INVESTIGATIONS ON OXOKETENE DITHIOACETALS : NEW CARBON - CARBON BOND FORMING REACTIONS AND THEIR FURTHER TRANSFORMATIONS TO NOVEL CARBOCYCLES AND HETEROCYCLES

By

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SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR

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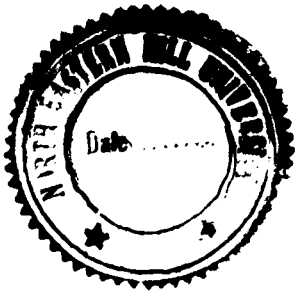
DOCTOR OF PHILOSOPHY



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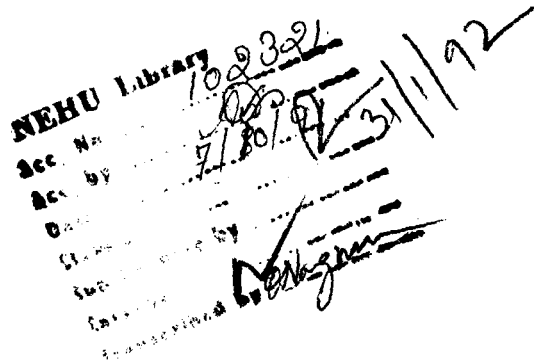
1989

chemistry



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

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4.	French Language	SPS - 601

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A C K N O W L E D G E M E N T

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Arun Kumar Gupta
17/10/89
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C O N T E N T S

PREFACE

Polarized ketene dithioacetals which can be easily prepared from a variety of active methylene compounds have been extensively explored in this laboratory for the development of new synthetic methods for a variety of heterocyclic and carbocyclic compounds. The α-oxoketene dithioacetals have also shown to be versatile intermediates for stereo- and regioselective carbon-hydrogen and carbon-carbon bond forming reactions involving metal hydrides and organometallic reagents respectively. Some interesting transformations involving reactions of organometallic reagents with α-oxoketene dithioacetals have been investigated in the present study.

The first Chapter gives an account of some of the recent transformations of α-oxoketene dithioacetals reported from this laboratory. The second Chapter of the thesis describes the interesting results involving reactions of propargylmagnesium bromide with α-oxoketene dithioacetals. Subsequent Lewis acid transformations of the alcohols thus formed has resulted in the development of a new synthetic method for aromatic annelation of easily available aliphatic precursors. The mechanisms and the scope of these transformations are described in detail.

The third Chapter is divided into two parts: Part 1 describes the reactions of α-oxoketene dithioacetals with lithioacetonitriles and the part II describe the reactions of α-oxoketene dithioacetals with β-substituted-β-lithioaminoacrylonitriles. The products arising out of these reactions, their mechanism, scope and limitation of the methodology developed are described in detail in this Chapter.

The fourth Chapter describes the studies of Diels-Alder cycloadditions reactions on vinylketene dithioacetals. A new efficient method of preparation of vinylketene dithioacetals from α-oxoketene dithioacetals have also been described.

