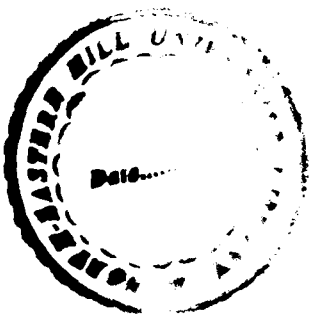
NEW SYNTHETIC ROUTES TO CARBOCYCLES AND HETEROCYCLES *VIA* ∝-OXOKETENE DITHIOACETALS



BY

KAUSHAL KISHORE

SUBMITTED

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IN

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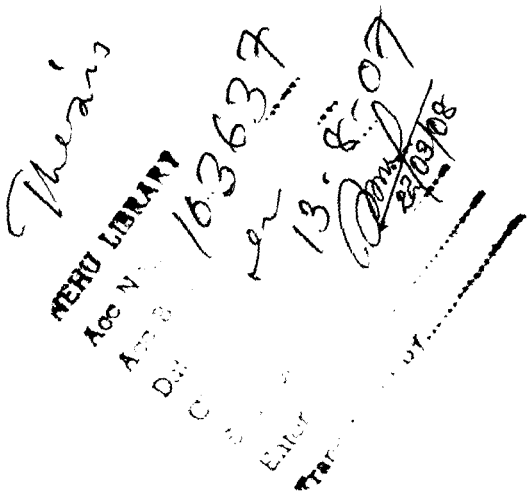
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This is being submitted to North-Eastern Hill University for the Degree of Doctor of Philosophy in Chemistry.

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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.

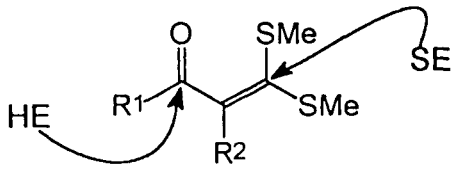
CHAPTER-I

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

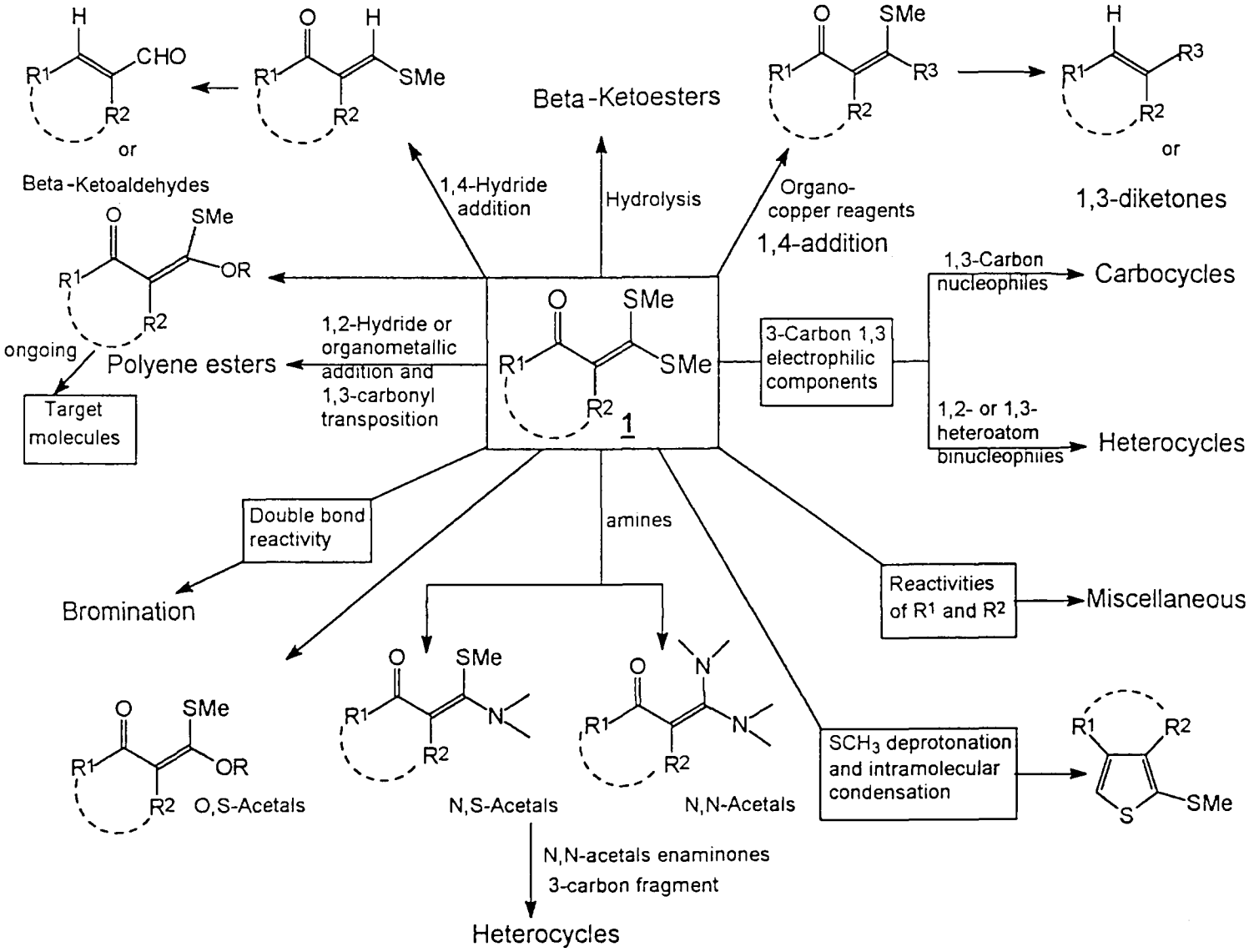
1

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-Ketoesters
1,4-Hydride addition
Hydrolysis
Organo-copper reagents
1,4-addition
or
Beta-Ketoaldehydes
or
1,3-diketones
1,2-Hydride or organometallic addition and 1,3-carbonyl transposition
Polyene esters
ongoing
Target molecules
3-Carbon 1,3 electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
Double bond reactivity
Bromination
amines
Reactivities of R1 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

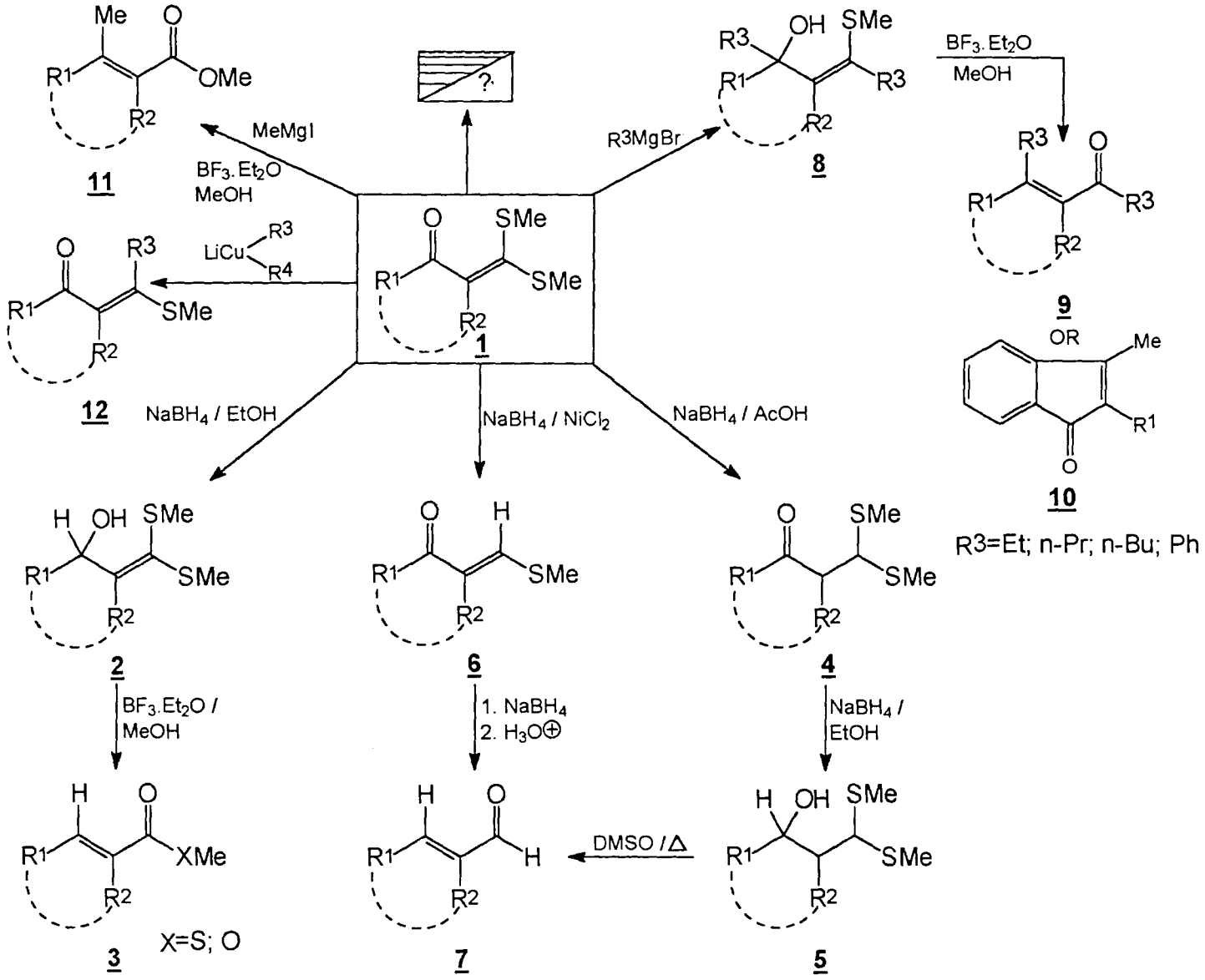
α-oxoketene dithioacetals which possess typical 1,3-electrophilic centres react with a number of heterobinucleophiles to yield 5-and 6-membered heterocycles.[12-24] When R^1 is alkyl, the acetal **1** undergoes deprotonation to give enolate anion which condenses with aldehydes to produce α-enoyl ketene 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

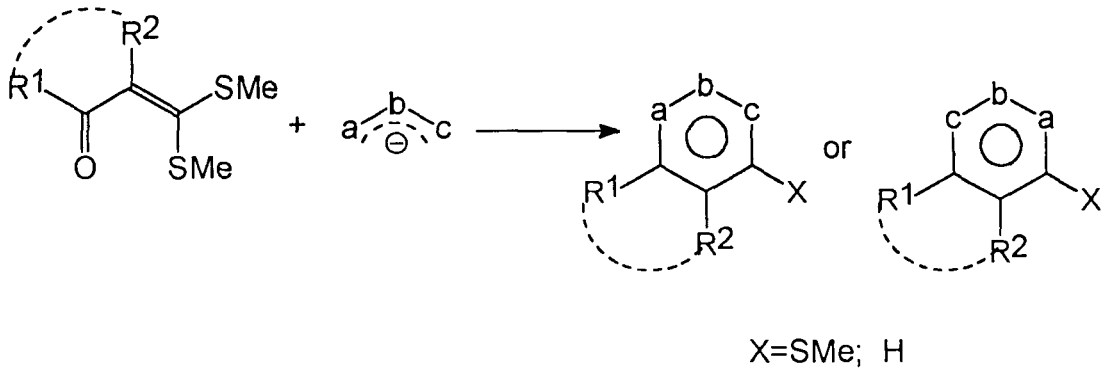

Me
O
OMe
R1
R2
11
MeMgI
BF3.Et2O
MeOH
?
R3MgBr
OH
SMe
R3
8
BF3.Et2O
MeOH
9
OR
Me
10
R3=Et; n-Pr; n-Bu; Ph
LiCu
R3
R4
12
SMe
1
NaBH4 / EtOH
NaBH4 / NiCl2
NaBH4 / AcOH
H
2
6
4
BF3.Et2O /
MeOH
1. NaBH4
2. H3O⊕
NaBH4 /
EtOH
XMe
3
X=S; O
7
DMSO /Δ
5

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



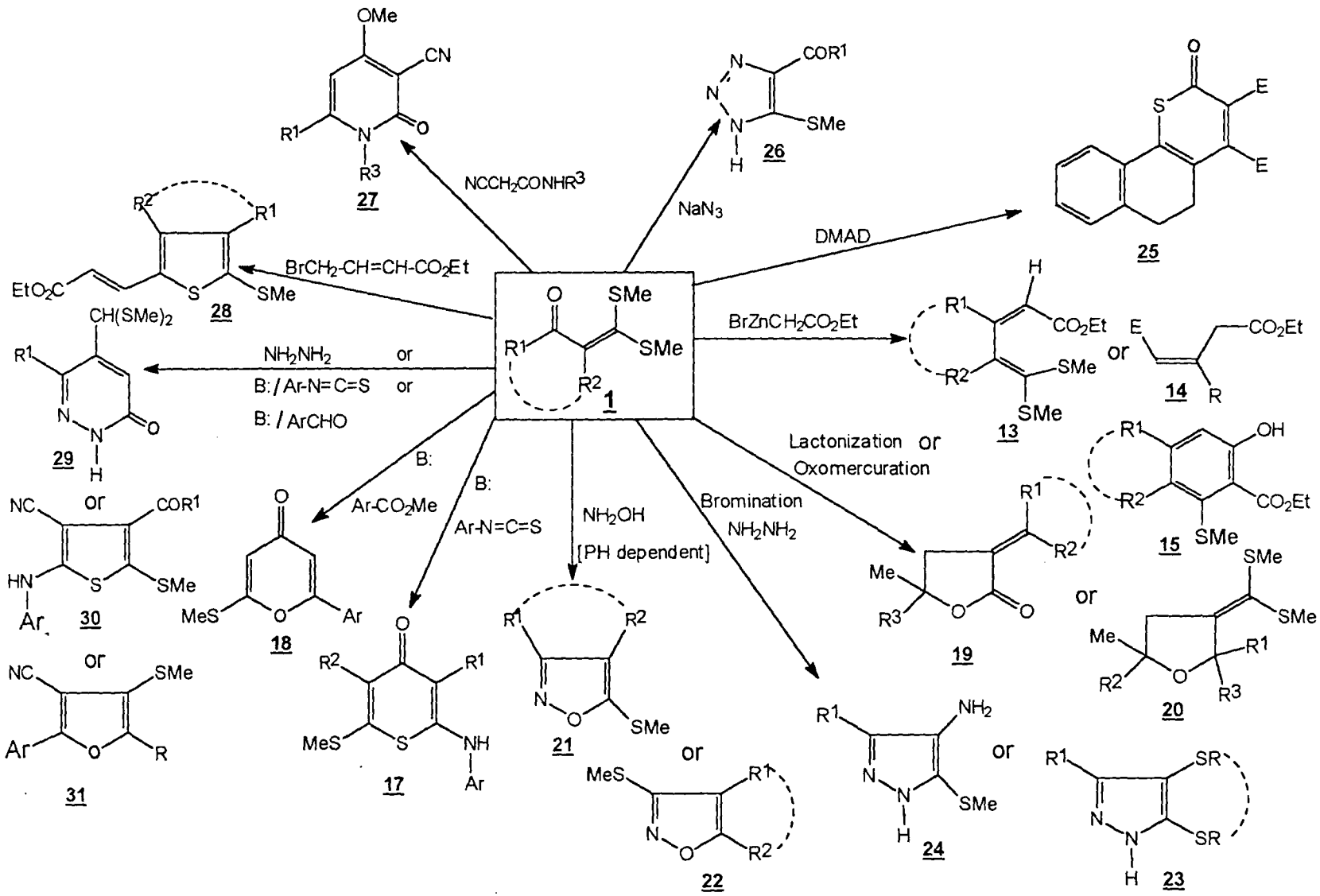
3 Carbon 1,3-binucleophiles and alpha-oxoketene dithioacetals approach for aromatic annelation

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

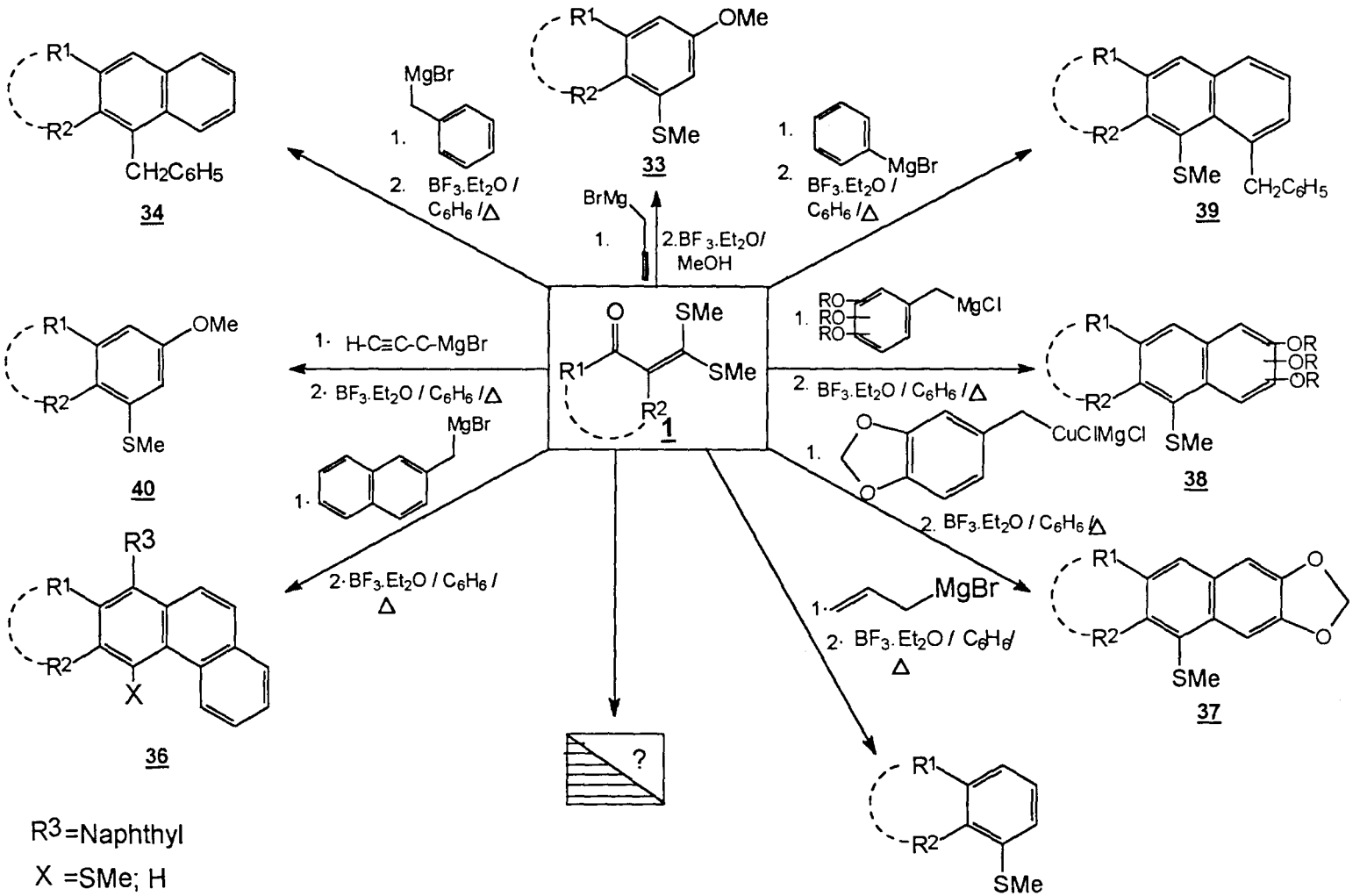

OMe
CN
R1
N
O
R3
27
NCCH2CONHR3
N
N
N
H
COR1
SMe
26
NaN3
O
S
E
E
25
DMAD
R2
R1
EtO2C
S
SMe
28
BrCH2-CH=CH-CO2Et
O
SMe
R1
SMe
R2
1
BrZnCH2CO2Et
H
R1
CO2Et
R2
SMe
SMe
13
or
E
CO2Et
14
R
CH(SMe)2
R1
N
N
O
H
29
NH2NH2 or
B: / Ar-N=C=S or
B: / ArCHO
B:
Ar-CO2Me
O
MeS
O
Ar
18
B:
Ar-N=C=S
O
R2
R1
MeS
S
NH
Ar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

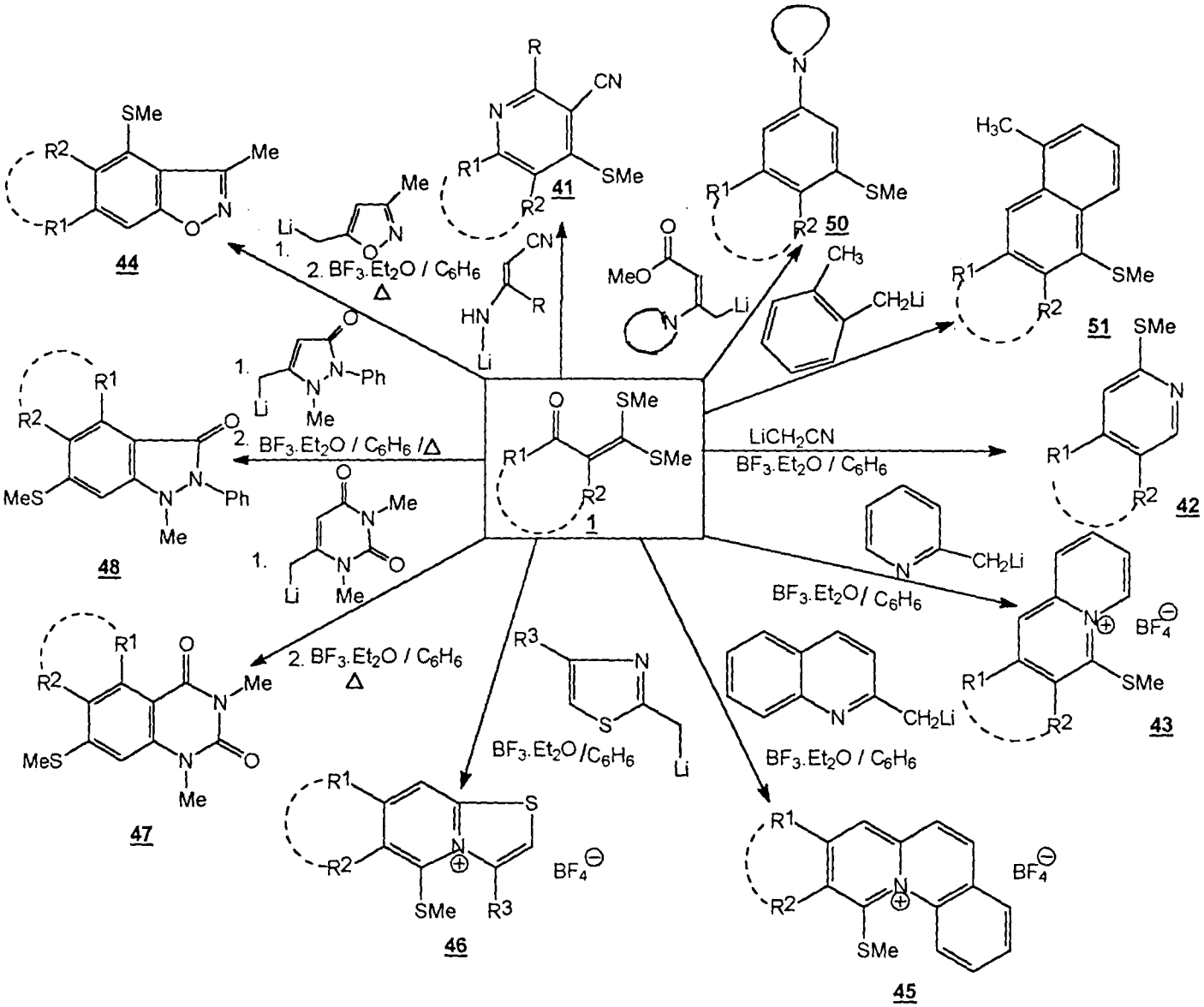

R1
R2
CH2C6H5
34
MgBr
1.
2. BF3.Et2O / C6H6 /Δ
R1
R2
OMe
SMe
33
BrMg
1.
2.BF3.Et2O/ MeOH
1.
MgBr
2. BF3.Et2O / C6H6 /Δ
R1
R2
SMe
CH2C6H5
39
R1
R2
OMe
SMe
40
1· H-C≡C-C-MgBr
2· BF3.Et2O / C6H6 /Δ
MgBr
1·
O
SMe
R1
SMe
R2
1
RO
RO
RO
1.
MgCl
2. BF3.Et2O / C6H6 /Δ
R1
R2
OR
OR
OR
SMe
38
O
O
1.
CuClMgCl
2. BF3.Et2O / C6H6 /Δ
R3
R1
R2
X
36
2·BF3.Et2O / C6H6 / Δ
?
1·
MgBr
2· BF3.Et2O / C6H6/ Δ
R1
R2
O
O
SMe
37
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
2. BF3.Et2O / C6H6 /Δ
LiCH2CN BF3.Et2O / C6H6
BF3.Et2O/ C6H6
BF3.Et2O/C6H6
BF3.Et2O / C6H6
41
42
43
44
45
46
47
48
50
51

Scheme-5

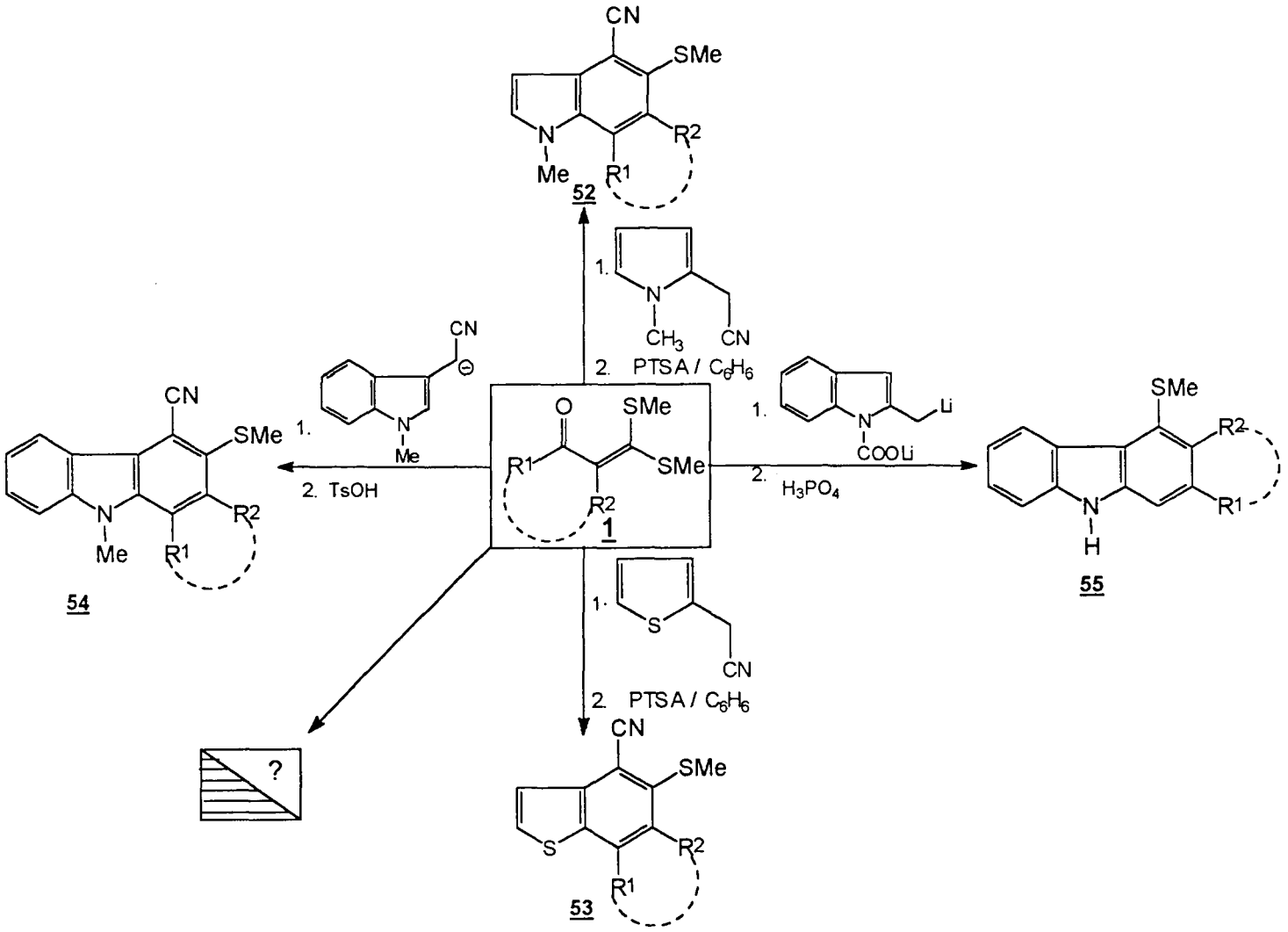
substituted and condensed indoles **52**.[51] This strategy was further extended for the synthesis of substituted benzothiophene **53**[52] by the reaction of thiophene 2-acetonitrile and various cyclic and acyclic α-oxoketene dithioacetals under similar conditions (*scheme*-6).

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:

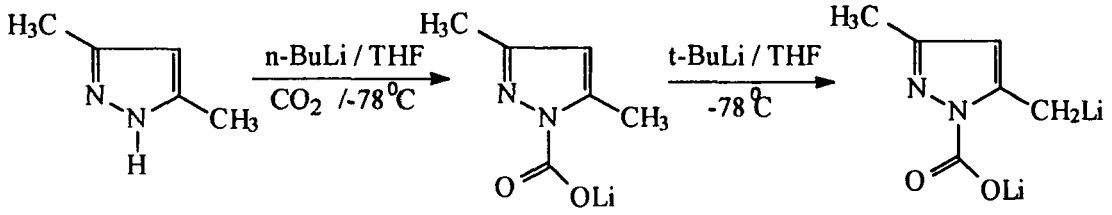
In continuation with above studies exploiting the synthetic potential of α-oxoketene dithioacetals which are easily accessible from a wide range of active methylene compounds, we further proposed to undertake to utilise these


CN
SMe
N
Me
R2
R1
52
1.
2. PTSA / C6H6
CN
1. TsOH
54
O
SMe
R1
SMe
R2
1
1.
2. H3PO4
COOLi
55
1.
2. PTSA / C6H6
?
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].

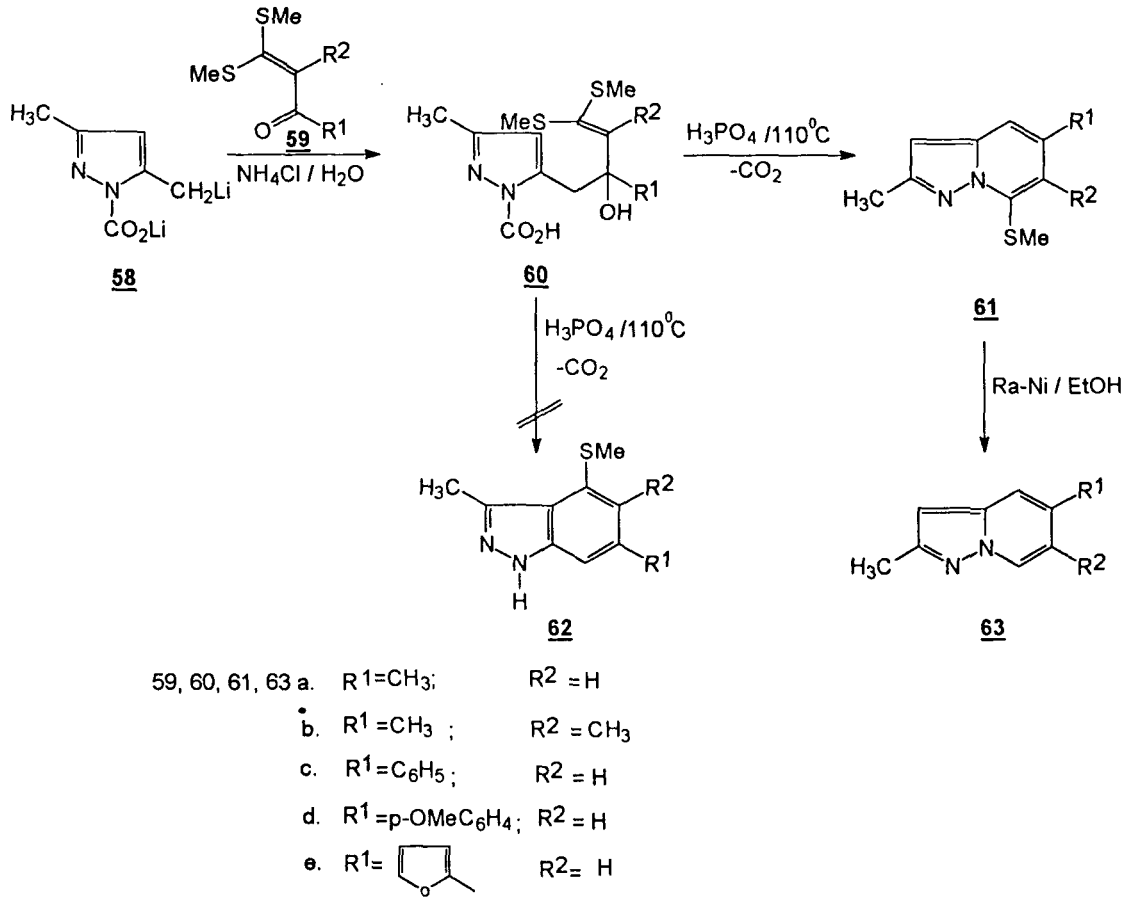


56 **57** **58**

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. $R^1=CH_3$; $R^2=H$

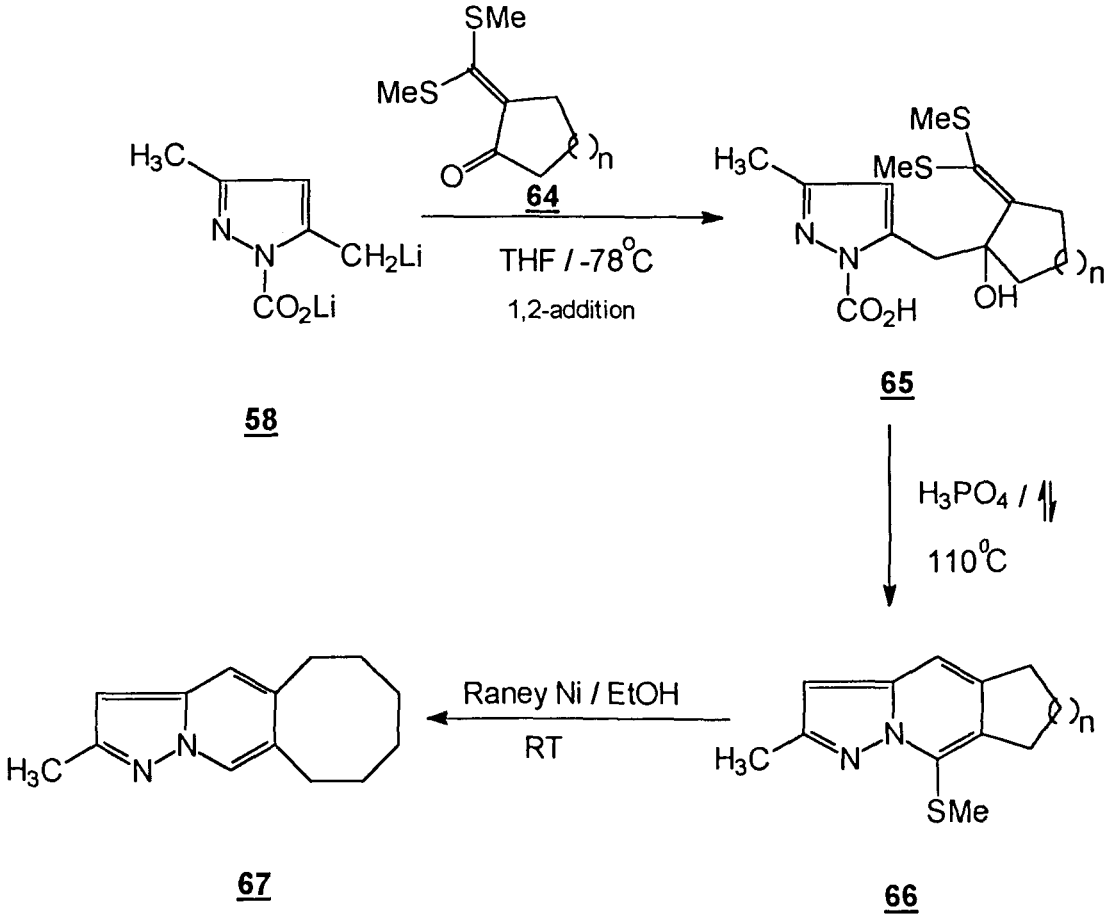
b. $R^1=CH_3$; $R^2=CH_3$

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

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

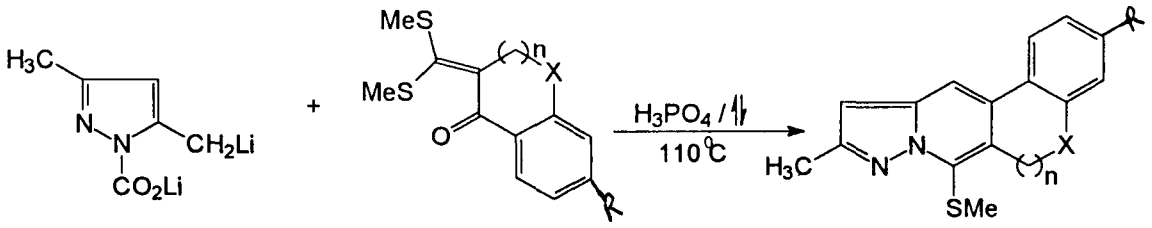
e. $R^1=$ $R^2=H$

Scheme-8



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

Scheme-9



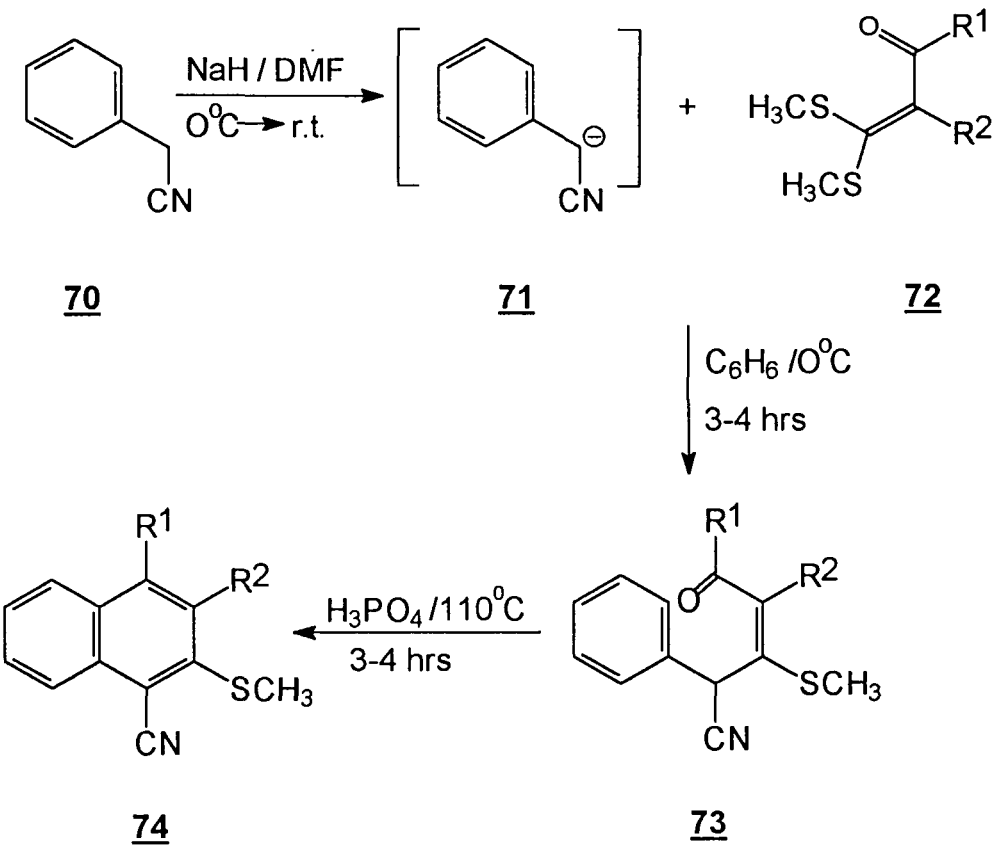
58 68 69

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

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

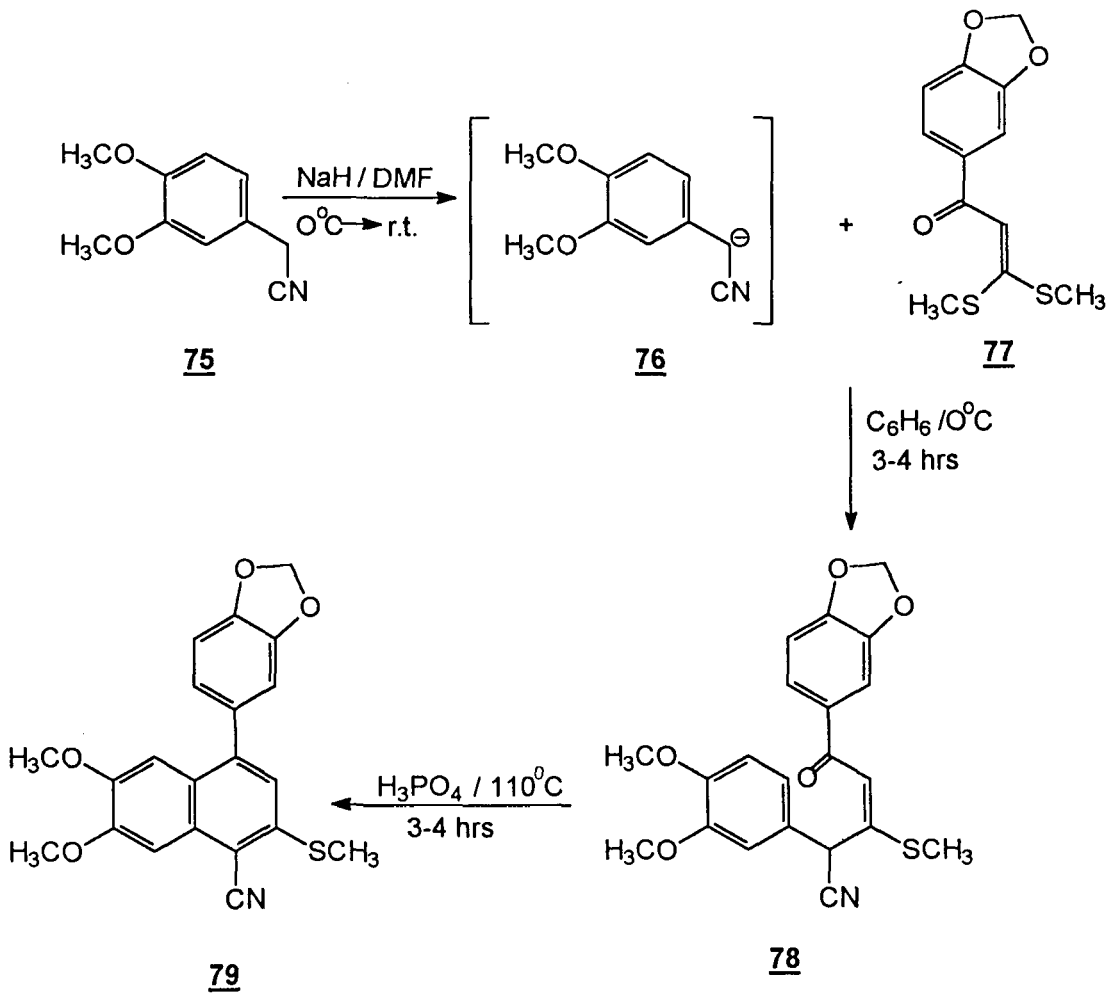
Scheme-10

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*).



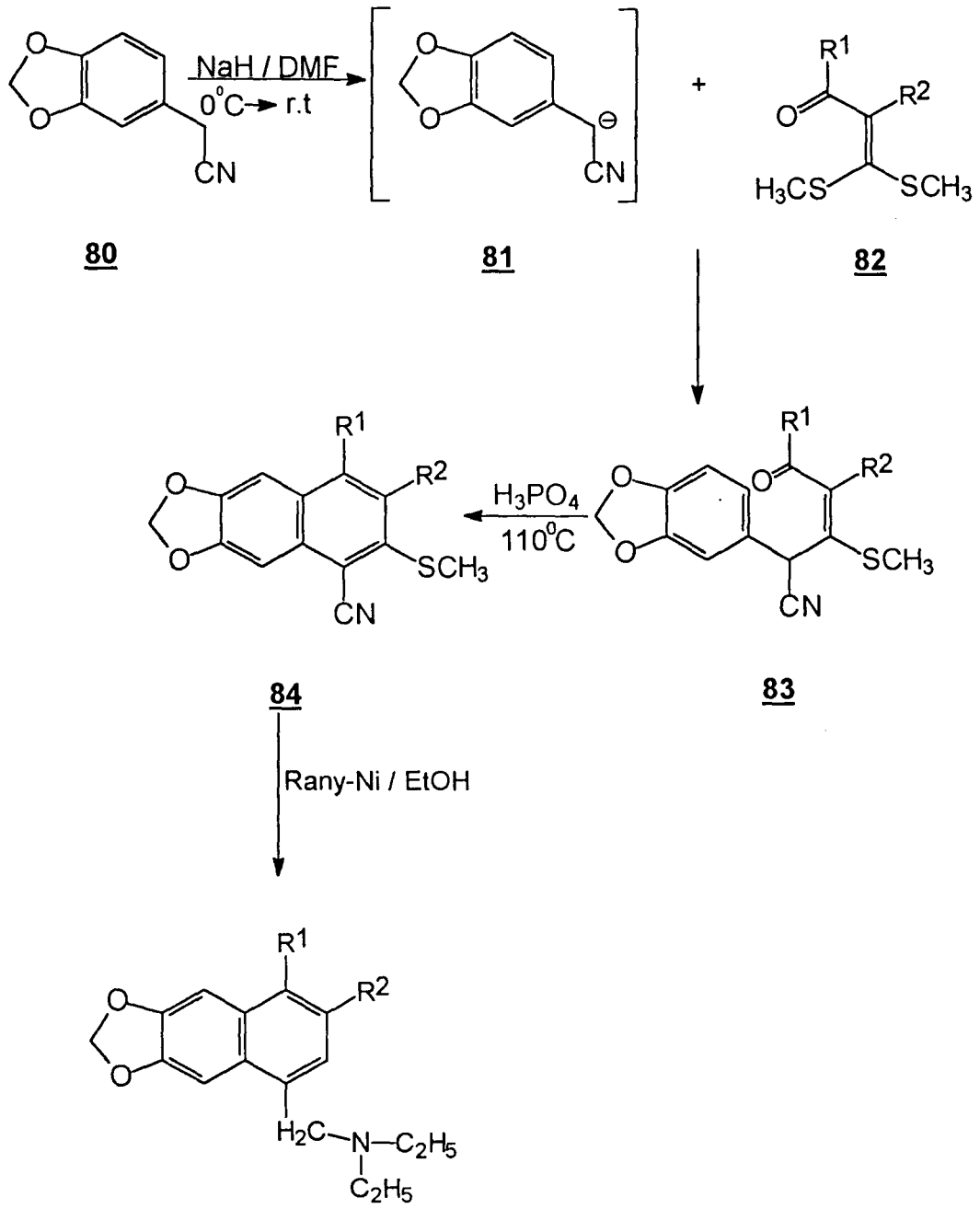
72, 73, 74	a.	$R^1 = CH_3$	$R^2 = H$
	b.	$R^1 = CH_3$	$R^2 = CH_3$
	c.	$R^1 = Ph$	$R^2 = H$
	d.	$R^1 = Ph$	$R^2 = Ph$
	e.	R^1 = p-Me Ph	$R^2 = H$
	f.	R^1 = p-OMe Ph	$R^2 = H$

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.

