene S,S- and N,S-acetals have been extensively used in this laboratory while the chemistry of O,S-acetals remains


or β-ketoaldehyde
1,4-
hydride
reduction
β-oxoesters
hydrolysis
1,4-
addition
(R^3)$_2$CuLi
or 1,3-diketone
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 R^1,R^2
Miscellaneous
S,O-acetals
unexplored
S, N-acetals
N,N-acetals
S-CH
deprotonation
and intramolecular
condensation
Thiophenes
enaminones or
3 Carbon fragments
Heterocycles

Scheme-1

unexplored. The corresponding S,O-acetals are now being reported by replacing one of the thiomethyl groups of oxoketene dithioacetals with alkoxide nucleophiles. The O,S-acetals can also be prepared directly by reacting enolate anions of active methylene ketones with alkyl xanthates followed by alkylation. Hydrides and organometallic reagents give 1,2-addition products typical of carbonyl function reactivity[18]. These additions can be directed in a 1,4-manner by suitably manipulating the reagent and reaction conditions[18-20]. Further transformations after the initial 1,2- or 1,4-additions are also reported. The oxoketene dithioacetals can further be utilized to introduce polyene functionality if R_1 in 1 is an alkyl group[4,21].

Extensive research has been done in the last twenty years to find out synthetic applications of 1 and a substantial amount of work has been published from our laboratory (Scheme 2). Thus the oxoketene dithioacetals 1 were shown to undergo facile 1,2-reduction with sodium borohydride to give the intermediate allylic alcohol which undergo facile solvolysis in the presence of boron trifluoride etherate to yield the corresponding highly regio and stereoselective ene esters 2 and 3 in high yields[22,23]. The ene ester synthesis was further extended to the addition of alkyl and aryl magnesium halides to study the scope of the method. They undergo either regioselective 1,2-addition to give the α-hydroxyketene dithioacetals or a sequential 1,4- and 1,2-additions to afford the β-hydroxyvinylsulfides. The boron trifluoride etherate catalyzed solvolysis or the hydrolysis of these carbinols yield α,β-unsaturated esters 3 or the corresponding ketone 4 (Scheme 2) in good yields[18]. During the hydrolysis of the addition products of grignard


12
13
2
3
or
4
or
5
NaBH$_4$ / NiCl$_2$
1. NaBH$_4$
2. BF$_3$·Et$_2$O / MeOH
R''MgX
1,3-SR shift
1
1. PhMgBr
2. BF$_3$·Et$_2$O
6
10
1,5-RS shift
R$_2$CuLi
BrZnCH$_2$CO$_2$Et
11
9
7
or
8

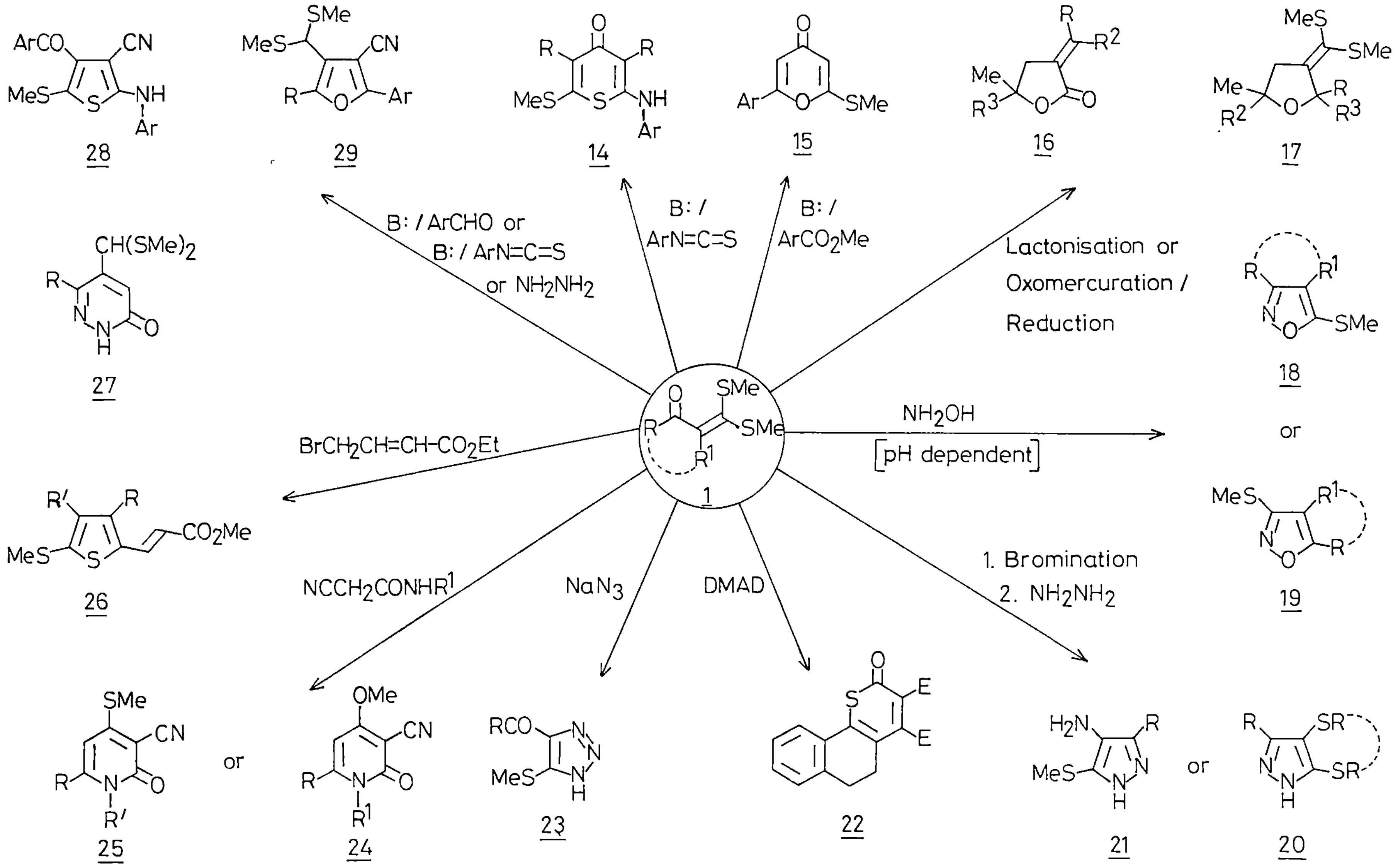
Scheme-2

reagents the systems with favourable cis geometry underwent intramolecular cyclization to yield 2,3-disubstituted indenones 5[18]. Similarly the oxoketene dithioacetals reacted with phenylmagnesium bromide followed by $BF_3.Et_2O$ treatment yielded the corresponding 1-methylthio-1-phenyl indane 6[24]. The Reformatsky reaction on dithioacetal 1 is reported to give the diene ester 7 and the β,γ-unsaturated ester 8[25]. Dieter and coworkers have shown that the dithioacetal 1 undergo chemo- and stereoselective conjugate additions with organocuprates to give the corresponding β-alkylthio-α,β-unsaturated ketones 9[19,20]. The oxoketene dithioacetals were also shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthio-alkenylketones 12[26]. These intermediates are hydrolysed to the α,β-unsaturated aldehydes 13. In another study from this laboratory, base catalyzed rearrangement of α-oxoketene dithioacetals derived from propiophenones are reported. The 2-alkylthiomethylacrylophenones 10 are formed by a 1,3-RS shift. A base assisted 1,5-RS shift to the diene 11 is also reported[27].

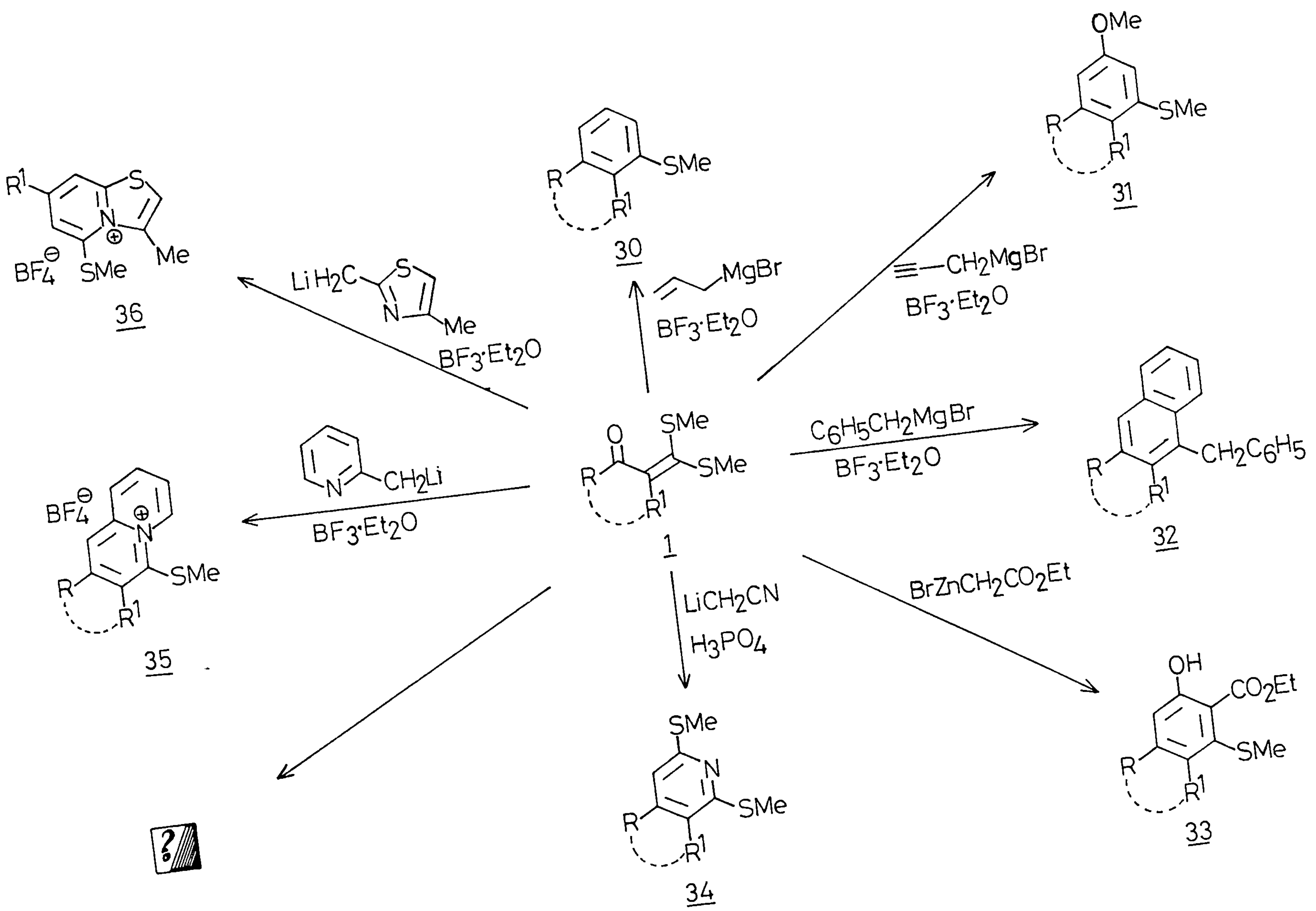
The α-oxoketene dithioacetals 1 have been extensively used as three carbon fragments and some times two carbon three atom units (N-C-C bond) in the construction of various heterocyclics. Thus the reaction of arylisothiocyanates with 1 or methyl benzoate is reported to yield the corresponding 2-arylamino-6-methylthio-thiopyran-4-one 14 and 2-methylthio-pyran-2-one 15 respectively[28,29]. The oxoketene dithioacetals have also been converted to the corresponding butyrolactones 16 and 17[30,31] and their reaction with hydroxylamine has been shown to be pH dependent yielding the regioisomers 18 and 19 in high yields[32]. The oxoketene dithioacetals were shown to undergo bromination (R^1=H) and the corresponding bromo oxoketene dithioacetals reacted with hydrazine hydrate to yield pyrazoles 20 and 21[33]. The reaction of 1 with DMAD initially underwent 2+2 cycloaddition followed by ring opening to yield the corresponding dienes. The oxoketene dithioacetals with tetralone however yielded 22 as one of the products involving interesting sequence of rearrangement[34]. The reaction of 1 with sodium azide and cyanoacetamide yield triazoles 23[35] and pyridines 24[36] respectively. Similarly the synthesis of heterocycles 26[37], 27[38], 28 and 29[39] were obtained by reacting 1 with appropriate reagents (Scheme 3).

The most important synthetic applications of 1 have been demonstrated by utilizing them in the development of new method of aromatic annelation. Some of these transformations are described in (Scheme 4). Allylmagnesium bromide has been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetals in high yield, which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives 30[40]. The approach is extended for the synthesis of other benzenoids 31, 32 and 33[41-43]. The method is further shown to be extremely versatile and found general application for the synthesis of pyridines, quinolizinium salts and fused thiazolo pyridinium compounds.

Thus when lithioacetonitrile was reacted with 1 the intermediate acetals underwent smooth ritter type intramolecular annelation with a new C-N bond formation to yield 34[44] in high yields. The 2-picollyllithium and 2-lithiomethylthiazole also reacted with 1 and yielded 35[45] and 36 in high yields. From these transformations it is apparent that oxoketene dithioacetals are versatile open-chain precursors with liberal structural


B: / ArCHO or
B: / ArN=C=S
or NH2NH2
B: /
ArN=C=S
B: /
ArCO2Me
Lactonisation or
Oxomercuration /
Reduction
NH2OH
[pH dependent]
or
1. Bromination
2. NH2NH2
DMAD
NaN3
NCCH2CONHR1
BrCH2CH=CH-CO2Et
1
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

Scheme-3

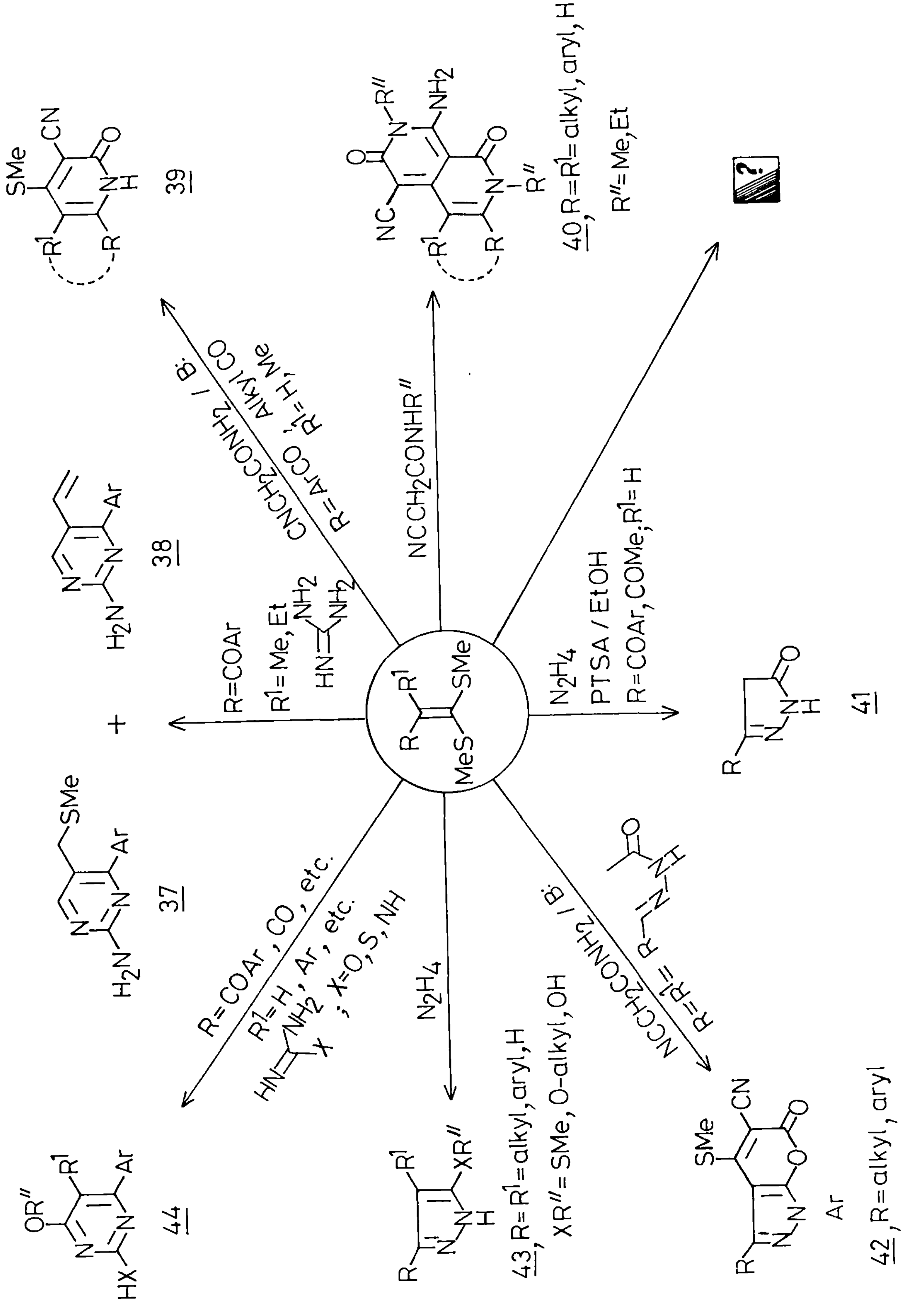

1
30
31
32
33
34
35
36
MgBr
BF3·Et2O
≡—CH2MgBr
BF3·Et2O
C6H5CH2MgBr
BF3·Et2O
BrZnCH2CO2Et
LiCH2CN
H3PO4
CH2Li
BF3·Et2O
LiH2C
Me
BF3·Et2O
SMe
OMe
CH2C6H5
OH
CO2Et
R
R1
BF4
Me
?

Scheme-4

flexibility for the construction of both the aromatic and heteroaromatic systems (Scheme 4).

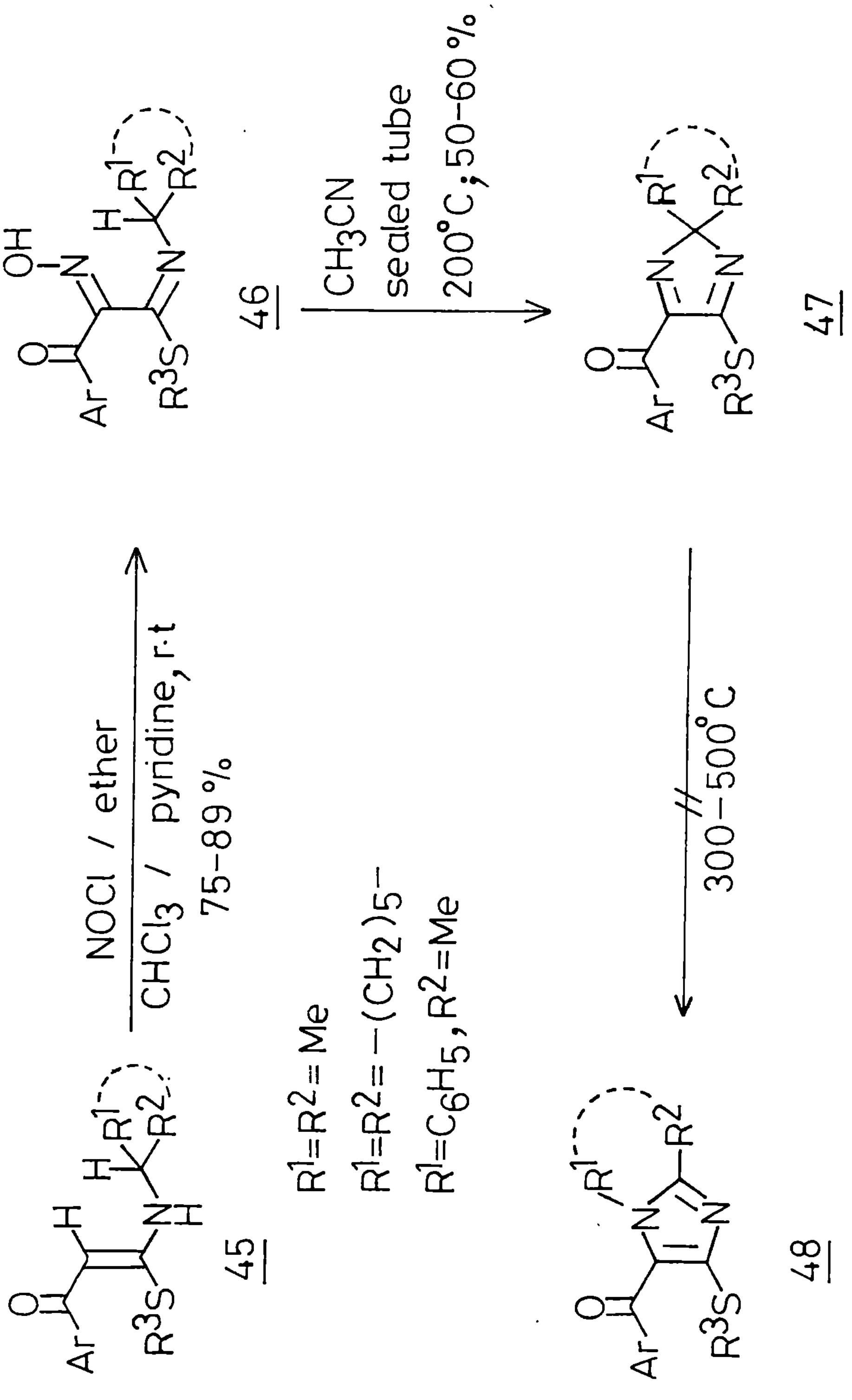
The oxoketene dithioacetals have also been used for the construction of a variety of heterocyclic compounds in our laboratory and these transformations are shown in Scheme 5[11,35b,46-49].

A brief survey of the important synthetic applications of oxoketene dithioacetals has been described and it is apparent that there is a potential still unexplored to develop further new methodologies to construct various biologically important heterocycles. It was therefore considered of interest to study the reaction of nitrosyl chloride with corresponding S,N-acetals 45 (Scheme 6) derived from alkylamines and cyclic alkylamines. The S,N-acetals yielded the corresponding hydroxiimino compounds 46 which were obtained in almost quantitative yields. These oximino compounds 46 underwent thermal cyclization to yield the 2,2-disubstituted 2H imidazoles 47 in good yields[50]. However attempts to rearrange the disubstituted 2H imidazoles to yield corresponding 1H imidazoles 48 were not successful. It was also considered of interest to study the reaction of aminoacetaldehyde diethylacetal 50 with various carbonimidodithioates 49. The preparation and properties of carbonimidodithioates though well explored their synthetic applications especially for the construction of five membered heterocyclics are not much explored. Thus when 1-N-aryl/alkyl carbonimidodithioates 49 were reacted with 50 in the presence of refluxing acetic acid the corresponding 1-N-aryl/alkyl imidazoles 51 were obtained in high yields[51]. The scope and limitations of this simple and facile methodology from easily accessible



MeS
SMe
R
R1
R=COAr
R1=Me, Et
HN=C(NH2)NH2
37
38
H2N
Ar
SMe
+
CNCH2CONH2 / B:
R=ArCO, Alkyl CO
R1=H, Me
39
CN
NCCH2CONHR″
40, R=R1=alkyl, aryl, H
R″=Me, Et
NC
NH2
N2H4
PTSA / EtOH
R=COAr, COMe; R1=H
41
NCCH2CONH2 / B:
R=R1=
42, R=alkyl, aryl
Ar
N2H4
43, R=R1=alkyl, aryl, H
XR″=SMe, O-alkyl, OH
R=COAr, CO, etc.
R1=H, Ar, etc.
HN=C(NH2)X ; X=O, S, NH
44
OR″
HX

Scheme-5

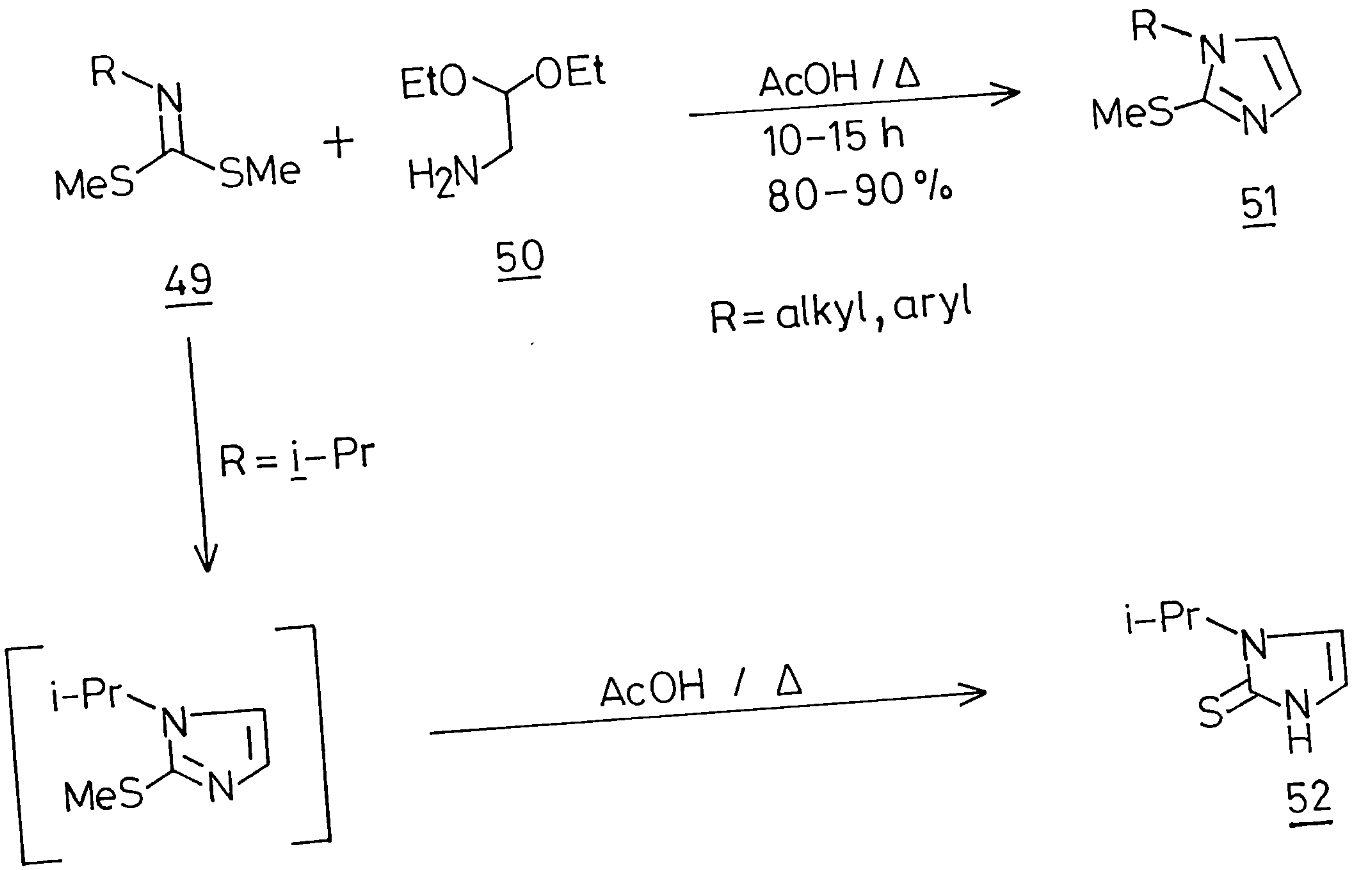

NOCl / ether
CHCl$_3$ / pyridine, r.t
75-89 %
$R^1=R^2=Me$
$R^1=R^2=-(CH_2)_5-$
$R^1=C_6H_5, R^2=Me$
45
46
CH$_3$CN
sealed tube
200°C; 50-60 %
47
300–500°C
48
Ar
R^{3}S
OH

Scheme-6

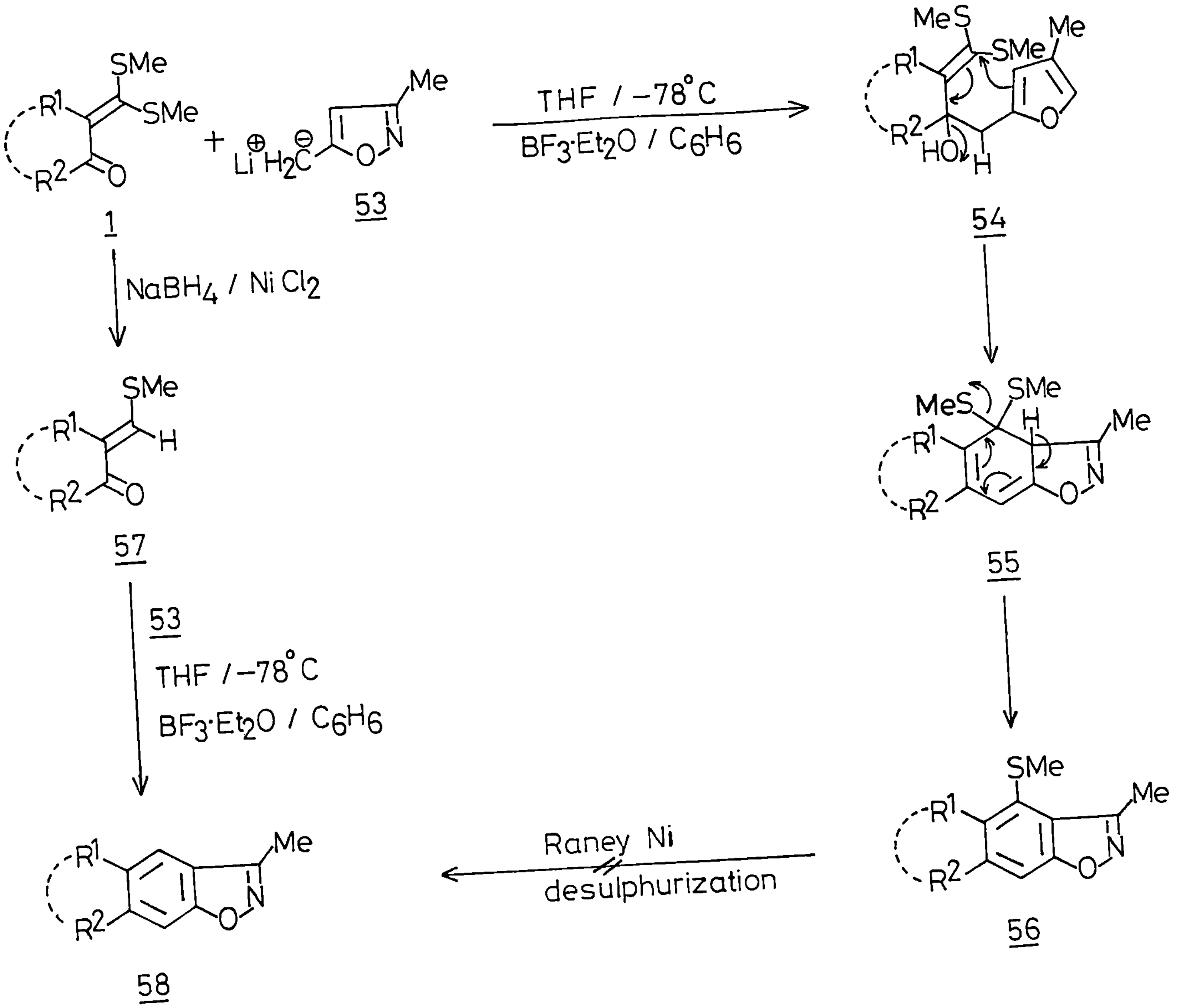
carbonimidodithioates have been described in Chapter II. When R was isopropyl group in 49 the methylthio group underwent rapid demethylation to yield the corresponding 1-isopropylimidazole-2(3H)-thione 52 (Scheme 7).

In continuation of our interest in exploring the reaction of 1 with various allyl and azaallylanions it was considered of interest to extend the methodology for the synthesis of 5-membered hetero aromatics. It is reported in the literature that the five membered heterocyclic ring is generally constructed on a preconstructed benzene ring. The approach for the synthesis of these heteroaromatics starting from preconstructed five membered heterocycles to yield the corresponding benzoheterocycles is not extensively investigated. Therefore 5-lithiomethylisoxazole was selected as an allylanion system to extend the aromatic annelation approach for the synthesis of benzisoxazoles 56. These results involve the first report of a new method for the synthesis of benzisoxazoles by constructing benzene ring from open-chain precursors on the preconstructed isoxazole ring (Scheme 8)[52].

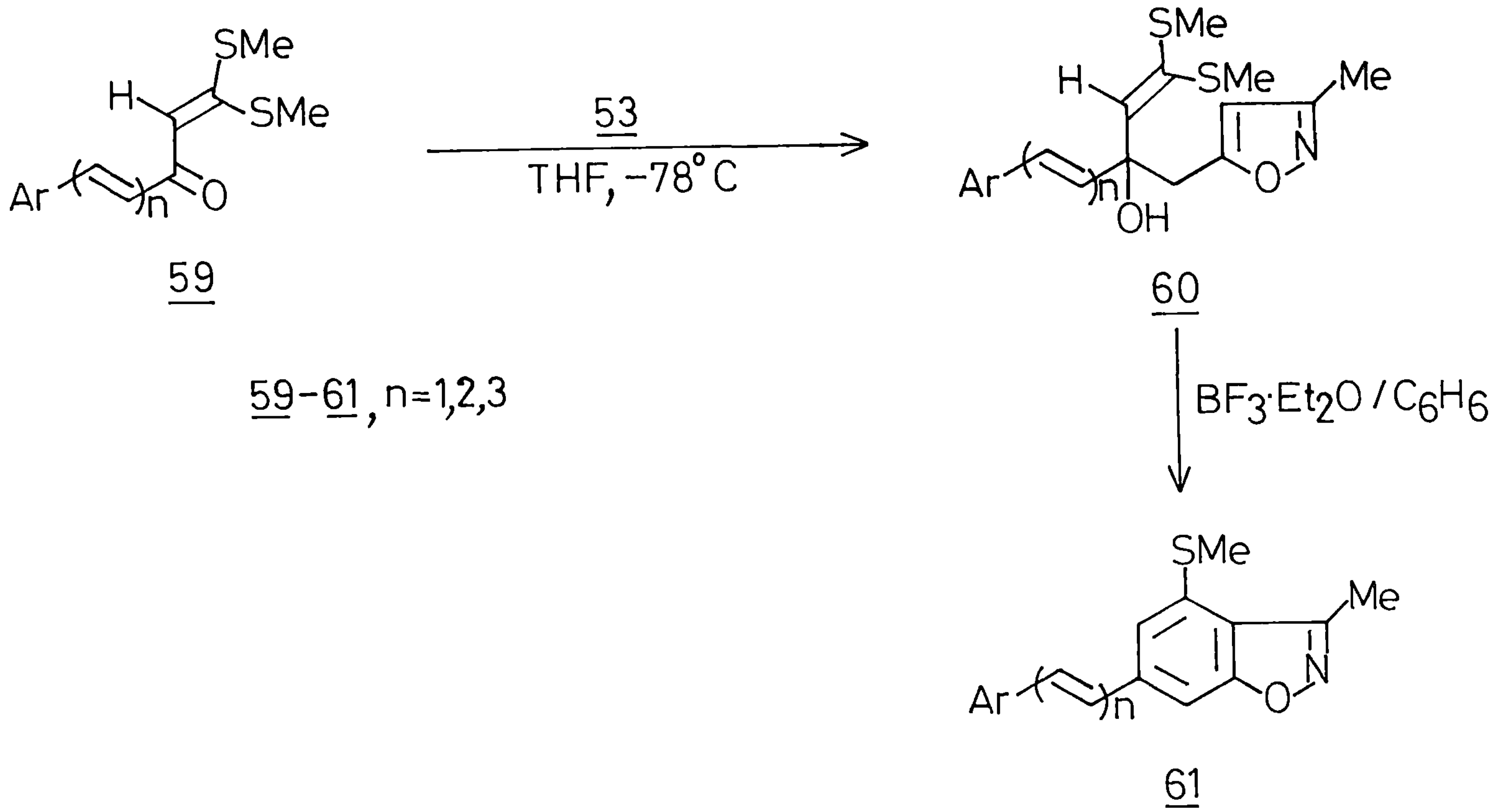
The results of this method are described in Chapter III. The 3-methyl-5-lithiomethylisoxazole 53 underwent smooth 1,2-addition at -78°C to quantitatively yield the carbinolacetal 54 followed by Lewis acid assisted annelation to afford the corresponding benzisoxazoles 56 in high yields. The β-methylthio-α,β-enones 57 obtained by our earlier reported method[26] from 1 also reacted with 53 to yield the corresponding sulfur free benzisoxazoles 58 in identical yields. The cinnamoylketene dithioacetals 59 similarly reacted with 53 to yield the corresponding benzisoxazoles 61 (Scheme 9). The detailed investigation of this reaction has been described in Chapter III.



Scheme–7


SMe
SMe
R1
R2
O
1
Li⊕ H2C⊖
O
N
Me
53
THF / –78°C
BF3·Et2O / C6H6
MeS
SMe
Me
HO
H
54
NaBH4 / Ni Cl2
SMe
H
57
MeS
SMe
H
55
53
THF / –78°C
BF3·Et2O / C6H6
SMe
56
Raney Ni
desulphurization
58

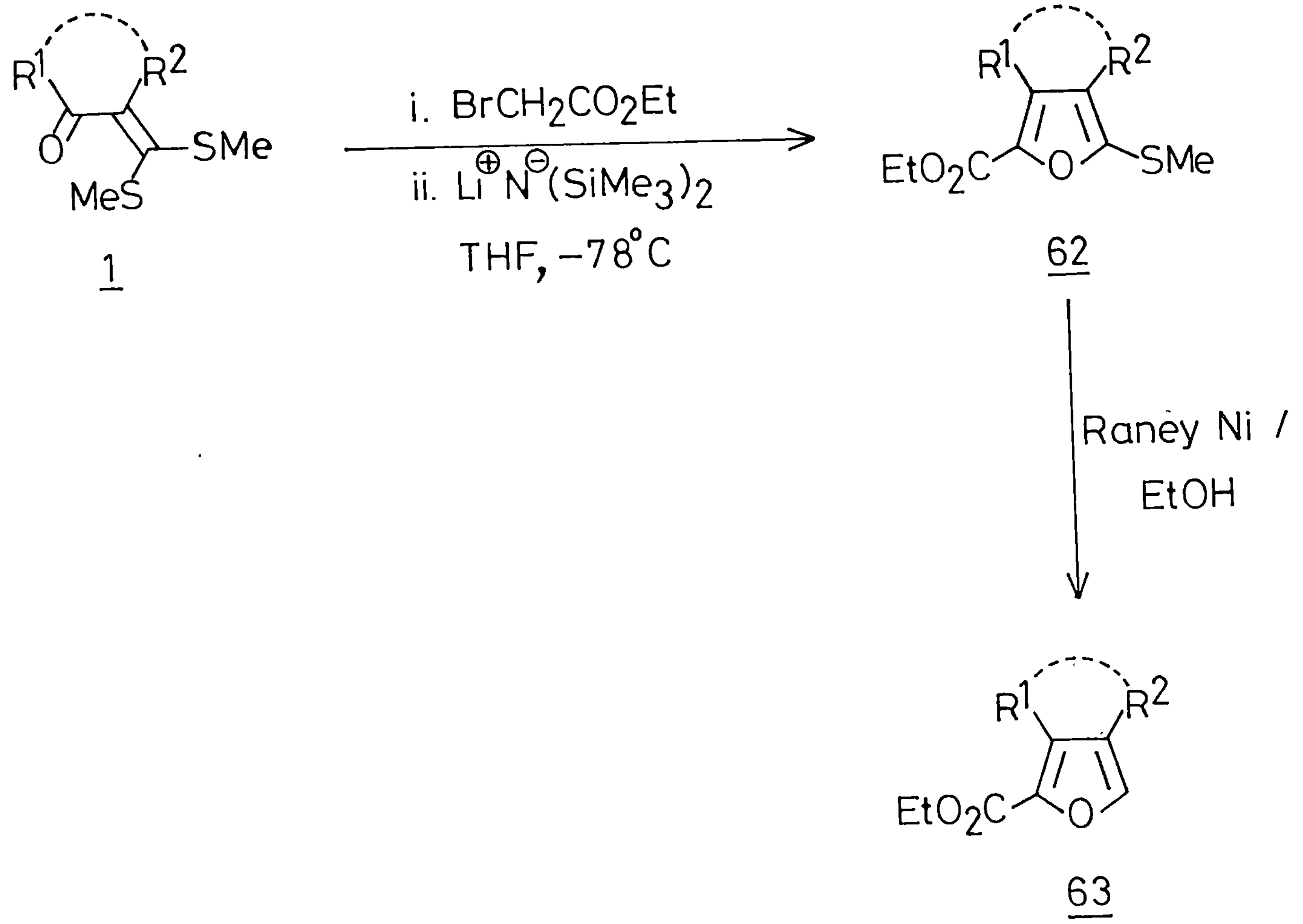
Scheme-8



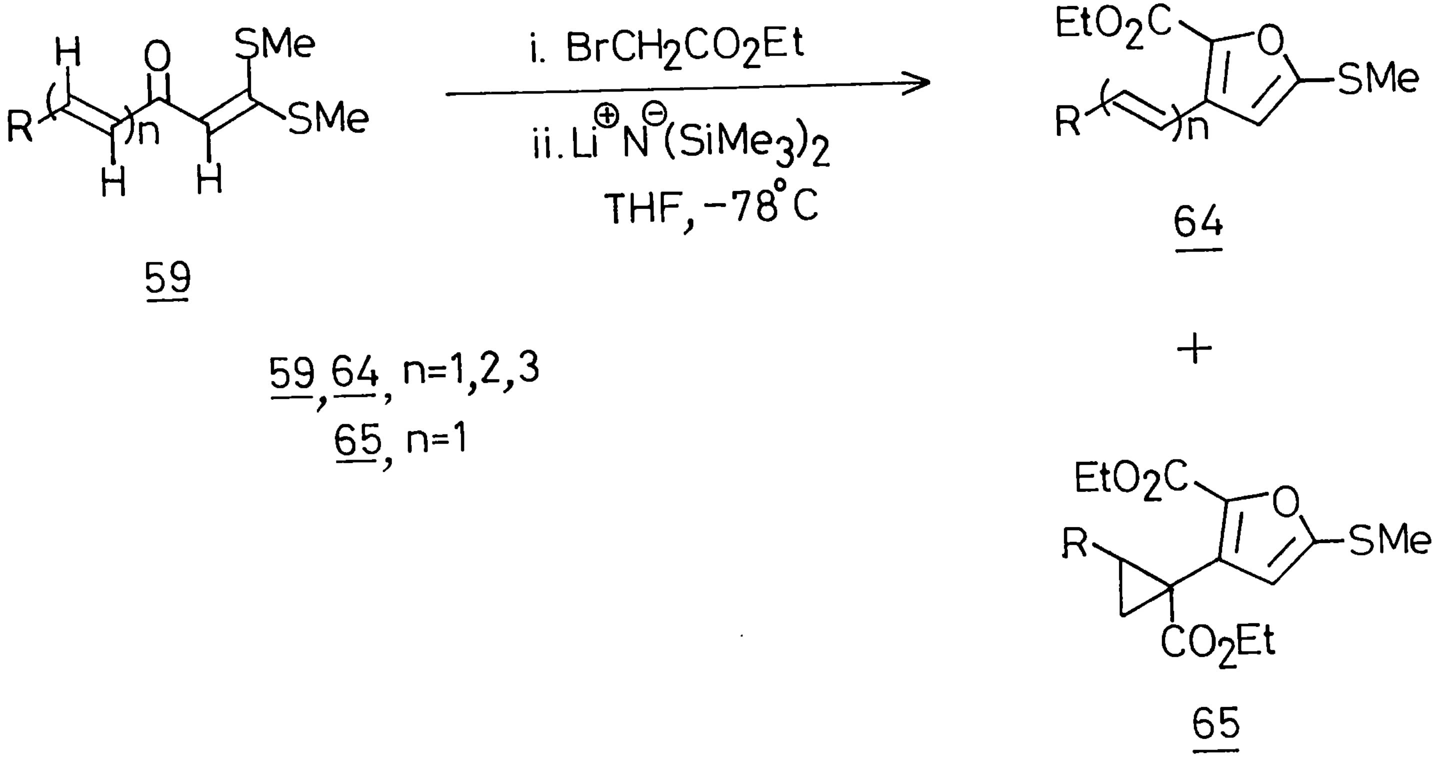
SMe
H
SMe
Ar
n
O
59
53
THF, −78° C
SMe
H
SMe
Me
Ar
n
OH
N
O
60
59–61, n=1,2,3
BF3·Et2O / C6H6
SMe
Me
Ar
n
N
O
61

Scheme–9

In the last Chapter the reaction of 1 with ethylbromoacetate under Darzen reaction conditions has been investigated. Thus when lithiobromoacetate anion was reacted with 1 at -78°C in tetrahydrofuran the furan carboxylates 62 were obtained in quantitative yields. The structures of 62 were established by spectral data as well as by subjecting them to Raney Nickel desulphuriaztion 63 to the known furan derivatives in some cases (Scheme 10)[53]. The reaction has been generalized by extending to cinnamoylketene dithioacetals 59 and the corresponding 64 and 65 were obtained in quantitative yields (Scheme 11). The scope and mechanism of these transformations have been discussed in the last Chapter of the thesis.


R1
R2
SMe
MeS
O
1
i. BrCH2CO2Et
ii. Li⊕N⊖(SiMe3)2
THF, –78°C
EtO2C
62
Raney Ni /
EtOH
63

Scheme–10



59, 64, n=1,2,3
65, n=1

Scheme–11

REFERENCES

1. C. Kelber, Chem. Ber.,43, 1252 (1910).
2. C. Kelber, A. Schwartz,Chem.Ber., 44, 1693 (1911).
3. C. Kelber, A. Schwarz, Chem. Ber.,45, 137 (1912).
4. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2187 (1962).
5. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2194 (1962).
6. M. Saquet, A. Thuillier, Bull. Soc. Chim. Fr.,1582 (1966).
7. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr.,1398 (1959).
8. R. Gompper, R.R. Schmidt, E. Kutter, Liebigs Ann. Chem. 684, 37 (1965).
9. E.J. Corey, R.H.K. Chen, Tetrahedron Lett. 3817 (1973).
10. I. Shahat, Y. Sasson, Tetrahedron Lett.,4207 (1973).
11. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 1779 (1976).
12. R.K. Dieter, J. Org. Chem., 46, 5031 (1981).
13. For a review see R.K. Dieter, Tetrahedron, 42, 3029 (1986).
14. R. Spitzner, M. Menzel, W. Schorth, Synthesis, 206 (1982).
15. R. Gompper, H. Schaefer, Chem. Ber., 100, 591 (1967).
16. D. Borrman, in Houben-Weyl, Methoden der Organischen Chemie, 4th Edn., E. Muller, Ed., Vol. VII, 14, Georg Thieme Verlag. Stuttgart, 421 (1966).
17. D.D. Rudorf, A. Schierhorn, M. Augustin Tetrahedron, 35, 551 (1979).
18. G. Singh, M.L. Purkayastha, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I, 1289 (1985).
19. R.K. Dieter, L.A. Silks, J.R. Fishpaugh, M.E. Kastner, J. Amer. Chem. Soc., 107, 4679 (1985).

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

21. B. Myrboh, C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 50 (1984).

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

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

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

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

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

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

28. L.W. Singh, H. Ila, H. Junjappa, Synthesis, 531 (1985).

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

30. A. Datta, S. Bhattacharjee, H. Ila, H. Junjappa, Synthesis, 725 (1988).

31. A. Datta, H. Ila, H. Junjappa, Tetrahedron, 43. 5367 (1987).

32. M.L. Purkayastha, H.Ila, H. Junjappa, Synthesis, 20 (1989).

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

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

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

36. 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).

37. A. Datta, H. Ila, H. Junjappa, Synthesis, 556 (1988).

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

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

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

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

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

43. A. Datta, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 497 (1988).

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

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

46. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 11911 (1976).

47. S.M.S. Chauhan, H. Junjappa, Synthesis, 880 (1974).

48. S.M.S. Chauhan, H. Junjappa, Synthesis, 798 (1975).

49. R.R. Rastogi, A. Kumar, H. Ila, H. Junjappa, J.C.S. Perkin Trans.I, 554 (1978).

50. D. PooranChand, H. Ila, H. Junjappa, Synthesis, 547 (1987).

51. D. PooranChand, H. Ila, H. Junjappa, Synthesis, 1136 (1987).

52. D. PooranChand, M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 501 (1988).

53. J.D. Prugh, A.C. Huitric, W.G. McCarthy, J. Org. Chem., 29, 1991 (1964).

CHAPTER II

A. REACTION OF β-METHYLTHIO-β-ISOPROPYLAMINO/CYCLOHEXYLAMINO/(α-PHENYL)ETHYLAMINO ACRYLOPHENONE S,N-ACETALS WITH NITROSYL CHLORIDE: A FACILE GENERAL ROUTE TO 2,2-DISUBSTITUTED 4-AROYL-5-ALKYLTHIO-2H-IMIDAZOLES*

B. REACTION OF DIMETHYL-N-ARYL-N-ALKYL CARBONIMIDODITHIOATES WITH AMINOACETALDEHYDE DIETHYL ACETAL: ONE POT SYNTHESIS OF 1-N-ARYL/ALKYL-2-METHYLTHIO IMIDAZOLES**

II.1 INTRODUCTION

The synthetic applications of various α-oxoketene S,N and N,N-acetals for the construction of a number of heterocyclic systems have been extensively investigated in this laboratory[1-8]. They have been shown to function as versatile three-carbon fragments

---

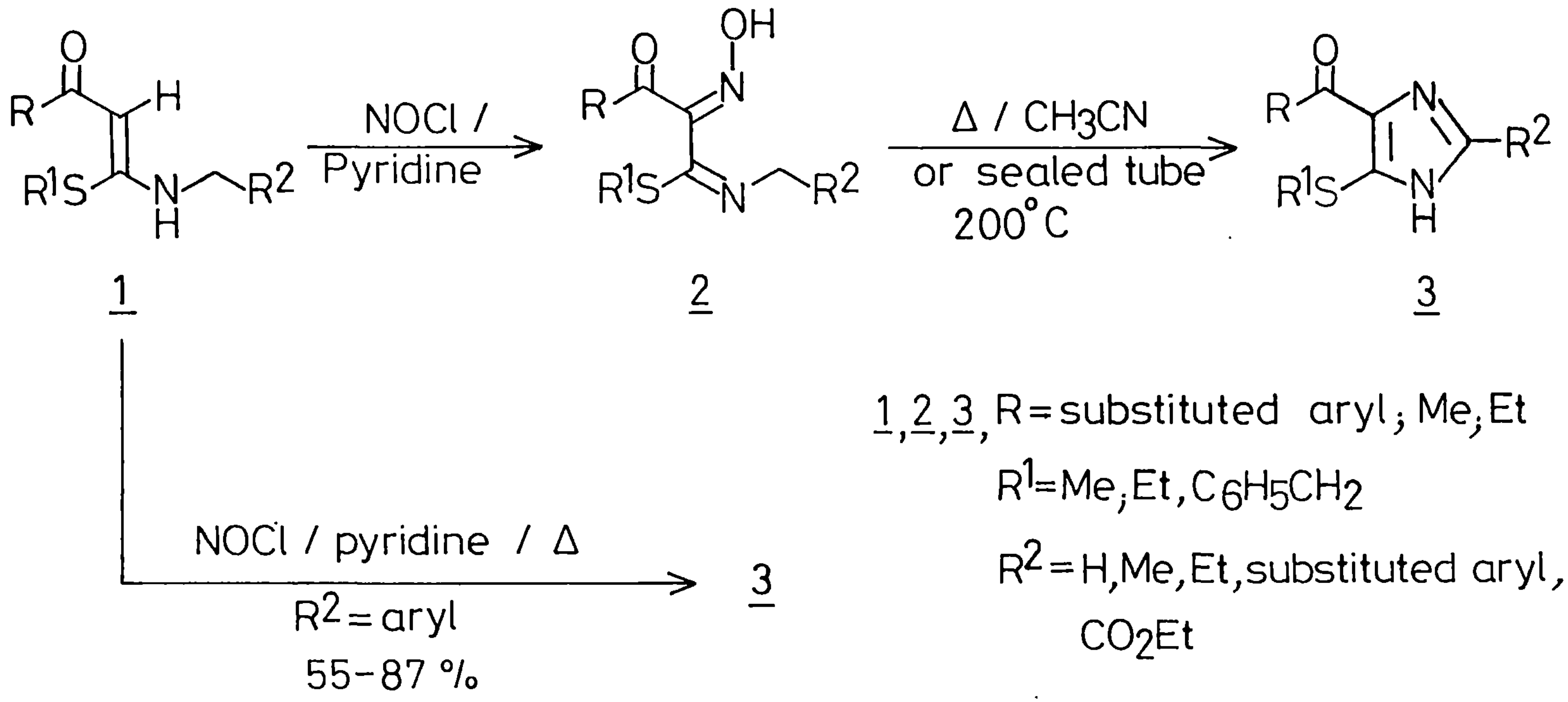
* D. Pooranchand, H. Ila, H. Junjappa, Synthesis, 547, 1987.