CHAPTER I

POLARIZED KETENE DITHIOACETALS: GENERAL INTRODUCTION

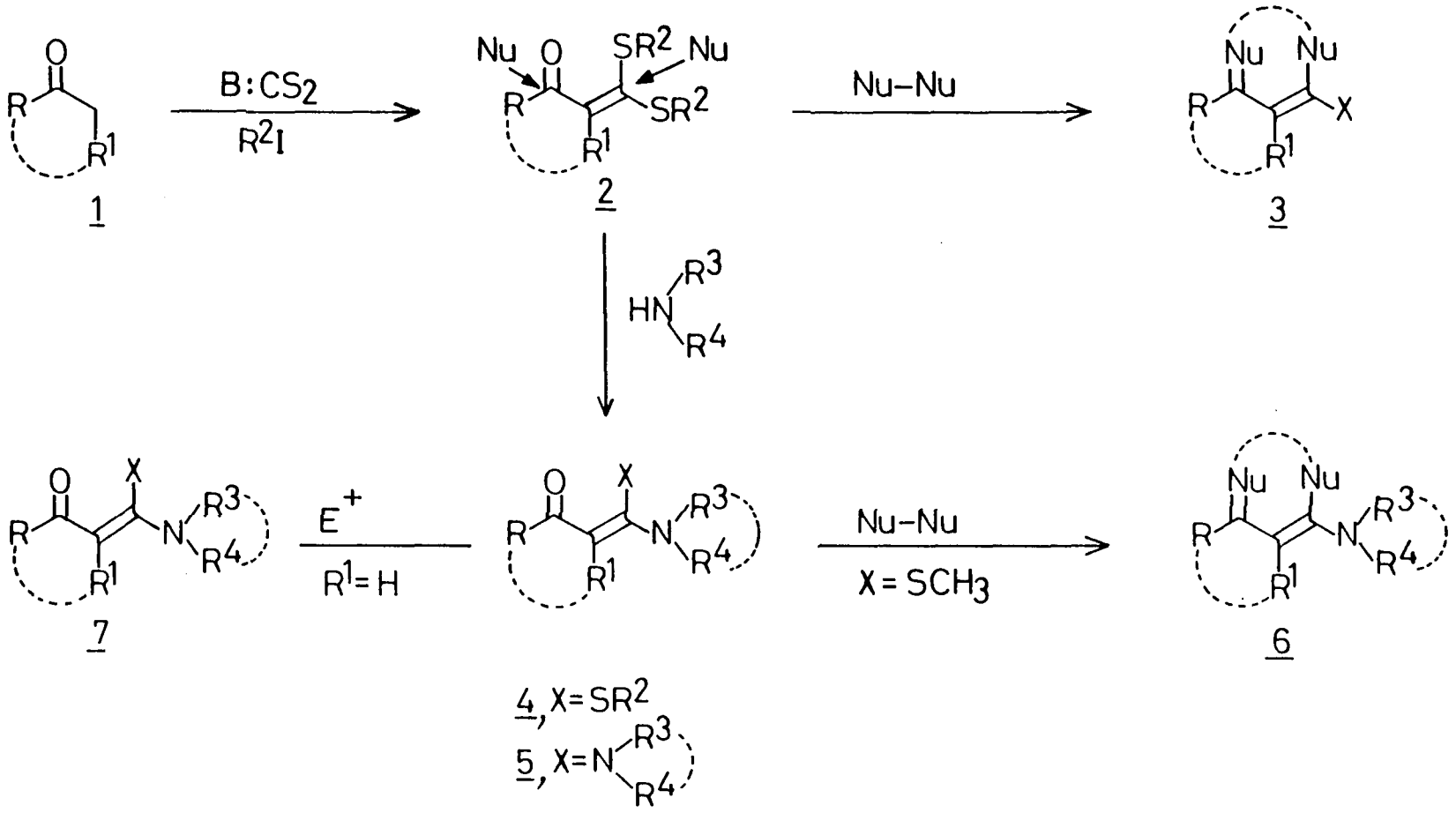
The α-oxoketene dithioacetals[1] are an important class of synthetic intermediates which can be prepared[2-10] by treating any active methylene compound of the general formula 1 with two equivalents of base and carbon disulphide followed by alkylation. The chemistry of α-oxoketene dithioacetals have been well documented[1,11]. They possess well defined physical properties and can be purified by any of the conventional purification methods. They are stable at room temperature and can withstand mild acidic and alkaline conditions. On the otherhand, the corresponding O,O-acetals are moisture sensitive and undergo hydrolysis under mild conditions[11,12].

The first synthesis of α-oxoketene dithioacetal was reported by Kelber and co-workers in 1910[13-15]. However, the chemistry of these intermediates

remained unexplored, until Thuillier and co-workers prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with carbon disulphide in the presence of base followed by alkylation[2-5]. Subsequently, several modifications have been made in choice of suitable bases maintaining the same conditions for obtaining higher yields of α-oxoketene dithioacetals[6-10].