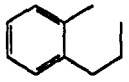


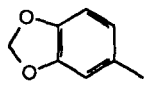
85. a. $R^1 = C_6H_5$ $R^2 = H$

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

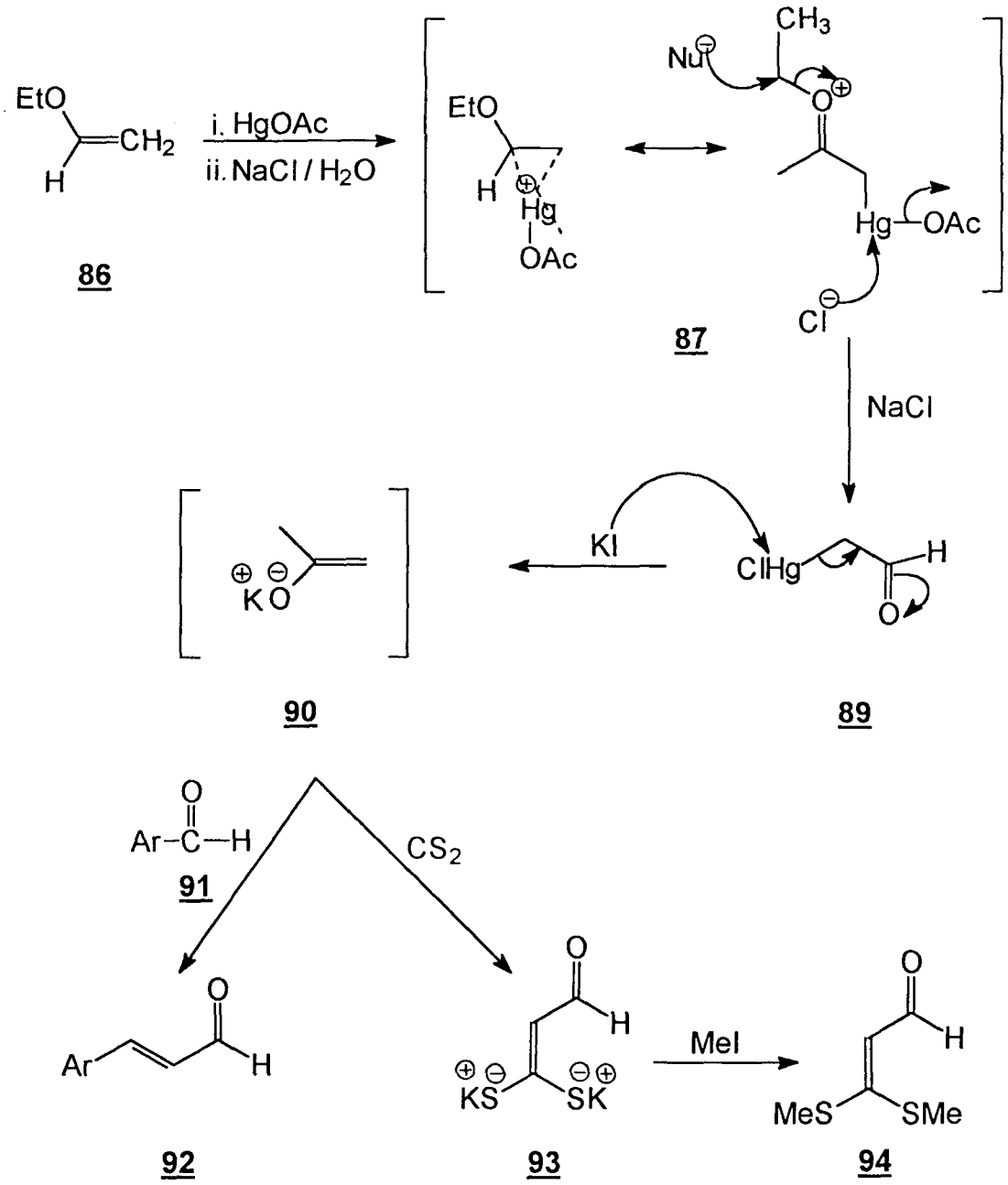
82,83,84. a. $R^1 = C_6H_5$ $R^2 = H$

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

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

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

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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CHAPTER-II

PREPARATION OF LITHIUM 5-LITHIOMETHYL-3-METHYLPYRAZOLE-1-CARBOXYLATE AND ITS REACTION WITH α-OXOKETENE DITHIOACETALS: A NEW GENERAL METHOD FOR SUBSTITUTED AND ANNELATED PYRAZOLO[1,5-*a*]PYRIDINES*

II. A INTRODUCTION:

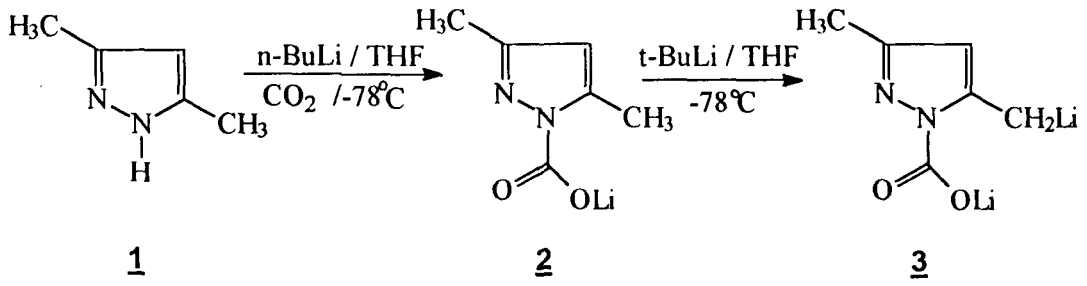
Metallation studies on *N*-methyl or *N*-benzyl pyrazoles have revealed that the *N*-alkyl protons preferentially undergo deprotonation to yield kinetically favoured carbanions which, at higher temperatures exchange protons from the pyrazole ring to give the thermodynamically stable 5-lithiopyrazole anions in high yields[1,2]. Reaction of these anions with various electrophiles has been examined and their formation is fully established. Also, 1,5-dimethyl and 1,3,5-trimethylpyrazoles have been shown to undergo exclusive *N*-methyl deprotonation in preference to any of the ring methyl protons[1,2,3].

---

*Kaushal Kishore, K. R. Reddy, J. R. Suresh, H. Ila and H. Junjappa, Tetrahedron (in press).

Thus to our knowledge no studies are reported in the literature on deprotonation of pyrazole ring methyl protons employing direct metallation technique. However, Katritzky and Akutagawa[4] have reported that the 2-methylindole, when protected as its 1-lithium carboxylate, readily underwent lithiation in the α-methyl carbon to afford the corresponding lithium 2-lithiomethylindole-1-carboxylate in excellent yield. The anion was reacted with various electrophiles to yield the corresponding 2-(substituted)methyl indoles in high yields. This was the first example of the use of carbon dioxide for protection, activation and deprotection sequence in a one pot reaction. We have successfully extended this protocol and reacted this anion with various α -oxoketene dithioacetals to yield the corresponding carbinol thioacetals followed by their cyclization in the presence of orthophosphoric acid to afford the corresponding *N-H* carbazoles in excellent yields[5].

We therefore, attempted this protocol on 3,5-dimethyl pyrazole **1** and observed that the corresponding Lithium-5-lithiomethyl-3-methylpyrazole-1-carboxylate **3** was formed in excellent yield and the anion was reacted with various α-oxoketene dithioacetals to yield the corresponding pyrazolo[1,5-*a*]pyridines involving cyclization through ring nitrogen rather than ring carbon of indazoles in high yields.The method constitutes first report on the construction of pyrazolo[1,5-*a*]pyridines directly from the pyrazole **1** through its dianion **3** and α-oxoketene dithioacetals.

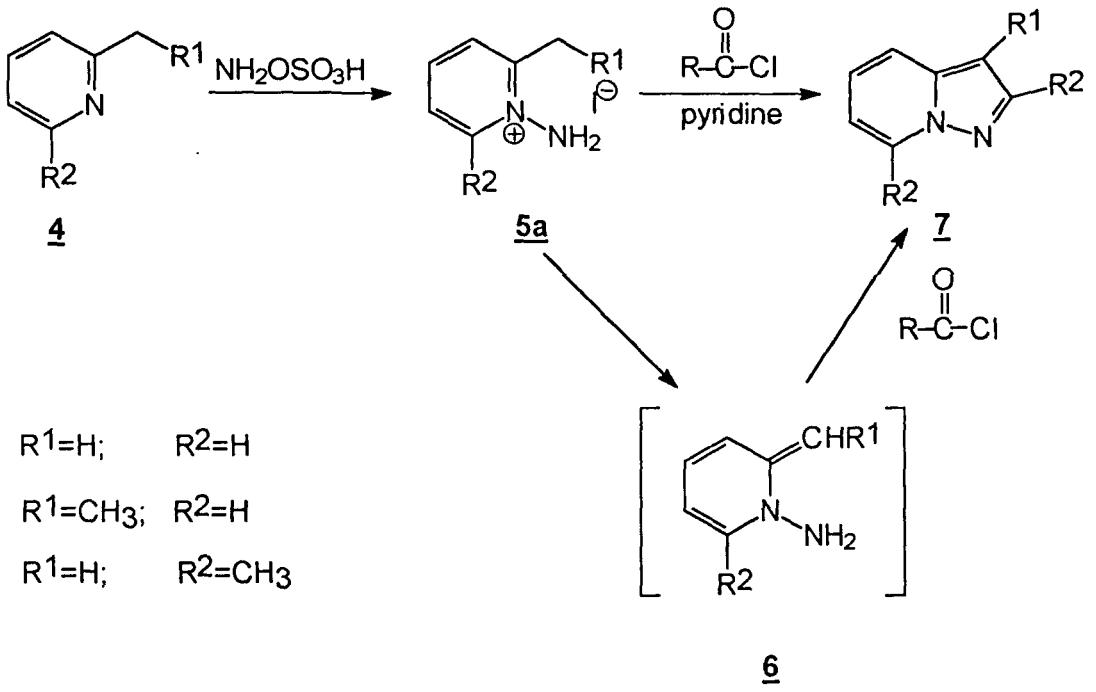


Scheme - 1

The chapter describes the results of these studies and a brief survey on the recent literature methods for the synthesis of pyrazolo[1,5-*a*]pyridines in the following section.

Chemistry of pyrazolo[1,5-*a*]pyridines has attracted the attention of many active research groups in recent years due to their wide variety of biological and pharmacological properties. Most of the methods described in the literature have used *N*-amino pyridinium salts as starting materials which are briefly discussed as follows.

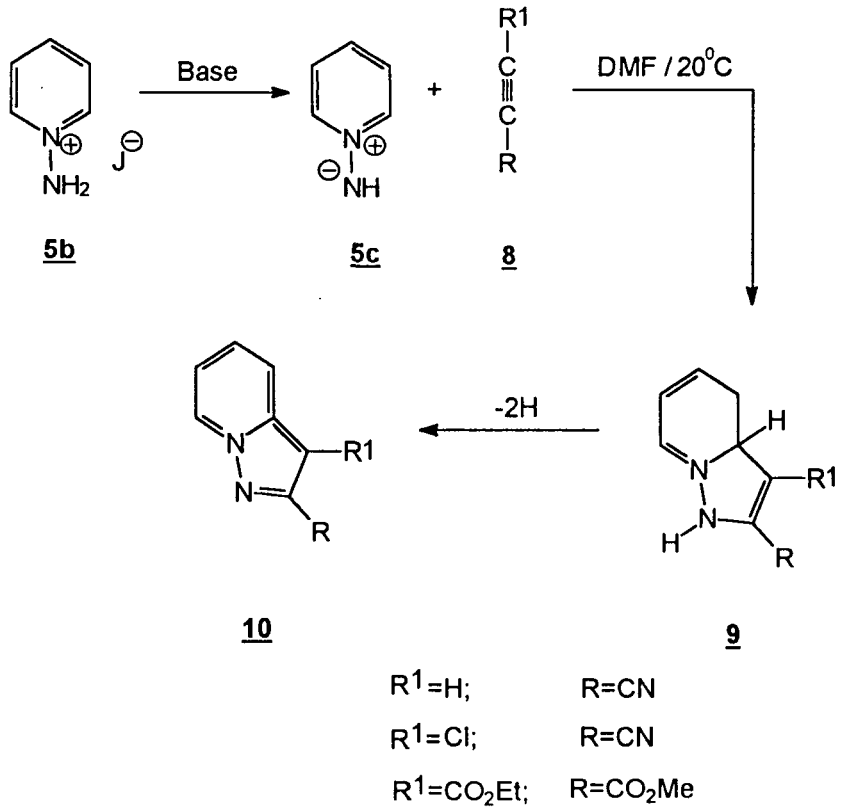
Potts and coworkers[6] reported a facile synthesis of pyrazolo[1,5-*a*]pyridines as formulated in *scheme-2*. The 2-alkyl-1-aminopyridinium salts **5a** were conveniently reacted with acyl or aroyl chlorides in the presence of pyridine as solvent when the corresponding pyrazolo[1,5-*a*]pyridines **7** were formed in moderate to good yields. The required 1-aminopyridinium salts **5** were prepared by direct amination of tertiary amines with hydroxylamine-*O*-sulfonic acid with various substituted pyridines (*Scheme-2*).



Scheme-2

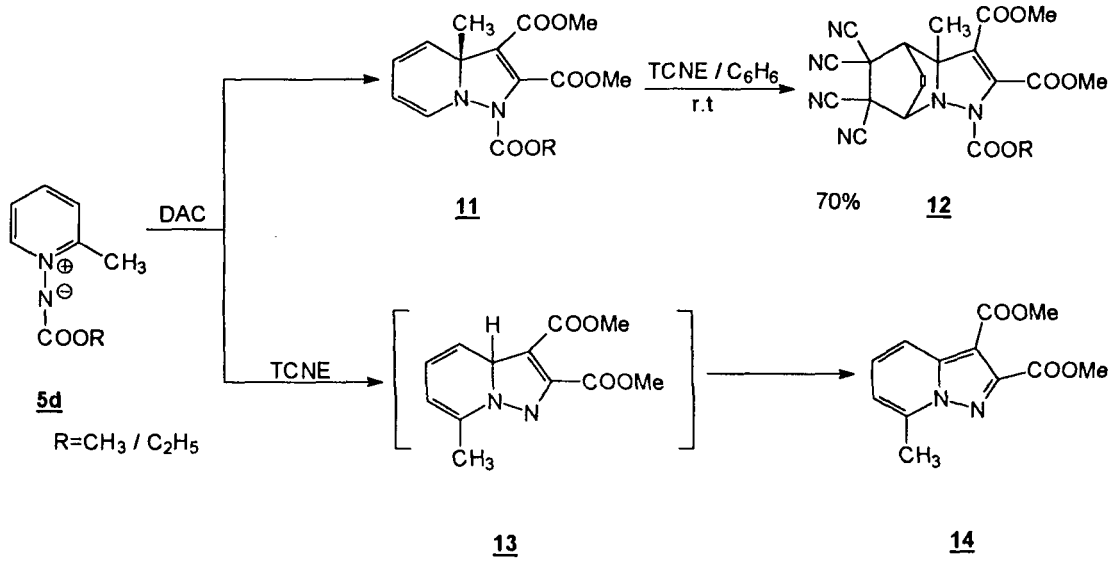
The *N*-Aminopyridinium iodide **5b** was treated with calcium hydroxide in dimethyl formamide to afford the corresponding ylids **5c**, which were used as 1,3-dipolar intermediates. These were then reacted with various acetylenic esters 8[7a-d] as effective dipolarophiles to afford the corresponding pyrazolo[1,5-*a*]pyridines **10** in good yields (*scheme-3*).

Several ring substituted 1-alkoxycarbonyl-iminopyridinium ylids[8] **5d** *scheme-4* were used in cycloaddition reaction as 1,3-dipolar species. **5d** was reacted with dimethyl acetylenedicarboxylate both in the absence and in the presence of tetracyanoethylene in benzene or acetonitrile medium.The reaction of **5d**



Scheme-3

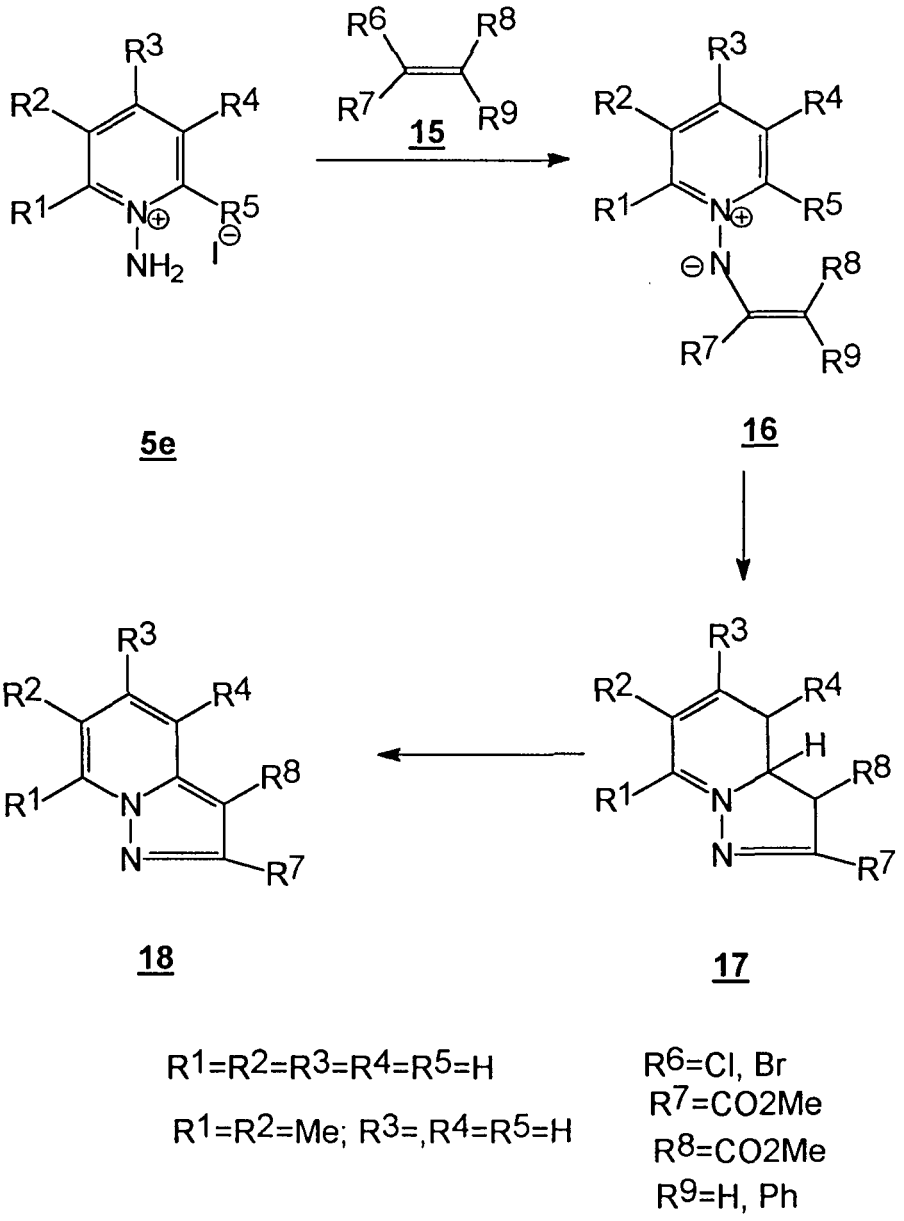
with dimethyl acetylenedicarboxylate gave the dihydropyrazolo[1,5-*a*]pyridines **11** as 1:1 adduct. The adduct was further reacted with tetracyano ethylene to afford the corresponding cycloadduct **12** in 70% yield. When **5d** was reacted with dimethyl acetylenedicarboxylate in the presence of tetracyanoethylene a mixture of **12** and **14** was formed whereas **14** being the minor product. It may be noted here that the reaction though mechanistically interesting its synthetic utility is not suitable for applying to the preparation of pyrazolo[1,5-*a*]pyridines.



Scheme-4

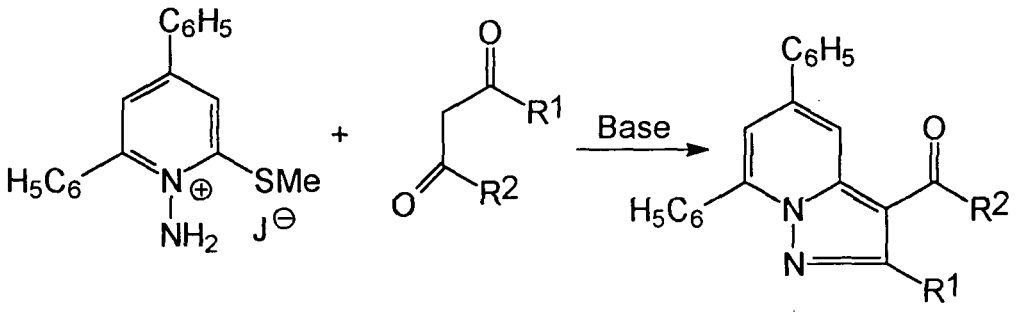
Sasaki and coworkers[9a-b] prepared a series of *N*-vinylpyridinium ylids **16** (*scheme-5*) from pyridinium *N*-imine hydriodides **5e** and dimethyl 1-chlorofumarate or maleate in the presence of potassium carbonate. The ylids **16** underwent cyclization in various solvents at room temperature to afford the corresponding dihydrocycloadducts **17** in moderate yields. These dihydro derivatives are stable in crystalline form while transforming rapidly to the pyrazolo[1,5-*a*]pyridine derivatives **18** in the presence of dehydrating agents. These reactions demonstrate that the 1,5-dipolar character is involved and useful for the preparation of these bridged nitrogen heteroaromatics.

Molina and coworkers[10a-b] develop a new strategy for the synthesis of pyrazolo[1,5-*a*]pyridine **20** as formulated in *scheme-6*. Thus, readily available



Scheme-5

1-amino- 4,6-diphenyl-2-methylthiopyridinium salts **5f** were reacted with 1,3-diketones **19** in the presence of base to afford the corresponding 2-substituted pyrazolo[1,5-*a*]pyridines **20**. It is to be noted that the presence of 2-phenyl group is essential for the preparation of **5f** from 2-thioxo-2*H*-pyrans whereas the corresponding methyl substituted pyridinium salts could not be used.



5f **19** **20**

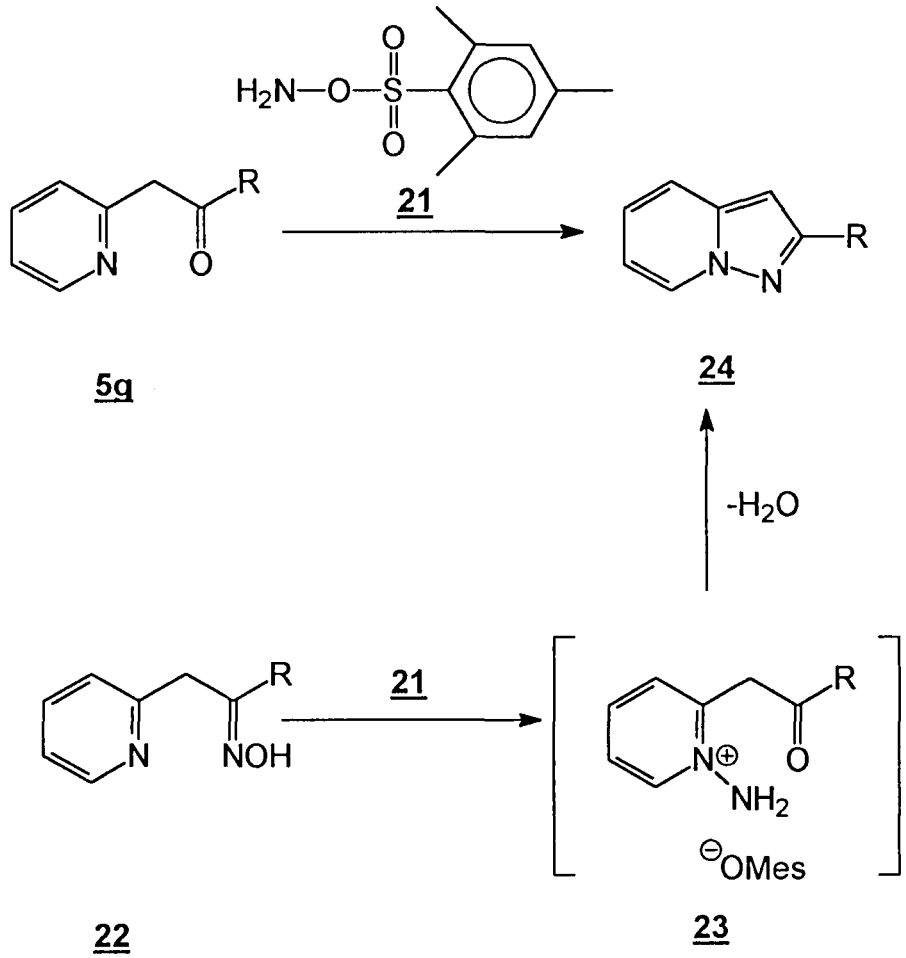
$R^1=CH_3$; $R^2=CH_3$

$R^1=Ph$; $R^2=OC_2H_5$

$R^1=OH$; $R^2=OC_2H_5$

Scheme-6

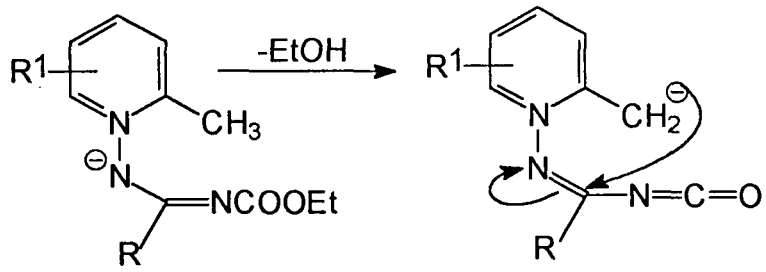
Tamura and coworkers[11] have developed a new approach for the synthesis of pyrazolo[1,5-*a*]pyridine as formulated in *scheme-7*. Thus oximes of 2-picolyl ketones when treated with *O*-mistylenesulfonylhydroxylamine directly cyclised through **23** to afford the corresponding pyrazolo[1,5-*a*]pyridine **24**. Kekehi and coworkers[12] have examined pyridinium ylids of the general formula **5h** in *scheme-8* under photochemical and thermal condition.These ylids on thermolysis yielded a mixture of **26** and **27** moderate yields. None of these experiments yielded the required pyrazolo[1,5-*a*]pyridines in desirable yields.



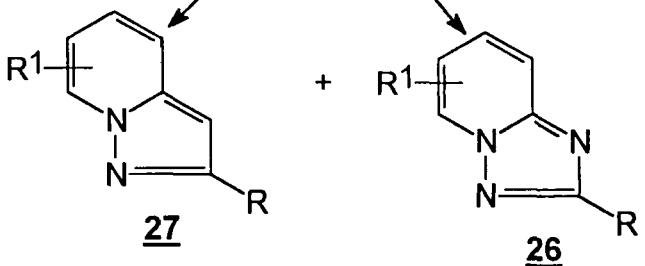
Scheme-7

In a synthetic scheme involving a reaction of pyridine as base with isonitrosoflavanone esters **29**, the pyrazolo[1,5-*a*]pyridine[13] **32** was formed through the sequence shown in *Scheme-9*. The method is not being attractive for its utility for the synthesis of these compounds.

Cyclopentadiene diazonium compound **33** was used as 1,3-dipolar species and reacted with acetylenic ester to give the corresponding spiro compound.

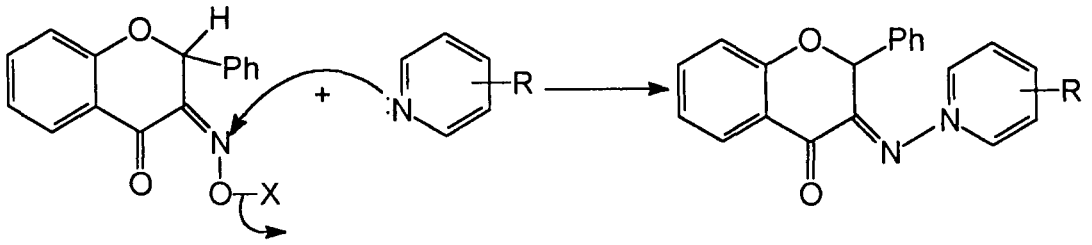


5h 25

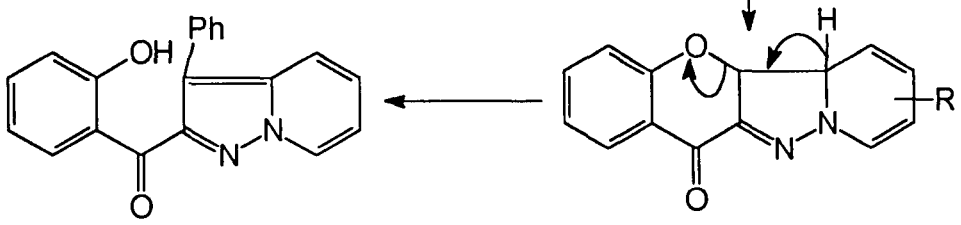


27 26

Scheme-8

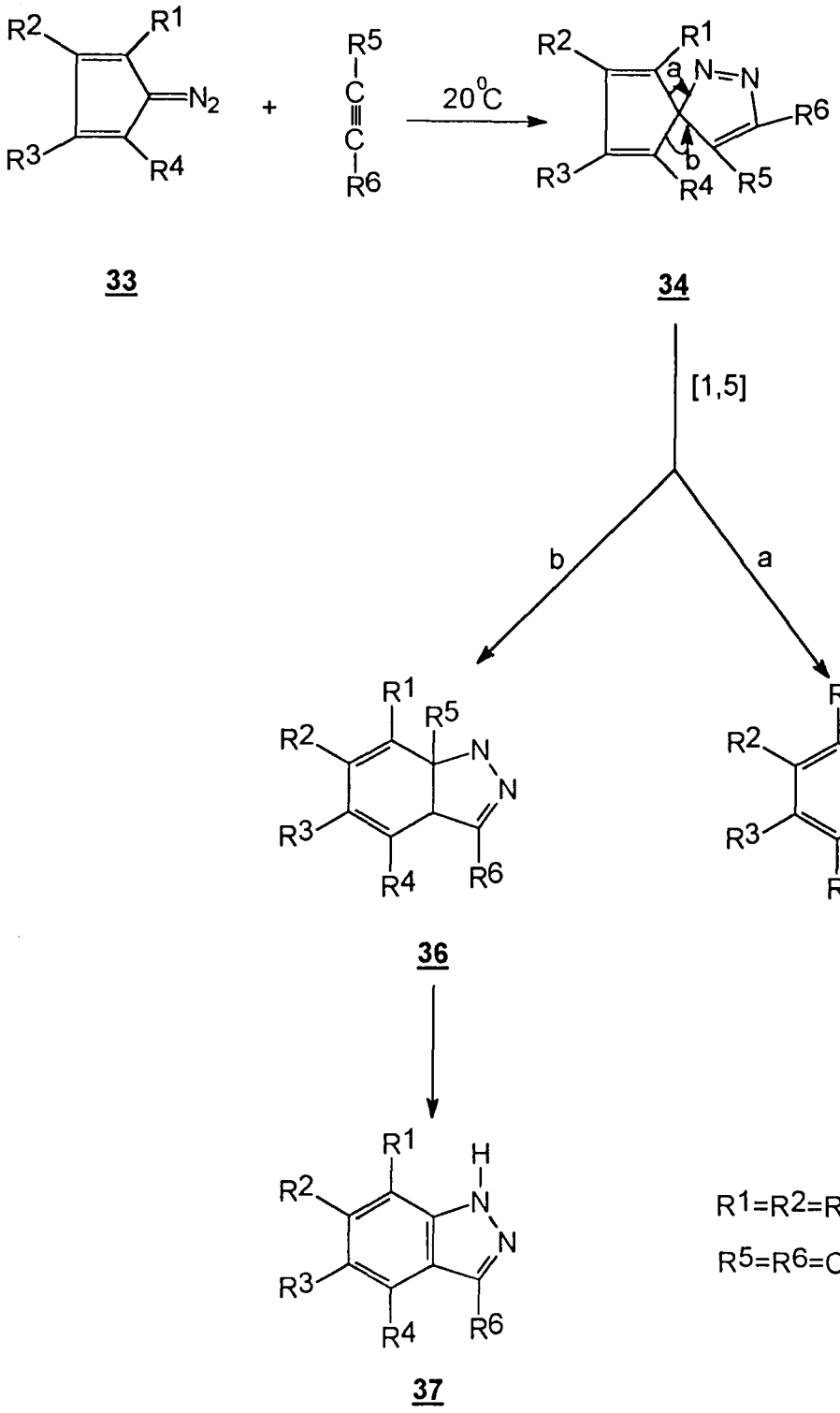


29 28 30



32 31

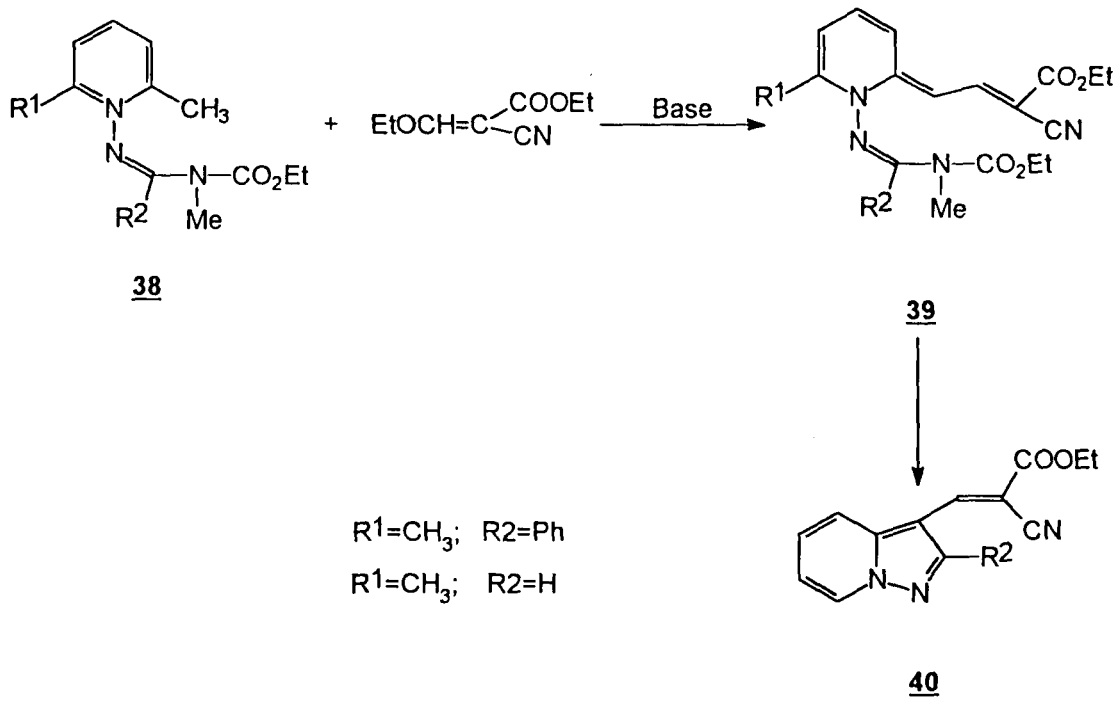
Scheme-9


R2
R1
N2
R3
R4
+
R5
C
C
R6
20°C
a
b
N=N
R6
R5
33
34
[1,5]
b
a
R1
R5
R2
R3
R4
R6
N
N
36
35
H
37
R1=R2=R3=R4=Ph
R5=R6=CO2Me

Scheme-10

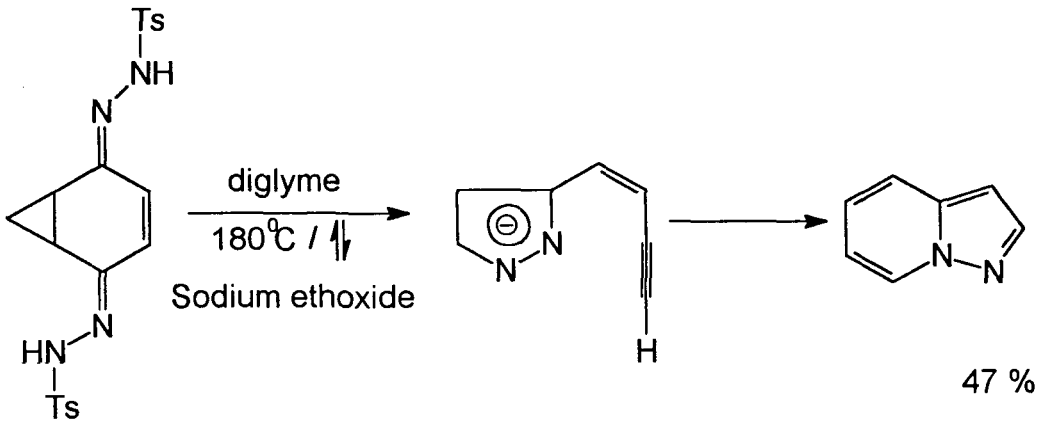
34. These spiro compounds underwent rearrangement to give a mixture of indazole **37** and pyrazolo[1,5-*a*]pyridine **35**[14a-b](*Scheme-10*).

2-Allylidene-1,2-dihydropyridine **38** possessing an electrophilic centre in the 1-substituent were prepared by the reaction of pyridinium salts with ethyl ethoxymethylene cyanoacetate in the presence of alkali. The reaction mixture on thermolyses gave 3-ethenyl pyrazolo[1,5-*a*]pyridines **40** in high yields[15a,b] (*scheme-11*).



Scheme-11

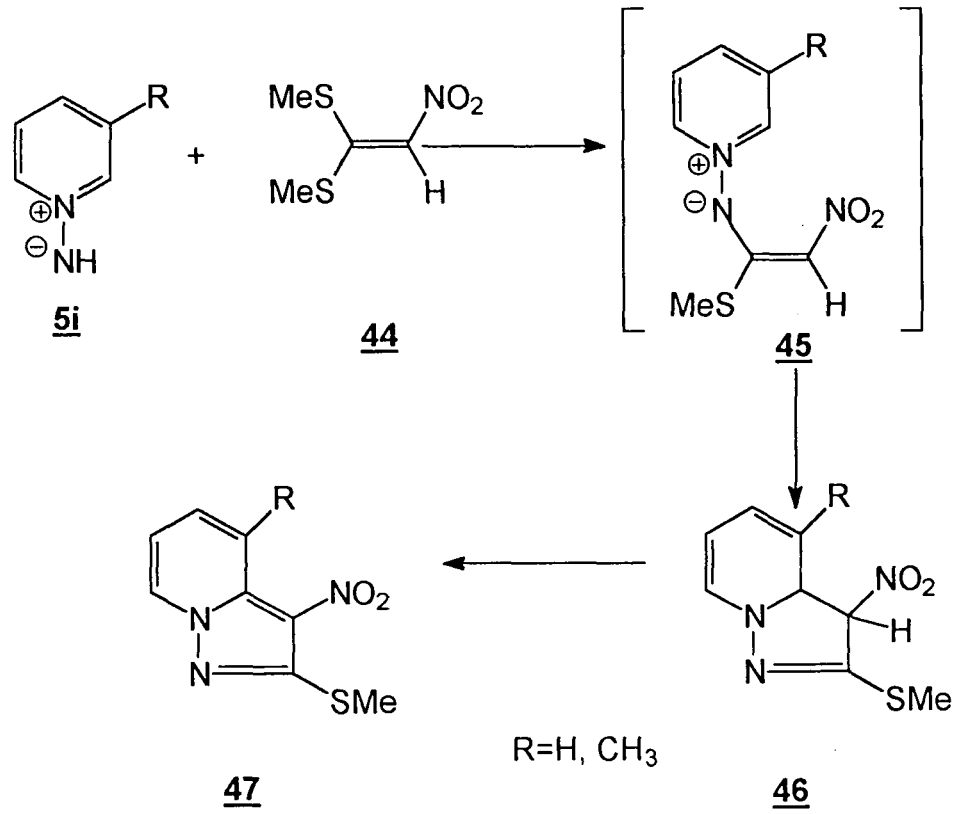
Chapleo and Dreiding[16] have made an interesting thermal studies on bis-*p*-toluenesulfonylhydrazone **41** (*scheme-12*) of homo-*p*-quinone which underwent rearrangement when its sodium salt was heated at 180^{0}C in diglyme to obtain pyrazolo[1,5-*a*]pyridine **43** in 47% yield.



41 **42** **43**

Scheme-12

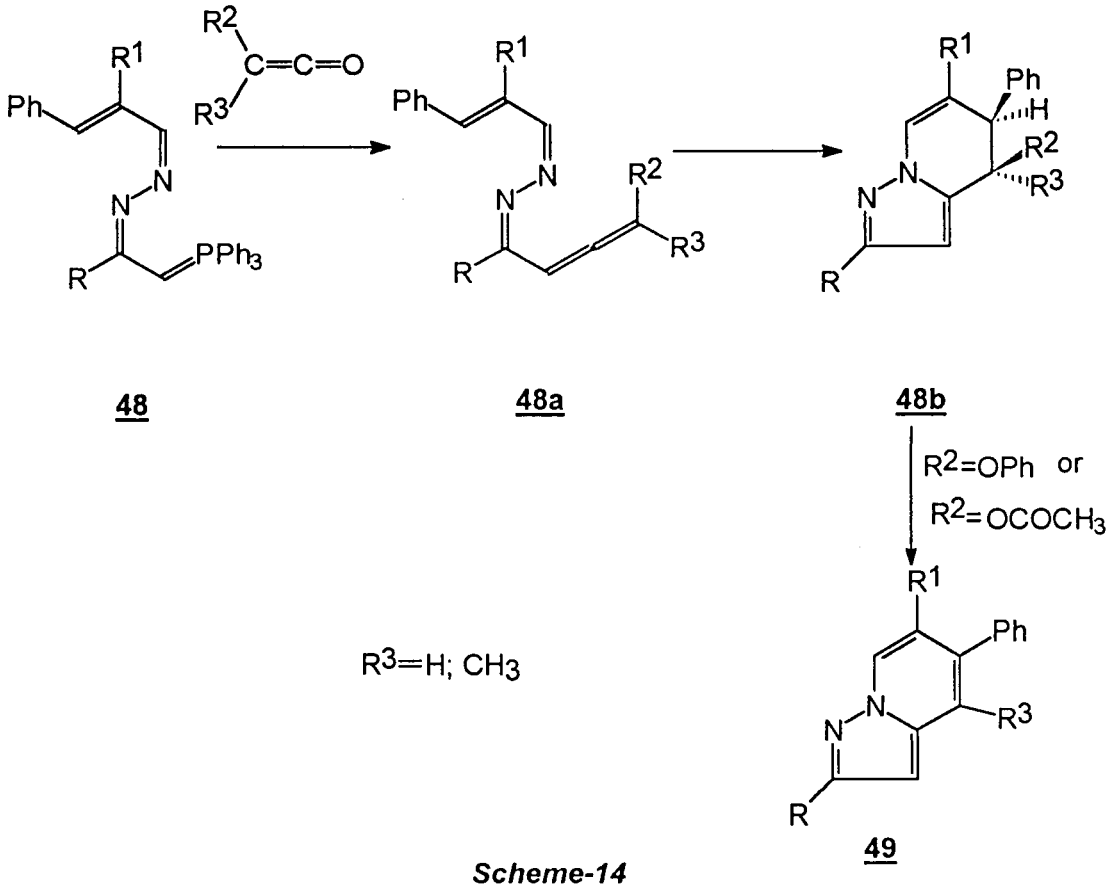
Kobayashi and coworkers[17a-b] reacted pyridinium *N*-imine **5i** with 2,2-bis(methylthio)-1-nitroethylene 44 to yield the corresponing 4-methyl-2-



5i **44** **45** **46** **47**

Scheme-13

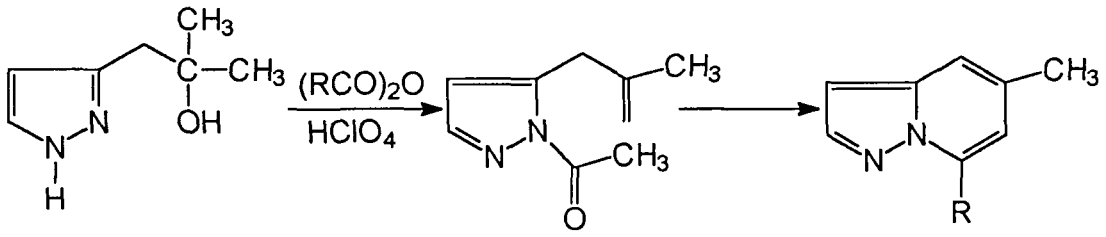
methylthio-3-nitro pyrazolo[1,5-*a*]pyridine **47** in good yield (*scheme-13*). Schweizers and coworkers[18] have reported the reaction of 3,4-diaza-2,4,6-hepta-(trienylidene)triphenyl phosphoranes **48** with ketenes to afford the corresponding 4,5-dihydropyrazolo[1,5-*a*]pyridine **48b**. If one of the substituents on the ketene is acetoxy, or phenoxy, elimination may occur to form the corresponding fully aromatized pyrazolo[1,5-*a*]pyridines **49** (*scheme-14*).



Scheme-14

In an interesting study Voshula and coworkers[19] have prepared pyrazole **50** by reacting hydrazine hydrate with 2,2-dimethyl 2,3-dihydropyranone-4. The pyrazole **50** on treatment with acid anhydride and perchloric acid yielded

pyrazolo[1,5-*a*]pyridine **52** probably involving the intermediacy of **51** (*scheme-15*). The reaction is important since it is the only report of its kind,



50 **51** **52**

R=CH_3; C_2H_5

Scheme-15

which does not involve the intermediacy of *N*-amino ylids encountered in the preceding examples. However, the method cannot be considered for its general application since it was observed as a by product in physico-chemical studies by the authors.

In the preceding brief review, we have described some of the major methods reported in the literature for the synthesis of pyrazolo[1,5-*a*]pyridines. It is to be noted that most methods were based on *N*-aminopyridinium salts or its ylids as intermediates with or without substituent on the pyridine ring. Thus there are no method in literature of any preparative importance that involves pyrazole as a starting material. The only method described in the literature belonging to this class is that due to Russian workers.[19]

It will be important if a method starting from simple pyrazole is developed to yield the pyrazolo[1,5-*a*]pyridines in high yields. We have successfully developed a new synthesis of pyrazolo[1,5-*a*]pyridines starting from 3,5-dimethyl 1-*H* pyrazole. These results are described in this section.