** D. Pooranchand, H. Ila, H. Junjappa, Synthesis, 1136, 1987.

towards various bifunctional nucleophiles to afford a variety of amino heterocycles, whereas in many of the reactions the enaminone functionality in these systems react with a variety of electrophiles to yield novel heterocyclic systems after subsequent transformations[9-11].

As a part of synthetic programme, these intermediates were recently shown to react with nitrosyl chloride to yield the corresponding nitroso derivatives in high yields. These nitroso compounds were shown to exist in their oximinoform and underwent thermal cyclocondensation to yield the corresponding 1H-imidazoles in good yields. The reaction was found to be general and could be extended, to construct, the corresponding thiazoles and the quinoxalines, when the substituent on nitrogen was aryl group[12]. It was further considered of interest that if the substrate S,N-acetals carry the isopropyl, cyclohexyl or α-phenylethyl substituent in the amino functionality, the reaction of such S,N-acetal with nitrosyl chloride should lead to the formation of 2,2-disubstituted 4-aroyl-5-alkylthio-2H-imidazoles. In the present investigation, a general method for the synthesis of this class of imidazoles has been investigated and the results of these studies are the main subject of this chapter.

The current developments on the chemistry of these group of imidazoles though not extensively investigated are described in the literature[13], with varying degrees of success. Some of these selected methods have been briefly reviewed so that the efficacy of the present methodology is better appreciated. Although imidazole ring on pyrimidine nucleus has been constructed by condensation of 5-nitroso-4-alkylamino derivatives[14-16], similar synthetic operations based on open-chain nitroso enamines or enaminones (or hydroxyiminoimines) to yield the corresponding imidazoles were not known in the literature. The scant literature on such transformations was primarily due to lack of appropriate open-chain nitroso enamine/enaminone precursors. This gap was successfully filled by Rahman, Ila and Junjappa[12] and they showed that the α-oxoketene S,N-acetals of the general formula 1 undergo facile nitrosation to yield the corresponding oximino acetals 2 in high yields, which were then cyclocondensed under thermal conditions to yield the corresponding 2,4,5-trisubstituted imidazoles 3 in high yields. The imidazoles 3 could also be obtained directly when 1 was reacted with nitrosyl chloride at elevated temperature (Scheme 1). When the substituent on the nitrogen was aryl group the corresponding hydroxyiminoimines 5 underwent ring closure through the participation of the aryl group to yield the quinoxalines 7 in high yields (Scheme 2). However when the S-alkyl group in 5 was replaced by benzyl group the reaction was deviated to yield the corresponding thiazoles 9. The S,N-acetals 1 also reacted with nitrosobenzene in the presence of acetic anhydride to yield the corresponding N-aryl imidazoles 14[17]. The probable mechanism for the formation of 14 has been described in Scheme 3. Thus the intermediate 10 formed by nucleophilic attack of β-carbon of S,N-acetal 1 to nitroso benzene undergoes dehydration in the acetic anhydride medium to give the diimine intermediate 11. Thermal 1,5-proton shift in 11 gives monoimine 12, which is ideally disposed for intramolecular cyclization to dihydroimidazole 13 which on subsequent dehydrogenation leads to 1-N-aryl imidazole 14. The construction of

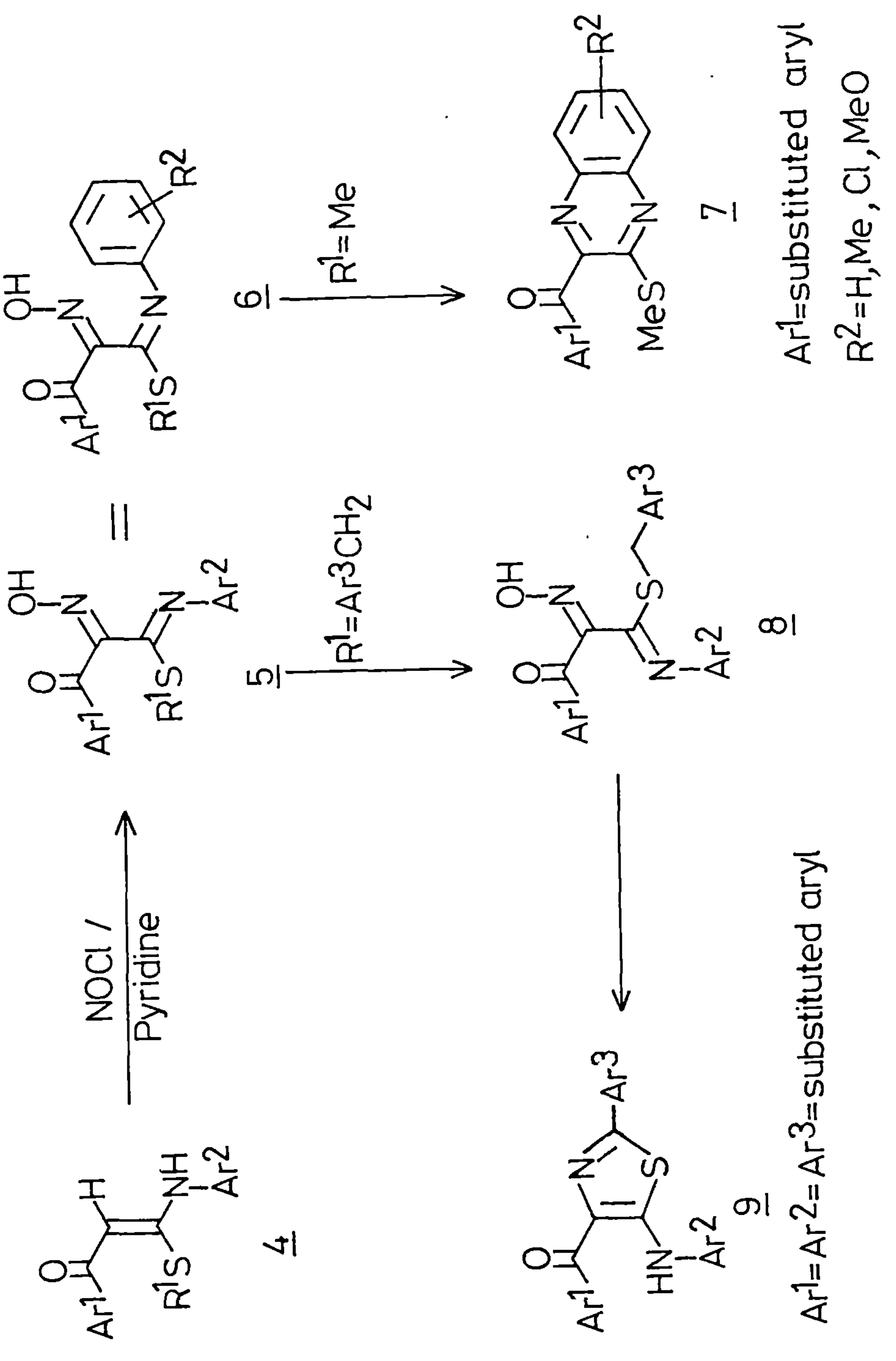


1, 2, 3, R = substituted aryl; Me; Et

R^1=Me; Et, $C_6H_5CH_2$

R^2 = H, Me, Et, substituted aryl, CO_2Et

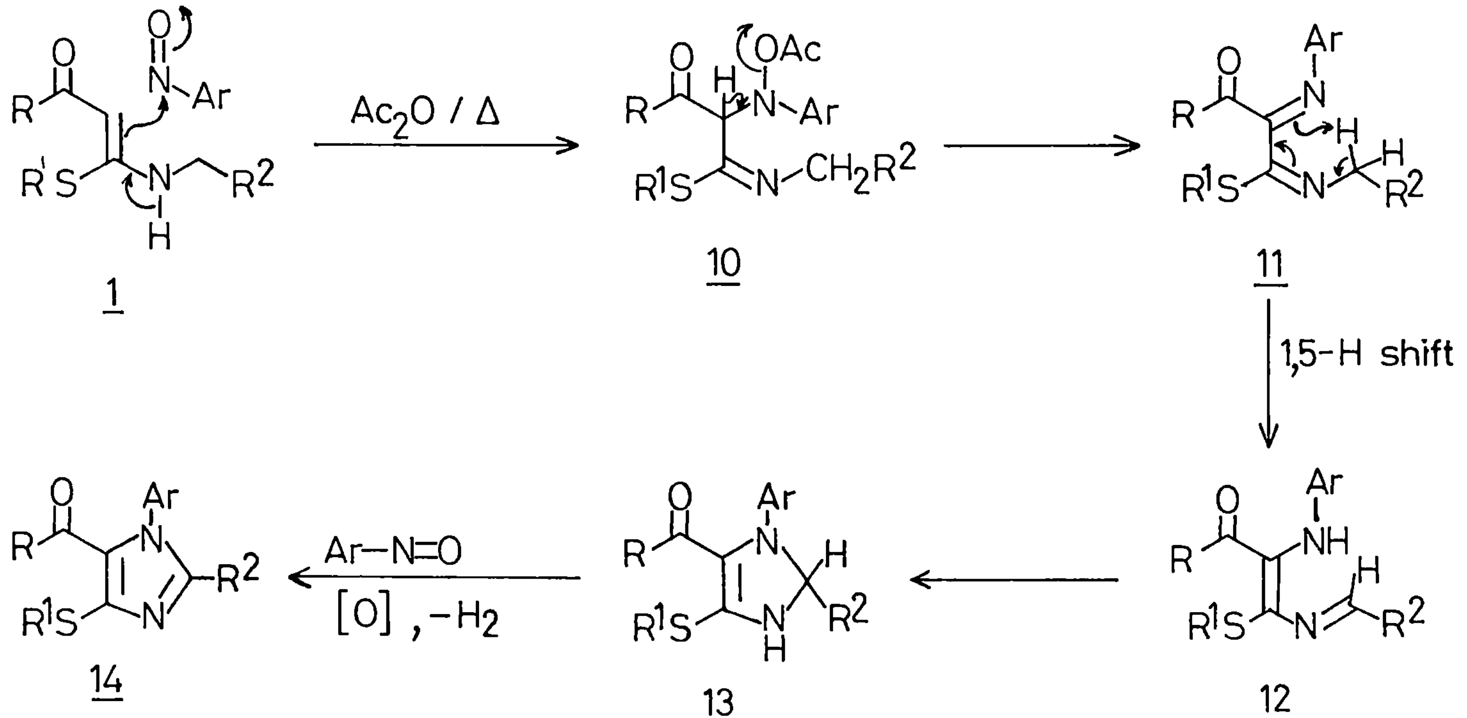
Scheme-1



Ar^1=substituted aryl
R^2=H,Me , Cl ,MeO

Ar^1=Ar^2= Ar^3=substituted aryl

Scheme-2



R = substituted aryl, Me ; R^1 = Me, Et, $PhCH_2$
R^2 = substituted aryl, H, Me ; Ar = C_6H_5, 4-MeC_6H_4; 70–85 % yield

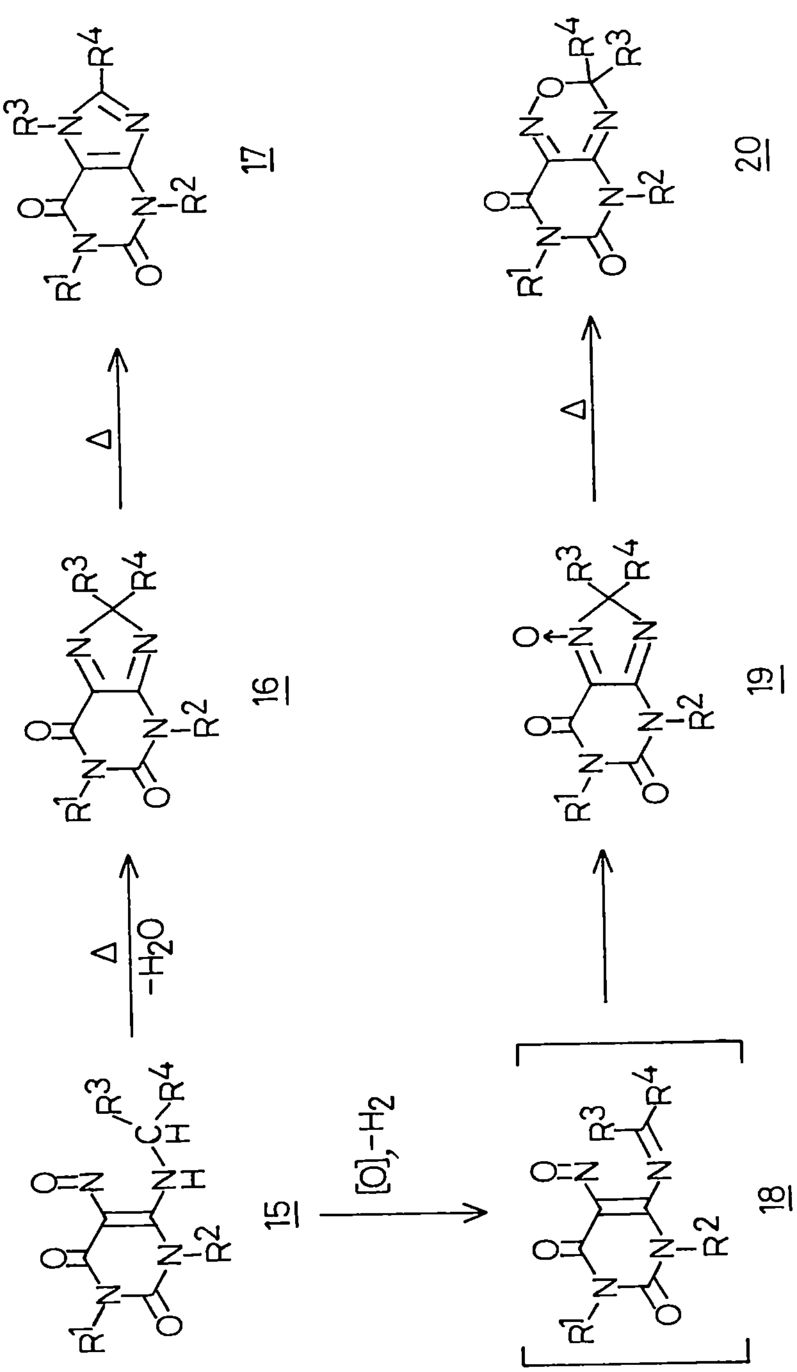
Scheme–3

2*H*-imidazole ring on the pyrimidine nucleus has been reported through 1,3-dimethyl-5-nitroso-4-secondary alkylamino uracil 15 which under thermal conditions yielded the corresponding 8,8-disubstituted xanthines 16 in high yields[18]. These intermediates undergo facile thermal rearrangement to 7,8-disubstituted xanthines 17. Dehydrogenation of 15 under mild conditions is reported to afford 8*H*-xanthine 7-N-oxide 19 via intermediate anil 18. The xanthine-N-oxide 19 isomerizes to fused oxadiazines 20 under thermal conditions (Scheme 4). One of the approaches for the synthesis of alkoxy or alkylthio 2*H*-imidazoles employs the reaction of acylnitrile 21 (Scheme 5) with hydrogen sulfide in the presence of ammonia and triethylamine to yield the corresponding hydroxythionamide 22 which on reaction with ketones yielded the corresponding 2*H*-imidazole-5-thione 23. These thiones were subsequently converted to the corresponding alkoxy imidazole 24 or acylthio 25 and thioalkyl 26 2*H*-imidazoles[13].

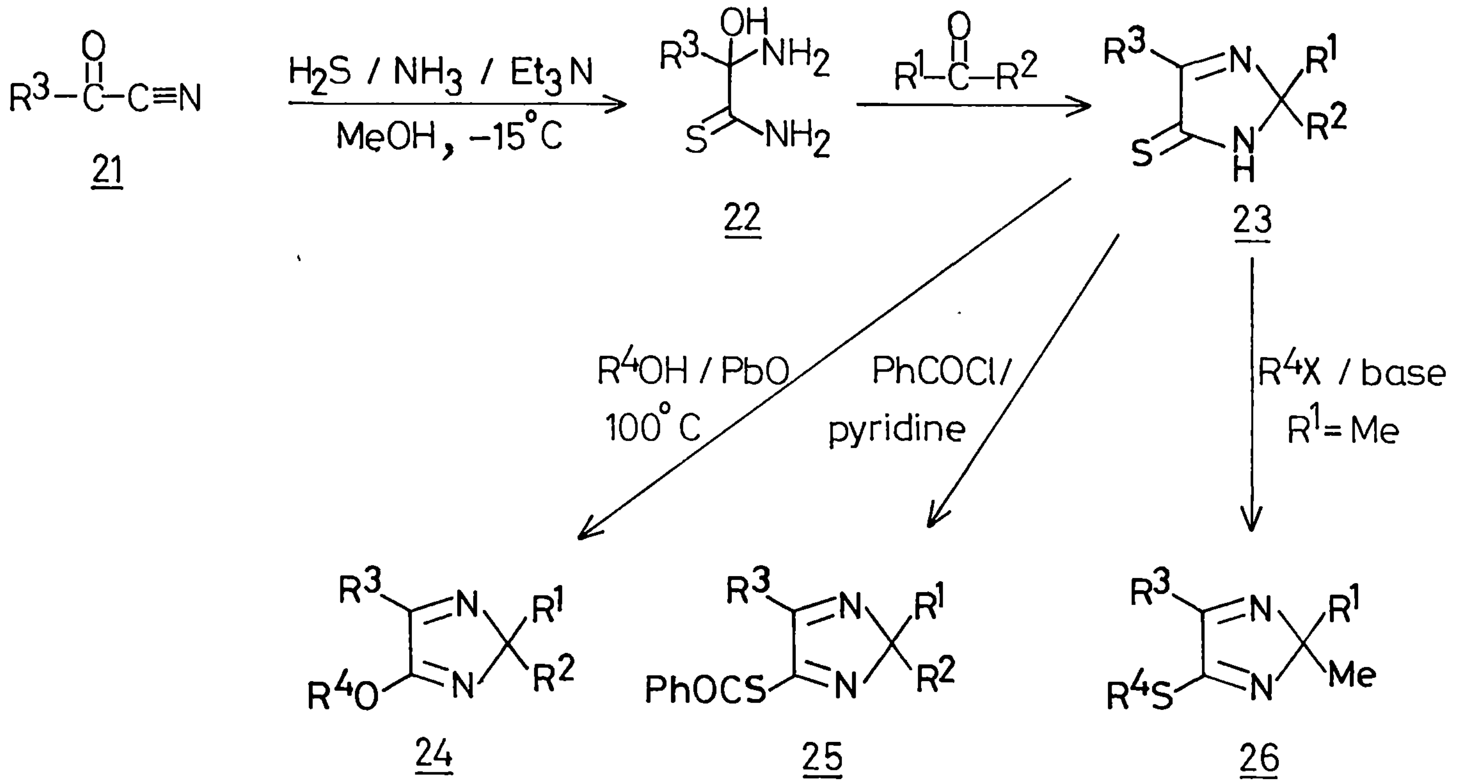
In another approach the 2*H*-imidazole thione 23 was converted to the corresponding imino chloride 27 by the reaction of 23 with sulfonyl chloride and the chlorine in 27 was subsequently replaced by thiophenol to yield the 2*H*-imidazole 28 (Scheme 6)[19].

The 2*H*-imidazoles, carrying substituents at, 4 and 5 positions have been shown to undergo thermal rearrangement involving the migration of one of the substituents at 2-position to the adjacent nitrogen atom to yield the corresponding 1-N-substituted-2,4,5-trisubstituted imidazoles 30 in moderate yields[20].

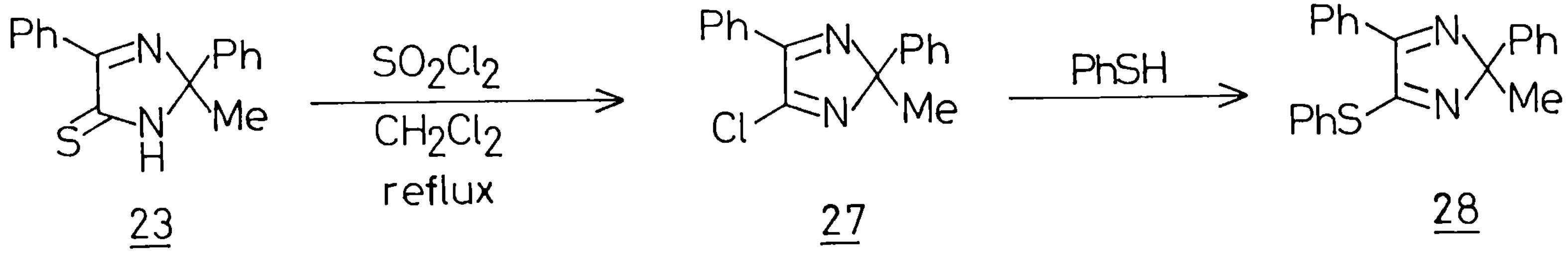
Similarly the 4,5-dicyano isoimidazole 31 underwent thermal rearrangement at 180°C to give 2-methyl-4,5-dicyano imidazole 32[21]. For thermal



Scheme-4


21
H2S / NH3 / Et3N
MeOH, −15°C
22
R1–C(O)–R2
23
R4OH / PbO
100° C
PhCOCl/
pyridine
R4X / base
R1 = Me
24
25
26

Scheme-5



Scheme-6

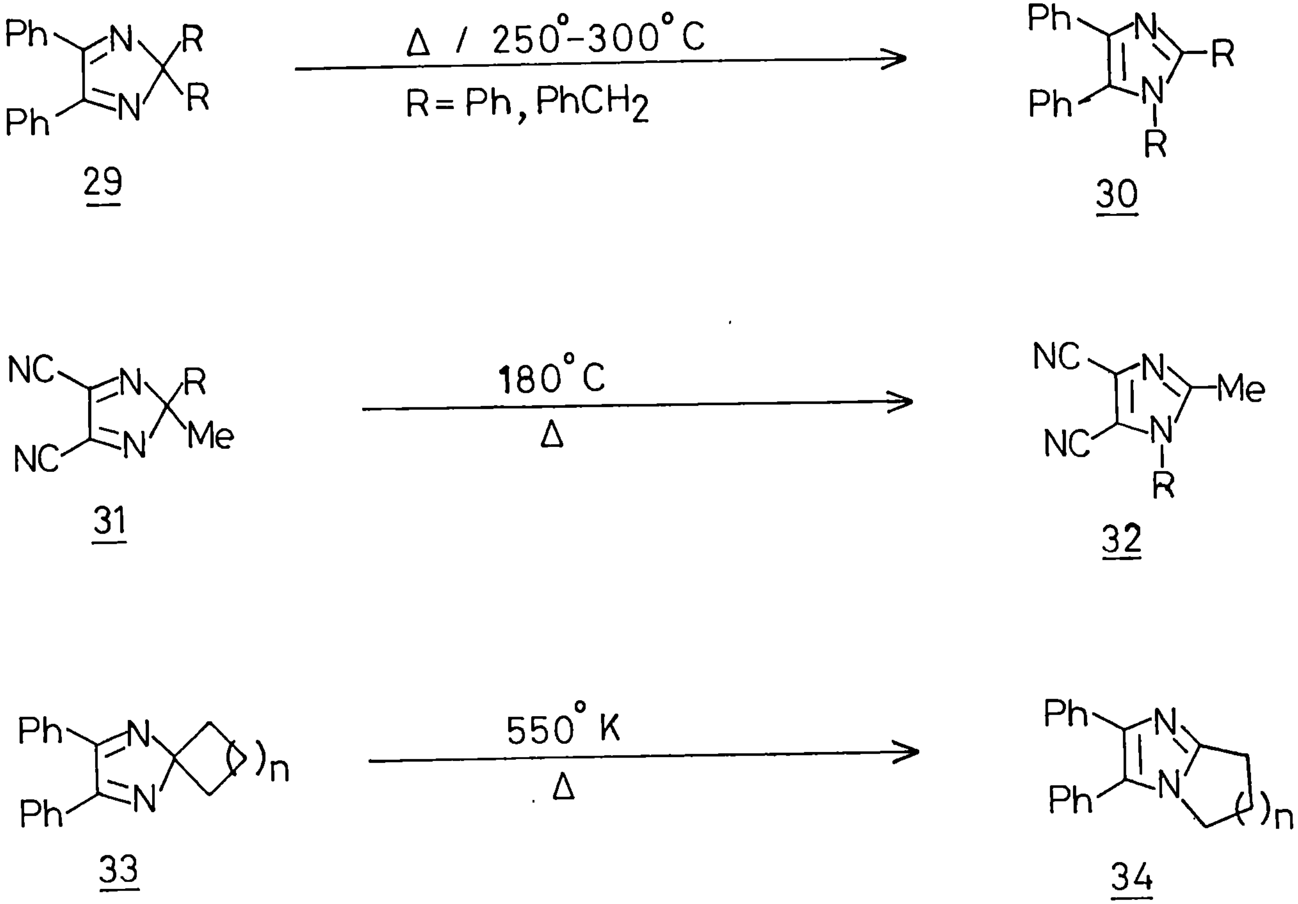
rearrangement the migratory aptitude of various groups were in the order Me $<$ Et $<$ nPr $\approx$ iPr. The spiroimidazoline 33 also underwent thermal rearrangement to yield the corresponding bicyclic imidazoles 34 (Scheme 7)[22].

It is apparent from the foregoing references, that the methods for the synthesis of 2H-imidazoles are few in number, particularly the approaches from the open-chain precursors (Scheme 5) involves many steps with poor overall yields of the product 2H-imidazoles.

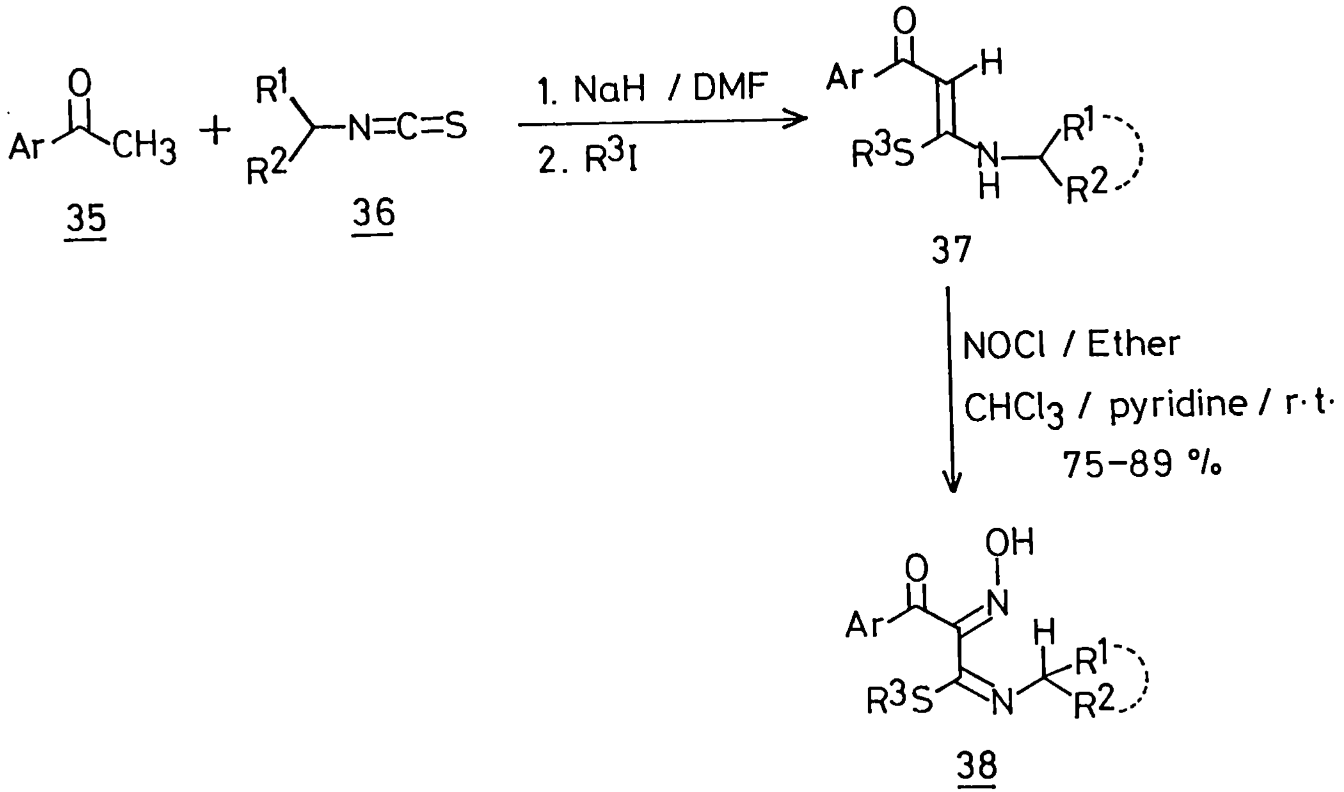
Interestingly, the construction of 2H-imidazoles on the appropriately substituted uracil 15 (Scheme 4) to yield the corresponding xanthine 16 appears to have not been extended to the open-chain precursors to construct the corresponding 2H-imidazoles. The lack of studies in these directions seems to be due to the non-availability of appropriate open-chain precursors. Therefore the present investigation considered these approaches appropriate so that a new general and efficient route for the synthesis of 2H-imidazoles may be developed. Also such an approach would provide opportunities to introduce substituents at all the possible three atoms of the product 2H-imidazoles. The results of the present investigation are described as follows.

II.2 RESULTS AND DISCUSSION

The S,N-acetals 37 required in the present investigation were conveniently prepared by reacting acetophenone 35 with the appropriate alkylisothiocyanate 36 in the presence of sodiumhydride in dimethylformamide in excellent yields (Scheme 8). The S,N-acetal 37a was obtained by reacting acetophenone with isopropylisothiocyanate. The compound 37a



Scheme–7



Scheme–8

was analyzed for $C_{13}H_{17}NOS$ (235.2) and showed in its i.r. spectrum (CCl_4) peaks at 3240, 1620, 1542 cm^{-1}. The 3240 cm^{-1} band was assigned to NH stretching vibrations while the 1623 cm^{-1} band was due to the carbonyl stretching frequency. The lower frequency of carbonyl group is attributed to the presence of β-amino group which interacts with the carbonyl group through lone pair of electrons. Further structural elucidation for 37a was obtained from its ^1H n.m.r. spectrum (CCl_4). The signal at δ 1.30(d,6H,J=7Hz) was due to six isopropyl methyl protons and the signal at δ 2.35(s,3H) was assigned to methylthio protons. The broad multiplet at δ 3.82 integrating for one proton was assigned to C$\underline{H}$ methine proton. The olefinic proton appeared as a singlet at δ 5.60 and the multiplet between δ 7.40-7.41(3H) and δ 7.80-7.85(2H) were attributed to five aromatic protons. The secondary amino proton appeared as broad doublet at δ 11.90 which was exchangeable with D_2O. Thus the structure of 37a was fully established. The other S,N-acetals 37b-1 required in the present investigation were not reported in the literature and were essentially prepared by extending the described method, in 80-90% overall yields. The analytical and spectral data of 37b-1 were in full agreement with the assigned structures and the data are reported in the experimental section.

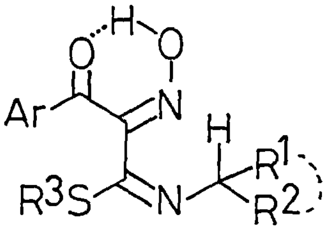
II.2.1 REACTION OF α-OXOKETENE S,N-ACETALS WITH NITROSYL CHLORIDE: SYNTHESIS OF α-HYDROXYIMINO-β-ALKYLIMINOKETONES (38a-1):

The S,N-acetal 37a was reacted with nitrosyl chloride in the presence of pyridine in chloroform when the corresponding hydroxyiminoimine 38a was obtained in 75% yield. The structure of the hydroxyiminoimine 38a (Scheme 8) was confirmed from its analytical and spectral data. It was analyzed for $C_{13}H_{16}N_2O_2S$ confirming the molecular weight 264.3. In its i.r. spectrum (KBr) it exhibited broad band at 3150 cm^{-1} which was assigned to the iminohydroxy group with intramolecular hydrogen bonding as shown in 39. In the earlier assignment also[23] it has been observed that the nitroso derivatives of enaminones exist in the tautomeric form with intramolecular hydrogen bonding. This structural assignment was further confirmed by shift in carbonyl frequency 1650 cm^{-1} where the nitrogen lone pair is in conjugation with the nitroso group, resulting in the higher carbonyl frequency. The hydroximino (tautomeric) structure of 38a was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6) (experimental). Thus the signal due to methine proton which appeared as broad band in 37 exhibited sharp septets at δ3.45 (0.5H, J=7Hz) and δ3.95 (0.5H, J=7Hz) indicating the absence of coupling between methine and NH protons[24], which exist in the tautomeric form 39. The chemical shift of hydroxyimino proton signal which appears between δ10.5-11.8 ppm in the ^1H n.m.r. spectrum of 38a supports the intramolecular hydrogen bonded structure[23]. The other signals confirmed the structural assignment of 38a which exists in hydrogen bonded form 39. The isopropyl methyl protons appears as two sharp doublets at δ1.50 (3H, J=7Hz) and δ2.48(3H, J=7Hz). Similarly the signal due to methylthio protons also appeared as two singlets at δ2.30(1.5H) and δ2.50(1.5H), showing the presence of two equivalent tautomeric forms of hydroxyiminoimine in DMSO-d_6*. The multiplet between δ7.28-7.80(3H) and δ7.80-8.20(2H)

---

* ^1H n.m.r. spectra of other hydroxyiminoimines which are soluble in $CDCl_3$ show only one signal for methylthio, isopropylmethyl and methine protons.

was assigned to aromatic protons. Apparently the nitroso derivatives of oxoketene S,N-acetals with a mobile hydrogen on the nitrogen atom exist in the hydroxyiminoimine tautomeric form. Similarly 38b-e were obtained in 82-86% overall yields, and their analytical and spectral data are described in the experimental section. The hydroxyimino ketones 38f-j derived from cyclohexylamine were also obtained in 81-89% overall yields. They were characterized by their ^{1}H n.m.r. spectrum ($CDCl_3$) which showed broad singlet with coupling($W\frac{1}{2}$=16Hz) indicating the absence of coupling between methine and NH protons[24]. A comparison of solid (KBr) and solution ($CHCl_3$) i.r. spectra of 38 did not show any shift of carbonyl and OH stretching frequency in the solution spectra, which points to an intramolecular hydrogen bonded structure 39 for 38. This is further supported by the chemical shift of hydroxyimino proton signal which appears between δ 10.5-11.8 ppm in ^{1}H n.m.r. spectra[23].



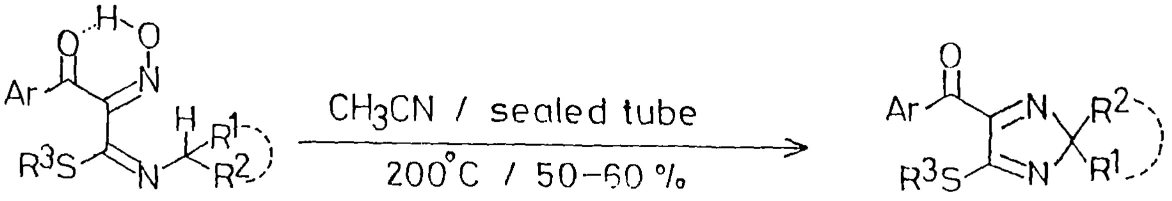
39

In conclusion the α-hydroxyimino-β-alkylimino ketones 38a-k thus prepared were fully characterized and shown to exist in their tautomeric hydroxyimino form.

II.2.2 THERMAL CYCLODEHYDRATION OF HYDROXYIMINOIMINES: SYNTHESIS OF NOVEL 2,2-DISUBSTITUTED-4-AROYL-5-ALKYLTHIO-2H-IMIDAZOLES (40a-l):

The hydroxyiminoimine 38a was heated at 200°C in a sealed tube for 1 hour and the reaction mixture after work up and purification yielded a product (m.p. 44-45°C) which was characterized as 2,2-dimethyl-4-benzoyl-5-methylthio-2H-imidazole in 50% yield (Scheme 9). The structure of 40a was elucidated from its analytical and spectral data. The compound was analyzed for $C_{13}H_{14}N_2OS$ and its mass spectrum exhibited molecular ion peak m/z 246(M^+,45%), and also showed characteristic mass fragmentation pattern and is given in the experimental section. The i.r. spectrum (KBr) displayed benzoyl carbonyl group at $\nu = 1660\ cm^{-1}$. The structure was elucidated from its ^1H n.m.r. spectrum ($CDCl_3$). Thus the signal at δ1.50 (s,6H) was assigned to the gemdimethyl protons and the methylthio protons appeared as singlet at δ2.48(3H). The two multiplets δ7.20-7.55(3H) and δ8.15-8.30(2H) represent the aromatic protons. The structure of 2H-imidazole 40a was thus confirmed. The imidazoles 40b-l were prepared in the analogous manner and were obtained in 50-60% overall yields. Their structures were fully confirmed by their analytical and spectral data (experimental).

The 2H-imidazoles 40 were subjected to thermal rearrangement with a view to study the possible migration of one of the substituents at 2-position. when 40a and b were heated at 300-500°C the expected rearranged products 1-N-alkyl/aryl-1H-imidazoles 41a or 41b were not detected (Scheme 10). In most of the cases either the unreacted starting materials were recovered or the reaction ended up in intractable tarry mixture. The rearrangements of this nature have been previously observed though in

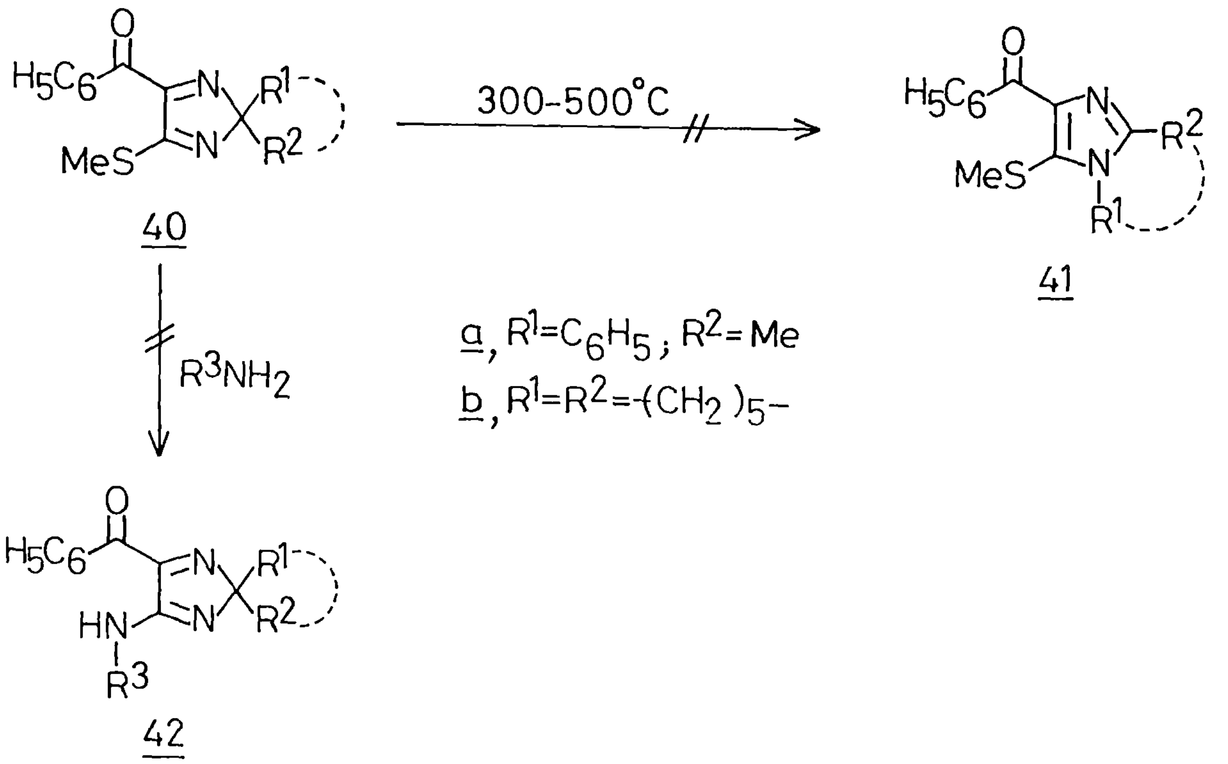


38 a-l

40 a-l

	Ar	R^1	R^2	R^3
a	C_6H_5	CH_3	CH_3	CH_3
b	4-MeC_6H_4	CH_3	CH_3	CH_3
c	4-MeOC_6H_4	CH_3	CH_3	CH_3
d	4-ClC_6H_4	CH_3	CH_3	CH_3
e	C_6H_5	CH_3	CH_3	C_2H_5
f	C_6H_5	$-(CH_2)_5-$		CH_3
g	4-MeC_6H_4	$-(CH_2)_5-$		CH_3
h	4-MeOC_6H_4	$-(CH_2)_5-$		CH_3
i	4-ClC_6H_4	$-(CH_2)_5-$		CH_3
j	C_6H_5	$-(CH_2)_5-$		C_2H_5
k	4-ClC_6H_4	C_6H_5	CH_3	CH_3
l	C_6H_5	C_6H_5	CH_3	CH_3

Scheme-9



a, $R^1=C_6H_5$; $R^2=Me$
b, $R^1=R^2=-(CH_2)_5-$

$R^3=Et, PhCH_2, Ph$; $R^1=R^2=Me$

Scheme-10

moderate yields[13]. The compound 40a was also treated with primary amines to see whether methylthio groups could be displaced by the corresponding amino group. The unreacted 40a was recovered and no displacement by amine was observed.

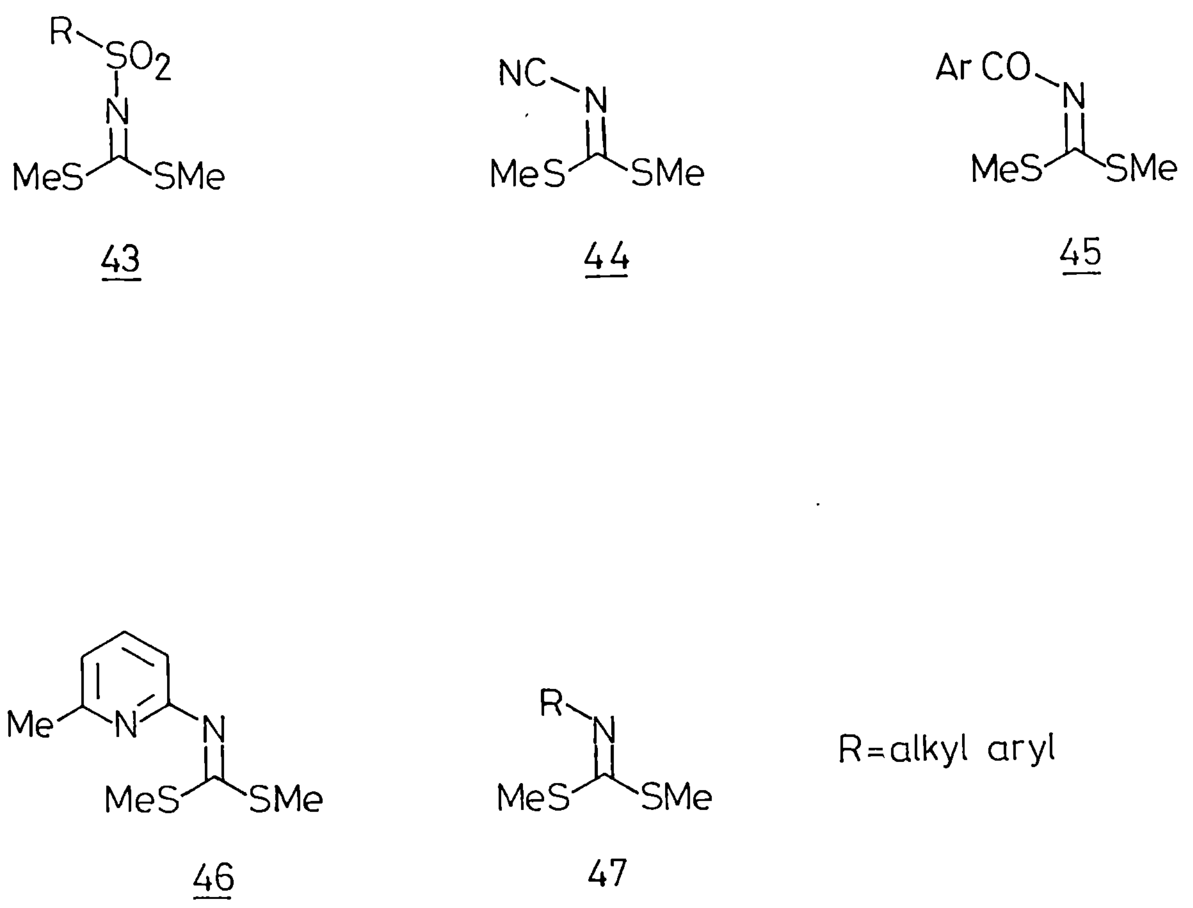
II.3 CONCLUSION

Thus from these results it is obvious that the hydroxyiminoimines prepared from substituted acetophenone derivatives constitute an important class of functionalized synthons, which provides an efficient versatile route for 2H-imidazoles from easily available starting materials.