The α-oxoketene dithioacetals can be visualized as masked β-ketoesters in which ester functionality is manifested as a ketene dithioacetal moiety. Alternatively, it may be considered as an α,β-unsaturated ketones containing a highly functionalized β-carbon. The α-oxoketene dithioacetals have been shown to be excellent 3-carbon fragments possessing 1,3-electrophilic centres with differing electrophilic properties, suitable for synthetic exploitation. They can further be converted to the corresponding ketene dihalogenides[16], S,N[17]- and N,N[18]-acetals making them more important precursors for a large variety of functionalized acetals. The α-oxoketene S,S-acetals, S,N- and N,N-acetals have been extensively used in this laboratory for developing a large number of new synthetic methods for both heterocyclic and carbocyclic systems (Scheme 1).

The carbonyl group of α-oxoketene dithioacetals have been shown to undergo sodium borohydride reduction to give the corresponding carbinolacetals which on subsequent acid catalysed treatment gave a number of rearranged products[19]. The 1,2-reduction of these intermediates was reinvestigated in our laboratory and the resulting carbinolacetals were shown to undergo smooth methanolysis in the presence of borontrifluoride etherate to afford highly regio-and stereoselective α,β-unsaturated methyl esters 8[20a], in high yields. Under controlled $BF_3.Et_2O$ catalysed hydrolysis the



Scheme 1

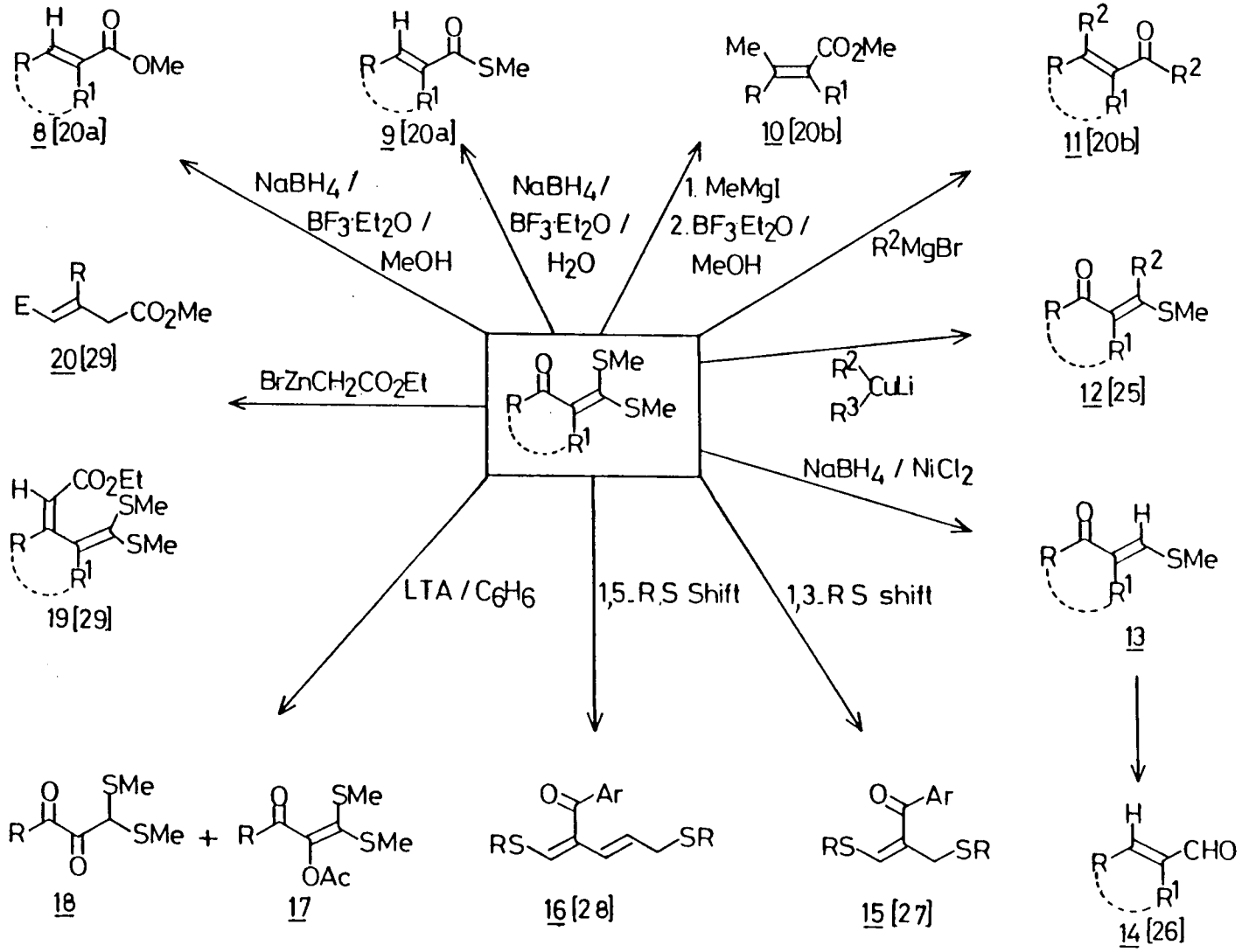
corresponding thiol ene esters 9[20a] were also obtained in high yields.