II.B. RESULTS AND DISCUSSION:

We have briefly discussed the formation of dianion **3** in the introductory part of this chapter. We have successfully generated the dianion **3** through direct deprotonation of the methyl group of 3,5-dimethyl-1-*H* pyrazole **1** following the method developed by Katritzky and coworkers[4]. Thus the 3,5-dimethyl pyrazole **1** was treated with *n*-butyl lithium and then carboxylated by passing analytical grade (99.9%) carbondioxide to obtain colourless suspension of lithium pyrazole-1-carboxylate **2**. The lithium-1-carboxylate **2** was further treated with *t*-butyl lithium at -78^{0}C to afford the lithium 5-lithiomethyl-3-methylpyrazole -1-carboxylate **3** in nearly quantitative yield.

The anion **3** was *insitu* treated with α-oxoketene dithioacetal **53** to yield the corresponding carbinolacetal **54** in excellent yield. The cabinolacetal was then treated with orthophosphoric acid to yield the cyclised product. The cyclisation could proceed either to give indaozle **57** if the cyclization goes through ring carbon or its isomeric product pyrazolo[1,5-*a*]pyridine **55, 59a** if the cyclisation goes through the ring nitrogen. The structure was established

on the basis of its spectral and analytical data that cyclisation proceeds to yield the corresponding pyrazolo[1,5-*a*]pyridine **55** in 78% yield.

IR (KBr): 1529, 1626, 2916, 2967, 2993 cm^{-1}.

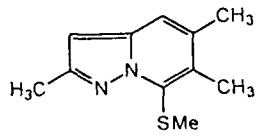
^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.22 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 2.47 (s, 3H, CH_3); 2.52 (s, 3H, SCH_3); 6.08 (s, 1H, H-3); 7.07 (s, 1H, H-4).

^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.06, 15.69, 16.70, 20.76, 95.54, 115.7, 124.95, 131.78, 133.05, 139.74, 150.04.

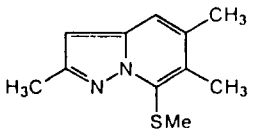
Mass (*m/z*; *%*) : 206 (M^+; 88.9); 172 (100).

Thus the IR spectrum of **55** did not display any peak due to *NH* group between 3200-3400 cm^{-1}. Also its ^1H NMR spectrum (300 *MHz*) did not show any D_2O exchangable signal between δ 8-14 characteristic of indazole and pyrazole ring *N-H*[20]. The pyrazolo[1,5-*a*]pyridine structure **55** was further supported by the presence of singlet at δ 6.08 due to *H*-3 proton in line with the earlier reported values.[21] In its ^{13}C NMR spectrum, **55** displayed characteristic *C*-3 signal at δ 95.54 confirming the structural assignment[22]. Dethiomethylation of **55** with Raney nickel afforded sulfur free **56** in 94% yield. The ^1H NMR spectrum of **56** established that the anion **3** has followed 1,2-addition mode to **53** since the ring protons *H*-4 and *H*-7 in **56** were observe as singlets. The other possible isomer 5-methylthiopyrazolopyridine isomer **59a** would have yielded, after desulfurization the corresponding 6,7-disubstituted

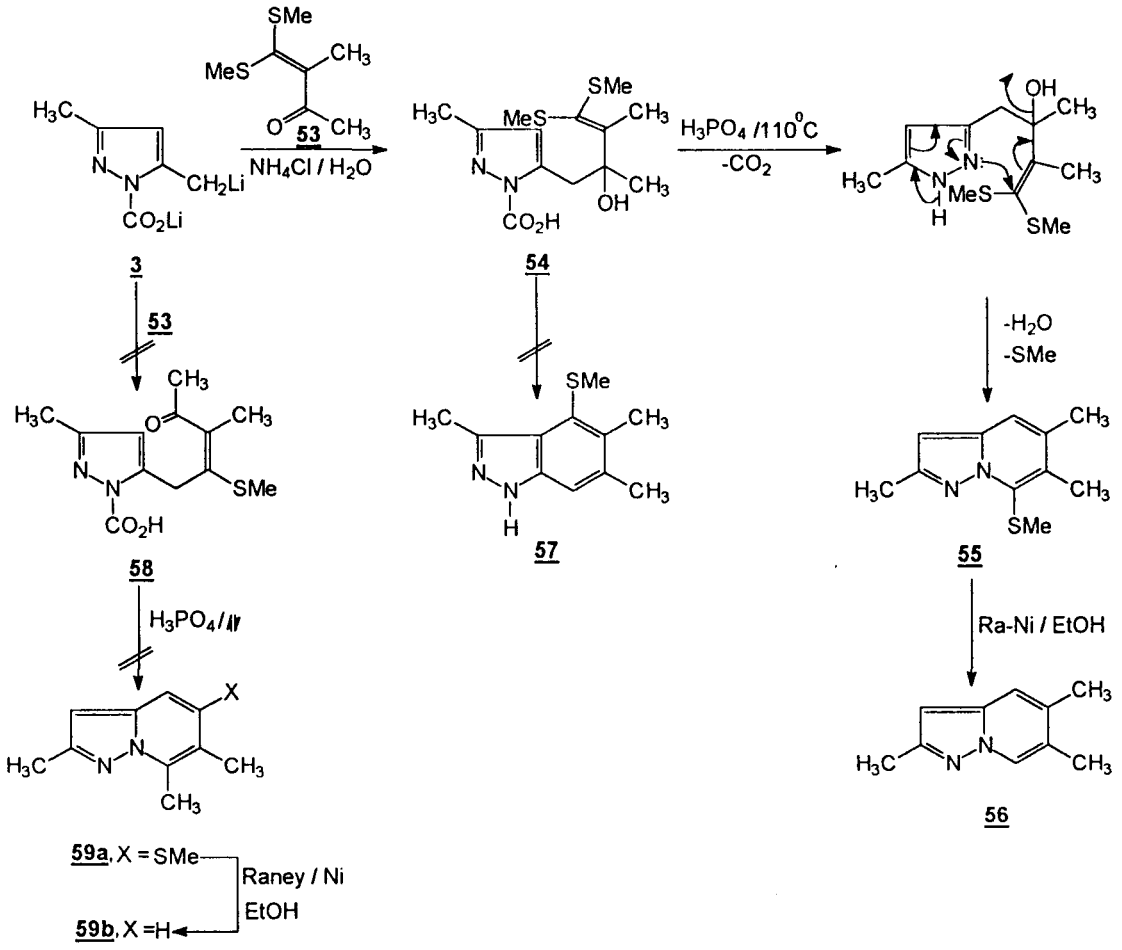
^1H NMR (300MHz, $CDCl_3$) Spectrum of 55



^{13}C NMR (75MHz, $CDCl_3$) Spectrum of 55

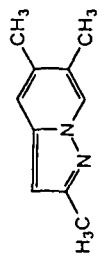


pyrazolopyridine **59b** for which the chemical shifts for *H*-4 and *H*-5 protons would have appeared as doublets through *o*-coupling. The presence of low field signal at δ 8.09 due to *H*-7 proton in the ^1H NMR spectrum of **56** is also in agreement with the reported values for these compounds[21,6] while no protons of the aromatic ring of indazole appears at such a high δ value[20]. The compound **56** showed in its mass spectrum, signal at 160 (100%) corresponding to the M^+ ion ($C_{10}H_{12}N_2$ (160.22).

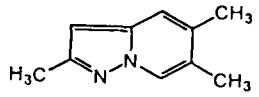


Scheme-16

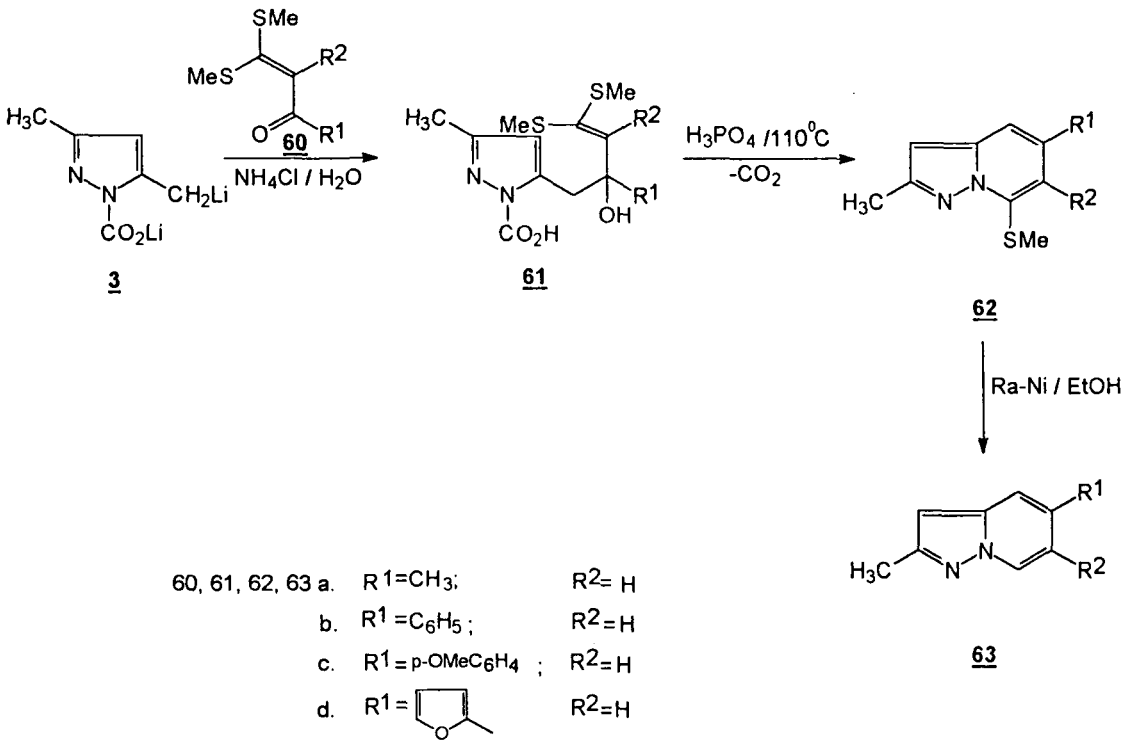
^1H NMR (300MHz, $CDCl_3$) Spectrum of 56



^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **56**

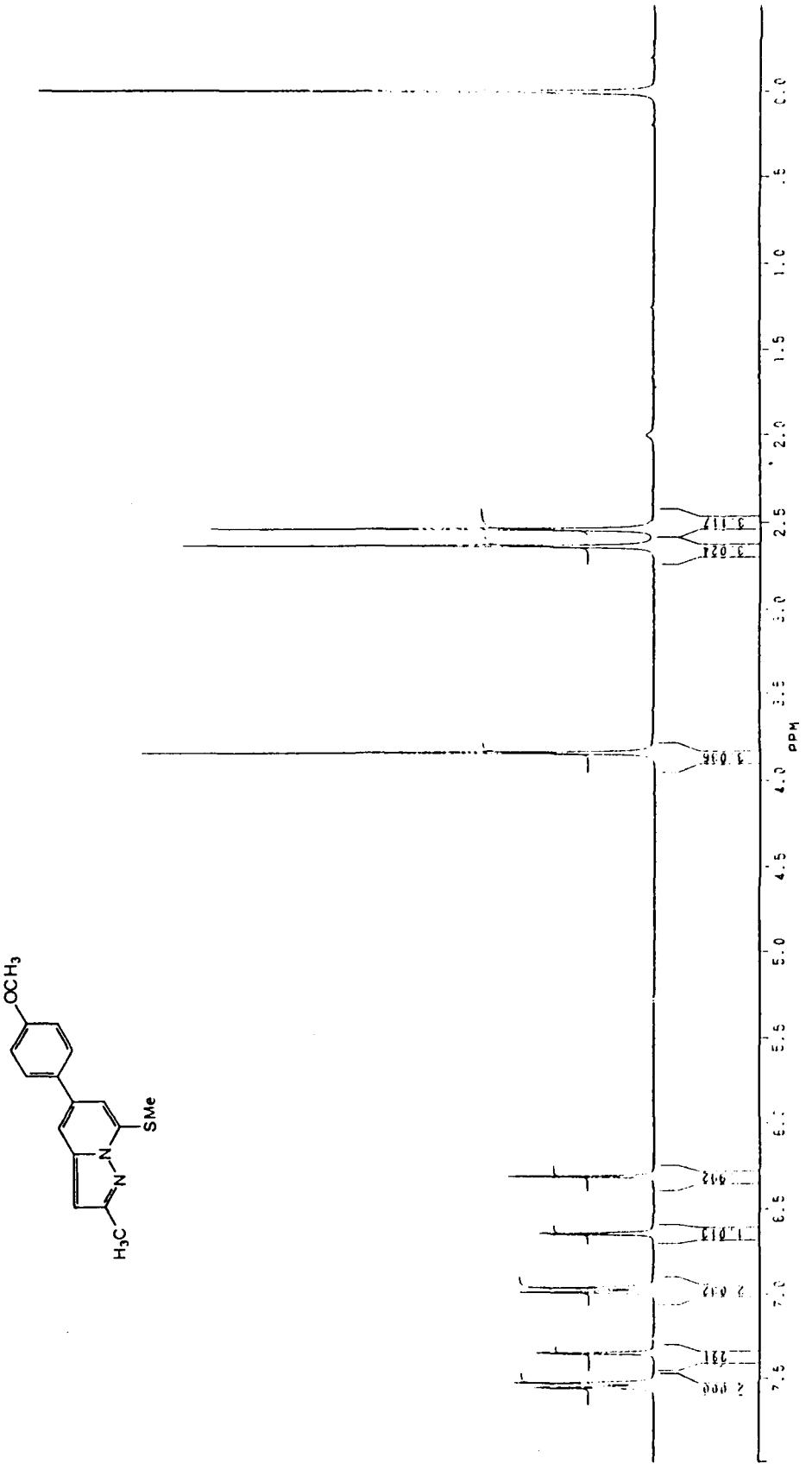


The anion **3** was next reacted with **60a-d** to give the corresponding carbinol acetals **61a-d** in near quantitative yields.These carbinol acetals underwent smooth cyclisation with orthophosphoric acid to afford the corresponding 2-methyl-7-methylthio substituted pyrazolo[1,5-*a*]pyridines **62a-d** in 60-82% over all yields. The methylthio pyrazolo[1,5-*a*]pyridines **62a-d** were also desulphurised using hydrogen and Raney-Ni to afford the corresponding sulphur free pyrazolo[1,5-*a*]pyridines **63a-c** in 80-88% over all yields. The structures **62a-d** and **63a-c** were fully confirmed by their analytical and spectral data which are described in the experimental section. The structure of **62c** was confirmed unequivocally by its *X*-ray crystal structure.



Scheme-17

^1H NMR (300MHz, $CDCl_3$) Spectrum of 62c



^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **62c**

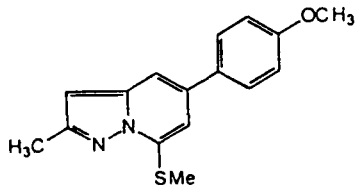


Table 1. Crystal data ,data collection and structure refinement for 1

Empirical formula	$C_{16}H_{16}N_2OS$
Formula weight	284.37
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 7.3200(10) Å α = 90° b = 9.816(2) Å β = 90° c = 39.490(8) Å γ = 90°
Volume	2837.5(9) $Å^3$
Z	8
Density (calculated)	1.331 Mg/m^3
Absorption coefficient	0.225 mm^{-1}
F(000)	1200
Crystal size	0.40 x 0.25 x 0.10 mm
Diffractometer used	STOE AED 2
Temperature	293(2) K
Wavelength	0.71073 Å
Monochromator	graphite
Measurement type	$\omega - \theta$
Standard reflections	3 measured every 60 minutes
θ range for data collection	2.06 to 22.50°
Index ranges	$0 \leq h \leq 7$, $0 \leq k \leq 10$, $0 \leq \ell \leq 42$
Reflections collected	1843
Independent reflections	1843 (R_{int} = 0.0000)
Observed reflection	1494 (I>2sigma(I))

Programs used	SHELXS-97 (Sheldrick, 1990), SHELXL-97 (Sheldrick, 1997)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1843 / 0 / 233
Goodness-of-fit on F^2	1.100
Final R indices [$I>2\sigma(I)$]	R1 = 0.0544, wR2 = 0.1465
R indices (all data)	R1 = 0.0709, wR2 = 0.1798
Hydrogen atoms	geom
Largest diff. peak and hole	0.318 and -0.387 $e\text{Å}^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [Å^2 x 10^3] for **1** . U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U(eq)
S	270(2)	1395(1)	2795(1)	65(1)
O	-103(3)	-3401(3)	4779(1)	55(1)
N(1)	-86(4)	2876(3)	3340(1)	46(1)
N(2)	-22(4)	3971(3)	3132(1)	53(1)
C(1)	-236(5)	5025(4)	3340(1)	52(1)
C(2)	-429(5)	4633(4)	3672(1)	52(1)
C(3)	-336(4)	3228(4)	3675(1)	43(1)
C(4)	-403(5)	2184(4)	3917(1)	48(1)
C(5)	-192(4)	857(4)	3821(1)	42(1)
C(6)	43(5)	563(4)	3472(1)	47(1)
C(7)	89(5)	1549(4)	3232(1)	48(1)
C(8)	-219(4)	-253(4)	4073(1)	43(1)
C(9)	-1274(5)	-182(4)	4364(1)	50(1)
C(10)	-1281(5)	-1202(3)	4604(1)	50(1)
C(11)	-217(4)	-2336(4)	4556(1)	46(1)
C(12)	837(5)	-2443(4)	4268(1)	49(1)
C(13)	841(5)	-1425(4)	4029(1)	49(1)
C(14)	327(9)	-428(5)	2752(1)	77(2)
C(15)	-224(6)	6436(4)	3204(1)	69(1)
C(16)	-1150(7)	-3303(5)	5084(1)	70(1)

Table 3. Bond lengths [Å] and angles [°] for 1 .

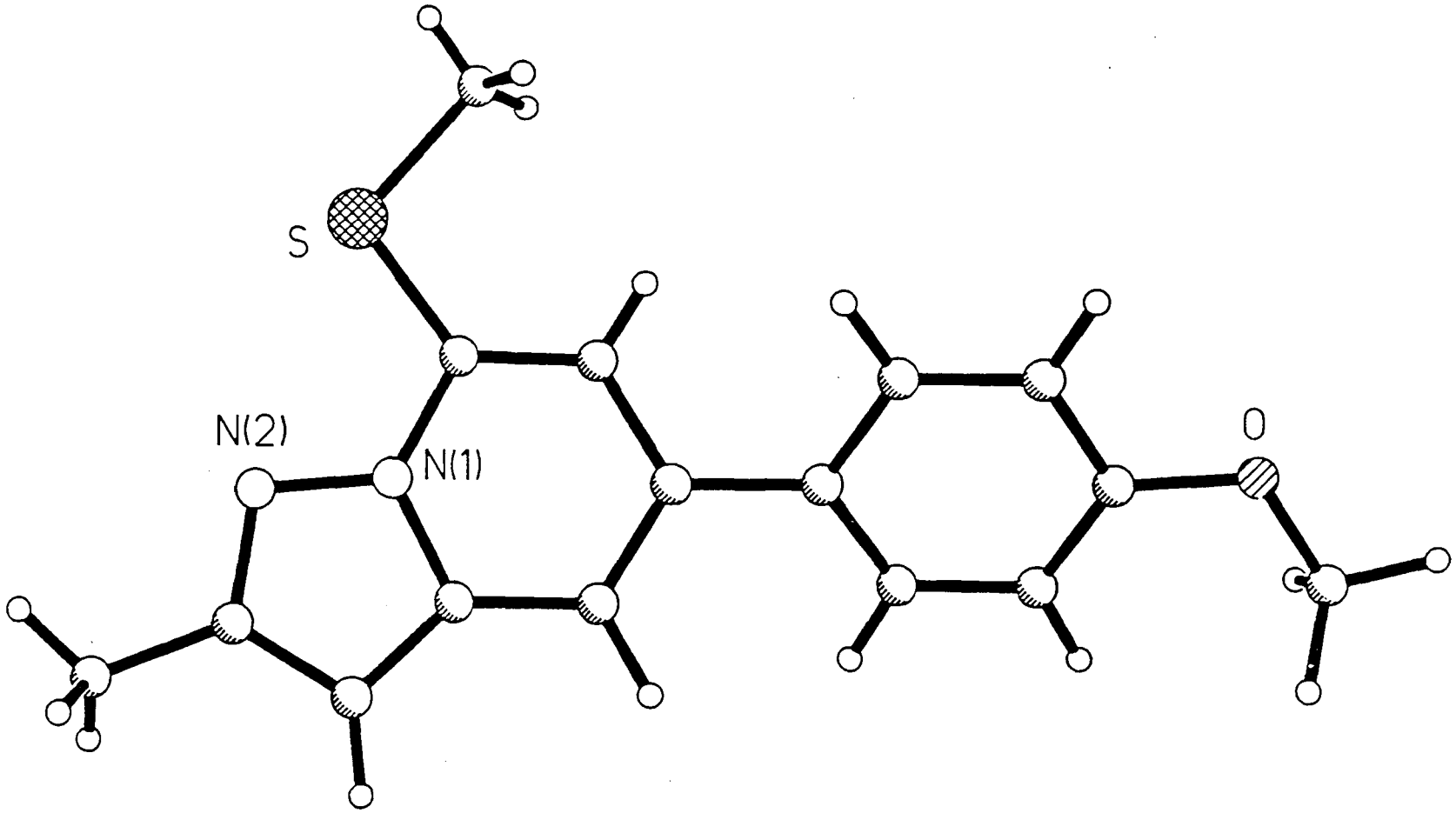
S-C(7)	1.738(4)	S-C(14)	1.797(5)
O-C(11)	1.367(4)	O-C(16)	1.431(5)
N(1)-N(2)	1.356(4)	N(1)-C(7)	1.377(5)
N(1)-C(3)	1.378(4)	N(2)-C(1)	1.330(5)
C(1)-C(2)	1.377(5)	C(1)-C(15)	1.485(5)
C(2)-C(3)	1.380(5)	C(3)-C(4)	1.403(5)
C(4)-C(5)	1.365(5)	C(5)-C(6)	1.419(5)
C(5)-C(8)	1.474(5)	C(6)-C(7)	1.356(5)
C(8)-C(9)	1.385(5)	C(8)-C(13)	1.399(5)
C(9)-C(10)	1.380(5)	C(10)-C(11)	1.371(5)
C(11)-C(12)	1.379(5)	C(12)-C(13)	1.377(5)
C(7)-S-C(14)	100.5(2)	C(11)-O-C(16)	117.2(3)
N(2)-N(1)-C(7)	123.9(3)	N(2)-N(1)-C(3)	112.8(3)
C(7)-N(1)-C(3)	123.3(3)	C(1)-N(2)-N(1)	103.8(3)
N(2)-C(1)-C(2)	112.5(3)	N(2)-C(1)-C(15)	120.2(4)
C(2)-C(1)-C(15)	127.3(4)	C(1)-C(2)-C(3)	106.4(3)
C(2)-C(3)-N(1)	104.5(3)	C(2)-C(3)-C(4)	137.2(3)
N(1)-C(3)-C(4)	118.3(3)	C(5)-C(4)-C(3)	120.3(3)
C(4)-C(5)-C(6)	118.5(3)	C(4)-C(5)-C(8)	121.1(3)
C(6)-C(5)-C(8)	120.4(3)	C(7)-C(6)-C(5)	122.5(3)
C(6)-C(7)-N(1)	117.1(3)	C(6)-C(7)-S	129.4(3)
N(1)-C(7)-S	113.5(3)	C(9)-C(8)-C(13)	117.0(3)
C(9)-C(8)-C(5)	121.9(3)	C(13)-C(8)-C(5)	121.1(3)
C(10)-C(9)-C(8)	122.4(3)	C(11)-C(10)-C(9)	119.5(3)
O-C(11)-C(10)	124.5(3)	O-C(11)-C(12)	115.9(3)
C(10)-C(11)-C(12)	119.5(3)	C(13)-C(12)-C(11)	120.9(3)
C(12)-C(13)-C(8)	120.7(3)		

Symmetry transformations used to generate equivalent atoms:

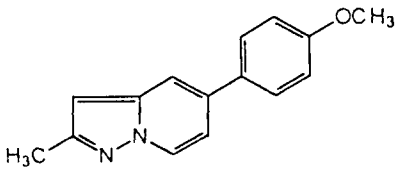
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 1 .
The anisotropic displacement factor exponent takes the form: $-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

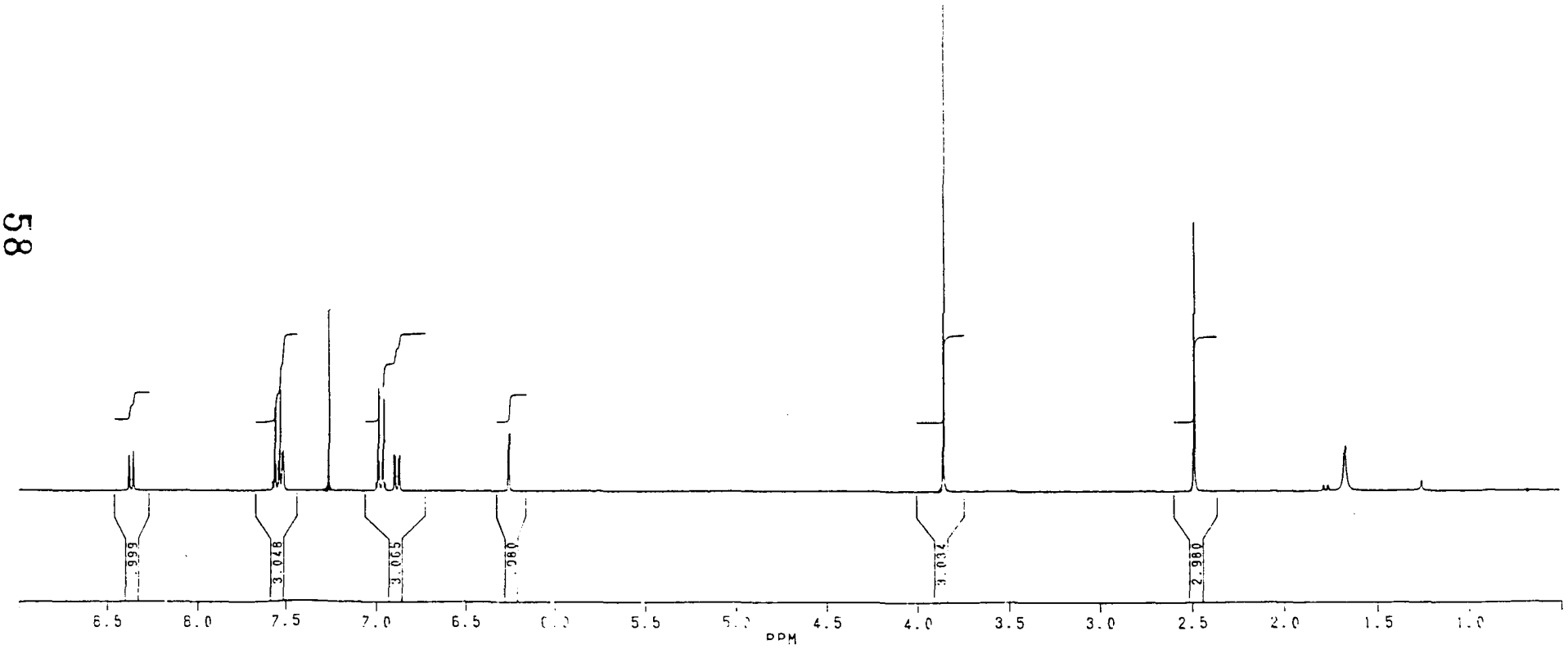
	U11	U22	U33	U23	U13	U12
S	110(1)	46(1)	40(1)	2(1)	3(1)	2(1)
O	65(2)	45(2)	55(2)	13(1)	5(1)	6(1)
N(1)	54(2)	39(2)	45(2)	3(1)	1(1)	-1(1)
N(2)	68(2)	39(2)	52(2)	7(2)	3(1)	-2(1)
C(1)	52(2)	41(2)	63(2)	1(2)	2(2)	0(2)
C(2)	59(2)	42(2)	55(2)	-10(2)	5(2)	1(2)
C(3)	41(2)	43(2)	46(2)	-2(2)	1(1)	0(2)
C(4)	52(2)	47(2)	45(2)	-1(2)	0(2)	1(2)
C(5)	41(2)	42(2)	43(2)	3(2)	0(1)	0(2)
C(6)	63(2)	34(2)	44(2)	-4(2)	1(2)	1(2)
C(7)	57(2)	39(2)	47(2)	-2(2)	-1(2)	-1(2)
C(8)	45(2)	40(2)	46(2)	1(2)	-3(1)	0(2)
C(9)	59(2)	45(2)	47(2)	4(2)	5(2)	7(2)
C(10)	59(2)	46(2)	45(2)	2(2)	4(2)	5(2)
C(11)	51(2)	41(2)	46(2)	4(2)	-3(2)	-3(2)
C(12)	51(2)	42(2)	54(2)	-1(2)	-3(2)	7(2)
C(13)	49(2)	48(2)	50(2)	1(2)	3(2)	3(2)
C(14)	137(5)	51(3)	44(3)	-7(2)	0(3)	7(3)
C(15)	87(3)	41(2)	80(3)	7(2)	4(2)	1(2)
C(16)	84(4)	61(3)	63(3)	18(2)	16(2)	7(2)

X-Ray molecular structure of 62c

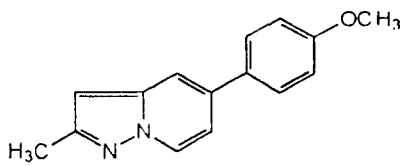


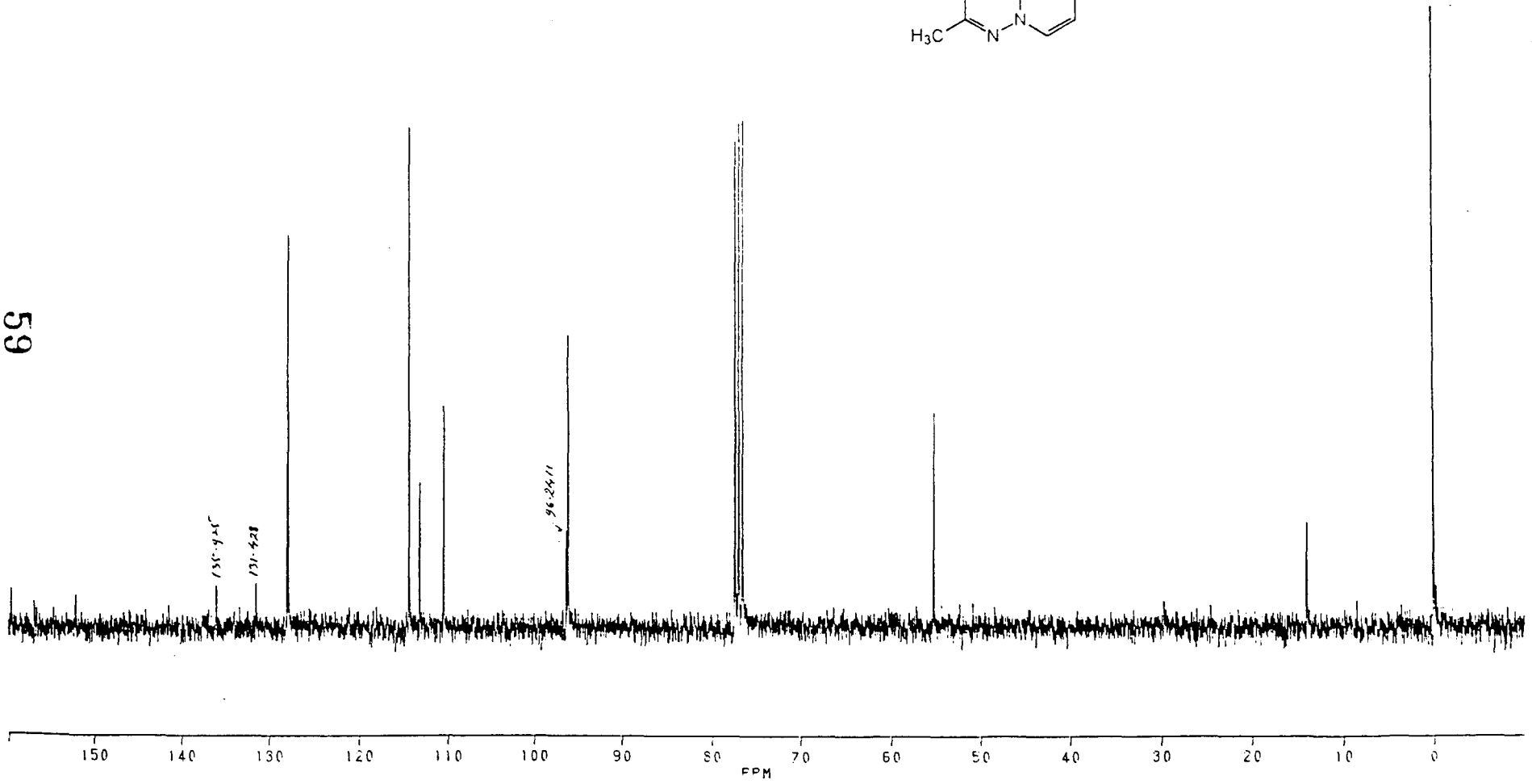
^1H NMR (300MHz, $CDCl_3$) Spectrum of 63c



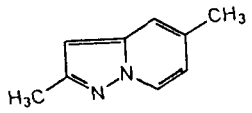


^{13}C NMR (75MHz, $CDCl_3$) Spectrum of <u>63c</u>

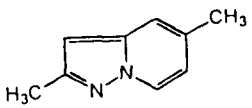




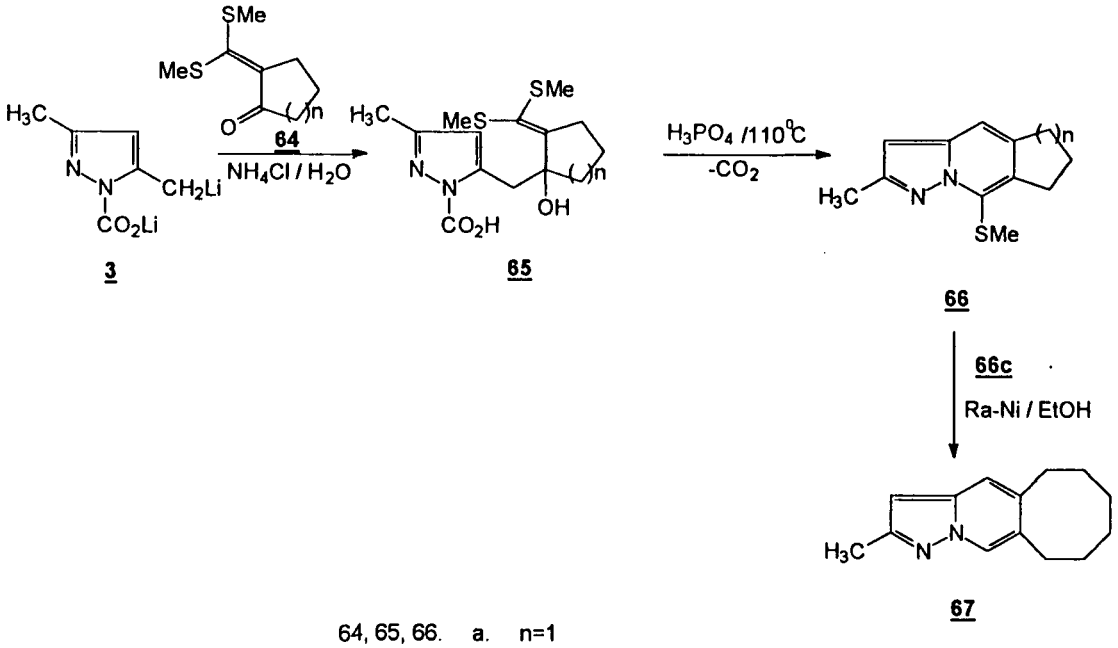
^1H NMR (300MHz, $CDCl_3$) Spectrum of 63a



^{13}C NMR (75MHz, $CDCl_3$) Spectrum of 63a



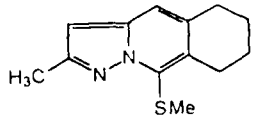
The anion **3** was then reacted with cyclic α-oxoketene dithioacetals **64a-c** derived from cyclopentanone, cyclohexanone and cyclooctanone respectively. The initial 1,2-addition followed as observed earlier to afford the corresponding carbinol acetals **65a-c** in high yields. These carbinol acetals were cyclised with orthophosophoric acid as described earlier to yield linearly fused pyrazolo[1,5-*a*]pyridines **66a-c** in 67-74% over all yields. All the cycloalkano pyridines **66a-c** were confirmed by their analytical and spectral data which are described in the experimental section. One of the pyrazolo[1,5-*a*]pyridine **66c** was subjected to desulphurization as described earlier to afford

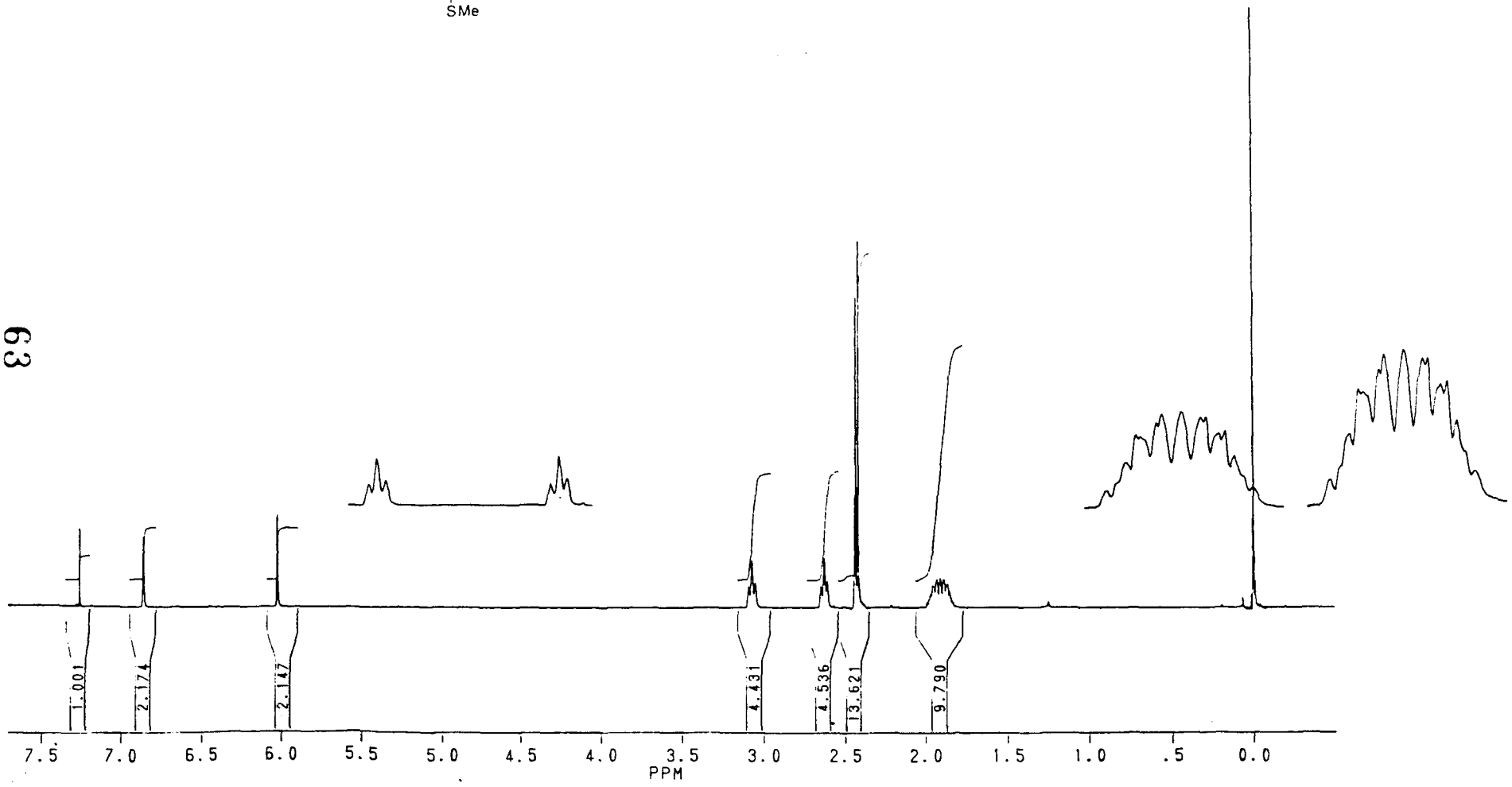


64, 65, 66. a. n=1
b. n=2
c. n=4

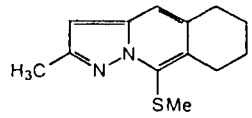
Scheme-18

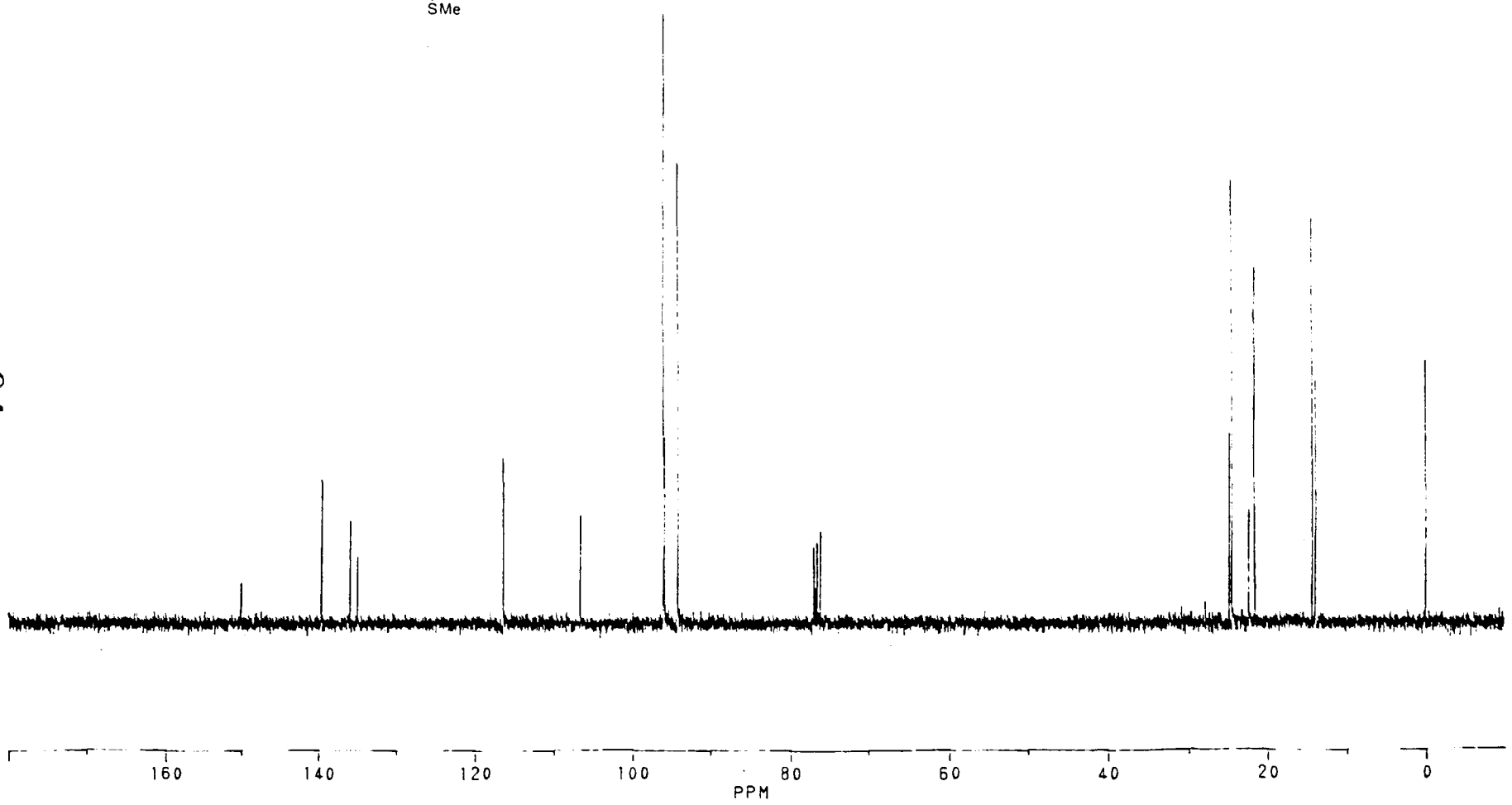
^1H NMR (300MHz, $CDCl_3$) Spectrum of 66b



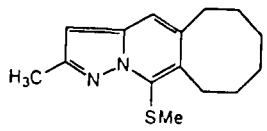


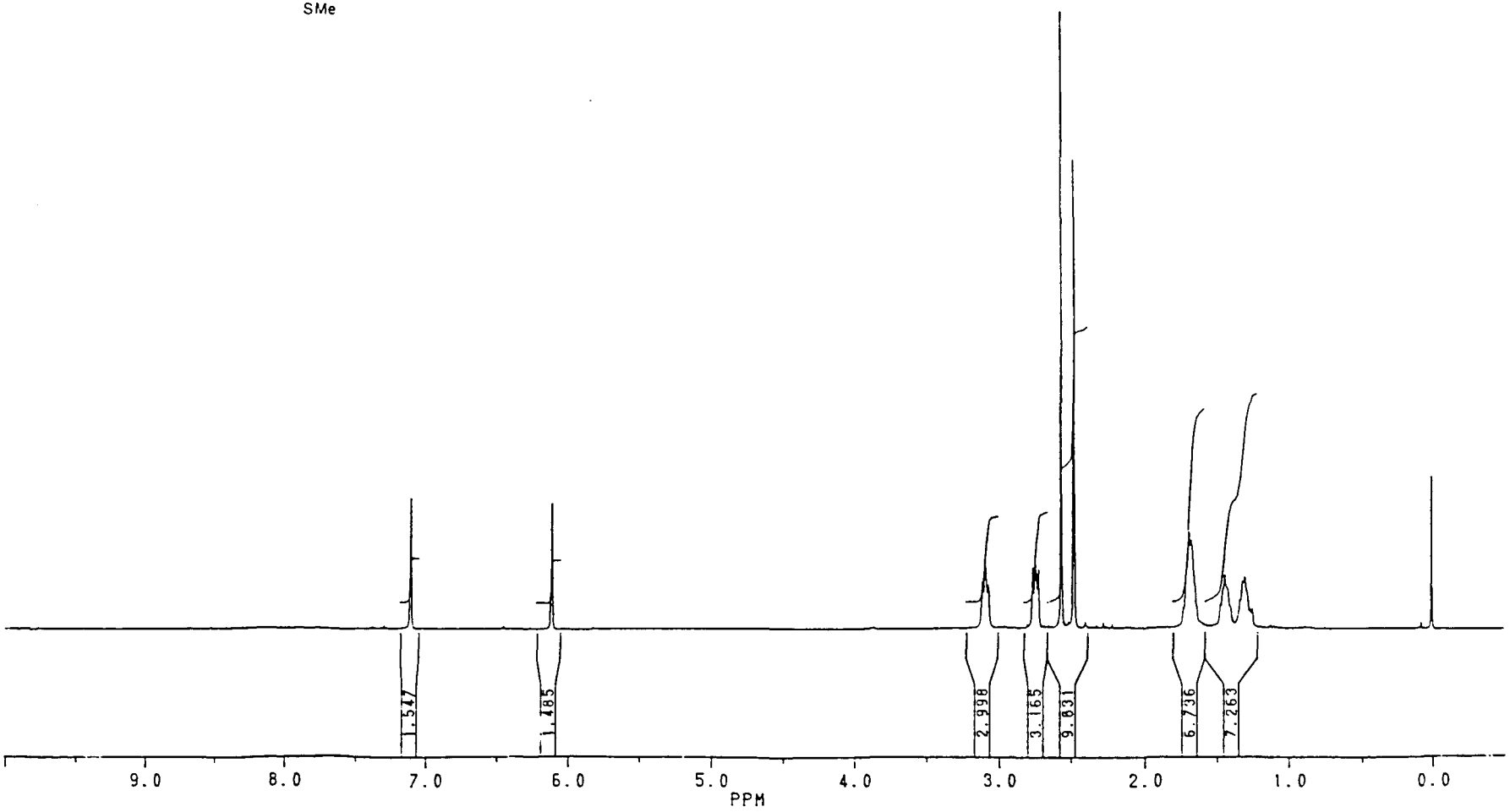
^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **66b**