II.4 REACTION OF DIMETHYL N-ARYL/N-ALKYL CARBONIMIDODITHIOATES WITH AMINOACETALDEHYDE DIETHYL ACETAL: ONE POT SYNTHESIS OF 1-N-ARYL AND 1-N-ALKYL-2-METHYLTHIOIMIDAZOLES:

II.4.1 INTRODUCTION

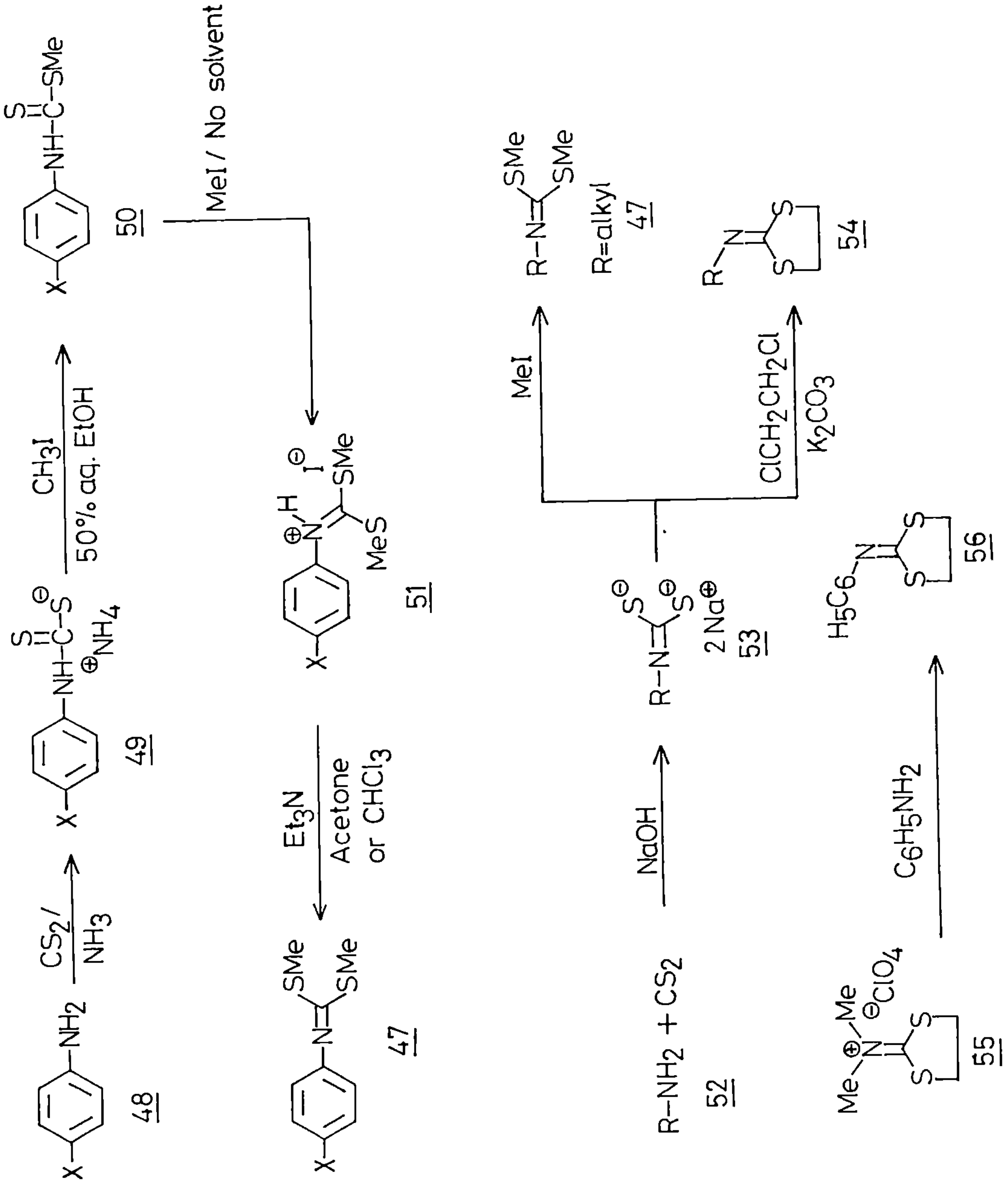
The preparation of dimethyl-N-aryl/N-alkyl carbonimidodithioates and their properties have been extensively reported in the literature[25-28]. However their synthetic applications for the construction of five membered heterocycles is relatively not much attended. On the other hand, their structural analogs with electron withdrawing groups on nitrogen such as 43[29], 44[30], and 45[31] (Scheme 11) have been extensively investigated. It was considered of special interest to explore the synthetic potential of this class of synthons for the construction of imidazoles through its reaction with aminoacetaldehyde diethylacetal in the presence of activating solvent such as acetic acid. In the present section reaction of carbonimidodithioates with aminoacetaldehyde diethyl acetal to yield the corresponding N-substituted-


R
SO2
N
MeS
SMe
43
NC
N
MeS
SMe
44
Ar CO
N
MeS
SMe
45
Me
N
N
MeS
SMe
46
R
N
MeS
SMe
47
R=alkyl aryl

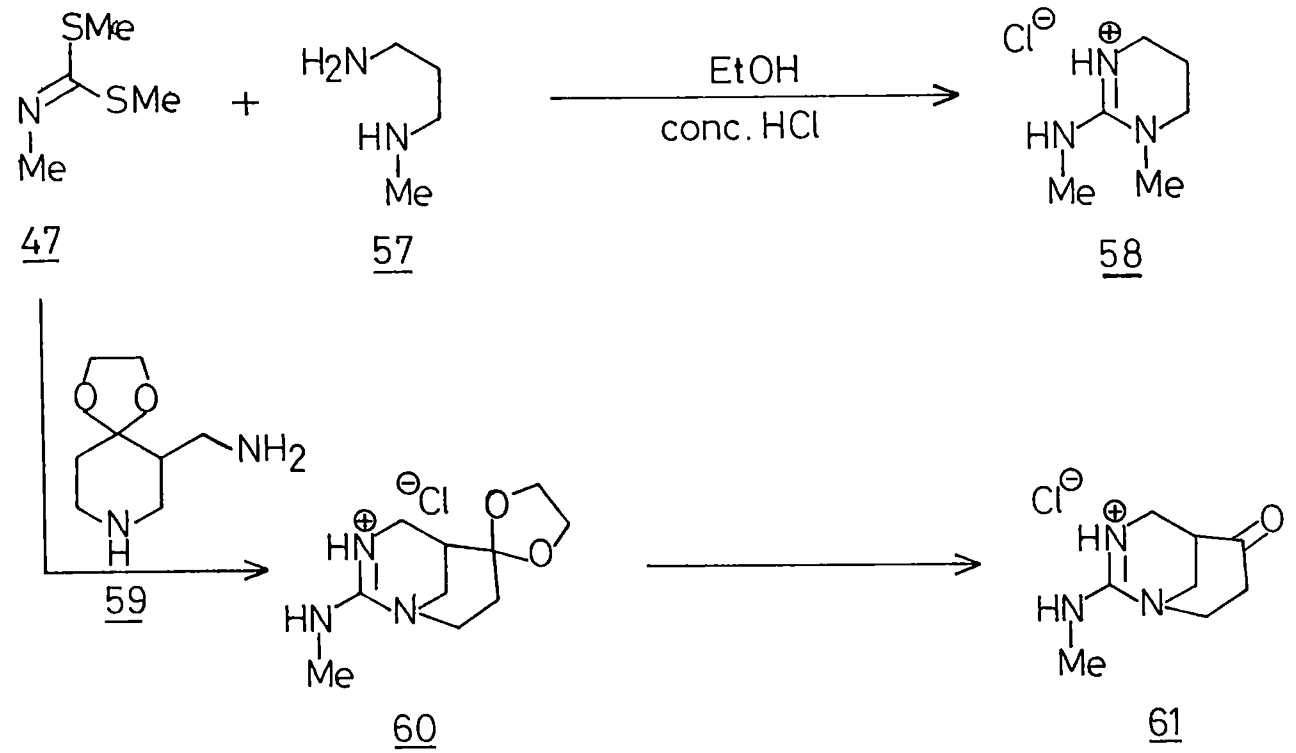
Scheme-11

2-methylthioimidazoles is presented. There appears to be no review on the synthesis and synthetic applications of these compounds and an attempt has been made to review the important synthetic methodologies for these compounds and their reported applications for the synthesis of heterocycles. The various methods for the preparation of carbonimidodithioates are described. The most general method for the synthesis of N-arylcarbonimidodithioates involves the reaction of various arylamines 48 (Scheme 12) with carbondisulfide and ammonia to give the ammonium dithiocarbamates 49. These were dimethylated in two steps to the immonium salts 51 and deprotonated to give 47 in excellent yields[27]. Similarly the alkylamines 52 undergo facile addition to carbon disulfide in the presence of sodiumhydroxide to yield the sodium salt of dithioates 53 which can be alkylated insitu to obtain the corresponding alkyl carbonimidodithioate 47. The cyclic carbonimidodithioates, 2-alkylimino-1,3-dithiolane 54 can be prepared by the reaction of 1,2-dichloroethane with the corresponding sodium N-alkyldithiocarbamate at 60°C in the presence of potassium carbonate. The 2-phenylimino-1,3-dithiolane 56 was prepared in 73% yield by the reaction of 2-dimethylamino-1,3-dithiol anylinium perchlorate with aniline[32].

The carbonimidodithioates can be an excellent source of one electrophilic carbon and accordingly undergo interesting cyclization reactions with appropriate binucleophiles. Thus dimethyl-N-alkyl-carbonimidodithioate 47 (Scheme 13) condensed with N-methyl-1,3-diaminopropane 57 in the presence of absolute ethanol and concentrated hydrochloric acid under reflux to give 1-methyl-2-(methylamino)-1,4,5,6-tetrahydro-


48
49
50
51
47
CS2/
NH3
CH3I
50% aq. EtOH
MeI / No solvent
Et3N
Acetone
or CHCl3
R=alkyl
47
52
53
54
55
56
R–NH2 + CS2
NaOH
2 Na⊕
MeI
ClCH2CH2Cl
K2CO3
C6H5NH2
ClO4
H5C6

Scheme-12

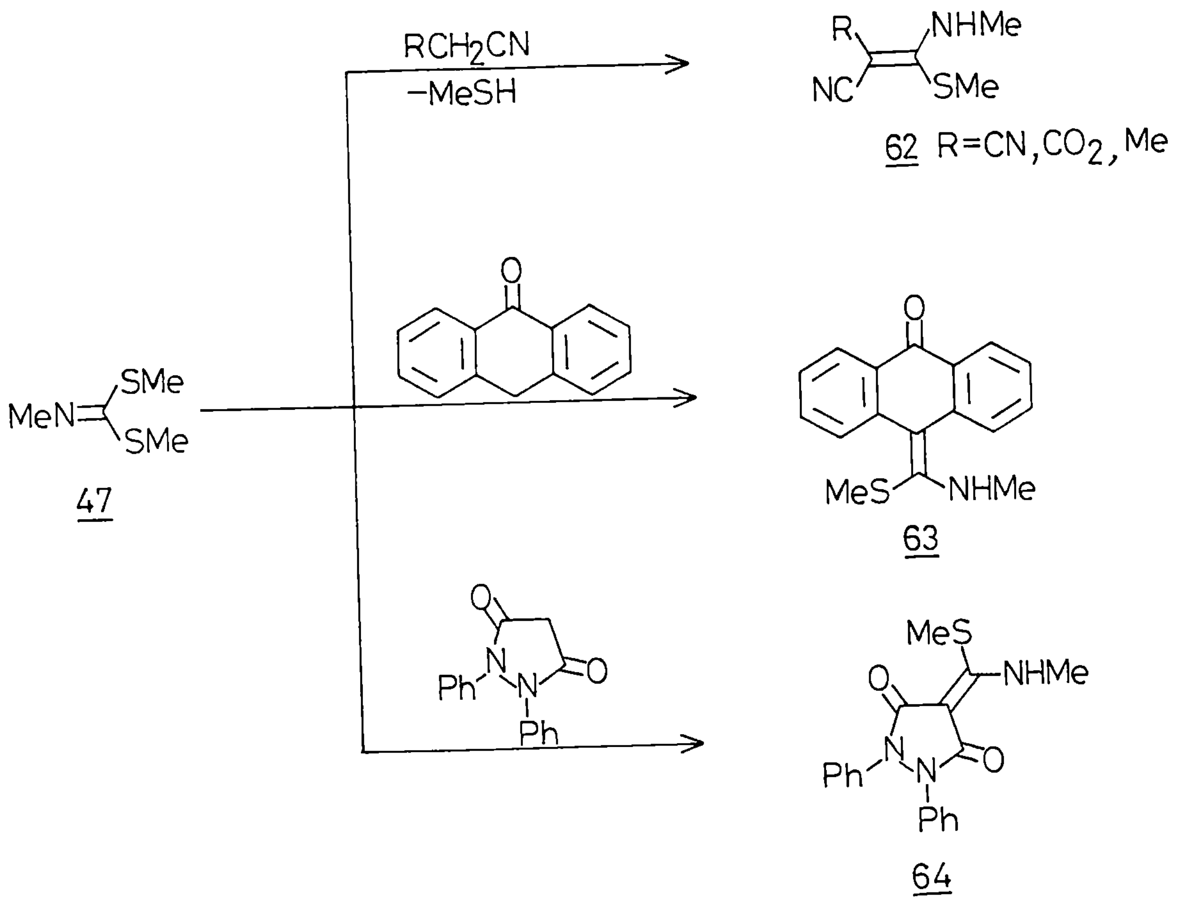

SMe
SMe
N
Me
47
+
H2N
HN
Me
57
EtOH
conc. HCl
Cl⊖
HN⊕
HN
N
Me
Me
58
NH2
N
H
59
⊖Cl
HN⊕
HN
N
Me
O
O
60
Cl⊖
HN⊕
HN
N
Me
O
61

Scheme-13

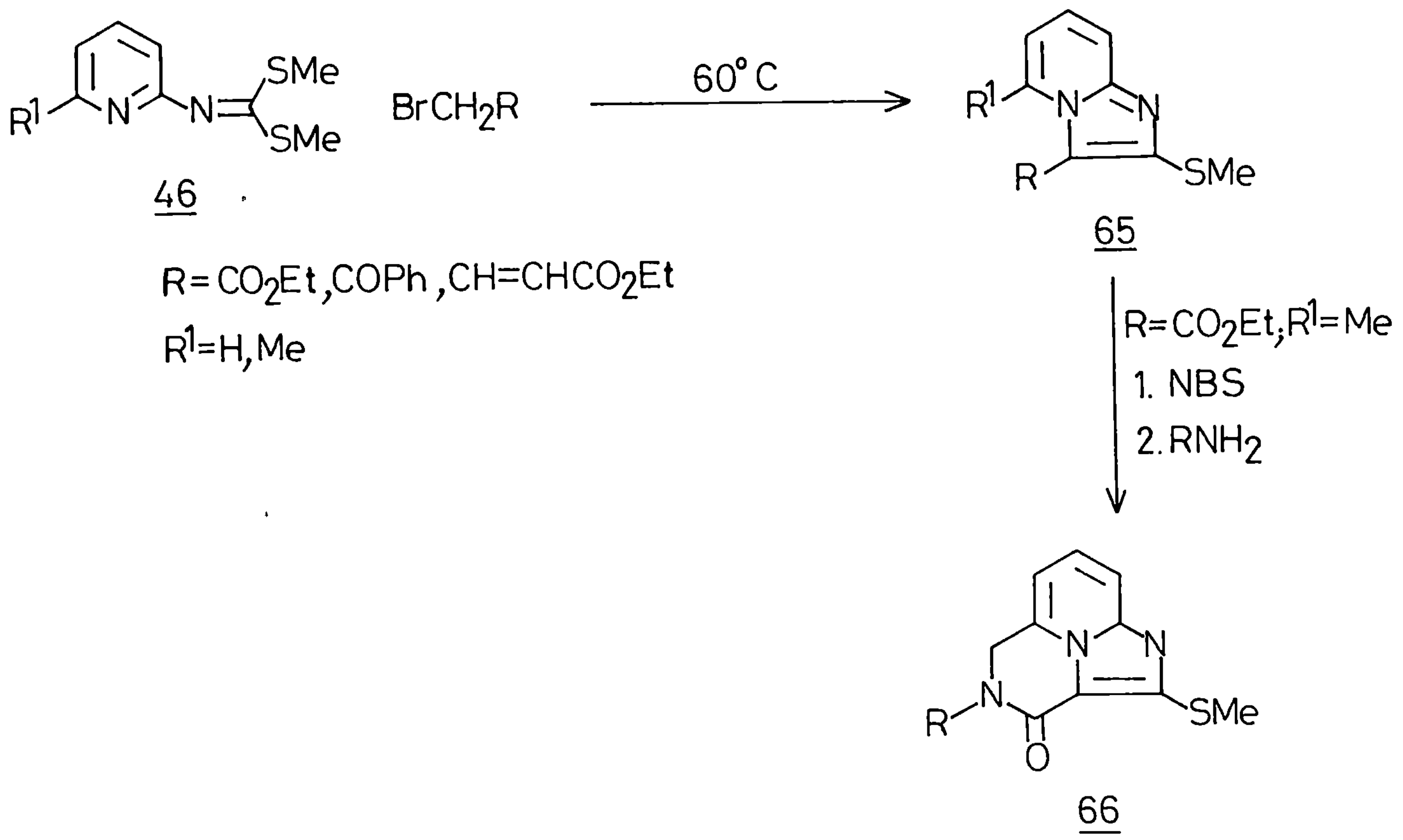
pyrimidine hydrochloride 58 in high yields. Similarly an interesting bicyclic heterocycle 2-(methylamino)-1,3-diazabicyclo[3.3.1]non-2-en-6-one hydrochloride 61 was reported to be formed by reacting 47 with 3-(aminomethyl)-4,4-ethylenedioxypiperidine 59 to yield initially ketal 60 which on hydrolysis yielded 61[33].

Carl and Wegler have reported the addition of compounds with acidic carbon hydrogen to 47 to give the corresponding S,N-acetals. Thus the active methylene compounds like malononitrile, anthrone and 1,2-diphenyl, pyrazolidine 3,5-dione gave the S,N-acetals, 3-methylamino-3-methylthio-2-cyano-methyl acrylate 62, 10-[methylamino-methylthio-methylene]9-anthrone 63 and 1,2-diphenyl-4-(methylamino-methylthio-methylene)pyrazolidine, 3,5-dione 64 respectively in good yields (Scheme 14)[34]. Similarly the carbonimidodithioate 46 derived from 2-aminopyridine reacts with haloacetate and haloketones to yield the corresponding 1-azaindolizines 65 in high yields (Scheme 15). Oxidation of 65 ($R=CO_2Et$; $R^1=H,Me$) by perphthalic acid gave the 2-methylsulfonyl derivatives. Bromination of 65 with N-bromosuccinimide followed by cyclization with ammonia and methylamine gave 66[35] in good yields. Similarly 47 also reacts with trichloroacetic acid where the trichloro carbanion generated after decarboxylation adds to the electrophilic carbon to yield the intermediate 67 which on loss of methanethiol yields the corresponding compound 68 (Scheme 16)[36].

The carbonimidodithioates are known to act as dienophiles in the cycloadditions of heterocumulenes[37]. Thus aroyl isothiocyanate 69 undergoes 4+2 cycloaddition with 47 to give oxadiazines 70 (Scheme 16).


MeN
SMe
SMe
47
RCH2CN
−MeSH
R
NHMe
NC
SMe
62 R=CN,CO2,Me
O
MeS
NHMe
63
O
N
N
Ph
Ph
O
64

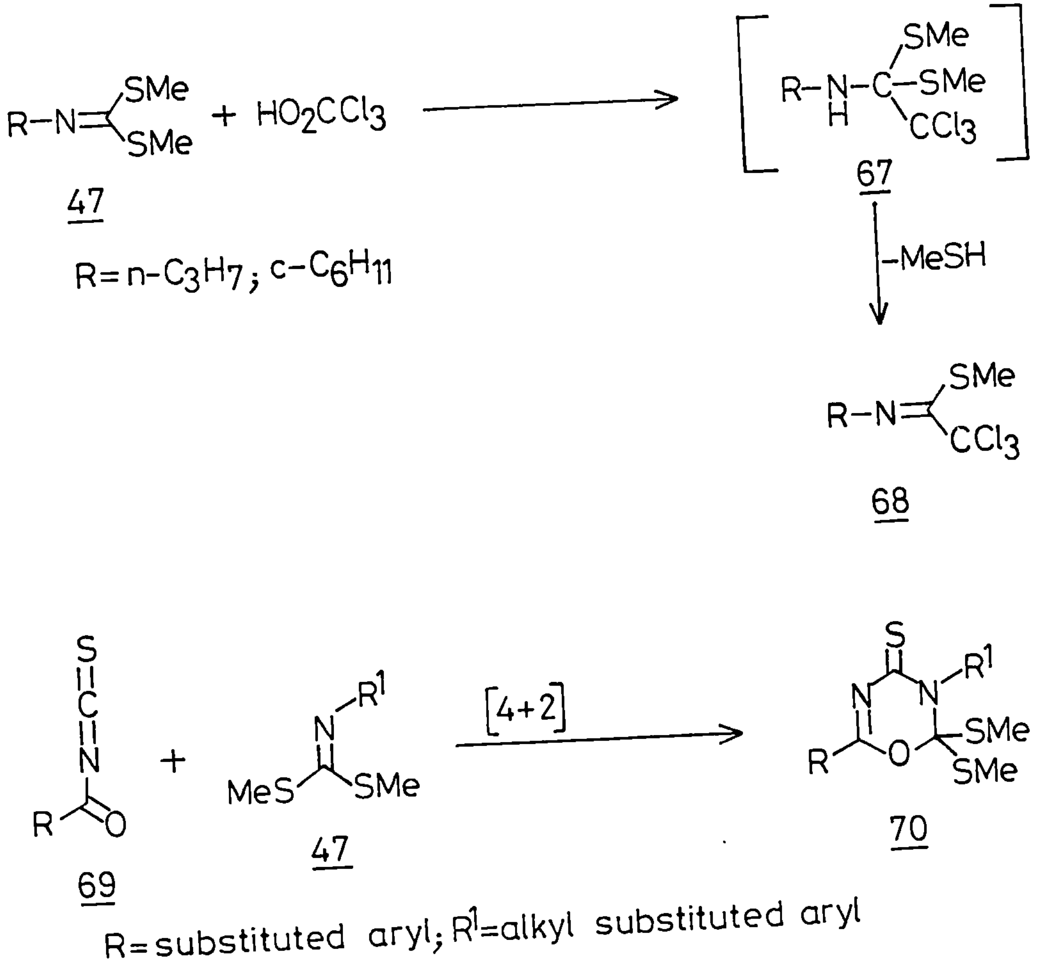
Scheme-14



$R = CO_2Et, COPh, CH{=}CHCO_2Et$

$R^1 = H, Me$

Scheme-15



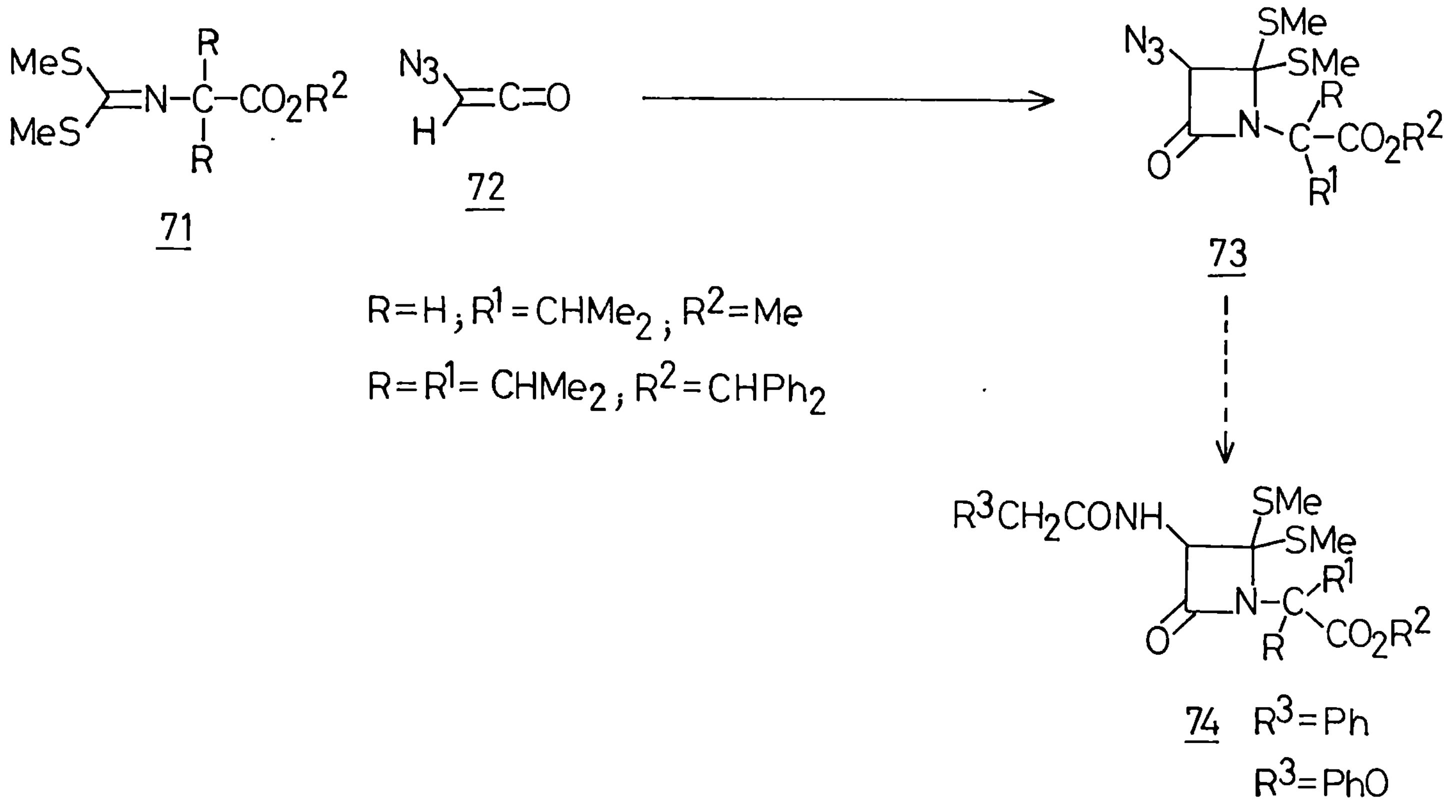
R=n-C_3H_7; c-C_6H_{11}

R=substituted aryl; R^1=alkyl substituted aryl

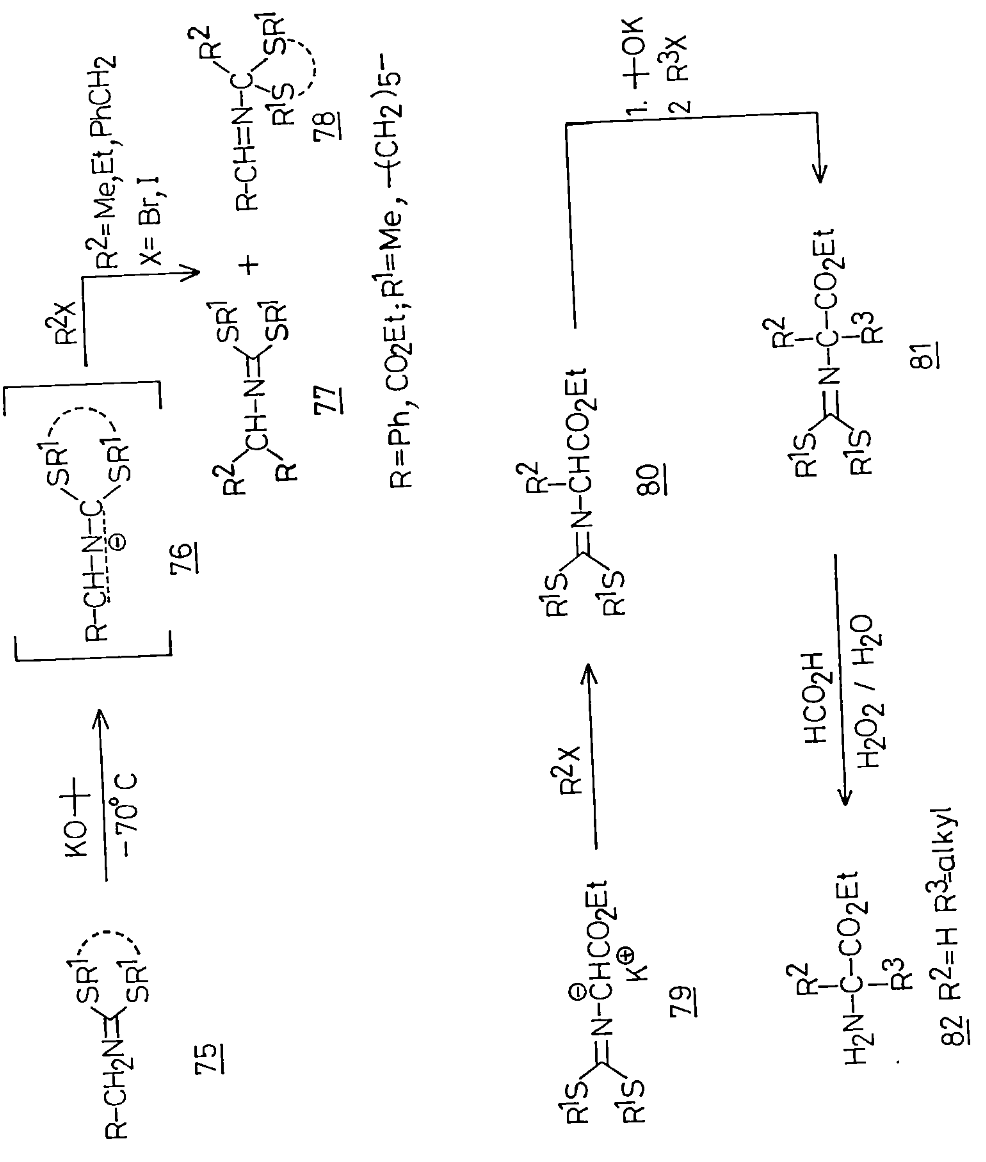
Scheme–16

The iminodithiocarbonate ester 71 derived from substituted glycinate undergoes 2+2 cycloaddition with azidoketene 72 to yield the corresponding β-lactams 73 which are subsequently transformed to 74 (Scheme 17)[38,39].

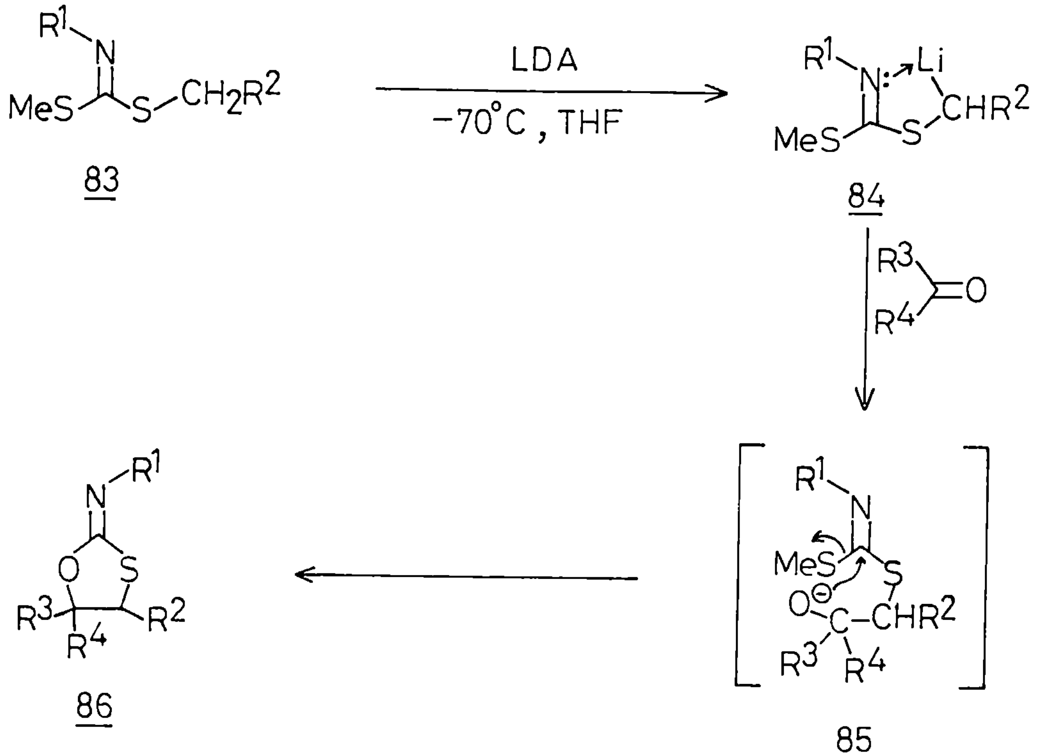
The carbonimidodithioates carrying N-arylmethylthio or alkyl group side-chain undergo deprotonation in the presence of potassium tertiary butoxide to give the corresponding ambident anions 76 which react with alkyliodides or benzylbromides with chain-extension to form the carbonic acid derivatives 77 and the isomeric orthocarboxylic acid derivative 78[40]. Dieter Hoppe has reported that the α-amino carbanions 79 obtained by the reaction of glycine ethyl esters with potassium tert-butoxide at -70°C afford chain-extended esters 80 on treatment with alkyliodides or benzylbromide between -60 and 0°C. Renewed metallation (without isolation of 80) and alkylation permits introduction of a second alkyl group to form the α-branched-α-amino acid derivatives 81. The 81 undergoes oxidative hydrolytic desulfuration with aqueous performic acid to the amino acid esters 82 (Scheme 18)[41]. Another interesting reaction of N-alkyl-iminodithiocarbamates is the metallation of S-alkylthio proton. Thus lithium diisopropylamide in tetrahydrofuran at -70°C preferentially abstracts an α-proton of the S-alkyl group from the iminocarbonic ester 83 to give [alkylimino (alkylthio)methylthio]alkyl lithium 84 which readily adds to aldehydes and ketones to yield the intermediate 85 which cyclize with the elimination of methanethiol to form 1,3-oxathiolanes 86 in good yields (Scheme 19)[42].



Scheme-17


75
76
77
78
79
80
81
82
KO-t-Bu
-70° C
R2X
R2=Me,Et,PhCH2
X= Br, I
R=Ph, CO2Et; R1=Me, -(CH2)5-
1. t-BuOK
2 R3X
HCO2H
H2O2 / H2O
82 R2=H R3=alkyl

Scheme–18



R^1= Me , Ph ; R^2= Ph; R^3= Me, Et, H, $PhCH_2$

R^4= Me, Et, CMe_3, Ph, C≡C–Ph, 2-naphthyl, hexyl, cyclopropyl

Scheme–19

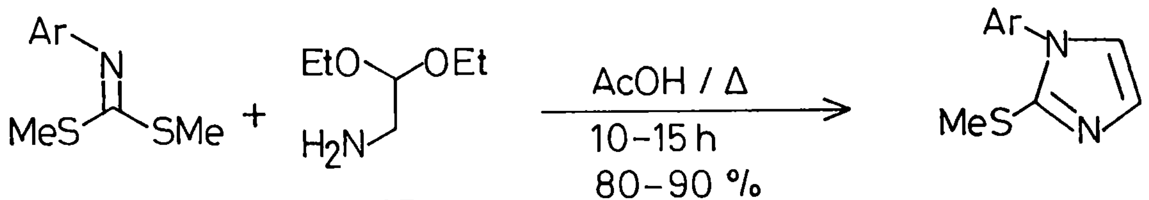
From the above brief survey it is evident that the synthetic applications of carbonimidodithioates are explored in a limited way, the applications still largely remain unexplored.

In the present investigation, the reactivity of carbonimidodithioates with aminoacetaldehyde diethyl acetal with a nucleophilic centre at one end and electrophilic centre on the other end has been studied so that the initial displacement reaction should yield an intermediate thiomethylene urea derivative which is likely to undergo intramolecular electrophilic ring closure followed by elimination of ethanol to yield the corresponding imidazole (Scheme 20).

II.4.2 RESULTS AND DISCUSSION

The required carbonimidodithiocarbonates 47a-i were prepared essentially by the reported method[27], and their structures were fully confirmed before they were reacted with 87.

In one of the typical experiments 47a was reacted with 87 in refluxing acetic acid to yield the product which was identified as 1-phenyl-2-methylthio imidazole 88a in 80% yield (Scheme 20). The imidazole has been reported earlier and it is found to be identical with that of the reported imidazole[43] (mixed m.p. superimposable i.r. and n.m.r. (see experimental section). It is of interest to note that 88a has been prepared earlier by treating N-phenylaminoacetaldehydeacetal 90 with potassiumthiocyanide 89 in the presence of dilute hydrochloric acid to yield the corresponding N-phenyl-2-mercapto-imidazole 91 in 54% yield, which on alkylation gave the thiomethyl imidazole 88a. The overall yield of 88a was 67%. The present method therefore provides



47 87 88

47, 88 a, Ar = C_6H_5
b, Ar = 4-MeC_6H_4
c, Ar = 4-$MeOC_6H_4$
d, Ar = 4-ClC_6H_4
e, Ar = 4-BrC_6H_4
f, Ar = 2-MeC_6H_4
g, Ar = 2-ClC_6H_4
h, Ar = 3-ClC_6H_4
i, Ar = 2,3,5-$(MeO)_3C_6H_2$

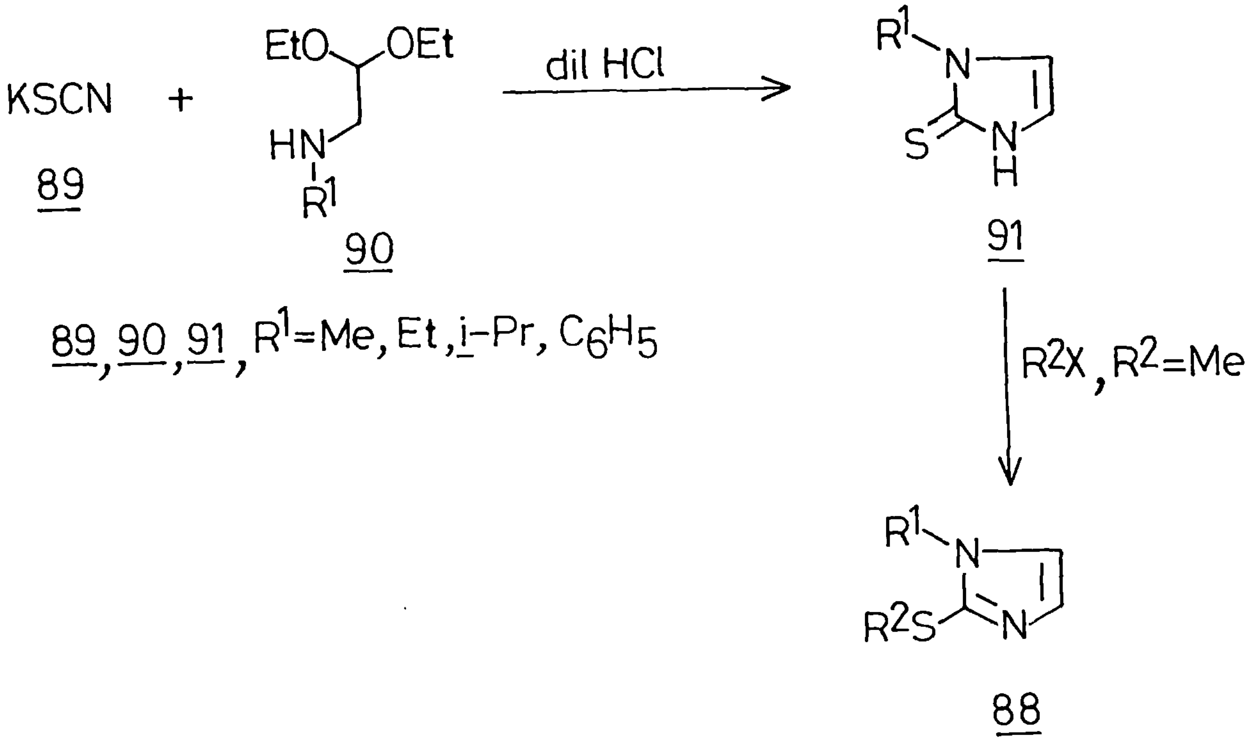
Scheme-20

improved yields of 88a in one pot reaction from easily accessable carbonimidodithioates (Scheme 21).

The reaction was found to be general for the other N-aryl-carbonimidodithioates 47b-i under similar reaction conditions and the overall yields of the corresponding N-aryl-imidazoles were around 80-90%. The analytical and spectral data are described in the experimental section. When the reaction was extended to the N-alkyl-carbonimidodithioates, 1-N-alkyl-2-methylthio imidazoles 88j-l, were obtained in good yields. However, the analogous reaction with the N-isopropyl derivative 47m afforded only 1-isopropylimidazole-2(3H)-thione 91. The desired imidazole 88m which was formed in low yield during the initial period (1h) of the reaction was found to undergo rapid demethylation to the thione 91 (monitored by TLC) probably due to steric hindrance[44]. This was further confirmed by refluxing 88m (prepared by a known procedure) in acetic acid for one hr, the thione 91 being obtained in nearly 95% yield (Scheme 22).

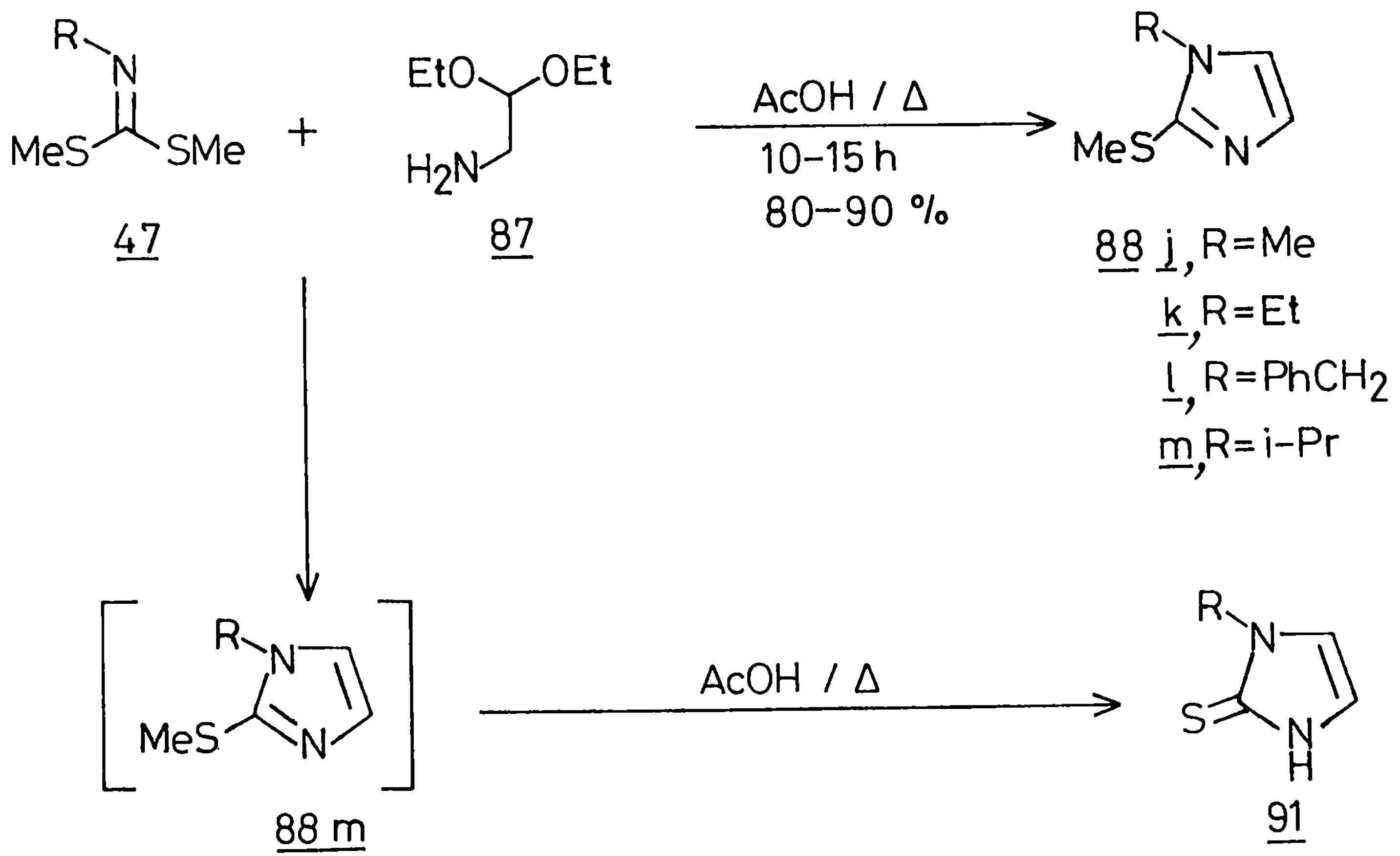
II.4.3 CONCLUSION

In summary, dimethyl N-aryl-and N-alkylcarbonimidodithioates are useful precursors of 1-aryl-, 1-methyl-, 1-ethyl- and 1-aralkyl-2-methylthioimidazoles (88a,j,k,l)which were earlier obtained by a two-step procedure involving synthesis of the corresponding imidazole-2(3H)thiones and their methylation[45-49]. The active methylthio group at position 2 of the imidazole ring can be replaced by carbon, nitrogen and oxygen nucleophiles thus widening the synthetic scope of the present method.



89, 90, 91, R^1=Me, Et, i-Pr, C_6H_5

Scheme-21


47
87
AcOH / Δ
10–15 h
80–90 %
88 j, R=Me
k, R=Et
l, R=PhCH2
m, R=i-Pr
88 m
AcOH / Δ
91

Scheme-22

II.5 EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point (capillary method) apparatus and are uncorrected. Infrared spectra were recorded on a 'Perkin-Elmer 297 spectrometer and i.r. frequencies have been reported in cm^{-1}. The ^{1}H n.m.r. spectra were recorded on a Varian EM-390, 90 MHz spectrometer and are reported in δ units downfield from Me_4Si. The mass spectra were recorded on Jeol D-300 spectrometer. and relative intensities are expressed in percentage. ^{13}C n.m.r. spectra were obtained on a Brucker WH-270 spectrometer. Carbon, hydrogen and nitrogen elemental analysis were done at RSIC, Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of acetophenone, 4-chloroacetophenone, 4-methoxyacetophenone, 4-methylacetophenone, amines, acetonitrile, dimethylformamide, pyridine chloroform, various anilines, carbondisulfide, aminoacetaldehydediethylacetal and acetic acid were purified before use. Isopropylisothiocyanate, cyclohexylisothiocyanate and (α-phenyl) ethylisothiocyanate were prepared according to the reported procedure[50,51].

The α-oxoketene S,N-acetals 37b-l were prepared according to the earlier reported procedure[52] which is given below.

General method for the preparation of S,N-acetals (37b-l):

To an ice cooled and well stirred suspension of sodium hydride (2.4g, 0.15 mol) (washed 2-3 times with dry benzene) in dry dimethylformamide (DMF) (50 ml), a solution of acetophenone (0.05 mol) in dry DMF (15ml) was added dropwise during 0.5 hr. A solution of isothiocyanate (0.05 mol) in dry DMF (25 ml) was then added and the reaction mixture was further stirred for 1.5-2 hr followed by subsequent addition of alkyl halide (0.05 mol) in DMF (15 ml). After further stirring for 2 hr. the reaction mixture was poured over crushed ice, neutralized with 20% acetic acid, extracted with chloroform (3x75 ml). The chloroform layer was washed with water (3x200 ml), dried (Na_2SO_4) and concentrated to give crude, S,N-acetals (37b-l) which were purified either by crystallization from benzene/hexane (1:1) or by passing through silica gel column using hexane/benzene (4:1) as eluent. The structures of these S,N-acetals were confirmed by their analytical and spectral data given below.

3-Isopropylamino-3-methylthio-1-phenyl-2-propen-1-one (37a); viscous liquid (TLC single spot); yield 91%; i.r. (KBr): ν_{max}= 3240, 1623, 1542 cm^{-1}; ^1H n.m.r. (CCl_4):δ 1.30[d,J=7Hz,6H,$(CH_3)_2CH$]; 2.35(s,3H, $SC\underline{H}_3$); 3.82(brm,1H$(CH_3)_2C\underline{H}$); 5.60(s,1$H_{olefinic}$); 7.04-7.41(m,3H_{arom}); 7.80-7.85(m,2H_{arom}); 11.90(brs,1H,NH,exchangeable with D_2O). (Found: C,66.21; H,7.24; N,6.00. Calc. for $C_{13}H_{17}NOS$(235.2): C,66.33; H,7.23; N,5.95%).

3-Isopropylamino-3-methylthio-1-(4-methylphenyl)-2-propen-1-one(37b); viscous liquid (TLC single spot); yield 92%; i.r.(KBr):ν_{max} = 3240, 1623, 1542 cm^{-1}; ^1H n.m.r.(CCl_4):δ1.25[d,J=7Hz,6H$(C\underline{H}_3)_2CH$]; 2.35(s, 3H,$C\underline{H}_3$); 2.33(s,3H,$SC\underline{H}_3$); 3.85[brm,1H$(C\underline{H}_3)_2CH$]; 5.45(s,1$H_{olefinic}$); 7.10(d,J=7Hz,A_2B_2,2H_{arom}); 7.75(d,J=7Hz,A_2B_2,2H_{arom});11.89(d,J=6Hz,1H,NH, exchangeable with D_2O. (Found: C,67.31; H,7.62; N,5.59. Calc. for $C_{14}H_{19}NOS$(249.35): C,67.43; H,7.67, N,5.61%).

3-Isopropylamino-3-methylthio-1-(4-methoxyphenyl)-2-propen-1-one (37c); viscous liquid (TLC single spot); yield 95%;i.r.(KBr): ν_{max} = 3239, 1613, 1522 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.30[d,J=7Hz,6H$(C\underline{H}_3)_2CH$]; 2.35(s, 3H,$SC\underline{H}_3$); 3.65(s,3H,$OC\underline{H}_3$); 3.82(brm,1H$(CH_3)_2C\underline{H}$]; 5.54(s,1H$_{olefinic}$); 6.75(d,J=7Hz,A_2B_2,2H$_{arom}$); 7.85(d,J=7Hz,A_2B_2,2H$_{arom}$); 11.85(d,J=6Hz, 1H,$N\underline{H}$,exchangeable with D_2O. (Found: C,63.20; H,7.25; N,5.20. Calc. for $C_{14}H_{19}NO_2S$ (265.35): C,63.36; H,7.21; N,5.27%).

3-Isopropylamino-3-methylthio-1-(4-chlorophenyl)-2-propen-1-one (37d); viscous liquid (TLC single spot); yield 89%; i.r.(KBr): ν_{max} = 3100, 1610, 1620, 1490 cm^{-1}; ^{1}H n.m.r.(CCl_4):δ1.22[d,J=7Hz,6H$(C\underline{H}_3)_2C\underline{H}$]; 2.32 (s,3H,$SC\underline{H}_3$); 3.82[brm,J=7Hz,1H$(C\underline{H}_3)_2CH$]; 5.42(s,1H$_{olefinic}$); 7.10-7.49 (m,2H$_{arom}$); 7.72-8.10(m,2H$_{arom}$); 11.80(brs,1H,$N\underline{H}$,exchangeable with D_2O). (Found: C,57.81; H,5.99; N,5.14. Calc. for $C_{13}H_{16}ClNOS$ (269.82): C,57.86; H,5.97; N,5.18%).

3-Isopropylamino-3-ethylthio-1-phenyl-2-propen-1-one (37e); viscous liquid (TLC single spot); yield 72%; i.r.(KBr): ν_{max} = 3200, 1600, 1620, 1542 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ1.17(t,J=7Hz,3H,$C\underline{H}_3CH_2$);1.20[d,J=7Hz,6H$(C\underline{H}_3)_2$ CH] ; 2.78(q,J=7Hz,2H,$CH_3C\underline{H}_2$); 3.90(brm, J=7Hz,1H$(CH_3)_2C\underline{H}$); 5.45(s, 1H$_{olefinic}$); 7.12-7.52(m,3H$_{arom}$); 11.88(brs,1H,$N\underline{H}$,exchangeable with D_2O). (Found: C,67.39; H,7.62; N,5.60. Calc. for $C_{14}H_{19}NOS$ (249.36): C,67.42; H,7.67; N,5.61%).

3-Cyclohexylamino-3-methylthio-1-phenyl-2-propen-1-one (37f); yellow solid; yield 83%; m.p. 79-80°C; i.r.(KBr): ν_{max} = 3400, 1540, 1470 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ1.15-2.15(m,10H,ring $C\underline{H}_2$); 2.45(s,3H,$SC\underline{H}_3$); 3.60(brm, 1H,$NC\underline{H}$); 5.51(s,1H$_{olefinic}$); 7.21-7.47(m,3H$_{arom}$); 7.68-7.90(m,2H$_{arom}$);

10.05(brs,1H,NH,exchangeable with D_2O). (Found: C,69.51; H,7.83; N,4.97. Calc. for $C_{16}H_{21}NOS$ (275.3): C,69.80; H,7.63;N,5.09%).m/z 275(M^+,25%).

3-Cyclohexylamino-3-methylthio-1-(4-methylphenyl)-2-propen-1-one (37g); pale yellow solid; yield 92%; m.p. 80°C; i.r.(KBr):ν_{max} = 1580, 1480 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.15-2.11(m,10H,ring CH_2); 2.20(s,3H,CH_3); 2.35(s,3H, SCH_3); 3.65(brm,1H,NCH); 5.52(s,1$H_{olefinic}$); 7.00-7.29(d,A_2B_2,2H_{arom}); 7.51-7.72(d,A_2B_2,2H_{arom}); 11.89(brs,1H,NH,exchangeable with D_2O). (Found: C,70.22; H,8.08; N,4.79; Calc. for $C_{17}H_{23}NOS$ (289.41): C,70.54; H,8.00; N,5.08%).

3-Cyclohexylamino-3-methylthio-1-(4-methoxyphenyl)-2-propen-1-one (37h); pale yellow solid; yield 96%; m.p. 71°C; i.r.(KBr):ν_{max} = 1600, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ1.20-2.12(m,10H,ring CH_2); 2.42(s,3H,SCH_3); 3.57(brm, 1H,NCH); 3.82(s,3H,OCH_3); 5.61(s,1$H_{olefinic}$); 6.82-7.30(m,2H_{arom}); 7.71-8.12(m,2H_{arom}); 11.90(brs,1H,NH,exchangeable with D_2O). (Found: C,63.29; H,7.19; N,5.07. Calc. for $C_{14}H_{19}NO_2S$ (265.35): C, 63.36; H,7.21; N,5.27%).

3-Cyclohexylamino-3-methylthio-1-(4-chlorophenyl)-2-propen-1-one (37i); pale yellow solid; yellow 81%; m.p. 74-75°C; i.r.(KBr):ν_{max} = 1562, 1468 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ1.81-2.21(m,10H,ring CH_2); 2.43(s,3H,SCH_3); 3.61(brm,1H,CH); 5.38(s,1$H_{olefinic}$);7.39(d,J=9Hz,2H_{arom}); 7.84(d,J=9Hz, 2H_{arom}); 11.98(brs,1H,NH,exchangeable with D_2O). (Found: C,62.29; H,6.34; N,4.70. Calc. for $C_{16}H_{20}ClNOS$ (309.7): C,62.00; H,6.46; N,4.52%). m/z 311 (M^+, 17%); 309 (M^+,45%).