The overall transformation is considered as a homologation of active methylene ketenes, involving 1,3-carbonyl transposition. However, the bulkier alkylmagnesium halides and the arylmagnesium halides added in a sequential 1,4-followed by 1,2-manner, affording the respective α,β-unsaturated ketones 10[20b] (Scheme 2). The 1,3-carbonyl transposition was further extended in this laboratory for the synthesis of diene esters[21].

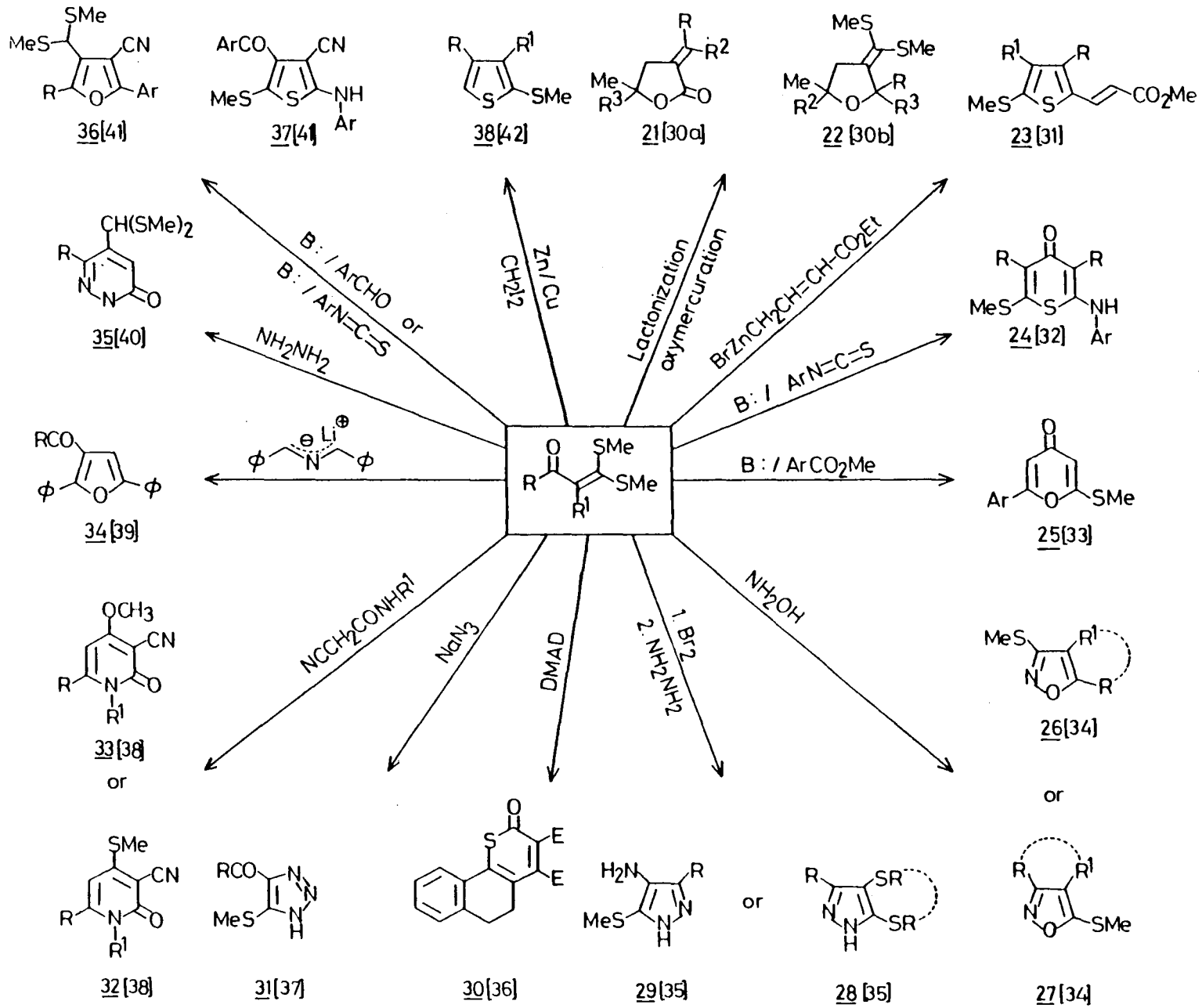
Dieter and co-workers[22-25] have shown that the dithioacetals 2 undergo chemo- and stereoselective 1,4-addition with organocuprates to give the corresponding β-alkylthio- α,β-unsaturated ketones 12[25]. The α-oxoketene dithioacetals were shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthioalkenyl ketones 13 which on hydrolysis yielded the corresponding α,β-unsaturated aldehydes 14[26] (Scheme 2).