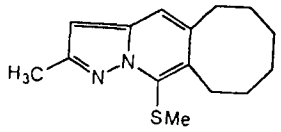


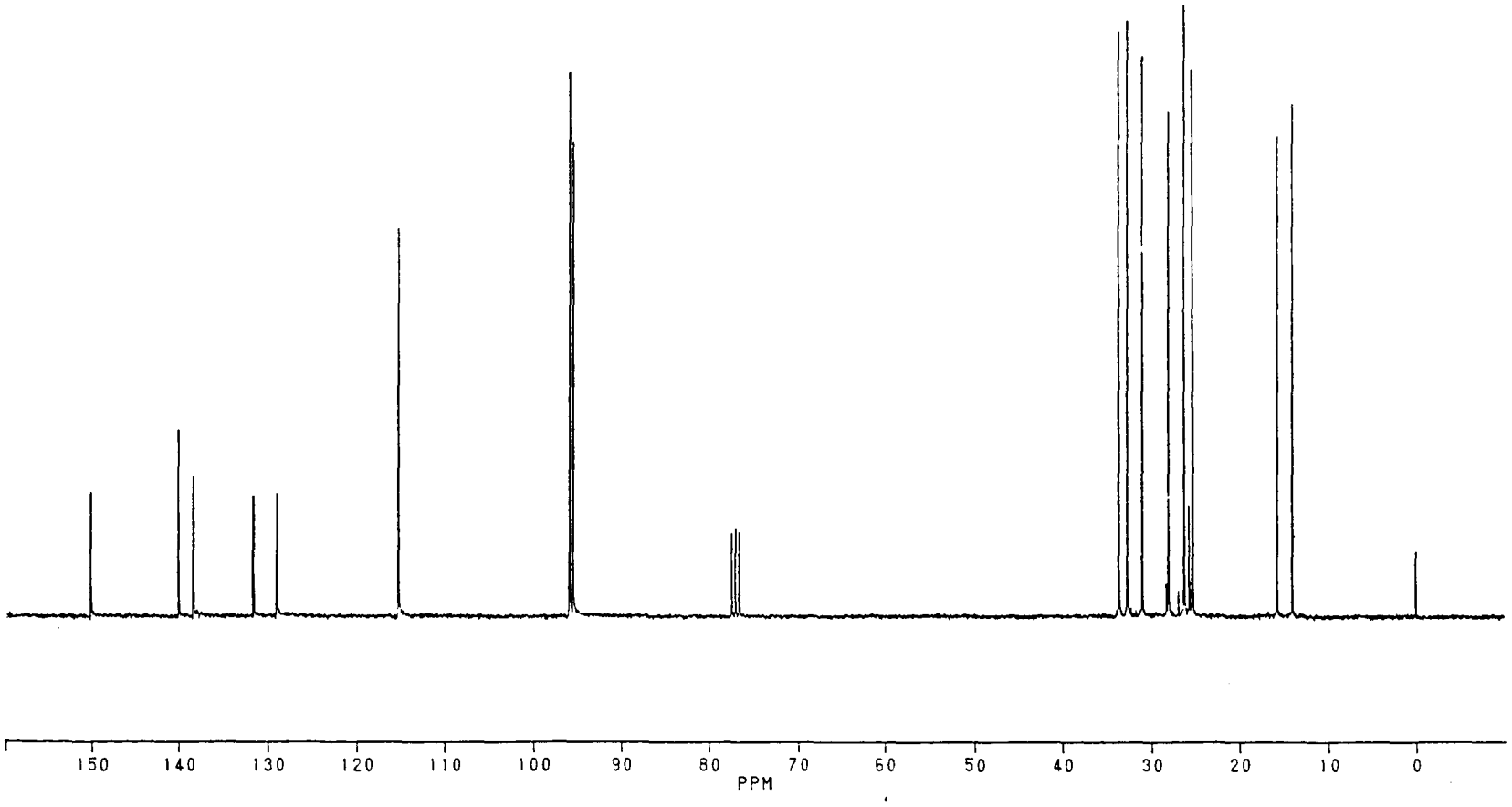
^1H NMR (300MHz, $CDCl_3$) Spectrum of <u>66c</u>





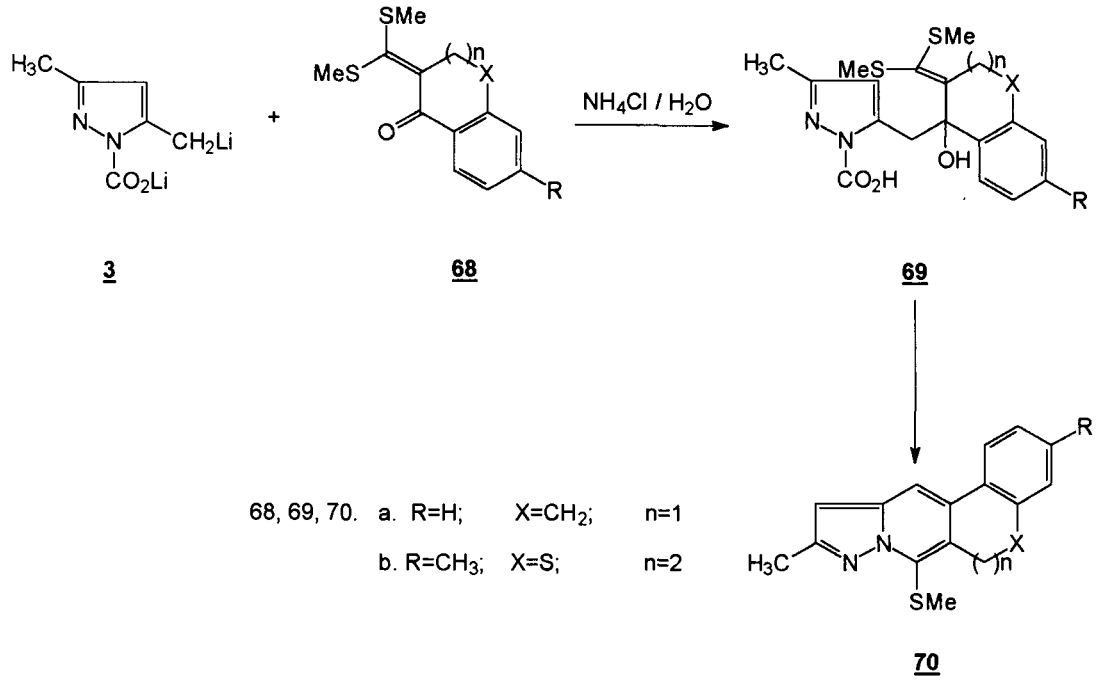
^{13}C NMR (75MHz, $CDCl_3$) Spectrum of 66c





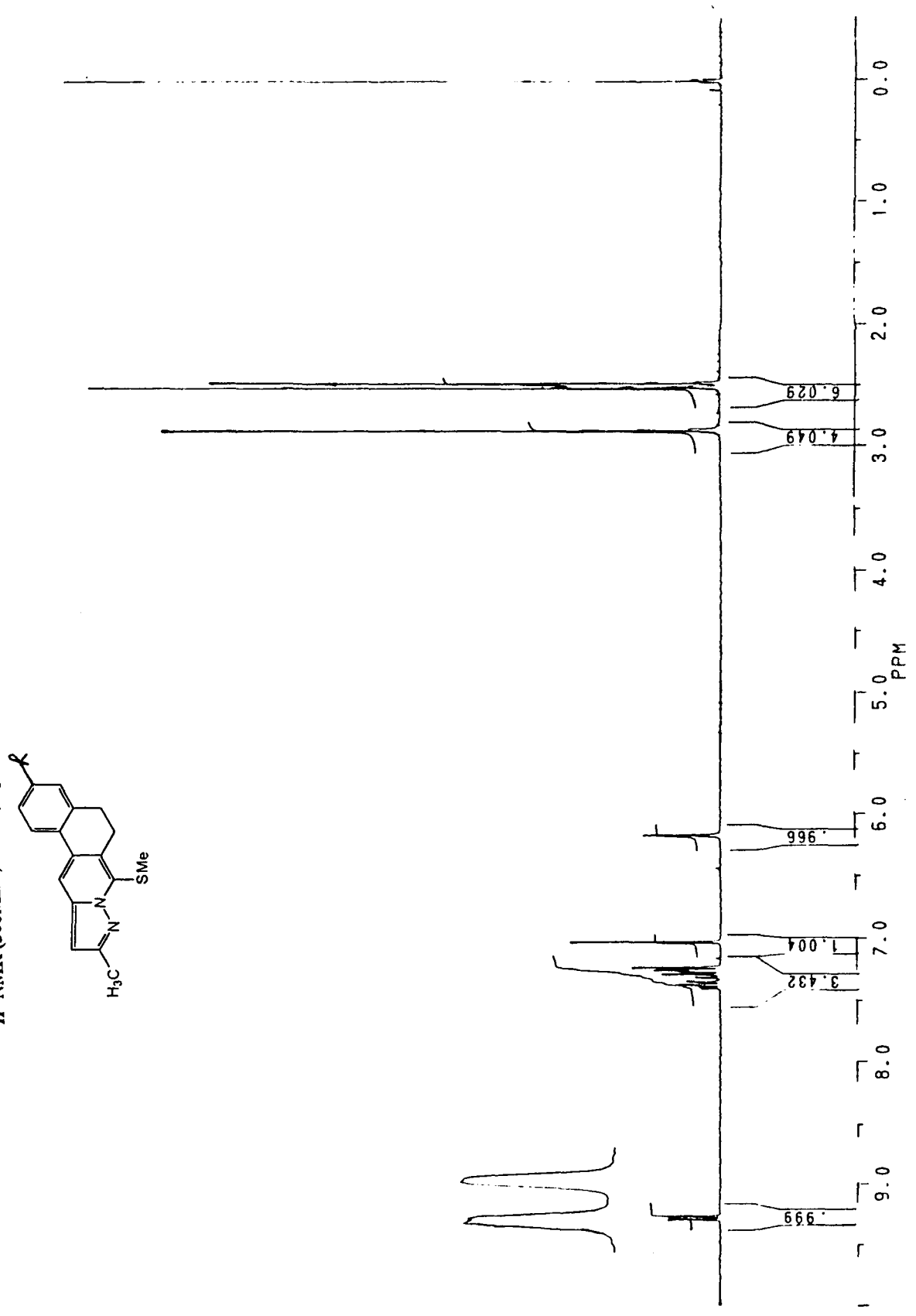
the corresponding 2-methyl cycloocta[*f*]pyrazolo[1,5-*a*]pyridine **67** in 91% yield (*scheme-18*).

The anion **3** was also reacted with α-oxoketene dithioacetals **68a** and **68b** derived from tetralone and 8-methyl-2,3,4,5-tetrahydrobenzo[*b*]thiophin-5-one under identical condition as described earlier. The intermediate carbinol acetals were also cyclized with orthophosphoric acid to afford the corresponding condensed substituted pyrazolo[1,5-*a*]pyridines **70a-b** in 63-71 % yields respectively. The structure of **70a-b** were fully established by their analytical and spectral data which were described in the experimental section (*scheme 19*).

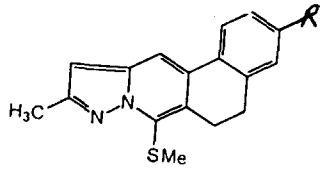


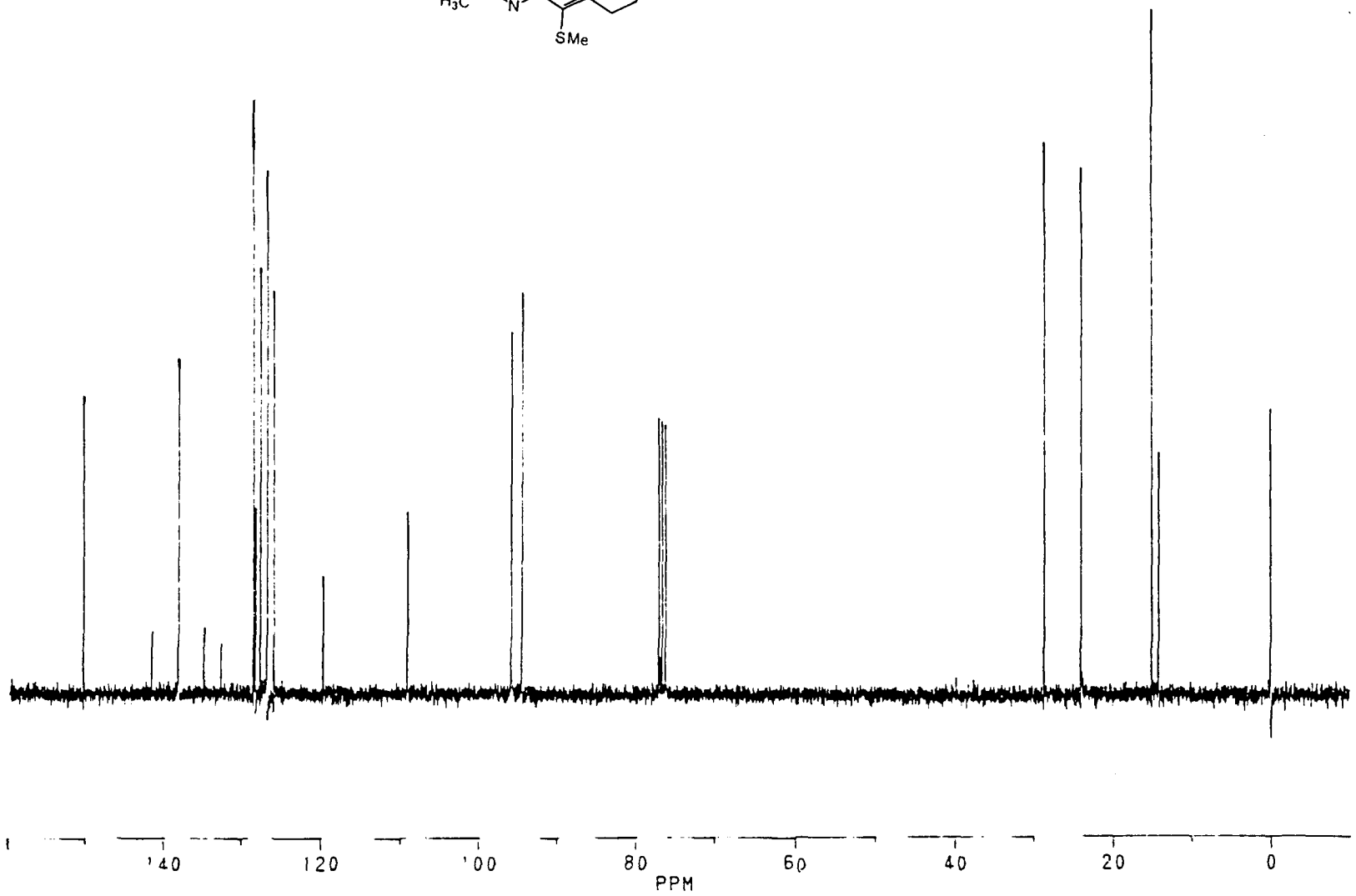
Scheme-19

^1H NMR (300MHz, $CDCl_3$) Spectrum of 70a

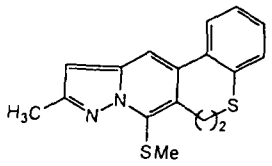


^{13}C NMR (75MHz, $CDCl_3$) Spectrum of <u>70a</u>

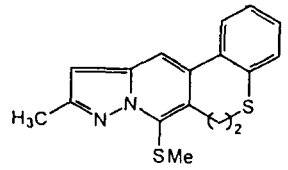




^1H NMR (300MHz, $CDCl_3$) Spectrum of 70b



^{13}C NMR (75MHz, $CDCl_3$) Spectrum of <u>70b</u>



II.C CONCLUSION:

We have, for the first time, successfully generated Lithium 5-lithiomethyl-3-methylpyrazole-1-carboxylate **3** using Kartritzky metallation approach involving carbon dioxide as protecting, activating, deprotecting system in one pot reaction. The anion **3** thus formed has been reacted with various α-oxoketene dithioacetals which follows 1,2-addition mode to yield the corresponding carbinol acetal which underwent cyclization in the presence of orthophosphoric acid to afford the corresponding substituted and annelated pyrazolo[1,5-*a*]pyridines rather than the corresponding indazoles. Many of the pyrazolo[1,5-*a*]pyridines are shown to be biologically important exhibiting antiinflammatory, antiallergic, bronchodilating and adenosine antagonist activity[23]. Thus, this is the first general method for the synthesis of pyrazolo[1,5-*a*]pyridines starting from simple pyrazole. Most of the reported methods for the synthesis of pyrazolo[1,5-*a*]pyridines involve construction of pyrazole moiety onto pyridine ring starting from 1-aminopyridinium derivatives. Thus the present method is the simplest with wide possible general application to a large variety of pyrazolo[1,5-*a*]pyridines which possibly a method of choice for the development of new products in this area.

II. D **EXPERIMENTAL SECTION:**

General:

Melting points were obtained on a "**Thomas Hoover** capillary melting point apparatus and are uncorrected. The Infrared Spectra were recorded on a **Perkin-Elmer model 983** spectrophotometer and its frequencies are expressed in cm^{-1}. The high resolution of ^{1}H NMR (300 *MHz*) and ^{13}C NMR (75.45 *MHz*) spectra were recorded on **Bruker ACF-300** Spectrometer. The chemical shifts (δ , *ppm*) and the coupling constant (J, *Hz*) are reported in the standard fashion with the help of solvent indicated with tetramethyl silane as the reference for interlock and $CDCl_3$ at δ 76.7 for ^{13}C NMR to explain the peak patterns. The following abbreviations are used like s=singlet, d=doublet, t=triplet, q= quartet, m= multiplet and br= broad. mass spectra were measured on a Joel JMS-D-300 Spectrometer. The molecular and base peaks as indicates by (M^+) and (%) respectively. Elemental analysis of carbon, Hydrogen and Nitrogen were carried out on a **Heraeus CHN-O**-Rapid analyser.

All reactions involving organolithium were performed in an oven dried (120^0C) glassware under masked dry Nitrogen or Argon atmosphere. Transfer of anhydrous solvents or mixtures were done through syringe using syringe-septum technique. Low temperature reactions were carried out in a bath made of ethylacetate and liquid nitrogen. Analytical thin layer chromatography

(**TLC**) were performed on glass plates coated with **ACMEs** silicagel containing 13% calcium sulphate as binder. Combination like benzene, ethylacetate-hexane, ethylacetate-benzene were used as eluents.

The visualisation of the reaction spots was identified by the exposure to iodine vapour or by spraying potassium permanganate (acidic) solution. **ACME**'s silica Gel (60-120 mesh) is used for column chromatography. Distilled solvents were used for column chromatography eluents. All solvents evaporations were done on steam bath.

Chemical and Reagents:

Commercially available hydrazine hydrate and acetylacetone were used. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl prior to use. Dry benzene was obtained by washing with concentrated H_2SO_4 followed by azeotropic distillation and then stored over sodium wire. *n*-BuLi/Hexane and *t*-BuLi/Hexane were purchased from **Aldrich**.

Commercially available ketones: acetone, ethylmethyl ketone, acetophenone, 4-methoxy acetophenone, cyclohexanone, cyclopentanone and cyclooctanone were purified by distillation under reduced pressure before use. 2-Acetyl furan, tetralone and 2,3,4,5-tetrahydrobenzo[*b*]thiepin-5-one[24] were prepared according to earlier reported procedure. The general experimental details for

the preparation of α-oxoketene dithioacetal[25] are described as below. Raney Ni (W4)[26] were prepared according to reported procedure.

General procedure for the preparation of α-oxoketene dithioacetals (53, 60, 64, 68).

A mixture of ketone (0.2mol) and carbondisulphide (0.2mol) was added drop-wise in ice cold and well stirred suspension of sodium *t*-butoxide (0.4mol) in dry benzene (200ml) and the reaction mixture was allowed to stir at ambient temp for 5-6 hrs. Neutral dimethyl sulphate (0.2mol) was then gradually added with stirring and cooling. The reaction mixture was stirred at room temperature for 6-8 hrs, and then it was poured into aqueous saturated ammonium chloride solution (250ml) and the layer were separated. The aqueous layer was extracted with benzene and the combined organic layer was washed with water, dried over Na_2SO_4 and then the solvent was distilled off on water bath. Trituration of the oily residue with hexane gave the dithioacetals as yellow crystalline solid in good yields. Liquid dithioacetals were purified by passing through silica gel column using hexane-ethylacetate as eluent. All the dithioacetals known were characterised by comparing their MP, NMR, IR with authentic data.

Preparation of 3,5-Dimethyl-1*H*-pyrazole (1):

3,5-Dimethyl *N-H* Pyrazole (mp.107^{0}C)was obtained from the acetyl acetone and hydrazine hydrate (98%) in ethanol under ice cold condition as mention in the procedure[27].

Procedure for the generation of Lithium 5-lithiomethyl-3-methylpyrazole-1-carboxylate (3) and its reaction with various α-oxoketene dithioacetals to form condensed substituted pyrazolo[1,5-*a*]pyridines:

To a solution of 3,5-dimethyl 1-*H* pyrazole **1** (15mmol) in 25 ml of dry tetrahydofuran solvent at -78^{0}C, *n*-Buli (16mmol) was added drop by drop with stirring under dry and inert atmosphere apparatus. The reaction mixture was then allowed to warm at room temperature and was stirred for 30 minutes. Analytical grade carbondioxide (99.9%) was then bubbled for 5 minutes at -78^{0}C when colourless suspension appeared indicating the formation of Lithium pyrazole-2-carboxylate. The excess of CO_2 and the solvent tetrahydrofuran were removed under reduced pressure to afford Lithium salt **2** as colourless solid. Freshly distilled THF (25ml) was added to the residue by maintaining the temperature at -78^{0}C. To this, *t*-BuLi (16mmol) was added drop by drop at -78^{0}C when a deep yellow colour was observed indicating dianion 3 was formed. The reaction mixture was stirred for 45 minutes at -78^{0}C and then a solution of α-oxoketene dithioacetals (15mmol) in 25ml of dry tetrahydrofuran

The reaction mixture was thenpoured into saturated NH_4Cl solution (2x100 ml) and extracted with chloroform (3x60 ml). The combined organic extracts were washed with water (2x50ml),dried over sodium sulphate and solvent removed under reduced pressure to obtain the crude carbinolthioacetals. The crude carbinolthioacetals were further treated with H_3PO_4 (5ml) at 120°C for 2-3 hrs and the reaction mixture after cooling was poured into ice cold saturated $NaHCO_3$ solution (250ml). The organic compound was then extracted with chloroform (3x50ml) and the combined organic extract was washed with water (2x50ml), dried over sodium sulphate and the solvent evapourated to give viscous mass. This was subjected to column chromatography over silica gel using ethylacetate-hexane (3:97) as eluent to give the expected pyrazolo[1,5-*a*]pyridine.

2,5,6-Trimethyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 55:

Colourless crystals; yield- 78%; mp.75-76°C (ether). IR (KBr): 1529, 1626, 2916, 2967, 2993 $cm.^{-1}$ ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.22 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 2.47 (s, 3H, CH_3); 2.52 (s, 3H, SCH_3); 6.08 (s, 1H, H-3); 7.07 (s, 1H, H-4). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.06, 15.69, 16.70, 20.76, 95.54, 115.7, 124.95, 131.78, 133.05, 139.74, 150.04. Mass (*m/z*; %) : 206 (M^+; 88.9); 172 (100). Anal. Calcd. for $C_{11}H_{14}N_2S$ (206.20): C, 64.02; H, 6.84; N, 13.59 %. Found: C, 64.32; H, 6.63; N, 13.84 %.

2,5-Dimethyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 62a:

Colourless crystals; yield-72%; mp. 99-100^{0}C(ether). IR (KBr): 1497, 1621, 2918, 2986 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.24 (s, 3H, CH_3); 2.37-2.46 (d, 6H, CH_3 and SCH_3); 6.07 (s, 1H, H-3); 6.15 (brs, 1H, H-6); 6.87 (s, 1H, H-4). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 13.87, 14.06, 21.17, 95.21, 108.64, 108.64, 111.27, 133.23, 138.31, 141.18, 151.28. Mass (*m/z*; %): 192 (M^+; 64.8) 159 (100). Anal. Calcd for $C_{10}H_{12}N_2S$ (192.28): C, 62.46; H, 6.29; N, 14.57%. Found: C, 62.92; H, 6.53; N, 14.78%.

2-methyl-5-phenyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 62b :

colourless crystals; yield- 80%; mp.133-135^{0}C(chloroform-hexane). IR (KBr): 1499, 1610, 2899, 2918, 2982 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3$): δ 2.52 (s, 3H, CH_3); 2.59 (s, 3H, SCH_3); 6.31 (s, 1H, H-3); 6.64 (s, 1H, H-4); 7.35-7.45 (m, 4H, ArH); 7.57-7.60 (d, 2H, ArH). ^{13}C NMR (300 *MHz*; $CDCl_3$): 14.19, 14.23, 97.06, 105.83, 110.04, 126.88, 127.94, 128.89, 136.40, 139.25, 139.39, 141.38, 152.28. Mass (*m/z*; %): 254 (M^+; 93.7) 221 (100). Anal. Calcd. for $C_{15}H_{14}N_2S$ (254.36): C, 70.83; H, 5.55; N, 11.01%. Found: C, 71.02; H, 5.48; N, 11.12%.

5-(4-Methoxyphenyl)-2-methyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine 62c: Light grey crystals; yield-82%; mp.152-153^{0}C (chloroform-hexane). IR (KBr) 1471, 1497, 1524, 1603, 2982, 2837, 2917 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3$): δ 2.53 (s, 3H, CH_3); 2.62 (s, 3H, SCH_3); 3.83 (s, 3H, OCH_3); 6.31 (s, 1H, H-

3); 6.63 (brs, 1H, H-6); 6.97 (d, J=8.7Hz, 2H, ArH); 7.34 (brs, 1H, H-4); 7.54 (d, J=8.7Hz, 2H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.28, 15.27, 55.39, 95.39, 109.70, 110.67, 113.61, 125.66, 128.05, 130.63, 134.98, 139.28, 142.45, 151.78, 160.51. Mass (*m/z*; %): 284 (M^+; 81.8) 251 (100).Anal calcd. for $C_{16}H_{16}ON_2S$ (284.38): C, 67.58; H, 5.67; N, 9.85%. Found: C, 67.83; H, 5.81; N, 10.31%.

2-methyl-5-furan-7-(methylthio) Pyrazolo[1,5-*a*]pyridine 62d:

Light yellow crystals; yield-60%; mp.88-89^{0}C (chloroform hexane). IR (KBr): 1614, 1658, 2916, 2986 cm^{-1}. ^1H NMR (90 *MHz*; $CDCl_3/CCl_4$): δ 1.1-1.2 (s, 3H, CH_3); 2.3-2.4 (s, 3H, SCH_3); 6.1 (s, 1H, H-3); 6.5 (s, 1H, H-4); 7.01-7.7 (d, 2H, ArH); 7.5 (s, 1H, ArH); 8.05 (s, 1H, ArH). Anal. calcd. for $C_{13}H_{11}ON_2S$ (244.31): C, 64.17; H, 11.09; O, 6.58;N, 11.51%. Found: C, 64.35; H, 11.17; O, 6.53; N, 11.59 %.

2-methyl-8-(methylthio)cyclopenta[d]pyrazolo[1,5-*a*]pyridine 66a:

colourless crystals; yield-67%; mp-87-88^{0}C (chloroform-hexane). IR (KBr): 1539, 1588, 1629, 1683, 2850, 2869, 2926, 2956 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.09-2.16 (m, 2H, CH_2); 2.49 (s, 3H, CH_3); 2.60 (s, 3H, SCH_3); 2.92 (t, 2H, CH_2); 3.04 (t, 2H, CH_2); 6.16 (s, 1H, H-3); 7.14 (s, 1H, H-4). ^{13}C NMR (75*MHz*; $CDCl_3/CCl_4$): 14.20, 15.44, 25.84, 31.48, 32.64, 95.91, 110.28, 133.34, 140.92, 150.46, 224.24. Mass (*m/z*; %): 218 (M^+; 48.2); 185

(100). Anal. calcd. for $C_{12}H_{14}N_2S$ (218.26): C, 66.04; H, 6.46; N, 12.82; Found: C, 65.89; H, 6.51; N, 12.93 %.

2-methyl-9-(methylthio)-5,6,7,8-tetrahydropyrazolo[1,5-*b*]isoquinoline 66b:

Colourless crystals; yield-74%; mp-98-100^{0}C (chloroform-hexane). IR (KBr): 1507, 1529, 2870, 2932, 2980 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 1.83-1.96 (m, 4H, $(CH_2)_2$); 2.42 (s, 3H, CH_3); 2.44 (s, 3H, SCH_3); 2.61-265 (brt, 2H, CH_2); 3.05-3.09 (brt, 2H, CH_2); 6.02 (s, 1H, H-3) 6.86 (s, 1H, H-4). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 13.93, 14.37, 21.54, 22.34, 24.51, 24.86, 94.20, 95.97, 106.70, 116.44, 134.95, 135.90, 139.56, 150.02. Mass (*m/z*; %): 232 (M^+; 100); 217 (37.6). Anal. Calcd for $C_{13}H_{16}N_2S$ (232.35): C, 67.20; H, 6.94; N, 12.06%. Found: C, 67.51; H, 7.28; N, 12.41%.

2-methyl-11-(methylthio)cycloocta[*d*]pyrazolo[1,5-*a*]pyridine 66c:

Light yellow crystals; yield-67%; mp.82-83^{0}C (chloroform-hexane). IR(KBr):1473, 1659, 1682, 2850, 2921cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 1.25-1.33 (brm, 2H, CH_2); 1.44-1.47 (brm, 2H, CH_2); 1.67-1.73 (brm, 4H, $(CH_2)_2$); 2.47(s, 3H, CH_3); 2.56 (s, 3H, SCH_3); 2.72-2.76 (brt, 2H, CH_2); 3.07-3.11 (brt, 2H, CH_2); 6.11 (s, 14, H-3); 7.1 (s, 1H, H-4). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.07, 15.77, 25.36, 26.94, 28.06, 31.02, 32.71, 33.67, 95.56, 115.27, 128.96, 131.58, 138.40, 140.08, 150.08. Mass (*m/z*; %):

260 (M^+; 7.4). Anal. Calcd. for $C_{15}H_{20}N_2S$ (260.40): C, 69.19; H, 7.74; N, 10.76%. Found: C, 69.32; H, 7.70; N, 10.83%.

5,6-dihydro-9-methyl-7-(methylthio)benzo[*f*]-pyrazolo[5,1-*b*]isoquinoline 70a:

Light green crystals; yield-63%; mp.107-108^{0}C (chloroform-hexane). IR(Kbr): 1445, 1556, 1568, 1614, 2851 2921 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.46 (s, 3H, CH_3); 2.50 (s, 3H, SCH_3); 2.85 (s, 4H, $(CH_2)_2$); 6.16 (s, 1H, H-10); 7.02 (s, 1H, H-11); 7.23-7.40 (m, 3H, ArH); 9.27-9.30 (d, J=8.1Hz, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.13, 15.03, 24.06, 28.72, 94.67, 96.04, 109.35, 119.93, 126.18, 126.97, 127.83, 128.46, 128.71, 132.79, 134.97, 138.26, 141.71, 150.37. Mass (*m/z*; %): 280 (M^+; 100). Anal. calcd. for $C_{17}H_{16}N_2S$ (280.39): C, 72.82; H, 5.75, N, 9.99%. Found: C, 72.69; H, 5.81; N, 9.93%.

6,7-Dihydro-3,10-dimethyl-8(-methylthio)benzo[*b*]pyrazolo[1',5'-1,6]-pyrido [4,3-*d*]thiepin 70b:

Colourless crystals; yield-64%; mp.190-192^{0}C(chloroform-hexane). IR (KBr): 1467, 1524, 1547, 1621, 2917, 2937 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.38 (s, 3H, CH_3); 2.51 (brs, 3H, CH_3); 2.62 (s, 3H, SCH_3); 2.90 (brm, 2H, CH_2); 3.45 (brm, 2H, CH_2); 6.28 (s, 1H, H-11); 7.14 (s, 1H, ArH); 7.26-7.36 (brs, 2H, ArH); 7.38 (brs, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.07, 15.74, 20.76, 29.34, 37.41, 95.94, 97.17, 115.42, 126.03, 128.41, 129.30,

130.91, 130.99, 135.51, 138.05, 138.10, 139.92, 142.07, 150.43. Mass (*m/z*; %): 326 (M^+; 2.6).

Anal calcd. for $C_{18}H_{18}N_2S_2$ (326.49): C, 66.22; H, 5.56; N, 8.58%. Found: C, 66.36; H, 5.67; N, 8.51%.

General Procedure for Dethiomethylation of 55, 62a,b,c, and 66c:

To a stirred solution of corresponding methylthiopyrazolo[1,5-*a*]pyridine (2.5 mmol) in ethanol (25 ml) was added Raney Nickel (**W4**, 3 times by weight) and the mixture was stirred at ambient temp for 2-3 hr (monitored by **TLC**). The reaction mixture was cooled filtered through **G-3** sintered funnel and the residue was washed with ethanol (3x10ml). Ethanol was distilled off and chloroform (25ml), was added into residue. The solution was thenwashed with water (2x25ml), dried overanhydrous sodium sulphate and concentrated to give crude products. Analytically pure compounds **56**, **63a,b,c and 67** were obtained by passing through a short length silicagel column using hexane as eluent.

2,5,6-Trimethyl pyrazolo[1,5-*a*]pyridine 56:

Colourless crystals; Yield-94%; mp.94^{0}C (chloroform-hexane). IR (KBr): 1529, 1626, 2916 cm.$^{-1}$ ^1H NMR (300*MHz*; $CDCl_3$): δ 2.17(s, 3H, CH_3); 2.22 (s, 3H, CH_3); 2.43 (s, 3H, CH_3); 6.06 (s, 1H, H-3); 7.10 (s, 1H, H-4); 8.09 (s, 1H, H-7). ^{13}C NMR (75*MHz*; $CDCl_3$) :15.86, 16.67, 19.46, 94.33, 115.55,

120.67, 125.65, 134.45, 140.31, 150.88. Mass (*m/z*; %) : 160 (M^+; 100). Anal. Calc. for $C_{10}H_{12}N_2$ (160.21): C, 74.96; H, 7.55; N, 17.48 %. Found: C, 75.23; H, 7.79; N, 17.50%.

2,5-Dimethyl pyrazolo[1,5-*a*]pyridine (63a):

Light yellow crystals; yield- 90 %; mp.79-80^{0}C (chloroform-hexane). IR (KBr): 1467, 1514, 1736, 2851, 2925 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.3 (s, 3H, CH_3); 2.44 (s, 3H, CH_3); 6.11 (s, 1H, H-3); 6.42-6.45 (dd, J=1.8, 7.1Hz, 1H, H-6); 7.11-7.12 (brs, 1H, H-4); 8.20 (d, J=7.1Hz, 1H, H-7). ^{13}C NMR (75*MHz*; $CDCl_3/CCl_4$): 13.9, 21.11, 94.89, 113.31, 115.55, 127.28, 133.77, 141.36, 151.60. Mass (*m/z*; %): 146 (M^+; 100). Anal. calcd. for $C_9H_{10}N_2$ (146.19): C, 73.93; H, 6.90; N, 19.16%. Found: C, 73.78; H, 6.91; N, 19.23%.

2-Methyl-5-phenyl pyrazolo[1,5-*a*]pyridne 63b:

white crystals; yield-85%; m p.121^{0}C (chloroform-hexane). IR (KBr): 1522, 1723, 2334, 2401, 2858, 2918 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3$): δ 2.45 (s, 3H, CH_3); 6.21 (s, 1H, H-3); 6.86 (dd, J=1.8, 7.2 Hz, 1H, H-6); 7.36-7.56 (m, 6H, ArH); 8.37 (d, J=7.1Hz, 1H, H-7). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.02, 96.24, 110.06, 113.78, 126.27, 126.45, 127.63, 127.78, 128.08, 128.43, 128.61, 135.85, 138.92, 140.85, 151.68. Mass (*m/z*; %) : 208 (M^+; 100). Anal calcd. for $C_{14}H_{12}N_2$ (208.26): C, 80.74 ; H, 5.80 ; N, 13.45%. Found: C, 81.07; H, 5.85 ; N, 13.39%.

5-(4-Methoxyphenyl)-2-methyl-pyrazolo[1,5-*a*]pyridine 63c:

Colourless crystals; yield-92%; mp.145^{0}C (chloroform-hexane). IR (KBr): 1630, 1692, 2915, 2932 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.48(s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.26 (s, 1H, H-3); 6.82-6.85 (dd, 1H, J=2, 7.3 Hz, H-6); 6.92-6.95 (d, 1H, J=8.8Hz, ArH); 7.47-7.52 (m, 1H, H-4); 7.55 (d, 2H, J=8.9 Hz, ArH); 8.32-8.34 (d, 1H, J=7.2Hz, H-7). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 13.89, 55.17, 96.23, 110.35, 113.04, 114.30, 127.72, 127.81, 131.29, 135.84, 141.34, 152.09, 159.63. Mass (*m z*; %): 238 (M^+; 100) 223(82). Anal calc. for $C_{15}H_{14}N_2O$ (238.29): C, 75.61; H, 5.92; N, 11.76%. Found: C, 75.96, H, 6.19; N, 12.03%.

2-methyl-cycloocta[d]pyrazolo[1,5-*a*]pyridine 67:

Colourless crystals; yield-91%; mp.76^{0}C (chloroform-hexane). IR (KBr): 1441, 1528, 1602, 2025, 2838, 2952 cm^{-1}. ^1H NMR (300 *MHz*, $CDCl_3/CCl_4$): δ 1.00-2.00 (brm, 8H, $(CH_2)_4$); 2.60-2.90 (m, 4H, $(CH_2)_2$); 2.39 (s, 3H, CH_3); 6.01 (s, 1H, H-3); 7.1 (s, 1H, H-4); 8.09 (s, 1H, H-11). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 13.73, 16.52, 19.30, 29.57, 52.96, 94.17, 115.4, 119.84, 125.55, 133.53, 139.95, 150.45. Mass (*m/z*; %): 214 (M^+; 100%). Anal. Calcd. for $C_{14}H_{18}N_2$ (214.31): C, 78.46; H, 8.46; N, 13.07%. Found : C, 78.54; H, 8.48; N, 13.09 %.

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CHAPTER- III

REACTION OF ARYL ACETONITRILES WITH α-OXOKETENE DITHIOACETALS: FORMATION OF ADDITION-ELIMINATION PRODUCTS AND THEIR ORTHOPHOSPORIC ACID ASSISTED CYCLISATION TO REGIOSELECTIVELY SUBSTITUTED NAPHTHALENES

III. A INTRODUCTION:

A brief review on the synthesis of Naphthalenes:

In **1984**, a new general method for aromatic annelation from open chain precursors was discovered in our laboratory[1]. The method mainly consisted of the reaction of allyl magnesium halides with α-oxoketene dithioacetals to afford the carbinol acetals in quantitative yields. These carbinolacetals were subsequently cyclised *insitu* in the presence of Lewis acids to afford the corresponding annelated benzeniod system.

The method was general and could be applied to a wide variety of allyl anions and α-oxoketene dithioacetals resulting in a versatile annelating protocol. Among others, benzyl Grignard reagents constituted an important group of allyl anion system which on reaction with α-oxoketene dithioacetals could afford the corresponding naphthalene derivatives. The intermediate carbinol acetals in these reactions underwent cyclisaton in acidic medium involving ring participation. The method was extensively explored with various allyl anions particularly benzyl Grignard reagents and lithiomethyl aromatics. However, the softer allyl or benzyl anions derived from phenyl acetonitriles were not reacted with α-oxoketene dithioacetals to explore their utility for the synthesis of naphthalenes and condensed variants. The formation of this anion from phenyl acetonitriles is possible under ordinary basic reaction condition and these anions should follow 1,4-addition-elimination sequence to yield the intermediates, which could be cyclised to the corresponding naphthalenes. We have investigated these reactions, which forms the part of this chapter.

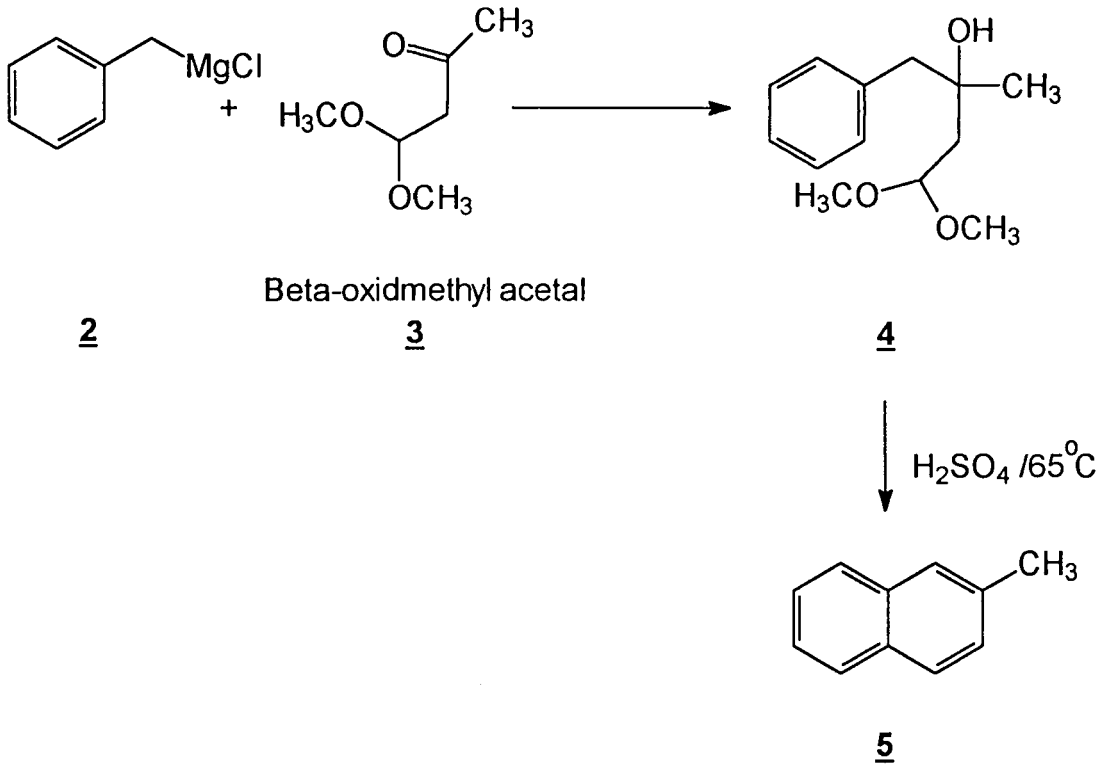
We briefly review some of the literature methods of naphthalenes synthesis to appreciate the efficacy of our methodology.

The classical method of naphthalenes synthesis involves reaction of benzene with succinic anhydride under Friedel-Craft's reaction condition to afford the

corresponding keto acids. The keto acid was subjected to Clemensen's reduction to yield the corresponding γ-phenyl propanoic acid, which was first converted into acid chloride and cyclised under Friedel-Craft's condition to afford the corresponding tetralone. The tetralone was then reduced and dehydrogenated to afford naphthalenes in poor yields.

Subsequently, a number of more practical direct synthesis of naphthalenes have been developed which are described as follows.

Kochetkov and coworkers[2] first reported the reaction of benzyl magnesium chloride **2** with β-oxodimethyl acetal **3** to afford initially the corresponding



Beta-oxidmethyl acetal

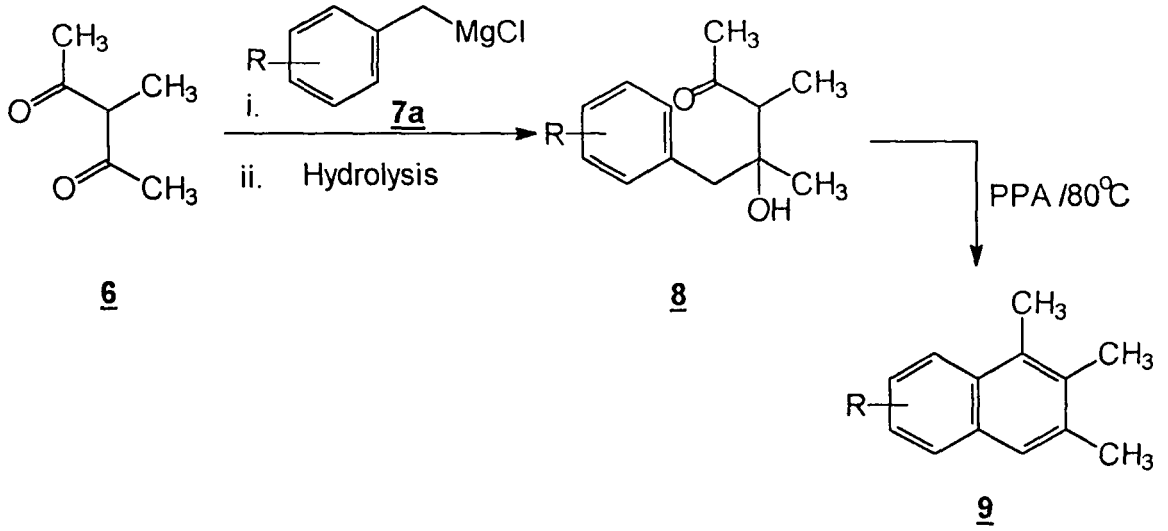
2 **3** **4**

5

Scheme-1

carbinol acetal **4** in high yield. This carbinolacetal was then cyclised in the presence of sulphuric acid to afford the corresponding 2-methyl naphthalenes **5** in good yield (*Scheme-1*).

Subsequently, this method was extended by Leitch and coworkers[3a] for the synthesis of di-and tri-methyl naphthalenes. They reacted benzyl magnesium chloride **7a** with 1,3-diketone **6** to afford the carbinols **8** in excellent yields which were subsequently cyclised using polyphosphoric acid to yield the corresponding 1,2,3-trimethyl substituted naphthalenes **9** in good yields (*Scheme-2*).

