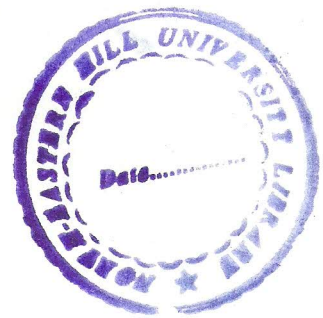
NEW SYNTHETIC ROUTES TO CARBOCYCLES AND HETEROCYCLES *VIA* ∝-OXOKETENE DITHIOACETALS



BY

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Shillong
April 1999

I, Kaushal Kishore, hereby declare that the subject matter of thesis is the record of work done by me, that the content of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else and that the thesis has not been submitted by me for any research degree in any other University / Institute.

This is being submitted to North-Eastern Hill University for the Degree of Doctor of Philosophy in Chemistry.

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WHAT LIES BHIND US
WHAT LIES BEFORE US
ARE TINY MATTERS
COMPARED TO
WHAT LIES WITHIN US.

-OLIVER WENDELL HOLMES

THESIS DEDICATED

TO

MY ***PARENTS,***

LATE ***GRAND MOTHER***

AND

LATE ***FATHER-IN-LAW***

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CONTENTS

PREFACE

Polarised ketene dithioacetals serve as a versatile 3-carbon fragments with ambident 1,3-dielectrophilic centres for designing and constructing heterocyclic as well as carbocyclic compounds. The differential electrophilicity of 1,3-carbon centres of these molecules have thoroughly been exploited in our laboratory resulting in a number of general synthetic routes for a wide range of organic molecules.

The present investigation has been aimed at examining some new interesting synthetic transformations of polarised ketene dithioacetals, the results of which are described in this thesis.

The thesis is divided into four chapters.

Chapter I deals with a brief review of the work done involving α-oxoketene dithioacetals to construct a wide range of heterocycles, carbocycles, aromatics and heteroaromatics.

Chapter II describes the generation and reaction of lithium 5-lithiomethyl-3-methylpyrazole-1-carboxylate with α-oxoketene dithioacetals for the synthesis of substituted and annelated pyrazolo[1,5-*a*]pyridines.

Chapter III consists of a new efficient regiocontrolled route to substituted naphthalenes by the base-catalysed reaction of substituted and unsubstituted phenyl acetonitriles with α-oxoketene dithioacetals.

Chapter IV describes the reaction of chloromercuriacetaldehyde with carbon disulphide and aromatic aldehydes in the presence of potassium iodide. This is a new general synthesis of β,β-bis(methylthio)acrolein, and cinnamaldehydes from carbon disulphide and benzaldehydes respectively in good to excellent yields.

Each chapter is further subdivided into introduction, results and discussion, conclusion, experimental section and references to support the entire documentation in the chapter.

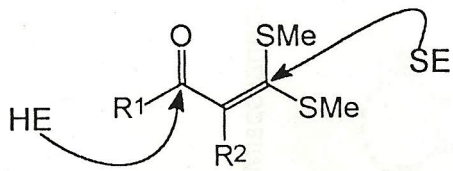
CHAPTER-I

POLARISED KETENE DITHIOACETALS AND THEIR SYNTHETIC POTENTIAL: A *BRIEF REVIEW*

I. A INTRODUCTION:

Synthetic organic chemistry is a continuing challenge to design and construct molecules from inexpensive resource materials. Related to this area, polarised ketene dithioacetals have been proved to be a versatile family of synthons which are among the simplest and potential synthetic intermediates in various transformations[1].

This class of the compounds can very easily be prepared from a variety of active methylene compounds by condensation of the corresponding enolate, with carbondisulphide or trithiocarbonate followed by alkylation of the



HE- Hard electrophiles
SE- Soft electrophiles

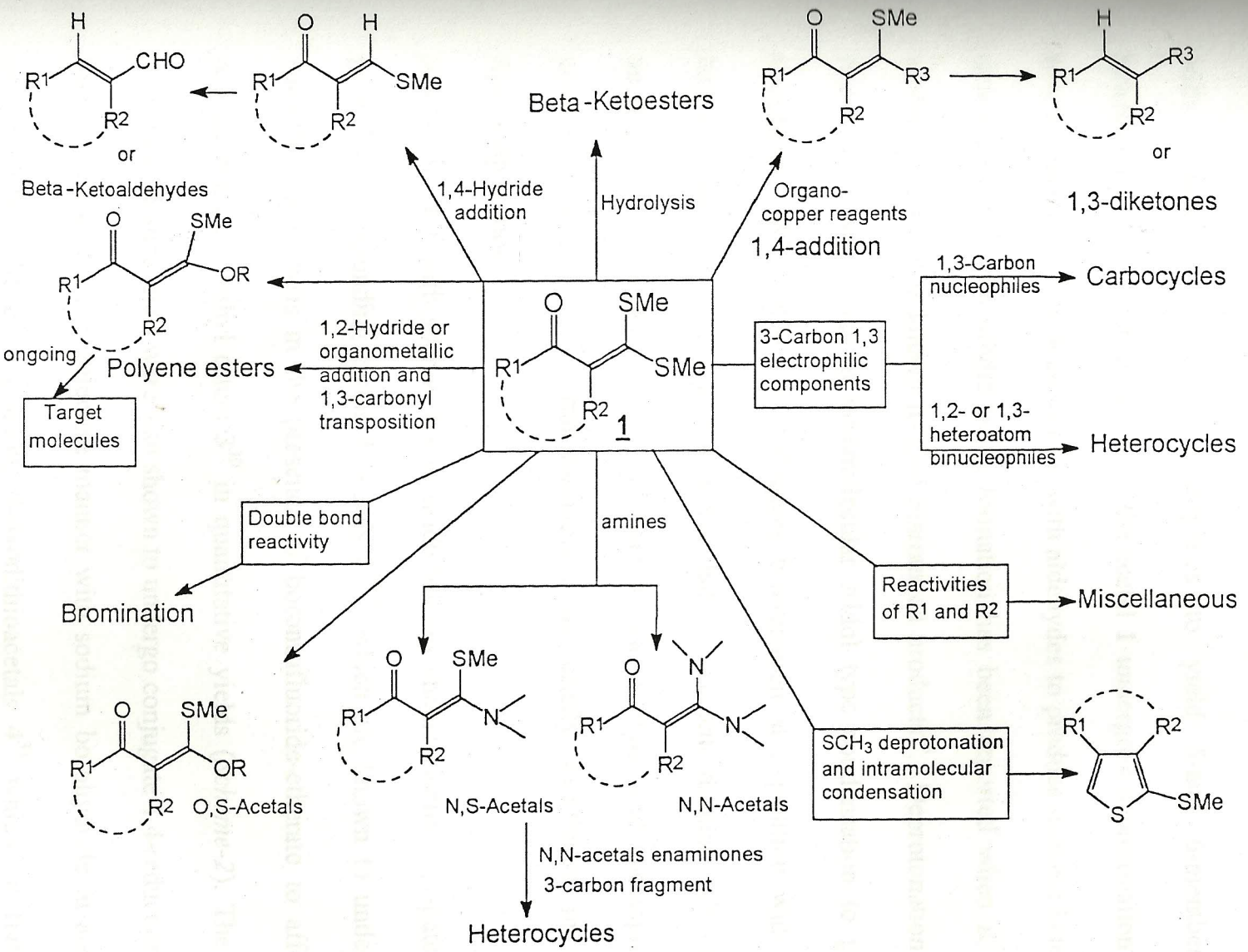
1

intermediate dithiolate species mostly in one pot operation in moderate to good yields[2-8]. They possess well defined physical properties either as crystalline solids or as distillable liquids. They are stable at room temperature and also under mild acidic and alkaline conditions.

In **1910**, Kelber and co-workers[9] had reported the first synthesis of α-oxoketene dithioacetals. However, the chemistry of these intermediates could draw very little attention until Thuillier et al. synthesised these compounds in higher yields using sodium amylate as base followed by alkylation[2,4]. With the passage of time, the reaction conditions were greatly improved by using different bases[3-8].

Today, a large number of α-oxoketene dithioacetals are known and have emerged as very useful synthetic intermediates during the last 25 years[1].