3-Cyclohexylamino-3-ethylthio-1-phenyl-2-propen-1-one (37j); viscous liquid; yield 90%; m.p. 60°C; i.r.(KBr):ν_{max} = 1620, 1480 cm^{-1}; ^1H n.m.r. (CCl_4):δ1.19(t,J=6.5Hz,3H,SCH_2CH_3); 1.00-2.14(m,10H,ring CH_2); 2.82(q, J=6.5Hz,2H,SCH_2CH_3); 3.58(brm,1H,NCH); 5.52(s,$1H_{olefinic}$); 7.20-7.31 (m,$3H_{arom}$); 7.60-7.81(m,$2H_{arom}$); 11.92(brs,1H,NH,exchangeable with D_2O). (Found: C,70.32; H,8.11; N,4.85. Calc. for $C_{17}H_{23}NOS$ (289.41): C,70.54; H,8.00; N,4.83%).

3-(α-Phenyl)ethylamino-3-methylthio-1-(4-chlorophenyl)-2-propen-1-one (37k); viscous liquid; yield 80%; i.r. (KBr):ν_{max}=1600, 1480 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.49(d,J=7Hz,3H,CH_3); 2.20(s,3H,SCH_3); 4.81(brm,1H, NCH); 5.52(s,$1H_{olefinic}$); 6.92-7.49(m,$7H_{arom}$); 7.62(m,$2H_{arom}$); 12.05 (d,J=6Hz,1H,NH,exchangeable with D_2O). (Found: C,65.21; H,5.42; N,4.22. Calc. for $C_{18}H_{18}ClNOS$ (331.89): C,65.14; H,5.46; N,4.21%).

The hydroxyiminoimines 38a-m were prepared by extending the following reported procedure.

General procedure for the preparation for α-hydroxyimino-β-alkyliminoketones (38a-m):

To an ice cooled and well stirred solution of S,N-acetal 37 (10 mmol) in dry pyridine (2 ml) and dry chloroform (25 ml), a solution of nitrosyl chloride (8g, 0.012 mol) in dry ether (5 ml), was added and the mixture was further stirred for 15 min. It was then diluted with ice cold water (50 ml), extracted with chloroform (50 ml), and the chloroform extract was washed with water (3x100 ml) dried with sodium sulfate and evaporated to give hydroxyiminoimines 38a-k as colourless solids, which were further purified by crystallization using benzene. The hydroxyiminoimine 38k was found to be unstable on prolonged keeping, at room temperature, whereas 38l was not isolated in pure form for spectral and analytical data and as such used for subsequent cyclization. The structures of hydroxyiminoimines were confirmed by their spectral and analytical data which were given below.

α-Hydroxyimino- β-isopropylimino- β-methylthio-propiophenone (38a); light yellow solid; yield 75%; m.p. 155°C; i.r.(KBr): ν_{max}=3150(Br), 1650, 1598 cm^{-1}; ^{1}H n.m.r.(DMSO-d$_6$):δ1.50(d,J=7Hz,3H,$C\underline{H}_3$); 2.48(d,J=7Hz, 3H,$C\underline{H}_3$); 2.30(s,1.5H,$SC\underline{H}_3$); 2.50(s,1.5H,$SC\underline{H}_3$); 3.45(sept,J=7Hz,0.5H, $CH(CH_3)_2$; 3.95(sept,J=7Hz,0.5H,$C\underline{H}(CH_3)_2$; 7.28-7.80(m,3H$_{arom}$); 7.80-8.20 (m,2H$_{arom}$). (Found: C,58.93; H,6.37; N,10.42. Calc. for $C_{13}H_{16}N_2O_2S$ (264.3): C,59.09; H,6.06; N,10.60%).

α-Hydroxyimino- β-isopropylimino- β-methylthio-(4-methyl)propiophenone (38b); light yellow solid; yield 82%; m.p. 120°C; i.r.(KBr): ν_{max} = 3137(br), 1650, 1600 cm^{-1}; i.r.(CHCl$_3$): ν_{max} = 3133(br), 1650, 1603 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$): δ 1.20(d,J=7Hz,6H,$C\underline{H}_3$); 2.24(s,3H,$SC\underline{H}_3$); 2.35(s,3H,$C\underline{H}_3$); 3.95 [sept,J=7Hz,1H,$C\underline{H}(CH_3)_2$]; 7.03(d,J=8Hz,A_2B_2,2H$_{arom}$); 7.82(d,J=8Hz,A_2B_2, 2H$_{arom}$); 10.95(brs,1H,OH,exchangeable with D_2O). (Found: C,60.17; H,6.38; N,9.93. Calc. for $C_{14}H_{18}N_2O_2S$ (278.4): C,60.43; H,6.47; N,10.07%).

α-Hydroxyimino- β-isopropylimino- β-methylthio-(4-methoxy)propiophenone (38c); light yellow solid; yield 85%; m.p. 140°C; i.r.(KBr): ν_{max} = 3137, 1650(m), 1600 cm^{-1}; i.r.(CHCl$_3$): ν_{max} = 2132, 1646, 1600 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$): δ 1.23(d,J=6.5Hz,6H,$C\underline{H}_3$); 3.85(s,3H,$OC\underline{H}_3$); 3.90[sept,J=6.5Hz, 1H,$C\underline{H}(CH_3)_2$]; 6.80(d,J=7.5Hz,A_2B_2,2H$_{arom}$); 8.05(d,J=7.5Hz,A_2B_2,2H$_{arom}$); 10.8(brs,1H,OH,exchangeable with D_2O). (Found: C,57.08; H,6.37; N,9.39. Calc. for $C_{14}H_{18}N_2O_3S$ (294.4): C,57.14; H,6.12; N,9.52%).

α-Hydroxyimino-β-isopropylimino-β-methylthio-(4-chloro)propiophenone (38d); light yellow solid; yield 86%; m.p. 160°C; i.r.(KBr): ν_{max} = 3145, 1655, 1588 cm^{-1}; i.r.($CHCl_3$): ν_{max} = 3143(w); 1652, 1592 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 1.20(d,J=7Hz,6H,$C\underline{H}_3$); 2.22(s,3H,$SC\underline{H}_3$); 3.90(sept,J=7Hz,1H,$NC\underline{H}$); 7.10-7.53(m,$2H_{arom}$); 7.71-8.15(m,$2H_{arom}$); 11.0(brs,1H,OH,exchangeable with D_2O). (Found: C,52.27; H,5.38; N,9.54. Calc. for $C_{13}H_{15}ClN_2O_2S$ (298.8): C,52.30; H,5.03; N,9.39%).

α-Hydroxyimino-β-isopropylimino-β-ethylthio-propiophenone (38e); light yellow solid; yield 83%; m.p. 120°C; i.r.(KBr): ν_{max} = 3129, 1658, 1584 cm^{-1}; i.r.($CHCl_3$): ν_{max} = 3132, 1655, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.18(t,J=7Hz,3H,$C\underline{H}_3CH_2$); 1.20(d,J=7Hz,6H,$C\underline{H}_3$); 2.68(q,J=7Hz,2H,$CH_3C\underline{H}_2$); 3.90(sept,J=7Hz,1H,$NC\underline{H}$); 7.10-7.68(m,$3H_{arom}$); 7.25-7.96(m,$2H_{arom}$); 11.60(brs,1H,OH,exchangeable with D_2O). (Found: C,60.13; H,6.25; N,10.33. Calc. for $C_{14}H_{18}N_2O_2S$ (278.4): C,60.43; H,6.47; N,10.07%).

α-Hydroxyimino-β-cyclohexylimino-β-methylthio-propiophenone (38f); light yellow solid; yield 85%; m.p. 132°C; i.r.(KBr): ν_{max} = 3125, 1660, 1600 cm^{-1}; i.r.($CHCl_3$): ν_{max} = 3122, 1658, 1597 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.05-2.23(m,10H,ring $C\underline{H}_2$); 2.48(s,3H,$SC\underline{H}_3$); 3.55(brs,1H,$NC\underline{H}$); 7.15-7.82(m,$3H_{arom}$); 8.13-8.52(m,$2H_{arom}$); 10.90(brs,1H,OH,exchangeable with D_2O). (Found: C,65.42; H,6.32; N,9.47. Calc. for $C_{16}H_{20}N_2O_2S$ (304.4): C,65.13; H,6.57; N,9.21%).

α-Hydroxyimino-β-cyclohexylimino-β-methylthio-(4-methyl)propiophenone (38g); light yellow solid; yield 88%; m.p. 135°C; i.r.(KBr): ν_{max} = 3113, 1647, 1596 cm^{-1}; i.r.($CHCl_3$): ν_{max} = 3115(w), 1647, 1592 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 0.89-2.00(brm,10H,ring $C\underline{H}_2$); 2.18(s,3H,$C\underline{H}_3$); 2.35(s,3H,$SC\underline{H}_3$);

3.56(brs,1H,NC$\underline{H}$); 7.08(d,J=8Hz,A_2B_2,2H_{arom}); 7.86(d,J=8Hz,A_2B_2,2H_{arom}); 10.70(brs,1H,O$\underline{H}$,exchangeable with D_2O). (Found: C,64.03; H,6.83; N,8.71. Calc. for $C_{17}H_{22}N_2O_2S$ (318.4): C,64.15; H,6.91; N,8.80%).

α-Hydroxyimino-β-cyclohexylimino-β-methylthio-(4-methoxy) propiophenone (38h); colourless solid; yield 83%; m.p. 175°C; i.r.(KBr):ν_{max} = 3120, 1643(m), 1600, 1588 cm^{-1}; i.r.($CHCl_3$): ν_{max} = 3118, 1643, 1600, 1588 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ1.05-2.20 (brm,10H,ring CH_2); 2.47(s,3H,SC$\underline{H}_3$); 3.55(brs,1H,NC$\underline{H}$); 3.82(s,3H, OC$\underline{H}_3$); 6.71-7.00(m,2H_{arom}); 7.82-8.05(m,2H_{arom}); 11.80(brs,1H,O$\underline{H}$, exchangeable with D_2O). (Found: C,61.30; H,6.38; N,8.50. Calc. for $C_{17}H_{22}N_2O_3$ (334.4): C,61.07; H,6.58; N,8.38%).

α-Hydroxyimino-β-cyclohexylimino-β-methylthio-(4-chloro) propiophenone (38i); colourless solid; yield 89%; m.p. 180°C; i.r. (KBr):ν_{max} = 3271, 1647, 1608, 1588 cm^{-1}; i.r.($CHCl_3$):ν_{max} = 3275(w), 1650, 1605, 1588 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ0.9-2.10(brm,10H,ring C$\underline{H}_2$); 2.20(s,3H,SC$\underline{H}_3$); 3.53(brs,1H,NC$\underline{H}$); 7.18(d,J=7.5Hz,A_2B_2,2H_{arom}); 7.72(d,J=7.5Hz,A_2B_2,2H_{arom}); 11.65(brs,1H,O$\underline{H}$,exchangeable with D_2O). (Found: C,58.25; H,5.78; N,8.03. Calc. for $C_{16}H_{19}ClN_2O_2$ (338.9): C,58.40; H,5.60; N,8.25%).

α-Hydroxyimino-β-cyclohexylimino-β-ethylthiopropiophenone (38j); colourless solid; yield 81%; m.p. 120°C; i.r.(KBr):ν_{max} = 3150, 1660, 1590 cm^{-1}; ^1H n.m.r.(DMSO-d_6):δ1.18(t,J=6.5Hz,3H,SCH_2C$\underline{H}_3$); 0.9-2.04(brm,10H,ring C$\underline{H}_2$); 2.73(q,J=6.5Hz,1.6H,SC$\underline{H}_2CH_3$); 3.10(q, J=6.5Hz,4H,SC$\underline{H}_2CH_3$); 3.62(brs,1H,NC$\underline{H}$); 7.10-7.62(m,3H_{arom}); 7.81-8.05

(m,2H_{arom}); 11.7(brs,1H,OH,exchangeable with D_2O). (Found: C,64.45; H,7.31; N,8.51. Calc. for $C_{17}H_{22}N_2O_2S$ (318.4): C,64.15; H,6.91; N,8.80%).

α-Hydroxyimino-β-(α-phenyl)ethylimino)-β-methylthio-(4-chloro) propiophenone (38k); colourless solid; yield 86%; m.p. 110°C; i.r. (KBr): ν_{max} = 3050(w), 1647, 1592 cm^{-1}; i.r.($CHCl_3$): ν_{max} = 3047(w), 1650, 1588 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.48(d,J=7Hz,3H, $C\underline{H}_3$); 2.00(s, 3H,$SC\underline{H}_3$); 4.81(q,J=7Hz,1H,NC$\underline{H}$); 6.85-7.48(m,7H_{arom}); 7.66(d,J=9Hz, 2H_{arom}); 10.8(brs,1H,O$\underline{H}$,exchangeable with D_2O). (found: C,60.21; H,4.51; N,7.41. Calc. for $C_{18}H_{17}ClN_2O_2S$ (360.9): C,60.00; H,4.72; N,7.71%).

General procedure for the preparation of 2,2-disubstituted-4-aroyl-5-alkylthio-2*H*-imidazoles (40a-l):

A solution of hydroxyiminoimine 38 (10 mmol) in acetonitrile (25 ml) is heated in a steel bomb at 200°C for 1 h. (monitored by TLC mobile phase:ethylacetate). The mixture is cooled poured into water (100 ml), extracted with chloroform (2x100 ml), dried with sodium sulfate and concentrated to give crude imidazoles 40a-l, which are further purified by chromatography, on silica gel column using hexane/ethylacetate (20:1) as eluent. The spectral and analytical data of the imidazoles are as follows.

2,2-Dimethyl-4-benzoyl-5-methylthio-2*H*-imidazole (40a); white solid; yield 50%; m.p. 44-45°C; i.r.(KBr): ν_{max} = 1660, 1600 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 1.50(s,6H,$C\underline{H}_3$); 2.48(s,3H,$SC\underline{H}_3$); 7.20-7.55(m,3H_{arom}); 8.15-8.30(m,2H_{arom}). (Found: C,63.62; H,5.40; N,11.50. Calc. for

$C_{13}H_{14}N_2OS$ (246.3): C,63.41; H,5.69; N,11.38%). m/z 246(M^+,45%); 231(32); 199(3); 141(8); 115(10); 105(100); 100(30).

2,2-Dimethyl-4-(4-methyl)benzoyl-5-methylthio-2*H*-imidazole (40b);

white solid; yield 58%; m.p. 102°C; i.r.(KBr): ν_{max} = 1660, 1604 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.60(s,6H,$C\underline{H}_3$); 2.40(s,3H,$SC\underline{H}_3$); 2.53(s,3H,$C\underline{H}_3$); 7.28(dd,J=8Hz,A_2B_2,$2H_{arom}$); 8.10(dd,J=8Hz,A_2B_2,$2H_{arom}$). (Found: C,64.38; H,6.32; N,10.48. Calc. for $C_{14}H_{16}N_2OS$ (260.4): C,64.61; H,6.15; N,10.76% . m/z 260(M^+,46%); 245(34); 213(10); 141(8); 119(100); 115(13); 100(45).

2,2-Dimethyl-4-(4-methoxy)benzoyl-5-methylthio-2*H*-imidazole (40c);

white solid; yield 58%; m.p. 102°C; i.r.(KBr): ν_{max} = 1645, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.50(s,6H,$C\underline{H}_3$); 2.41(s,3H,$SC\underline{H}_3$); 3.80(s,3H,$OC\underline{H}_3$): 6.88(d,J=7Hz,A_2B_2,$2H_{arom}$); 8.21(d,J=7Hz,A_2B_2,$2H_{arom}$). (Found: C,60.63; H,5.90; N,10.39, Calc. for $C_{13}H_{13}ClN_2OS$ (280.8): C,60.86; H,5.79; N,10.14%). m/z 276(M^+,30%); 261(34); 229(1); 141(3); 135(100); 115(7); 100(34).

2,2-Dimethyl-4-(4-chloro)benzoyl-5-methylthio-2*H*-imidazole (40d);

white solid; yield 60%; m.p. 99-100°C; i.r.(KBr): ν_{max} = 1660, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.58(s,6H,$C\underline{H}_3$); 2.50(s,3H,$SC\underline{H}_3$); 7.48(dd,J=8Hz, A_2B_2,$2H_{arom}$); 8.25(dd,J=8Hz,A_2B_2,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$/TMS): δ 14.5($S\underline{C}H_3$); 2.41(2-$\underline{C}H_3$); 104.8($\underline{C}$-2); 128.9($\underline{C}$-3',phenyl); 131.00 ($\underline{C}$-2',phenyl); 133.4($\underline{C}$-4',phenyl C-Cl); 140.9($\underline{C}$-1',phenyl); 158.5 ($\underline{C}$-4); 163.5($\underline{C}$-5); 187.0 ppm(C=O). (Found: C,55.68; H,4.73; N,10.17. Calc. for $C_{13}H_{13}ClN_2OS$ (280.8): C,55.51; H,4.62; N,9.96%). m/z 282, 280(M^+,11,28%); 267,265(10,26); 235,233(5,13), 141(30), 141, 139(75,100), 155(11), 100(32).

2,2-Dimethyl-4-benzoyl-5-ethylthio-2H-imidazole (40e); viscous semisolid; yield 55%; i.r.(KBr): ν_{max} = 1660, 1598 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$): δ 1.35(t,J=7Hz,3H,SCH_2CH_3); 1.55(s,6H,CH_3); 3.10(q,J=7Hz, 2H,SCH_2CH_3); 7.28-7.66(m,3H_{arom}); 8.15-8.41(m,2H_{arom}). (Found: C,64.90; H,6.52; N,9.55. Calc. for $C_{14}H_{16}N_2OS$ (260.4): C,64.61; H,6.15; N,10.76%). m/z 260(M^+,16%); 245(59); 199(13); 155(48); 129(7); 105(100); 100(50).

2,2-Cyclopentamethylene-4-benzoyl-5-methylthio-2H-imidazole (40f); white solid; yield 52%; m.p. 41-42°C; i.r.(KBr): ν_{max} = 1665, 1600 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.05-2.20(m,10H,ring CH_2); 2.50(s,3H,SCH_3); 7.15-7.52(m,3H_{arom}); 8.15-8.31(m,2H_{arom}). (Found: C,67.40; H,6.52; N,9.55. Calc. for $C_{16}H_{18}N_2OS$ (286.4): C,67.13; H,6.29; N,9.79%). m/z 286(M^+,56%); 239(26); 181(26); 155(10); 140(25); 105(100).

2,2-Cyclopentamethylene-4-(4-methyl)benzoyl-5-methylthio-2H-imidazole (40g); white solid; yield 58%; m.p. 101°C; i.r.(KBr): ν_{max} = 1660, 1608 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.10-2.15(m,10H,ring CH_2); 2.40(s,3H,SCH_3); 2.55(s,3H,CH_3); 7.18(dd,J=7Hz,A_2B_2,2H_{arom}); 8.10 (dd,J=7.5Hz,A_2B_2,2H_{arom}). (Found: C,67.81; H,6.48; N,9.64. Calc. for $C_{17}H_{20}N_2OS$ (300.4): C,68.00; H,6.66; N,9.33%). m/z 300(M^+,54%); 253 (21); 181(15); 155(5); 140(24); 119(100).

2,2-Cyclopentamethylene-4-(4-methoxy)benzoyl-5-methylthio-2H-imidazole (40h); viscous semisolid; yield 57%; i.r.(KBr): ν_{max}= 1655, 1596 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.20-2.18(brs,10H,ring CH_2); 2.45(s, 3H,SCH_3); 3.83(s,3H,OCH_3); 6.86(d,J=9Hz,A_2B_2,2H_{arom}). (Found: C,64.34; H,6.52; N,8.51. Calc. for $C_{17}H_{20}N_2O_2S$ (316.4): C,64.55; H,6.32; N,8.86%). m/z 316(M^+,38%); 269(8); 181(16); 155(22); 140(95); 135(100).

2,2-Cyclopentamethylene-4-(4-chloro)benzoyl-5-methylthio-2H-imidazole (40i); white solid; yield 59%; m.p. 106°C; i.r.(KBr): ν_{max} = 1668, 1595 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.30-2.10(m,10H,ring $C\underline{H}_2$); 2.50(s,3H,$SC\underline{H}_3$); 7.46(d,J=8.5Hz,A_2B_2,$2H_{arom}$); 8.25(d,J=8.5Hz, A_2B_2,$2H_{arom}$). (Found: C,59.92; H,5.45; N,8.43. Calc. for $C_{16}H_{17}ClN_2OS$(320.8): C,59.80; H,5.29; N,8.72%). m/z 322, 320(M^+, 14,40%); 275, 273(8,19); 181(80); 155(14); 140(80); 141,139(40,100).

2,2-Cyclopentamethylene-4-benzoyl-5-ethylthio-2H-imidazole (40j); viscous semisolid; yield 56%; i.r.(KBr): ν_{max} = 1660, 1596 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.40(t,J=7Hz,3H,$SCH_2C\underline{H}_3$); 1.40-2.20(brs,10H, ring CH_2); 3.10(q,J=7Hz,2H,$SC\underline{H}_2CH_3$); 7.20-7.68(m,$3H_{arom}$); 8.13-8.35 (m,$2H_{arom}$). (Found: C,68.28; H,6.39; N,9.66. Calc. for $C_{17}H_{20}N_2OS$ (300.4): C,68.00; H,6.66; N,9.33%). m/z 300(M^+,28%); 239(12); 195(35); 169(17); 141(15); 105(100).

2-Phenyl-2-methyl-4-(4-chloro)benzoyl-5-methylthio-2H-imidazole (40k); white solid; yield 58%; m.p. 95°C; i.r.(KBr): ν_{max} = 1660, 1580 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.75(s,3H, $C\underline{H}_3$); 2.58(s,3H, $C\underline{H}_3$); 7.12-7.78(m, $7H_{arom}$); 8.26(d,J=9Hz,A_2B_2,$2H_{arom}$). (Found: C,63.44; H,4.52; N,8.48. Calc. for $C_{18}H_{15}ClN_2OS$ (342.8): C,63.15; H,4.38; N,8.18%); m/z 344, 342(M^+,20,50%); 297, 295(33,70); 203(55); 177(56); 162(57); 141, 139(27,58).

2-Phenyl-2-methyl-4-benzoyl-5-methylthio-2H-imidazole (40l); white solid; yield 55%; m.p. 87°C; i.r.(KBr): ν_{max} = 1655, 1593 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.75(s,3H,$C\underline{H}_3$); 2.70(s,3H,$SC\underline{H}_3$); 7.05-7.92(m, $8H_{arom}$); 8.15-8.38(m,$2H_{arom}$). ^{13}C n.m.r.($CDCl_3$/TMS): δ 14.6($S\underline{C}H_3$);

27.5(2-$\underline{C}H_3$); 108.1($\underline{C}$-2); 126.8; 127.8; 128.3; 128.5, 130.6($\underline{C}$-2', $\underline{C}$-3', $\underline{C}$-4' of phenyl and $\underline{C}$-2',$\underline{C}$-3' of 4-benzoyl); 134.2($\underline{C}$-4' of 4-benzoyl); 135.1($\underline{C}$-1' of 2-phenyl); 139.8($\underline{C}$-1' of 4-benzoyl); 158.7 ($\underline{C}$-4); 164.5($\underline{C}$-5); 188.2 ppm(C=O). (Found: C,70.44; H,5.49; N,9.41. Calc. for $C_{18}H_{16}N_2OS$ (308.4): C,70.12; H,5.19; N,9.09%). m/z 308 (M^+,5%); 261(10); 203(64); 177(70); 162(80); 105(100).

II.6 The dimethyl-N-aryl-and N-alkyl carbonimidodithioates were prepared according to the reported procedure[25-28].

General procedure for the preparation of 1-N-aryl and 1-N-alkyl-2-methylthioimidazoles (88a-l):

A solution of the dimethyl N-aryl-or N-alkyl carbonimidodithioate 47 (10 mmol) and aminoacetaldehyde diethylacetal 87(2g, 15 mmol) in acetic acid (10 ml) was heated to boiling for 10-15 hr. Then acetic acid was removed under vacuum and the residue was dissolved in $CHCl_3$ (50 mL). This solution was washed with H_2O (3x30 mL), dried (Na_2SO_4), and evaporated to give the crude product 88 which was purified by column chromatography on silica gel using EtOAc/hexane (1:4) as eluent and crystallized from CH_2Cl_2.

The structures of the imidazoles were confirmed by their spectral and analytical data which are given below.

The products 88j-l[43,48] were characterized by comparison of their i.r. and ^1H n.m.r. spectral data with reported values as well as by mass spectra and micro analyses.

1-Phenyl-2-methylthioimidazole (88a); white solid, reaction time 10h; yield 80%; m.p. 55°C; lit. m.p. 53-54°C. (Found: C,63.38; H,5.45;

N, 14.97. Calc. for $C_{10}H_{10}N_2S$ (190.1): C,63.15; H, 5.26; N,14.76%). m/z 190(100%).

1-(4-Methylphenyl)-2-methylthioimidazole (88b); white solid; reaction time 10h; yield 89%; m.p. 75°C; i.r.(KBr): ν_{max} = 3160, 3010, 1510, 1440 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.39(s,3H,$C\underline{H}_3$); 2.54(s,3H,$SC\underline{H}_3$); 7.00 (s,1H,$\underline{H}$-4); 7.03(s,1H,$\underline{H}$-5); 7.31(s,4H_{arom}). (Found: C,64.99; H,5.71; N,13.90. Calc. for $C_{11}H_{12}N_2S$ (204.2): C,64.70; H,5.88; N,13.72%), m/z 204(M^+,61%).

1-(4-Methoxyphenyl)-2-methylthioimidazole (88c); white solid; reaction time 11h; yield 85%; m.p. 100°C; i.r.(KBr): ν_{max} = 3120, 3000, 1510, 1442 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.45(s,3H,$SC\underline{H}_3$); 3.76(s,3H,$OC\underline{H}_3$); 6.70-7.29(m,6H,$\underline{H}$-4, $\underline{H}$-5, 4H_{arom}). (Found: C,60.28; H,5.61; N,12.90. Calc. for $C_{11}H_{12}N_2OS$ (220.2): C,60.00; H,5.45; N,12.72%). m/z 220 (M^+,60%).

1-(4-Chlorophenyl)-2-methylthioimidazole (88d); white solid; reaction time 10h; yield 81%; m.p. 110-112°C; i.r.(KBr): ν_{max} = 3120, 2900, 1480, 1435 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.50(s,3H,$SC\underline{H}_3$); 7.98(s,1H,$\underline{H}$-4); 7.07(s,1H,$\underline{H}$-5); 7.32(m,4H_{arom}). (Found: C,53.65; H,4.24; N,12.26. Calc. for $C_{10}H_9ClN_2S$ (224.6): C,53.42; H,4.00; N,12.46%). m/z 224, 226(M^+,100,96%).

1-(4-Bromophenyl)-2-methylthioimidazole (88e); white solid; reaction time 10h; yield 90%; m.p. 97°C; i.r.(KBr): ν_{max} = 3095, 2925, 1481, 1440 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.50(s,3H,$SC\underline{H}_3$); 7.00(s,1H,$\underline{H}$-4); 7.05 (s,1H,$\underline{H}$-5); 7.00-7.65(m,4H_{arom}). (Found: C,44.78; H,3.42; N,10.48. Calc. for $C_{10}H_9BrN_2S$ (269.1): C,44.59; H,3.34; N,10.40%). m/z 268,270 (M^+,35,10%).

1-(2-Methylphenyl)-2-methylthioimidazole (88f); oil; reaction time 15 h. yield 82%; i.r.(KBr):ν_{max} = 3102, 3024, 1490, 1458 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$):δ2.51(s,3H,SC$\underline{H}_3$); 6.81(s,1H,$\underline{H}$-4); 6.96(s,1H,$\underline{H}$-5); 7.0 -7.40(m,4H$_{arom}$). (Found: C,69.91; H,5.97; N,13.97. Calc. for $C_{11}H_{12}N_2S$ (204.2): C,64.70; H,5.88; N,13.72%). m/z 204(M$^+$,38%).

1-(2-Chlorophenyl)-2-methylthioimidazole (88g); oil; reaction time 16h. yield 83%: i.r.(KBr):ν_{max} = 3100, 3051, 1590, 1480, 1435 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$):δ2.50(s,3H,SC$\underline{H}_3$); 6.84(s,1H,$\underline{H}$-4); 6.94(s,1H,$\underline{H}$-5); 7.0-7.55(m,4H$_{arom}$). (Found: C,53.63; H,4.22; N,12.21. Calc. for $C_{10}H_9ClN_2S$ (224.6): C,53.42; H,4.00; N,12.46%). m/z 224, 226(M$^+$, 80, 35%).

1-(3-Chlorophenyl)-2-methylthioimidazole (88h); white solid; reaction time 10h. yield 80%; m.p. 45°C; i.r.(KBr):ν_{max}= 3108, 3092, 1590, 1482, 1473 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$):δ2.51(s,3H,SC$\underline{H}_3$): 6.90(s,2H,$\underline{H}$-4 and $\underline{H}$-5); 7.00-7.35(m,4H$_{arom}$). (Found: C,53.29; H,4.29; N,12.16. Calc. for $C_{10}H_9ClN_2S$ (224.6): C,53.42; H,4.00; N,12.46%). m/z 224, 226(M$^+$,81, 79%).

1-(2,4,5-trimethoxyphenyl)-2-methylthioimidazole (88i); white solid; reaction time 10h. yield 81%; m.p. 120°C; i.r.(KBr):ν_{max} = 3110, 3095, 1595, 1509, 1443 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$):δ2.51(s,3H,SC$\underline{H}_3$); 3.71(s,3H,OC$\underline{H}_3$); 3.73(s,6H,OC$\underline{H}_3$); 6.50(s,2H,$\underline{H}$-4 and $\underline{H}$-5); 6.90(s, 2H$_{arom}$). (Found: C,55.92; H,5.59; N,10.28. Calc. for $C_{13}H_{16}N_2O_3S$ (280.1): C,55.71; H,5.71; N,10.00%). m/z 280(M$^+$,93%).

1-Methyl-2-methylthioimidazole (88j); oil; reaction time 11h. yield 80%. (Found: C,46.61; H,5.58; N,22.22. Calc. for $C_5H_8N_2S$ (128.0): C,46.87; H,6.25; N,21.87%). m/z 128 (M^+,100%).

1-Ethyl-2-methylthioimidazole (88k); oil; reaction time 12h. yield 80%. (Found: C,50.42; H,7.31; N,19.98. Calc. for $C_6H_{10}N_2S$ (142.0): C,50.70; H,7.04; N,19.71%). m/z 142 (M^+,100%).

1-Benzyl-2-methylthioimidazole (88l); oil; reaction time 15h, yield 85%; i.r.(KBr): ν_{max} = 3100, 3058, 1492, 1450, 1425 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 2.52(s,3H,SC$\underline{H}_3$); 5.00(s,2H,$C_6H_5C\underline{H}_2$); 6.72(s,1H,$\underline{H}$-4); 6.90 (s,1H,$\underline{H}$-5): 6.90-7.30(m,5H_{arom}). (Found: C,64.46; H,6.96; N,13.46. Calc. for $C_{11}H_{12}N_2S$ (204.21): C,64.70; H,5.89; N,13.70%) m/z 204(M^+,100%).

1-Isopropylimidazole-2(3H)-thione; General procedure:

A solution of dimethyl N-isopropylcarbonimidodithioate 87m (1.50g, 15 mmol) in acetic acid (10 mL) is heated to boiling for 20h. until compound 87m has been consumed completely (TLC, EtOAc/benzene 1:4) work-up as in general procedure gives the thione 89 as pale coloured crystals (from CH_2Cl_2); 100g(75%); m.p. 169-70°C (Lit. m.p. 168-69°C, superimposable i.r. and n.m.r. spectra. (Found: C, 51.25; H,6.56; N,19.61. Calc. for $C_6H_9N_2S$ (141.13): C,51.05; H,6.42; N,19.83%). m/z 141 (M^+,60%).

REFERENCES

1. S.M.S. Chauhan, H. Junjappa, Synthesis, 880 (1974).
2. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 1911 (1976).
3. S.M.S. Chauhan, H. Junjappa, Synthesis, 789 (1975).
4. R.R. Rastogi, A. Kumar, H. Ila, H. Junjappa, J. Chem. Soc. Chem. Commun., 645 (1975).
5. A. Kumar, H. Ila, H. Junjappa, J. Chem. Soc. Chem. Commun., 592 (1976).
6. A. Kumar, H. Ila, H. Junjappa, Synthesis, 324 (1976).
7. R.R. Rastogi, A. Kumar, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I, 549 (1978).
8. A. Kumar, H. Ila, H. Junjappa, J. Chem.Soc. Perkin Trans.I., 857 (1978).
9. R. Gompper, H. Schaefer, Chem. Ber.,100, 591 (1967).
10. V. Aggarwal, G. Singh, H. Ila, H. Junjappa, Synthesis, 214 (1982).
11. A. Rahman, J.N. Vishwakarma, R.D. Yadav, H. Ila, H. Junjappa, Synthesis, 247 (1984).
12. A. Rahman, H. Ila, H. Junjappa, J. Chem. Soc. Chem. Commun.,430 (1984).
13. For a recent review on 2H-imidazoles see: Sammes, M.P. Katritzky,A.R., in: Advances in Heterocyclic Chemistry, Katritzky, A.R., ed., Vol. 35, Academic Press, New York, 1984, p. 347, 381.
14. H. Fuchs, M. Gottlieb, W. Pfleiderer, Chem. Ber.,111, 982 (1978).
15. E. Bohler and W. Pfleiderer, Angew. Chem. Int. Ed.,4, 146 (1965).
16. W. Pfleiderer and G. Nubel, Liebeg Ann. 631, 168 (1960).
17. A. Rahman, R.T. Chakrasali, H. Ila, H. Junjappa, Ind. J. Chem., 24B, 463 (1985).
18. H. Goldner, G. Dietz and E. Carstens, Liebigs Ann. Chim, 692, 134 (1966).
19. F. Asinger, D. Neuray, A. Saus, J. Graber, U. Lames, Monatshefte Chemie, 103, 406 (1972).

20. M. Weiss, J. Am. Chem. Soc, 74, 5193 (1952).

21. R.W. Begland, D.R. Hartter, J. Org. Chem., 37, 4136 (1972).

22. J.H.M. Hall, T.R. Fogg, H. Guttmann, J. Org. Chem., 40, 2562 (1975).

23. P.C. Cherry, W.R.T.Cottrell, G.D. Meakins, E.E. Richards, J. Chem. Soc., 459 (1968).

24. G.O. Dubek, R.H. Holm, J. Am. Chem. Soc., 84, 2691 (1962).

25. J. Garin, V. Martinez, J. Mayoral, E. Melendez, F. Merchan, Synthesis, 961 (1981).

26. J. Garin, E. Melendez, F.L. Merchan, C. Tejel, T. Tejero, Synthesis, 375 (1983).

27. Liden N, J. Sandstrom, Tetrahedron, 27, 2893-2901 (1971).

28. Delepine, M. Bull. Soc. Chim, Fr.,3, 27, 807 (1902).
Fromm, E., Block M. Ber. Dtsch. Chem. Ges., 32, 2219 (1899).

29. R. Gompper, W. Hagele, Chem. Ber.,99, 2885 (1966).

30. T. Suyama, K. Odo, J. Synth. Org. Chem. Japan, 29, 65 (1971).

31. M. Sato, N. Fukada, M. Kurauchi, T. Takeshima, Synthesis, 554 (1981).

32. T. Nakai, Y. Ueno, M. Okawara, Bull. Chem. Soc. Japan, 43, 156, 162(1970).

33. R.A. Houghten, R.A. Simpson, R.N. Hanson, H. Rapport, J. Org. Chem., 44, 4536 (1979).

34. C. Metzer, R. Wegler, Chem. Ber., 101, 1131 (1968).

35. K. Kurata, H. Awaya, Y. Tominaga, Yoshinori, Matsuda, Chem. Abs., 90, 22892 (1979).

36. C. Metzer, R. Wegler, Chem. Abs., 68, 86828q. (1968).

37. K. Milzner, K. Seckinger, Helv. Chim. Acta, 57, 1614 (1974).

38. D.F. Sullivan, D.Scopes, A.F. Kluge, J.A. Edwards, J. Org. Chem., 41, 1112 (1976).

39. C. Metzer, R. Wegler, Chem. Ber.,101, 1120 (1968).

40. D. Hoppe, Angew. Chem. Inter. Ed., 14, 424 (1975).

41. D. Hoppe, Angew. Chem. Inter. Ed., 426 (1975).

42. D. Hoppe, R. Follmann, Liebigs Ann. Chem.,1779 (1980).

43. J. Kister, G. Assef, J. Metzger, Can. J. Chem., 57, 813 (1979).

44. J. Kister, G. Assef, G. Mille, G. Metzger, Can. J. Chem. 57, 822 (1979).

45. M.R. Grimmet, in: Comprehensive Heterocyclic Chemistry, Vol. 5, Part 4A, K.T. Potts,(ed), Pergamon Press, Oxford, 1984 p. 473.

46. G. Reuben, E. Kornfeld, K.C. Mclaughlin, R.C. Anderson, J. Am. Chem. Soc., 71, 4000 (1949).

47. W.N. Cannon, C. E. Powell, R.G. Jones, J. Org. Chem.,22, 1323 (1957).

48. I.B. Simon, I.I. Kovtunovskaya, Endokrinol, 18, 355 (1961); Chem. Abs. 58, 7921 (1963).

49. P. Hassanaly, H.J.M. Dori, J. Metzger, Synthesis, 253 (1977).

50. A text book of Practical Organic Chemistry by A.I. Vogel, pp. 736, ELBS and Longman (1978).

51. J.E. Hodgrins,M.G. Ettlinger; J. Org. Chem, 21, 404 (156).

52. A. Kumar, V. Aggarwal, H. Ila, H. Junjappa, Synthesis, 748 (1980).

CHAPTER III

CYCLOAROMATIZATION OF α-OXOKETENE DITHIOACETALS WITH 3-METHYL-5-LITHIOMETHYL ISOXAZOLE: A NEW GENERAL METHOD FOR THE SYNTHESIS OF SUBSTITUTED AND ANNELATED 1,2-BENZISOXAZOLES*

III.1 INTRODUCTION

The α-oxoketene dithioacetals have been a subject of intense investigation in this laboratory. They possess 1,3-electrophilic centres with differential electrophilicity and undergo either 1,2- or 1,4-regioselective additions depending on the nature of the nucleophiles[1]. The differential reactivity pattern has been fully exploited by a number of workers leading to many novel transformations

---

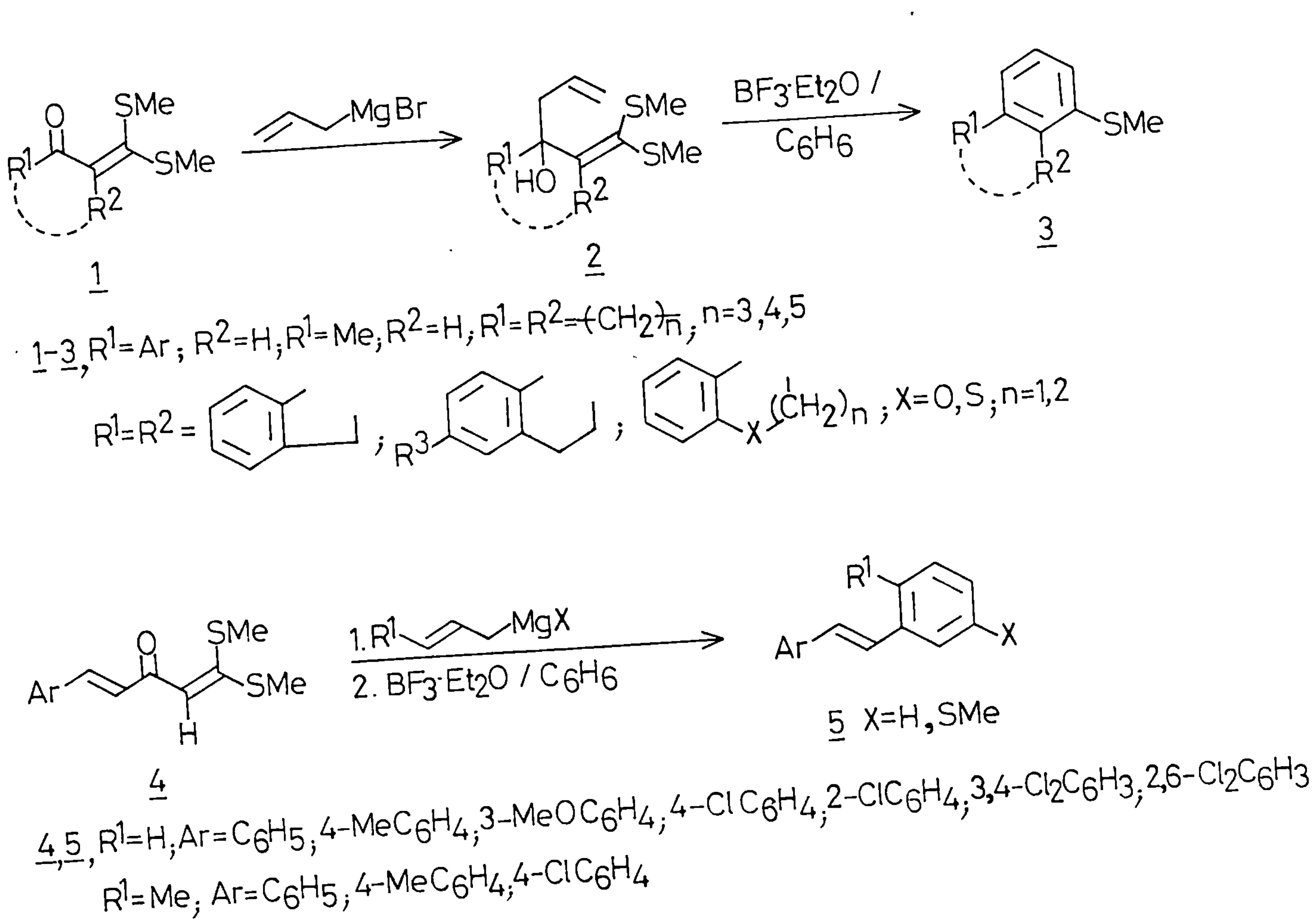
* D. Pooranchand, M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett., 501 (1988).

involving new C-C bond formation. Thus the organomanganesium reagents have been shown to undergo both 1,2- or 1,4-addition[2], whereas various organolithium compounds exhibit high regioselectivity yielding compounds arising through 1,2-additions[3]. Also the organocuprates have been shown to add in a regioselective 1,4-manner[4].

The foregoing discussion displays the reports on C-C bond forming reactions via α-oxoketene dithioacetals, which results in ring forming reactions leading to aromatic and heteroaromatic systems. The general strategy involves 1,2-addition of a suitable carbon nucleophile to α-oxoketene dithioacetals to give the allylic alcohols which on subsequent Lewis acid assisted cationic cyclization form six membered ring followed by aromatization. The overall reaction can be generally termed as aromatic annelation or cycloaromatization. The present method involves the union of two three atom fragments one with 1,3-electrophilic and other with 1,3-nucleophilic centres.

The α-oxoketene dithioacetals <u>1</u> were shown to undergo facile 1,2-reduction with sodiumborohydride to give the intermediate alcohols which undergo facile solvolysis in the presence of boron trifluoride etherate to give the corresponding ene esters[5]. The ene ester synthesis was further extended to the addition of alkyl and arylmagnesium halides to study the scope of the method[2]. Interestingly when allylmagnesium bromide was added to α-oxoketene dithioacetals <u>1</u>, exclusive 1,2-addition took place to afford the corresponding alcohol acetals <u>2</u> in nearly quantitative yields, which were shown to undergo intramolecular cationic cycloaromatization to the aromatic compounds <u>3</u>[6]. The reaction appears to proceed through intramolecular π-participation of the allylic double bond to form a cationic species which on elimination of methyl mercaptan yield the aromatized product 3 (Scheme 1). The formation of these benzenoids from the α-oxoketene dithioacetals derived from wide structural variants of active methylenes ketones, provides unique one pot reaction to yield regiospecifically substituted aromatic ring systems. The method has been shown to be general for both aliphatic and aromatic substituents in the open-chain precursors. The oxoketene dithioacetals derived from fused ring systems yield the corresponding condensed aromatic systems in identical yields. Similarly the reaction of α-cinnamoylketene dithioacetals 4 with allyl and crotyl magnesium bromide is also reported to give regiospecifically substituted trans stilbenes 5 in good yields (Scheme 1)[7]. This approach of stilbene synthesis is of considerable synthetic importance for it allows one of the benzene rings with appropriate, substituents suitably placed in the open-chain precursors.

A benzoannelation approach for the synthesis of fused thioresorcinol dimethylethers is also reported[8] by the reaction of propargyl magnesium bromide with α-oxoketene dithioacetals 1 prepared from cyclic ketones. It was considered of interest that the cyclization proceeds by the intramolecular participation of the propargyl triple bond in the carbinol acetal 6 with concommitant attack of methanol on the incipient vinyl cation, followed by loss of methyl mercaptan to yield the thioresorcinol dimethylethers 7 in good yields (Scheme 2). However when the oxoketene dithioacetal derived from cyclopentanone 8 was reacted with



1 2 3

1-3, R^1=Ar; R^2=H; R^1=Me; R^2=H; R^1=R^2=$-(CH_2)_n-$; n=3,4,5

R^1=R^2= ; R^3 ; ; $(CH_2)_n$; X=O,S; n=1,2

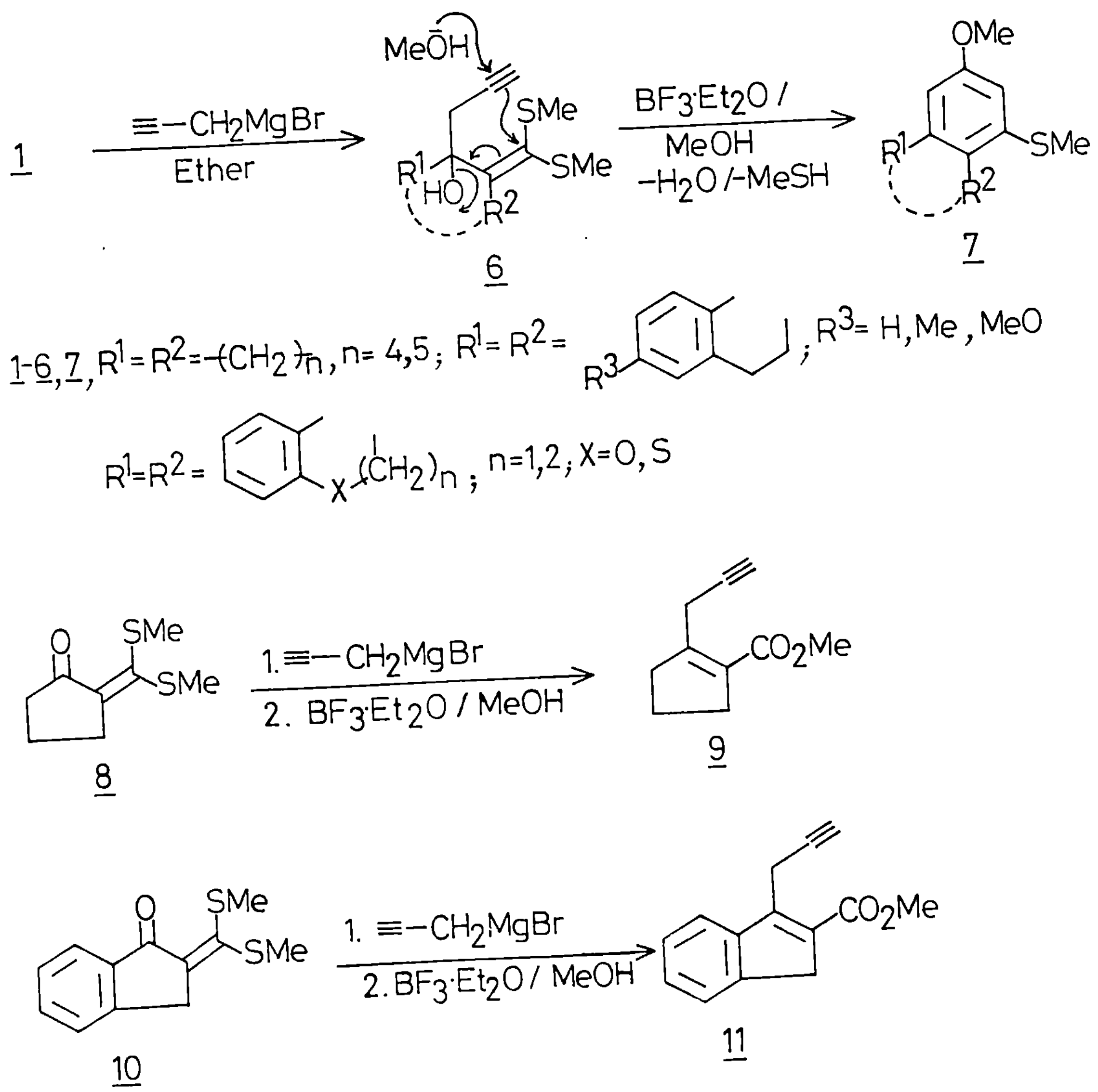
4

5 X=H, SMe

4,5, R^1=H; Ar=C_6H_5; 4-MeC_6H_4; 3-MeOC_6H_4; 4-ClC_6H_4; 2-ClC_6H_4; 3,4-$Cl_2C_6H_3$; 2,6-$Cl_2C_6H_3$

R^1=Me; Ar=C_6H_5; 4-MeC_6H_4; 4-ClC_6H_4

Scheme-1

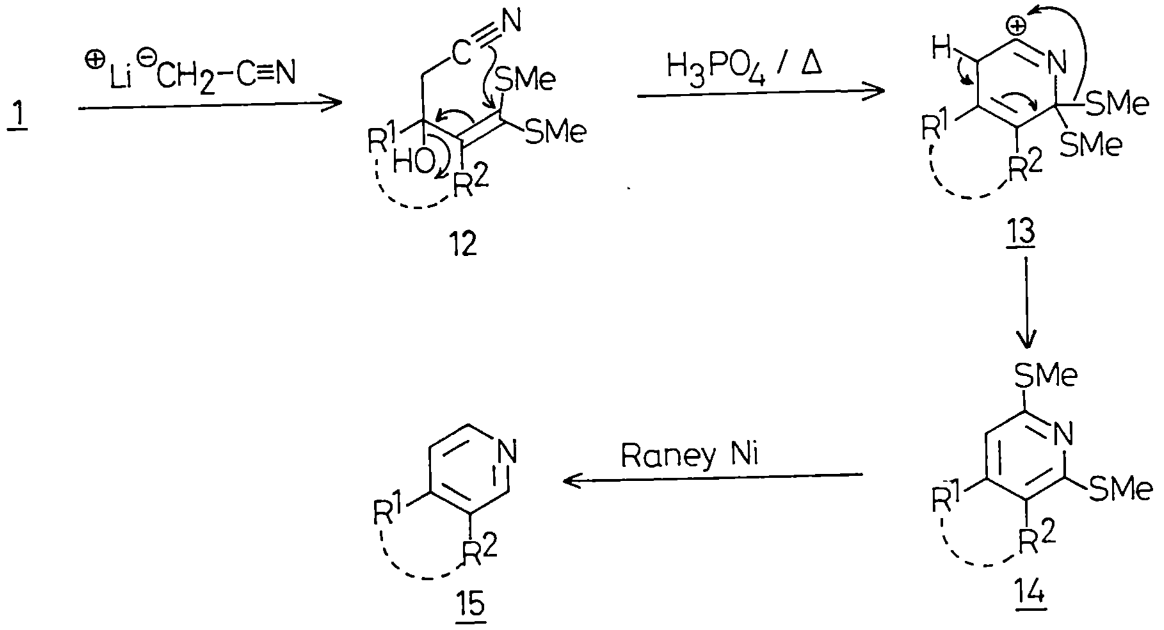

1
≡—CH2MgBr
Ether
MeOH
SMe
SMe
R1
HO
R2
6
BF3·Et2O /
MeOH
-H2O /-MeSH
OMe
SMe
R1
R2
7
1-6, 7, R1=R2=-(CH2)n, n= 4,5; R1= R2=
R3
; R3= H, Me, MeO
R1=R2=
X
(CH2)n ; n=1,2; X=O, S
O
SMe
SMe
8
1. ≡—CH2MgBr
2. BF3·Et2O / MeOH
CO2Me
9
O
SMe
SMe
10
1. ≡—CH2MgBr
2. BF3·Et2O / MeOH
CO2Me
11

Scheme-2

propargylmagnesium bromide, the corresponding allyl alcohol though formed in quantitative yield failed to undergo the described cationic aromatic annelation to give the corresponding indanes, instead the corresponding propargyl ene esters 9 arising from solvolysis of mercaptal functionality was obtained. Similarly the oxoketene dithioacetal 10 derived from indanone underwent addition with propargylmagnesium bromide to yield the ene ester 11. The failure of the cycloaromatization in these systems appears to be due to unfavourable geometry of the five membered rings.