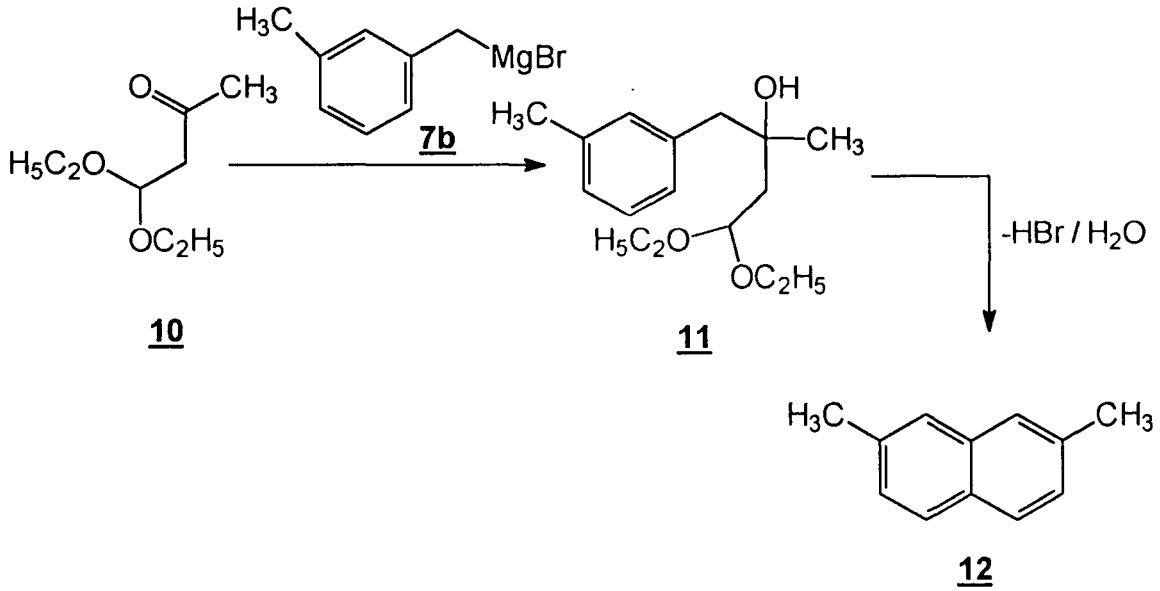


6 **8** **9**

Scheme-2

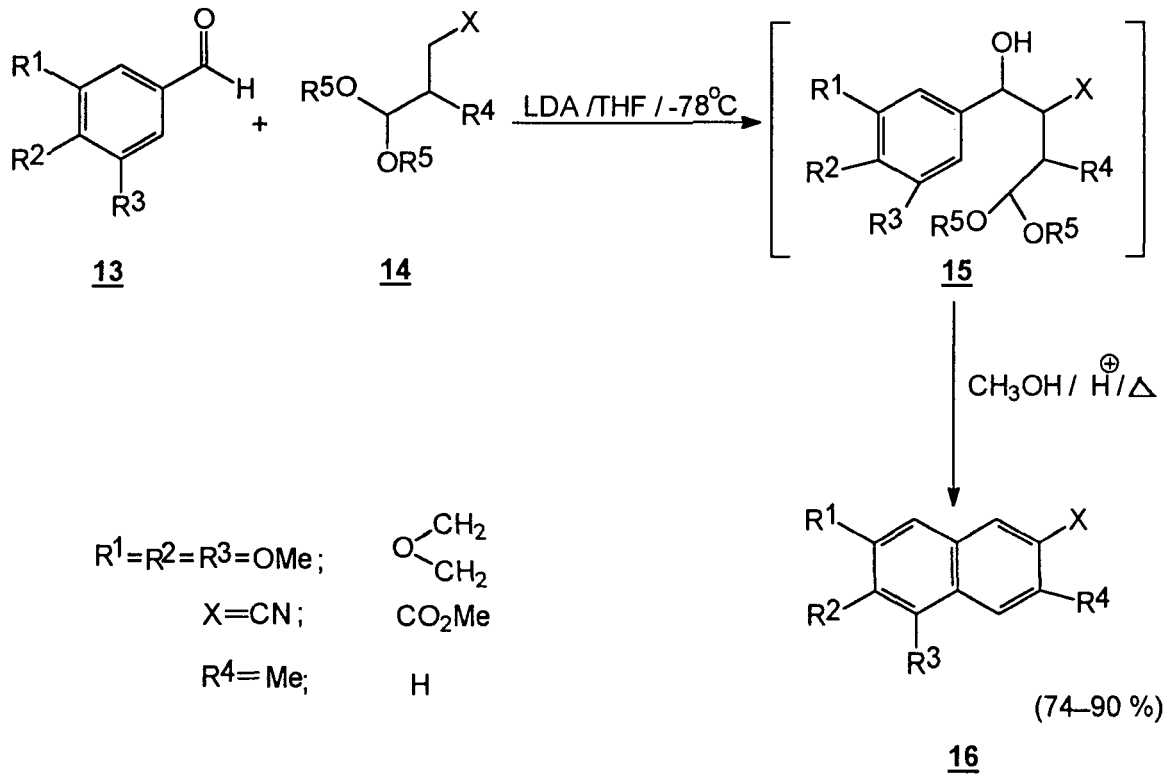
Similarly, the 3-methyl benzyl magnesium bromide **7b** was reacted with β-oxoacetal **10** to afford the corresponding 1,2-adduct carbinol acetal **11** in high

yield. The carbinol was then cyclised in the presence of aqueous hydrobromic acid to yield the corresponding 1,6-dimethyl naphthalene **12**[3b] (*Scheme-3*).



Scheme-3

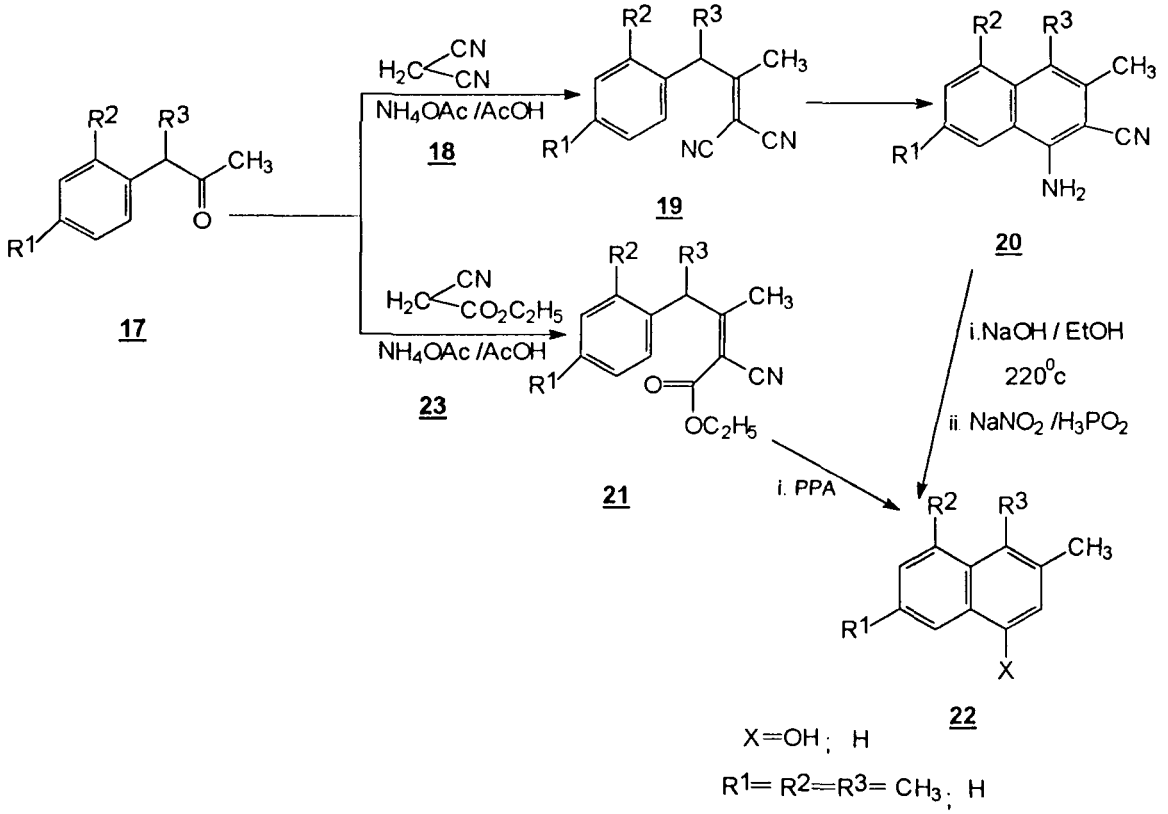
Roth and coworkers[4] reported highly functionalised naphthalenes synthesis which consisted the following steps. α-Lithio derivatives of 3-substituted 4,4-dialkoxy butanonitriles **14** were reacted with substituted benzaldehydes **13** in the presence of Lithium di-isopropyl amide at -78^{0}C when the corresponding carbinol acetals **15** were formed in excellent yields. These carbinol acetals were then cyclised in the prescene of methanol and dilute sulphuric acid to afford the corresponding naphthalenes **16** (*Scheme-4*) in 74-90% overall yields.



Scheme-4

Siphol and co-workers[5] used ylidinemalonodinitriles for the construction of naphthalene rings from the phenyl acetone (*Scheme-5*). The malonitrile **18** was condensed with phenyl acetone **17** in the presence of acetic acid and ammonium acetate to afford the corresponding yilidins **19** which were easily cyclised in the presence of polyphosphoric acid to yield the corresponding naphthalenes **20**. The yilidin **21** obtained by condensation of cyanoacetate **23** with phenyl acetone **17**

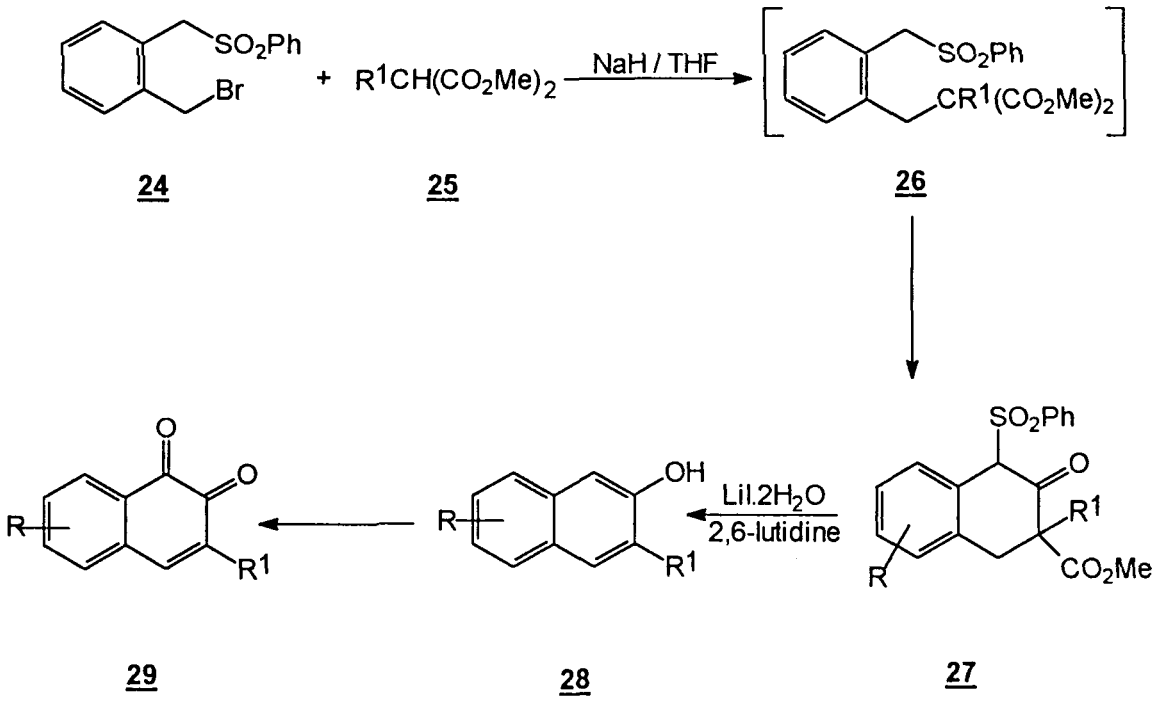
was also cyclised under similar reaction condition to afford the corresponding naphthalenes **22**.



Scheme-5

Ghera and coworkers[6] have reported annelation reaction leading to the synthesis of highly substituted naphthalene derivatives. The method is applicable to the synthesis of 1,2- and 1,4-naphthoquinones. The reaction of 1-[(phenylsulfonyl) methyl]-2-(bromomethyl)benzene **24** with monosubstituted malonic ester **25** to afford the corresponding 1-(phenylsulfonyl)-2-oxo-3-(methoxycarbonyl)-1,2,3,4-

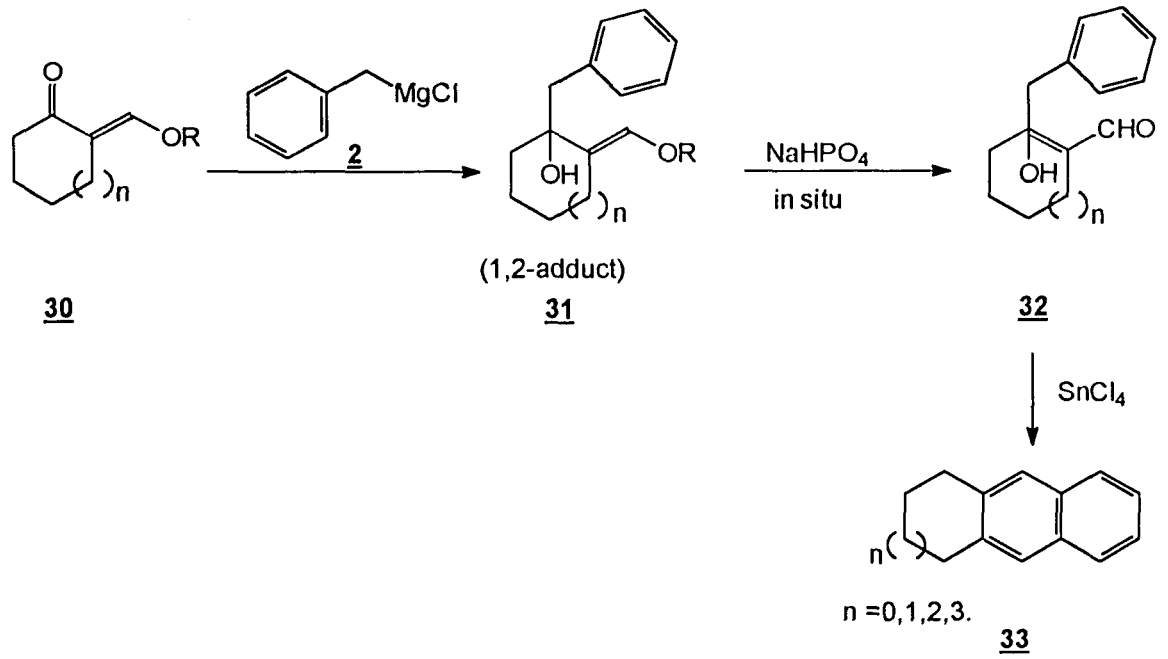
tetrahydronaphthalenes **27** in high yields. These compounds were subsequently hydrolysed in one step to afford the corresponding naphthols **28** which were oxidised to afford 1,2-naphthoquinones **29** (*Scheme-6*).



Scheme-6

Tius and coworkers[7a] developed a new method for the synthesis of naphthalenes and their condensed variants as formulated in *scheme-7*. The benzyl magnesium chloride **2** was reacted with various cyclic and open chain α,β-unsaturated vinyl ether **30** to afford the corresponding carbinols **31** which on hydrolysis yielded the corresponding aldehydes **32**. These aldehydes were then cyclised in the presence

of tin tetrachloride to afford the corresponding 2,3-cycloalkano naphthalenes **33** in good yields.

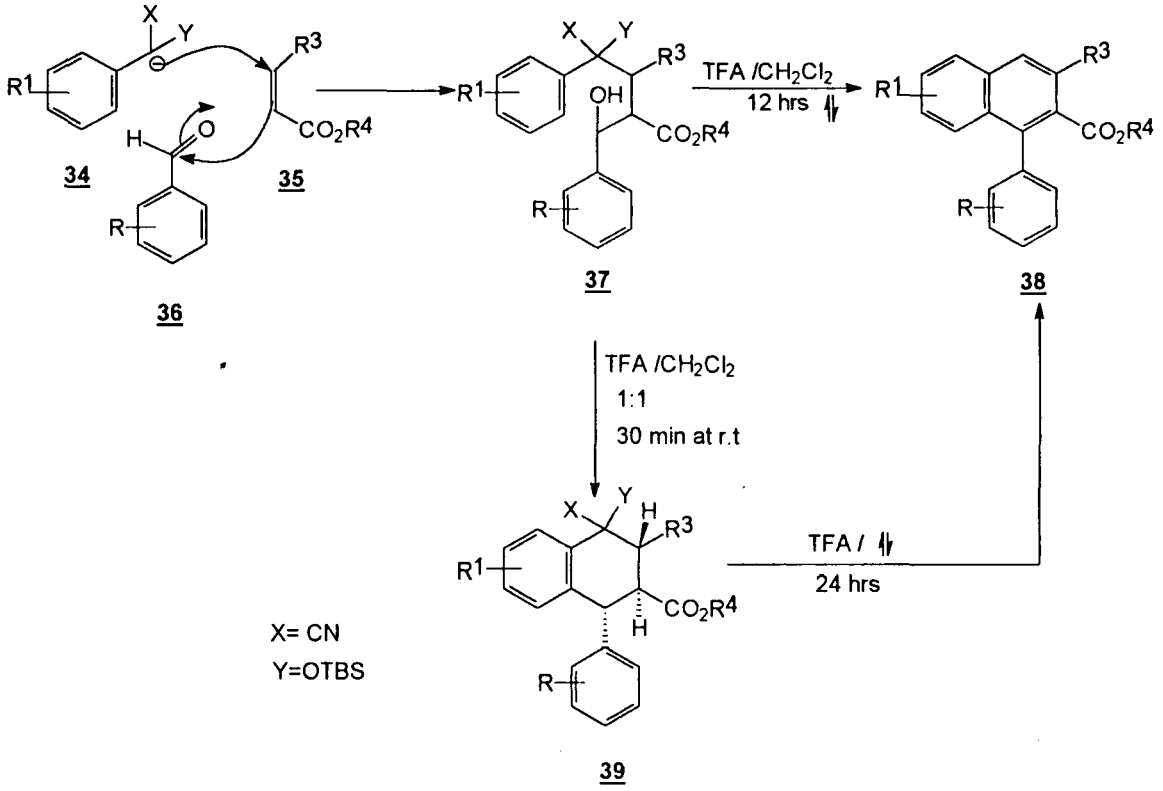


30 31 32 33

Scheme-7

A new two step synthesis of aryl naphthalenes lignans of general structure **38** (*scheme-8*) from O-t-butyldimethylsilyl cyanohydrins **34** developed by Ogiku and coworkers[9] involves tandem conjugate addition of cyanohydrine anion **34** to α,β-unsaturated esters **35** in the presence of various aldehydes **36** to afford the corresponding carbinols **37** in excellent yields. These carbinols were then

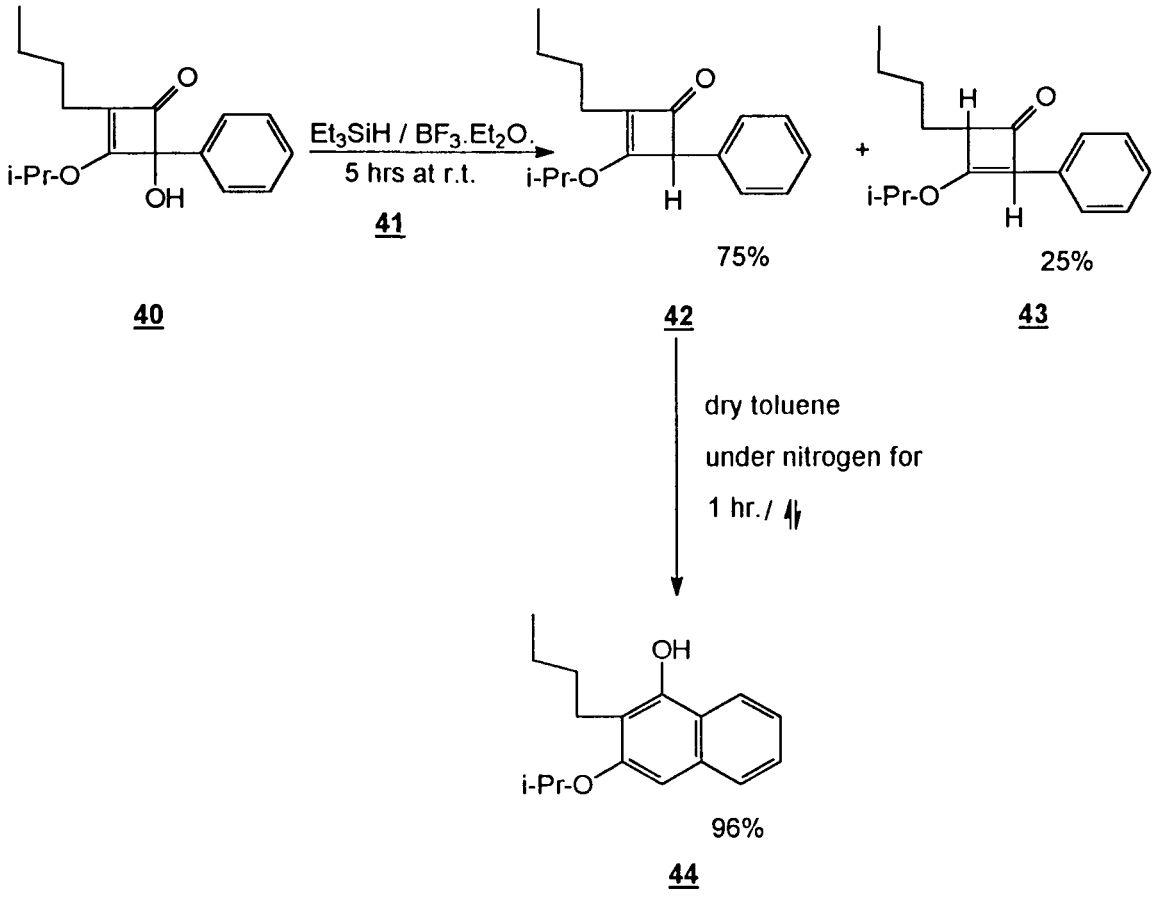
cyclised in the presence of chloroacetic acid to afford the corresponding naphthalenes **38**. The method was applied for the synthesis of a number of naturally occurring lignans[10].



Scheme-8

Moore and coworkers[11] developed a highly regioselective synthesis of substituted naphthalenes in excellent yields following the protocol as depicted in *scheme- 9*. The cyclobutenone method involves the construction of **40** by reacting Gillmann's reagents to substituted cyclobutenediones. These butenones were dehydrated to

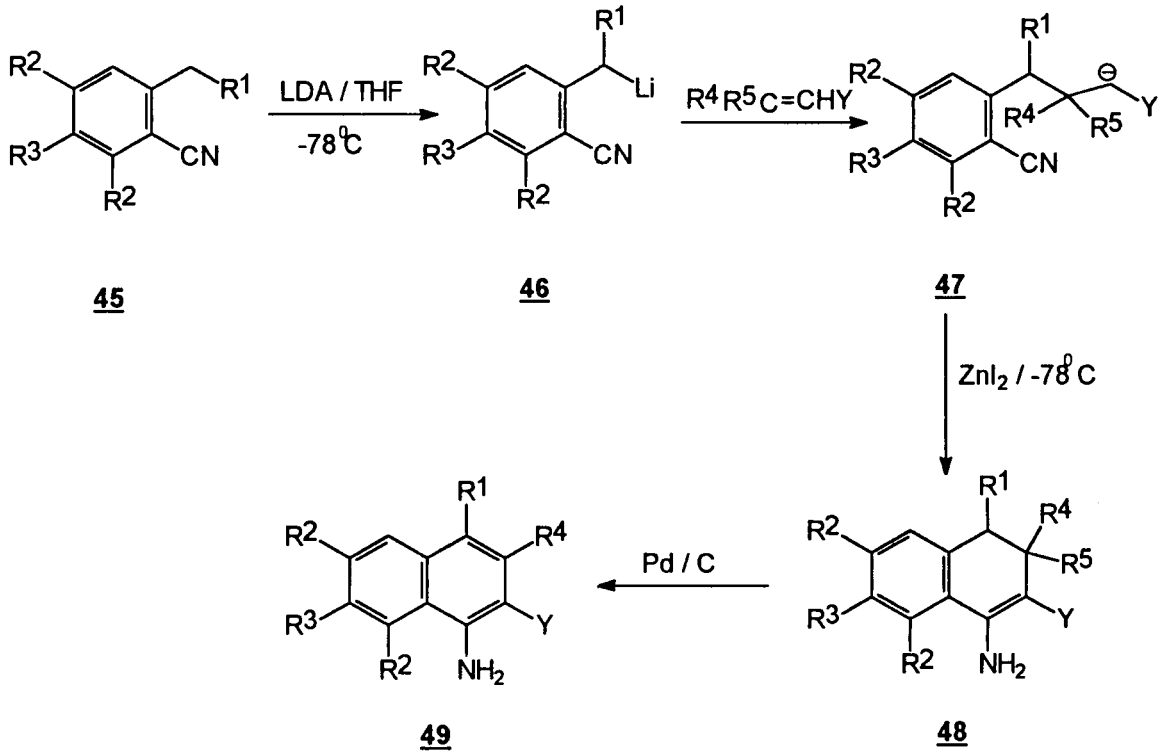
afford the corresponding mixture of **42** and **43**, which were rearranged to naphthols **44** in refluxing toluene.



Scheme-9

Kobayashi and coworkers[12] have developed an efficient general method for the preparation of 1-amino-2-naphthalene-carboxylic derivatives **49** by the reaction of

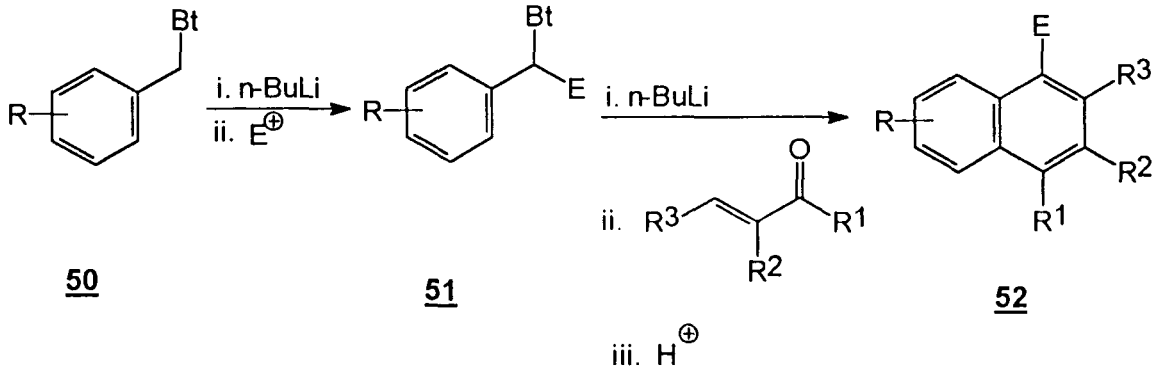
2-(α-lithioalkyl)benzonitriles **46**, generated *insitu* by the treatment of 2-alkyl benzonitrile **45** with LDA in diglyme, with α,β-unsaturated carboxylates and nitriles followed by the treatment of zinc iodide and palladium carbon in 54-94% yields (*Scheme-10*).



Scheme-10

Katritzky and coworkers[13] have recently reported a general synthetic route for polysubstituted naphthalenes and phenanthrenes. Their strategy involves lithiation of (benzotriazol-1-ylmethyl)benzenes **50** and naphthalenes, and subsequent 1,4-addition to α,β-unsaturated aldehydes and ketones. These 1,4-adducts **51** thus

obtained underwent intramolecular cyclodehydration induced by acetic acid-hydrobromic acid or polyphosporic acid to give the corresponding polysubstituted naphthalenes **52** and phenanthrenes in moderate to good yields (*Scheme-11*).

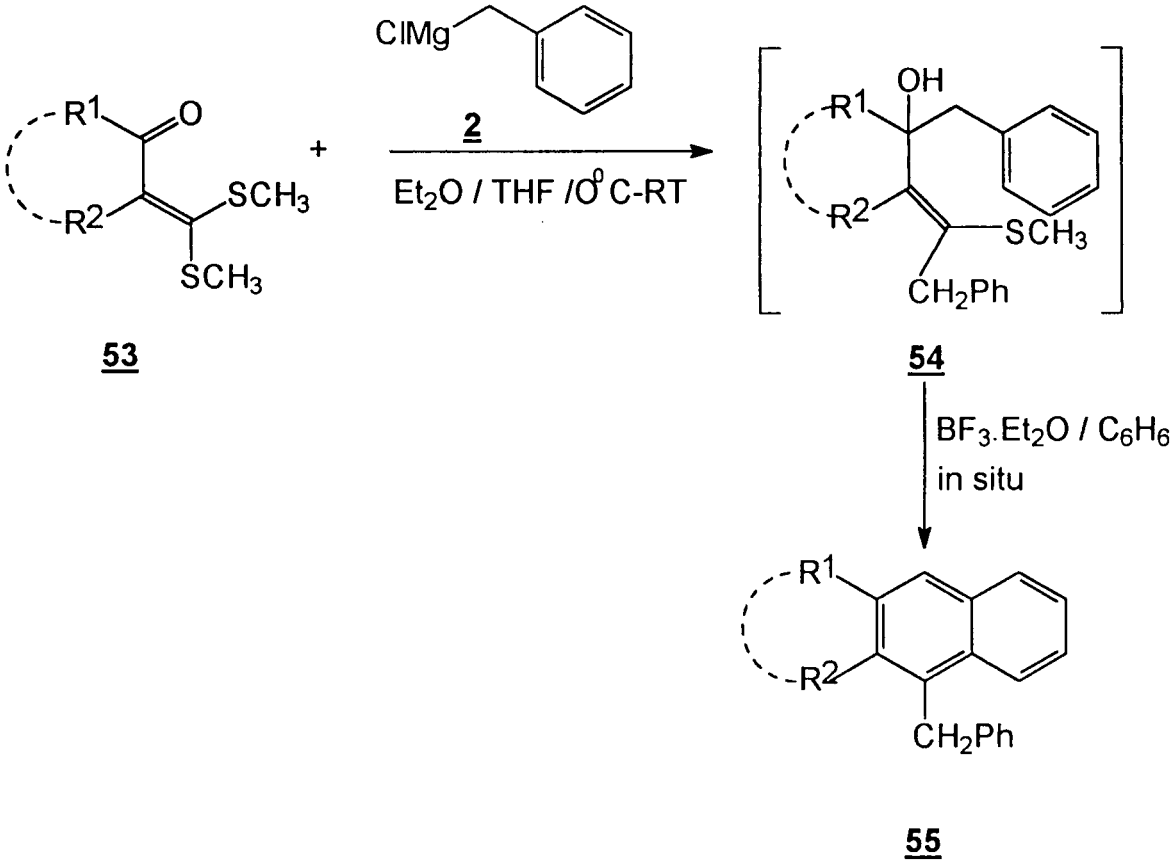


R= OMe; Me E= Me; Et
R^1=Me; H; Ph
R^2=H; Ph
R^3=Ph; Et

Scheme-11

In **1986**, the reaction of benzyl magnesium chloride **2** with α-oxoketene dithioacetals **53** was first reported from our laboratory[14]. When one equivalent of benzyl magnesium chloride **2** was reacted with α-oxoketene dithioacetals **53** the carbinol acetals **54** were obtained which subjected to $BF_3.Et_2O/C_6H_6$ to yield the corresponding benzyl substituted naphthalenes **55** in 30% yields. After the structural elucidation it was found that the benzyl magnesium chloride **2** followed the sequential 1,4-and 1,2-addition mode to afford **54**. Thus resulting in lower

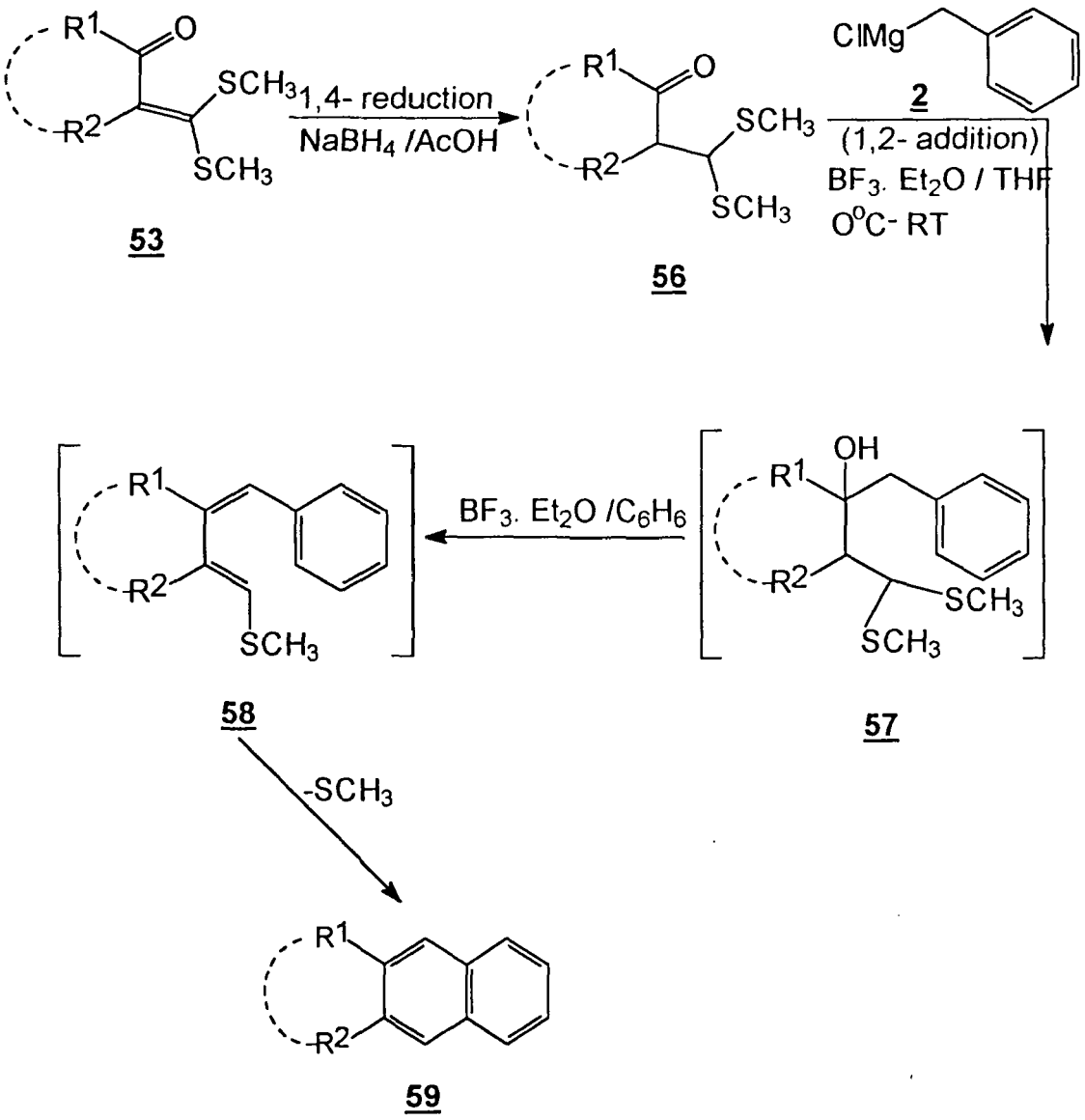
yield of naphthalenes. When excess of benzyl magnesium chloride **2** was reacted with α-oxoketene dithioacetals **53** the benzyl naphthalenes **55** were obtained in excellent yields. Thus the benzyl magnesium chloride **2** did not follow exclusively 1,2-addition even when one equivalent of the reagent was used (*scheme-12*).



53 **54** **55**

Scheme-12

To circumwent this handicap some successful attempts were made as follows: The α-oxoketene dithioacetals were subjected to a series of controlled reduction process to reduce the mercapto double bond selectively. Thus the α-oxoketene

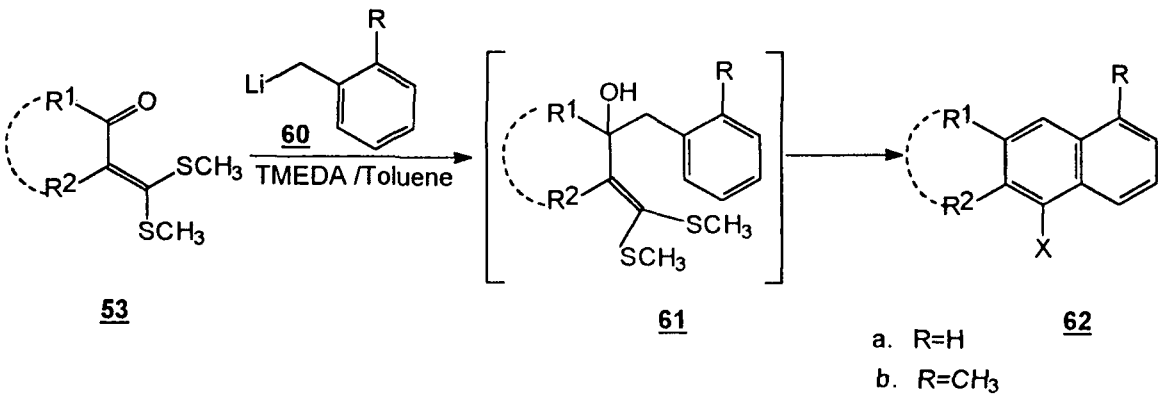


53 56 57 58 59

Scheme-13

dithioacetals **53** when subjected to sodium borohydride in the presence of acetic acid the corresponding β-oxodithioacetals **56** were formed in excellent yields. Alternatively, the β-oxodithioacetals **56** were also formed from α-oxoketene dithioacetals **53** using Zinc and acetic acid as reducing medium. The β-oxo-dithioacetals thus obtained were reacted with benzyl Grignard reagents in the 1,2-fashion to afford the corresponding carbinols **57** in excellent yields. These carbinols underwent $BF_3.Et_2O$ cyclisation to afford the corresponding sulphur free naphthalenes[15] **59** (*scheme-13*) in high yields. The method was generally applicable and yields were high.

Subsequently, it was shown that lithiomethyl benzene **60** *scheme-14* reacts with α-oxoketene dithioacetals **53** directly to afford exclusively the corresponding carbinol acetals **61** following exclusively 1,2-addition mode. These carbinols were then cyclised as described earlier to afford the corresponding methylthio naphthalenes[16] **62** in 80-90% overall yields. The methylthio group was removed under Raney-nickel desulphurisation to afford the sulphur free naphthalenes in high yields. Thus lithiomethyl aromatics follow 1,2-addition mode to **53** and 1,4-adducts were not observed even in traces.



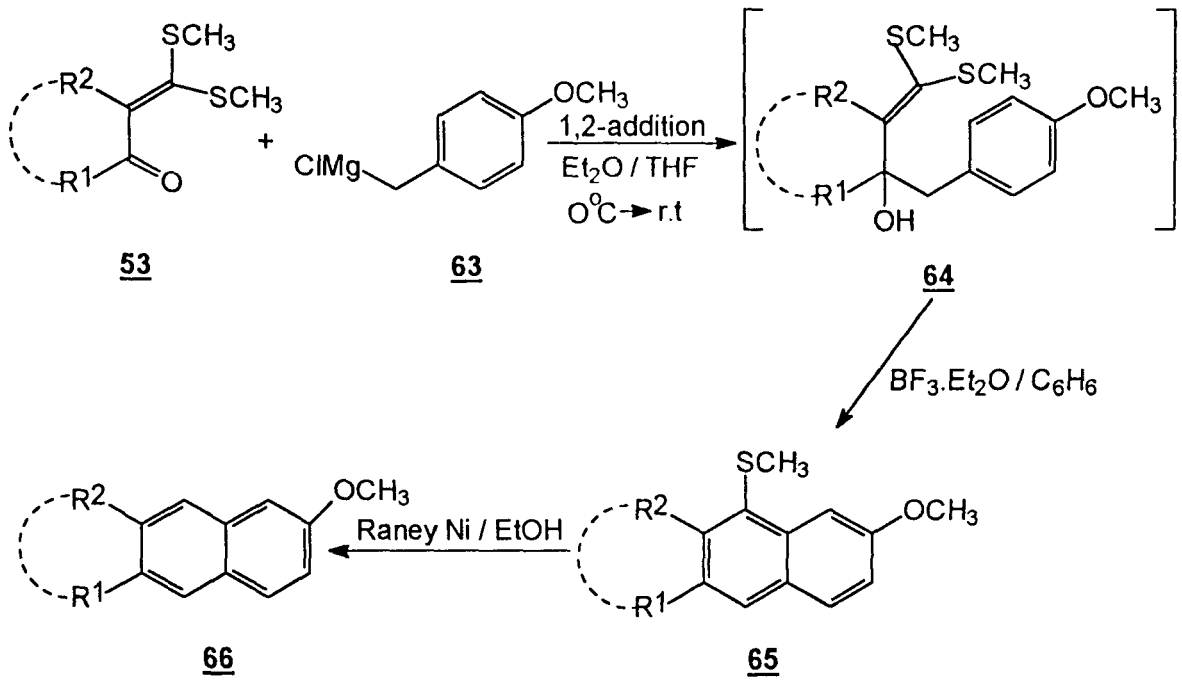
Scheme-14

In summary, it can be generalised about the reactivity of benzyl anions as follows: The benzyl magnesium chloride reacts with α-oxoketene dithioacetals **53** in a sequential 1,4- and 1,2-mode following 1,4-addition in the initial step. Thus the anion appears to behave as a soft nucleophile involving charge distribution over the benzene ring. Thus this anion follows orbital controlled 1,4-addition and then reacted with α,β-unsaturated enones. On the other hand the lithiomethyl benzene derivatives follow the 1,2-addition mode to give the carbinol acetals manifesting the properties of a hard nucleophile. It is possible that the highly electropositive lithium atom tightly binds the negative charge, which is less easily distributed over the ring.

Consequently, these anions follow charge controlled 1,2-addition mode with **53**. We have observed this trend with few exception where the steric consideration play a dominent role. For example, lithiomethyl reagent derived from ortho

xylene follows sequential 1,4-and 1,2-mode. Otherwise lithiomethyl aryl anions uninversally follow charge controlled 1,2-addition mode.

On the basis of these findings alkoxy substituted benzyl Grignard reagents **63** were expected to follow charge controlled 1,2-mode on **53** due to the resisting power of the electron donating substituents of any charge movements from exo-cyclic source. Thus benzyl anions in these systems is less likely to be resonating over the ring and follow the charge controlled 1,2-addition mode with **53**. In most cases this trend is clearly demonstrated in our laboratory, that the alkoxy substituted benzyl Grignard reagents follow 1,2-addition mode with **53** (*Scheme-15*) to afford the corresponding substituted naphthalenes[17] **66**.



53 63 64 65 66

Scheme-15

Similarly, phenyl acetonitrile anions should behave as a soft nucleophile and follow orbital controlled 1,4-addition-elimination sequence. Heterocyclic acetonitriles such as *N*-methylpyrrole-2-acetonitrile[18a], thiophene-2-acetonitrile [18b] and indole-3-acetonitrile[19] have followed 1,4-addition-elimination sequence and the resulting intermediates have been cyclised using different Lewis acids.

The reaction of phenyl acetonitriles with α-oxoketene dithioacetals should follow 1,4-addition-elimination sequence and the intermediates are excellent precursors for the synthesis of highly substituted naphthalenes. These studies are described in the following chapter.

III. B RESULTS AND DICUSSION:

In the preceding section we have described the general methods available for the synthesis of naphthalenes and their derivatives[20-23]. It is already contemplated that the phenyl acetronitrile anions should follow 1,4-addition sequence when reacted with α-oxoketene dithioacetals **53**, thus permitting the synthesis of a large number of precursors. It may be noted that it was not possible to arrest the reaction of benzyl magnesium chloride with α-oxoketene dithioacetals **53** in the second step. The carbinol acetals obtained were the outcome of addition of benzyl magnesium chloride to α-oxoketene dithioacetals **53** in sequentially 1,4- and 1,2-

fashion. On the other hand benzyl cyanide anions react with α-oxoketene dithioacetals **53** to yield the corresponding open chain addition-elimination products which can further be cyclised to afford the corresponding naphthalenes. Although a wide variety of phenyl acetonitriles can be applied for the synthesis of naphthlenes, we have selected a limited number of these intermedites to examine the reactivity of α-oxoketene dithioacetals **53**.

In a typical experiment, to a stirred solution of phenyl acetonitrile **67** (dry dimethyl formide in the prescene of sodium hydride) was added dropwise the α - oxoketene dithioacetal **53f** (dissolved in benzene), maintaining the temperature at 0°C. The reaction mixture was stirred for additional six to eight hours at room temperature. The reaction mixture after work up yielded the corresponding addition-elimination product **69f** (*scheme-16*) in 75 % yield.

The open chain intermediate **69f** was isolated and purified for analysis. The structure was confirmed from its analytical and spectral data as follows:

4-cyano-1-(p-methoxyphenyl)-3-(methylthio)- 4-phenyl-2-buten-1-one 69f:

Yellow coloured solid;Yield-75%; mp-151-152°C;(Chloroform-hexane).IR (KBr): 1645,1704, 2229, 2908, 3149 cm^{-1}. ^{1}H NMR (300 *MHz*; $CDCl_3/CCl_4$): δ 2.4 (s, 3H, SCH_3); 3.8 (s, 3H, OCH_3); 6.6. (s, 1H, ArH); 6.8-7.0 (d, 2H, ArH); 7.24- 7.38 (m, 6H, ArH); 7.75-7.76 (d, 2H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3/CCl_4$): 14.72,

54.99, 96.08, 114.12, 118.27, 123.27, 123.70, 127.17, 128.05, 128.55, 129.54, 130.01, 133.43, 155.25, 157.78, 159.20, 161.60. Mass (*m/z*; %): 323 (M^+; 76.6%). Anal calc. for $C_{19}H_{17}O_2NS$ (323.41): C, 70.56; H, 5.29; N, 4.33 %. Found: C, 70.59; H, 5.30; N, 4.34 %.