A brief sketch of synthetic utility of α-oxoketene dithioacetals is depicted in *Scheme-1*. 1,2-Addition products are obtained[10] on treatment with hydrides and organometallic reagents but this sequence could be manipulated to follow 1,4-path by suitably manipulating the reagent and reaction conditions[10,11]. The


Beta-Ketoaldehydes
or
Beta-Ketoesters
1,4-Hydride addition
Hydrolysis
Organo-copper reagents
1,4-addition
or
1,3-diketones
1,3-Carbon nucleophiles
Carbocycles
3-Carbon 1,3 electrophilic components
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
1,2-Hydride or organometallic addition and 1,3-carbonyl transposition
Polyene esters
ongoing
Target molecules
1
Double bond reactivity
Bromination
amines
Reactivities of R1 and R2
Miscellaneous
O,S-Acetals
N,S-Acetals
N,N-Acetals
SCH3 deprotonation and intramolecular condensation
N,N-acetals enaminones
3-carbon fragment
Heterocycles

Scheme-1

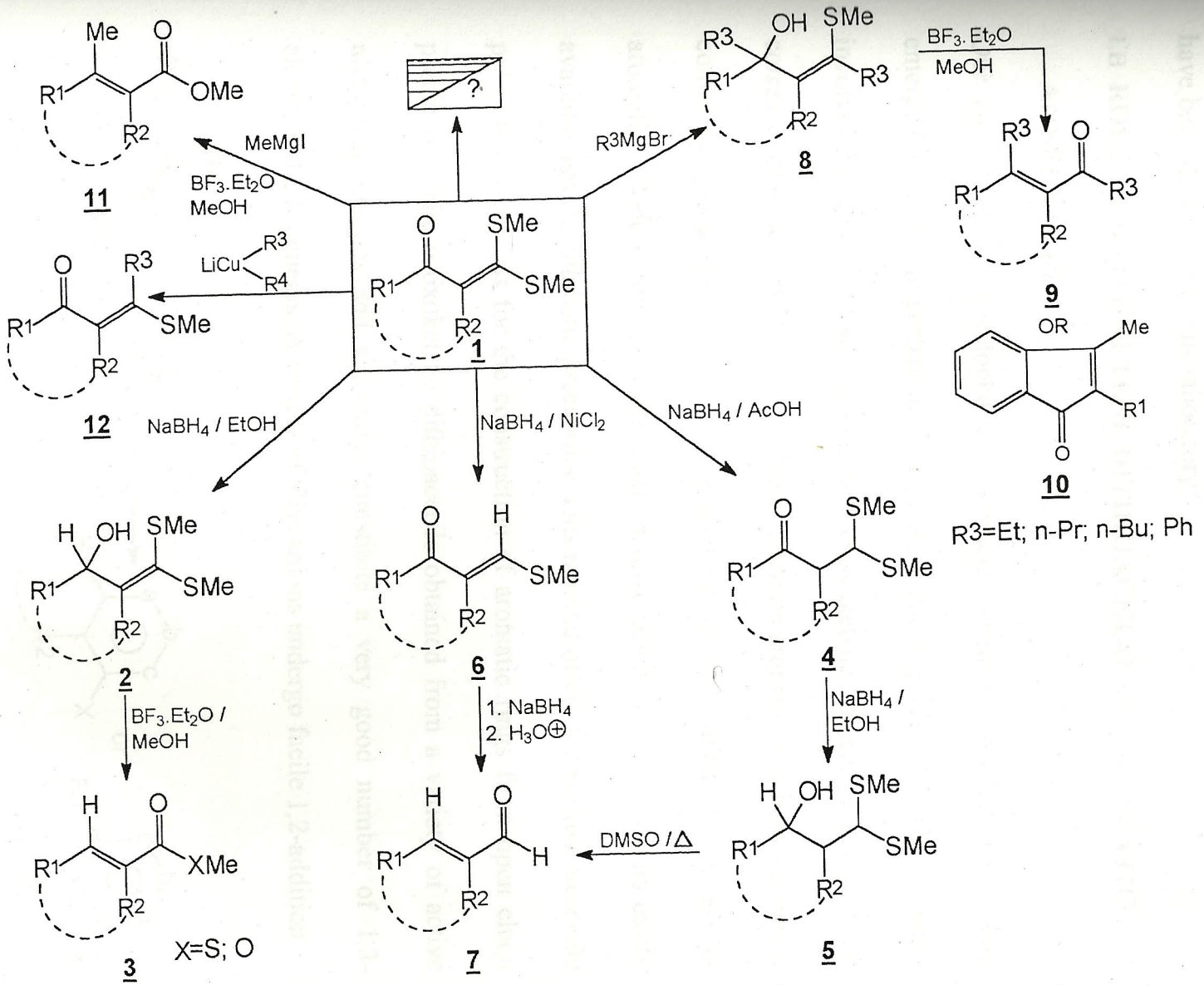
α-oxoketene dithioacetals which possess typical 1,3-electrophilic centres react with a number of heterobinucleophiles to yield 5-and 6-membered heterocycles.[12-24] When R^1 is alkyl, the acetal **1** undergoes deprotonation to give enolate anion which condenses with aldehydes to produce α-enoyl ketene dithioacetals[2b,25]. An allylic anion formation has been reported when R^2 is methyl group and is known to give rearranged products[26]. Deprotonation of thiomethyl group leads to intramolecular Aldol type condensation to give thiophene[27]. When R^2=*H*, it undergoes bromination at α-position with *N*-bromosuccinimide[28]. Thus it is apparent that α-oxoketene dithioacetals form an important class of synthons with reactive electrophilic and nucleophilic centres. Some important transformations are briefly mentioned in the following section.

Reduction of **1** with sodium borohydride follows chemoselective 1,2-path to give the corresponding carbinol acetals **2**[29,30] which are known to undergo smooth methanolysis in the presence of borontrifluoride-etherate to afford α,β-unsaturated methyl esters **3**[30] in quantitative yields (*Scheme-2*). The α-oxoketene dithioacetals were also shown to undergo conjugate 1,4-reduction in highly regio-and chemoselective manner with sodium borohydride in acetic acid to afford the corresponding β-oxodithioacetals **4**[31] which on further $NaBH_4$ treatment in ethanol give the carbinolacetals **5**. On further heating in DMSO it affords the corresponding α,β-unsaturated aldehydes **7**[32] in high

yields. The α,β-unsaturated aldehydes can also be obtained from α-oxoketene dithioacetals by the treatment of nickel boroide ($NiCl_2/NaBH_4$) to give the corresponding β-methylthio alkenyl ketones **6**[33] which can subsequently be transformed to α,β-unsaturated aldehydes **7**[33].

The Grignard and organolithium reagents undergo either regioselective 1,2-addition to afford the α-hydroxyketene dithioacetals or a sequential 1,4-and 1,2-addition to afford the β-hydroxyvinyl sulfides **8**[10]. The borontrifluoride-etherate catalysed solvolysis or the hydrolysis of these carbinols yield either β-substituted α,β-unsaturated esters **11** or the corresponding ketones **9** (Scheme-2) in good yields. However, when the R^1 is alkyl or aryl group the open chain cinnamates were not obtained, instead the corresponding 2,3-disubstituted indenones **10** were formed[10]. Dieter et al. have reported the chemo- and stereoselective addition of organocuprates to α-oxoketene dithioacetals **1**. It is known to undergo conjugate addition to give β-alkylthio-β-substituted α,β-unsaturated ketones **12**[11].

S,N and *N,N* acetals which possess also 1,3-electrophilic centres can be considered as vinylogous amides if they derived from ketones and as vinylogous amines if they derived from the other active methylene compounds. They are stable and behave as enamines. The α-oxoketene *S,N*- and *N,N*-acetals behave as enamines in the Nenitzescu Indole synthesis[34]. The chemistry and the synthetic potential of *S,N*- and *N,N*-acetals have been

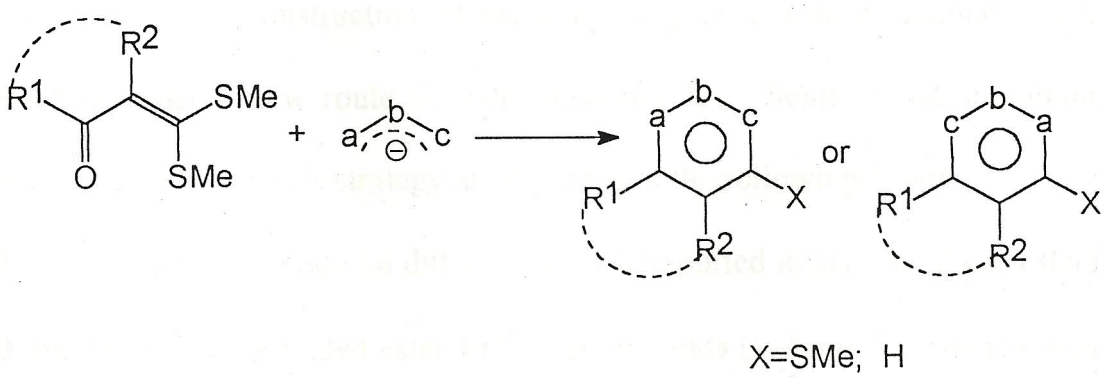

Me
O
OMe
R1
R2
11
MeMgI
BF3.Et2O
MeOH
?
R3MgBr
OH
SMe
R3
8
BF3.Et2O
MeOH
9
OR
Me
R1
10
R3=Et; n-Pr; n-Bu; Ph
LiCu
R3
R4
12
SMe
1
NaBH4 / EtOH
NaBH4 / NiCl2
NaBH4 / AcOH
H
2
BF3.Et2O /
MeOH
3
X=S; O
6
1. NaBH4
2. H3O⊕
7
DMSO /Δ
4
NaBH4 /
EtOH
5

Scheme 2

reviewed[1b] and a number of synthetic routes *via* this *N,N*- and *S,N*- acetals have been developed in this laboratory.