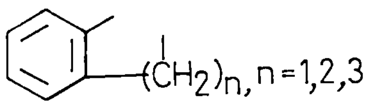
Interestingly the idea of acetonitrile nucleophile participation through the terminal double bond was extended usefully for the synthesis of pyridine derivatives. Thus lithioacetonitrile underwent smooth 1,2-addition to 1 to give the corresponding allyl alcohol 12 in nearly quantitative yields. The alcohol thus obtained underwent smooth intramolecular cyclization through the formation of new C-N bond with concurrent migration of thiomethyl group to yield the corresponding 2,6-bis(methylthio)-3,4-substituted or annelated pyridine derivatives 14 (Scheme 3), in high yields which on Raney Nickel desulfurization yielded the parent compound 15 in quantitative yield[9]. The method has been extended to a number of substituents to prove the efficacy of its synthetic potential.

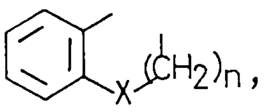
The reaction of benzylmagnesium chloride with oxoketene dithioacetals was considered of special interest since the corresponding allyl alcohol should undergo cycloaromatization through the participation of aromatic ring double bond yielding corresponding naphthalene and other fused ring systems. However when benzylmagnesium halide was reacted with 1



1, 12-15, R^1 = Ar; R^2 = H; R^1 = Me, Et; R^2 = H; R^1 = Me, Et; R^2 = Me, n Bu

R^1 = 2-furyl, 2-thienyl, 2- or 3-pyridyl; R^2 = H

$R^1 = R^2 = (CH_2)_n$, n = 3,4,5 ; $R^1 = R^2 =$  $(CH_2)_n$, n = 1,2,3

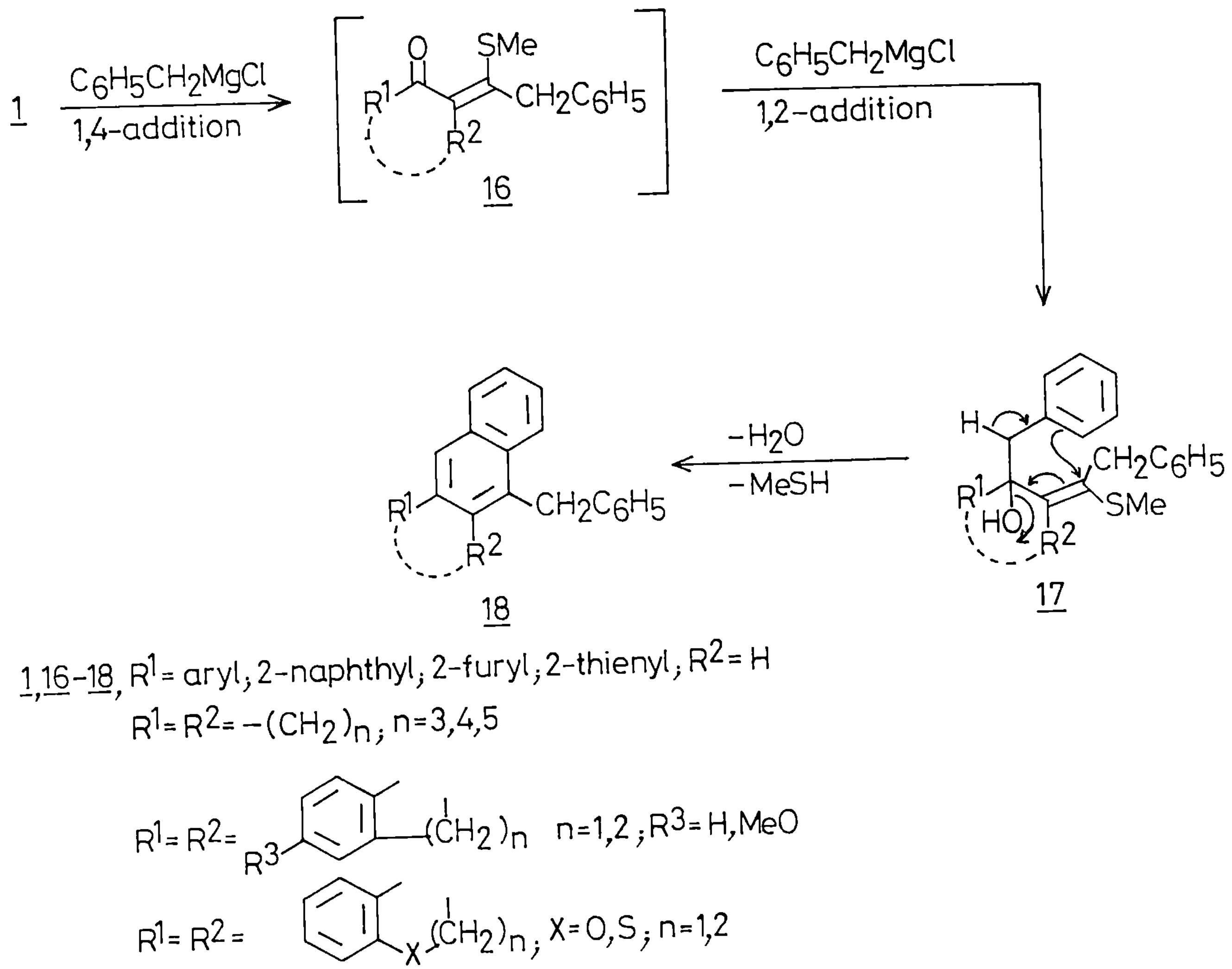
$R^1 = R^2 =$  $(CH_2)_n$, X = O, S; n = 1,2

Scheme-3

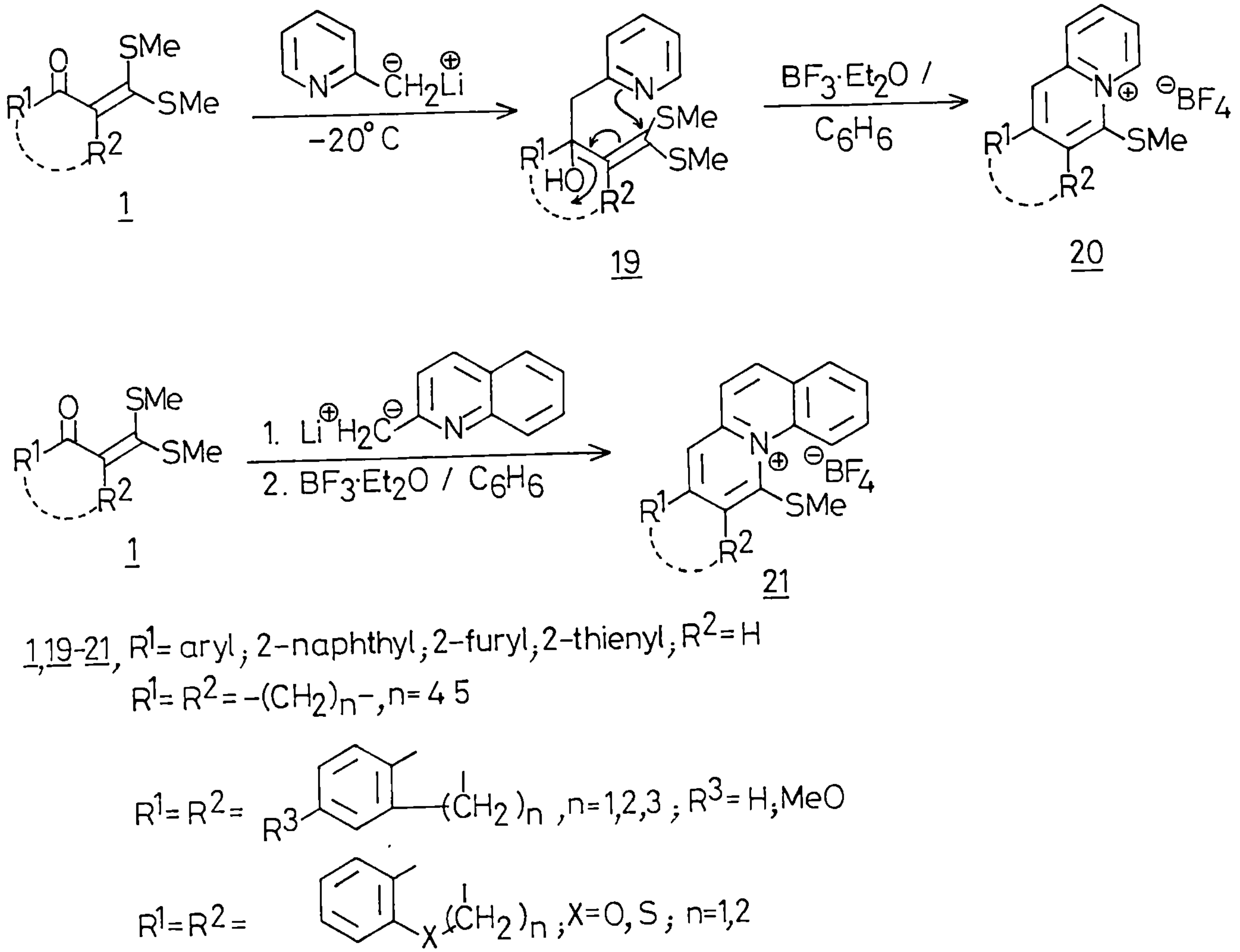
it underwent initial 1,4-conjugate addition to yield the corresponding more reactive ketone 16, followed by 1,2-addition, finally leading to the formation of naphthoannelated product 18 through 17 with benzyl group as substituent in place of thiomethyl group. This method is shown to be of general application, not only to naphthalene derivatives but also to many polycyclic hydrocarbons depending on the structure of 1 (Scheme 4)[10].

The aromatic annelation was further extended to construct bridge head nitrogen compounds of the general formula 21 (Scheme 5). Thus 2-picolyllithium was selected as representative of lithio-3-azaallyl system with α-oxoketene dithioacetals, to enhance the scope of the method for aromatic annelation and further extend it to important heteroaromatic annelation. Thus 2-picolyllithium underwent facile 1,2-addition with 1 to give the expected allyl alcohols 19 in nearly quantitative yields (Scheme 5)[11]. These carbinol acetals when directly subjected to cycloaromatization in the presence of boron trifluoride etherate formed the quinolizinium ring systems 20 involving new C-N bond formation in high yields. Similarly when 2-lithiomethyl quinoline was reacted with 1 the corresponding quinolizinium fluoroborate salt 21 was obtained in high yields[12]. The generality of the method has been shown to be applicable to many structural variants of α-oxoketene dithioacetals.

Interestingly unlike benzylmagnesium chloride, when α-naphthylmethylmagnesium halide was reacted with 1, only 1,2-adduct 22 was formed in high yields which underwent facile boron trifluoride assisted ring


1
C6H5CH2MgCl
1,4-addition
O
SMe
R1
CH2C6H5
R2
16
C6H5CH2MgCl
1,2-addition
H
R1
HO
R2
CH2C6H5
SMe
17
-H2O
-MeSH
R1
R2
CH2C6H5
18
1,16-18, R1= aryl; 2-naphthyl; 2-furyl; 2-thienyl; R2= H
R1=R2= -(CH2)n; n=3,4,5
R1= R2=
R3
(CH2)n n=1,2 ; R3= H,MeO
R1= R2=
X
(CH2)n ; X=O,S ; n=1,2

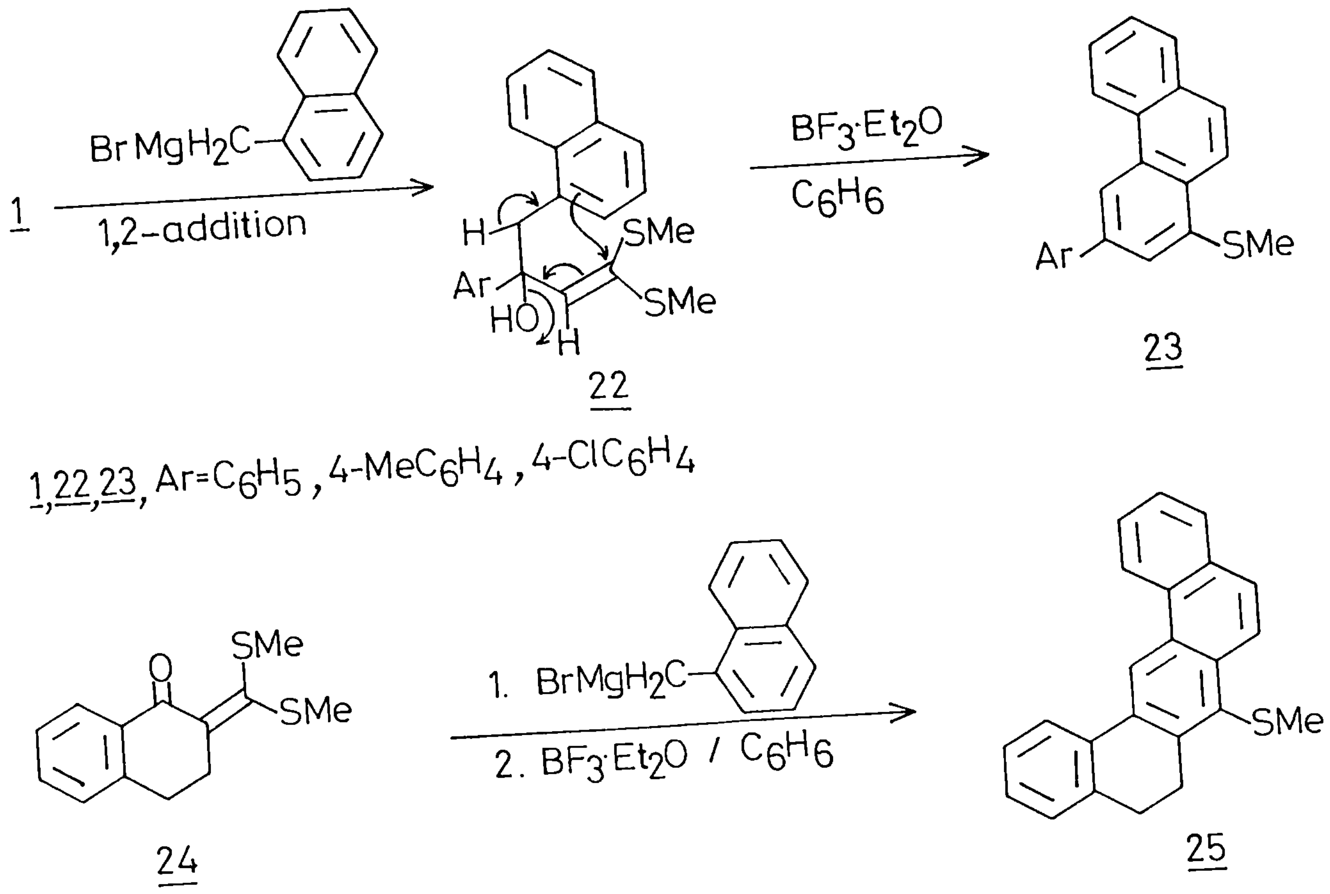
Scheme-4


SMe
SMe
O
R1
R2
1
N
CH2Li
−20° C
19
HO
BF3·Et2O /
C6H6
N⊕
⊖BF4
20
1. Li⊕H2C⊖
2. BF3·Et2O / C6H6
21
1,19-21, R1= aryl; 2-naphthyl; 2-furyl; 2-thienyl; R2= H
R1= R2= -(CH2)n-, n= 4 5
R1= R2=
R3
(CH2)n, n=1,2,3; R3= H; MeO
R1=R2=
X
(CH2)n; X=O, S; n=1,2

Scheme-5

closure to yield the corresponding thiomethylphenanthrene 23 in high yields (Scheme 6)[13]. Thus the oxoketene dithioacetals 1 are of considerable synthetic importance as useful precursors, for the synthesis of regiospecifically substituted phenanthrene derivatives in one pot synthetic operations. When the reagent was reacted with oxoketene dithioacetal derived from tetralone 24 the corresponding dihydro-1,2-naphthophenanthrene 25 was obtained in high yields. These reactions amply demonstrate that the aromatic annelation is possible to construct benzenoids, naphthalenes, anthracenes, phenanthrenes, benzanthracenes, naphthophenanthrenes and many other condensed aromatic systems starting from appropriately substituted oxoketene dithioacetals.

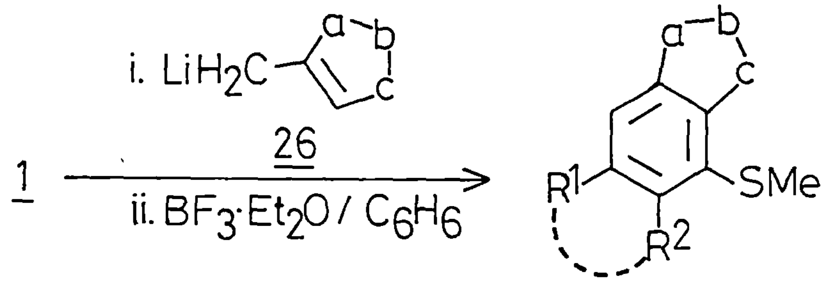
In the preceeding examples it has been shown that the aromatic or heteroaromatic annelation is possible for the construction of the aromatics and heteroaromatics and its possible extension to construct aromatic ring over the five membered heterocycles would provide an alternative efficient approach for the synthesis of important class of benzoheterocycles. The reported approaches for the synthesis of this class of compounds generally involve the construction of five membered heterocycles over the preconstructed benzene ring. Though this approach has been extensively investigated it requires often highly functionalized benzene derivatives, which are not always easy to make in overall high yields. Thus it was contemplated to extend the aromatic annelation approach to yet another broad based plan to explore the possibilities of annelating the aromatic ring over the preconstructed five membered heterocycles. Such an approach would



1,22,23, Ar=C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4

Scheme-6

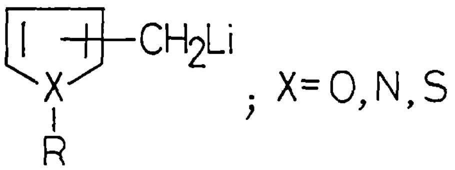
provide possibly easy general methods for the synthesis of benzoheterocycles. As a part of this programme the reaction of 3-methyl-5-lithiomethylisoxazole with α-oxoketene dithioacetals 1 has been investigated to yield the corresponding substituted and annelated 1,2-benzisoxazoles in high yields. The broad approach envisaged in the present investigation is described in Scheme 7.



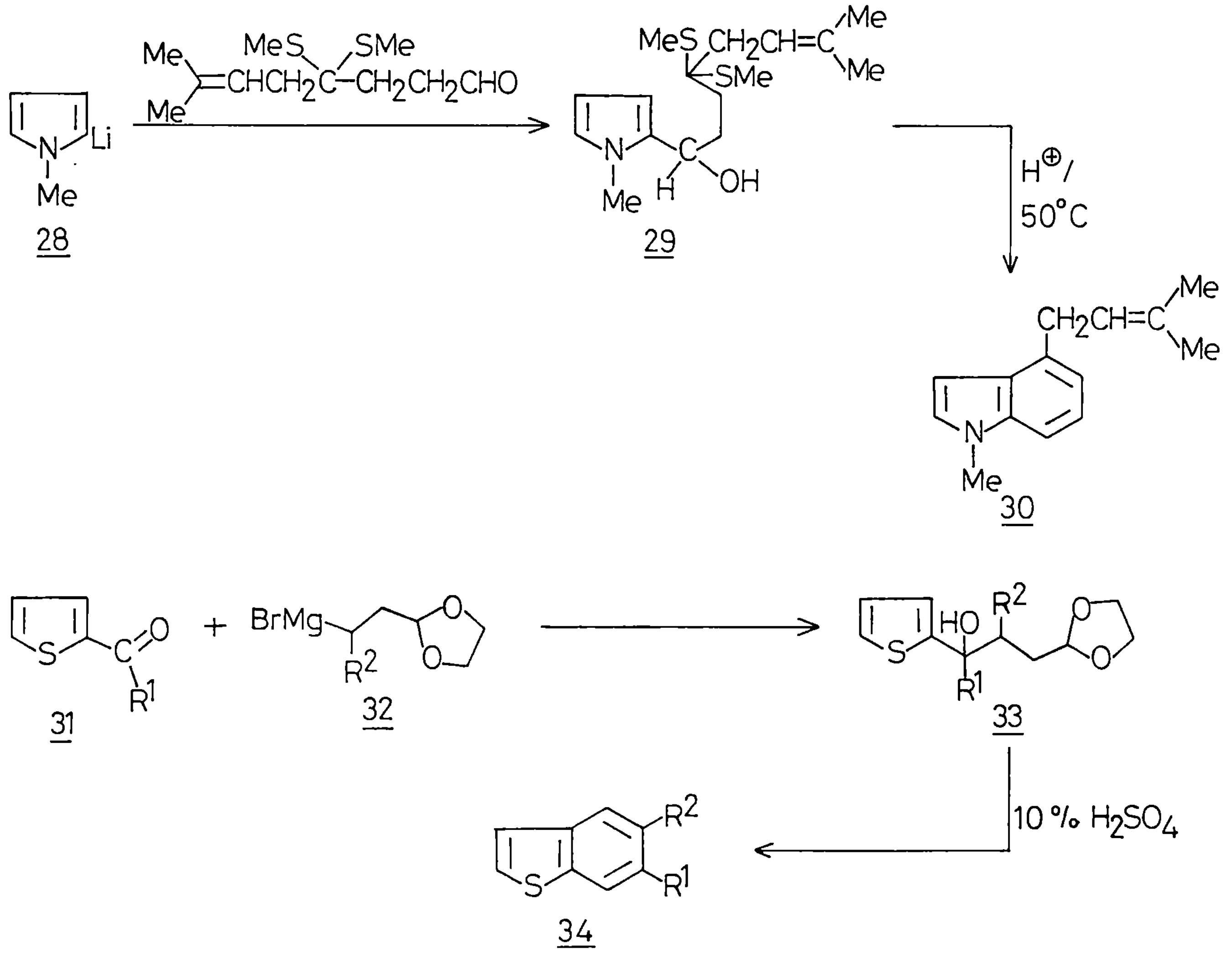
27

Scheme 7

However the success of the general approach envisaged in the present investigation will depend upon the availability of lithiomethyl heterocycles of the general formula.



A few classical approaches indeed are reported in the literature for the construction of benzene ring over the five membered heterocycles. For example the reaction of 2-lithio-N-methyl pyrrole 28 with functionalized ketals to yield the corresponding alcohols 29 (Scheme 8) have been shown to afford after acid assisted ring closure to the 4-(3-methyl-2-butenyl) indole 30[14]. Similarly the grignard reagent 32 was shown to react with 2-arylthiophenes and the resulting ketal alcohols 33 were found to undergo acid catalyzed ring closure to



R^1= H; Me; Et; Pr^i, Bu^t; R^2= H, Me

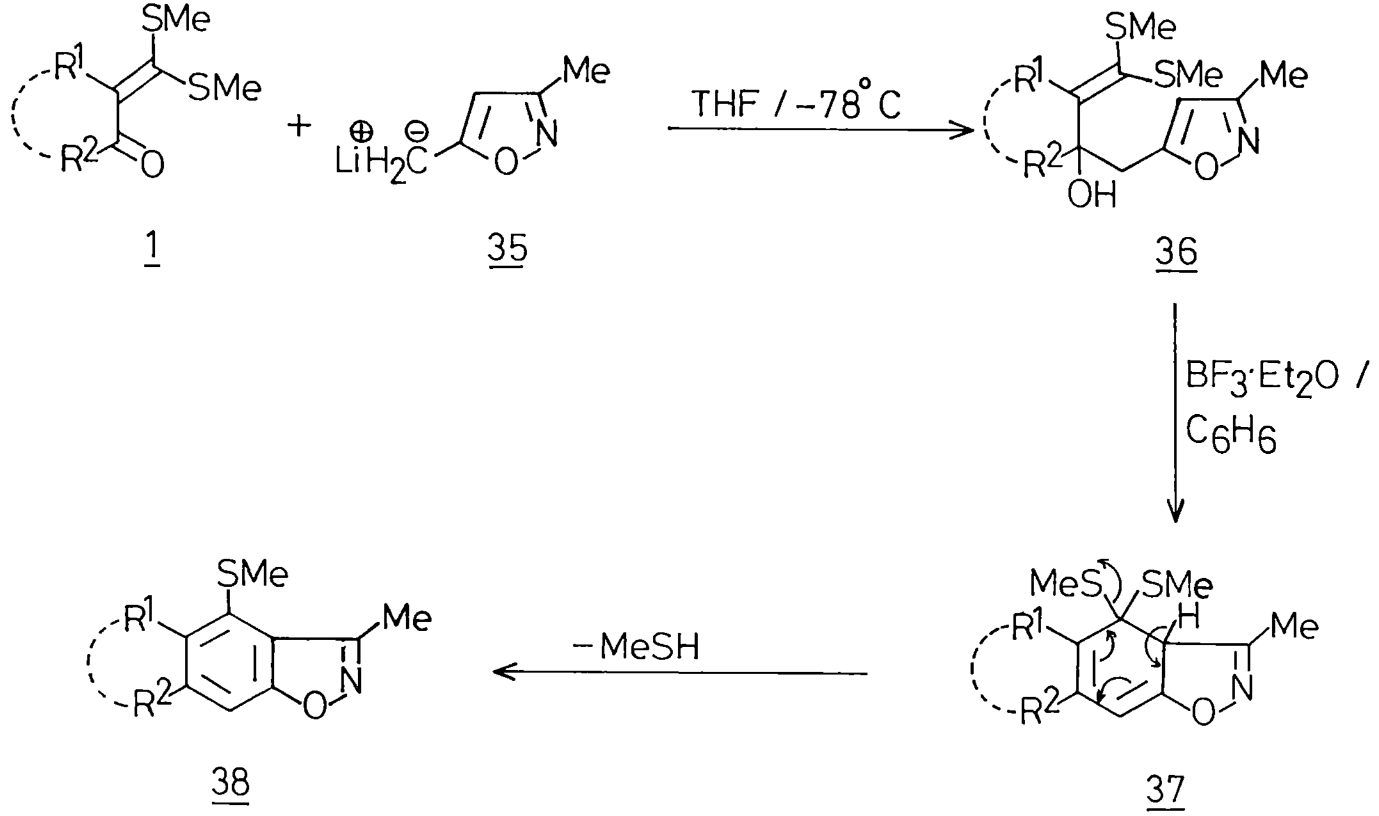
Scheme 8

yield the corresponding benzo[b] thiophenes 34 in good yields (Scheme 8)[15].

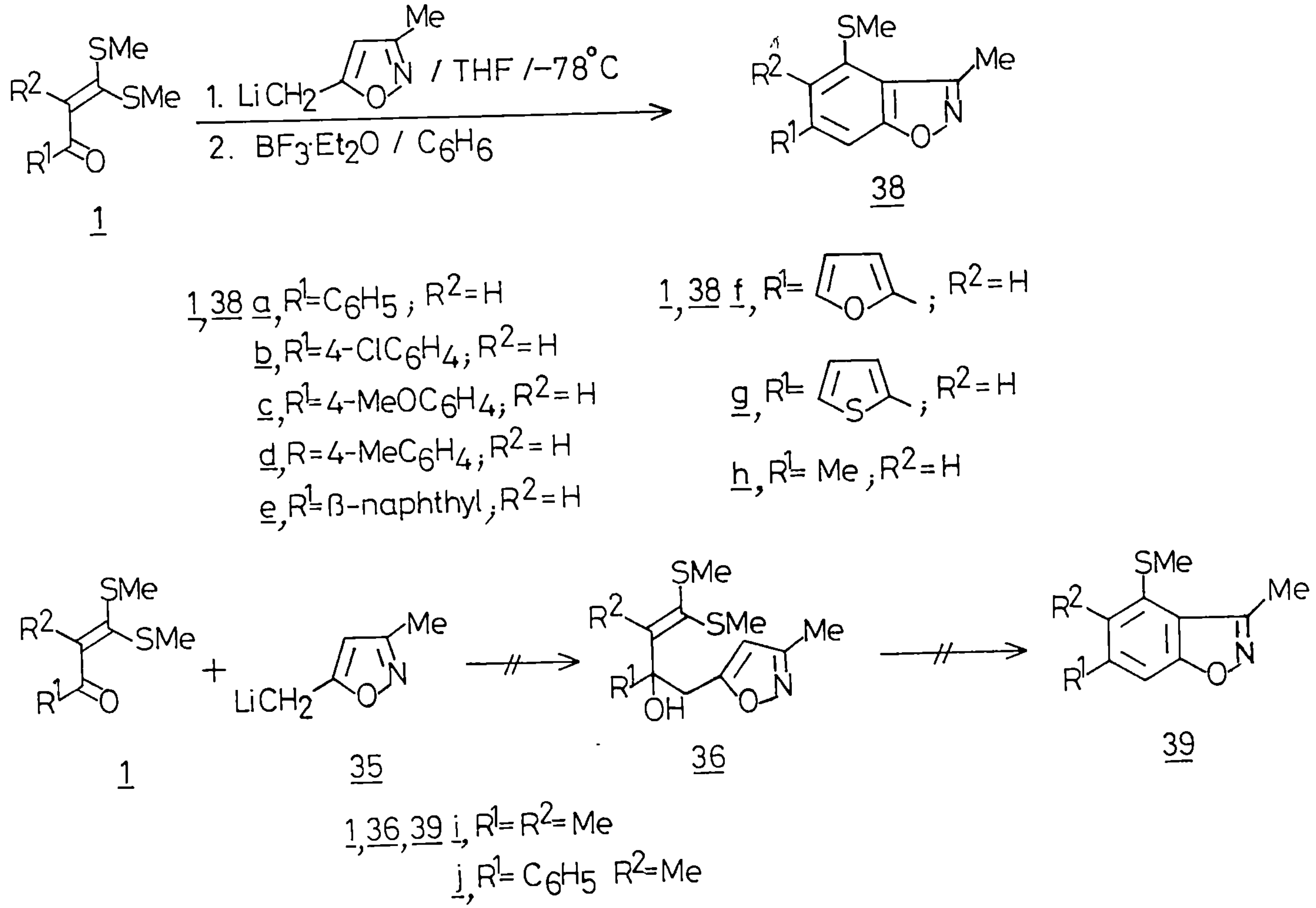
III.2 RESULTS AND DISCUSSION

In the present investigation 3-methyl-5-lithiomethyl isoxazole was selected as an allylanion system and as a representative of the 5-membered heterocycles in general. Thus anion 35 underwent facile 1,2-addition to yield the corresponding allyl alcohol 36 in near quantitative yields and the alcohol was insitu cycloaromatized in the presence of boron trifluoride etherate by the elimination of methylmercaptan from 37 to yield the corresponding benzisoxazole 38 (Scheme 9). Results of the detailed investigation are described herein.

When 1a was reacted with 3-methyl-5-lithiomethyl isoxazole 35 at -78°C, the corresponding carbinol acetal 36 was formed in quantitative yield which was directly subjected to cyclization in the presence of boron trifluoride etherate in refluxing benzene to give the colourless crystalline product characterized as 3-methyl-4-methylthio-6-phenyl-1,2-benzisoxazole 38a in 73% yield (Scheme 10). The structure of this compound was assigned on the basis of analytical and spectral data. Thus it was analyzed for $C_{15}H_{13}NOS$ and its mass spectrum displayed molecular ion peak at m/z 255 (M^+,100%). Its infrared spectrum (KBr) exhibited bands at 1600, 1566, 1425, 1388, 1345 cm^{-1}, where the 1600 band was due to C=N group. The ^1H n.m.r. (CCl_4) spectrum of 38a showed a singlet (3H) at δ 2.50 which was assigned to the methyl protons. The signal at δ 2.68 appeared as a singlet (3H) and was attributed to the methylthio protons. The


SMe
SMe
R1
R2
O
1
+
LiH2C
Me
N
O
35
THF / -78° C
SMe
SMe
Me
R1
R2
OH
N
O
36
BF3·Et2O /
C6H6
MeS
SMe
H
R1
R2
Me
N
O
37
-MeSH
SMe
R1
R2
Me
N
O
38

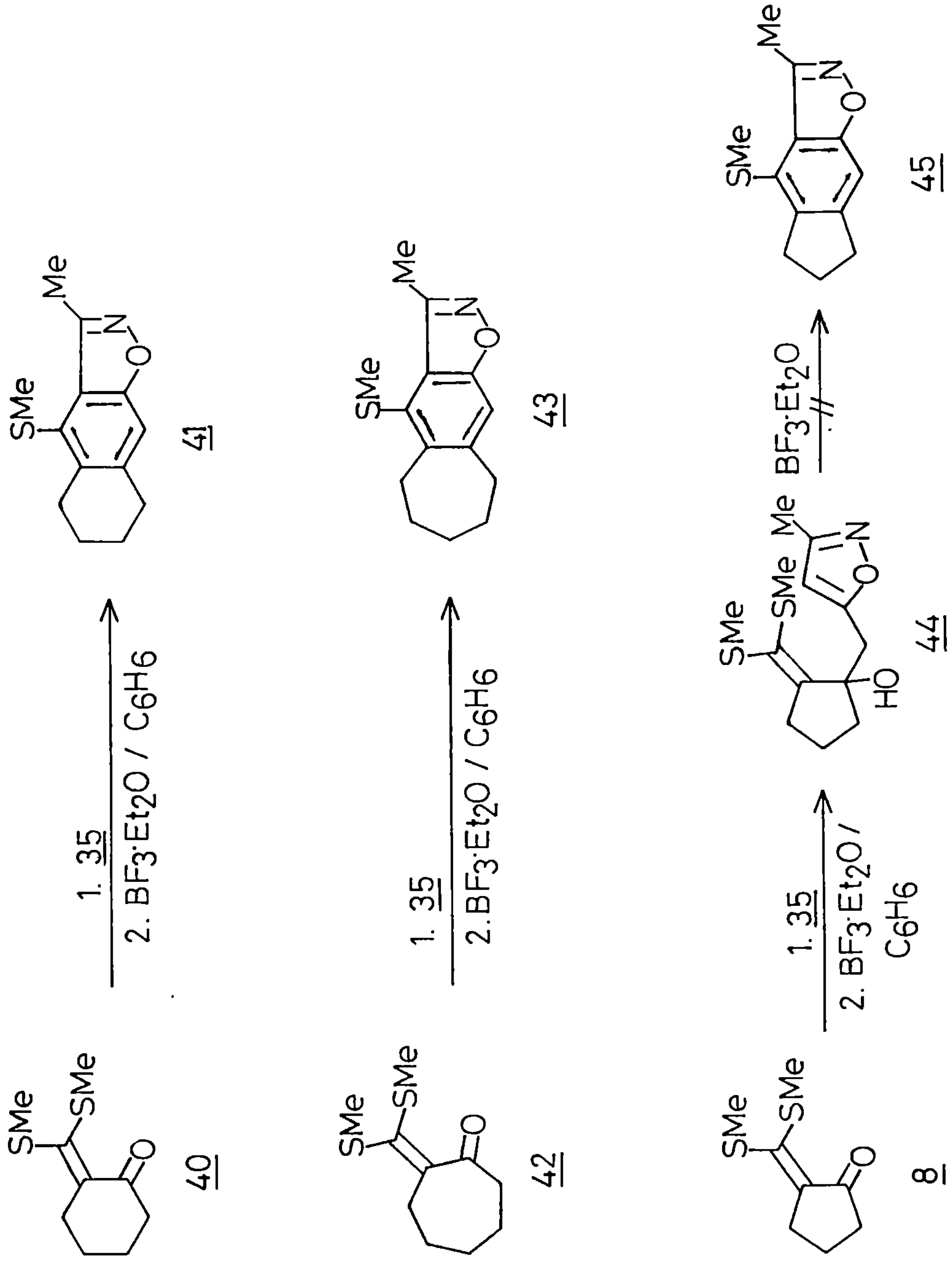
Scheme-9


SMe
SMe
R2
R1
O
1
1. LiCH2 / THF /–78°C
Me
N
O
2. BF3·Et2O / C6H6
SMe
R2
Me
R1
N
O
38
1, 38 a, R1=C6H5 ; R2=H
b, R1=4-ClC6H4; R2=H
c, R1=4-MeOC6H4; R2=H
d, R=4-MeC6H4; R2=H
e, R1=β-naphthyl ; R2=H
1, 38 f, R1= ; R2=H
O
g, R1= ; R2=H
S
h, R1= Me ; R2=H
1
+
LiCH2
35
36
OH
39
1, 36, 39 i, R1=R2=Me
j, R1= C6H5 R2=Me

Scheme-10

broad singlet at δ 7.02 was assigned to the H-7 proton whereas the aromatic protons appeared as broad multiplet between δ 7.20-7.67(6H). The structure of 38a was also confirmed by its ^{13}C n.m.r. spectrum which showed signals at δ 11.47(CH_3), 17.23(CH_3S), 103.80(C-7), 114.59 (C-5), 125.45, 127.24, 128.35(CH,arom), 128.36, 140.20, 142.66, 142.41 (quaternary c), 159.71(C-3), 168.07(C-8). Thus the structural assignment of 38a was fully confirmed. The method was found to be quite general and a number of benzisoxazoles 38b-h were obtained in 54-68% overall yields by reacting 35 with the corresponding α-oxoketene dithioacetals 1b-h. The structures of all these benzisoxazoles were fully confirmed by their analytical and spectral data and are given in the experimental section.

The oxoketene dithioacetals derived from ethyl methyl ketone 1i and propiophenone 1j failed to yield the desired alcohols 36i and 36j and therefore corresponding benzisoxazoles 39i and 39j could not be isolated. It appears that the α-methyl protons of 1i and 1j undergo rapid competitive deprotonation to give the allyl anions that do not participate in the reaction sequence (Scheme 10). However, the cyclic oxoketene dithioacetals also underwent the sequence of reaction to yield the corresponding benzisoxazoles. Thus oxoketene dithioacetal 40 derived from cyclohexanone reacted with 3-methyl-5-lithiomethylisoxazole 35 and underwent cycloaromatization to yield the corresponding 3-methyl-4-methylthio-5,6,7,8-tetrahydronaphtho[b]isoxazole 41 in 65% yield (Scheme 11). The analytical and spectral data of 41 are in confirmity with the assigned structure. Similarly the oxoketene dithioacetals 42 derived from cycloheptanone also reacted with 35 to yield 43 in 67%

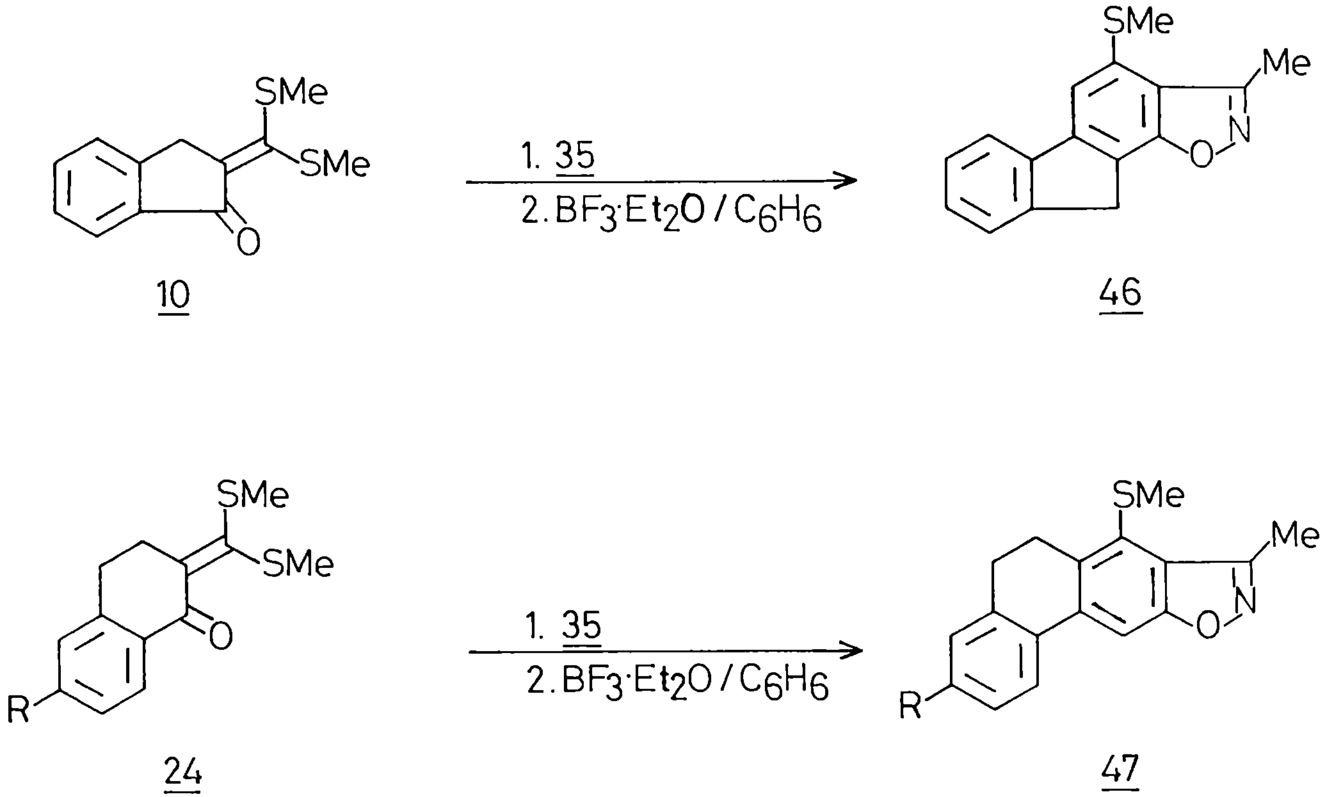

40
41
42
43
8
44
45
SMe
Me
1. 35
2. BF$_3$·Et$_2$O / C$_6$H$_6$
2. BF$_3$·Et$_2$O / C$_6$H$_6$
BF$_3$·Et$_2$O
HO

Scheme-11

yield. The spectral and analytical data in favour of 43 were given in the experimental section. The α-oxoketene dithioacetal 8 derived from cyclopentanone though yielded the alcohol 44, failed to undergo cycloaromatization under the described conditions to yield the corresponding isoxazole 45. No well defined compound could be isolated from the reaction mixture (Scheme 11). However in an analogous reaction condition oxoketene dithioacetal derived from indanone 10 did react with 35 and underwent cyclization to yield the corresponding fused ring isoxazole 46 in 57% yield. The analytical and spectral data of 46 are in agreement with the assigned structure (experimental). Similarly the oxoketene dithioacetals 24a-b also reacted with isoxazole to yield the corresponding 5,6-annelated benzisoxazoles 47a-b in 76% and 78% yields respectively (Scheme 12). The analytical and spectral data of these compounds are described in the experimental section.

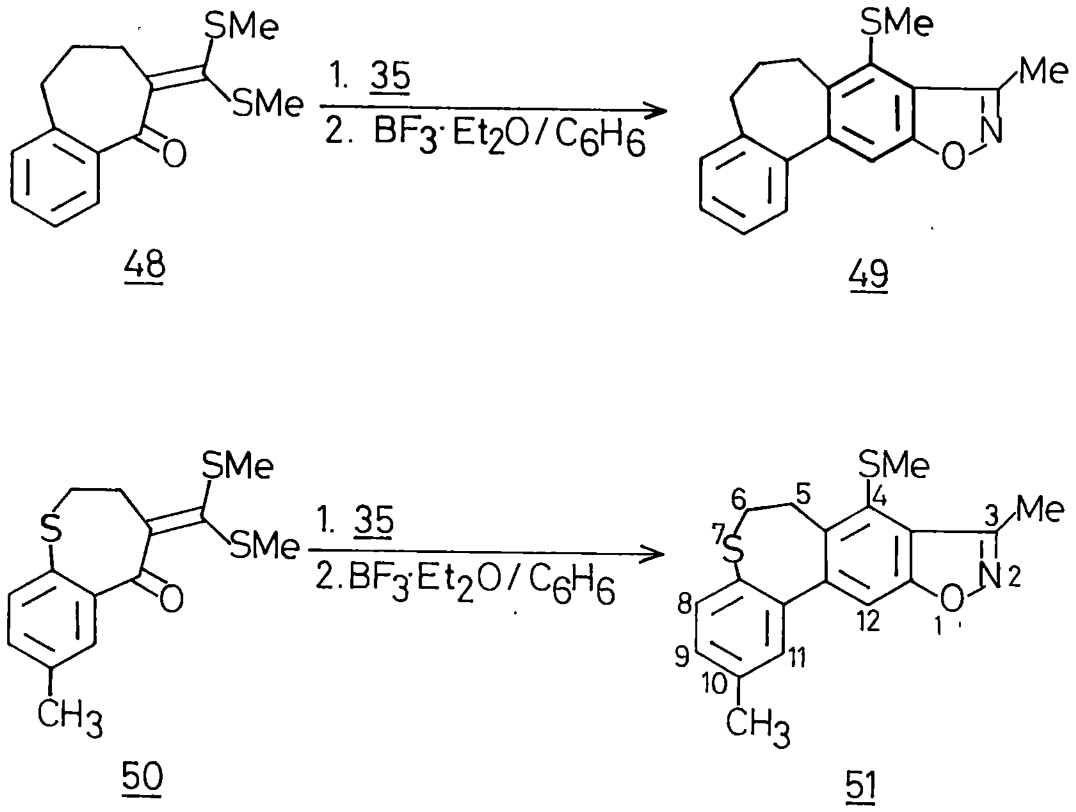
The oxoketene dithioacetals 48 and 50 similarly yielded fused benzisoxazoles 49 and 51 in 69% and 81% yields respectively (Scheme 13) whose analytical and spectral data are described in experimental section.

In a few cases the validity of benzoannelation over the isoxazole ring was examined on β-methylthio-α-β-unsaturated enones 52 so that the product isoxazoles are formed without thiomethyl group on the ring. Thus the oxoketene dithioacetals 1a-c were subjected to Nickel boride reduction as reported in one of our earlier papers[16] to yield the corresponding β-methylthio-α-β-unsaturated ketones 52a-c in 60-70% overall yields (Scheme 14). These compounds were confirmed for their

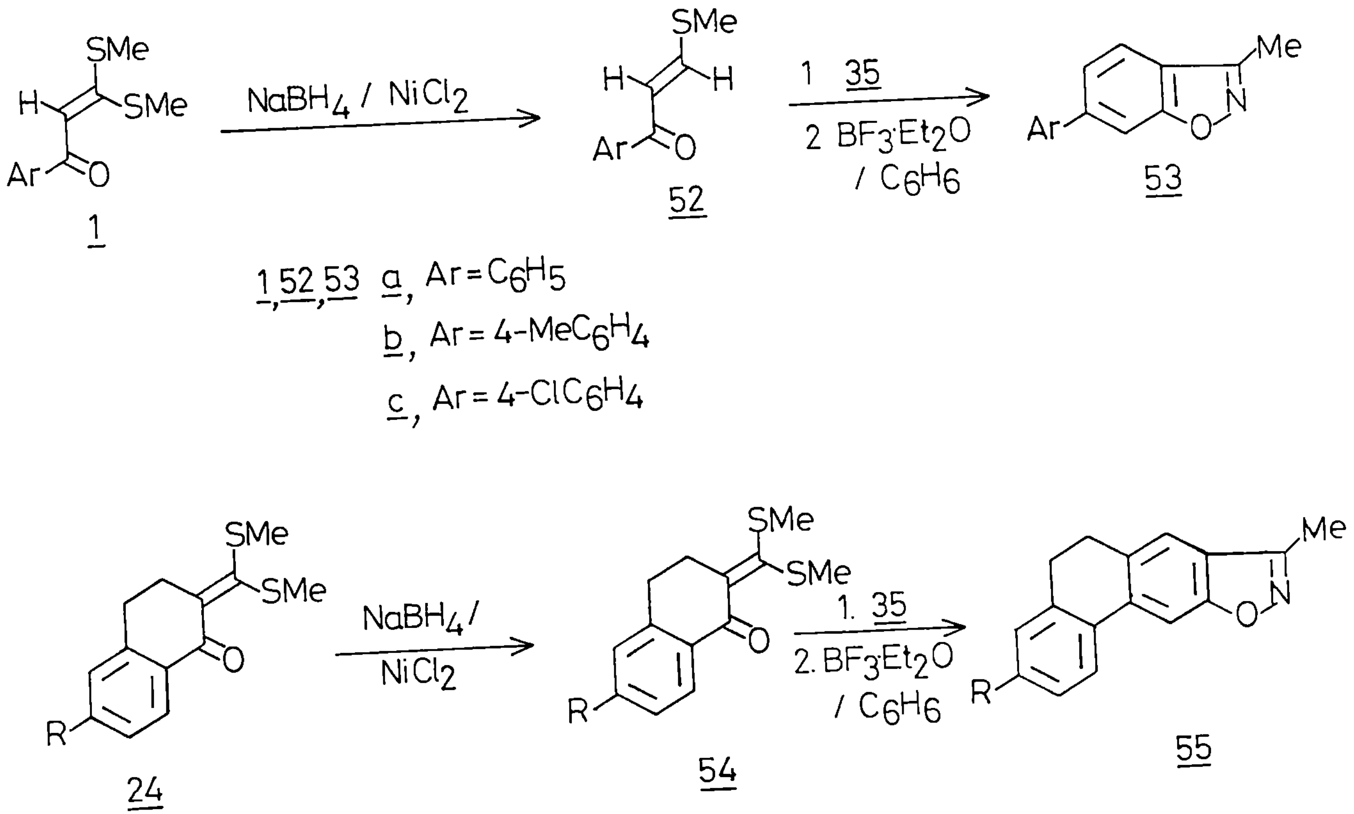


24, 47 a, R=H
b, R=MeO

Scheme-12


SMe
SMe
O
1. 35
2. BF3·Et2O/C6H6
48
SMe
Me
N
O
49
SMe
SMe
S
O
CH3
1. 35
2.BF3·Et2O/C6H6
50
SMe
Me
1
2
3
4
5
6
7
8
9
10
11
12
S
N
O
CH3
51

Scheme-13



1,52,53 a, Ar = C_6H_5
b, Ar = 4-MeC_6H_4
c, Ar = 4-ClC_6H_4

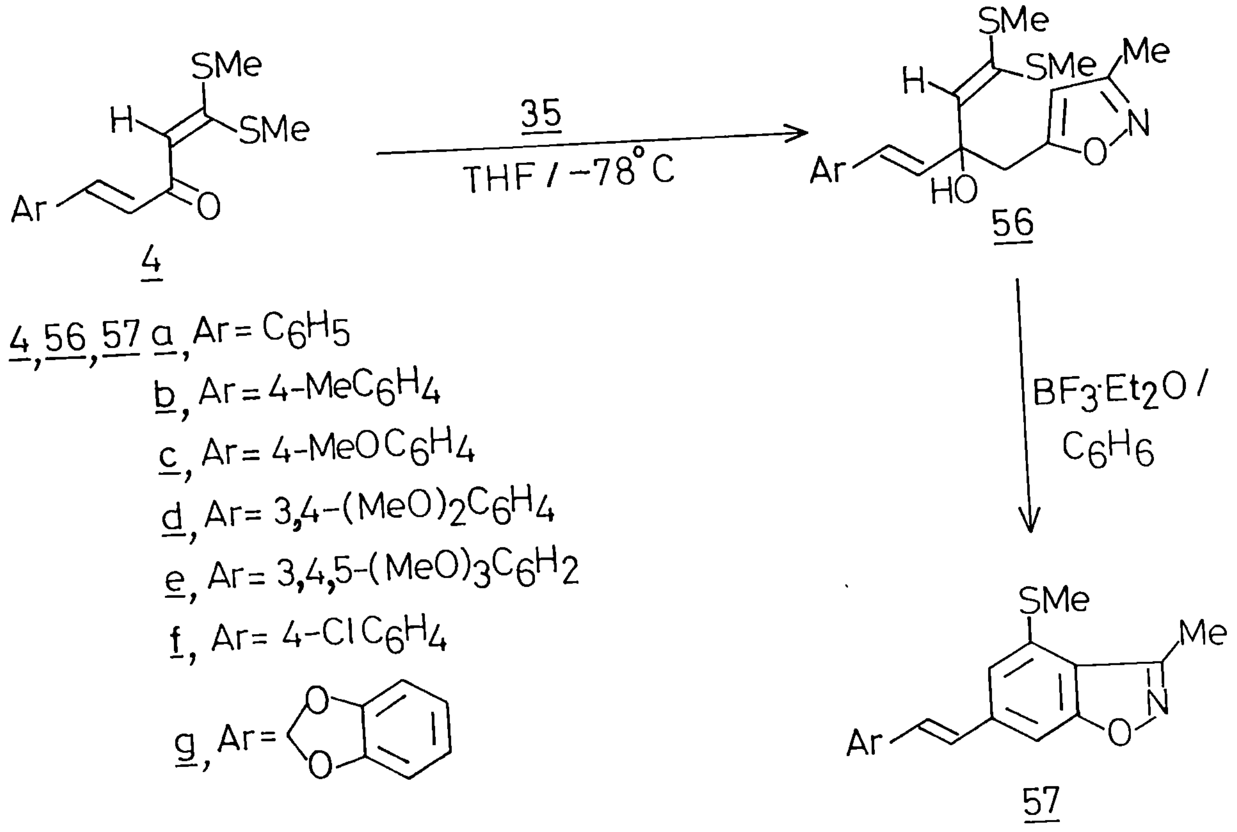
24,54,55 a, R=H
b, R=MeO

Scheme-14

structural authenticity and reacted with 3-methyl-5-lithiomethyl isoxazole and the corresponding sulfur free benzisoxazole 53a-c were obtained in 70-90% overall yields. The absence of thiomethyl singlet at δ 2.68 fully confirmed the formation of sulphur free benzisoxazoles. The analytical and spectral data of these compounds are described in the experimental section. Similarly 54a-b were formed from 24a-b in 75-85% yields as per reported method and when reacted with isoxazole 35 the corresponding 5,6-annelated benzisoxazoles 55a-b were obtained in 85% and 88% overall yields. The absence of thiomethyl signal and the other spectral data (experimental) confirmed the formation of benzisoxazoles.