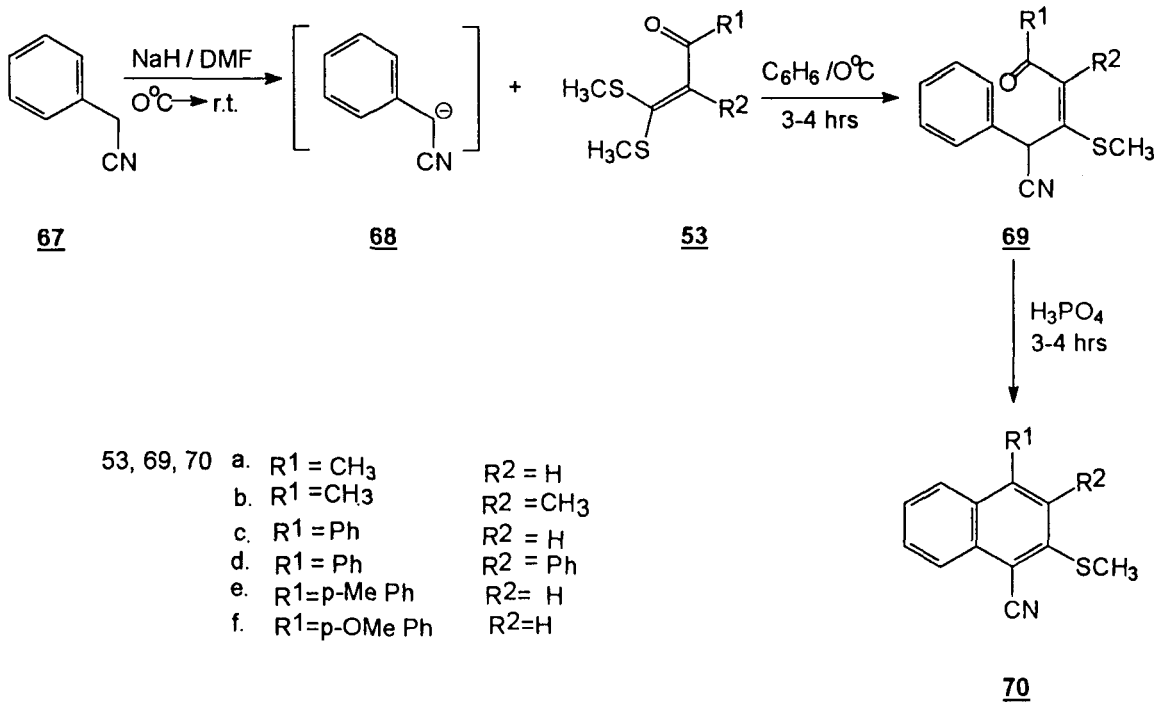
Apparently, it is clear the anion **68** is added to the α-oxoketene dithioacetals **53f** in the 1,4-fashion following addition-elimination sequence to give the open chain intermediate **69f**. There was no trace of 1,2-addition product in the reaction mixture. The stable open chain precursors **69f** were characterized only in a few cases to confirm the course of reactions. In most other cases in this work it is presumed the open chain intermediate is in accordance of these observations and directly followed the cyclisation step. When the open chain precursor **69f** was cyclised in the presecence of ortho phosporic acid the reaction mixture after work up yielded the corresponding 1-cyno-2-methylthio-4-(p-methoxyphenyl) naphthalene **70f** in 67% yield. The structure of **70f** was established on the basis of its analytical and spectral data as follows:

1-Cyano-2-methylthio-4-(p-methoxyphenyl)naphthalene <u>70f</u>:

Light Yellow Crystals; mp.151^{0}C; Yield-67% (Chloroform-hexane). IR(KBr): 1578, 2209, 2851, 2918 cm.$^{-1}$ ^1H NMR (90 *MHz*; $CDCl_3$): δ 2.4 (s, 3H, SCH_3); 3.8 (s, 3H, OCH_3); 6.6 (s, 1H, ArH); 6.9-7.1 (d, 2H, ArH); 7.4-7.6 (s, 5H, ArH);

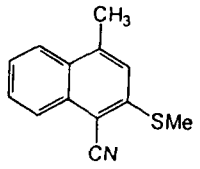
7.8-7.9 (d, 1H, ArH). Anal. Calcd for $C_{19}H_{15}ONS$ (305.39): C, 74.73; H, 4.95; N, 4.59%. Found: C, 74.82; H, 4.96; N, 4.60%.

Similarly, anion **68** was reacted with α-oxoketene dithioacetals **53a** to **53e** to afford initially the corresponding open chain addition and elimination products **69a-69e** in overall excellent yields. These open chain precursors were cyclised without identification as described earlier to afford the corresponding naphthalenes **70a-70e** in 62-75% overall yields. The structures of all the naphthalenes **70a** to **70e** were established by their analytical and spectral data,which are described in the experimental section.

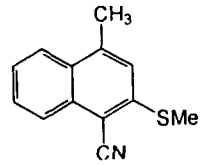


Scheme-16

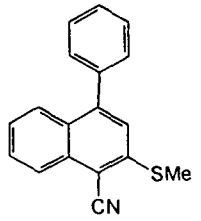
^1H NMR (300MHz, $CDCl_3$) Spectrum of **70a**

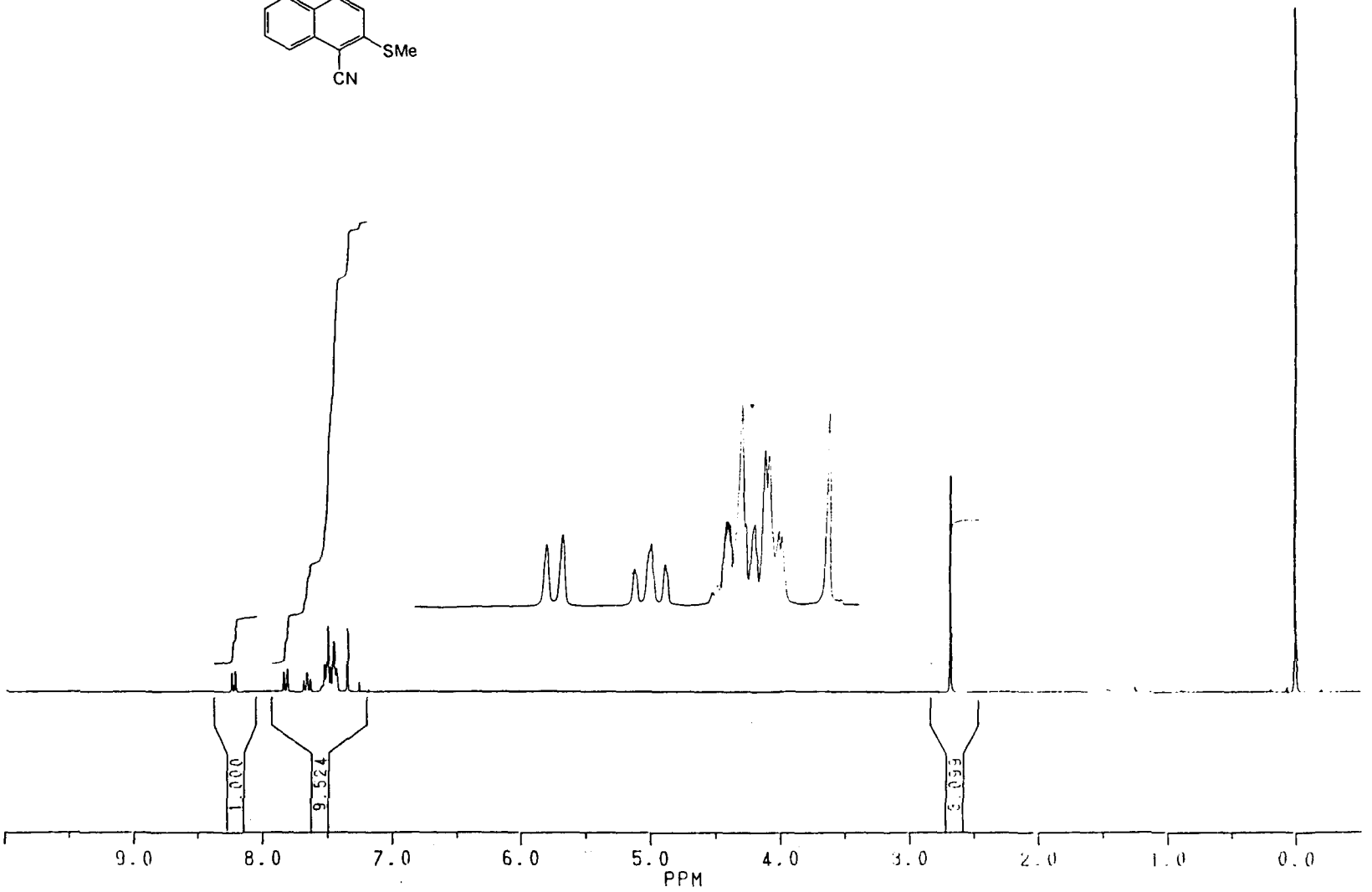


^{13}C NMR (75MHz, $CDCl_3$) Spectrum of 70a

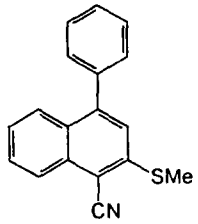


^1H NMR (300MHz, $CDCl_3$) Spectrum of <u>70c</u>

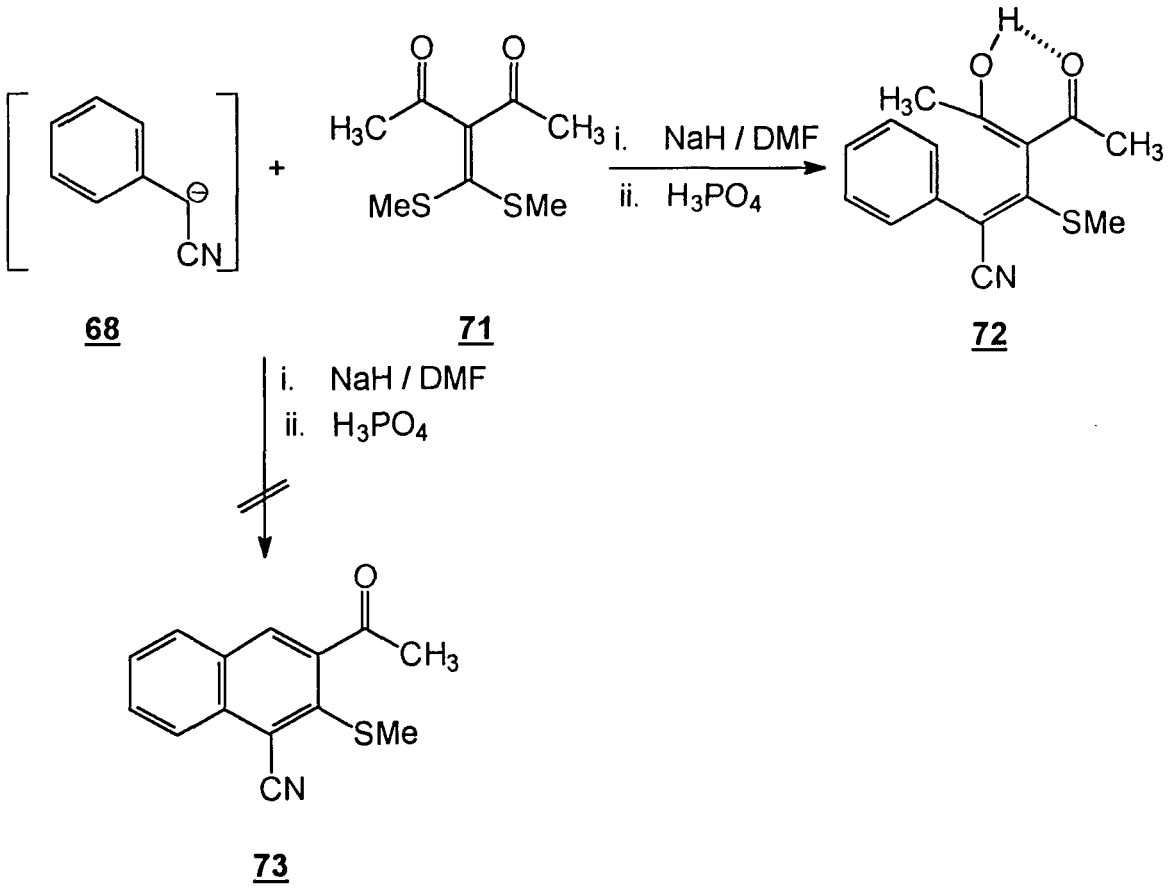




^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **70c**

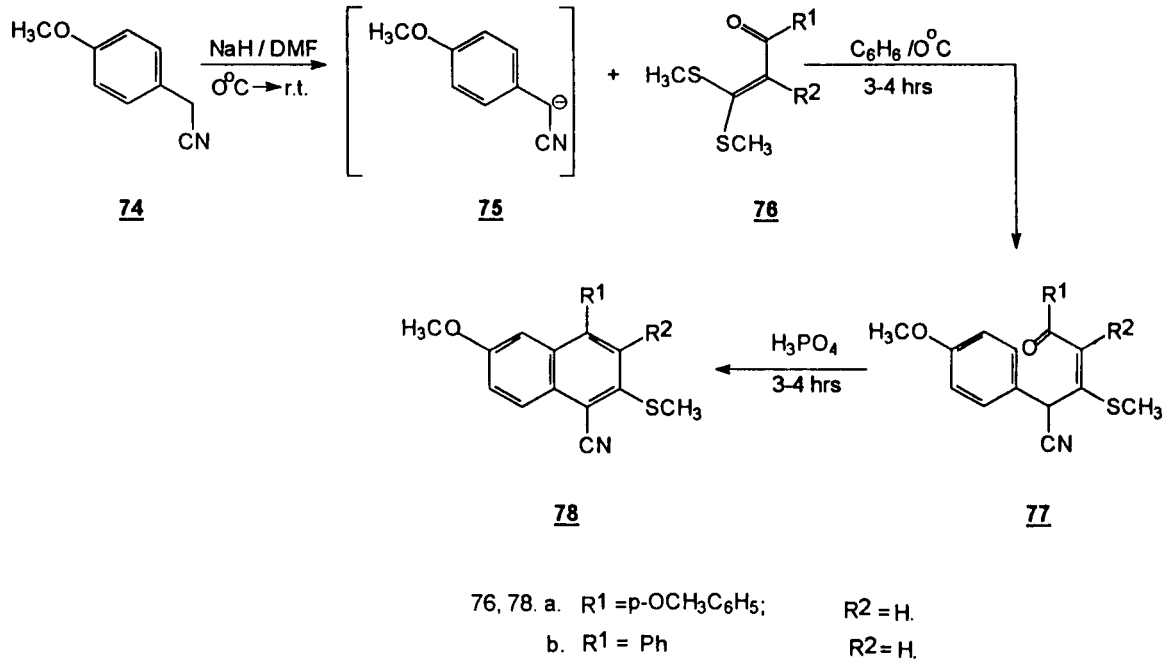


However, when anion **68** was reacted with mercaptal **71** derived from 2,4-pentanedione the intermediate addition-elimination products **72** failed to undergo ring closure to afford the naphthalene **73** *scheme-17*. It is quiet likely that the open chain precursor is highly resonance stablised hydrogen bonded cyclic product as shown in **72** and fails to undergo cyclisation under the described reaction condition.



Scheme-17

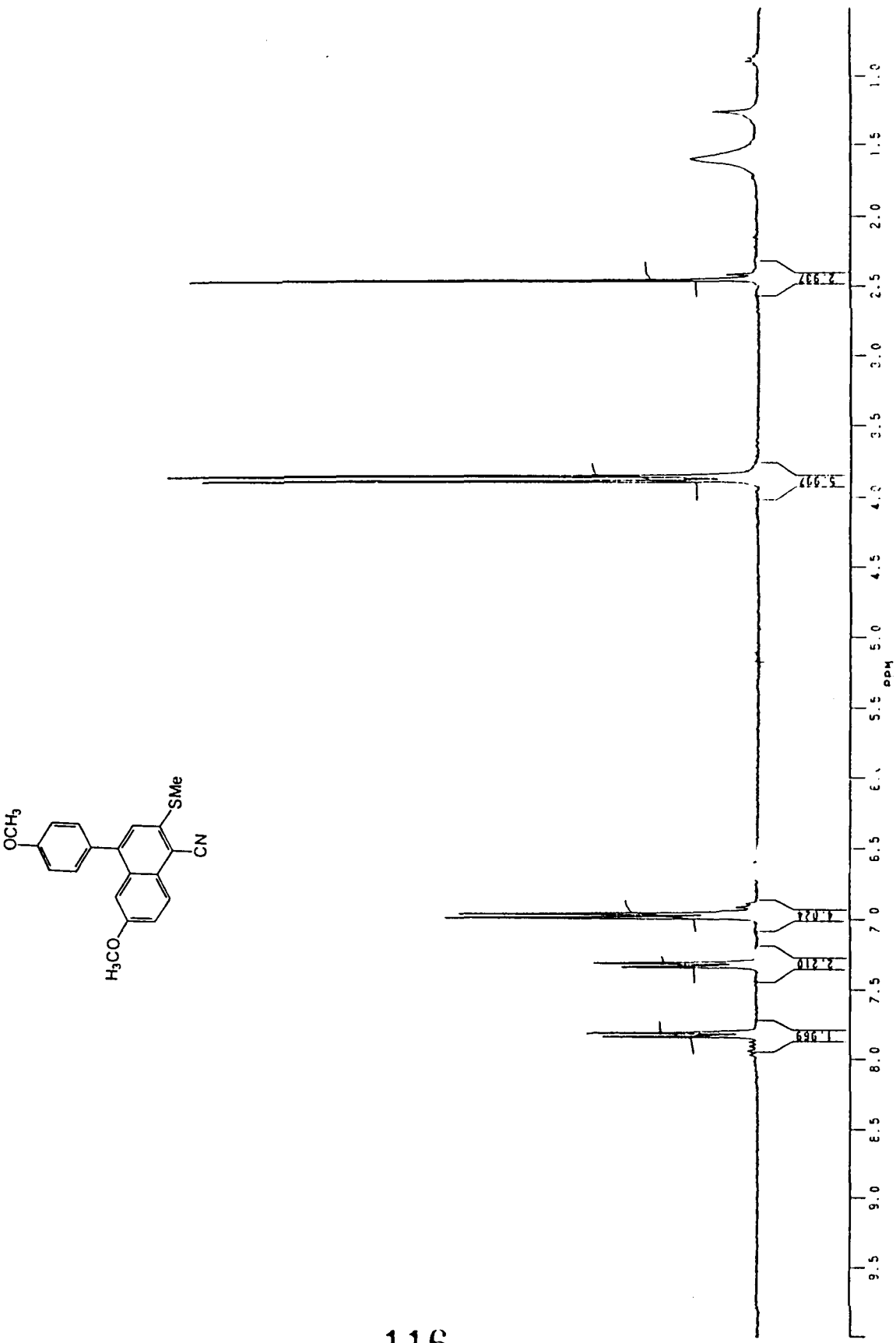
p-Methoxy phenyl acetonitrile **74** was similarly reacted with mercaptal **76** derived from substituted acetophenones to afford the open chain intermediate **77** which was directly cyclised with ortho phosphoric acid to afford the corresponding naphthalenes **78** in 63-72% yields. The structure of naphthalenes **78** as established on the basis of its analytical and spectral data as explained in experimental section (*Scheme-18*).



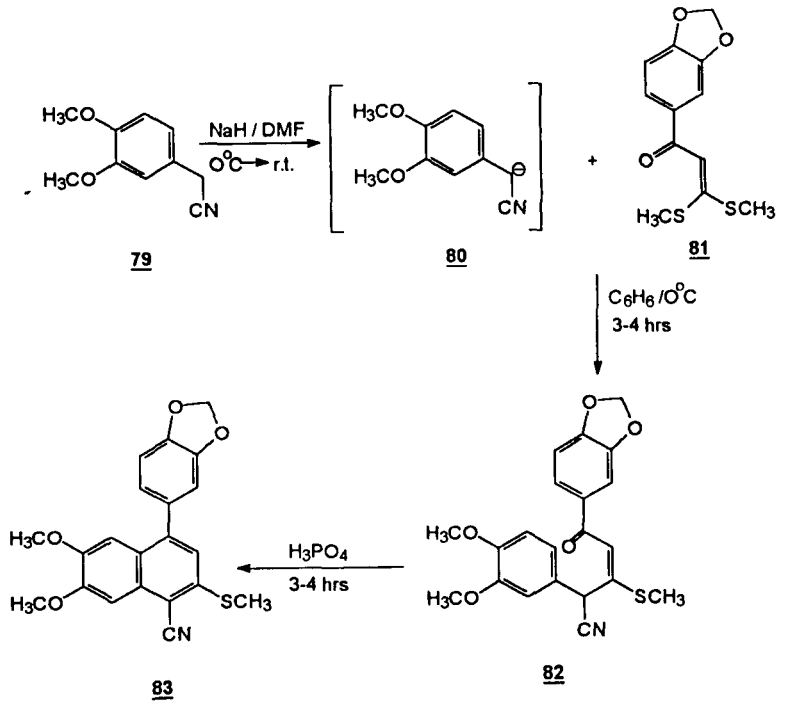
Scheme-18

In the next experiment the reaction of 3,4-dimethoxyphenylacetonitrile **79** with 3,4-methylenedioxyacetophenone mercaptal **81** so that the product naphthalene is close to some of the natural lignans. The open chain intermediate **82** obtained as

^1H NMR (300MHz, $CDCl_3$) Spectrum of 78a



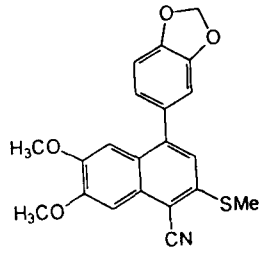
described earlier was cyclised in the presence of ortho phosphoric acid to afford the corresponding naphthalene **83** in 72% yield. The structure of this naphthalene was established by its analytical and spectral data described in experiment section (Scheme-19).

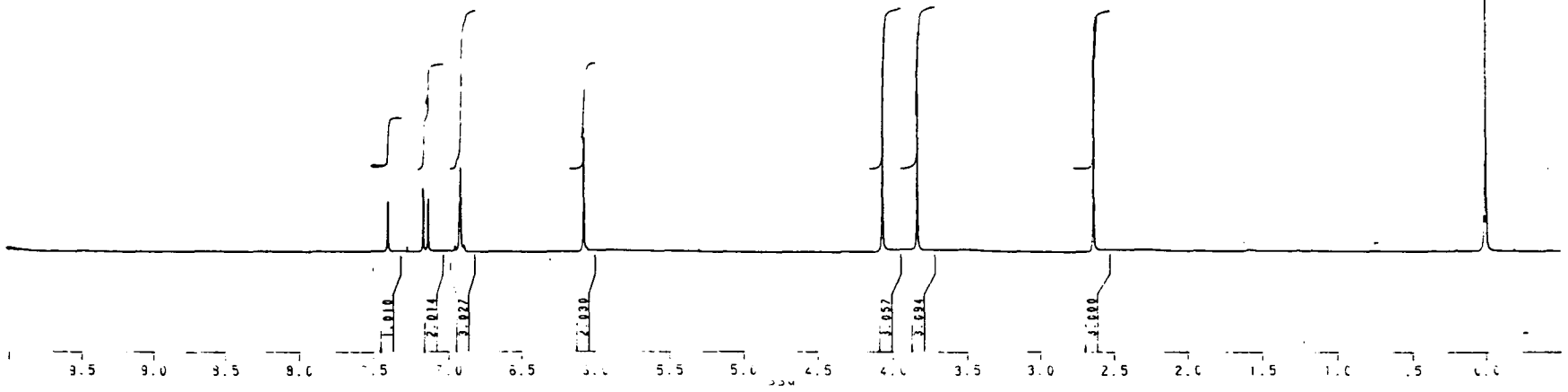


Scheme-19

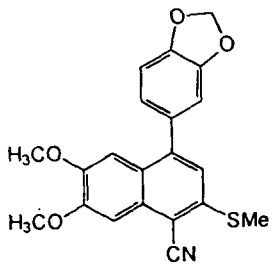
The presence of methylenedioxy structure in many natural lignans prompted us to react 3,4-methylenedioxyphenyl acetonitrile **84**. The anion **85** was reacted with **86a,b** to give the corresponding open chain addition-elimination product **87a,b**

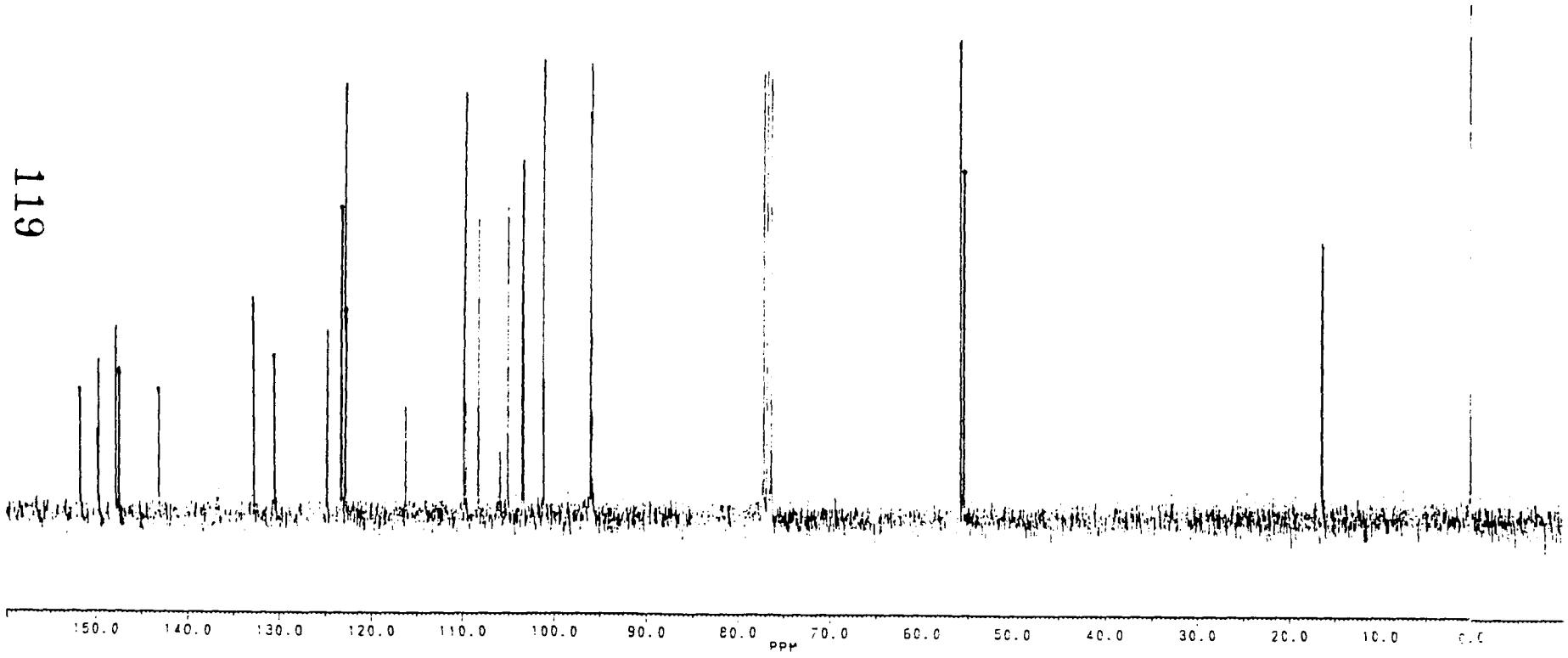
^1H NMR (300MHz, $CDCl_3$) Spectrum of **83**

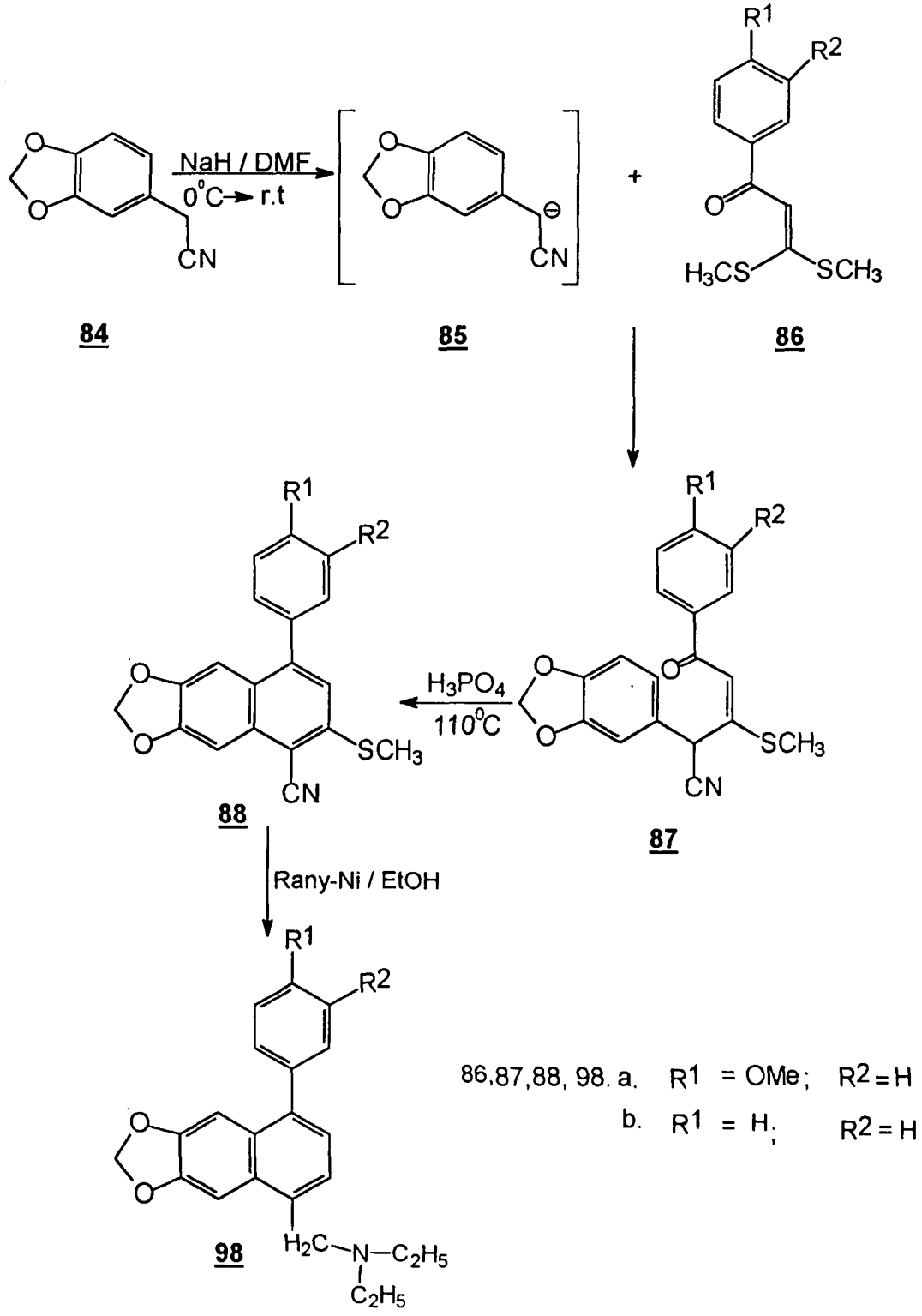




^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **83**





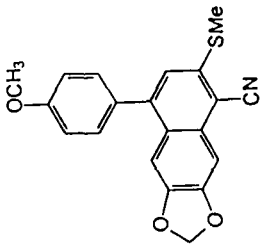


86,87,88, 98. a. R1 = OMe; R2 = H

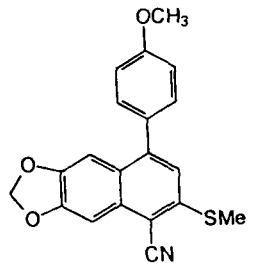
b. R1 = H; R2 = H

Scheme-20

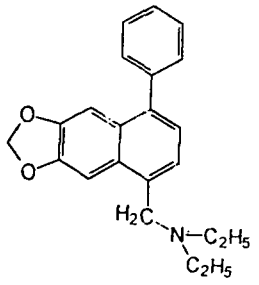
^1H NMR (300MHz, $CDCl_3$) Spectrum of 88a



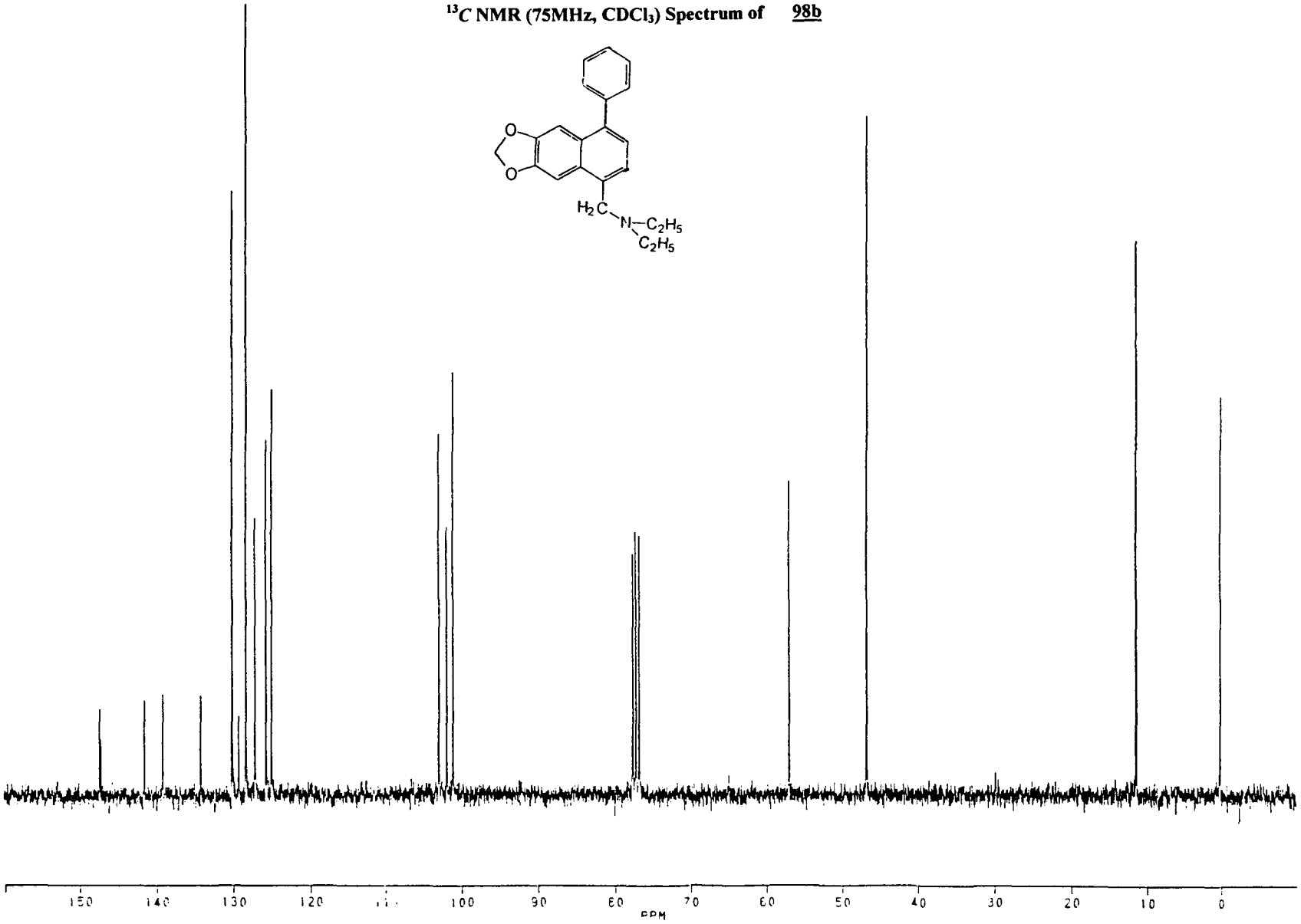
^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **88a**



^1H NMR (300MHz, $CDCl_3$) Spectrum of **98b**

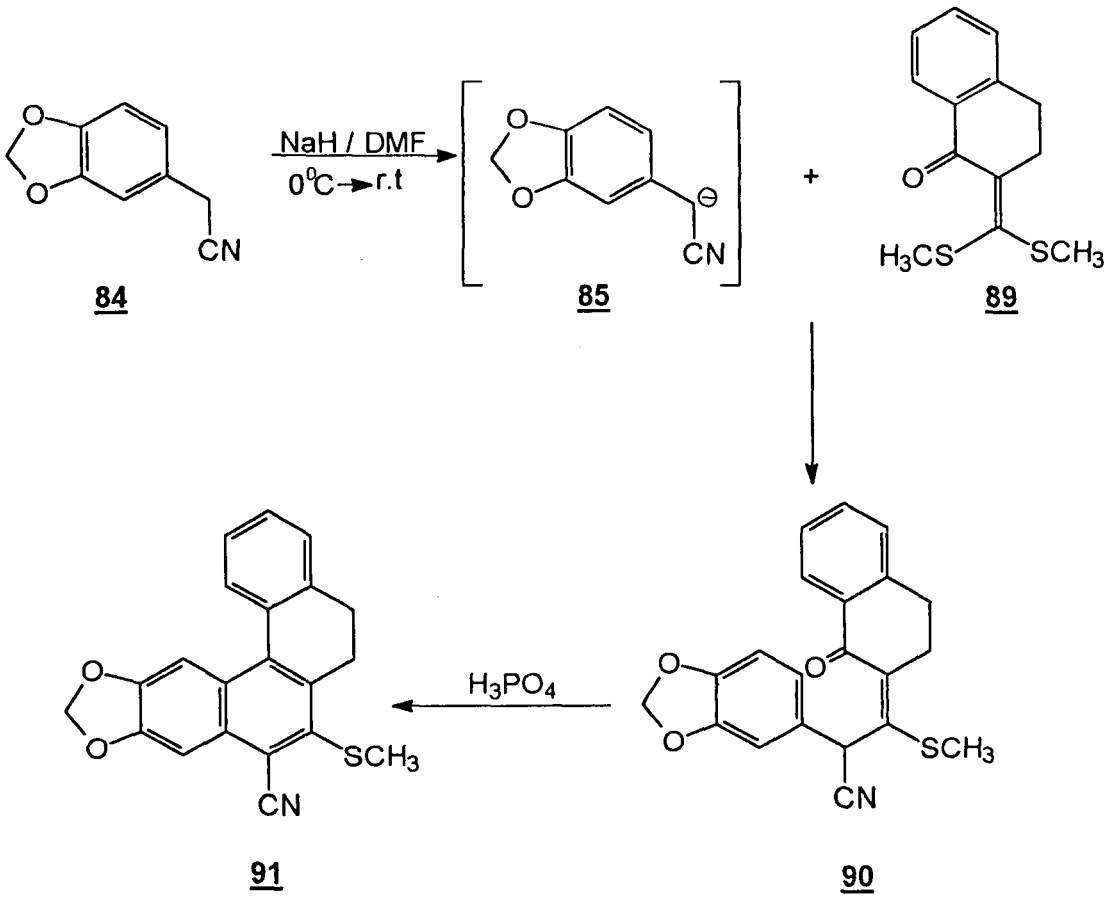


^{13}C NMR (75MHz, $CDCl_3$) Spectrum of **98b**



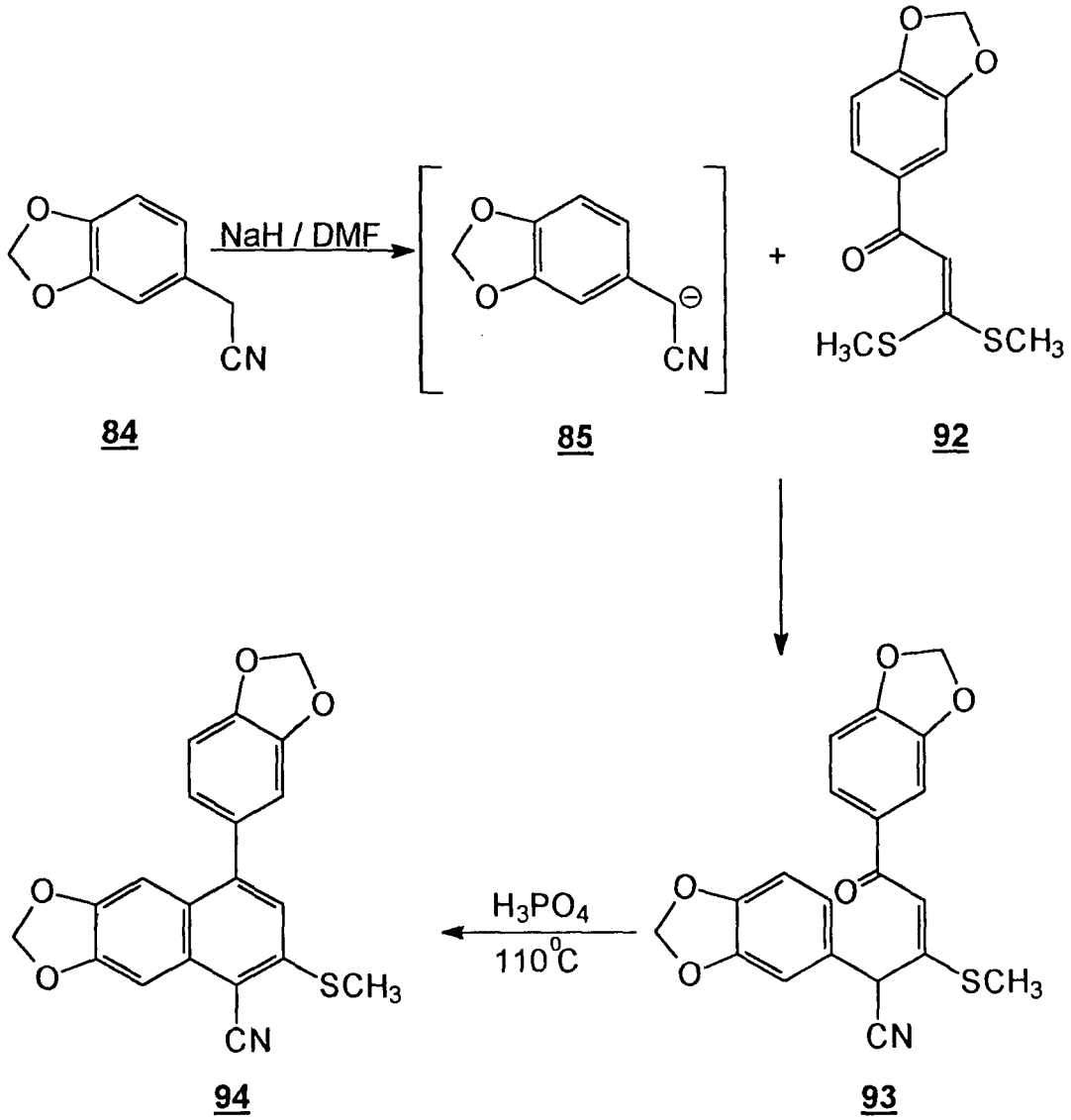
which were directly cyclised in the presence of ortho-phosphoric acid to afford the corresponding naphthalenes **88a,b** in 69-72 % yields. The structure of **88a,b** were established by its analytical and spectral data as mentioned in the experimental section (*Scheme-20*).

The methylenedioxyphenyl acetonitrile **84** was also reacted with tetralone mercaptal **89** to afford the corresponding open chain precursor **90** in excellent yield, which was directly cyclised to give the corresponding condensed



Scheme-21

naphthalene **91** product in 68% yield. The structure was established by its spectral and analytical data, which are mention in the experimental section (*Scheme-21*). Similarly, methylenedioxyphenyl acetonitrile anion **85** was reacted with **92** as described and cyclised earlier to afford the corresponding naphthalene **94** in 80%



Scheme-22

yield. The structure was confirmed by its spectral and analytical data (*scheme-22*).

III.C CONCLUSION:

In summary, we have demonstrated a new general method for the synthesis of naphthalenes based on easily accessible phenyl acetonitriles. The method is applicable to a wide variety of these starting materials.

It is shown that the reaction stops at 1,4-addition-elimination stage and open chain precursor can be easily cyclised in the presence of orthophosphoric acid. Many natural lignans contain this molecule which can now be easily prepared by aromatic annelation methodology.

III.D EXPERIMENTAL SECTION:

General:

Melting points were determined on a **Thomas Hoover** melting point apparatus. IR spectra were recorded on a **Perkin Elmer 983** Spectrophotometer. ^{1}H NMR (90 *MHz*) were recorded on **Varian EM-390** spectrometer. High resolution ^{1}H NMR (300*MHz*), ^{13}C NMR (76.7 *MHz*) spectra were recorded on **Bruker ACF- 300** spectrometer. The chemical shifts (*ppm*) and the coupling constants (*Hz*) are reported in the standard fashion with reference to tetramethylsilane as internal lock (for ^{1}H NMR) and the central line (76.9*ppm*) of $CDCl_3$ (for ^{13}C NMR). The

analytical data follows some of the appropriate abbreviations to explain the peak pattern like s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet br=broad. Mass spectra (MS) were measured on a **Jeol JMS-D 300** Mass spectrometer. Masses are reported in units of mass over charge (*m/z*), the molecular and base peaks are indicated by (M^+) and (%) respectively. Elemental analysis were carried out on a **Heraeus CHN-O**-Rapid analyzer.

All reactions were performed in oven dried (120^0C) glasswares under a dry argon/nitrogen atmosphere. Analytical thin layer chromatography (**TLC**) were performed on glass plates coated with **ACME's** silicagel and various combinations of ethylacetate-hexane, ethylacetate-benzene, benzene were used as eluents for monitoring the reactions.

Visualisation of spots was accomplished by exposure to iodine vapour or by potassium permanganate (acidic) solution. **ACME's** silica gel (60-120 mesh) is used for column chromatography and solvents were used after simple distillation of commercial grade. All solvent evaporation were done using a steam bath.

Chemicals and Reagents

Magnesium turnings (**SISCO**) were used for all Gringnard reactions which were carried out under an Argon/nitrogen atmosphere. Dry benzene[24a] was obtained by shaking with concentration H_2SO_4 followed by azeotropic distillation and stored

over sodium wire. Dry ether[24b] was obtained by keeping over $CaCl_2$ (fused) and stored over sodium wire. Dry dimethylformamide was obtained by distilling over CaH_2 under reduced pressure. Dry Tetrahedrofuran (THF) was obtained by distilling sodium benzophenone ketyl[25].

Starting materials:

Commercially available ketones: acetophenone, 4-methoxy acetophenone, acetone, ethyl methyl ketone, 2,4-pentene-dione, tetralone,[26a] 5,8-dimethoxy tetralone[26b] (m.p.58-62^{0}C) and 3,4-(methylenedioxy)benzaldehyde were used without purification. Raney-nickel (**W4**)[27] was prepared according to the reported procedure.

General procedure for the preparation of α-oxoketene dithioacetals[28] is described in the experimental section of Chapter II. All the ketene dithioacetals used for the present investigation were prepared using this procedure and characterized by physical and analytical spectral data.

General procedure for the preparation of α-dithioacetals from substituted benzaldehydes:

To a solution of methyl magnesium iodide (0.2 mol, prepared by reacting 0.2 mol of magnesium with methyl iodide in dry ether), appropriate benzaldehyde (0.2 mol) in dry THF was added under ice cold conditions. The resulting reaction

mixture was further stirred at room temperature for 2 to 3 hours (monitored by TLC) and then it was poured into aqueous saturated ammonia chloride solutions (2x100ml), extracted with chloroform (3x50ml), combined organic layer was washed with water, dried over anhydrous sodium sulfate and then solvent removed to give the crude alcohol.

To a solution of the above alcohol (0.05mol) in 300 ml of acetone, 51 ml of Jones reagent (prepared by adding concentrated sulfuric acid to chromic trioxide in water) was added with constant stirring keeping the temperature below 10°C and the reactions mixture stirred for one hour at room temperature. Excess of Jones reagent was then decomposed by adding 10 ml of methanol and the reaction mixture was poured into 200 ml of water. Extraction was carried out with ether (3x100ml) and the organic layer was washed with 5% $NaHCO_3$ solution, then with water (3x50ml), dried over anhydrous Na_2SO_4 and the solvent evapourated to give the crude ketone which could be purified by column chromatography.

These ketones were converted into α-oxoketene dithioacetals by following the standard procedure and their authencity could be ascertained by melting point, IR and NMR spectral data.

General Procedure for the preparation of substituted phenyl acetonitriles:

To a stirred solution of substituted benzaldehyde (0.1mol) in ethanol (50ml) was added sodium borohydride (0.3mol) at regular intervals of time by maintaining

the temperature below 5^0C and the mixture was further stirred at ambient temperature for two hours (monitored by TLC). Ehtanol was evaporated on water bath and extracted with chloroform, dried over sodium sulfate and solvent evaporated to give alcohol.

0.01mol of $SOCl_2$ and 1ml of pyridine were added to a solution of 0.01 mol benzyl alcohol in 20ml dry benzene and the mixture was stirred at room temperature for 45 minutes. It was then poured into cold water extracted with chloroform, organic layer dried over anhydrous Na_2SO_4 and the solvent evaporated to give crude benzyl chloride.

A mixture of crude benzyl chloride (0.01mol) and sodium cynide (0.03mol) in 15 ml DMF was stirred at room temperature for one hour (monitored by TLC) and then was poured over 100ml of water and extracted with benzene (3x50 ml),organic layer washed with water (4x50ml) and dried over Na_2SO_4. Evaporation of the solvent to give the crude nitrile which was purified by column chromatography (ethyl acetate + hexane, 1:9). The nitriles obtained by the above procedure could be confirmed by melting point, IR, NMR data.