I.B ROLE OF α-OXOKETENE DITHIOACETALS IN AROMATIC ANNELATION:

Our laboratory has developed the aromatic annelation strategy which has emerged as a very important area of great synthetic potential[36]. This strategy involves the reaction of allyl anions with α-oxoketene dithioacetals to give the corresponding benzenoids, naphthalenes, polyclic aromatic and heteroaromatic compounds in good yields. The overall process was aimed at creating an aromatic or heteroaromatic system with diverse structural features from easily available acyclic aliphatic precursors. This method offers for the first time one pot reaction process for the construction of aromatic rings from open chain precursors. The α-oxoketene dithioacetals obtained from a variety of active methylene ketones and aldehydes constitute a very good number of 1,3-electrophilic fragments. A variety of allyl anions undergo facile 1,2-addition



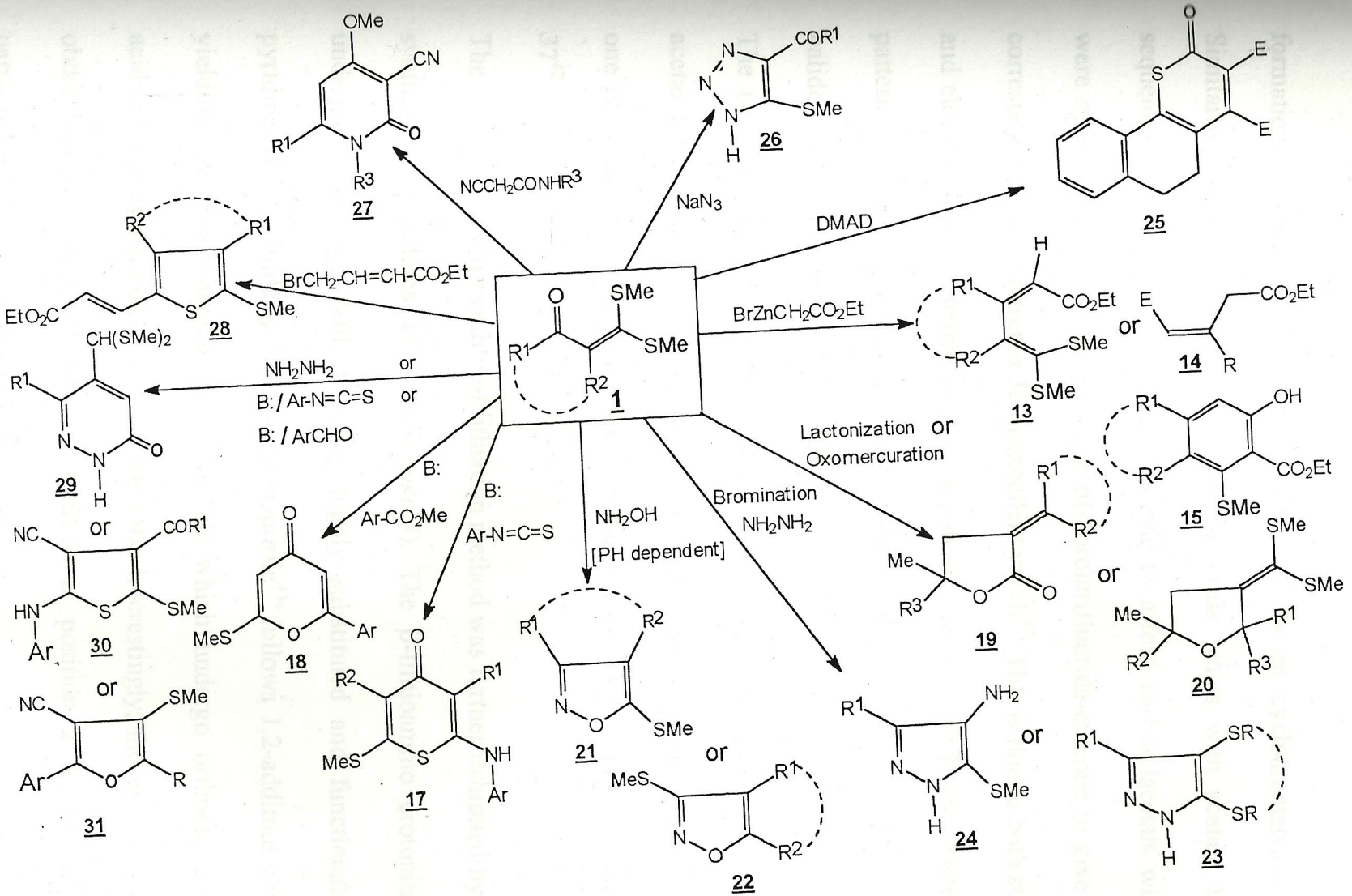
3 Carbon 1,3-binucleophiles and alpha-oxoketene dithioacetals approach for aromatic annelation

on the α-oxoketene dithioacetals to give the corresponding carbinolacetals in very high yields which when treated with Lewis acids *insitu* get cyclised to yield the corresponding benzoannelated products. Thus a large number of benzenoids, naphthalenes, phenanthrenes, anthracenes, benzanthracenes and many other condensed aromatics with a variety of structural features have been synthesised by choosing appropriate allyl, benzyl, 1- or 2-naphthylmethyl anions and α-oxoketene dithioacetals. This approach for the synthesis of substituted benzenes is novel because of the fact that literature methods involve substitution reaction on aromatic ring which are not free from limitations due to rigid aromatic orientation. In our approach the desired substituents could be placed either in the open chain dielectrophilic fragments or in the binucleophilic fragments or in both depending upon the requirement. Thus a control could be exercised on the position of the substituents in the product. Also a variety of 1-or 3-heteroatom binucleophiles can be used to incorporate one or more heteroatoms in the aromatic rings. Another variation is the successful construction of aromatic ring over a heteroaromatic ring which provides a new route for benzoheterocycles. Some of the important results derived from this strategy are depicted in the following *Schemes*.

The Reformatsky reaction on dithioacetals **1** is reported to give the diene esters **13** and the α,β-unsaturated ester **14**[37] in good yields (*Scheme*-3). The reaction of arylisothiocyanates or methyl benzoate with **1** is reported to yield the

corresponding 2-arylamino-6-(methylthio)thiopyran-4-one **17** and 2-(methylthio)-6-arylpyran-4-one **18** respectively[15,16]. The α-oxoketene dithioacetals have also been converted to the corresponding butyrolactones **19** and **20**[18,22] and their reaction with hydroxylamine has been shown to be pH dependent yielding the regioisomers **21** and **22** in high yields[24]. The α-oxoketene dithioacetals were shown to undergo bromination (R^2=*H*) and the corresponding bromo-oxoketene dithioacetals reacted with hydrazine hydrate to yield pyrazoles **23** and **24**[17]. The reaction of **1** with DMAD initially underwent (2+2) cycloaddition followed by ring opening to yield the corresponding dienes. The oxoketenedithioacetal derived from tetralone on reaction with DMAD yielded **25** as one of the products involving interesting sequence of rearrangement.[14] The reaction of α-oxoketene dithioacetals with sodium azide and cyanoacetamide yield triazoles **26**[20] and pyridines **27**[12,13] respectively. Similarly the synthesis of heterocycles **28**[21], **29**,[19] **30** and **31**[23] were obtained by reacting **1** with appropriate reagents as shown in *Scheme*-3.