The approach of stilbene synthesis was extended to benzisoxazole synthesis as depicted in Scheme 15. Thus the cinnamoylketene dithioacetal 4a was reacted with isoxazole 35 to yield the corresponding allyl alcohol 56a in quantitative yield and cyclized in the presence of boron trifluoride etherate to yield the corresponding 6-styryl benzisoxazole 57a in 68% yield. the structure of 57a was confirmed from its analytical and spectral data. Thus it was analyzed for $C_{17}H_{15}NOS$ and its mass spectrum showed the molecular ion peak at m/z 281 (M^+,100%). The spectral data of 57a were described in experimental section. The 6-styryl benzisoxazoles 57b-g were also obtained similarly from the corresponding cinnamoylketene dithioacetals 4b-g in 60-70% overall yields (Scheme 15). The structures of these compounds were confirmed from their analytical and spectral data (experimental).

Interestingly, although dienoylketene dithioacetal 58 failed to undergo cyclocondensation with allylmagnesium halide the 3-methyl-5-lithiomethyl

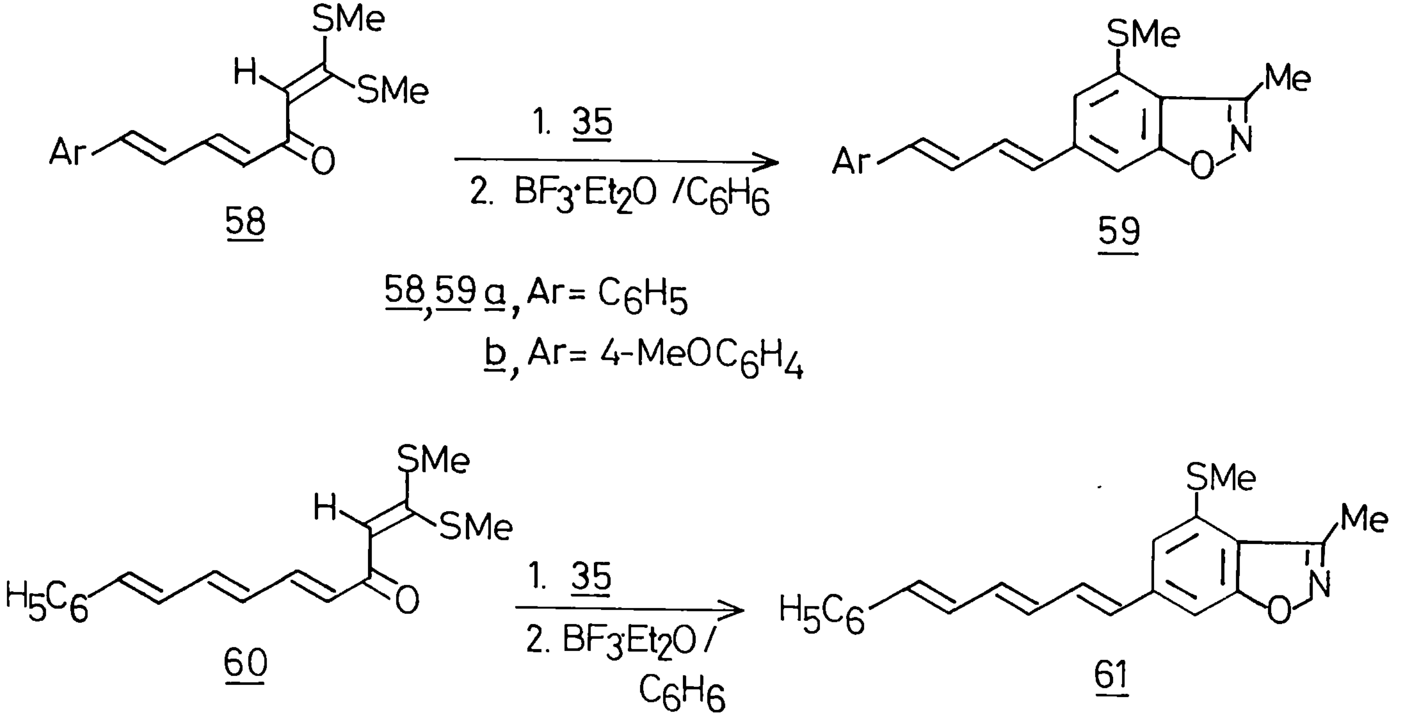

SMe
H
SMe
Ar
O
4
35
THF / −78° C
SMe
H
SMe
Me
N
O
Ar
HO
56
BF3·Et2O /
C6H6
SMe
Me
N
O
Ar
57
4, 56, 57 a, Ar = C6H5
b, Ar = 4-MeC6H4
c, Ar = 4-MeOC6H4
d, Ar = 3,4-(MeO)2C6H4
e, Ar = 3,4,5-(MeO)3C6H2
f, Ar = 4-ClC6H4
g, Ar =
O
O

Scheme-15

isoxazole 35 reacted smoothly with 58a-b in near quantitative yields followed by cyclocondensation to yield the corresponding 6-(4-aryl-1,3-butadienyl)benzisoxazoles 59a-b in 55% and 65% yields respectively. The structural assignment of both 59a and b are in agreement with the spectral data and are described in experimental section. The 6-(6-phenyl-1,3,5-hexatrienyl)benzisoxazole 61 was similarly obtained by reacting 35 with 60 (Scheme 16). The structure of 61 was confirmed by its analytical and spectral data.

III.3 CONCLUSION

Thus, it has been demonstrated that the oxoketene dithioacetals with diverse structural features react with 3-methyl-5-lithiomethyl isoxazole resulting in the synthesis of hitherto unreported benzisoxazoles in high yields. Starting from benzene derivatives, apparently the synthesis of these benzisoxazoles is uneconomic, tedious and involve many steps with possible overall poor yields of the product benzisoxazoles. The present method therefore makes a definite contribution for the synthesis of benzisoxazoles in high yields in one step from oxoketene dithioacetals. Conceptually this approach can be extended to any five membered heterocycles to build aromatic ring over five membered heterocycles. However, the success and the extension of this methodology to other five membered heterocycles largely depends upon the possibility of regiospecific generation of lithiomethyl anions which are not always easy to generate since these heterocycles undergo ring deprotonation in preference to methyl side-chain deprotonation. The further work in this direction is in progress in our laboratory.


SMe
H
SMe
Ar
O
58
1. 35
2. BF3·Et2O /C6H6
SMe
Me
Ar
N
O
59
58,59 a, Ar= C6H5
b, Ar= 4-MeOC6H4
SMe
H
SMe
H5C6
O
60
1. 35
2. BF3·Et2O /
C6H6
SMe
Me
H5C6
N
O
61

Scheme-16

III.3 EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point (capillary method) apparatus and are uncorrected. ^1H n.m.r. spectra were recorded on a Varian EM-390, 90 MHz spectrometer and the chemical shift values are expressed as δ(ppm) downfield from Me_4Si as internal standard. ^{13}C n.m.r. spectra were recorded on a 67.89 MHz Brucker WH-270 spectrometer. I.r. and mass spectra were recorded on a Perkin-Elmer 297 spectrometer and a Jeol D-300 mass spectrometer respectively. Carbon, hydrogen and nitrogen elemental analysis were done at RSIC, Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of acetone, acetophenone, 4-methylacetophenone, 4-methoxyacetophenone, 4-chloroacetophenone, 2-acetylnaphthalene, 2-acetylfuran, 2-acetylthiophene, cyclopentanone, cyclohexanone, cycloheptanone, 1-tetralone, 6-methoxytetralone, benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, piperonaldehyde were purified before use wherever necessary. The cyclic ketones i.e. 1-indanone[17], 1-benzsuberanone[18], benzthiepenone[19], 4-methoxycinnamaldehyde, 5-phenyl-2,4-pentadienal[20], and 3,5-dimethylisoxazole[21] were prepared according to the reported procedure.

The known α-oxoketene dithioacetals 1a-j, 8, 10, 24, 40, 42, 48, 50, β-methylthio-α-β-unsaturated enones 52a-c, 54a-b, 1,1-bis (methylthio)-1,4-pentadiene-3-ones 4a-g, 1,1-bis(methylthio)-7-aryl-1,4,6-heptatriene 3-ones 58a-b and 1,1-bis(methylthio)-

9-aryl,1,4,6,8-nonatetraene-3-one 60[16,22-27] were prepared according to the reported procedures given below.

General method for the preparation of α-oxoketene dithioacetals (1a-j, 8, 10, 24, 40, 42, 48, 50):

A mixture of ketone (0.2 mol) and carbondisulphide (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 stir 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 stir at room temperature for 6-10 hr. The reaction mixture was poured over ammonium chloride solution (250 ml) and the layers were separated. The aqueous layer was extracted with benzene (100 ml) and the 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. The physical and spectral data were compared with that of reported values.

General method for the preparation of 2-methylthio-1-alkenyl ketones (52a-c, 54a-b):

To a stirring suspension of nickel chloride hexahydrate (0.16 mol) in ethanol (150 ml), sodium borohydride (0.2 mol) was slowly added (15 min.). Fresh addition was made only when effervescene due to evolution of hydrogen has stopped. The mixture was further stirred for 10 min. and a solution of ketene S,S-acetal 1 (0.06 mol) in ethanol (50 ml) was added to the black suspension and the mixture was further stirred at room temperature for 10 min. It was then heated under reflux in an oil bath with stirring (9-36 hr), until the starting material has disappeared completely (TLC). The mixture was filtered hot through a sintered funnel and the black residue was washed with boiling chloroform (3x200 ml). The combined filtrate was washed with water (2x300 ml), the organic layer dried with sodium sulphate and evaporated to give a dark brown viscous liquid which was then purified by column chromatography. Elution with hexane/benzene (9:1). 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 compounds (4a-g, 58a-b, 60):

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 amount of ethanol was added dropwise over a period of 5 minutes. The reaction mixture was brought to room temperature stirred for 4-5 hrs. The mixture was diluted with cold water (100 ml) and the solid separated out was filtered, washed with water (4x100 ml) and dried. The physical and spectral data were found to be in confirmity with that of reported values.

3,5-Dimethyl isoxazole:

To a solution of hydroxylamine hydrochloride (7g) in water (15 ml) in a 100 ml round bottomed flask a solution of acetylacetone (10g) in ethanol (10 ml) was added. The mixture was heated under reflux until a negative ferric chloride test is given (ca 1 hr) and the reaction mixture was poured into cold water (60 ml). Extracted with ether, dried (Na_2SO_4), and distilled. B.P. 140-142°C.

Generation and reaction of 3-methyl-5-lithiomethyl isoxazole with oxoketene dithioacetals; General procedure:

To a stirred solution of freshly distilled 3,5-dimethyl isoxazole (0.015 mol) in dry THF (25 ml), butyllithium (0.015 mol) was added under nitrogen atmosphere at -78°C. The solution was stirred for 30 min. and a solution of 1 (0.01 mol) in THF (25 ml) was added to 35 at -78°C, stirred for 1 hr, slowly warming the mixture to room temperature. The reaction mixture was poured over saturated ammonium chloride solution. The aqueous layer was extracted with ether (2x50 ml) and the combined organic layer was washed with water (100 ml), dried (Na_2SO_4) and evaporated to give the crude alcohol 36 in nearly quantitative yield.

General procedure for the cycloaromatization of hydroxy dithioacetals; Synthesis of substituted and annelated 1,2-benzisoxazoles (38a-h, 41, 43, 46-47, 49, 51, 53a-c, 55a-b, 57a-g, 59, 61):

To a solution of crude alcohol 36 in dry benzene (50 ml), boron trifluoride etherate (2 ml) was added and the reaction mixture was refluxed with stirring for 1 hr. The reaction mixture was cooled and poured over cold saturated $NaHCO_3$ solution, extracted with chloroform (2x50 ml), washed with water, dried (Na_2SO_4) and evaporated to give a viscous residue which was purified by passing through silica gel column (hexane as eluent) to give 38 as colourless crystals (chloroform).

The spectral and analytical data of the 1,2-benzisoxazoles are given below.

3-Methyl-4-methylthio-6-phenyl-1,2-benzisoxazole (38a); colourless crystals; yield 73%; m.p. 70°C; i.r.(KBr): ν_{max} = 1600, 1566, 1425, 1388, 1345 cm^{-1}; ^1H n.m.r.(CCl_4): δ 2.50(s,3H,$C\underline{H}_3$); 2.68(s,3H,$SC\underline{H}_3$); 7.02(brs,1H,$\underline{H}$-7); 7.20-7.67(m,6H_{arom}); ^{13}C n.m.r.($CDCl_3$): δ11.47($\underline{C}H_3$); 17.23($S\underline{C}H_3$); 103.80, 114.59 ($\underline{C}$-7 and $\underline{C}$-5); 125.45, 127.24, 128.35, ($C\underline{H}$, phenyl); 128.36, 140.20, 142.66, 142.41 (quaternary $\underline{C}$); 159.71 ($\underline{C}$-3); 168.07($\underline{C}$-8). (Found: C,70.42; H,5.11; N,5.44. Calc. for $C_{15}H_{13}NOS$(255.31): C,70.56; H,5.13; N,5.48%). m/z 255(M^+,100%).

3-Methyl-4-methylthio-6-(4-chlorophenyl)-1,2-benzisoxazole (38b); colourless crystals; yield 66%; m.p. 155°C; i.r.(KBr): ν_{max} = 1600, 1575, 1430, 1390, 1335 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.56(s,3H,$C\underline{H}_3$); 2.68(s,3H,$SC\underline{H}_3$); 7.02(brs,1H,$\underline{H}$-7); 7.21-7.67(m,6H_{arom}). (Found: C,62.03; H,4.13; N,4.80. Calc. for $C_{15}H_{12}ClNOS$ (289.76): C,62.17; H,4.17; N,4.83%). m/z 289(M^+,60%).

3-Methyl-4-methylthio-6-(4-methoxyphenyl)-1,2-benzisoxazole (38c); colourless crystals; yield 68%; m.p. 130°C; i.r.(KBr): ν_{max} = 1600, 1580, 1430, 1345, 1385 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.60(s,3H,$C\underline{H}_3$); 2.70(s,3H,$SC\underline{H}_3$); 3.80(s,3H,$OC\underline{H}_3$); 7.02(brs,1H,$\underline{H}$-7); 6.80-6.93(d, J=7Hz,A_2B_2,2H_{arom}); 7.33-7.63(d,J=7Hz,A_2B_2,2H_{arom}); 7.36(s,1H_{arom}). (Found: C,67.15; H,5.22; N,4.88. Calc. for $C_{16}H_{15}NO_2S$ (285.34): C,67.34; H,5.29; N,4.90%). m/z 285(M^+,100%).

3-Methyl-4-methylthio-6-(4-methylphenyl)-1,2-benzisoxazole (38d); colourless crystals; yield 65%; m.p. 120°C; i.r.(KBr): ν_{max} = 1600, 1580, 1425, 1385, 1345 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.40(s,3H,$C\underline{H}_3$);

2.56(s,3H,C$\underline{H}_3$); 2.66(s,3H,SC$\underline{H}_3$); 7.03(brs,1H,$\underline{H}$-7); 7.16-7.53 (m,5H_{arom}). (Found: C,71.24; H, 5.60; N,5.18. Calc. for $C_{16}H_{15}NOS$ (269.35): C,71.34; H,5.61; N,5.19%). m/z 269(M^+,100%).

3-Methyl-4-methylthio-6-(2-naphthyl)-1,2-benzisoxazole (38e); colourless crystals; yield 64%; m.p. 145°C; i.r.(KBr):ν_{max} = 1600, 1590, 1425, 1380, 1345 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ2.60(s,3H,C$\underline{H}_3$): 2.73(s,3H,SC$\underline{H}_3$); 7.10(brs,1H,$\underline{H}$-7); 7.26(s,1H_{arom}); 7.36-7.66(m,3H_{arom}); 7.72-8.01(m,4H_{arom}). (Found: C,74.58; H,4.92;N,4.50. Calc. for $C_{19}H_{15}NOS$ (305.37): C,74.72; H,4.95; N,4.58%). m/z 305(M^+,100%).

3-Methyl-4-methylthio-6-(2-furyl)-1,2-benzisoxazoles (38f); colourless crystals; yield 59%; m.p. 85°C; i.r.(KBr): ν_{max} = 1601, 1517, 1429, 1387, 1347 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.56(s,3H,C$\underline{H}_3$); 2.66(s, 3H,SC$\underline{H}_3$); 6.43(m,1H,$\underline{H}$-4'); 6.73(d,J=3Hz,1H,$\underline{H}$-3'); 7.20(s,1H,$\underline{H}$-7); 7.56(d,J=3Hz,2H,$\underline{H}$-5 and $\underline{H}$-5'). (Found: C,63.55; H,4.48; N,5.69. Calc. for $C_{13}H_{11}NO_2S$ (245.28): C,63.65; H,4.52; N,5.70%). m/z 245 (M^+,100%).

3-Methyl-4-methylthio-6-(2-thienyl)-1,2-benzisoxazole (38g); colourless crystals; yield 61%; m.p. 125°C; i.r.(KBr):ν_{max} = 1602, 1573, 1427, 1388, 1341 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.63(s,3H,C$\underline{H}_3$); 2.76(s, 3H,SC$\underline{H}_3$); 7.10-7.30(m,2H_{arom}); 7.41-7.62(m,3H_{arom}). (Found: C,59.63; H,4.19; N,5.32. Calc. for $C_{13}H_{11}NOS_2$ (261.34): C,59.74; H,4.24; N,5.35%). m/z 261(M^+,100%).

3-Methyl-4-methylthio-6-methyl-1,2-benzisoxazole (38h); colourless crystals; yield 54%; m.p. 85°C; i.r.(KBr): ν_{max} = 1601,1517,1429,1387, 1347 cm^{-1}; 1H n.m.r.($CDCl_3$):δ2.43(s,3H,C$\underline{H}_3$); 2.51(s,3H,C$\underline{H}_3$); 2.68

(s,3H,SC$\underline{H}_3$); 7.01(brs,1H,$\underline{H}$-7); 6.86(s,1H$_{arom}$). (Found: C,62.02; H,5.68; H,5.68; N,7.20. Calc. for $C_{10}H_{11}NOS$ (193,26): C,62.14; H,5.73; N,7.24%). m/z 193(M^+,100%).

3-Methyl-4-methylthio-5,6,7,8-tetrahydronaphtho[b]isoxazole (41); colourless crystals; yield 65%; m.p. 42°C; i.r.(KBr): ν_{max} = 1605, 1580, 1430, 1330, 1300 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ1.61-1.98(m,4H,ring C$\underline{H}_2$); 2.34(s,3H,C$\underline{H}_3$); 2.66(s,3H,SC$\underline{H}_3$); 2.60-3.13(m,4H, ring C$\underline{H}_2$); 7.01(brs,1H$_{arom}$). (Found: C,66.80; H,6.47; N,6.02. Calc. for $C_{13}H_{15}NOS$ (233.32): C,66.91; H,6.48; N,6.00%). m/z 233 (M^+,92%).

3-Methyl-4-methylthio-6,7,8,9-tetrahydro-5H-cyclohepta[b]benzisoxazole (43); colourless crystals; yield 67%; m.p. 62°C; i.r.(KBr): ν_{max} = 1600, 1580, 1430, 1380, 1300 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.30-1.80(m, 6H,ring C$\underline{H}_2$); 2.13(s,3H,C$\underline{H}_3$); 2.53(s,3$\underline{H}$,SC$\underline{H}_3$); 2.83(m,2H,ring C$\underline{H}_2$); 7.01(brs,1H$_{arom}$). (Found: C,67.86; H,6.88; N,5.62. Calc. for $C_{14}H_{17}NOS$(247.35): C,67.97; H,6.92; N,5.65%). m/z 247(M^+,100%).

3-Methyl-4-methylthio-5$\underline{H}$-indano[2,1-b]benzisoxazole (46); colourless crystals; yield 57%; m.p. 160°C; i.r.(KBr): ν_{max} = 1600, 1588, 1420, 1388, 1320 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.36(s,3H,C$\underline{H}_3$); 2.73(s,3H,SC$\underline{H}_3$); 3.99(brs,2H,ring C$\underline{H}_2$); 7.26-7.50(m,3H$_{arom}$); 7.63-7.83(m,2H$_{arom}$). (Found: C,71.80; H,4.88; N,5.21. Calc. for $C_{16}H_{13}NOS$ (267.26): C,71.90; H,4.90; N,5.23%). m/z 267(M^+,89%).

3-Methyl-4-methylthio-5,6-dihydrophenanthro[2,1-b]isoxazole (47a); colourless crystals; yield 76%; m.p.152°C; i.r.(KBr): ν_{max} = 1600, 1585, 1513, 1430, 1380, 1330, 1300 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.30(s, 3H,C$\underline{H}_3$); 2.80(s,3H,SC$\underline{H}_3$); 2.72-3.43(m,A_2B_2,4H,C$\underline{H}_2$); 7.16-7.38(m,3H$_{arom}$);

7.60-7.83(m,2H_{arom}); ^{13}C n.m.r.($CDCl_3$): δ 12.75($C\underline{H}_3$); 20.14($SC\underline{H}_3$); 26.04($C\underline{H}_2$); 29.16($C\underline{H}_2$); 105.61, 124.88, 127.24, 127.97, 128.60($\underline{C}H_{arom}$); 123.03, 128.91, 134.24, 134.26, 138.17, 138.26, 155.83, 162.50 (quaternary $\underline{C}$). (Found: C,72.45; H,5.29; N,4.92. Calc. for $C_{17}H_{15}NOS$ (281.36): C,72.56; H,5.37; N,4.97%). m/z 281(M^+,100%).

3-Methyl-4-methylthio-8-methoxy-5,6-dihydrophenanthro[2,1-b] isoxazole (47b); colourless crystals; yield 78%; m.p. 135°C; i.r. (KBr): ν_{max} = 1600, 1580, 1512, 1420, 1385, 1325, 1300 cm^{-1}; ^{1}H n.m.r.($CDCl_3$):δ 2.33(s,3H,$C\underline{H}_3$); 2.83(s,3H,$SC\underline{H}_3$); 2.73-3.36(m,A_2B_2, 4H,$C\underline{H}_2$); 3.83(s,3H,$OC\underline{H}_3$); 6.63-6.93(m,2H_{arom}); 7.56-7.86(m,2H_{arom}). (Found: C,69.31; H,5.48; N,4.08. Calc. for $C_{18}H_{17}NO_2S$ (311.38): C,69.42; H,5.50; N,4.49%). m/z 311(M^+,100%).

3-Methyl-4-methylthio-6,7-dihydro-5H-benzocyclohepta[2,1-b] benzisoxazole (49); colourless crystals; yield 69%; m.p. 175°C; i.r.(KBr): ν_{max} = 1600, 1560, 1430, 1390, 1345 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$):δ2.23-2.36(brs,4H,ring $C\underline{H}_2$); 2.86(s,3H,$SC\underline{H}_3$); 3.43-3.96 (m,2H,ring $C\underline{H}_2$); 7.36-7.83(m,5H_{arom}). (Found: C,73.07; H,5.78; N,4.71. Calc. for $C_{18}H_{17}NOS$ (295.38): C,73.18; H,5.80; N,4.73%). m/z 295 (M^+,100%).

3-Methyl-4-methylthio-10-methyl-5,6-dihydrobenzothiepino[2,1-b] benzisoxazole (51); colourless crystals; yield 81%; m.p. 185°C; i.r.(KBr): ν_{max} = 1600, 1580, 1430, 1380, 1320 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$):δ 2.43(s,3H,$C\underline{H}_3$); 2.46(s,3H,$SC\underline{H}_3$); 2.36-2.73(m,1H,$C\underline{H}$, benzylic); 2.83-3.16(m,1$\underline{H}$,$C\underline{H}$,benzylic); 3.43-3.63(m,1H,$SC\underline{H}$); 3.83-4.13(m,1H,$SC\underline{H}$); 7.16-7.53(m,4H_{arom}). (Found: C,85.99; H,4.88; N,4.05.

Calc. for $C_{18}H_{16}NOS_2$ (327.44): C,66.02; H,4.92; N,4.27%). m/z 327(M^+,100%).

3-Methyl-6-phenyl-1,2-benzisoxazole (53a); colourless crystals; yield 87%; m.p.62°C; i.r.(KBr): ν_{max} = 1600, 1580, 1500, 1430, 1390, 1340 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ2.60(s,3H,$C\underline{H}_3$); 7.26-7.93(m, $8H_{arom}$). (Found: C,78.35; H,4.52; N,5.78. Calc. for $C_{14}H_{11}NO$ (209.23): C,78.46; H,4.55; N,5.80%). m/z 241(M^+,100%).

3-Methyl-6-(4-methylphenyl)-1,2-benzisoxazole (53b); colourless crystals; yield 82%; m.p. 134°C; i.r.(KBr): ν_{max} = 1600, 1560, 1420, 1380,1320 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.36(s,3H,$C\underline{H}_3$); 2.56(s,3H,$C\underline{H}_3$); 7.16-7.33(m,$2H_{arom}$); 7.43-7.76(m,$5H_{arom}$). (Found: C,80.58; H,5.78; N,6.24. Calc. for $C_{15}H_{13}NO$ (223.25): C,80.69; H,5.86; N,6.27%). m/z 223(M^+,100%).

3-Methyl-6-(4-chlorophenyl)-1,2-benzisoxazole (53c); colourless crystals; yield 79%; m.p. 102°C; i.r.(KBr): ν_{max} = 1600, 1555, 1420, 1375, 1320 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 2.56(s,3H,$C\underline{H}_3$); 7.23-7.96(m,$7H_{arom}$). (Found: C,68.88; H,4.08; N,5.72. Calc. for $C_{14}H_{10}ClNO$ (243.72): C,68.98; H,4.10; N,5.74%). m/z 243(M^+,40%).

3-Methyl-5,6-dihydrophenanthro[2,1-b]isoxazole (55a); colourless crystals; yield 85%; m.p. 105°C; i.r.(KBr): ν_{max} = 1620, 1595, 1430, 1380, 1320 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.53(s,3H,$C\underline{H}_3$): 2.73-3.03(m,4$\underline{H}$,ring $C\underline{H}_2$); 7.16-7.46(m,$4H_{arom}$); 7.66-7.93(m,$2H_{arom}$). (Found: C,81.56; H,5.48; N,5.92. Calc. for $C_{16}H_{13}NO$ (235.26): C,81.67; H,5.56; N,5.95%). m/z 235(M^+,90%).

3-Methyl-8-methoxy-5,6-dihydro-phenanthro[2,1-b]isoxazole (55b); colourless crystals; yield 88%; m.p.130°C; i.r.(KBr): ν_{max} = 1600, 1556, 1488, 1440, 1345, 1250 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.46(s,3H, $C\underline{H}_3$); 2.66-3.03(m,4H,ring $C\underline{H}_2$); 3.83(s,3H,$OC\underline{H}_3$); 6.50-6.93(m,$3H_{arom}$); 7.53(brs,$1H_{arom}$); 7.93(d,$1H_{arom}$). (Found: C,76.85; H,5.68; N,5.23. Calc. for $C_{17}H_{15}NO_2$ (265.29): C,76.96; H,5.69; N,5.27%). m/z 265 (M^+,100%).

3-Methyl-4-methylthio-6-styryl-1,2-benzisoxazole (57a); pale yellow crystals; yield 68%. m.p. 145-149°C; i.r.(KBr): ν_{max} = 1600, 1570, 1510, 1430, 1390, 1350 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.60(s,3H,$C\underline{H}_3$); 2.70(s,3H,$SC\underline{H}_3$); 2.03-7.26(m,3H,$2H_{arom}$+$1H_{olefinic}$); 7.36-7.83(m, 6H,$5H_{arom}$+$1H_{olefinic}$). (Found: C,72.45; H,5.04; N,4.92. Calc. for $C_{17}H_{15}NOS$ (281.35): C,72.56; H,5.37; N,4.97%). m/z 281(M^+,100%).

3-Methyl-4-methylthio-6(4-methylstyryl)-1,2-benzisoxazole (57b); pale yellow crystals; yield 71%; m.p. 135°C; i.r.(KBr): ν_{max} = 1600, 1599, 1570, 1500, 1450 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ2.33(s,3H,$C\underline{H}_3$); 2.63 (s,3H,$C\underline{H}_3$); 2.66(s,3H,$SC\underline{H}_3$); 7.03-7.30(m,$2H_{olefinic}$+$1H_{arom}$); 7.30-7.56(m,$5H_{arom}$). (Found: C,73.07; H,5.78; N,4.71. Calc. for $C_{18}H_{17}NOS$ (295.38): C,73.18; H,5.80; N,4.73%). m/z 295(M^+,100%).

3-Methyl-4-methylthio-6(4-methoxystyryl)-1,2-benzisoxazole (57c); yellow crystals; yield 78%; m.p. 139°C; i.r.(KBr): ν_{max} = 1600, 1590, 1500, 1440, 1380 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.60(s,3H,$C\underline{H}_3$); 2.70(s, 3H,$SC\underline{H}_3$); 3.76(s,3H,$OC\underline{H}_3$); 6.76-7.03(m,A_2B_2,$4H_{arom}$+$1H_{olefinic}$); 7.16-7.56(m,A_2B_2,$2H_{arom}$+$1H_{olefinic}$). (Found: C,69.31; H,5.48; N,4.45. Calc. for $C_{18}H_{17}NO_2S$ (311.38): C,69.42; H,5.50; N,4.49%). m/z 311(M^+,100%).

3-Methyl-4-methylthio-6-[4-(3,4-dimethoxystyryl)]-1,2-benzisoxazole (57d); yellow crystals; yield 62%; m.p. 134°C; i.r.(KBr): ν_{max}= 1600, 1580, 1500, 1440, 1380 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$): δ 2.46(s,3H,C$\underline{H}_3$); 2.66 (s,3H,SC$\underline{H}_3$); 3.93(d,6H,OC$\underline{H}_3$); 6.23(brs,2H,1H$_{arom}$+1H$_{olefinic}$); 6.36-6.66(m,2H$_{arom}$); 6.83-7.36(m,3H,2H$_{arom}$+1H$_{olefinic}$). (Found: C,66.71; H,5.58; N,4.00. Calc. for $C_{19}H_{19}NO_3S$ (341.4): C,66.83; H,5.60; N,4.10%). m/z 341(M$^+$,92%).

3-Methyl-4-methylthio-6-[4-(3,4,5-trimethoxystyryl)]-1,2-benzisoxazole (57e); yellow crystals; yield 63%; m.p. 179°C; i.r.(KBr): ν_{max} = 1600, 1590, 1505, 1420, 1380 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$): δ 2.63(s,3H,C$\underline{H}_3$); 2.73(s,3H,SC$\underline{H}_3$); 3.86-4.16(m,9H,OC$\underline{H}_3$); 6.93(brs,2H,1H$_{arom}$+1H$_{olefinic}$); 7.23(brs,2H$_{arom}$); 7.43-7.66(m,2H,1H$_{arom}$+1H$_{olefinic}$). (Found: C,64.54; H,5.68; N,3.74. Calc. fo $C_{20}H_{21}NO_4S$ (371.43): C,64.66; H,5.69; N,3.76%). m/z 371(M$^+$,100%).

3-Methyl-4-methylthio-6-(4-chlorostyryl)-1,2-benzisoxazole (57f); pale yellow crystals; yield 60%; m.p. 120°C; i.r.(KBr): ν_{max} = 1600, 1580, 1430, 1410 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$): δ 2.56(s,3H,C$\underline{H}_3$); 2.66(s,3H, SC$\underline{H}_3$); 6.93-7.13(m,3H,2H$_{arom}$+1H$_{olefinic}$); 7.33-7.63(m,5H,4H$_{arom}$+ 1H$_{olefinic}$). (Found: C,64.53; H,4.42; N,4.41. Calc. for $C_{17}H_{14}ClNOS$ (315.84): C,64.64; H,4.43; N,4.43%). m/z 315 (M$^+$,40%).

3-Methyl-4-methylthio-6-(3,4-methylenedioxystyryl)-1,2-benzisoxazole (57g); yellow crystals; yield 59%; m.p. 188°C; i.r.(KBr): ν_{max}= 1600, 1580, 1500, 1480, 1400 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$): δ 2.63(s,3H,C$\underline{H}_3$); 2.73(s,3H,SC$\underline{H}_3$); 5.93(brs,2H,O-CH$_2$-O); 6.73-7.40(m,5H$_{arom}$+2H$_{olefinic}$). (Found:C,66.31; H,4.58; N,4.28. Calc. for $C_{18}H_{15}NO_3S$ (325.36): C,66.44; H,4.64; N,4.30%). m/z 325(M$^+$,100%).

3-Methyl-4-methylthio-6(4-phenyl-1,3-butadienyl)-1,2-benzisoxazole (59a); yellow crystals; yield 55%; m.p. 153°C; i.r.(KBr): ν_{max} = 1605, 1599, 1440, 1400, 1340 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.56(s,3H,$C\underline{H}_3$); 2.66 (s,3H,$SC\underline{H}_3$); 6.60-7.30(m,$4H_{olefinic}$); 7.13-7.56(m,$7H_{arom}$). (Found: C,74.07; H,5.53; N,4.54. Calc. for $C_{19}H_{17}NOS$ (307.39): C,74.23; H,5.57; N,4.55%). m/z 307(M^+,100%).

3-Methyl-4-methylthio-6-[4-(4-methoxyphenyl)-1,3-butadienyl]-1,2-benzisoxazole (59b); deep yellow crystals; yield 65%; m.p. 162°C; i.r.(KBr): ν_{max} = 1600, 1580, 1510, 1395, 1355 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.56(s,3H,$C\underline{H}_3$); 2.66(s,3H,$SC\underline{H}_3$); 3.83(s,3H,$OC\underline{H}_3$); 6.66-7.33(m, 7H,$3H_{arom}$+$4H_{olefinic}$); 7.20-7.50(m,$3H_{arom}$). (Found: C,70.99; H,5.59; N,4.12. Calc. for $C_{20}H_{19}NO_2S$ (337.41): C,71.18; H,5.68; N,4.14%). m/z 337(M^+,100%).

3-Methyl-4-methylthio-6-(6-phenyl-1,3,5-hexatrienyl)-1,2-benzisoxazole (61); deep yellow crystals; yield 55%; m.p. 172°C; i.r.(KBr): ν_{max}= 1600, 1570, 1435, 1400, 1335 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.63(s,3H,$C\underline{H}_3$); 2.73(s,3H,$SC\underline{H}_3$); 6.43-6.93(m,$6H_{olefinic}$); 7.20-7.56(m,$7H_{arom}$). (Found: C,75.51; H,5.71; N,4.17. Calc. for $C_{21}H_{19}NOS$ (333.42): C,75.64; H,5.74; N,4.19%); m/z 333(M^+, 100%).

REFERENCES

1. For a review, see R.K. Dieter, Tetrahedron, 42, 3029 (1986).
2. G. Singh, M.L. Purkayastha, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I., 1289 (1985).
3. R.K. Dieter, Y. Jenkitkasemwong, Lin, J.W. Dieter, J. Org. Chem., 49, 3183 (1984) and references therein.
4. R.K. Dieter, J.R. Fishpaugh, M.E. Kastner, J. Am. Chem. Soc.,107, 4679 (1985).
5. B. Myrboh, H. Ila and H. Junjappa, J. Org. Chem., 48, 5327 (1983).
6. G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., 25, 5095 (1984).
7. C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 50 (1984).
8. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett.,28, 1459 (1987).
9. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett.,29, 6633 (1988).
10. M.P. Balu, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., 27, 117 (1986).
11. M.P. Balu, H.Ila, H. Junjappa, Tetrahedron Lett., 28, 3023 (1987).
12. A.K. Gupta, H. Ila, H. Junjappa, unpublished results.
13. M.P. Balu, H. Ila, H. Junjappa, unpublished results.
14. M. Natsume and H. Muratake, Tetrahedron Lett., 36, 3477-3480 (1979).
15. H.J. J. Loozen and E.F. Godofroi, J. Org. Chem., 38, 1056 (1973).
16. B. Myrboh, L.W. Singh, H. Ila,H. Junjappa, Synthesis, 307 (1982).
17. J. Koo, J. Am. Chem. Soc., 75, 1891 (1953).
18. R.C. Gilmore, W.J. Horton, J. Am. Chem. Soc.,73, 1411 (1951).
19. D. Huckle, I.M. Lockhart, N.E. Webb, J.Chem. Soc.(C), 2252 (1971).
20. M.P. Reddy, G.S. Krishnarao, Synthesis, 815 (1980).

21. Practical Heterocyclic Chemistry, A.O. Fitton, R.K. Smalley, ed., Academic Press, New York (1968), p. 28.

22. A. Kumar, Ph.D. Thesis submitted to Agra University, Agra, India (1978).

23. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2182 (1962).

24. S. Apparao, S.S. Bhattacharji, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I., 641 (1985).

25. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 1779 (1976).

26. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2187 (1962).

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

CHAPTER IV

DARZEN'S CONDENSATION ON α-OXOKETENE DITHIOACETALS: A NEW VERSATILE SYNTHESIS OF 3,4-SUBSTITUTED-2-FUROATES

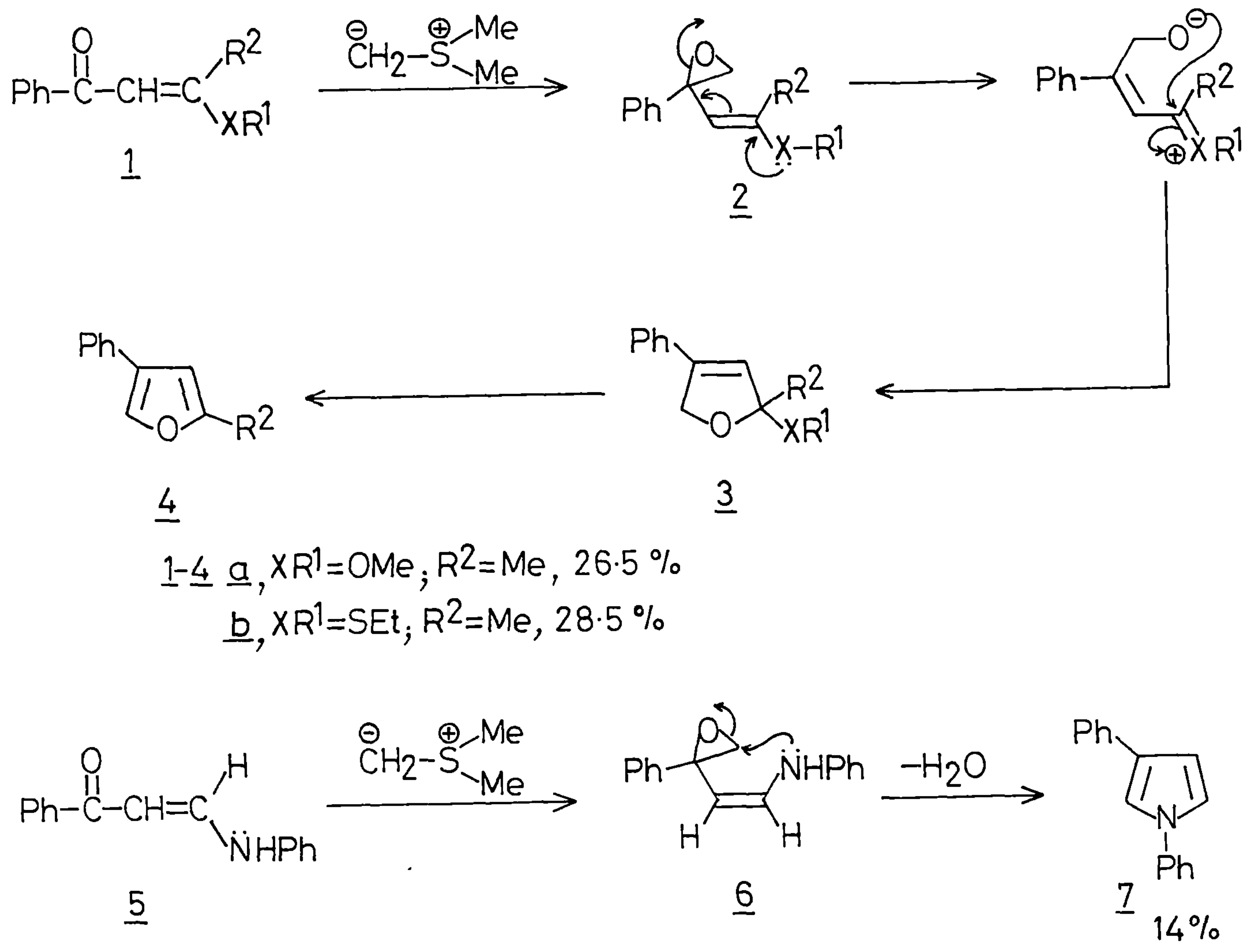
IV.1 INTRODUCTION

The α-oxoketene dithioacetals of the general formula 8 have been shown to undergo either 1,2- or 1,4-conjugate addition to yield the respective regioselective adducts in high yields[1]. Thus they undergo metal hydride reduction in 1,2-fashion to give the corresponding allyl alcohols, which are subsequently converted to the corresponding ene esters, aldehydes or ketones depending on the nature of the substituent at the β-position in 8[2]. The oxoketene dithioacetals generally yield the corresponding esters under these conditions, while the corresponding β-methylthio and β-alkyl-β-methylthio, α-β-unsaturated ketones yield the aldehydes and ketones respectively[3,4]. These reactions have been further extended to the addition of carbon nucleophiles. Thus it has been shown that, the methylmagnesium iodide undergoes regioselective 1,2-addition, while the higher alkyl and aryl grignard reagents yield the products through sequential 1,4- and 1,2-additions[5].

In the preceeding chapter, the addition of allylmagnesium halide is shown to undergo 1,2-addition followed by cycloaromatization to yield the corresponding aromatic ring systems[6]. The method has been shown to be highly general and its further applications to construct the corresponding aromatic ring systems over the isoxazole has been successfully demonstrated[7]. There have been many instances of this nature where a functionalized nucleophile can be made to add in 1,2-fashion to α-oxoketene dithioacetals and were subsequently transformed to synthetically useful products.

The Darzen's condensation on α-oxoketene dithioacetals was considered of particular interest since it should add in 1,2-fashion to yield the epoxide which under appropriate reaction conditions can be rearranged to the corresponding furan derivatives. In the present work thus the reaction has been investigated with lithiobromoacetate and the results are described in this chapter. The literature retrieval reveals that there are few related reactions with α-oxoketene dithioacetals leading to 5-membered heterocycles particularly the furans and pyrroles. Some of these transformations are reviewed herein.

Nishio and coworkers first reported the reaction of dimethylsulfonium methylide (DMSM) with <u>1</u> and observed that the reagent undergoes regioselective 1,2-addition to yield the corresponding epoxy derivatives <u>2</u> which on rearrangement gave the corresponding furans <u>4</u> (Scheme 1).

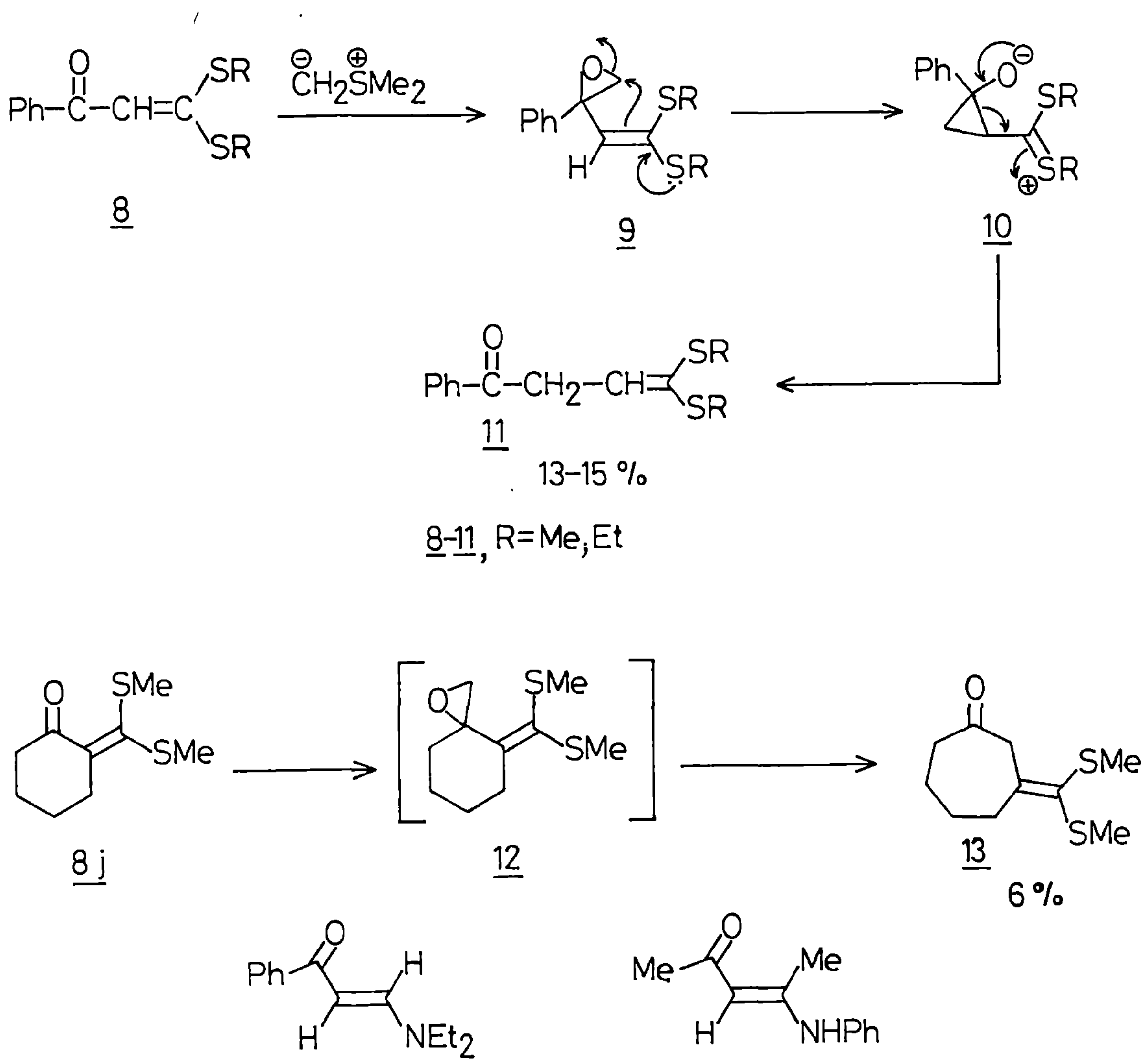


1-4 a, XR^1=OMe; R^2=Me, 26·5 %
b, XR^1=SEt; R^2=Me, 28·5 %

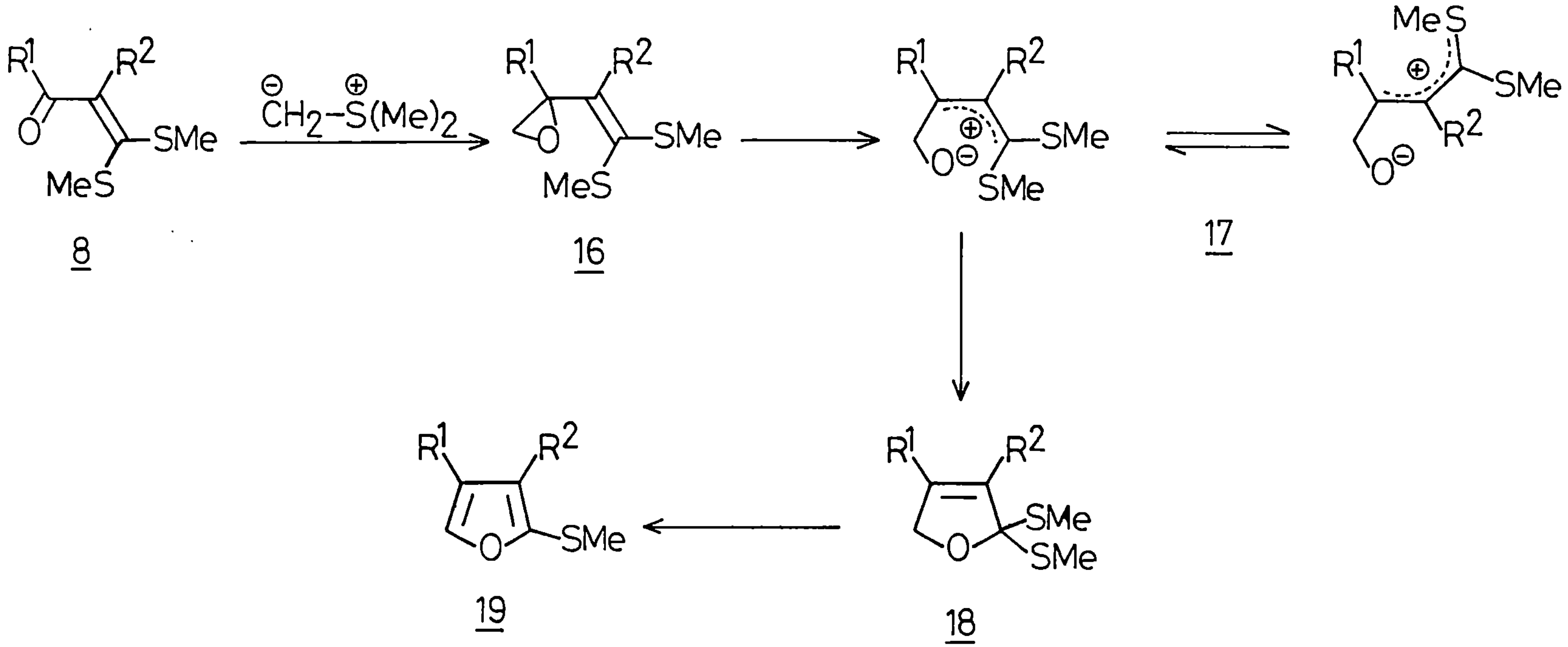
Scheme-1

The yields in these cases were however moderate. Interestingly these authors have also reacted β-anilino-α-β-unsaturated ketones 5 with dimethylsulfonium methylide (DMSM) to yield the corresponding pyrroles 7[8]. Also the reaction path could lead to methylene insertion as described in Scheme 2 to yield the corresponding homologus γ, γ, bisalkylthio-β, γ-unsaturated ketones 11 in low yields. Similarly cyclic acetal 8j yielded the corresponding cycloheptanone 13 in 6% yield (Scheme 2).