General procedure for the reaction of substituted phenyl acetonitriles with α-oxoketene dithioacetals:

Phenyl acetonitrile (0.01mol) was added dropwise to an ice-cold and well stirred suspension of NaH (0.04mol) in dry benzene 15ml and 3 ml of DMF. The

reaction mixture was allowed to stir at ambient temperature for 45 minutes, when it attains brown colour. A solution of α-oxoketene dithioacetal (0.01mol) was added with stirring and cooling, and the reaction mixture was allowed to stir at room temperature for 5-6 hrs (monitor by TLC). The reaction mixture was poured over aqueous saturated NH_4Cl solution (250ml) and the aqueous layer was extracted with benzene (3x50ml) and combined benzene extracts were washed with water (4x50ml), dried over sodium sulphate and solvent evaporated to give the crude product which was purified by passing through silica gel column using hexane:ethylacetate (7:3) as eleuent. The carbinol acetals were characterized through melting points, ^1H NMR, IR and mass spectra analyser.

To the crude carbinol acetal (50mmol), orthophosphoric acid (75mmol) was added and the reaction mixture was stirred under reflux for 2-3 hrs. After the reaction was completed (monitored by TLC), it was cooled to room temperature and poured into ice cold saturated sodium bicarbonate solution (100ml) slowly, extracted with chloroform/benzene (3x25ml) and washed the organic layer with water (2x50ml), dried over Na_2SO_4 and concentrated to give the crude product which was chromatographed on silicagel using hexane and ethylacetate in the ratio of 9:1 as eluent. The structure of the product thus obtained were assigned on the basis of spectral and analytical data.

1-Cyano-2-methylthio-4- methylnaphthalene 70a:

Colourless crystals; Yield-63%; mp.132-133^{0}C (chloroform-hexane). IR (KBr): 1582, 2213, 2381, 2918 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3$): δ 2.32 (s, 3H, CH_3); 2.39 (s, 3H, SCH_3); 6.91 (s, 1H, ArH); 7.21 (t, 1H, ArH); 7.31 (t, 1H, ArH); 7.62 (d, 1H, ArH); 7.79 (d, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 16.10, 20.08, 116.36, 124.19, 124.74, 125.07, 126.53, 128.33, 130.02, 133.33, 140.70, 143.95. Anal. Calcd for: $C_{13}H_{11}NS$ (213.30) C, 73.20; H, 5.19; N, 6.56 %. Found: C, 73.30; H, 5.20; N, 6.57%.

1-Cyano-2-methylthio-3,4-dimethylnaphthalene 70b:

Light yellow crystalline; Yields-62%; mp.98^{0}C (Chloroform-hexane). IR (KBr): 1561, 1615, 2313, 2909, 2952 cm^{-1} . ^1H NMR (90 *MHz*; $CDCl_3$): δ 2.4 (s, 3H, CH_3); 2.7-2.8 (d, 6H, CH_3 and SCH_3); 7.6-7.7 (dd, 2H, ArH); 8.05- 8.3 (dd, 2H, ArH). Anal. Calcd for: $C_{14}H_{13}NS$ (227.33): C, 73.97; H, 5.76; N, 6.16%. Found: C, 74.07; H, 5.77; N, 6.17%.

1-Cyano-2-methylthio-4- phenylnaphthalene 70c:

White crystalline; Yields-75%; mp.175^{0}C (chloroform-hexane). IR (KBr): 1508, 1602, 2213, 2838, 2958 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3/CCl_4$): δ 2.67 (s, 3H, SCH_3); 7.34 (s, 1H, ArH); 7.42-7.51 (m, 6H, ArH); 7.62-7.67 (t, 1H, ArH); 7.80-

7.82 (d, 1H, ArH); 8.20- 8.23 (d, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 15.91, 124.06, 124.79, 126.44, 126.75, 128.21, 128.42, 128.77, 129.08, 129.49, 138.86. Anal. Calcd for : $C_{18}H_{13}NS$ (275.37); C, 78.51; H, 4.76; N, 5.08 %. Found: C, 78.62; H, 4.77; N, 5.09 %.

1-Cyano-2-methylthio-3,4-diphenylnaphthalene 70d:

Light Yellow crystalline; Yields-62%; mp.204^{0}C (chloroform-hexane). IR (KBr): 1438, 1482, 2211, cm^{-1}. ^1H NMR (300 *MHz*; $CCl_4/CDCl_3$): δ 2.31,(s, 3H, SCH_3) 7.0-7.02 (m, 4H, ArH); 7.13-7.24 (m, 6H, ArH); 7.42-7.63(m, 3H, ArH); 8.31-8.34 (d, 1H, ArH). ^{13}C NMR (75*MHz*; $CDCl_3$): 19.60, 115.02, 116.33, 125.14, 126.89, 127.10, 127.30, 127.42, 127.61, 127.65, 128.44, 130.19, 130.43, 131.77, 132.99, 137.59, 138.35, 141.56, 141.82, 143.79, 180.11. Anal.Calcd for $C_{24}H_{17}NS$ (351.47): C, 82.02; H, 4.87; N, 3.98 %. Found: C, 82.12; H, 4.88; N, 3.99 %.

1-Cyano-2-methylthio-4-(p-methylphenyl)naphthalene 70e:

Colourless crystals; Yield 65%; mp.133^{0}C(chloroform-hexane). IR (KBr): 1568, 2206, 2925,3032 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3$): δ 2.39 (s, 3H, CH_3); 2.40 (s, 3H, SCH_3); 7.27-7.29 (m, 7H, ArH); 7.76-7.79 (d, 2H, ArH). ^{13}C NMR (75*MHz*; $CDCl_3$): 15.45, 21.56, 111.35, 117.57, 128.18, 128.37, 128.77, 128.85, 129.47,

132.86, 133.78, 144.99, 153.27, 194.05. Anal. Calcd for $C_{19}H_{15}NS$ (289.40): C, 78.85, H, 5.22, N, 4.84%. Found: C, 78.96, H, 5.23, N, 4.85%.

3[(2-Cyano-2-phenyl-1-methylthio)ethenyl]-2,4-pentanedione 72:

Light Yellow crystalline; Yields-76%; mp.124^{0}C (chloroform-hexane). IR (KBr): 1420, 1568, 1817, 2193, 2999 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3$): δ 2.12 (s, 3H, CH_3); 2.14 - 2.23 (d, 6H, CH_3 and SCH_3); 7.41-7.56 (m, 5H, ArH); 6.67 (s, 1H, OH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 15.42, 22.86, 30.60, 53.02, 109.84, 112.17, 117.32, 128.55, 128.62, 129.01, 132.69, 154.06, 172.06, 190.31. Anal. Calcd for $C_{15}H_{15}O_2NS$ (259.35): C, 69.47; H, 5.83; N, 5.40%. Found: C, 69.56; H, 5.84; N, 5.41%.

1-Cyano-2-methylthio-4-p-methoxy phenyl-6-methoxy naphthalene 78a:

Yellow coloured solid;Yield-72%; mp.133-135^{0}C(chloroform-hexane). IR (KBr): 1575, 1615, 1709, 2932 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3/CCl_4$): δ 2.44, (s, 3H, SCH_3); 3.83 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 6.6 (s, 1H, ArH); 6.95- 6.98 (m, 4H, ArH), 7.3 (d, 2H, ArH); 7.80-7.83 (d, 2H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 15.05, 55.10, 55.36, 97.25, 108.4, 113.93, 114.36, 123.88, 125.04, 127.42, 131.36, 132.08, 139.07, 160.5, 163.03. Anal. Calcd for : $C_{20}H_{16}O_2NS$ (335.42): C, 71.62; H, 5.11; N, 4.17%. Found: C, 71.70; H, 5.12; N, 4.18%.

1-Cyano-2-methylthio-4-phenyl-6-p-methoxy naphthalene 78b:

Light yellow crystalline; Yields-63%; mp.158^{0}C (chloroform-hexane). IR (KBr): 1605, 2249, 2260, 2910, 2942 cm^{-1}. ^1H NMR (90*MHz*; $CDCl_3/CCl_4$): δ 2.4 (s, 3H, SCH_3); 3.8 (s, 3H, OCH_3); 6.6-6.7 (d, 1H, ArH), 6.9-7.1 (d, 1H, ArH); 7.4-7.7 (m, 5H, ArH); 7.8-8.0 (d, 1H, ArH). Anal. Calcd for $C_{19}H_{15}ONS$ (305.40): C, 74.42; H, 4.95; N, 4.59%. Found: C, 74.82; H, 4.96; N. 4.60%.

1-Cyano-2-methylthio-4-[(3',4'-methelenedioxy)phenyl]-6,7-dimethoxy naphthalene 83:

White crystals; Yields-72%; mp.218-220^{0}C (chloroform-hexane). IR (KBr): 1616, 2186, 2205, 2924, 3013 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3/CCl_4$): δ 2.63 (s, 3H, SCH_3); 3.83 (s, 3H, OCH_3); 4.06 (s, 3H, OCH_3); 6.07 (s, 2H, CH_2); 6.92 (s, 3H, ArH); 7.13-7.16 (d, 2H, ArH); 7.39 (s, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 16.38, 55.62, 55.91, 101.22, 103.48, 105.18, 106.03, 108.40, 109.75, 116.34, 122.87, 123.26, 124.89, 130.65, 133.11, 140.51, 143.15, 147.62, 147.86, 149.79, 151.83. Mass (*m/z*; %): 379 (M^+; 100%). Anal. Calcd for $C_{21}H_{17}O_4NS$ (379.43): C, 66.48; H, 4.52; N. 3.69%. Found: C, 66.55; H, 4.53; N. 3.7%.

1-Cyano-2-methylthio-4-(*p*-methoxyphenyl)-6,7-(methylenedioxy)naphthalene 88a:

Light yellow crystals; yields-72%; mp-160-162^{0}C(chloroform-hexane). IR: (KBr): 1637, 1996, 2211, 2915 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3$): δ 2.61 (s, 3H, SCH_3); 3.89 (s, 3H, OCH_3); 6.06 (s, 2H, CH_2); 7.02-7.05 (d, 2H, ArH); 7.12 (s, 1H, ArH); 7.18 (s, 1H, ArH); 7.32-7.35 (d, 2H, ArH); 7.49 (s, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 15.36, 55.42, 101.50, 101.87, 103.26, 114.10, 116.54, 123.46, 126.71, 130.66, 131.66, 132.21, 141.16, 144.23, 148.31, 150.15, 159.72. Mass (*m/z*; %): 349 (M^+;100%). Anal. Calcd for $C_{20}H_{15}O_3NS$ (349.12); C, 68.74; H, 4.33; N, 4.01%. Found: C, 68.76; H, 4.33; N, 4.01%.

1-Cyano-2-methylthio-4-phenyl-6,7-(methylenedioxy)naphthalene 88b:

Light yellow crystalline;Yields-69%; mp.180^{0}C (chloroform- hexane). IR (KBr): 1612, 1709, 1994, 2218, 2917 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3/CCl_4$): δ 2.62 (s, 3H, SCH_3); 6.07 (s, 2H, CH_2); 7.06 (s, 1H, ArH); 7.18 (s, 1H, ArH); 7.32 (s, 1H, ArH); 7.37-7.40 (m, 2H, ArH); 7.45-7.53 (m, 3H, ArH). Mass (*m/z*; %): 319 (M^+; 100%). Anal. Calcd for $C_{19}H_{13}O_2NS$ (319.38): C, 71.45; H, 4.10; N, 4.38%. Found: C, 71.53; H, 4.11; N, 4.39%.

5-Cyano-7,8-dihydro-2,3-methylenedioxy-6-(methylthio)benzo[*a*]-phenanthrene 91:

Light Yellow crystalline; Yields-68%; mp.170-171^{0}C (chloroform-hexane). IR (KBr) : 1636, 2217, 2902, 2916 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3$/ CCl_4): δ 2.51

(s, 3H, SCH_3); 2.77-2.81 (t, 2H, CH_2); 3.17 (Br, 2H, CH_2); 6.11 (s, 2H, CH_2); 7.24-7.36 (m, 3H, ArH), 7.59 (s, 1H, ArH); 7.68-7.73 (m, 2H, ArH). ^{13}C NMR (75*MHz*; $CDCl_3/CCl_4$): 13.35, 27.65, 29.18, 101.42, 102.36, 102.87, 114.54, 116.62, 125.97, 126.75, 127.50, 128.12, 128.86, 131.54, 133.14, 136.71, 136.93, 138.28, 139.86, 149.05. Mass (*m/z*; %): 345 (M^+; 100%). Anal. Calcd for: $C_{21}H_{15}ONS$ (345.42): C, 73.02; H, 4.37; N, 4.06%. *Found*: C, 73.11; H, 4.38; N, 4.07%.

1-Cyano-2-methylthio-4-(3',4'-methylenedioxy)phenyl-6,7-(methylenedioxy) naphthalene 94:

Light yellow cyrstals; yields-80%; mp.200-202^{0}C(chloroform-hexane). IR (KBr): 1536, 1553, 1611, 2206, 2921 cm^{-1}. ^1H NMR (90*MHz*; $CDCl_3/CCl_4$): δ 2.6 (s, 3H, SCH_3); 6.1-6.2 (Br, 4H, CH_2); 6.9 (s, 3H, ArH); 7.1-7.3 (m, 2H, ArH); 7.5-7.6 (d, 1H, ArH). Mass (*m/z*; %): 363 (M^+; 38%). Anal. Calcd for $C_{20}H_{13}O_4NS$ (363.09): C, 66.09; H, 3.60; N, 3.85%. Found: C,67.12; H, 3.55; N, 3.87%.

1,4-Dimethoxy-5,6-dihydro-7-methylthio-8-cyano-10,11-(methylenedioxy) naphthalene 97:

Light yellow crystalline; Yields-58%; mp.168^{0}C (chloroform-hexane). IR (KBr): 1676, 2247, 2744, 2831, 3133 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 2.1-2.3 (Br, 4H, $(CH_2)_2$); 2.5-3.0 (Br, 5H, SCH_3 and CH_2); 3.7- 3.9 (s, 6H, $(OCH_3)_2$); 6.7-7.3 (m,

4H, ArH). Anal. Calcd. for $C_{23}H_{19}O_4NS$ (405.47): C, 68.13; H, 4.72; N, 3.45%. Found: C, 68.21; H, 4.73; N, 3.46%.

General procedure for dethiomethylation:

To a stirred solution of methylthio naphthalene (2.5mol) in ethanol (25ml) was added Raney Nickel (**W4**, 3 times by weight) and the mixture was stirred at ambient temperature for 6-8 hrs (monitored by **TLC**). The reaction mixture was filtered through **G-3** cintered funnel and the residue was washed with ethanol (3x10ml). The bulk of the ethanol was distilled off and chloroform (20ml) was added. The solution was washed with water (2x25ml), dried over Na_2SO_4 and evapourated. Analytically pure compounds were obtained by passing through a short length silicagel column using hexane as eluent.

1-(Diethylaminomethyl)-4-(p-methoxyphenyl)-6,7-methylenedioxynaphthalene 98a:

Colourless crystalline; Yield-71%; mp.106^{0}C (chloroform-hexane). IR (KBr): 1456, 1532, 2346, 2945, 3398 cm^{-1}. ^1H NMR (300*MHz*; $CDCl_3$): δ 1.08-1.12 (t, 6H, $(CH_3)_2$); 2.60-2.63 (q, 4H, $(CH2)_2$); 3.87 (s, 5H, OCH_3 and CH_2); 5.99 (s, 2H, CH_2); 7.05 (d, 2H, ArH), 7.18-7.33 (m, 5H, ArH); 7.76 (s, 1H, ArH). ^{13}C NMR (75*MHz*; $CDCl_3$): 11.27, 29.66, 46.59, 55.20, 56.75, 96.09, 100.83, 101.76, 102. 83,113.90, 124.82, 125.74, 129.34, 130.71, 133.71, 135.19, 138.77, 147.04,

158.74. Anal. Calcd for: $C_{23}H_{25}O_2N$(363.45): C, 76.01; H, 6.93, N, 3.85%. Found: C, 76.10; H, 6.94; N, 3.86%.

1-(Diethylaminomethyl)-4-phenyl-6,7-methylenedioxynaphthalene 98b:

Colourless crystalline; Yield-67%; mp.101^{0}C (chloroform-hexane). IR(KBr): 1467, 1575, 2797, 2958, 3422 cm^{-1}. ^1H NMR (300 *MHz*; $CDCl_3/CCl_4$) : δ 1.06-1.12 (t, 6H, $(CH_3)_2$); 2.57-2.64 (q, 4H, $(CH_2)_2$); 3.89 (s, 2H, CH_2); 5.98 (s, 2H, CH_2); 7.17-7.44 (Br, 8H, ArH); 7.79 (s, 1H, ArH); 7.79 (s, 1H, ArH). ^{13}C NMR (75 *MHz*; $CDCl_3$): 11.35, 46.66, 56.86, 100.95, 101.76, 102.80, 124.93, 125.65, 127.05, 128.24, 129.12, 129.99, 134.09, 139.05, 141.42, 147.09, 147.26. Anal. Calcd for : $C_{22}H_{23}O_2N$ (333.43): C,79.25; H,6.95; N,4.20%. Found: C, 79.35, H, 6.96, N, 4.21 %.

III. E REFERENCES AND NOTES:

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CHAPTER-IV

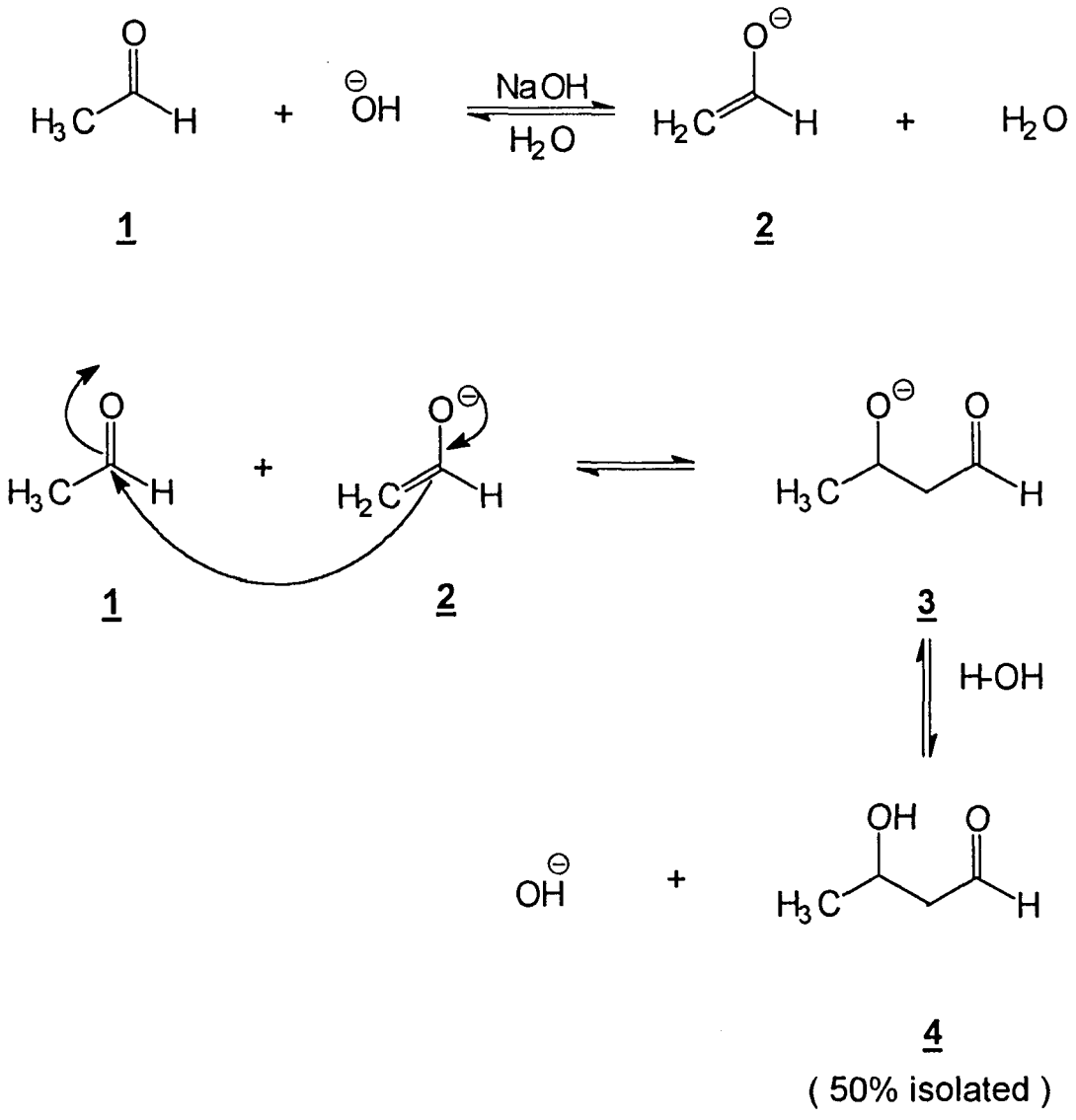
IODIDE ION INDUCED CONDENSATION OF CHLOROMERCURI -ACETALDEHYDE WITH CARBONDISULPHIDE AND AROMATIC ALDEHYDES : A NEW GENERAL SYNTHESIS OF β, β-BIS(METHYL THIO)ACROLEIN AND CINNAMALDEHYDES

IV.A INTRODUCTION:

***A brief review on Aldol condensation and related reactions*:**

Addition of enolate anions to carbonyl group constitutes an important carbon-carbon bond formation reaction generally known as Aldol condensation[1a]. Generally, when two aldehyde molecules undergo aldol condensation in the presence of a base, one of the aldehyde molecules **1** undergoes deprotonation to yield the corresponding enolate anion **2** which spontaneously attacks the carbonyl

carbon of the other aldehyde to afford the corresponding Aldol 4 in 50% yield after acidification. Thus in overall reaction, the proton-abstraction step is generally considered as the rate determining step[2-6](*Scheme-1*).



Scheme-1

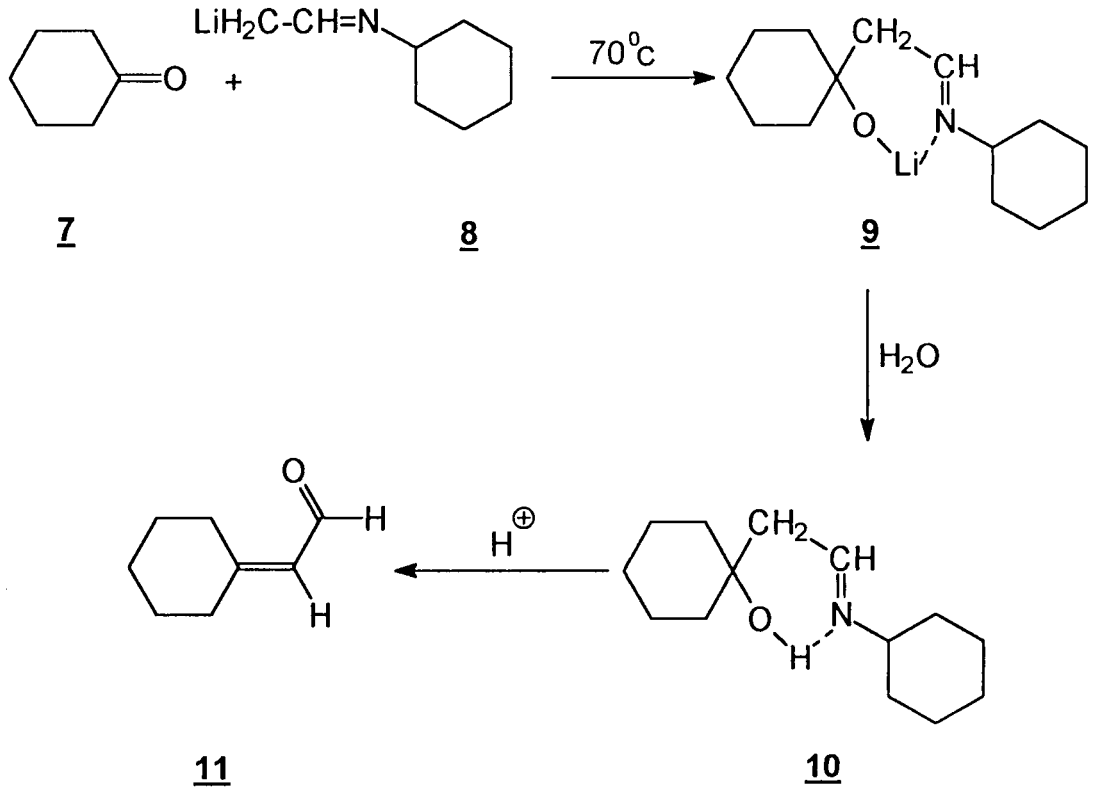
Many variations of Aldol condensation involving base-catalysed addition of enolate anion of one component to an aldehyde or ketone as the carbonyl component have been reported in the literature. For example, Knoevenagel reaction, Perkin reaction, Darzens condensation, Wittig reaction etc. fall under general Aldol condensation categories.

THE SCOPE OF ALDOL CONDENSATION:

When two molecules of same aldehyde such as acetaldehyde etc. are taking part in Aldol reaction, the reaction is quite feasible allowing conversion of many aldehydes to the corresponding aldols. The best catalysts employed in this reaction are a variety of organic bases and basic ion exchange resins. On the other hand if the condensation is taking place between two ketones, the equilibrium lies to the left and the reaction is feasible only if the equilibrium can be shifted. In most general cases the condensation between different aldehydes is also possible, if one of the aldehydes does not contain α-hydrogen, like aromatic aldehydes. Only the crossed product is the major compound formed in these reactions. This type of crossed aldol condensations are called Claisen Schmidt reaction[8-10]. Similarly, condensation between an aromatic aldehyde and an aromatic or aliphatic ketone are among the most popular Aldol reactions known in the literature.

In many reactions, Aldol condensations are employed for the preparation of α,β-

unsaturated aldehydes. The classical reaction is based on the Aldol condensation if the intermediate aldols contain an α-hydrogen atom, which are readily dehydrated to give the corresponding olefins. However, high yields of self condensation reaction products become prominent in these reactions. Thus the best way to condense two different aldehydes or carbonyl compounds is to involve what is known as directed Aldol condensation[11] which generally eliminates self condensation products. Ketones are also used in the directed Aldol condensation. For example, protected acetaldehydecyclohexylimine is deprotonated by

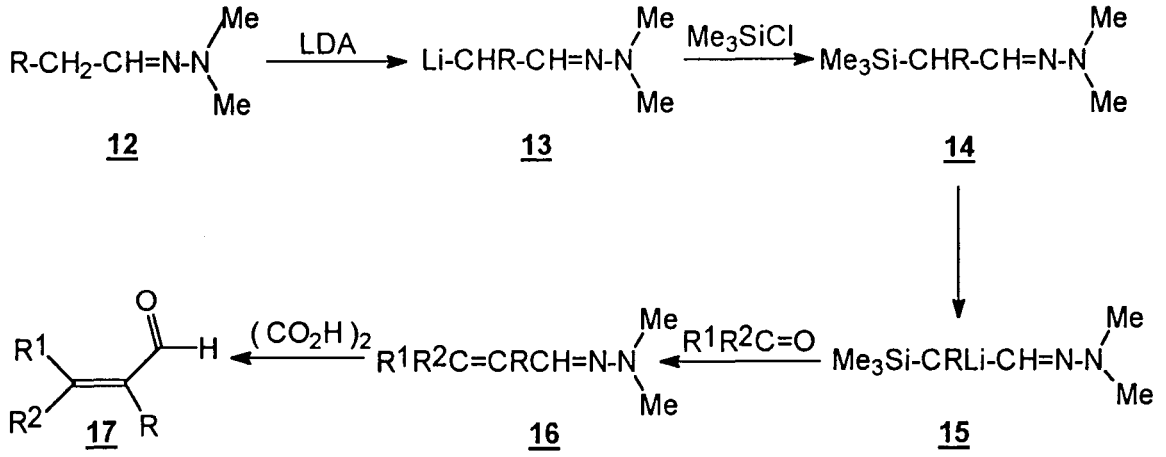


7 8 9 10 11

Scheme-2

metallation to afford the corresponding lithio derivatives **8** which generally attacks more electrophilic cyclohexanone carbonyl group to afford the corresponding intermolecular aldol **10** followed by dehydration and hydrolysis simultaneously to afford the condensation product **11** (*Scheme-2*).

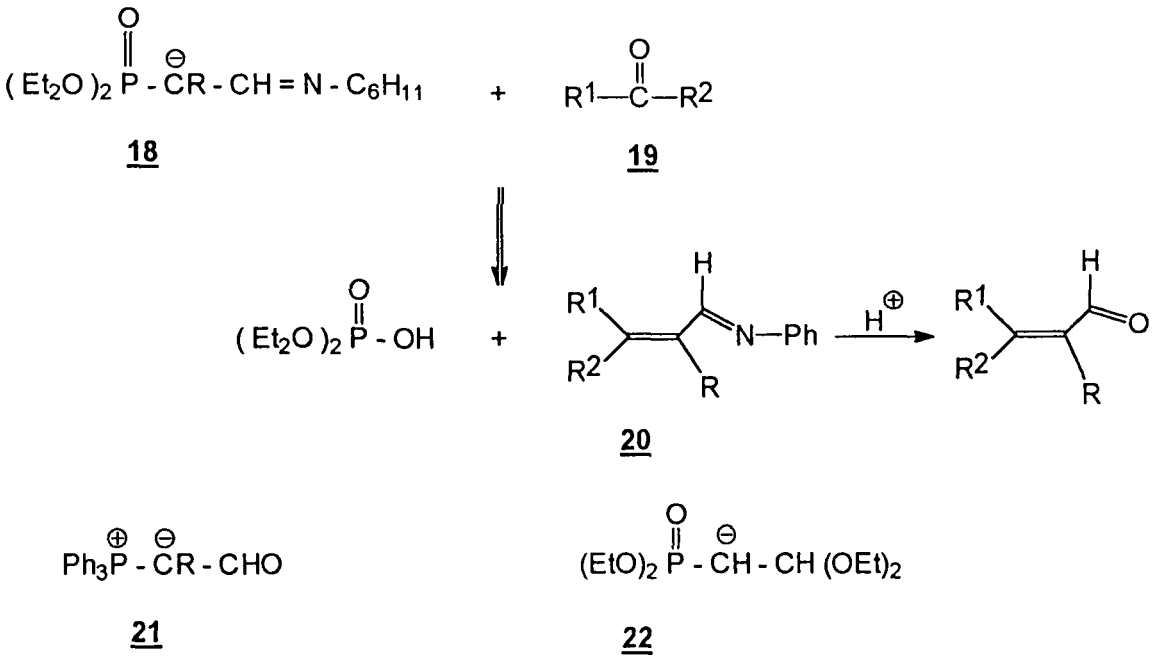
Many variations of directed Aldol condensations have thus been developed in the recent years which are used successfully in complex synthetic programms. The other variation includes a ketone or an aldehyde which can be condensed with silyl aldimine or silyl dimethyl-hydrazone to give a product which can be easily which can be easily transformed into α,β-unsaturated olefinic aldehyde **17**[12](*Scheme-3*).



Scheme-3

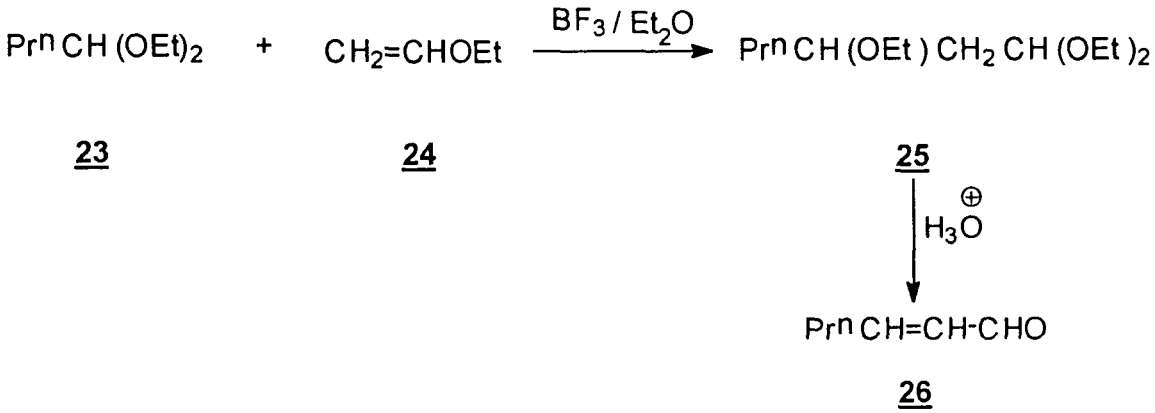
Similarly, carbonyl carbon atom of an aldehyde or ketone can also be transformed into α,β-unsaturated olefinic aldehyde by means of the phosphonate anion **18**[13].

The other phosphorous ylides employed for the synthesis of ene-aldehydes are **21**[14] and**22**[15](*Scheme-4*).



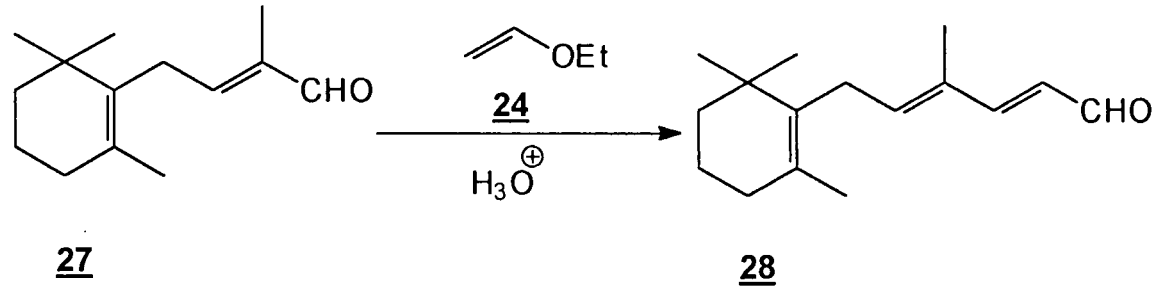
Scheme-4

The α,β-unsaturated aldehyde **26**[16] can also be prepared by directly reacting vinyl ethers with aldehyde acetals in the presence of $BF_3.Et_2O$ as depicted in *Scheme-5*.



Scheme-5

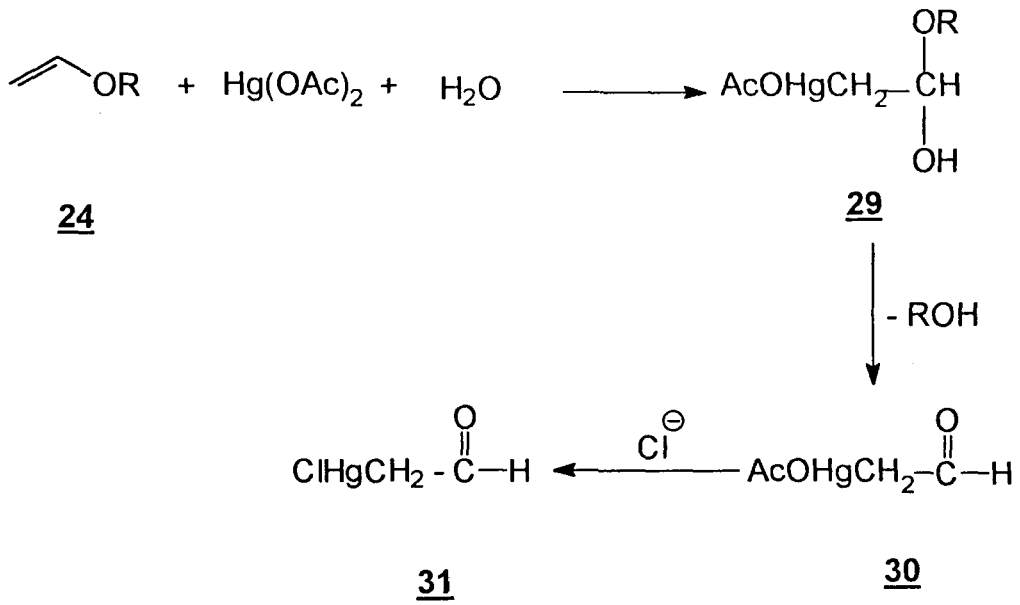
This method is applicable for the synthesis of olefinic aldehyde like carotenoid and vitamin A **28**[17] as shown in *scheme-6*.



27 **28**

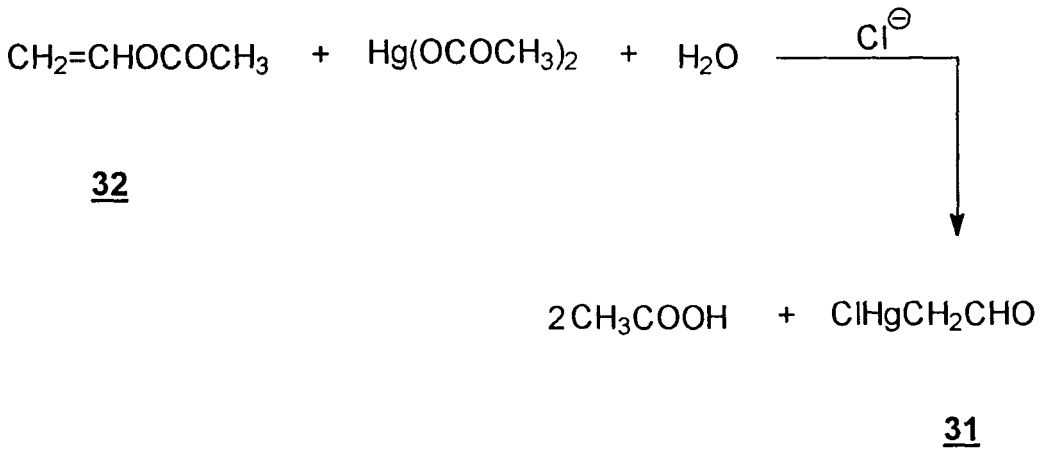
Scheme-6

During the course of our studies on new synthetic methods for polyene aldehydes[31a,b] and ester[32], we considered of interest to investigate condensation of chloromercuriacetaldehyde (a stable compound obtained by reaction of vinyl ester with mercuric acetate or mercuric chloride) with various aldehydes to give ene-aldehydes. Our literature survey revealed that Nesmeyanov and coworkers[18] have reacted vinylethers with mercuric acetate or mercuric chloride in aqueous medium to give double bond addition product **29** obeying Markovnikov's rule. The product **29** eliminates the elements of alcohol and forms a solution of acetoxymercuriacetaldehyde **30** which precipitates with chloride readily to afford the corresponding solid chloromercuriacetaldehyde **31** (*Scheme-7*).



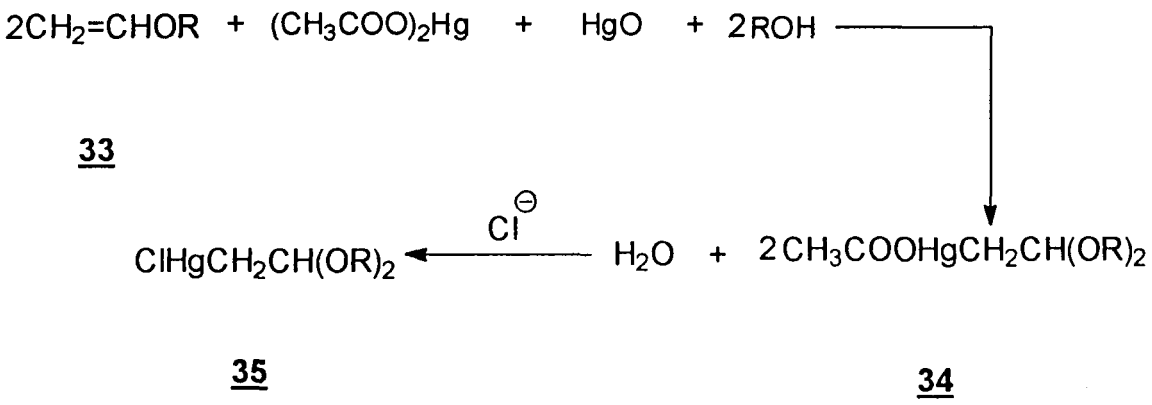
Scheme-7

Similarly, the chloromercuriacetaldehyde **31** has also been prepared from vinyl acetate **32**[19,20] under identical condition in quantitative yields as formulated in *Scheme-8*.



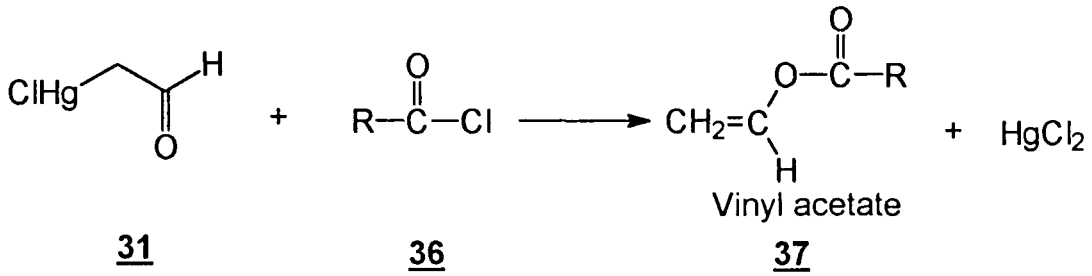
Scheme-8

Nesmeyanov etal. have also reacted vinylether **33** with mercuric acetate in the presence of alcohols and mercuric oxide to afford the corresponding chloromercuriacetaldehyde acetals **35**[21,22] which can also be transformed into chloromercuriacetaldehyde **31** (*Scheme-9*).



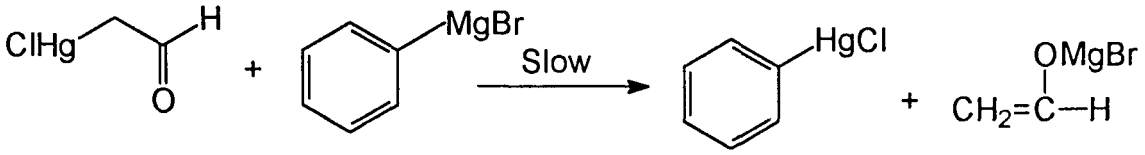
Scheme-9

The reaction of chloromercuri-acetaldehyde **31** as enolate equivalent has also been investigated by the same workers.Thus chloromercuriacetaldehyde **31** has been reacted with alkyl or aryl acid chlorides **36** to afford the corresponding vinyl acetates **37**[19] in 40-56% overall yields (*Scheme-10*).



Scheme-10

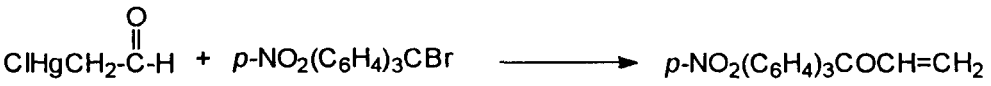
Chloromercuriacetaldehyde **31** has also been reacted with benzylmagnesium bromide to afford the corresponding acetaldehyde enolate magnesium bromide **40**[25] (*Scheme-11*).



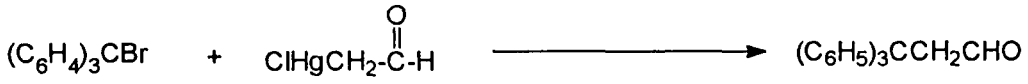
31 **38** **39** **40**

Scheme-11

Similarly, tri(*p*-nitrophenyl)bromomethane reacts with chloromercuriacetaldehyde to obtain tri(*p*-nitrophenyl)methylvinyl ether **42**. This reaction is a convenient method for the synthesis of vinylether of tri(*p*-nitrophenyl)methylvinyl ether **42**[19]. However, triphenyl bromomethane **43** when reacted with chloromercuri-



31 **41** **42**



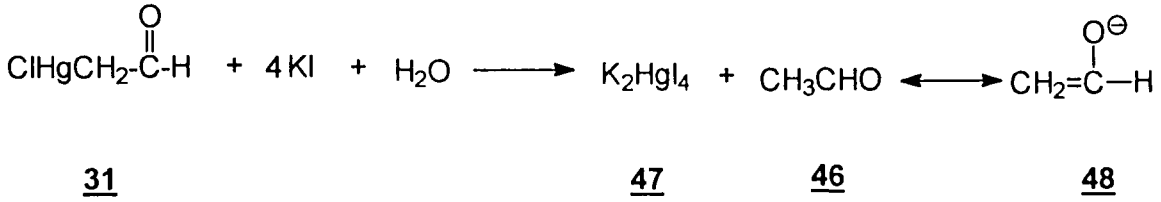
43 **31** **44**

Scheme-12

acetaldehyde **31**, the corresponding triphenyl methyl acetaldehyde **44**[26](*Scheme-12*) was obtained in excellent yields. The reaction represent ambident nucleophilic reactivity of chloromercuriacetaldehyde **31**with halides.

IV. B RESULTS AND DICUSSION:

In the preceding section we have described some prominent examples of directed aldol condensation and some reactions of vinyl ether with mercuric chloride to afford the corresponding chloromercuriacetaldehyde **31**. It was contemplated that this molecule should be a potential source of acetaldehyde anion *via* carbon mercury bond cleavage in the presence of potassium iodide[27] to afford the required acetaldehyde enolate **48** (*Scheme-13*) which is free to react with any electrophile that may be incorporated into the reaction mixture.

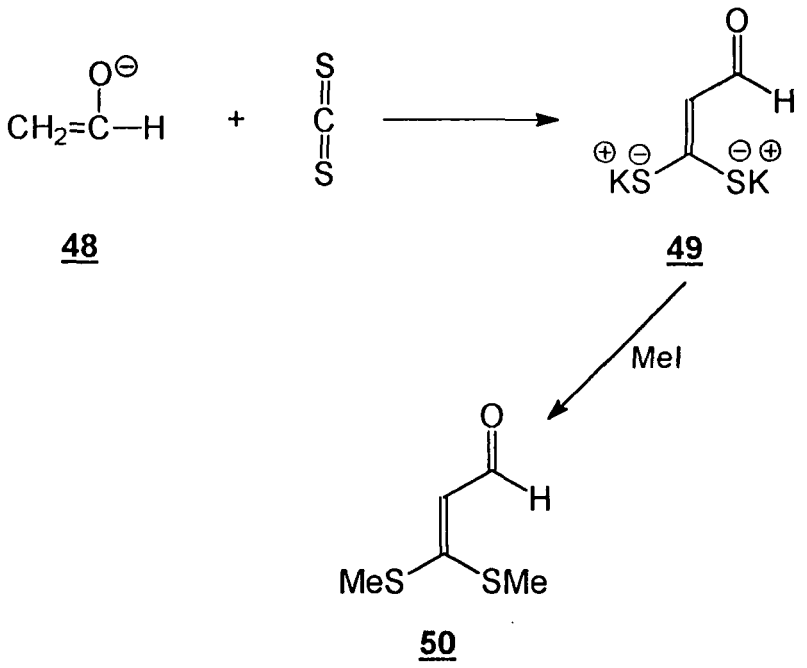


Scheme-13

a. Reaction of chloromercuriacetaldehyde with carbondisulphide: Synthesis of β,β-bis(methylthio)acrolein

If the reaction is carried out in the presence of carbon disulphide it is possible toprepare the corresponding α-oxoketene dithioacetal **50** through this route. We

have indeed achieved this new method of synthesis of **50** and other reactions of directed indeed achieved this new method of synthesis of **50** and other reactions of directed Aldol condensation of this anion **48** which are described in this section as shown in *Scheme-14*.