In an another study from this laboratory, base catalysed rearrangement of α-oxoketene dithioacetals derived from propiophenones was reported to give 15[27]. A base assisted 1,5-RS shift was observed to yield the dienes 16[28] in good yields. The LTA oxidation of α-oxoketene dithioacetals afforded the corresponding α-acetoxyketene dithioacetals 17 and the diketones 18 in good yields. The Reformatsky reagent derived from ethyl bromoacetate undergoes 1,2-addition to give carbinolacetals and their further transformations to yield the corresponding diene 19 and 1,3-propene dicarboxylate 20 has also been reported[29] (Scheme 2).

The Scheme 3 outlines the synthetic outcome of α-oxoketene dithioacetals for the synthesis of various substituted and fused five membered and six membered heterocycles which have been developed in this laboratory[30-42].


8 [20a]
9 [20a]
10 [20b]
11 [20b]
NaBH4 / BF3·Et2O / MeOH
NaBH4 / BF3·Et2O / H2O
1. MeMgI 2. BF3·Et2O / MeOH
R2MgBr
20 [29]
BrZnCH2CO2Et
R2 R3 CuLi
12 [25]
19 [29]
NaBH4 / NiCl2
LTA / C6H6
1,5-R.S Shift
1,3-R.S shift
13
18
17
16 [28]
15 [27]
14 [26]