Okazaki and coworkers[9] further investigated the work of Nishio and coworkers and observed that the DMSM reacts with 8 in 1,2-fashion to yield the corresponding epoxides 16, which were insitu rearranged to the corresponding furans 19 (Scheme 3) in good yields. They also isolated the epoxide 16 in some cases, to prove the mechanistic pathway from 8 → 16 → 19. The reaction has been shown to be applicable to a number of structural variants of oxoketene dithioacetals with favourable high yields. The scope of the reaction has been demonstrated by extending the method for the synthesis of natural product perilline 21 which contains furan ring. Thus the oxoketene dithioacetal 8a was first converted to 20 by subjecting it to appropriate alkylation in the presence of LDA. The oxoketene dithioacetal 20 was then converted to perilline 21 by treating with dimethylsulfonium methylide and subsequent Raney Nickel desulfurization of the resulting 2-methyl furan (Scheme 4). The same intermediate 8a was first converted into 4-methylfuran 22 and the dimethylallyl side chain was introduced through its 5-lithio derivatives to yield the corresponding furan 23 which on Raney Nickel desulfurization yielded the natural product rose furan 24. Several

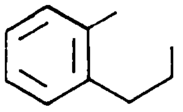

Ph–C–CH=C
O
SR
SR
8
$\overset{\ominus}{C}H_2\overset{\oplus}{S}Me_2$
Ph
O
H
SR
SR
9
Ph
O
SR
SR
10
Ph–C–CH2–CH=
O
SR
SR
11
13–15 %
8-11, R=Me; Et
O
SMe
SMe
8 j
O
SMe
SMe
12
O
SMe
SMe
13
6 %
Ph
O
H
H
NEt2
14
Me
O
Me
H
NHPh
15

Scheme-2

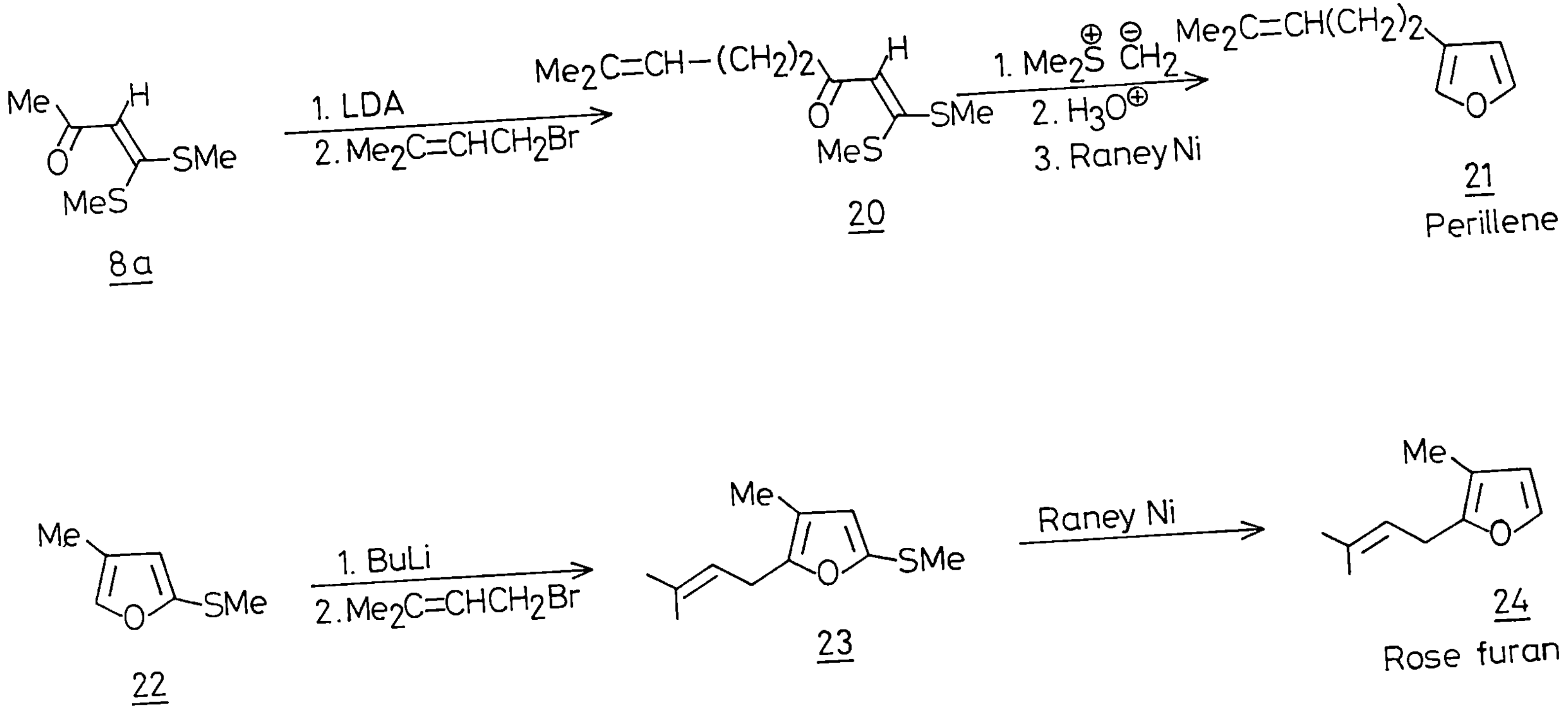


R^1=Ph, R^2=H; R^1=R^2=–$(CH_2)_4$–; R^1=Me, R^2=H; R^1=H, R^2=Ph;

R^1=Me_2C=$CH(CH_2)_2$, R^2=H; R^1=Me, R^2= Me_2C=$CHCH_2$;

R^1=R^2= 

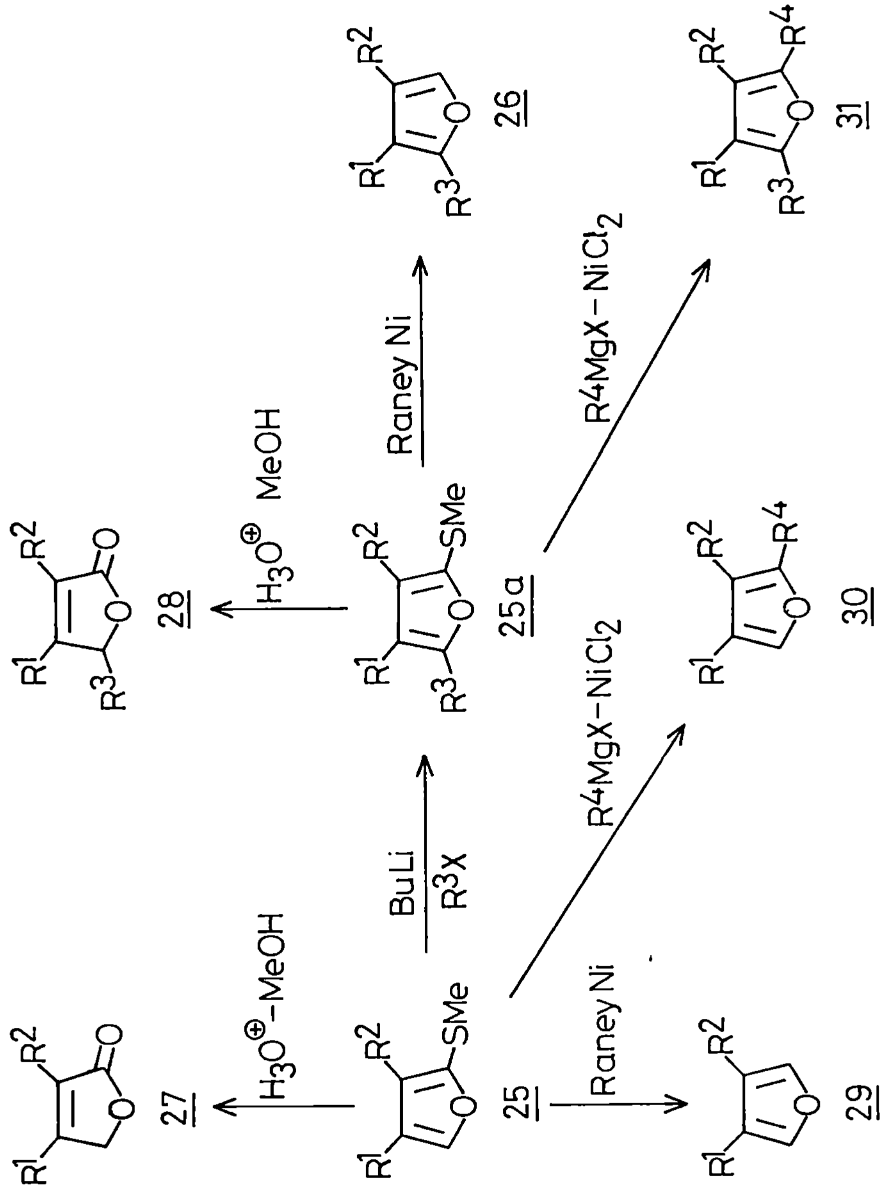
Scheme-3


Me
H
SMe
MeS
O
8a
1. LDA
2. Me2C=CHCH2Br
Me2C=CH−(CH2)2
H
O
SMe
MeS
20
1. Me2S CH2
2. H3O
3. Raney Ni
Me2C=CH(CH2)2
O
21
Perillene
Me
SMe
O
22
1. BuLi
2. Me2C=CHCH2Br
Me
O
SMe
23
Raney Ni
Me
O
24
Rose furan

Scheme-4

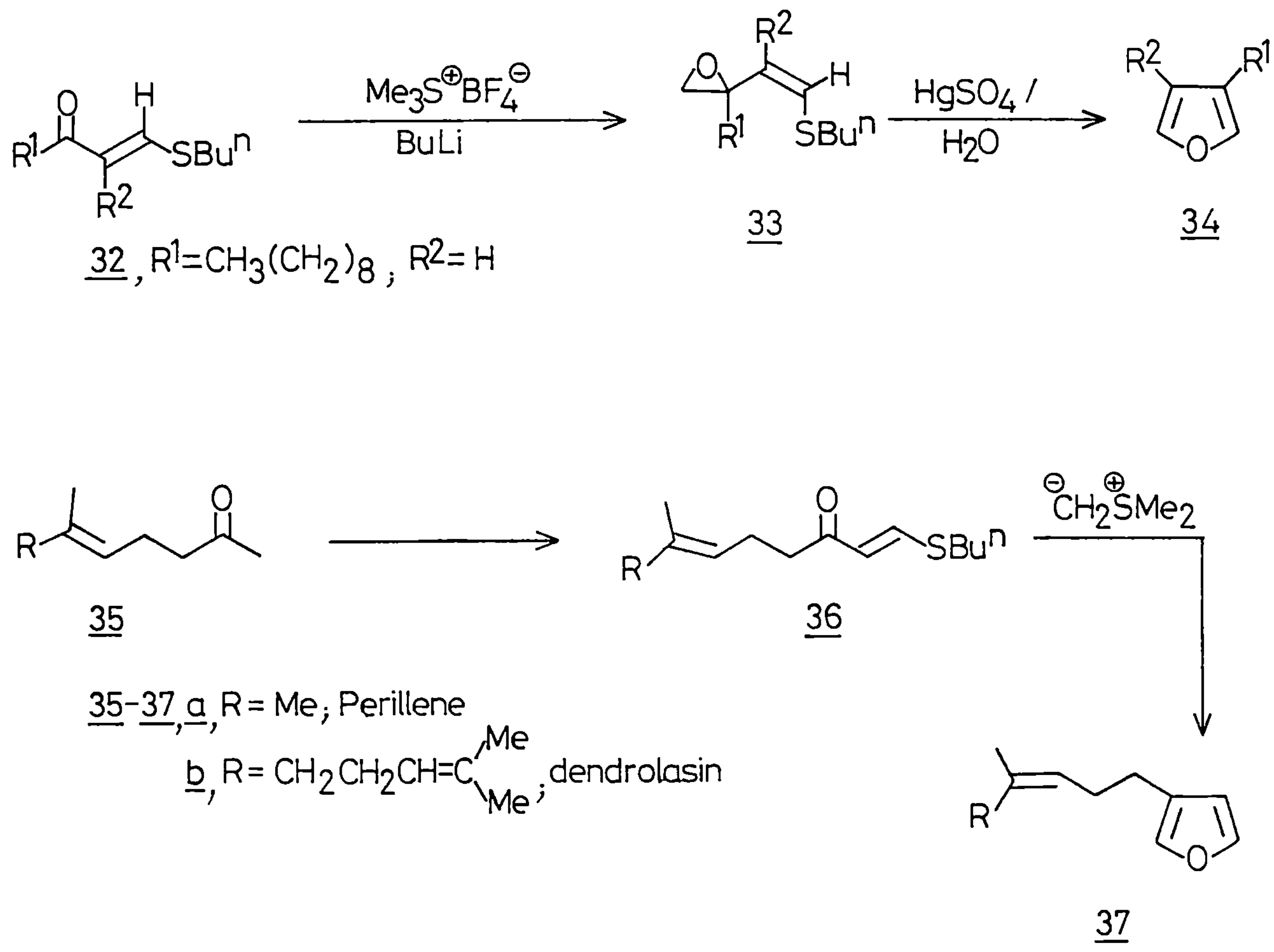
useful conversions by extending this method involving furan ring have been illustrated by Okazaki et al.[9]. The furan 25 (Scheme 5) has also been subjected to hydrolysis to yield the corresponding butenolides 27 in good yields, and it can further be deprotonated at 5-position followed by alkylation to yield furans 25a which are also converted to the corresponding butenolides 28. The furans 25 and 25a were desulfurized to yield the corresponding sulfur free furans 26 and 29. The thiomethyl group was also displaced by alkyl groups in the presence of alkyl grignard reagents and Nickel chloride to yield the corresponding 1,2,3-tri and 1,2,3,4-tetra substituted furans 30 and 31 respectively (Scheme 5). Earlier to these studies Spencer and Garst developed a method for furan synthesis fron n-butylthiomethylene ketones and extended their method for the synthesis of natural furans perilline and dendrolasine. Thus the β-alkylthio ketones 32 were reacted with methylide (DMSM) to yield the furans 34 (Scheme 6) in moderate yields[10]. The method was extended to the synthesis of natural product perilline 37 (Scheme 6) from commercially available ketones 35 and their subsequent conversion to 36 followed by furan ring formation.

The reaction of β-ketoacetals with α-chloroacetate under the Darzen reaction conditions to yield the corresponding glycldic esters 39 (Scheme 7) followed by thermal rearrangement to afford the corresponding 3-substituted-furan-2-carboxylates 41 has been reported[11]. This is the first report that β-keto-acetals have been investigated for the synthesis of not so easily accessible 3-substituted furans through glycidic ester pathway under Darzen reaction conditions.



R^1=Ph, R^2=H, R^3=R^4=Me; R^1=R^2=$(CH_2)_4$; R^3=R^4=Me

Scheme-5

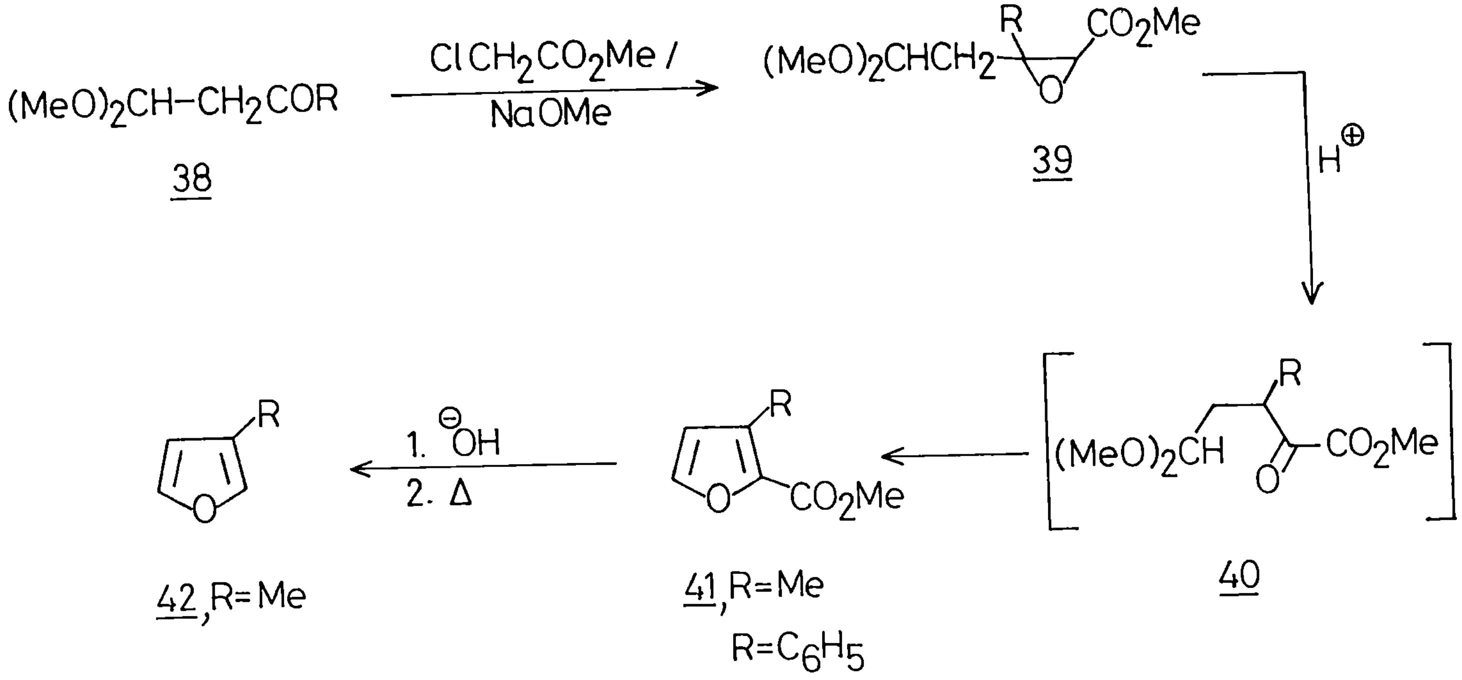


32, $R^1 = CH_3(CH_2)_8$; $R^2 = H$

35-37 a, R = Me; Perillene

b, R = $CH_2CH_2CH{=}C(Me)_2$; dendrolasin

Scheme-6

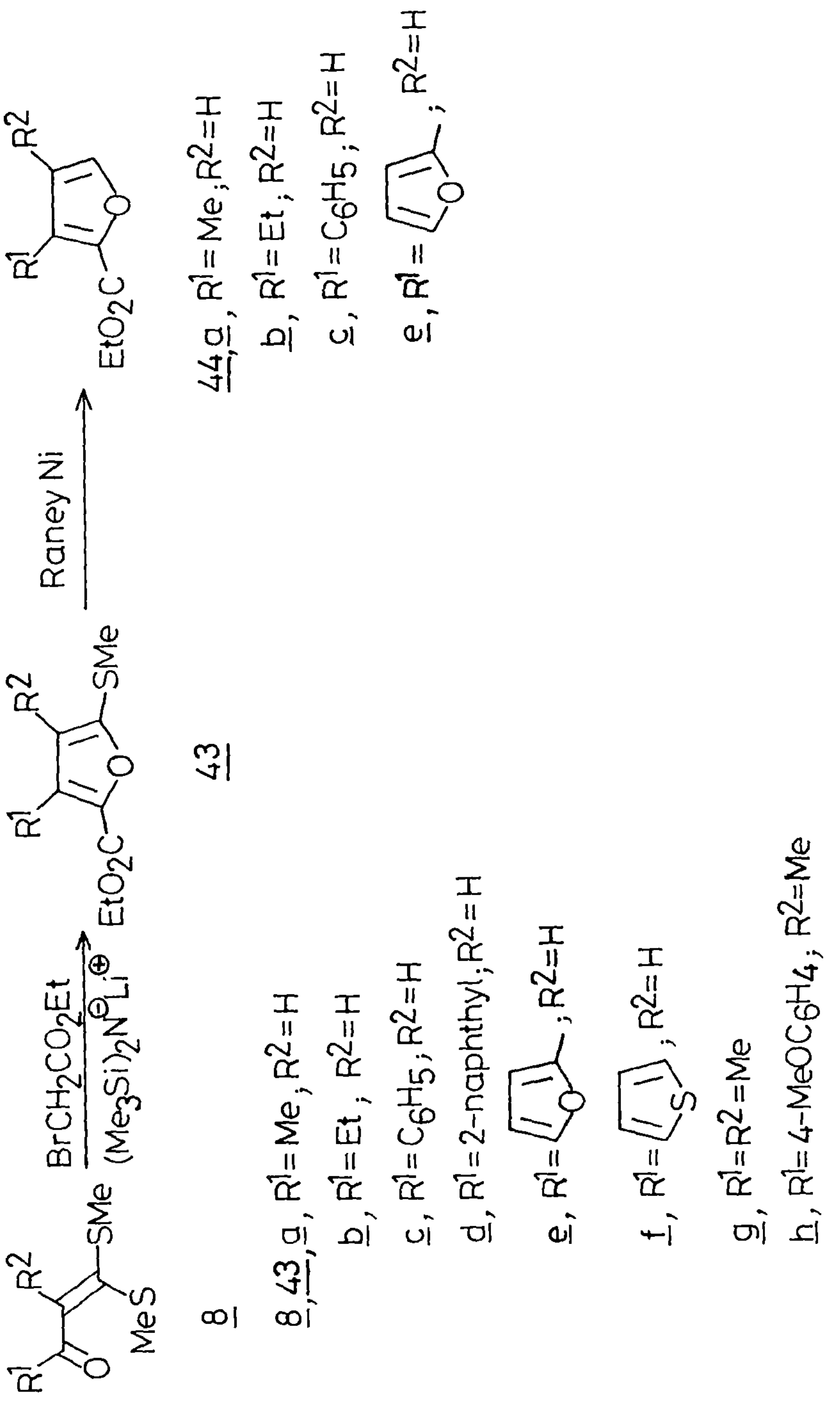

(MeO)$_2$CH–CH$_2$COR
38
ClCH$_2$CO$_2$Me /
NaOMe
(MeO)$_2$CHCH$_2$
R
CO$_2$Me
O
39
H$^{\oplus}$
(MeO)$_2$CH
R
CO$_2$Me
O
40
R
O
CO$_2$Me
41, R=Me
R=C$_6$H$_5$
1. $^{\ominus}$OH
2. Δ
R
O
42, R=Me

Scheme-7

In the light of these studies, it was considered of interest to study the reactivity of oxoketene dithioacetals 8 under Darzen reaction conditions with a view to develop a methodology for the synthesis of substituted and annelated furans through α-oxoketene dithioacetals.

IV.2 RESULTS AND DISCUSSION

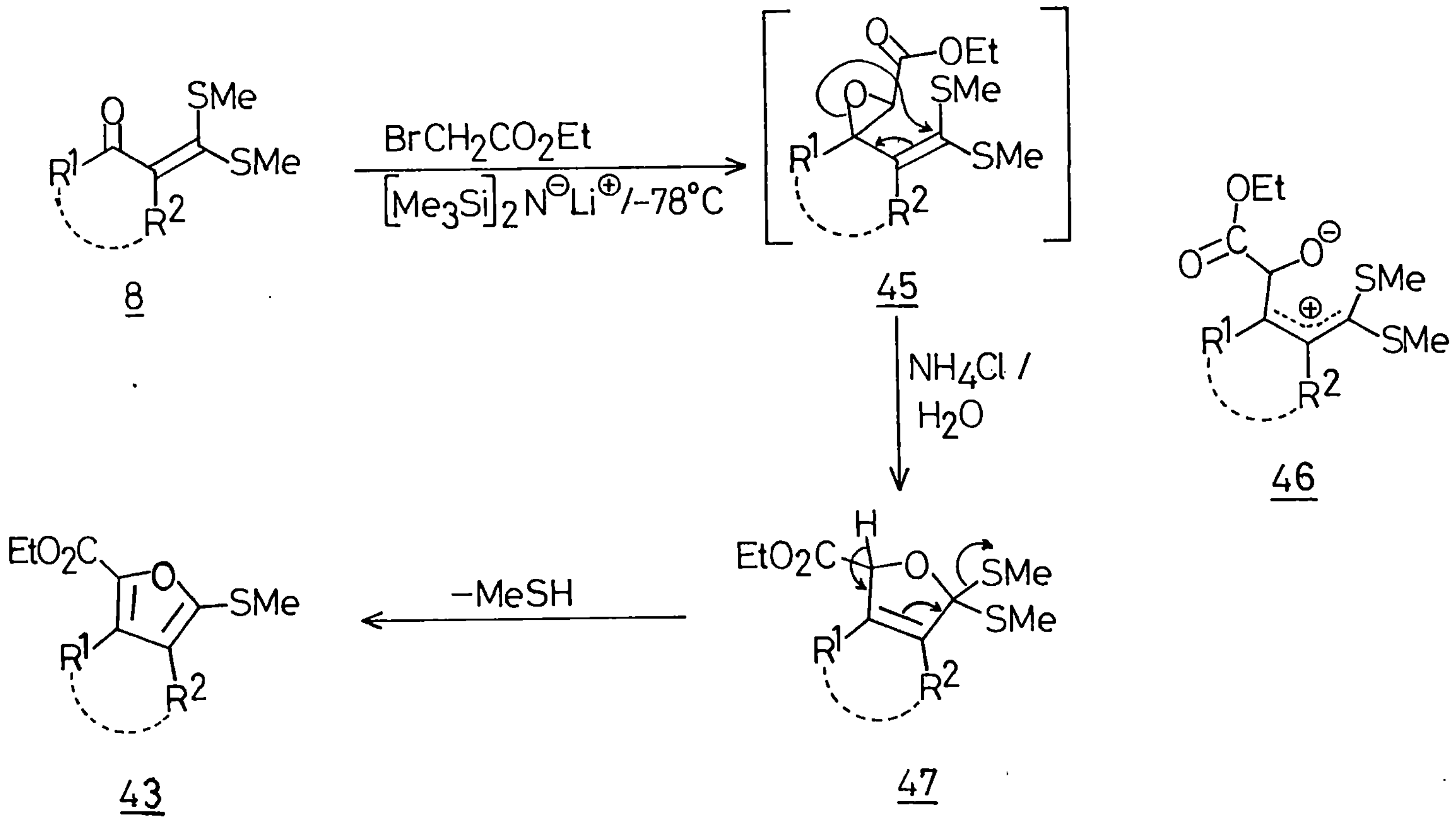
The α-oxoketene dithioacetals 8a-p, 48a-h, 55a-b and 58a-b and 60 have been synthesized as per reported methods[12-24], from this laboratory and their structures were fully confirmed before they were employed for these transformations. The oxoketene dithioacetal 8a was reacted with bromoacetate anion which was generated by treating ethylbromoacetate with lithium bis(trimethylsillyl)amide[25] at -78°C in tetrahydrofuran. Work up and purification of the reaction mixture yielded the corresponding ethyl 3-methyl-5-methylthio-furan-2-carboxylate 43a in 55% yield (Scheme 8). The structure of 43a was confirmed from its analytical and spectral data. Thus it was analyzed for $C_9H_{12}O_3S$ and exhibited in its mass spectrum the molecular ion peak at m/z 200 (M^+,100%) confirming its molecular weight and the formula. In its i.r. spectrum (CCl_4) the peak at 1710 cm^{-1} was assigned to the ester carbonyl group. The structure was further confirmed from its ^1H n.m.r. spectrum ($CDCl_3$). The triplet (3H) at δ 1.33(J=7Hz) was assigned to the methyl protons of the ethyl group. The singlet (3H) at δ 2.33 was attributed to methyl protons while the other singlet (3H) at δ 2.54 was due to methylthio protons. The quartet (2H) at δ 4.24(J=7Hz) was assigned to methylene protons of the ethoxy group. The ring H-4 proton of the furan ring appeared


R1 R2 SMe MeS O
8
BrCH2CO2Et
(Me3Si)2N⊖Li⊕
EtO2C R1 R2 SMe O
43
Raney Ni
EtO2C R1 R2 O
8, 43 a, R1=Me, R2=H
b, R1=Et, R2=H
c, R1=C6H5, R2=H
d, R1=2-naphthyl, R2=H
e, R1= (2-furyl), R2=H
f, R1= (2-thienyl), R2=H
g, R1=R2=Me
h, R1=4-MeOC6H4, R2=Me
44 a, R1=Me, R2=H
b, R1=Et, R2=H
c, R1=C6H5, R2=H
e, R1= (2-furyl), R2=H

Scheme–8

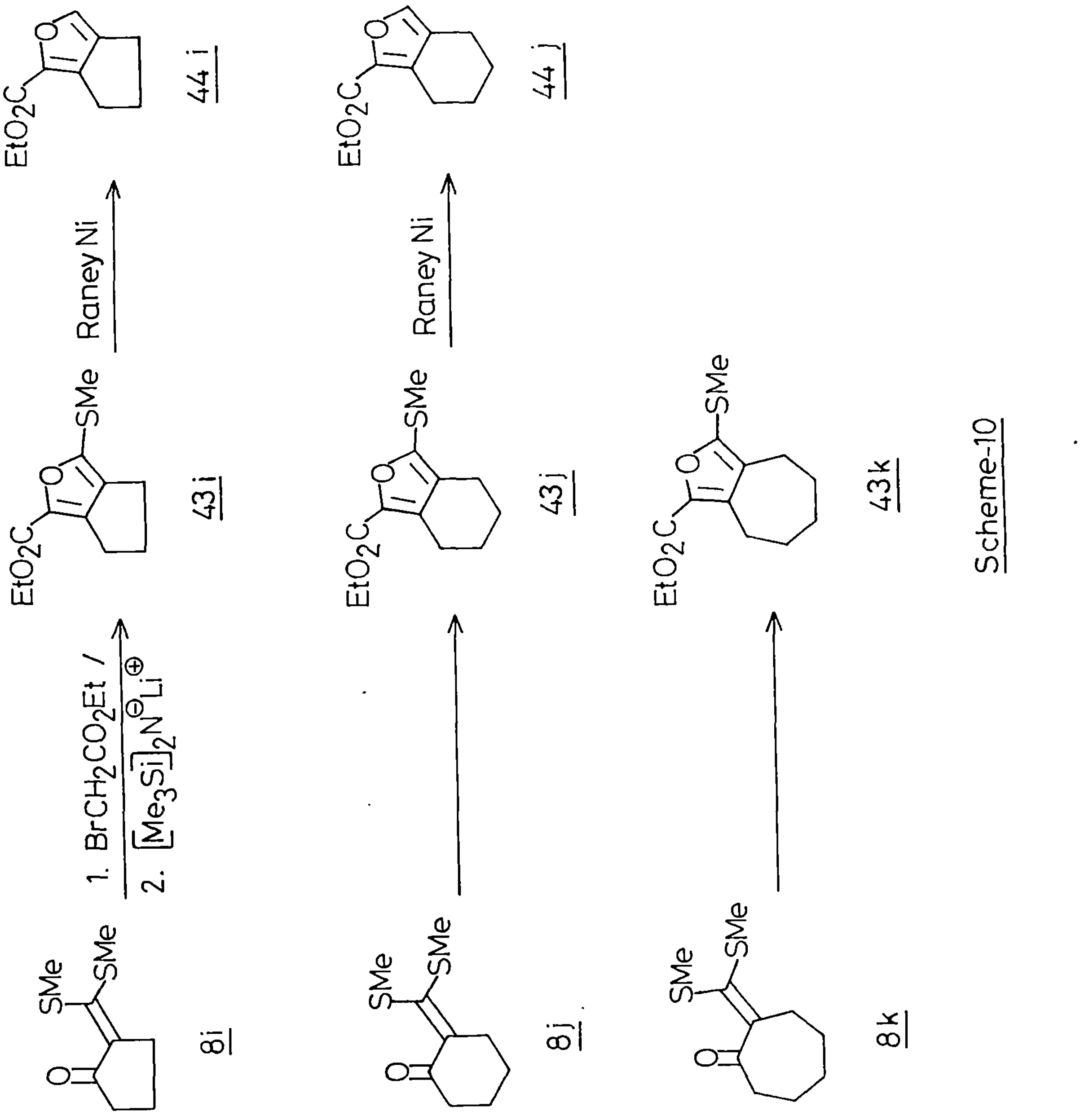
as singlet at δ 6.09. Further structural confirmation for the product was obtained by Raney Nickel desulfurization of the furan 43a which afforded the known ethyl 3-methyl-furan-2-carboxylate 44a whose spectral data was found to be in confirmity with that of the known product[26]. The other furans, 3-substituted 43b-f and 3,4-disubstituted 43g-h furans were similarly obtained from the corresponding 8b-h using the described reaction conditions in 50-70% overall yields. The structural assignment of all the furans 43b-h have been confirmed by their analytical and spectral data and are described in the experimental section. Some of these thiomethyl furans 43b, c and e were subjected to Raney Nickel desulfurization when the corresponding sulfur free furans 44b-c and e (Scheme 8) were obtained in 60-80%, overall yields. The analytical and spectral data of 44b, c and e are given in the experimental section. The probable mechanism of the formation of furan 43 is shown in Scheme 9. The lithiobromoacetate anion undergoes 1,2-addition with 8 to yield the epoxide 45, which on subsequent rearrangement and elimination of methylmercaptan affords the product furan 43. Our attempts to isolate either glycidic ester 45 or the dihydrofuran 47 intermediates under varying conditions were however not successful.

The cyclic oxoketene dithioacetals 8i-p (Scheme 10,11,12) were next investigated with a view to extend the method for the synthesis of the corresponding furan carboxylates annelated at 3- and 4-positions. Thus when 8i was reacted with bromoacetate anion, generated as described earlier, the corresponding ethyl 7-methylthio-cyclopenta[c] furan-2-

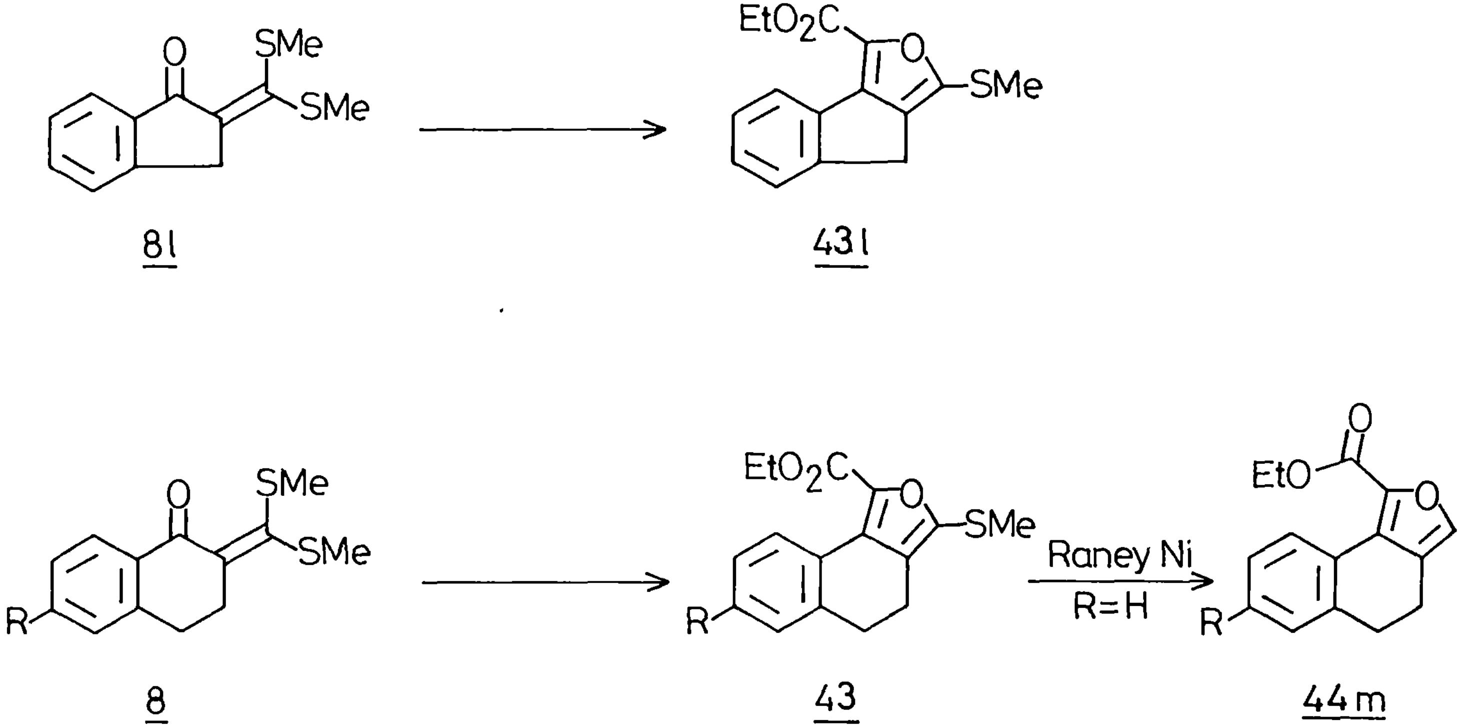


8
BrCH$_2$CO$_2$Et
[Me$_3$Si]$_2$N$^\ominus$Li$^\oplus$/-78°C
45
NH$_4$Cl /
H$_2$O
46
47
−MeSH
43

Scheme-9

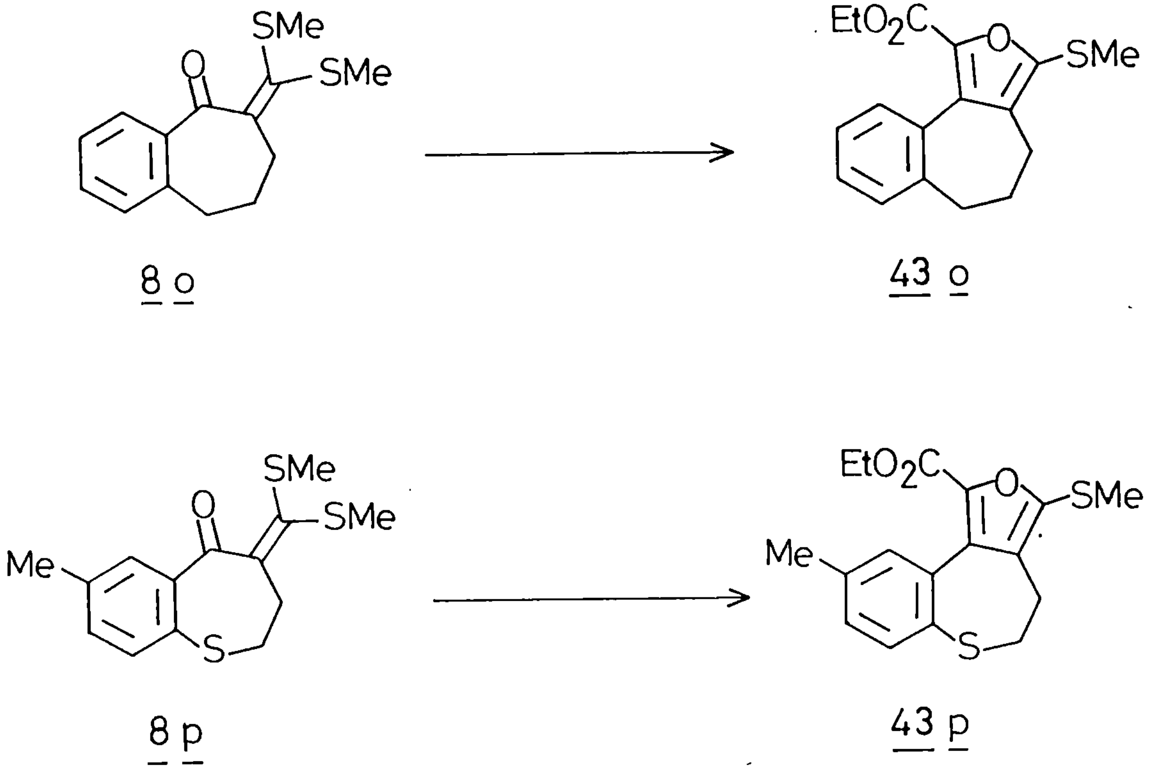

8i
1. BrCH$_2$CO$_2$Et /
2. [Me$_3$Si]$_2$N$^\ominus$Li$^\oplus$
43i
Raney Ni
44 i
8j
43j
Raney Ni
44 j
8k
43k
SMe
EtO$_2$C
O

Scheme-10



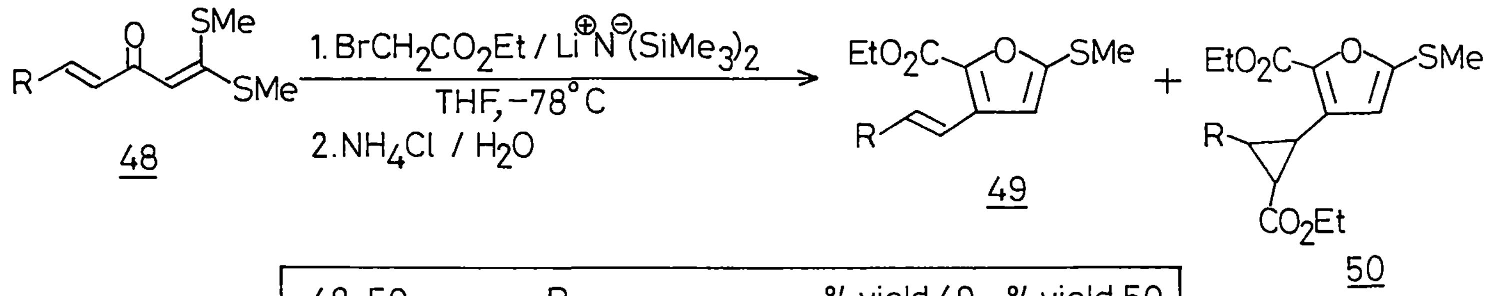
8, 43 m, R=H
n, R=OMe

Scheme-11

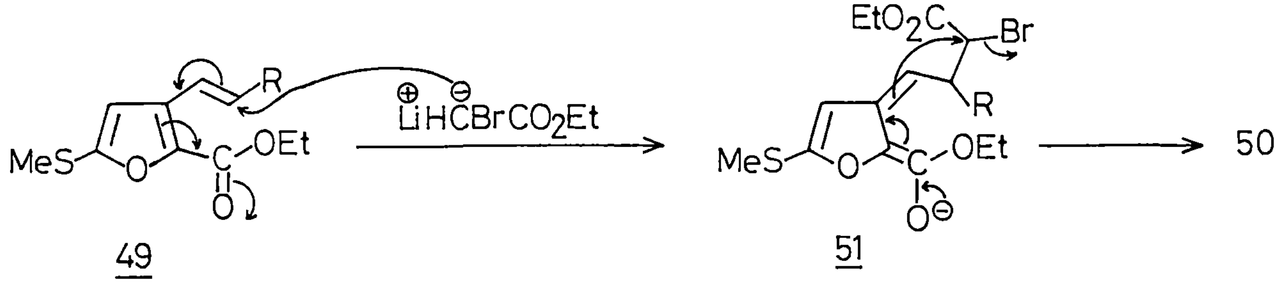


Scheme-12

carboxylate was obtained in 58% yield. The structure of 43i was confirmed from its analytical and spectral data and found to be in agreement with the assigned structure. These results are described in the experimental section. The furan 43i was also subjected to Raney Nickel desulfurization when the corresponding sulfur free furan 44i was obtained in 70% yield. Similarly the oxoketene dithioacetals 8j-p derived from appropriate cyclic ketones yielded the corresponding furans 43j-p (Scheme 10,11,12) in 50-60% overall yields. The analytical and spectral data of 43j-p were in confirmity with the assigned structures and are described in the experimental section. The furans 43j and 43m were desulfurized to yield the corresponding sulfur free furans 44j and 44m in quantitative yields and their structure was confirmed by its analytical and spectral data (experimental). In order to further generalize the reaction, the Darzen's condensation was next examined on α-cinnamoylketene dithioacetals 48a-h. These systems are of particular interest since the bromoacetate anion is likely to attack either one of the electrophilic carbons and consequently yield a mixture of products (Scheme 13). Thus when 48a was reacted with bromoacetate anion the reaction mixture after work-up revealed that it contains two compounds. The structural assignment showed that the ethyl 3-styryl-5-methylthio-furan-2-carboxylate 49a was formed in 20% yield whereas the other product was characterized as ethyl 3-(2-carbethoxy-3-phenyl-cycloprop-1-yl)-5-methylthio-furan-2-carboxylate 50a in 42% yield. The structure of 49a was elucidated from its analytical and spectral data. It was analyzed for $C_{16}H_{16}O_3S$ and exhibited in its mass spectrum the molecular ion peak at m/z 288 (M^+,100%). In its i.r. spectrum (CCl_4) the band



48, 50	R	%yield 49	%yield 50
a	C_6H_5	20	42
b	4-MeOC$_6$H$_4$	25	48
c	3,4-(MeO)$_2$C$_6$H$_3$	55	28
d	3,4,5-(MeO)$_3$C$_6$H$_2$	60	30
e	3,4-methylenedioxyC$_6$H$_3$	22	43
f	4-ClC$_6$H$_4$	—	67
g	4-MeC$_6$H$_4$	—	58
h	Me	—	67

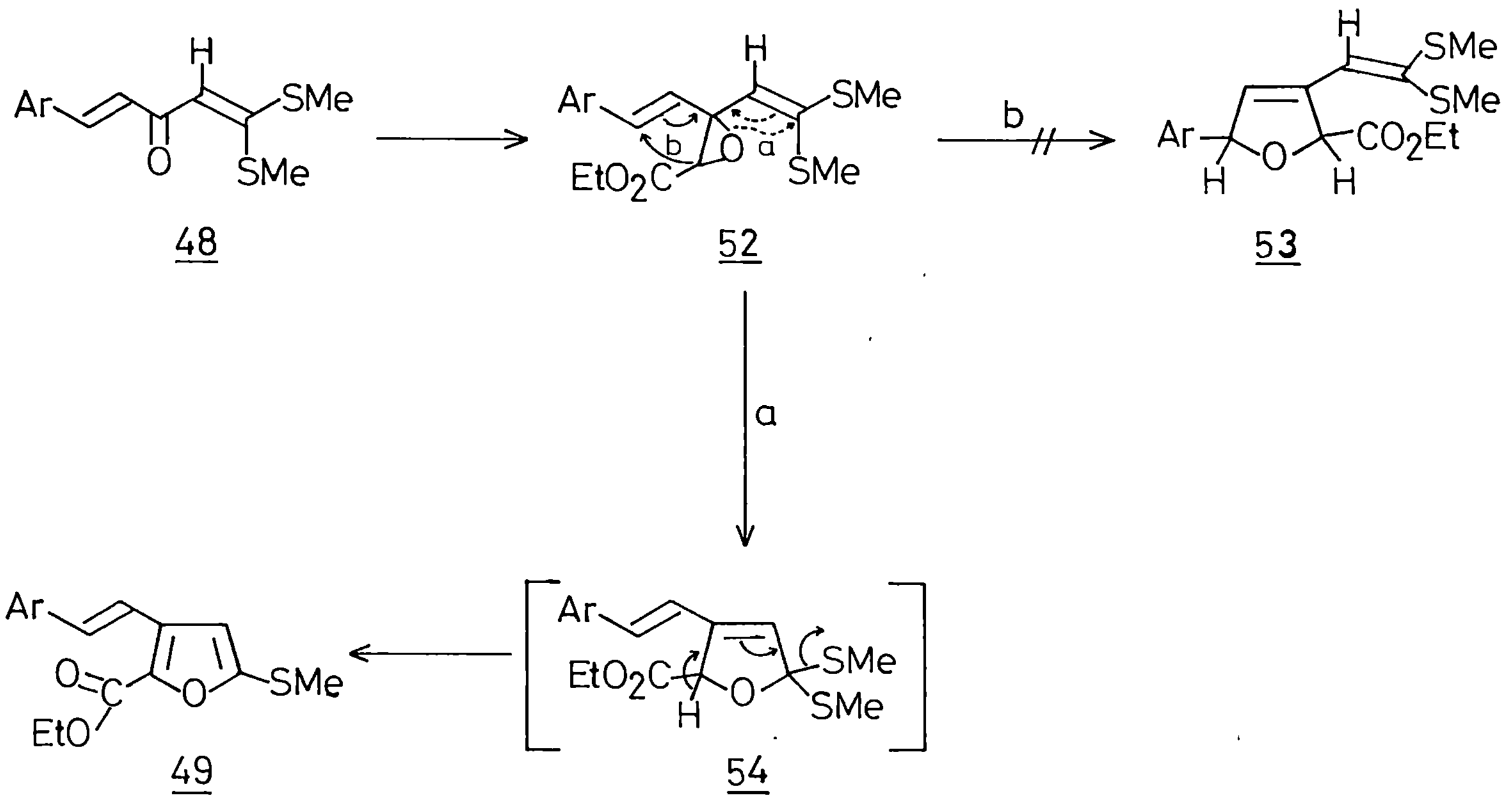


Scheme-13

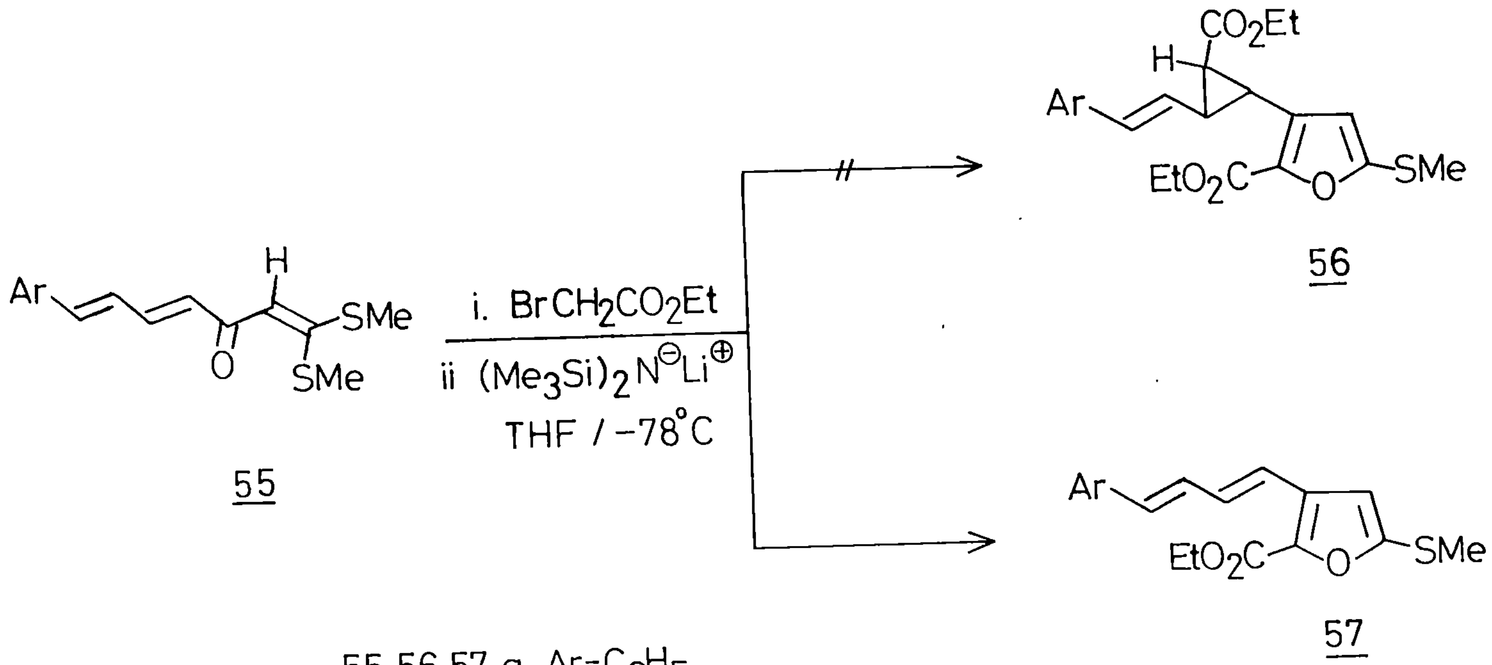
at 1690 was assigned to ester carbonyl function. The structure was further confirmed from its ^{1}H n.m.r. spectrum (CCl_4). The signal due to ethoxy protons appeared as triplet (3H, J=7Hz) and quartet (2H,J=7Hz) at δ1.33 and δ4.33 respectively. Whereas the singlet at δ2.46(3H) was assigned to methylthio protons. The H-4 ring proton appeared as singlet at δ6.56. The multiplet between δ7.16-7.56 was assigned to five aromatic protons. The styryl protons appeared as characteristic doublets (J=16Hz) at δ 6.83 and δ7.60 respectively. The structure of 50a was confirmed from its analytical and spectral data. It was analyzed for $C_{20}H_{22}O_5S$ and exhibited the molecular ion peak at m/z 374 (M^+,30%). The band at 1720 cm^{-1} in its i.r. spectrum was assigned to ester carbonyl group. The structure was further confirmed by its ^{1}H n.m.r. spectrum ($CDCl_3$). The methyl protons of the two ethoxy groups appeared as overlapping triplets between δ 1.13-1.56. The signal at δ 2.50 appeared as singlet and was assigned to methylthio protons. The three cyclopropyl protons appeared as three multiplets between δ 2.26-2.43, δ 2.83-3.03 and δ 3.23-3.46 respectively. The furan ring proton H-4 was observed at δ 6.40. The five aromatic protons appeared as broad singlets around δ 7.13-7.46. The yield of 50a could be further increased by extending the reaction time beyond eight hours. It was possible to isolate only 50a without 49a as a contaminant on prolonged reaction time and with excess of lithiobromoacetate. It was therefore concluded that the formation of 50a is taking place from 49a through cyclopropanation as depicted in 51 through 49 to 50 (Scheme 13). The probable mechanism for the formation of 50a can be explained as follows, the initially formed styryl substituted furan 49 undergoes nucleophilic addition at the α-position of the styryl group, which has enhanced electrophilicity due to π-electron delocalization over the carbonyl group of the carbethoxy moiety to yield the intermediate 51 which then cyclizes with the elimination of the bromide ion to afford the product 50a. The cinnamoylketene dithioacetals 48b-e gave under the above described conditions the corresponding furans 49b-e and the cyclopropyl furans 50b-e in varying yields (Scheme 13) respectively. However, the acetals 48f and 48g afforded only the corresponding cyclopropyl furans 50f and 50g exclusively. Similarly the corresponding α-butenoyl oxoketene dithioacetal 48h afforded only the cyclopropyl furan 50h exclusively in 67% yield. The products obtained in these reactions were separated by column chromatography in pure form and the structural assignment was confirmed by their analytical and spectral data which are described in the experimental section.