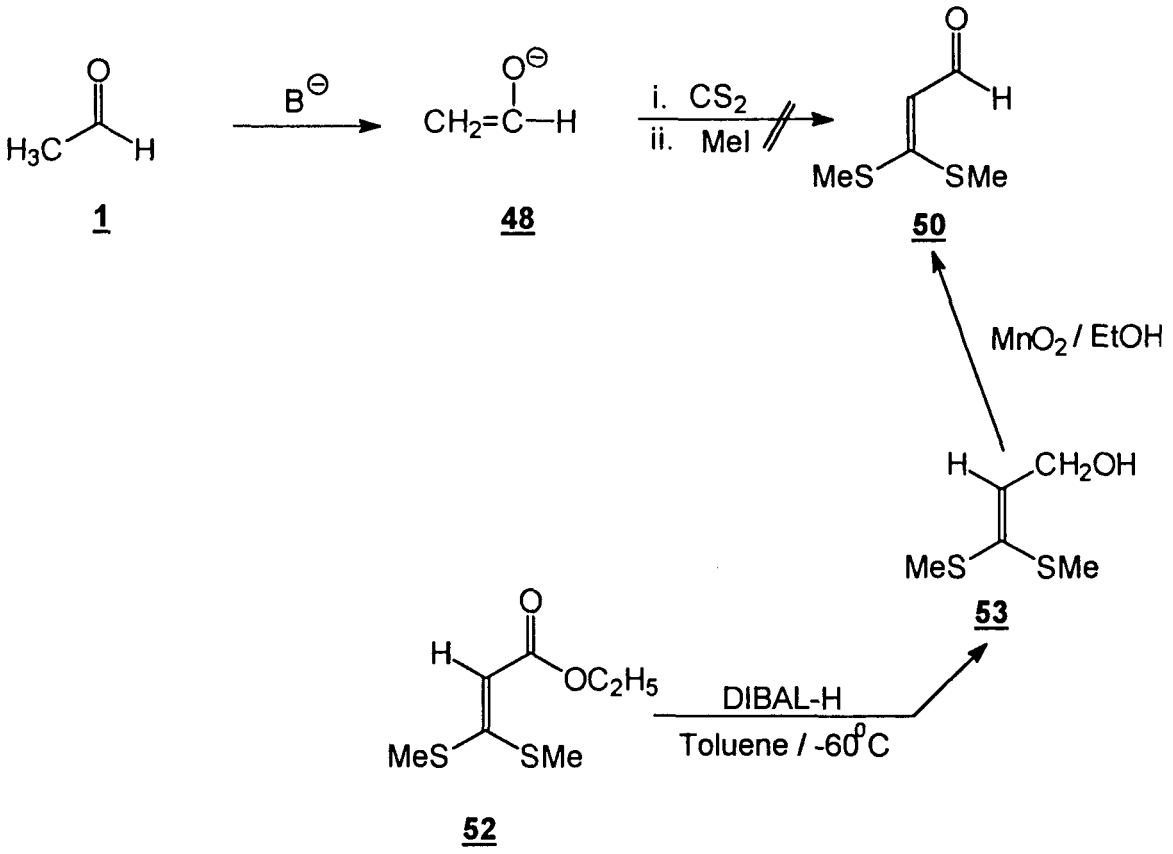


48 **49** **50**

Scheme-14

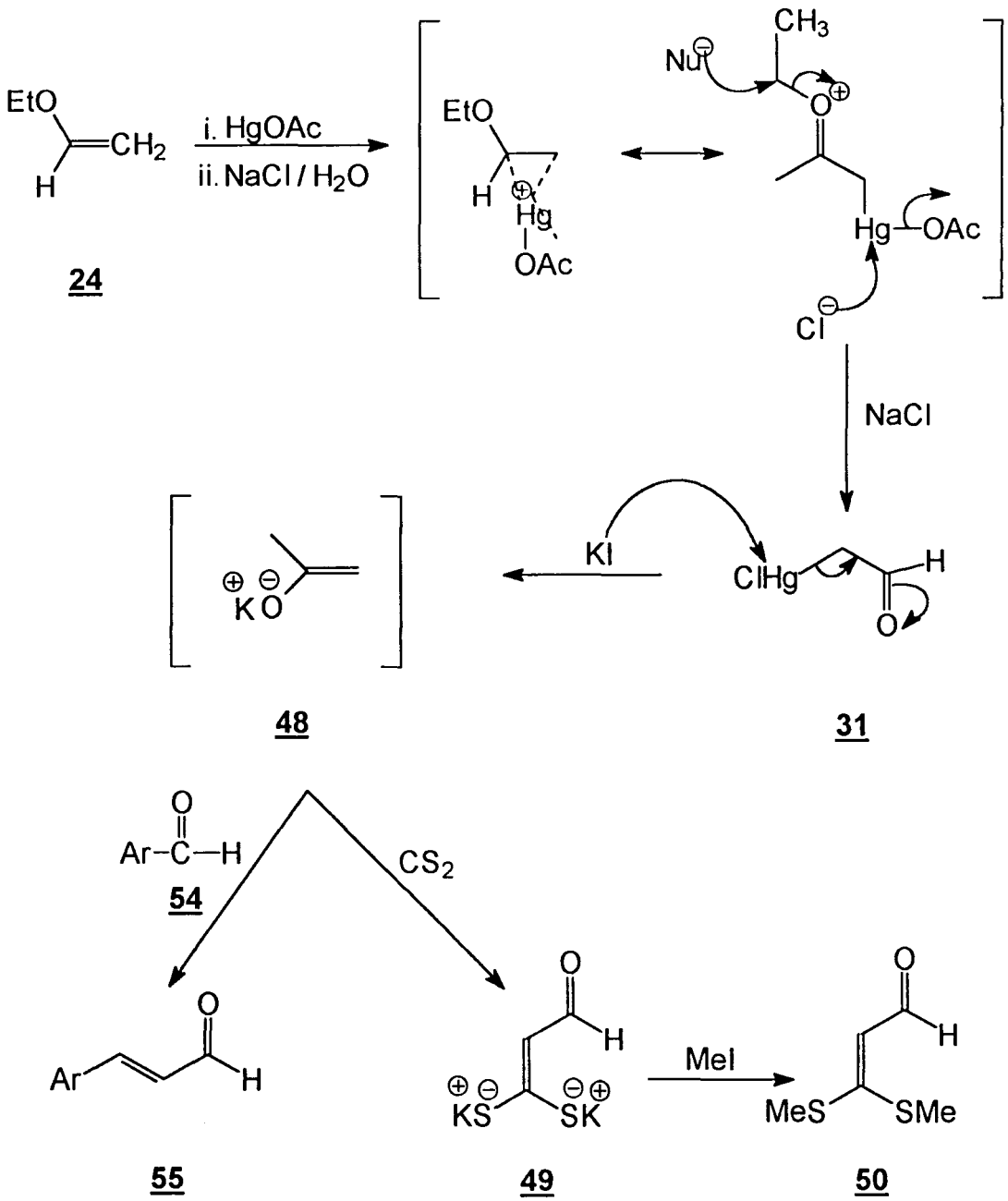
The acetaldehyde mercaptal **50** has been known in the literature involving multi-step operation. Dieter and coworkers[28] first reported the synthesis of **50** as formulated in *Scheme-15*.

Thus mercaptal from β-ketoester was treated with sodium ethoxide at room temperature to knock off the acetyl group to afford the corresponding ethyl 3,3-bis(methylthio)propenoate **52** which was reduced with diisobutylaluminum hydride to yield the corresponding 3,3-bis(methylthio)-2-propen-1-ol **53**. The alcohol was then subjected to manganese dioxide oxidation to afford the corresponding 3,3-bis(methylthio)propenal **50**.



Scheme-15

We have achieved the synthesis of 3,3- bis(methylthio)propenal **50** in one pot by a better way of trapping the enolate anion **48** with carbondisulphide followed by alkylation (*Scheme-16*). The possible mechanism governing the formation of enolate anion **48** is depicted in *Scheme-16*. The vinylethyl ether **24** is known to react with mercuric chloroacetate in the presence of sodium chloride to afford the corresponding mercuriacetaldehyde **31** in excellent yields. This is further reacted with potassium iodide, when the mercury carbon bond is broken to afford the corresponding acetaldehyde enolate **48** which has been trapped with carbon disulphide, to afford the corresponding dithioate **49** followed by alkylation to yield the mercaptal 50%. In a typical experiment, the anion **48** was generated in the presence of carbon disulphide using dimethylformamide as aprotic solvent. The reaction mixture was dipped into oil bath at 90°C when the bulky mercury chloroacetaldehyde spontaneously decomposed **49** to enolate and reacted with carbon disulphide to yield the corresponding potassium salt **49** which was *insitu* alkylated with methyl iodide to afford the corresponding acetaldehyde mercaptal **50** in 40 % yield. The structure of **50** was fully confirmed by its analytical data which is given as follows.


EtO
CH2
H
i. HgOAc
ii. NaCl / H2O
24
EtO
H
Hg
OAc
Nu
CH3
O
Hg
OAc
Cl
NaCl
KI
ClHg
H
O
K O
48
31
Ar–C–H
O
54
CS2
Ar
O
H
55
KS
SK
O
H
49
MeI
MeS
SMe
O
H
50

Scheme-16

3,3-Bis(methylthio) propenal 50:

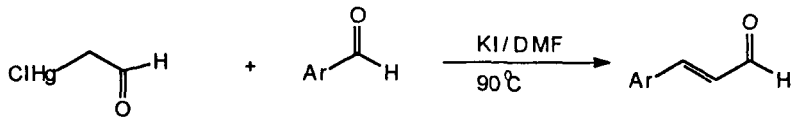
Viscous liquid; yield- 40 % (chloroform-hexane). IR (CCl_4): 1650, 2740, 2830, 2940, 3012 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 2.45 (s, 3H, SCH_3); 2.57 (s, 3H, SCH_3); 6.10 (d, 1H, CH); 9.6 (d, 1H, CHO). ^{13}C NMR (300MHz; CCl_4): 16.45, 16.67, 121.1, 167. 6, 186.8. Anal. Calcd .for $C_5H_8OS_2$ (148.25): C, 40.5; H, 5.44; O, 10.79 %. Found: C, 40.58; H, 5.45; O, 10.81%.

The reaction of chloromercuriacetaldehyde **31** with various aromatic aldehydes in the presence of potassium iodide to give cinnamaldehydes is described in this section.

b. **Reaction of chloromercuriacetaldehyde with aromatic aldehydes: Synthesis of cinnamaldehydes**.

In a typical experiment, one equivalent chloromercuriacetaldehyde **31** was treated with potassium iodide in the presence of benzaldehyde **54a** at 70°C. The reaction mixture after work up yielded the corresponding cinnamaldehyde **55a** in 85% yield. The structure of cinnamaldehyde was confirmed by superimposeable IR and comparison with data from literature. In a series of experiments, it was examined to see the different iodides and different solvents in terms of yields. It may be noted that yields were not high if solvents other than DMF were used (see ***table-1***). Similarly, potassium iodide salt is better than lithium iodide to improve the yields.

Therefore, the best yields were obtained in potassium iodide as a salt and dimethyl formamide as solvent. In all other subsequent reactions, the optimised reaction condition using dimethyl formamide and potassium iodide were used.

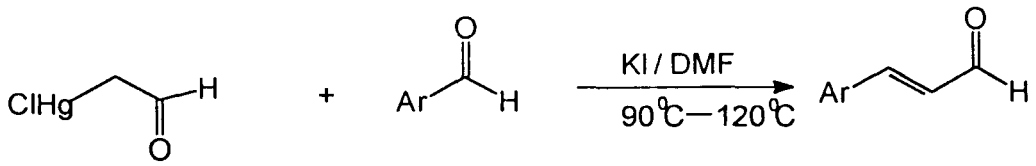


31 **54** **55**

Salts	Solvent	% Yields
LiI	MeCN	38
LiI	DMSO	45
LiI	DMF	40
KI	DMSO	70
KI	DMF	85
KI	MeCN	62

Table-1

Under similar reaction condition various aldehydes **54b-j** were reacted with **31** to afford the corresponding ene-aldehydes[29] **55b-j** in 60-90% overall yields (see *Table-2-4*).The ene-aldehydes thus obtained have their spectral and analytical data identical with those described in literature. The reaction was then extended to ketones. For example when acetone **54k** was treated with **31** under the same reaction condition, crotonaldehyde **55k** was obtained in 65% yield. The



31 54 55

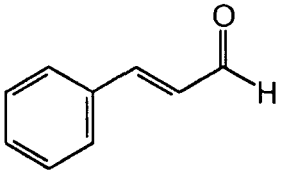
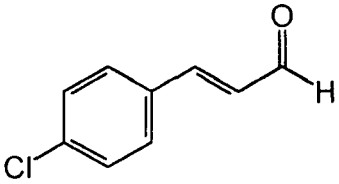
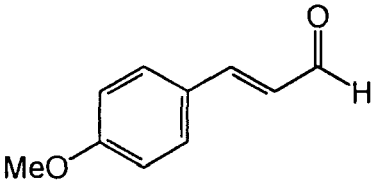
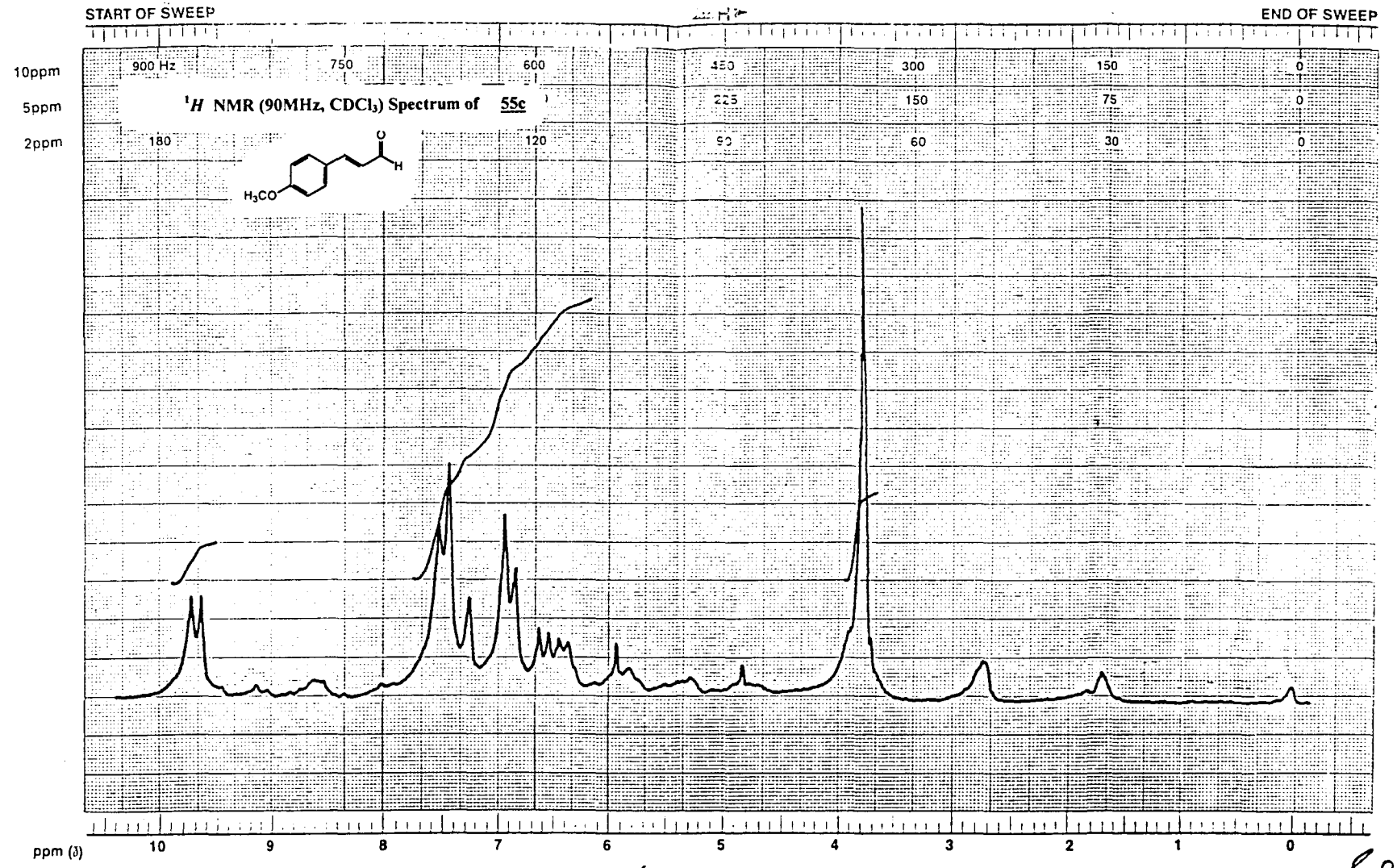
S. No.	Ar	Products	% Yield
54a	Ph	 55a	85
54b	p-Cl C_6H_4	 55b	80
54c	p-OMe C_6H_4	 55c	60

Table-2



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DECOUPLE POS. _____ ppm
DECOUPLING POWER _____ mG

SPECTRUM AMPL. 10
FILTER 0.1 sec
RF POWER 0.1 mG

SWEEP TIME 5 min
SWEEP WIDTH 10 ppm
END OF SWEEP _____ ppm

NUCLEUS _____
ZERO REF. _____
SAMPLE TEMP. _____ °C

SAMPLE : KK-200
SIGNAL IN THE OFFSET YES/NO
SOLEVNT : $CDCl_3$

OPERATOR _____
DATE 16.10.92
SPECTRUM NO. _____

OFFSET RECORDED FROM _____ TO _____

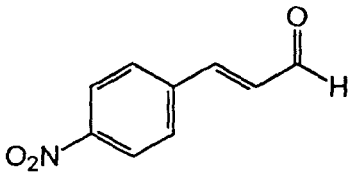
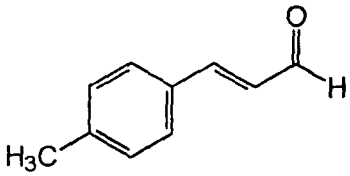
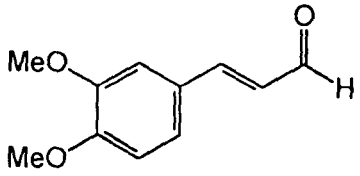
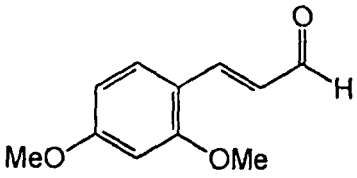
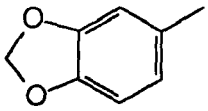
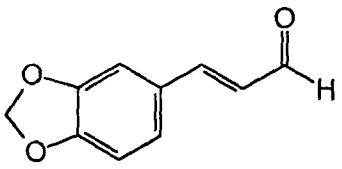
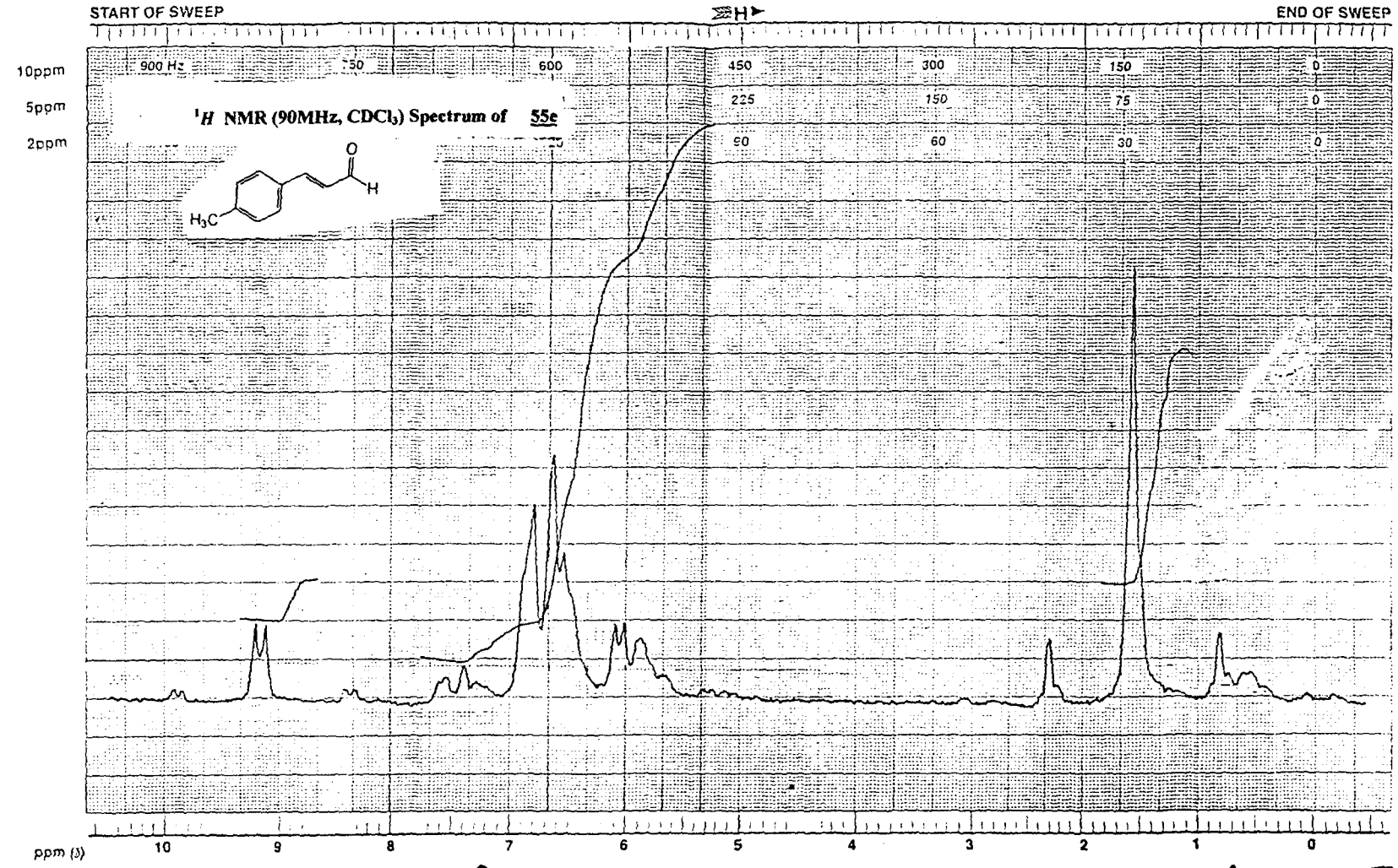
S. No.	Ar	Products	% Yield
54d	p-NO_2-C_6H_5	 55d	75
54e	p-CH_3-C_6H_5	 55e	67
54f	3,4-OMe-C_6H_4	 55f	65
54g	2,4-OMe-C_6H_4	 55g	70
54h		 55h	60

Table-3



EM-390 90 MHz NMR SPECTROMETER

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LOCK POWER _____ mG
DECOUPLE POS. _____ ppm
DECOUPLING POWER _____ mG

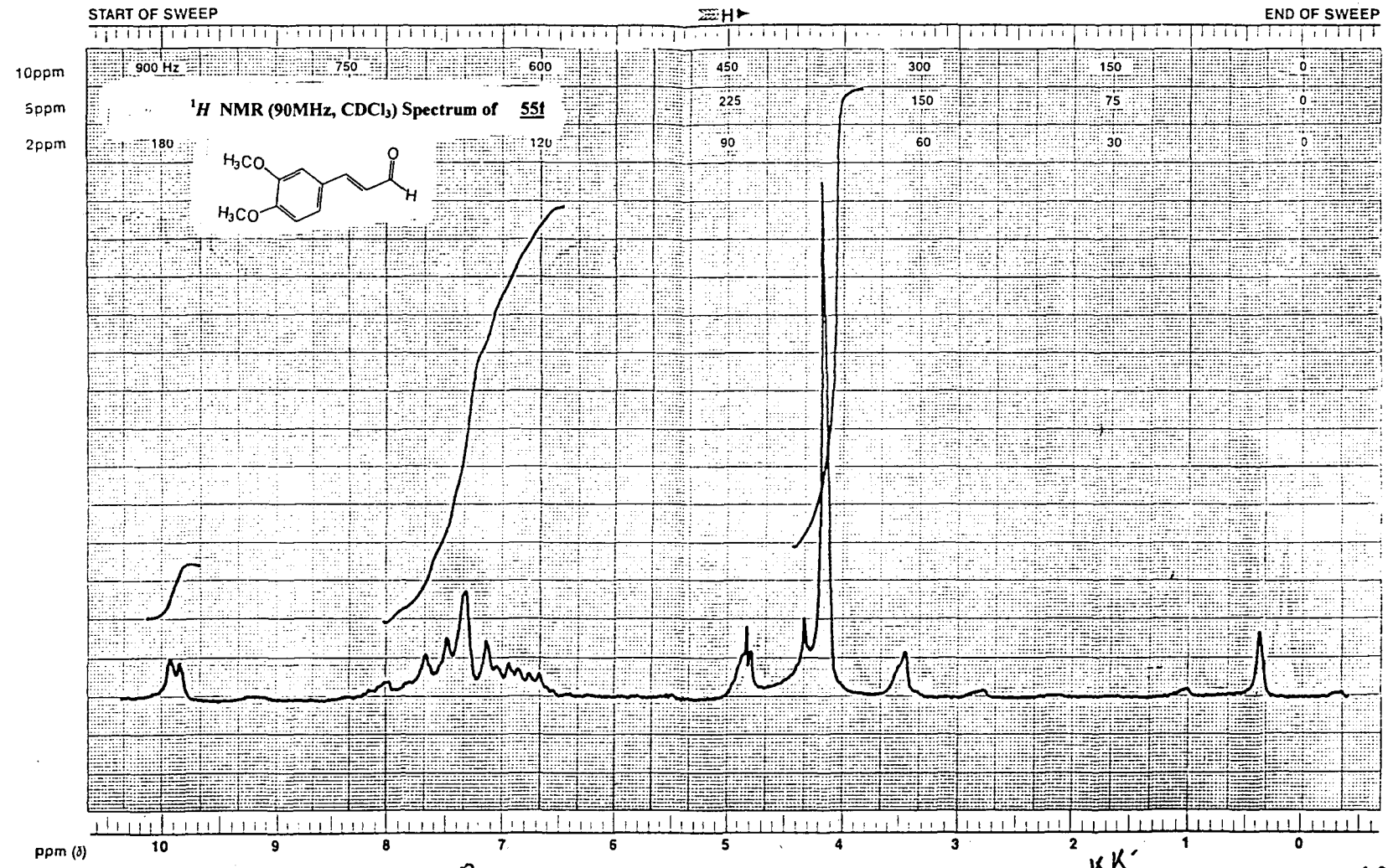
SPECTRUM AMPL. 0.2mm
FILTER 0.1 sec
RF POWER 0.1 mG

SWEEP TIME 5 min
SWEEP WIDTH 10 ppm
END OF SWEEP _____ ppm
OFFSET RECORDED FROM _____ TO _____

NUCLEUS _____
ZERO REF. _____
SAMPLE TEMP. _____ °C

SAMPLE : KK-016
SIGNAL IN THE OFFSET YES/NO
SOLEVNT : Cosely.

OPERATOR _____
DATE 12.1.89.
SPECTRUM NO. _____



EM-390 90 MHz NMR SPECTROMETER

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LOCK POWER _____ mG
DECOUPLE POS. _____ ppm
DECOUPLING POWER _____ mG

SPECTRUM AMPL. 100
FILTER 0.1 sec
RF POWER 0.1 mG

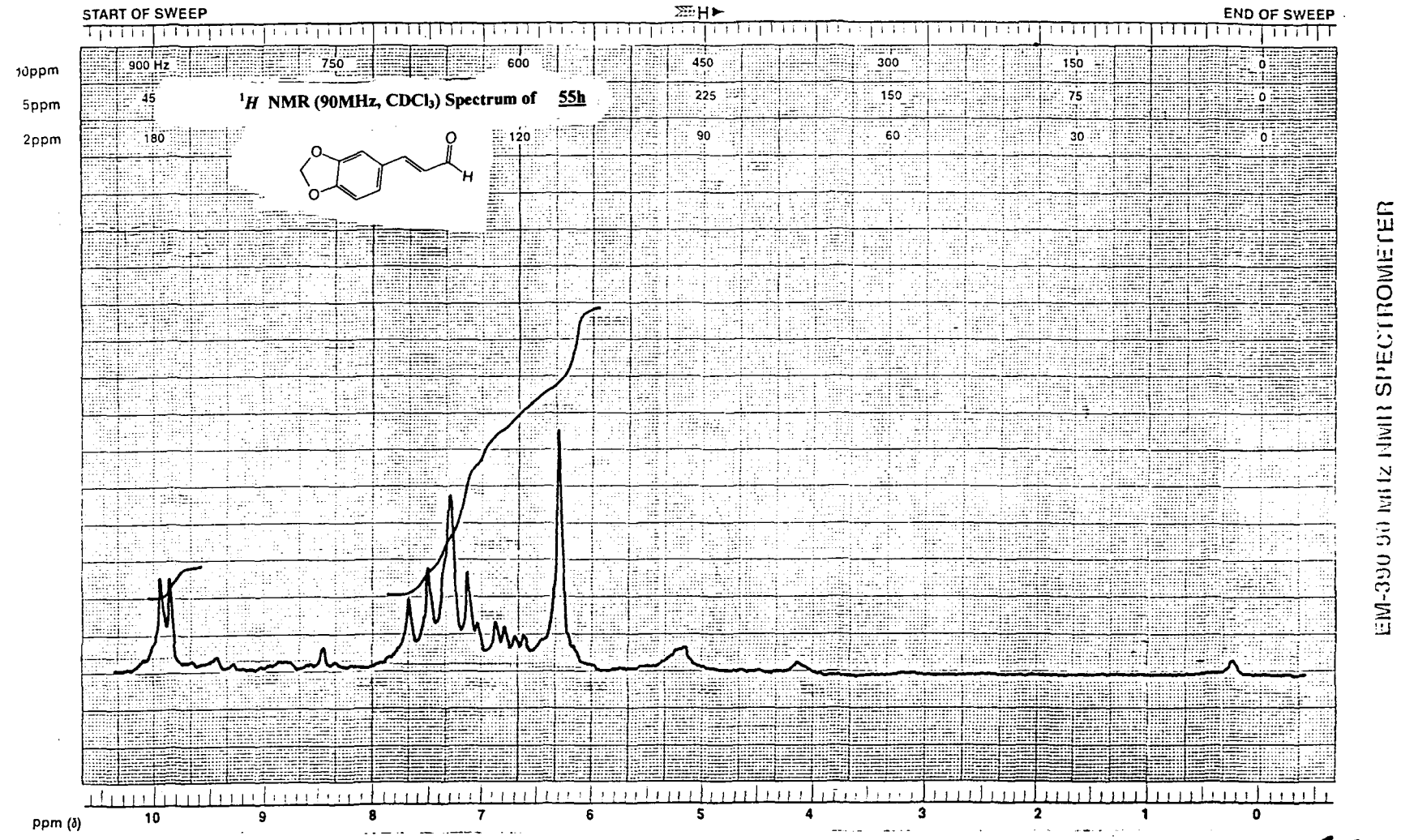
SWEEP TIME 5 min
SWEEP WIDTH 10 ppm
END OF SWEEP _____ ppm

NUCLEUS _____
ZERO REF. _____
SAMPLE TEMP. _____ °C

SAMPLE : KK. 202
SIGNAL IN THE OFFSET YES/NO
SOLEVNT : CDCl3

OPERATOR _____
DATE 16.10.98
SPECTRUM NO. _____

OFFSET RECORDED FROM _____ TO _____



EM-390 90 MHz NMR SPECTROMETER

LOCK POS. _____ ppm
LOCK POWER _____ mG
DECOUPLE POS. _____ ppm
DECOUPLING POWER _____ mG

SPECTRUM AMPL. 100
FILTER 0.1 sec
RF POWER 0.1 mG

SWEEP TIME 5 min
SWEEP WIDTH 10 ppm
END OF SWEEP _____ ppm

NUCLEUS _____
ZERO REF. _____
SAMPLE TEMP. _____ °C

SAMPLE : KK-201
SIGNAL IN THE OFFSET YES/NO
SOLEVNT : CDCl3

OPERATOR _____
DATE 16.10.98
SPECTRUM NO. _____

OFFSET RECORDED FROM _____ TO _____

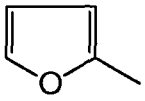
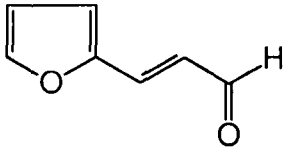
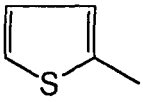
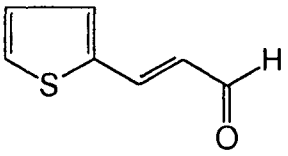
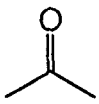
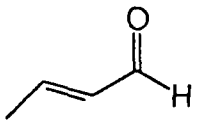
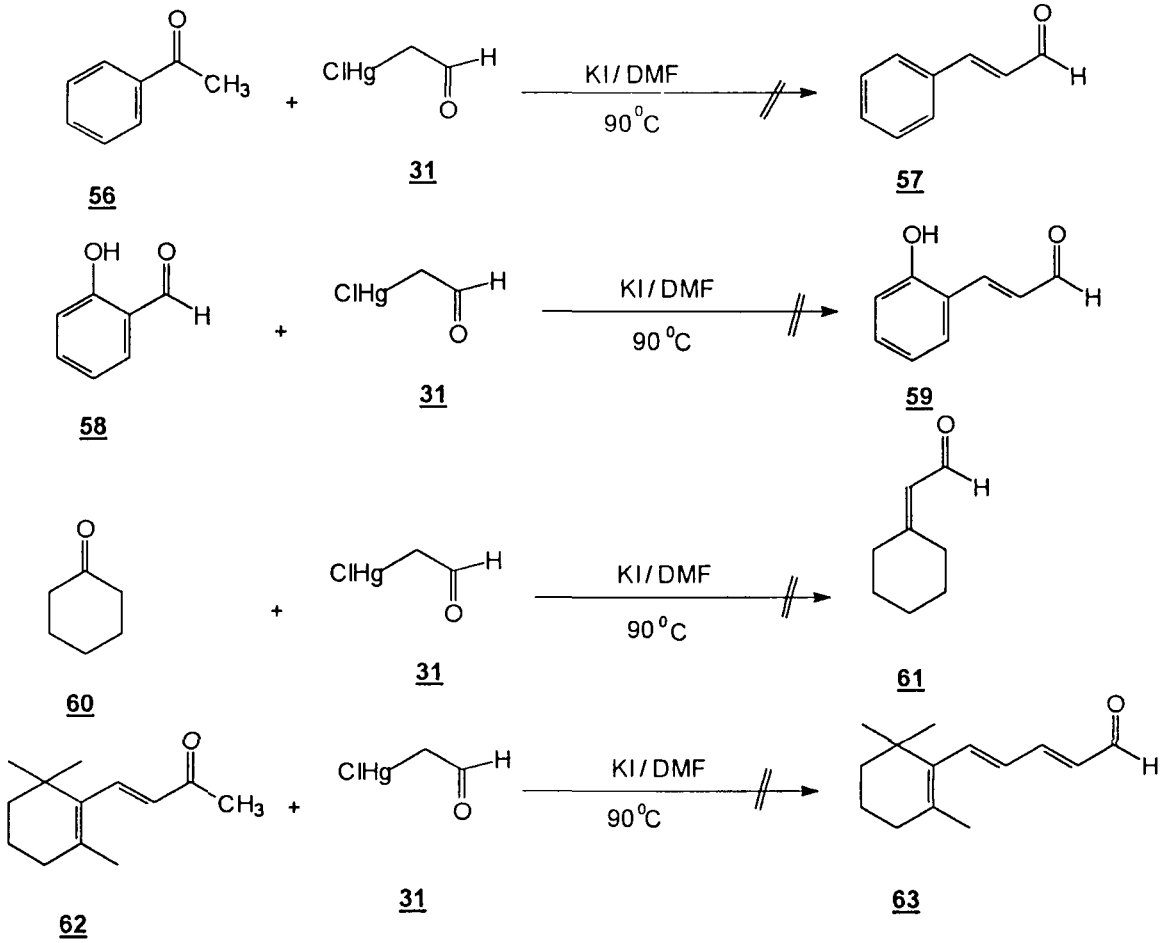
S. No.	Ar	Products	% Yield
54i		 55i	65
54j		 55j	90
54k		 55k	65

Table-4

crotanaldehyde[30] **55k** thus obtained was identical in spectral and analytical data with those described in the literature. Similarly, when acetophenone **56**, 2-hydroxybenzaldehyde **58** cyclohexanone **60** and β-ionone **62** were reacted with **31** under the described reaction conditions were not formed and the reaction resulted an intractable tar (*Scheme-17*). It is apparent that the reaction is best accomplished from aldehydes. Only acetone **54k** among the ketones reacted with **31** giving good yields.



Scheme-17

IV.C CONCLUSION:

In conclusion, we have for the first time shown that the chloromercuri acetaldehyde is an excellent source of acetaldehyde enolate anion which could be used for the synthesis of ene-aldehydes. Most aromatic aldehydes have yielded the corresponding olefinic aldehydes in good quantity. However, its reaction with ketones with one exception was not successful. The anion is also used for the preparation of β,β-bis(methylthio)acrolein **50** which is an important synthon useful for many synthetic operations. The method is much simpler than most directed aldol synthesis using particularly acetaldehyde. Therefore, it should prove superior to all the methods described in the literature.

IV. D EXPERIMENTAL SECTION:

General:

Melting point were determined on a "**Thomas Hoover**" capillary melting point apparatus and are uncorrected. The Infra red spectra were recorded on a **Perkin-Elmer 983** Spectrometer. ^{1}H NMR (*90MHz*) spectra were recorded on **Varian EM-390**. The chemical shifts (*ppm*) and the coupling constants (*Hz*) are reported in the standard fashion with reference to tetramethyl silane. Analytical thin layer chromatography (**TLC**) were performed on glass plates coated with **ACME's** silica gel containing 13% calcium sulphate as binder and various combination of

ethylacetate-hexane, ethylacetate-benzene and benzene were used as eluents. Iodine vapour, acidic potassium permanganate solution were used to visualise chromatograms. Column chromatography was performed on (60-120 mesh) silica gel purchased from **ACME's**. Solvents for chromatography were used after simple distillation of commercial materials. All solvents evaporation were done using a steam bath.

Chemicals and Reagents:

N,N-dimethyl formamide (**Aldrich**) of bottle grade quality was dried over calcium hydride, distilled and stored over molecular sieves (**5A**). Similarly, dimethyl sulphoxide dried over calcium hydride and distilled. Potassium iodide, lithium iodide, lithium chloride, mercurous acetate were purchased from **Aldrich**. Carbon disulphide purchased from **SD's**.

Starting Materials:

The commercial sample of vinyl methyl ether, benzaldehyde, *p*-chloro-benzaldehyde, *p*-nitro benzaldehyde, *p*-methoxy benzaldehyde, *p*-methyl benzaldehyde, 3,4-dimethoxy benzaldehyde, 3,4-methylenedioxy benzaldehyde, thiophene, furan, acetone, β-ionone, cyclohexanone, acetophenone were used as such.

Preparation of chloro(2-oxoethyl)mercury or chloromercuriacetaldehyde 31:

To a solution of 31.8gm (0.1M) of mercuric acetate in 150 ml of water, 7.2 gm (0.1M) of methyl vinyl ether is added drop by drop with stirring. After the addition was completed stirring was further continued for 15 minutes and then a saturated solution containing 5.8 gm (0.1M) of sodium chloride was added when a white precipitate was formed instantaneously which was filtered and recrystallised from water to give crystalline chloromercuriacetaldehyde in 68 % yields which melted at 130^0C to correspond with authentic data.

Preparation of β,β-bis(methylthio) acrolein 50:

To a solution of 2.79gm (0.01M) chloromercuriacetaldehyde in dimethyl formamide (15ml) was added 0.76 ml (0.01M) of carbon disulphide with 5ml of dimethyl formamide at room temperature with stirring. After 30 minutes the temperature was raised to 90^0C and then 4.74 gm (0.03M) of potassium iodide was added at a time when the reaction mixture develops a light yellow colour which turns light red within two minutes. 1.26ml (0.01M) of dimethyl sulphate was added at a time and the resulting reaction mixture was stirred for 10-15 minutes. It was then cooled and poured over cold water (200ml) and extracted with ether (3x50ml). The combined organic extract was washed with water, dried over

sodium sulphate and solvent distilled off to give the desired β,β-bis(methylthio) acrolein in 40% yields.

Preparation of ene-aldehydes:

To a stirred mixture of 1.06 gm (0.01M) of benzaldehyde and 4.74 gm (0.03ml) of potassium iodide in DMF, 2.79 gm (0.01M) chloromercuriacetaldehyde was added in small portions at 30°C. After five minutes a red layer separated, the resulting reaction mixture was poured over water, extracted with ether (3x60ml) and then the organic layer was washed with water (2x100ml), dried over sodium sulphate and the solvent evaporated to give ene-aldehydes in 60-90% yields.

3-phenyl-2-propenal 55a:

Yellow liquid; yield-85% (chloroform-hexane). IR (KBr): 1629, 1689, 2737, 2817, 3066, 3348 cm^{-1}. ^1H NMR (90*MHz*; CCl_4): δ 6.6.-6.8 (d, 2H, CH); 7.4-7.7 (Br, 4H, ArH);8.1-8.4 (Br, 1H, ArH); 97-9.85 (d, 1H, CHO). Anal. calcd. for C_9H_8O (132.16): C, 81.79; H, 6.10; O, 12.11%. Found: C, 81.89; H, 6.11; O, 12.12 %.

3-(4-chlorophenyl)-2-propenal 55b:

Prisms needles; yield-80%; mp.62-64°C (chloroform-hexane). IR (KBr): 1602, 1676, 1790, 2220, 2918, 3073 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 6.3-6.6 (d, 2H, CH); 6.9 (d, 1H, ArH); 7.4-7.6 (m, 3H, ArH); 9.4-9.5 (d, 1H, CHO). Anal. calcd.

for C_9H_7OCl (166.61): C, 64.88; H, 4.23; O, 9.6 %. Found: C, 65.12; H, 4.25; O, 9.64 %.

3-(4-methoxy phenyl)-2-propenal 55c:

Light yellow crystals; yields-60%; mp.76-78^{0}C (chloroform-hexane). IR (KBr): 1669, 2838, 2938, 3314 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 3.8 (s, 3H, OCH_3); 6.4 (dd, 1H, CH); 6.75-7.80 (m, 5H, CH); 9.55-9.75 (d, 1H, CHO). Anal. Calcd. for $C_{10}H_{10}O_2$ (162.19): C, 74.05; H, 6.21; 0.19.7%. Found: C, 74.14; H, 6.22; O, 19.7%.

3-(4-nitrophenyl)-2-propenal 55d:

Light yellow crystals; Yield-75%; mp.139-140^{0}C (chloroform-hexane). IR (KBr): 1658, 1676, 2232, 2908 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 5.6-5.7(d, 2H, CH); 6.6-6.7 (d, 1H, ArH); 7.3-7.6 (m, 3H, ArH); 9.6-9.7 (d, 1H, CHO). Anal. calcd. for $C_9H_7O_3N$ (177.16): C, 61.02; H, 3.980, 27.09 %. Found: C, 61.07; H, 3.99; O, 27.12 %.

3-(4-methylphenyl)-2-propenal 55e:

Light yellow crystal; Yield-67%; mp.38-39^{0}C (chloroform). IR (KBr): 1608,1668, 2750, 2824, 3052 cm^{-1} . ^1H NMR (90*MHz*; CCl_4): 1.6 (s, 3H, CH_3) 5.6-6.2 (d, 1H, CH); 6.2-7.01(m, 5H, CH and ArH); 9.1-9.3 (d, 1H, CHO). Anal. Calc. for: $C_{10}H_{10}O$: C, 81.76; H, 7.35; O, 10.9%. Found: C,82.1; H, 7.15; O,11.1%.

3,4-dimethoxy phenyl-2-propenal 55f: Light yellow crystalline; yield 65%; mp.72-73^{0}C (chloroform hexane). IR (KBr): 1682, 2838, 2932, 3778 cm^{-1} . ^1H NMR (90 *MHz*; CCl_4): δ 3.9 (s, 6H, $(OCH_3)_2$); 6.6-7.90 (m, 5H, CH and ArH), 9.6-9.8 (d, 1H, CHO). Anal. calcd. for $C_{11}H_{12}O_3$(192.21): C, 68.74; H, 6.29; O, 24.97%. Found: C, 68.81; H, 6.30; O, 24.99%.

2,4-dimethoxy phenyl 2-propenal 55g:

Light yellow crystalline; yields-70%; mp.67-68^{0}C (chloroform-hexane). IR (KBr): 1680, 2835, 2930, 3775 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 3.9 (s, 6H, $(OCH_3)_2$); 6.5-7.4 (m, 5H, ArH); 9.5-9.7 (d, 1H, CHO). Anal. calcd. for $C_{11}H_{12}O_3$ (192.21): C, 68.74; H, 6.29; O, 24.97%. Found: C, 68.81; H, 6.30; O, 24.99%.

3,4 dioxymethylene phenyl-2-propenal 55h:

Pale yellow crystalline; yields-60%; mp.85-86^{0}C (chloroform-hexane). IR (KBr): 1669, 2253, 2710, 3073 cm^{-1}. ^1H NMR (90*MHz*; CCl_4): δ 6.05 (s, 2H, CH_2); 6.20-7.7 (m, 5H, CH and ArH); 9.6-9.7 (d, 1H, CHO). Anal. calcd. for $C_{10}H_8O_3$ (176.17): C, 68.18; H, 4.58; O, 27.24% Found: C, 68.24; H, 4.59; O, 27.27%.

3-(2-Furanyl)-2-propenal 55I:

Light yellow solid; yields-95%; mp.55-57^{0}C (chloform-hexane) IR (KBr): 1642, 2945, 3778 cm^{-1}. ^1H NMR (90 *MHz*; CCl_4): δ 5.4-5.5 (d, 1H, CH); 6.1 (s, 1H, CH); 6.4-6.8 (m, 2H, ArH); 7.0-7.4 (m, 1H, ArH); 9.5 (s, 1H, CHO). Anal. calcd for

$C_7H_6O_2$(122.12): C, 68.85; H, 4.95; O, 26.20%. Found: C, 68.91; H, 4.96; O, 26.23%.

3-(2-thioanyl)-2-propenal 55j:

Yellow viscous liquid; yield-90% (chloroform-hexane). IR (CCl_4):1467, 1582, 1647, 1857, 2947 cm^{-1}. ^1H NMR (90 MHz; CCl_4): δ 5.4-5.7 (d, 1H, CH); 6.2-6.8 (m,3H, CH and ArH); 7.3-7.5(d, 1H, ArH); 9.7 (s, 1H, CHO). Anal. calcd. for C_7H_6OS (138.19): C,60.84; H, 4.38; O, 11.58%. Found: C, 60.92; H, 4.38; O, 11.59%.

Crotonaldehyde 55k :

Yellow liquid, yield-65%. IR (KBr): 1658, 1718, 2267, 2313, 2947cm^{-1}. ^1H NMR (90*MHz*; CCl_4): δ 1.8 (s, 3H, CH_3); 6.1-6.2 (d, 1H, CH); 6.8-7.0 (dd, 1H, CH); 9.6-9.7 (d, 1H, CHO). Anal. calcd. for C_4H_6O (70.09): C, 68.55; H, 8.62; O, 22.83%. Found: C, 68.63; H, 8.63; O, 22.85%.

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