Allyl magnesium bromide has been shown to react with **1** in exclusively 1,2 fashion to give the corresponding carbinol acetal in high yields which undergo $BF_3.Et_2O$ catalysed cyclisation to obtain substituted and fused benzene derivatives.[38] This approach could successfully be extended for the synthesis of other benzenoids **33**,[39] **34**,[40] **36**[41](*Scheme-4*). However, benzyl magnesium chloride undergoes 1,4-addition followed by 1,2-addition leading to the

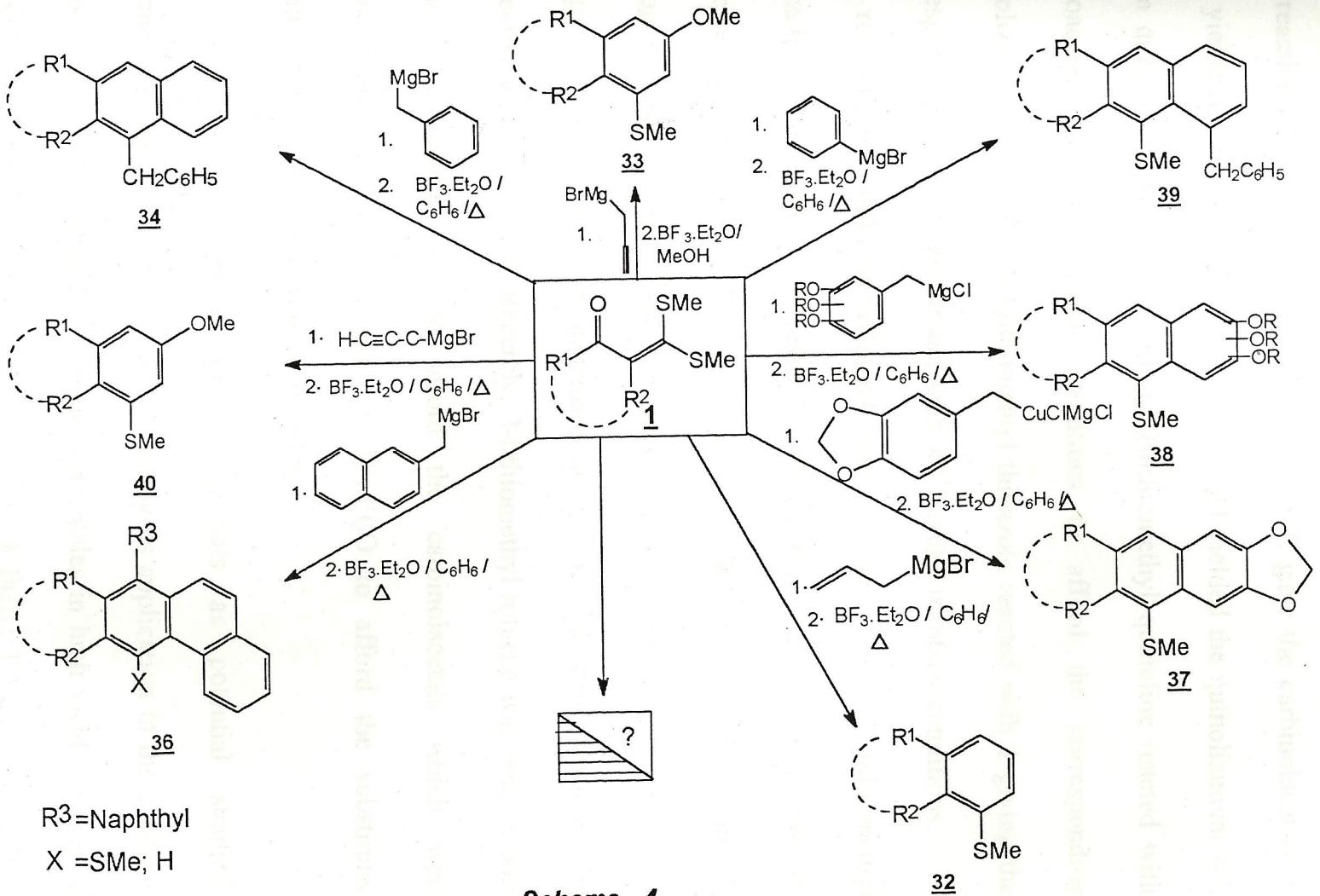

OMe
CN
R1
N
O
R3
27
NCCH2CONHR3
COR1
N
N
N
H
SMe
26
NaN3
O
S
E
E
25
DMAD
R2
R1
EtO2C
S
SMe
28
BrCH2-CH=CH-CO2Et
O
SMe
R1
SMe
R2
1
BrZnCH2CO2Et
H
R1
CO2Et
R2
SMe
SMe
13
or
E
CO2Et
14
R
CH(SMe)2
R1
N
N
H
O
29
NH2NH2
or
B: / Ar-N= C=S
or
B: / ArCHO
B:
Ar-CO2Me
B:
Ar-N=C=S
NH2OH
[PH dependent]
Lactonization or
Oxomercuration
Bromination
NH2NH2
R1
OH
R2
CO2Et
SMe
15
R1
R2
Me
R3
O
O
19
or
SMe
SMe
Me
R1
R2
O
R3
20
NC
or
COR1
HN
S
SMe
Ar
30
O
MeS
O
Ar
18
R2
R1
MeS
S
NH
Ar
17
R1
R2
N
O
SMe
21
or
MeS
R1
N
O
R2
22
R1
NH2
N
N
H
SMe
24
or
R1
SR
N
N
H
SR
23
NC
or
SMe
Ar
O
R
31

Scheme-3

formation of benzyl substituted naphthalenes **34** on cycloaromatisation.[40] Similarly, 2-naphthylmethyl magnesium chloride reacts with acetals **1** in sequential 1,4-mode followed by 1,2-mode to afford carbinolacetals which were cycloaromatized in the presence of borontrifluoride-etherate to give the corresponding phenanthrenes **36** in excellent yields[41]. This is due to both steric and electronic factors which play an important role in the different reactivity patterns of benzyl, 1-naphthyl methyl and 2-naphthylmethyl magnesium halides with α-oxoketene dithioacetals.

The behaviour of 3,4-methylenedioxybenzyl organocopper reagents towards acetal **1** is unique which underwent 1,2-addition and cycloaromatisation, in one pot reaction to yield the corresponding condensed aromatic naphthalene **37**[42].

The versatility and generality of lithiation method was further exhibited by the synthesis of pyridines **41**, **42** (*Scheme-5*). The β-lithioamino crotonitriles undergo 1,4-addition with **1** giving highly substituted and functionalised pyridine **41**.[43a,b] Similarly, the lithioacetonitrile[43c] follows 1,2-addition with **1** yielding the corresponding carbinolacetals which undergo orthophosphoric acid assisted cyclisation giving pyridines **42**. Interestingly, the pyridines thus obtained containing methylthio substituents at position 2 and 6 and no participation of nucleophiles was observed.