As a further proof of the proposed mechanism for the formation of 50 from 49, 49a was reacted with bromoacetate anion in the presence of base and the corresponding cyclopropyl furan 50a thus formed was found to be identical with the original compound.

Apparently the glycidic ester intermediate 52 formed under Darzen reaction conditions (Scheme 14) rearranges involving mercapto double bond path-a leading to 49. The dihydrofuran 53 (path-b) involving epoxy ring participation with the styryl double bond was therefore ruled out. Interestingly when the (5-aryl-2,4-pentadienoyl)ketene dithioacetals 55a-b (Scheme 15) were treated with ethyl bromoacetate


Ar
O
H
SMe
SMe
48
Ar
EtO2C
O
H
SMe
SMe
a
b
52
b
Ar
O
H
H
CO2Et
H
SMe
SMe
53
a
Ar
EtO2C
H
O
SMe
SMe
54
Ar
O
C
EtO
O
SMe
49

Scheme-14

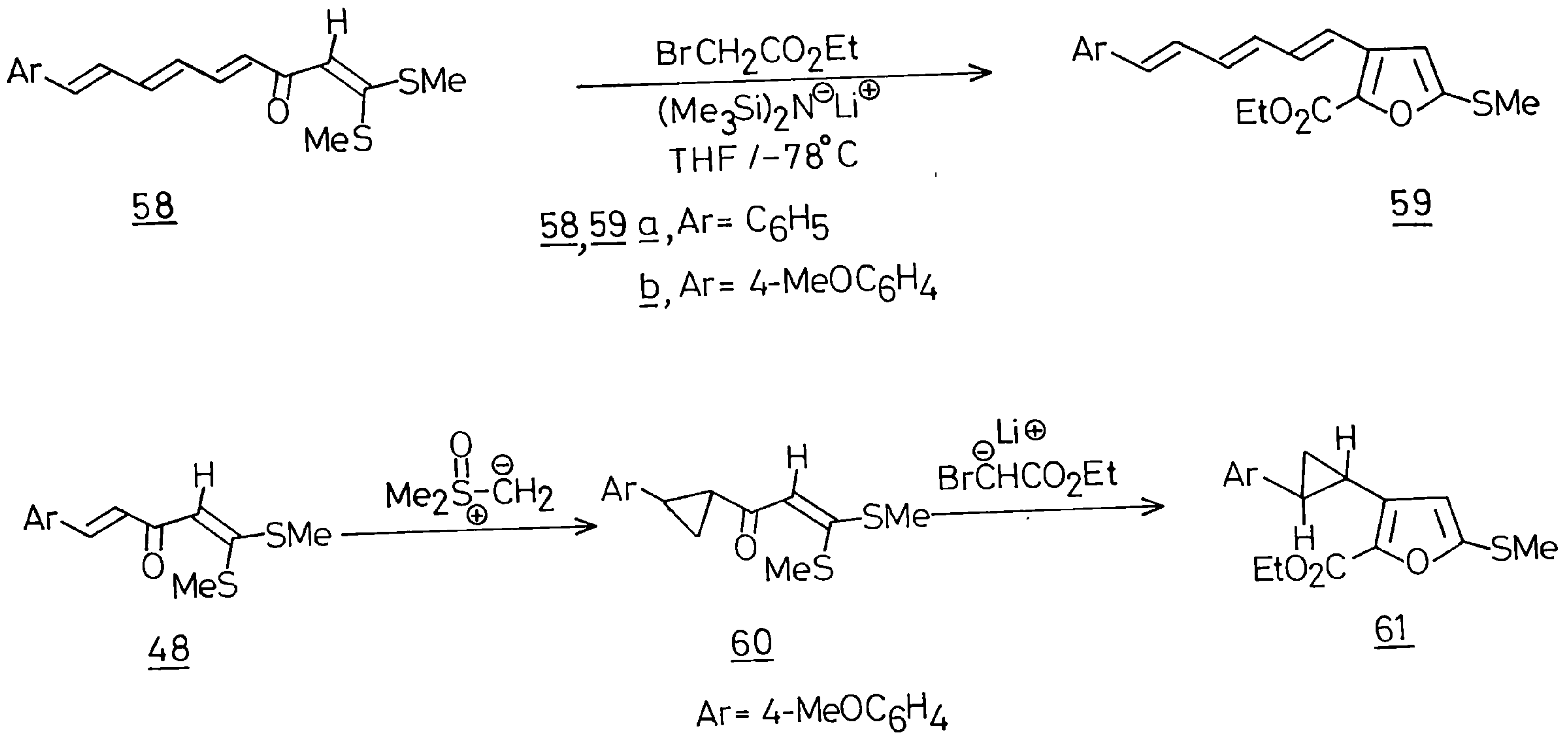


$\underline{55}$, $\underline{56}$, $\underline{57}$ $\underline{a}$, Ar=C_6H_5
$\underline{b}$, Ar=4-MeOC_6H_4

Scheme-15

anion under similar reaction conditions only the corresponding ethyl 3-(4-phenyl-1,3-butadienyl)-5-methylthio-furan-2-carboxylate 57a and ethyl 3-[4-(4-methoxyphenyl)-1,3-butadienyl]-5-methylthiofuran-2-carboxylate 57b were obtained in 52% and 51% yields respectively. The cyclopropanation of one of the side chain double bonds to yield the cyclopropylfuran 56 was not detected in both the reactions. The structures of 57a and 57b were confirmed from their analytical and spectral data which were in agreement with the proposed structure. Similarly the α-(7-aryl-2,4,6-heptatrienoyl)ketene dithioacetals 58a and 58b underwent the described transformation with ethyl bromoacetate anion to yield the corresponding ethyl 3-(6-phenyl-1,3,5-hexatrienyl)-5-methylthio-furan-2-carboxylate 59a and ethyl 3-[6-(4-methoxyphenyl)-1,3,5-hexatrienyl]-5-methylthio-furan-2-carboxylate 59b in 58% and 49% yields respectively (Scheme 16) and the structural assignment was confirmed from their analytical and spectral data (experimental). Apparently the reaction conditions are mild enough to introduce acid sensitive polyenyl functionalities over the furan ring.

In one of the experiments the α-cyclopropyl oxoketene dithioacetal 60 (Scheme 16) formed from 48 using dimethyl oxosulfonium methylide was subjected to bromoacetate condensations under similar reaction conditions, when the furan 61 was formed in 65% yield. The structure was assigned by its analytical and spectral data which are described in the experimental section. This experiment suggests that the preconstructed cyclopropane ring can be retained during the course of these transformations from 60 to 61.


Ar
SMe
MeS
O
H
58
BrCH$_2$CO$_2$Et
(Me$_3$Si)$_2$N$^{\ominus}$Li$^{\oplus}$
THF / -78° C
58,59 a, Ar= C$_6$H$_5$
b, Ar= 4-MeOC$_6$H$_4$
EtO$_2$C
59
48
Me$_2$S(O)$^{\oplus}$-CH$_2^{\ominus}$
60
Li$^{\oplus}$
Br$\overset{\ominus}{C}$HCO$_2$Et
61
Ar= 4-MeOC$_6$H$_4$

Scheme-16

IV.3 CONCLUSION

This transformation provides an easy pathway for the synthesis of furans. A large number of structural variants of α-oxoketene dithioacetals have been shown to undergo Darzen's condensation with ethyl bromoacetate generally in the presence of the base lithium bis(trimethylsillyl)amide under very mild reaction conditions leading to insitu spontaneous ring expansion to form the hitherto unreported furans carrying substituent at 3 and 4 positions. The illustrations suggest further possibilities of Darzen condensation with systems other than carbethoxy group so that the methodology can be efficiently used for the synthesis of 3,4-substituted furans. The thiomethyl group at 5-position is of considerable synthetic potential since it can undergo hydrolytic cleavage to yield the corresponding butenolides. It can also be replaced by alkyl groups in the presence of Raney Nickel catalyst so that the functional group manipulation will further enhance the synthetic utility of the described methodology.

IV.3 EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point (capillary method) apparatus and are uncorrected. ^{1}H n.m.r. spectra were recorded on a Varian EM-390, 90 MHz spectrometer and the chemical shift values are expressed as δ(ppm) downfield from Me_4Si as internal standard. I.r. and mass spectra were recorded on a Perkin-Elmer 297 spectrometer and a Jeol D-300 mass spectrometer respectively. Carbon and hydrogen analysis were done at RSIC, Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of acetone, ethylmethylketone, acetophenone, 2-acetylnaphthalene, 2-acetylfuran, 2-acetylthiophene, cyclopentanone, cyclohexanone, cycloheptanone, 1-tetralone, 6-methoxytetralone, propiophenone, benzaldehyde, 4-tolualdehyde, anisaldehyde, 4-chlorobenzaldehyde, piperonal, 2,3-dimethoxybenzaldehyde, 3,4,6-trimethoxybenzaldehyde, cinnamaldehyde and ethylbromoacetate were purified before use wherever necessary. The cyclic ketones i.e. 1-indanone, 1-benzsuberanone, benzthiepenone, 4-methoxycinnamaldehyde, 5-phenyl-2,4-pentadienal, 5-(4-methoxyphenyl)-2,4-pentadienal were prepared according to the reported procedure. The known α-oxoketene dithioacetals 8a-p α-cinnamoylketene dithioacetals 48a-h, 5-aryl, 1,1-bis(methylthio)-7-aryl-1,4,6-heptatriene-3-ones 55a-b and 1,1-bis(methylthio)-9-aryl, 1,4,6,8-nonatetraene-3-ones 58a-b were prepared according to the reported procedure[12-23], which was described in the Chapter III (experimental).

The unknown dithioacetal 8b was also prepared by known procedure and was characterized with the help of spectral and analytical data given below.

3,3-Bis(methylthio)-1-ethyl-2-propen-1-one (8b); pale yellow solid; yield 60%; m.p. 48°C; i.r.(KBr): ν_{max} = 1650, 1500 cm^{-1}; ^1H n.m.r. (CCl_4): δ 1.03(t,J=7Hz,3H,CH_2CH_3); 2.83(s,6H,SCH_3); 2.30(q,J=7Hz,2H, CH_2CH_3); 5.83(s,$1H_{olefinic}$). (Found: C,47.91; H,6.82. Calc. for $C_7H_{12}OS_2$ (176.17): C,47.72; H,6.86%). m/z 176(M^+,100%).

General procedure[24] for the preparation of cyclopropylketene dithioacetal (60):

A solution of 50% aqueous NaOH (50 ml) was introduced beneath a solution of the substrate (0.01 mol) and the phase transfer catalyst (TBAI) (0.013 mol) in dichloromethane (50 ml). Trimethylsulfoxonium iodide (0.011 mol) was added and the mixture was maintained at 45-50°C with vigorous stirring for 16-24 hr. (monitored by t.l.c.). The layers were separated and the organic layer was evaporated. The residue was diluted with EtOAc and the precipated catalyst was removed by filteration. The ethyl acetate solution was evaporated and chromatographed over silica gel column using 5% EtOAc-hexane as eluent.

3,3-Bis(methylthio)-1-[2-(4-methoxyphenyl)cyclopropyl]-2-propen-1-one (60); pale yellow solid (CH_2Cl_2-hexane); yield 92%; m.p. 96-97°C i.r.(KBr): ν_{max} = 1621, 1492 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.14-1.37(m, 1H,CH_2,cyclopropyl); 1.52-1.80(m,1H,CH_2,cyclopropyl); 1.79-2.04(m, 1H,CH,cyclopropyl); 2.41(s,3H,SCH_3); 2.43(s,3H,SCH_3); 2.34-2.58(m, 1H,CH,cyclopropyl, merged with SCH_3); 3.75(s,3H,OCH_3); 6.16(s,$1H_{olefinic}$);

6.76(d,J=9Hz,2H_{arom}); 7.00(d,J=9Hz,2H_{arom}).(Found: C,65.02; H,6.76. Calc. for $C_{15}H_{18}O_2S_2$ (294.29): C,65.18; H,5.84%). m/z 294(M^+,24%).

General procedure for the synthesis of 3/4 substituted and annelated furoates (43a-p, 49a-e, 50a-h, 57a-b, 59a-b and 61):

To a nitrogen flushed 100 ml three necked flask equipped with nitrogen inlet, septum inlet and magnetic stirrer was added a solution of lithium bis(trimethylsilyl)amide (3.4g, 0.02 m) in dry THF (15 ml) and the flask was cooled to -78°C. A solution of ethyl α-bromoacetate (3.4g, 0.02 m) in dry THF (10 ml) was then added dropwise (5 min.) to the cooled mixture and stirred for 10 mins. The corresponding dithioacetal (0.01 m) dissolved in dry THF (20 ml) was then added over a period of 10 mins, and the mixture was stirred at -78°C for 30 mins. followed by further stirring at room temperature for 12 hrs. The reaction mixture was poured over saturated NH_4Cl solution(100 ml), extracted with ether (3x50 ml), the combined organic layer washed with water (1x100 ml), dried anhyd. Na_2SO_4) and the solvent was removed to give the crude product which was further purified by passing through neutral alumina column. Elution with hexane yielded the pure products in good yields.

Ethyl 3-methyl-5-methylthio-furan-2-carboxylate (43a); viscous liquid; yield 55%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.33(t, J=6Hz,3H,$CH_2\underline{CH_3}$); 2.23(s,3H,$\underline{CH_3}$); 2.45(s,3H,$S\underline{CH_3}$); 4.24(q,J=6Hz,2H, $\underline{CH_2}CH_3$); 6.09(s,1H,$\underline{H}$-4). (Found: C,53.82; H,6.00. Calc. for $C_9H_{12}O_3S$ (200.25): C,53.97; H,6.04%). m/z 200(M^+,100%).

Ethyl 3-ethyl-5-methylthio-furan-2-carboxylate (43b); viscous liquid; yield 55%; i.r.(CCl_4): ν_{max} = 1700 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.03-1.53 (m,6H,$CH_2C\underline{H}_3$); 2.46(s,3H,$SC\underline{H}_3$); 2.76(q,J=7Hz,2H,$C\underline{H}_2CH_3$); 4.22(q,J=7Hz, 2H,$C\underline{H}_2CH_3$); 6.06(s,1H,$\underline{H}$-4). (Found: C,56.15; H,6.60. Calc. for $C_{10}H_{14}O_3S$ (214.27): C,56.05; H,6.58%). m/z 214(M^+,100%).

Ethyl 3-phenyl-5-methylthio-furan-2-carboxylate (43c); white solid; yield 62%; m.p. 49-50°C; i.r.(KBr): ν_{max} = 1700 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ1.22(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.50(s,3H,$SC\underline{H}_3$); 4.22(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 6.42(s,1H,$\underline{H}$-4); 7.22-7.60(m,5H_{arom}). (Found: C,64.22; H,5.31. Calc. for $C_{14}H_{14}O_3S$ (262.31): C,64.09; H,5.37%). m/z 262 (M^+,100%).

Ethyl 3-(2-naphthyl)-5-methylthio-furan-2-carboxylate(43d); viscous liquid; yield 61%; i.r.(CCl_4): ν_{max} = 1720 cm^{-1}; ^{1}H n.m.r. (CCl_4): δ 1.24(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.54(s,3H,$SC\underline{H}_3$); 4.22(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 6.52(s,1H,$\underline{H}$-4); 7.32-8.02(m,7H_{arom}). (Found: C,69.35; H,5.10. Calc. for $C_{18}H_{16}O_3S$ (312.37): C,69.20; H,5.16%). m/z 312(M^+,100%).

Ethyl 3-(2-furyl)-5-methylthio-furan-2-carboxylate (43e); viscous liquid; yield 65%; i.r.(CCl_4): ν_{max} = 1720 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.36(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.46(s,3H,$SC\underline{H}_3$); 4.32(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 6.36-6.40(d,J=2Hz,1H,$\underline{H}$-4'); 6.66(s,1H,$\underline{H}$-4); 7.34(d,J=2Hz,$\underline{H}$-3'); 7.54(d,J=3Hz,1H,$\underline{H}$-5'). (Found: C,57.28; H,4.72. Calc. for $C_{12}H_{12}O_4S$ (252.28): C,57.12; H,4.79%). m/z 252(M^+,100%).

Ethyl 3-(2-thienyl)-5-methylthio-furan-2-carboxylate (43f); viscous liquid; yield 63%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.36(t,J=7Hz,3H,$CH_2C\underline{H}_3$); 2.46(s,3H,$SC\underline{H}_3$); 4.36(q,J=6Hz,2H,$C\underline{H}_2CH_3$);

6.56(s,1H,H-4); 7.06(m,1H,H-4'); 7.35(d,J=2Hz,1H,H-3'); 7.76(d, J=2Hz,1H,H-5'). (Found: C,53.81; H,4.46. Calc. for $C_{12}H_{12}O_3S_2$(268.34): C,53.70; H,4.50%). m/z 268(M^+,100%).

Ethyl 3,4-dimethyl-5-methylthio-furan-2-carboxylate (43g); viscous liquid; yield 45%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.40(t,J=7Hz,3H,CH_2CH_3); 2.18(s,3H,CH_3); 2.48(s,6H,SCH_3,CH_3); 4.20(q,J=7Hz,2H,CH_2CH_3). (Found: C,56.13; H,6.52. Calc. for $C_{10}H_{14}O_3S$ (214.27): C,56.05; H,6.58%). m/z 214(M^+,100%).

Ethyl 3-(4-methoxyphenyl)-4-methyl-5-methylthio-furan-2-carboxylate (43h); viscous liquid; yield 40%; i.r.(CCl_4): ν_{max} = 1715 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.21(t,J=7Hz,3H,CH_2CH_3); 1.90(s,3H,CH_3); 2.48 (s,3H,SCH_3); 3.78(s,3H,OCH_3); 4.10(q,J=7Hz,2H,CH_2CH_3); 6.79-7.20 (m,$4H_{arom}$). (Found: C,62.88; H,5.90. Calc. for $C_{16}H_{18}O_4S$ (306.36): C,62.72; H,5.92%). m/z 306(M^+,100%).

Ethyl 6-methylthio-cyclopenta[c]furan-2-carboxylate (43i); viscous liquid; yield 58%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^1H n.m.r.(CCl_4): δ1.39(t,J=6Hz,3H,CH_2CH_3); 2.29-2.99(m,6H,ring CH_2); 2.49(s,3H,SCH_3); 4.28(q,J=6Hz,2H,CH_2CH_3). (Found: C,58.48; H,6.26. Calc. for $C_{11}H_{14}O_3S$ (226.28): C,58.32; H,6.28%). m/z 226(M^+,100%).

Ethyl 7-methylthio-cyclohexa[c]furan-2-carboxylate (43j); white solid; yield 60%; m.p. 45-47°C; i.r.(KBr): ν_{max} = 1690 cm^{-1}; ^1H n.m.r.(CCl_4): δ1.34(t,J=6Hz,3H,CH_2CH_3); 1.60-1.82(m,4H,ring CH_2); 2.42(s,3H,SCH_3); 2.31-2.82(m,4H,ring CH_2); 4.20(q,J=6Hz,2H,CH_2CH_3). (Found: C,59.82; H,6.68. Calc. for $C_{12}H_{16}O_3S$ (240.31): C,59.97; H,6.71%). m/z 240(M^+, 100%).

Ethyl 8-methylthio-cyclohepta[*c*]furan-2-carboxylate (43k); viscous liquid; yield 59%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.36(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 1.44-1.86(m,6H,ring $C\underline{H}_2$); 2.42(s,3H,$SC\underline{H}_3$); 2.42-2.62(m,2H,ring $C\underline{H}_2$); 2.84-3.02(m,2H,ring $C\underline{H}_2$); 4.26(q,J=6Hz,2H, $C\underline{H}_2CH_3$). (Found: C,61.49; H,7.10. Calc. for $C_{13}H_{18}O_3S$ (254.33): C,61.38; H,7.13%). m/z 254 (M^+,100%).

Ethyl 2-methylthio-3*H*-indano[2,1-*c*]furan-8-carboxylate (43l); viscous liquid; yield 56%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.44(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.56(s,3H,$SC\underline{H}_3$); 3.70(s,2H,ring $C\underline{H}_2$); 4.44(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 7.20-7.46(m,$3H_{arom}$); 8.13-8.23(m,$1H_{arom}$). (Found: C,65.57; H,5.12. Calc. for $C_{15}H_{14}O_3S$ (274.32): C, 65.67; H,5.14%). m/z 274 (M^+,100%).

Ethyl 2-methylthio-3,4-dihydro-naphtho[2,1-*c*]furan-9-carboxylate (43m); viscous liquid; yield 69%; i.r.(CCl_4): ν_{max} 1700 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$): δ 1.34(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.44(s,3H,$SC\underline{H}_3$); 2.52-2.94(m,4H, ring $C\underline{H}_2$); 4.36(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 7.14-7.36(m,$3H_{arom}$); 8.46-8.64 (m,$1H_{arom}$).(Found: C,66.79; H,5.53. Calc. for $C_{16}H_{16}O_3S$ (288.35): C,66.64; H,5.59%). m/z 288(M^+,100%).

Ethyl 2-methylthio-6-methoxy-3,4-dihydronaphtho[2,1-*c*]furan-9-carboxylate (43n); viscous liquid;yield 69%; i.r.(CCl_4): ν_{max} = 1700 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.36(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.42(s,3H, $SC\underline{H}_3$); 2.53-2.88(m,4H,ring $C\underline{H}_2$); 3.72(s,3H,$OC\underline{H}_3$); 4.30(q,J=6Hz,2H, $C\underline{H}_2CH_3$); 6.58-6.85(m,$2H_{arom}$); 8.48-8.60(m,$1H_{arom}$). (Found: C,64.20; H,5.62, Calc. for $C_{17}H_{18}O_4S$ (318.23): C,64.15; H,5.65%). m/z 318 (M^+,100%).

Ethyl 2-methylthio-4,5-dihydro-3*H*-benzocyclohepta[2,1-*c*]furan-9-carboxylate (43o); viscous liquid; yield 55%; i.r.(CCl_4): ν_{max}= 1700 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.30(t,J=6Hz,3H,$CH_2\underline{CH_3}$); 1.78-2.24(m,2H,ring CH_2); 2.16-2.64(m,4H,ring $\underline{CH_2}$); 2.50(s,3H,$S\underline{CH_3}$); 4.20(q,J=6Hz,2H,$\underline{CH_2}CH_3$); 7.24-7.32(m,3H$_{arom}$); 7.44-7.64(m,1H$_{arom}$). (Found: C,67.68; H,5.90. Calc. for $C_{17}H_{18}O_3S$ (302.37): C,67.52; H,5.99%). m/z 302(M$^+$,100%).

Ethyl 2-methylthio-8-methyl-3,4-dihydro-benzothiepino[2,1-*c*]furan-10-carboxylate (43p); viscous liquid; yield 52%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 1.31(t,J=6Hz,3H,$CH_2\underline{CH_3}$); 2.36(s,3H, $\underline{CH_3}$); 2.50(s,3H,$S\underline{CH_3}$); 2.57-2.71(m,2H,ring $\underline{CH_2}$); 2.81-3.36(m,2H, $S\underline{CH_2}$); 4.31(q,J=6Hz,2H,$\underline{CH_2}CH_3$); 7.01-7.72(m,3H$_{arom}$). (Found: C,61.21; H,5.38. Calc. for $C_{17}H_{18}O_3S_2$(334.43): C,61.05; H,5.42%). m/z 334(M$^+$,100%).

Reductive Desulphurization of (43a-c,e, 43i,j and 43m): 2-Carbethoxy-3-substituted and 3/4 annelated furans (44a-c,e, 44i,j and m);

General procedure:

To a solution of the appropriate methylthiofuran (0.005 m) in ethanol (25 ml) freshly prepared W_4 Raney Nickel (0.5g) was added and the reaction mixture was stirred at room temperature for 1h. It was then filtered through Kieselguhr, washed with hot chloroform (3x15 ml), and the solvent is evaporated from the combined filtrate to give the crude desulphurized product, which was further purified by passing through neutral alumina column (elution with hexane). The spectral and analytical data of furans thus obtained are given below.

Ethyl 3-methyl-furan-2-carboxylate (44a); viscous liquid; yield 83%; i.r.(CCl_4): ν_{max} = 1700 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.36(t,J=6Hz,3H,$CH_2\underline{CH_3}$);

2.30(s,3H,C$\underline{H}_3$); 4.30(q,J=6Hz,2H,C$\underline{H}_2$CH$_3$); 6.26(d,J=3Hz,1H,$\underline{H}$-4); 7.36(d,J=3Hz,1H,$\underline{H}$-5). (Found:C,62.42; H,6.48. Calc. for $C_8H_{10}O_3$ (154.16): C,62.32; H,6.53%).

Ethyl 3-ethyl-furan-2-carboxylate (44b); viscous liquid; yield 82%; i.r.(CCl$_4$):ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$):δ1.03-1.66(m,6H, CH$_2$C$\underline{H}_3$); 2.83(q,J=7Hz,2H,C$\underline{H}_2$CH$_3$); 4.30(q,J=7Hz,2H,C$\underline{H}_2$CH$_3$); 6.36 (d,J=3Hz,1H,$\underline{H}$-4); 7.43(d,J=3Hz,1H,$\underline{H}$-5). (Found: C,64.38; H,7.09. Calc. for $C_{19}H_{12}O_3$ (168.19): C,64.26; H,7.19%). m/z 168(M$^+$,25%).

Ethyl 3-phenyl-furan-2-carboxylate (44c); viscous liquid; yield 87%; i.r.(CCl$_4$):ν_{max} = 1705 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$):δ1.26(t,J=6Hz,3H, C$\underline{H}_2$CH$_3$); 4.36(q,J=6Hz,2H,C$\underline{H}_2$CH$_3$); 6.63(d,J=2Hz,1H,$\underline{H}$-4); 7.36(d, J=2Hz,1H,$\underline{H}$-5); 7.43-7.70(m,5H$_{arom}$). (Found: C,72.38; H,5.54. Calc. for $C_{13}H_{12}O_3$(216.23): C,72.20; H,5.59%). m/z 216(M$^+$,95.8%).

Ethyl 3-(2-furyl)-furan-2-carboxylate (44e); viscous liquid; yield 76%; i.r.(CCl$_4$):ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$):δ1.36(t,J=6Hz, 3H,CH$_2$C$\underline{H}_3$); 4.33(q,J=6Hz,2H,C$\underline{H}_2$CH$_3$); 6.33-6.56(m,1H,$\underline{H}$-4'); 6.83(d, J=3Hz,$\underline{H}$-4); 7.40(d,J=3Hz,2H,$\underline{H}$-3', $\underline{H}$-5); 7.50(d,J=3Hz,1H,$\underline{H}$-5'). (Found: C,63.22; H,4.79.Calc. for $C_{11}H_{10}O_4$ (206.19): C,64.07; H,4.88%). m/z 206(M$^+$,100%).

Ethyl cyclopenta[c]furan-2-carboxylate(44i); viscous liquid; yield 70%; i.r.(CCl$_4$):ν_{max} = 1710 cm^{-1}; ^{1}H n.m.r.(CCl$_4$): δ1.33(t,J=6Hz. 3H,CH$_2$C$\underline{H}_3$); 2.23-2.93(m,6H,ring C$\underline{H}_2$); 4.20(q,J=6Hz,2H,C$\underline{H}_2$CH$_3$); 7.10 (s,1H$_{olefinic}$). (Found: C,66.78; H,6.68. Calc. for $C_{10}H_{12}O_3$ (180.20): C,66.64; H,6.71%). m/z 180(M$^+$,40.6%).

Ethyl cyclohexa[c]furan-2-carboxylate(44j); viscous liquid; yield 85%; i.r.(CCl_4): ν_{max} = 1700 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.36(t,J=6Hz, 3H,CH_2CH_3); 1.50-1.86(m,4H,ring CH_2); 2.40-2.63(m,2H,ring CH_2); 2.73-2.92(m,2H,ring CH_2); 4.33(q,J=6Hz,2H,CH_2CH_3); 7.26(s,$1H_{olefinic}$). (Found: C,68.11; H,7.06. Calc. for $C_{11}H_{14}O_3$ (194.22): C,68.02; H,7.26%).

Ethyl 3,4-dihydro-naphtho[2,1-c]furan-2-carboxylate (44m); viscous liquid; yield 80%; i.r.(CCl_4): ν_{max} = 1700 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.36(t,J=6Hz,3H,CH_2CH_3); 2.53-2.93(m,4H,ring CH_2); 4.33(q,J=6Hz, 2H,CH_2CH_3); 7.03-7.33(m,$3H_{arom}$.$1H_{olefinic}$); 8.36-8.63(m,$1H_{arom}$). (Found: C,74.25; H,5.80. Calc. for $C_{15}H_{14}O_3$ (242.26): C,74.36; H,5.82%). m/z 242(M^+,100%).

Ethyl 3-styryl-5-methylthio-furan-2-carboxylate (49a); viscous liquid; yield 20%; i.r.(CCl_4): ν_{max} = 1690 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.33(t, J=6Hz,3H,CH_2CH_3); 2.46(s,3H,SCH_3); 4.33(q,J=6Hz,2H,CH_2CH_3); 6.56(s, 1H,H-4): 6.83(d,J=16Hz,$1H_{olefinic}$); 7.16-7.56(m,$5H_{arom}$); 7.60(d, J=16Hz,$1H_{olefinic}$). (Found: C,66.49; H,5.50. Calc. for $C_{16}H_{16}O_3S$ (288.35): C,66.64; H,5.59%). m/z 288(M^+,100%).

Ethyl 3-(4-methoxystyryl)-5-methylthio-furan-2-carboxylate (49b); viscous liquid; yield 25%; i.r.(CCl_4): ν_{max} = 1669 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 1.43(t,J=7Hz,3H,CH_2CH_3); 2.53(s,3H,SCH_3); 3.86(s,3H,OCH_3); 4.40(q,J=7Hz,2H,CH_2CH_3); 6.66(s,1H,H-4); 6.83-7.03(m,$2H_{arom}$+$1H_{olefinic}$); 7.33-7.60(m,$2H_{arom}$+$1H_{olefinic}$). (Found: C,64.21; H,5.63. Calc. for $C_{17}H_{18}O_4S$ (318.37): C,64.12; H,5.69%). m/z 318(M^+,21%).

Ethyl 3-(3,4-dimethoxystyryl)-5-methylthio-furan-2-carboxylate(49c); white solid; yield 55%; m.p. 98°C; i.r.(KBr): ν_{max} = 1680 cm^{-1}; ^1H n.m.r. ($CDCl_3$):δ1.30(t,J=7Hz,3H,CH_2CH_3); 2.40(s,3H,SCH_3); 3.76(s, 6H,OCH_3); 4.33(q,J=7Hz,2H,CH_2CH_3); 6.66(s,1H,H-4); 6.80-7.53(m, $3H_{arom}+1H_{olefinic}$); 7.86(d,J=16Hz,$1H_{olefinic}$). (Found: C,62.19; H,5.72. Calc. for $C_{18}H_{20}O_5S$ (348.40): C,62.04; H,5.78%). m/z 348 (M^+,73%).

Ethyl 3-(3,4,5-trimethoxystyryl)-5-methylthio-furan-2-carboxylate (49d); white solid; yield 60%; m.p. 100°C; i.r.(KBr): ν_{max} = 1680 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.36(t,J=6Hz,3H,CH_2CH_3); 2.46(s,3H,SCH_3); 3.86(s, 3H,OCH_3); 3.90(s,6H,OCH_3); 4.43(q,J=6Hz,2H,CH_2CH_3); 6.66(s,1H,H-4); 6.76-6.89(m,$2H_{arom}$); 6.86(d,J=16Hz,$1H_{olefinic}$); 7.90(d,J=16Hz,$1H_{olefinic}$). (Found: C,60.18; H,5.77. Calc. for $C_{19}H_{22}O_6S$ (378.43): C,60.29; H,5.86%). m/z 378(M^+,100%).

Ethyl 3-(3,4-methylenedioxystyryl)-5-methylthio-furan-2-carboxylate (49e); viscous liquid; yield 22%; i.r.(CCl_4): ν_{max} = 1720 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.46(t,J=6Hz,3H,CH_2CH_3); 2.46(s,3H,SCH_3); 4.36(q, J=6Hz,2H,CH_2CH_3); 5.93(s,2H,O-CH_2-O); 6.56(s,1H,H-4); 6.66-7.33(m, $3H_{arom}+1H_{olefinic}$); 7.50(d,J=16Hz,1H,cyclopropyl). (Found: C,61.32; H,4.76. Calc. for $C_{17}H_{16}O_5S$ (332.36): C,61.43; H,4.85%). m/z 332 (M^+,100%).

Ethyl 3-(2-carbethoxy-3-phenylcycloprop-1-yl)-5-methylthio-furan-2-carboxylate (50a); viscous liquid; yield 42%; i.r.(CCl_4): ν_{max} = 1720 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.13-1.56(m,6H,CH_2CH_3); 2.50(s,3H,SCH_3); 2.26-2.43(m,1H,cyclopropyl); 2.83-3.03(m,1H,cyclopropyl); 3.23-3.46

(m,1H,cyclopropyl); 6.46(s,1H,H-4); 7.13-7.46(brs,5H_{arom}). (Found: C,64.05; H,5.83. Calc. for $C_{20}H_{22}O_5S$ (374.38): C,64.15; H,5.92%). m/z 374(M^+,24%).

Ethyl 3-[2-carbethoxy-3(4-methoxyphenyl)cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50b);viscous liquid;yield 48%;i.r.(CCl_4):ν_{max}=1715 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 0.93(t,J=7Hz,3H,CH_2CH_3); 1.23(t,J=7Hz,3H,CH_2CH_3); 2.03(m,1H,cyclopropyl); 2.43(s,3H,SCH_3); 2.53-2.73(m,1H,cyclopropyl); 3.56-3.73(m,1H,cyclopropyl); 3.80(q,J=7Hz,2H,CH_2CH_3); 4.36(q,J=7Hz, 2H,CH_2CH_3); 6.10(s,1H,H-4); 6.83(d,J=7Hz,A_2B_2,2H_{arom}); 7.30(d,J=7Hz, A_2B_2,2H_{arom}). (Found: C,62.24; H,5.94. Calc. for $C_{21}H_{24}O_6S$ (404.46): C,62.35; H,5.98%). m/z 404(M^+,100%).

Ethyl 3-[2-carbethoxy-3-(3,4-dimethoxyphenyl)cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50c); viscous liquid; yield 28%; i.r.(CCl_4):ν_{max} = 1720 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.03(t,J=6Hz,3H, CH_2CH_3); 1.33(t,J=6Hz,3H,CH_2CH_3); 2.33-2.40(m,1H,cyclopropyl); 2.46(s,3H,SCH_3); 2.83-2.96(m,1H,cyclopropyl); 3.60-3.73(m,1H,cyclopropyl); 3.53-4.03(m,2H,CH_2CH_3+3H OCH_3); 6.16(s,1H,H-4); 6.73-7.06 (m,3H_{arom}). (Found: C,60.69; H,6.00. Calc. for $C_{22}H_{26}O_7S$ (434.49): C,60.81; H,6.03). m/z 434(M^+,16%).

Ethyl 3[2-carbethoxy-3-(3,4,5-trimethoxyphenyl)cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50d); white solid; yield 30%; m.p. 110°C; i.r.(KBr): ν_{max} = 1715 cm^{-1}; ^1H n.m.r.(CCl_4):δ 1.03(t,J=6Hz, 3H,CH_2CH_3); 1.43(t,J=6Hz,3H,CH_2CH_3); 2.00-2.26(m,1H,cyclopropyl); 2.46(s,3H,SCH_3); 2.60-2.83(m,1H,cyclopropyl); 3.13-3.53(m,1H, cyclopropyl); 3.63-4.16(m,9H$(OCH_3)_3$+2H,CH_2CH_3); 4.46(q,J=6Hz,2H,

$C\underline{H}_2CH_3$); 6.16(s,1H,$\underline{H}$-4); 6.66(brs,$2H_{arom}$). (Found: C,59.35; H,6.01. Calc. for $C_{23}H_{28}O_8S$ (464.51): C,59.46; H,6.07%), m/z 464(M^+,74%).

Ethyl 3-[2-carbethoxy-3-(3,4-methylenedioxyphenyl)cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50e); viscous liquid; yield 43%; i.r.(CCl_4):ν_{max} = 1710 cm^{-1}; ^1H n.m.r.(CCl_4):δ 1.03(t,J=7Hz,3H, $C\underline{H}_2CH_3$); 1.36(t,J=7Hz,3H,CH_2CH_3); 2.10-2.30(m,1H,cyclopropyl); 2.46 (s,3H,$SC\underline{H}_3$); 2.53-2.70(m,1H,cyclopropyl); 3.50-3.73(m,1H,cyclopropyl); 3.86(q,J=7Hz,$C\underline{H}_2CH_3$); 4.40(q,J=7Hz,2H,$C\underline{H}_2CH_3$); 5.96(s,2H,methylene O-CH_2-O); 6.13(s,1H,$\underline{H}$-4); 6.66-6.96(m,$3H_{arom}$). (Found: C,60.15; H,5.28. Calc. for $C_{21}H_{22}O_7S$ (418.45): C,60.27; H,5.30%). m/z 418 (M^+,100%).

Ethyl 3-[2-carbethoxy-3-(4-chlorophenyl)cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50f); viscous liquid; yield 67%; i.r.(CCl_4): ν_{max} = 1720 cm^{-1}; ^1H n.m.r.(CCl_4):δ 1.00(t,J=7Hz,3H,$CH_2C\underline{H}_3$); 1.36 (t,J=7Hz,3H,$C\underline{H}_2CH_3$); 2.13-2.33(m,1H,cyclopropyl); 2.46(s,3H,$SC\underline{H}_3$); 2.53-2.76(m,1H,cyclopropyl); 3.56-3.76(m,1H,cyclopropyl); 3.96(q, J=7Hz,2H,$C\underline{H}_2CH_3$); 4.36(q,J=7Hz,2H,$C\underline{H}_2CH_3$); 6.13(s,1H,$\underline{H}$-4); 7.20-7.43(brs,$4H_{arom}$). (Found: C,64.21; H,5.57. Calc. for $C_{20}H_{21}ClO_5S$ (408.23): C,64.32; H,5.66%). m/z 408,410 (M^+,59%,23%).

Ethyl 3-[2-carbethoxy-3-(4-methylphenyl)-cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50g); viscous liquid; yield 58%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.03(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 1.36(t,J=6Hz,3H,$CH_2C\underline{H}_3$); 2.10-2.30(m,1H,cyclopropyl); 2.23(s,3H, $C\underline{H}_3$); 2.36(s,3H,$SC\underline{H}_3$); 2.60-2.79(m,1H,cyclopropyl); 3.63-3.80(m, 1H,cyclopropyl); 3.96(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 4.29(q,J=6Hz,2H,$C\underline{H}_2CH_3$);

6.00(s,1H,H-4); 6.83-7.33(m,4H_{arom}). (Found: C,64.79; H,6.18. Calc. for $C_{21}H_{24}O_5S$ (388.46): C,64.92; H,6.22%). m/z 388(M^+,79,4%).

Ethyl 3-[2-carbethoxy-3-(4-methyl)-cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (50h); viscous liquid; yield 67%; i.r.(CCl_4): ν_{max} = 1720 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.13-1.63(m,6H,CH_2CH_3+3H,CH_3); 1.63-2.03(m,2H,cyclopropyl); 2.46(s,3H,SCH_3); 2.76-2.96(m,1H,cyclopropyl); 3.93-4.53(m,4H,CH_2CH_3); 5.93(s,1H,H-4), (Found: C,57.60; H,6.42. Calc. for $C_{15}H_{20}O_5S$ (312.15): C,57.71; H,6.45%). m/z 312 (M^+,62%).

Ethyl 3-(4-phenyl-1,3-butadienyl)-5-methylthio-furan-2-carboxylate (57a); viscous liquid; yield 52%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.43(t,J=6Hz,3H,CH_2CH_3); 2.50(s,3H,SCH_3); 4.40 (q,J=6Hz,2H,CH_2CH_3); 6.60(s,1H,H-4); 6.73-7.13(m,3H,1H_{arom}+2$H_{olefinic}$); 7.26-7.63(m,4H_{arom}+2$H_{olefinic}$). (Found: C,68.90; H,5.74. Calc. for $C_{18}H_{18}O_3S$ (314.38): C,68.76; H,5.77%). m/z 314(M^+,79%).

Ethyl 3-[4-(4-methoxyphenyl)-1,3-butadienyl]-5-methylthio-furan-2-carboxylate (57b); viscous liquid; yield 51%; i.r.(CCl_4): ν_{max} = 1710 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.40(t,J=7Hz,3H,CH_2CH_3); 2.53(s,3H, SCH_3); 3.83(s,3H,OCH_3); 4.43(q,J=7Hz,2H,CH_2CH_3); 6.60(s,1H,H-4); 6.66-6.96(m,2H_{arom}+2$H_{olefinic}$); 7.26-7.50(m,2H_{arom}+2$H_{olefinic}$). (Found: C,66.15; H,5.82. Calc. for $C_{19}H_{20}O_4S$ (344.41): C,66.25; H,5.85%). m/z 344(M^+,17%).

Ethyl 3-(6-phenyl-1,3,5-hexatrienyl)-5-methylthio-furan-2-carboxylate (59a); viscous liquid; yield 58%; i.r.(CCl_4): ν_{max} = 1700 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.36(t,J=6Hz,3H,CH_2CH_3); 2.50(s,3H,SCH_3); 4.36

(q,J=6Hz,2H,$C\underline{H}_2CH_3$); 6.36-6.96(m,$7H_{olefinic}$); 7.23-7.63(m,$5H_{arom}$). (Found: C,70.44; H,5.88. Calc. for $C_{20}H_{20}O_3S$ (340.42): C,70.55; H,5.92%). m/z 340(M^+,44%).

Ethyl 3-[6-(4-methoxyphenyl)-1,3,5-hexatrienyl-furan-2-carboxylate(59b); viscous liquid; yield 49%; i.r.(CCl_4):ν_{max} = 1705 cm^{-1}; ^1H n.m.r. ($CDCl_3$):δ 1.36(t,J=7Hz,3H,$CH_2C\underline{H}_3$); 2.46(s,3H,$SC\underline{H}_3$); 3.76(s,3H,$OC\underline{H}_3$); 4.36(q,J=7Hz,2H,$C\underline{H}_2CH_3$); 6.36-6.93(m,$5H_{olefinic}$+$3H_{arom}$); 7.06-7.46 (m,$2H_{arom}$+$1H_{olefinic}$). (Found: C,67.18; H,5.96. Calc. for $C_{21}H_{22}O_4S$ (470.45): C,68.08; H,5.98%). m/z 370(M^+,15%).

Ethyl 3-[2-(4-methoxyphenyl)-cycloprop-1-yl]-5-methylthio-furan-2-carboxylate (61); viscous liquid; yield 65%; i.r.(CCl_4):ν_{max} = 1720 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.23(t,J=7Hz,3H,$C\underline{H}_2CH_3$); 2.03-2.42(m, 3H,cyclopropyl); 2.46(s,3H,$SC\underline{H}_3$); 2.60-2.76(m,1H,cyclopropyl); 3.83(s,3H,$OC\underline{H}_3$); 4.36(q,J=7Hz,2H,$C\underline{H}_2CH_3$); 6.10(s,1H,$\underline{H}$-4); 6.83(d, J=7Hz,A_2B_2,$2H_{arom}$); 7.30(d,J=7Hz,A_2B_2,$2H_{arom}$). (Found: C,65.35; H,5.72. Calc. for $C_{18}H_{19}O_4S$ (331.33): C,65.24; H,5.77%). m/z 331 (M^+,23%).

REFERENCES

1. For a review, see R.K. Dieter, Tetrahedron, 42, 3029 (1986).
2. B. Myrboh, H. Ila, H. Junjappa, J. Org. Chem., 48, 5327 (1983).
3. R.E. Ireland, J.A. Marshall, J. Org. Chem., 27, 1620 (1962).
4. T. Nishio and Y. Omote, Synthesis, 390, 392 (1980).
5. G. Singh, M.L. Purkayastha, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I., 1289 (1985).
6. G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett., 25, 5095 (1984).
7. M.P. Balu, D. Pooranchand, H. Ila, H. Junjappa, Tetrahedron Lett., 24, 501 (1988).
8. T. Nishio, M. Sugawara, Y. Omote, J. Het. Chem., 815 (1979).
9. R. Okazaki, Y. Negishi and N. Inamoto, J. Org. Chem., 49, 3819 (1984).
10. M.E. Garst, T.A. Spencer, J. Am.Chem. Soc., 250 (1973).
11. D.M. Burness, J. Org. Chem., 21, 102 (1956).
12. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 1911 (1976).
13. A. Kumar, H. Ila, H. Junjappa, J. Chem. Soc. Chem. Commun., 592 (1976).
14. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 1398 (1959).
15. J. Koo, J. Am. Chem. Soc.,75, 1891 (1953).
16. M. Saquet, A. Thuillier, Bull. Soc. Chim. Fr., 15882 (1966).
17. A. Kumar, Ph.D. Thesis submitted to Agra University, Agra, India (1978).
18. K.T. Potts, M.J. Cipullo, P. Ralli and G. Theodoris, J. Org. Chem., 47, 3027 (1982).
19. S. Apparao, S.S. Bhattacharjee, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I., 641 (1985).
20. a. A. Kumar, H. Ila, H. Junjappa, J. Chem. Res (S), 268 (1979).
    b. A. Kumar, H. Ila, H. Junjappa, J. Chem. Res (M), 3001 (1979).

21. A. Thuillier, J. Vialle, *Bull. Soc. Chim. Fr.*, 2182 (1962).

22. L.W. Singh, Ph.D. Thesis submitted to North-Eastern Hill University, Shillong, India (1987).

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

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

25. E.H. Amonou-Neizer, R.A. Shaw, D.O. Skovlin, B.C. Smith, *J. Chem. Soc.*, 2997 (1965).

26. J.D. Prugh, A.C. Huitric, W.C. McCarthy, *J. Org. Chem.*, *29*, 1991 (1964).