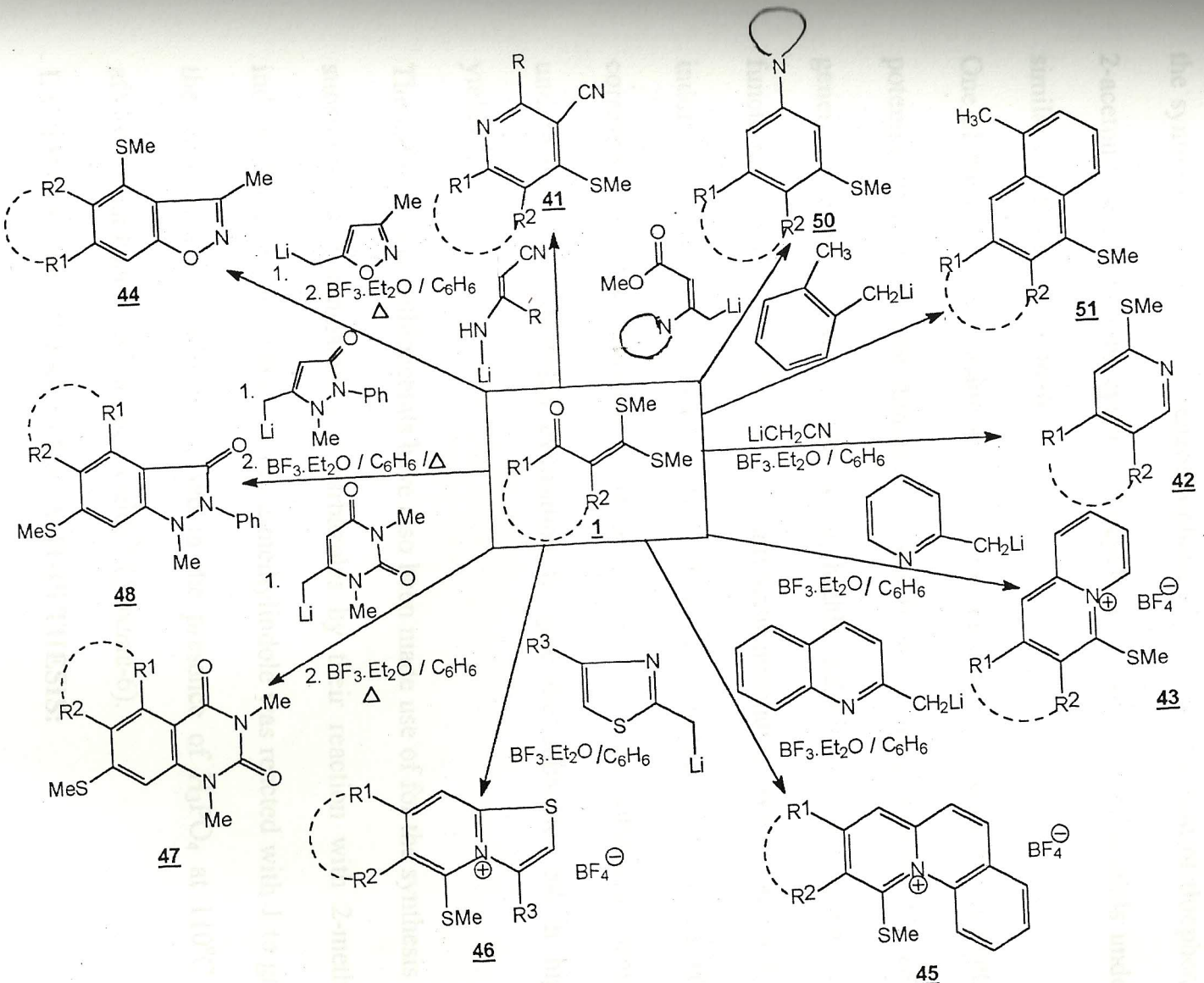

R1
R2
CH2C6H5
34
MgBr
1.
2. BF3.Et2O / C6H6 /Δ
R1
R2
OMe
SMe
33
1.
2. MgBr
BF3.Et2O / C6H6 /Δ
R1
R2
SMe
CH2C6H5
39
BrMg
1.
2.BF3.Et2O/ MeOH
O
SMe
R1
SMe
R2
1
RO
RO
RO
1. MgCl
2. BF3.Et2O / C6H6 /Δ
R1
R2
OR
OR
OR
SMe
38
1. H-C≡C-C-MgBr
2. BF3.Et2O / C6H6 /Δ
R1
R2
OMe
SMe
40
MgBr
1.
2. BF3.Et2O / C6H6 / Δ
1.
CuClMgCl
2. BF3.Et2O / C6H6 /Δ
R1
R2
SMe
37
R3
R1
R2
X
36
1.
MgBr
2. BF3.Et2O / C6H6/ Δ
?
R1
R2
SMe
32
R3=Naphthyl
X =SMe; H

Scheme - 4

The reaction of 2-picolyllithium with **1** at -30°C gave the carbinolacetals in high yields which in the presence of $BF_3.Et_2O$ yielded the quinolizinium salt **43** in quantitative yields[44a]. Similarly 2-lithiomethyl quinoline reacted with dithioacetals **1** under similar conditions to afford the corresponding quinolizinium salts **45**[44b]. 2-Lithiomethyl thioazole reacted with **1** giving the corresponding thioazolopyridinium salts **46**[45] under identical conditions.

The reaction of 6-lithiomethyluracil and 1-phenyl-2-methyl-3-lithiomethyl pyrazoline-5-one with dithioacetals **1** took place in 1,4-fashion to give the corresponding quinozolines **47**[46] and indazolones **48**[47] respectively. Similarly, lithiomethyl isooxazoles[48,49] and lithiomethyl aminocrotonates[47] reacted with **1** to give the corresponding benziosoxazoles **44** and aminobenzenes **50** respectively in high yields. Recently, 2-lithiomethyl toluene was reacted with α-oxoketene dithioacetals to afford the carbinolacetals which were cycloaromatized in the presence of $BF_3.Et_2O$ to afford the substituted naphthalenes **51**[50] (*Scheme*-5) in high yields.

The versatility of α-oxoketene dithioacetals as potential synthetic intermediates has further been exemplified by its application in the synthesis regiospecifically substituted and condensed indoles in high yields. A number of cyclic and acyclic dithioacetals underwent a facile 1,4-addition with 1-methyl pyrrole-2-acetonitrile in the presence of NaH to give the corresponding adducts. These adducts were cycloaromatised in the presence of PTSA to give


1. 2. BF3.Et2O / C6H6 Δ
LiCH2CN BF3.Et2O / C6H6
BF3.Et2O / C6H6
2. BF3.Et2O / C6H6 Δ
BF3.Et2O /C6H6
BF3.Et2O / C6H6
2. BF3.Et2O / C6H6 /Δ
1
41
42
43
44
45
46
47
48
50
51

Scheme-5

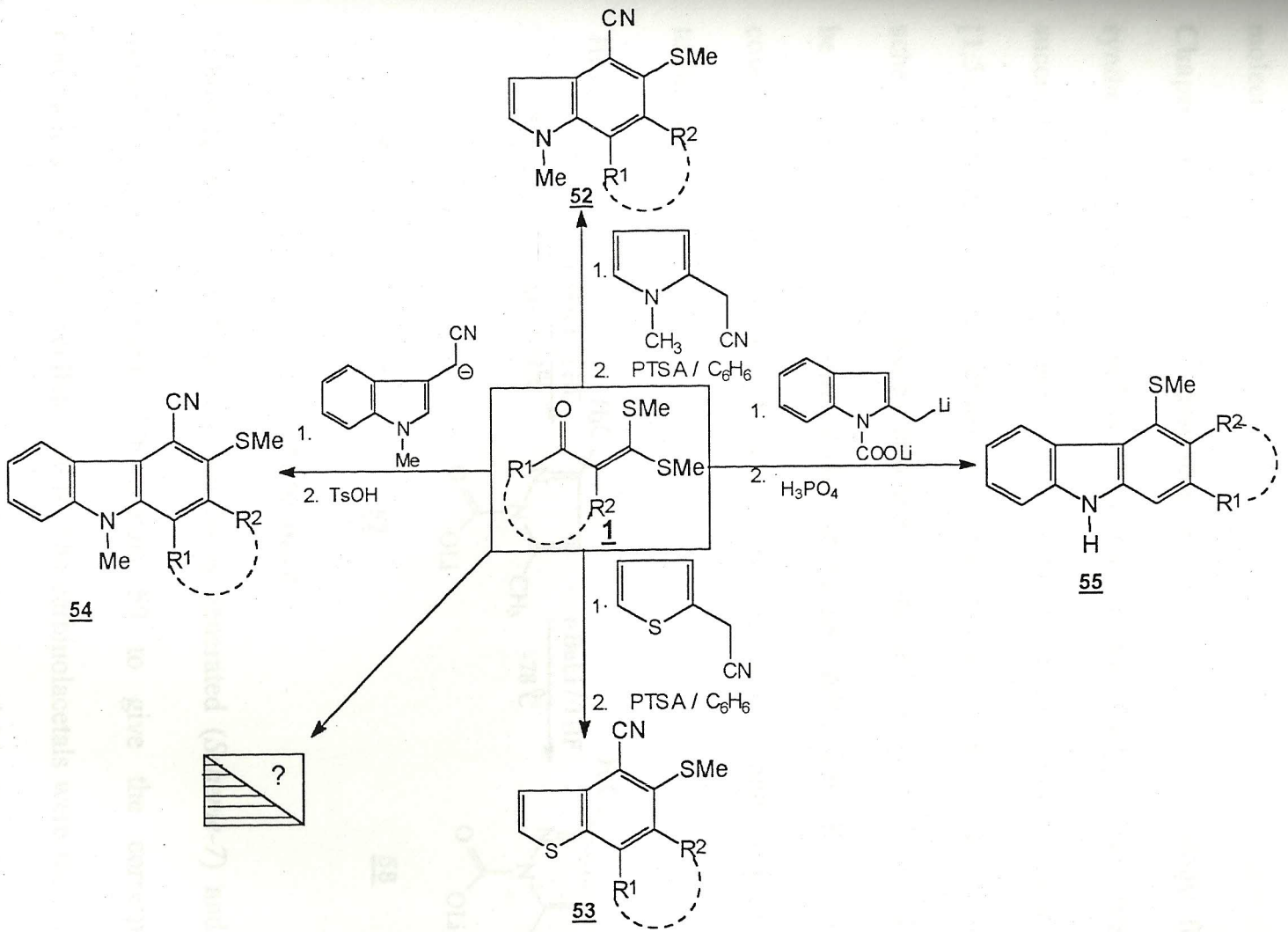
substituted and condensed indoles **52**.[51] This strategy was further extended for the synthesis of substituted benzothiophene **53**[52] by the reaction of thiophene 2-acetonitrile and various cyclic and acyclic α-oxoketene dithioacetals under similar conditions (*scheme*-6).

One of the most recent achievements of our laboratory utilising the synthetic potential of α-oxoketene dithioacetals has been the development of a new general method for the synthesis of highly substituted, condensed and functionalised carbazoles **54** via, heteroaromatic annelation. When 1-methyl-3-indole acetonitrile was reacted with **1** in the presence of NaH/DMF, corresponding 1,4-addition-elimination products were obtained which underwent PTSA catalysed cyclisation to give the cabazoles **54** in high yields[53].

The α-Oxoketene dithioacetals have also been made use of for the synthesis of substituted and annelated *N-H* carbazoles by their reaction with 2-methyl indole. The dianion generated from 2-methylindole was reacted with **1** to give the carbinol acetals which cyclised in the presence of H_3PO_4 at 110°C to afford *NH* carbazoles **55** in good yields[54] (*Scheme*-6).

I. C THE WORK PRESENTED IN THIS THESIS:

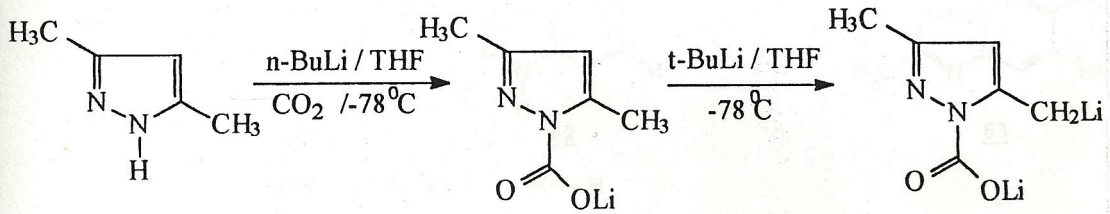
In continuation with above studies exploiting the synthetic potential of α-oxoketene dithioacetals which are easily accessible from a wide range of active methylene compounds, we further proposed to undertake to utilise these


CN
SMe
N
Me
R1
R2
52
1.
CH3
CN
2. PTSA / C6H6
CN
1.
N
Me
2. TsOH
O
SMe
R1
SMe
R2
1
1.
N
Li
COOLi
2. H3PO4
SMe
R2
N
H
R1
55
CN
SMe
N
Me
R1
R2
54
1.
S
CN
2. PTSA / C6H6
?
CN
SMe
S
R2
R1
53

Scheme-6

synthons for the development of new synthetic routes to arrive at new molecules.

Chapter II of the thesis describes a new general methodology for the synthesis of substituted and condensed pyrazolo[1,5-*a*]pyridines. We have successfully developed a new synthetic route for the synthesis of pyrazolo [1,5-*a*]pyridines using 3,5-dimethyl-1*H*-pyrazole as the substrate. In order to acheive the goal we needed 5-lithiomethyl-3-methyl-1*H*-pyrazole which could be obtained from 3,5-dimethyl-1*H*-pyrazole following Katritzky and coworkers methodology of activation, protection and deprotonation technique[56].

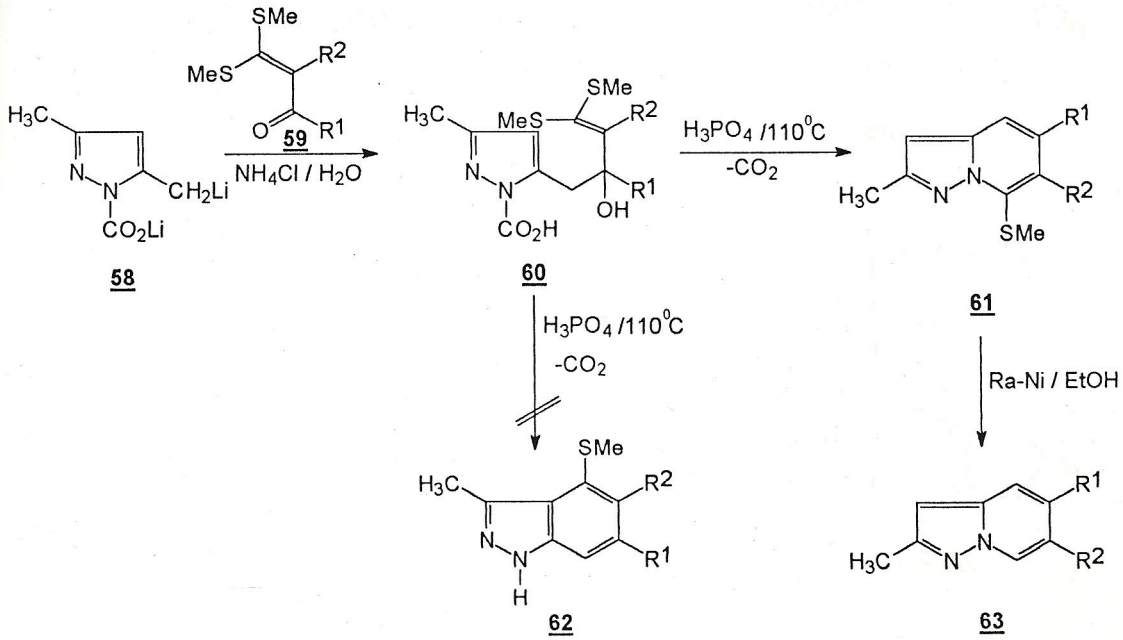


56 **57** **58**

Scheme-7

Following this method the dianion **58** is generated (*Scheme-7*) and *insitu* treated with α-oxoketene dithioacetals **59** to give the corresponding carbinolacetals **60** in excellent yields. The carbinolacetals were then cyclised in the presence of orthophosphoric acid to yield the corresponding pyrazolo[1,5-*a*]pyridines **61**. The alternative possible product indazole **62** was not formed.

The compounds **61** were further desulphurised in the presence of Rany-Nickel to afford the corresponding condensed and substituted pyrazolo[1,5-*a*]pyridines **63** (*Scheme*-8,9,10).



59, 60, 61, 63 a. R^1=CH_3; R^2 = H

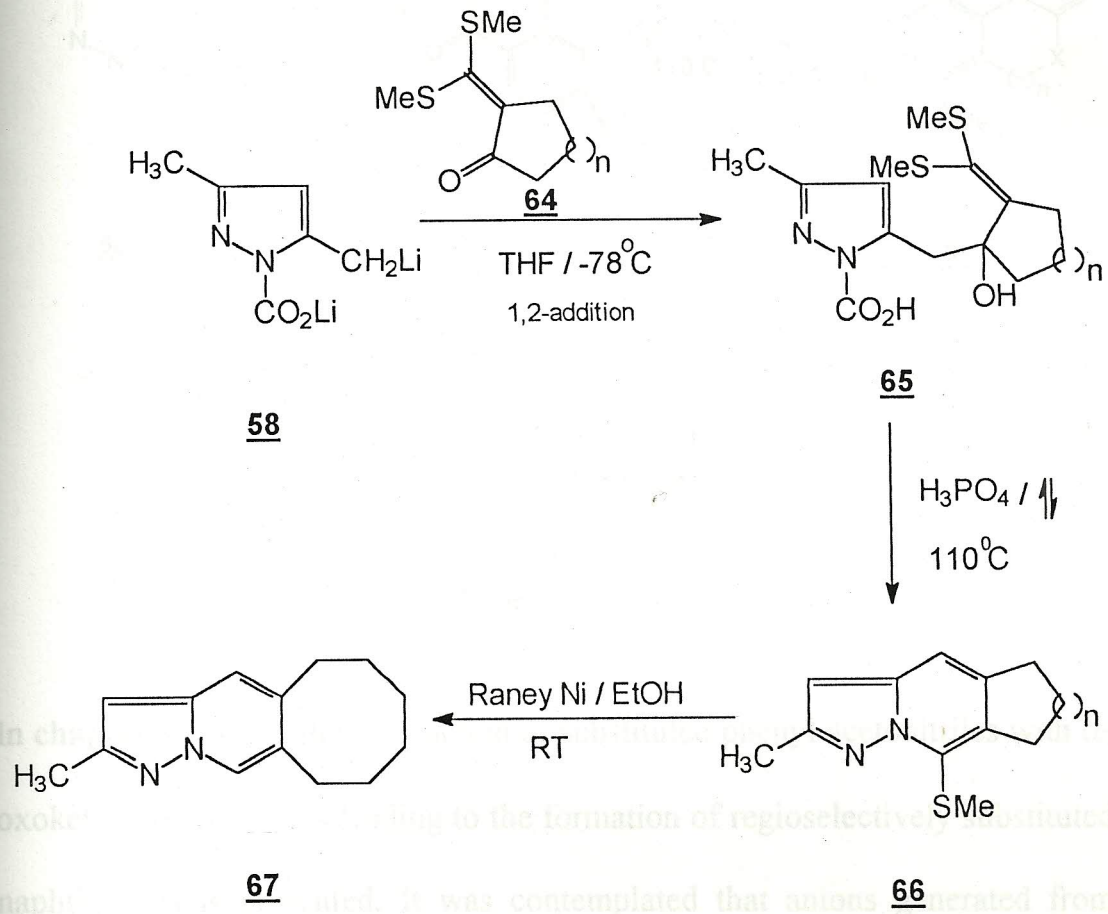
b. R^1 = CH_3 ; R^2 = CH_3

c. R^1 = C_6H_5 ; R^2 = H

d. R^1 = p-$OMeC_6H_4$; R^2 = H

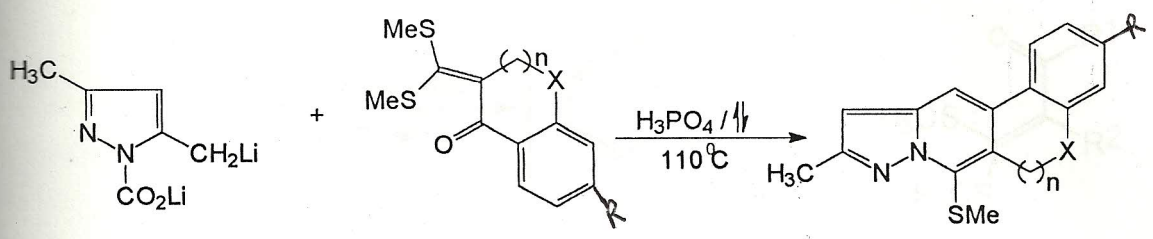
e. R^1=  R^2= H

Scheme-8



64, 65 ,66 a. n=1
b. n=2
c. n=4
67 n=4

Scheme-9



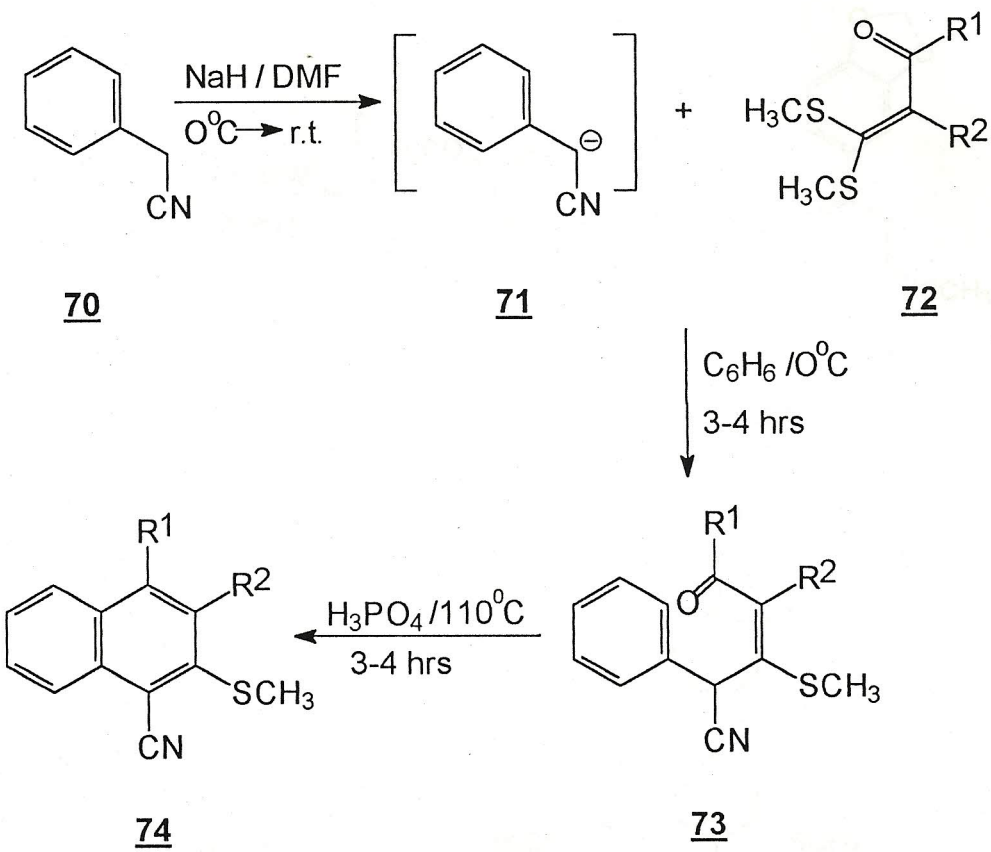
58 68 69

68, 69 a : $X=CH_2$, R=H, n=1

b: X= S, R= CH_3 n=2

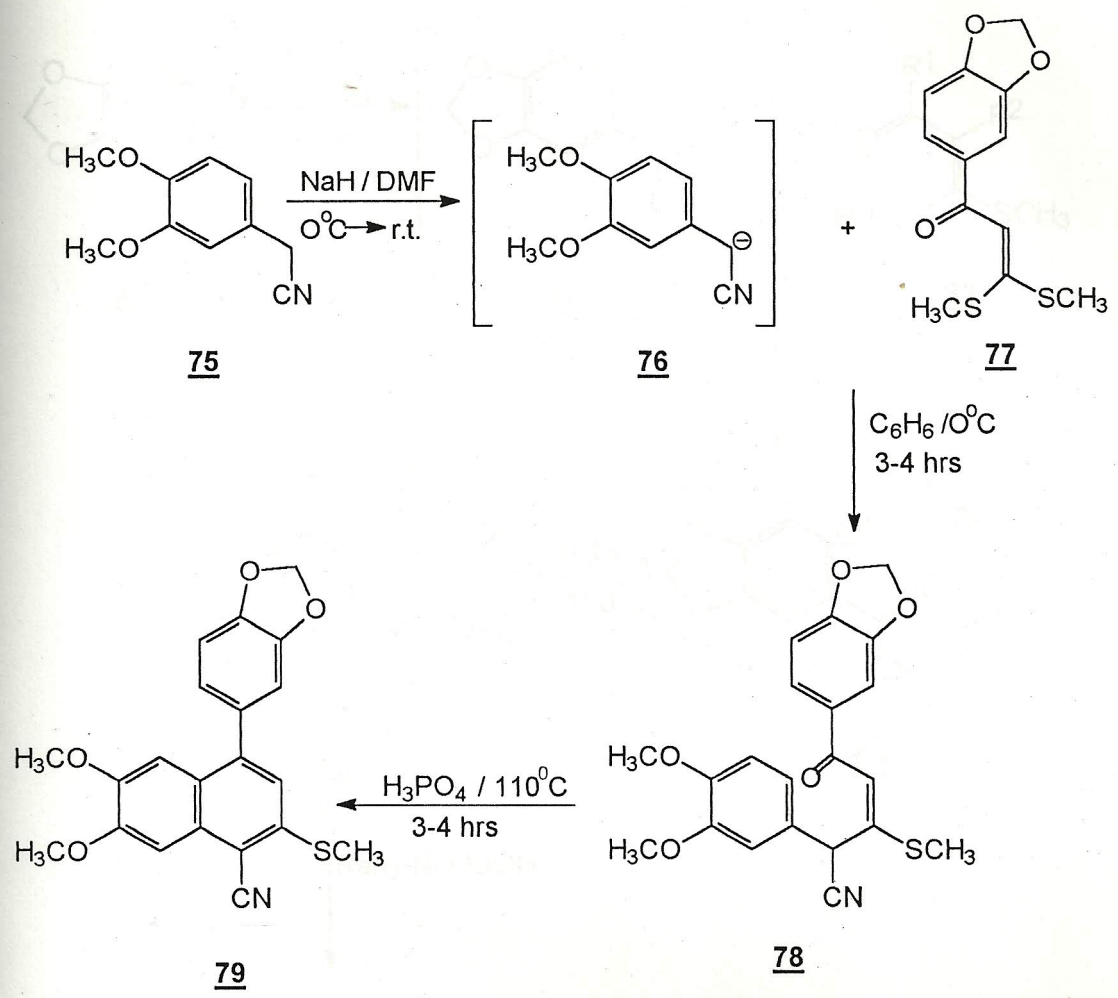
Scheme-10

In **chapter III** of the thesis, reaction of substituted phenyl acetonitriles with α-oxoketene dithioacetals leading to the formation of regioselectively substituted naphthalenes is presented. It was contemplated that anions generated from substituted phenyl acetonitriles should add to α-oxoketene dithioacetals in 1,4-fashion. Thus when we generated the anion from substituted phenyl acetonitriles in the presence of sodium hydride and reacted with α-oxoketene dithioacetals, addition-elimination products were obtained in good yields. These addition-elimination products underwent orthophosphoric acid assisted cyclodehydration to give the desired regioselectively substituted naphalenes (*Scheme-11-13*).



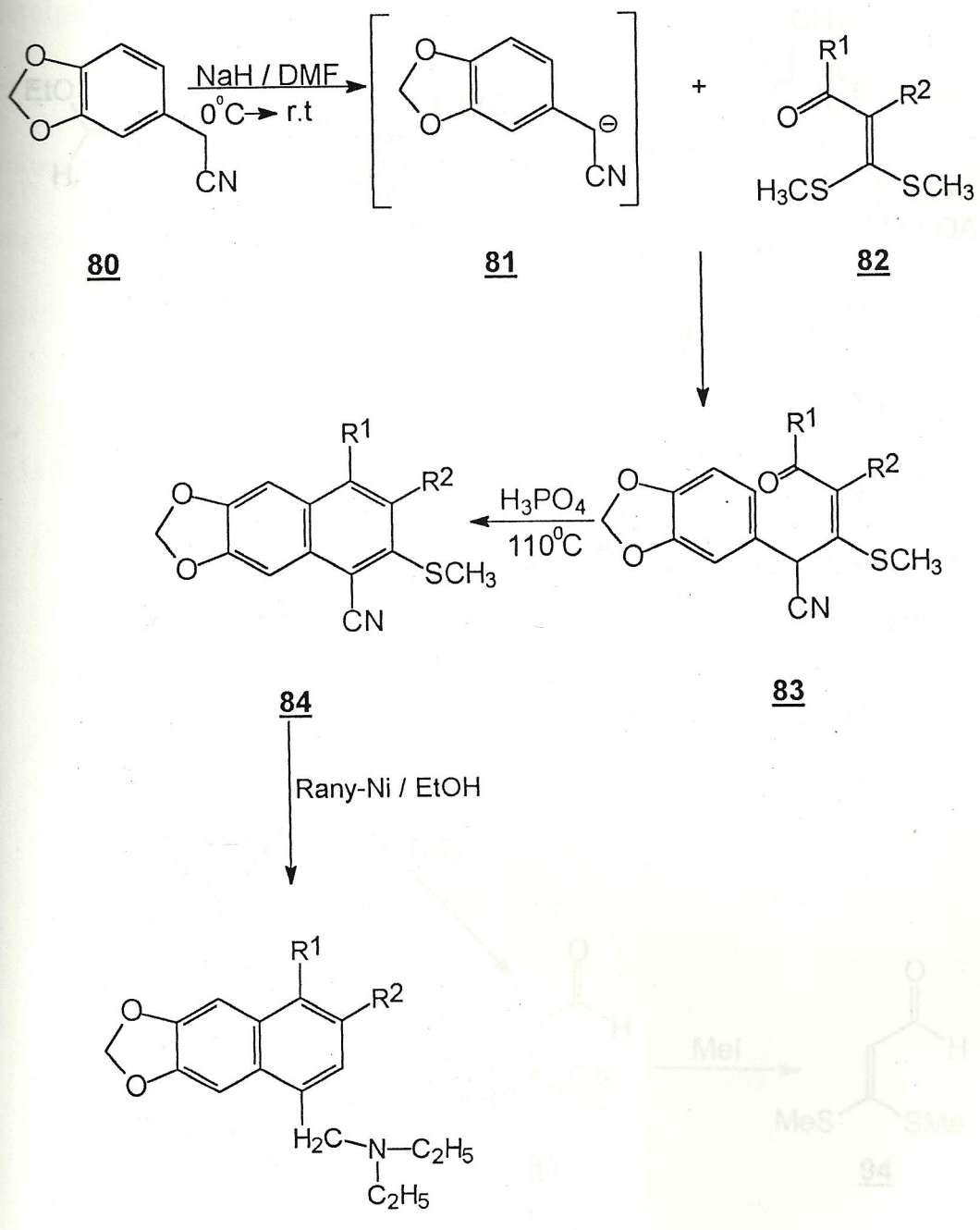
72, 73, 74	a.	$R^1 = CH_3$	$R^2 = H$
	b.	$R^1 = CH_3$	$R^2 = CH_3$
	c.	$R^1 = Ph$	$R^2 = H$
	d.	$R^1 = Ph$	$R^2 = Ph$
	e.	R^1 = p-Me Ph	$R^2 = H$
	f.	R^1 = p-OMe Ph	$R^2 = H$

Scheme-11



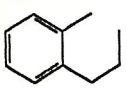
Scheme-12

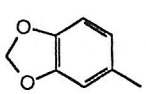
In **chapter IV** of this thesis, we have for the first time shown that chloromercury acetaldehyde **89** *Scheme-14* is an excellent source of acetaldehyde enolate anion which could be used for the synthesis of α,β-unsaturated aldehydes. Chloro(2-oxoethyl)mercury was synthesised by reacting mercuric acetate with methyl vinyl ether **86** in the presence of sodium chloride when a white precipitate was formed which was filtered and recrystallised from water for further use.



82,83,84. a. $R^1 = C_6H_5$ $R^2 = H$

b. $R^1 = p\text{-}OMeC_6H_4$ $R^2 = H$

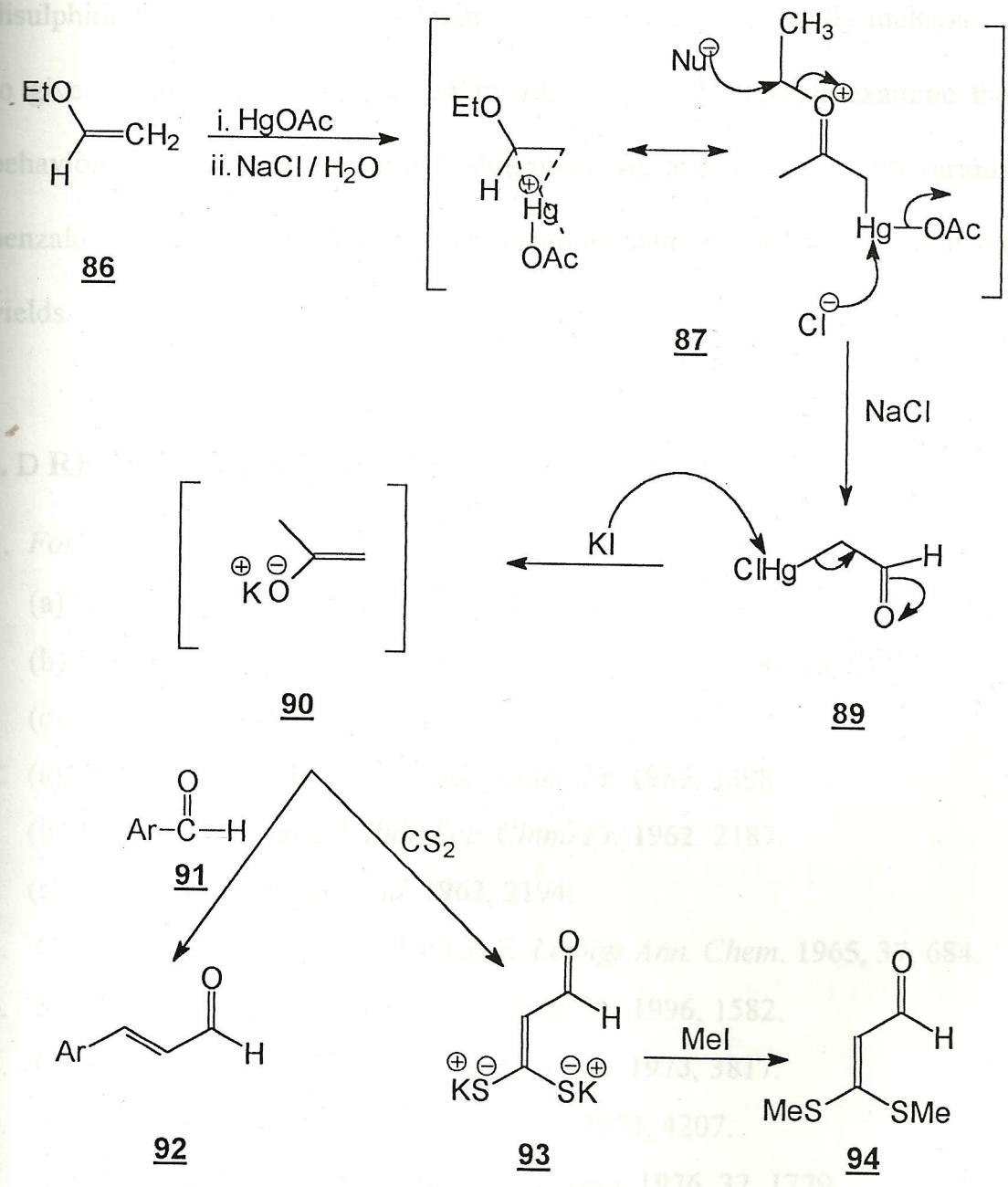
c. R^1 =  $R^2 = H$

d. R^1 =  $R^2 = H$

85. a. $R^1 = C_6H_5$ $R^2 = H$

b. $R^1 = p\text{-}OMeC_6H_4$ $R^2 = H$

Scheme-13



Scheme-14

In order to examine the synthetic potential of acetaldehyde enolate anion obtained from chloromercury acetaldehyde, we reacted this with carbon

disulphide using dimethyl formamide as solvent and subsequently methylated to give acetaldehyde mercaptal **94** in 40% yields. To further examine the behaviour of this anion we reacted chloromercury acetaldehyde with various benzaldehydes which yielded the corresponding cinanamaldehydes **92** in good yields.

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