Scheme 2

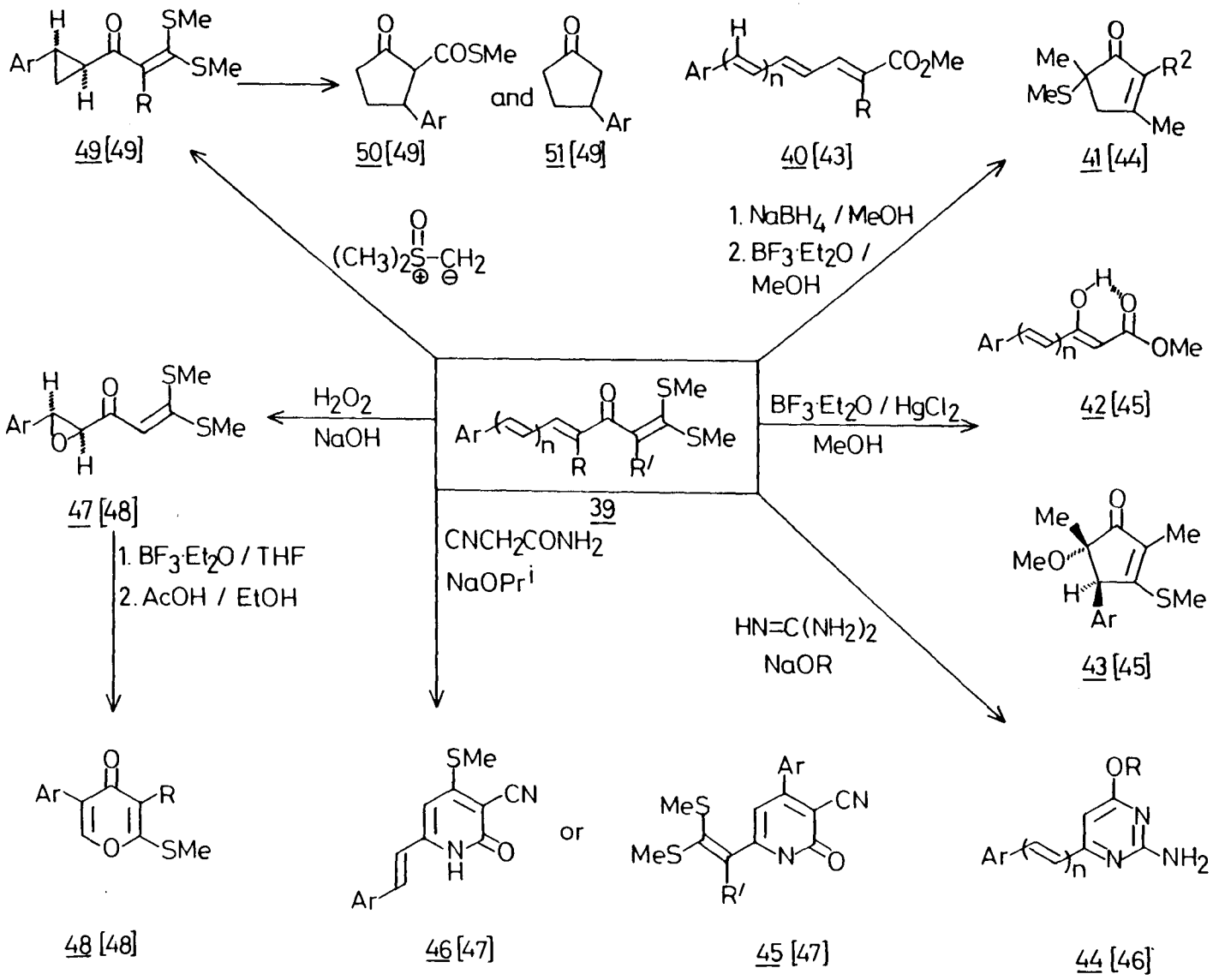

36[41]
37[41]
38[42]
21[30a]
22 [30b]
23 [31]
35[40]
24[32]
34[39]
25[33]
33[38]
or
26[34]
or
32[38]
31[37]
30[36]
29[35]
or
28 [35]
27[34]
B: / ArCHO or
B: / ArN=C=S
NH2NH2
Zn/Cu
CH2I2
Lactonization
oxymercuration
BrZnCH2CH=CH-CO2Et
B: / ArN=C=S
B: / ArCO2Me
NCCH2CONHR1
NaN3
DMAD
1. Br2
2. NH2NH2
NH2OH

Scheme 3

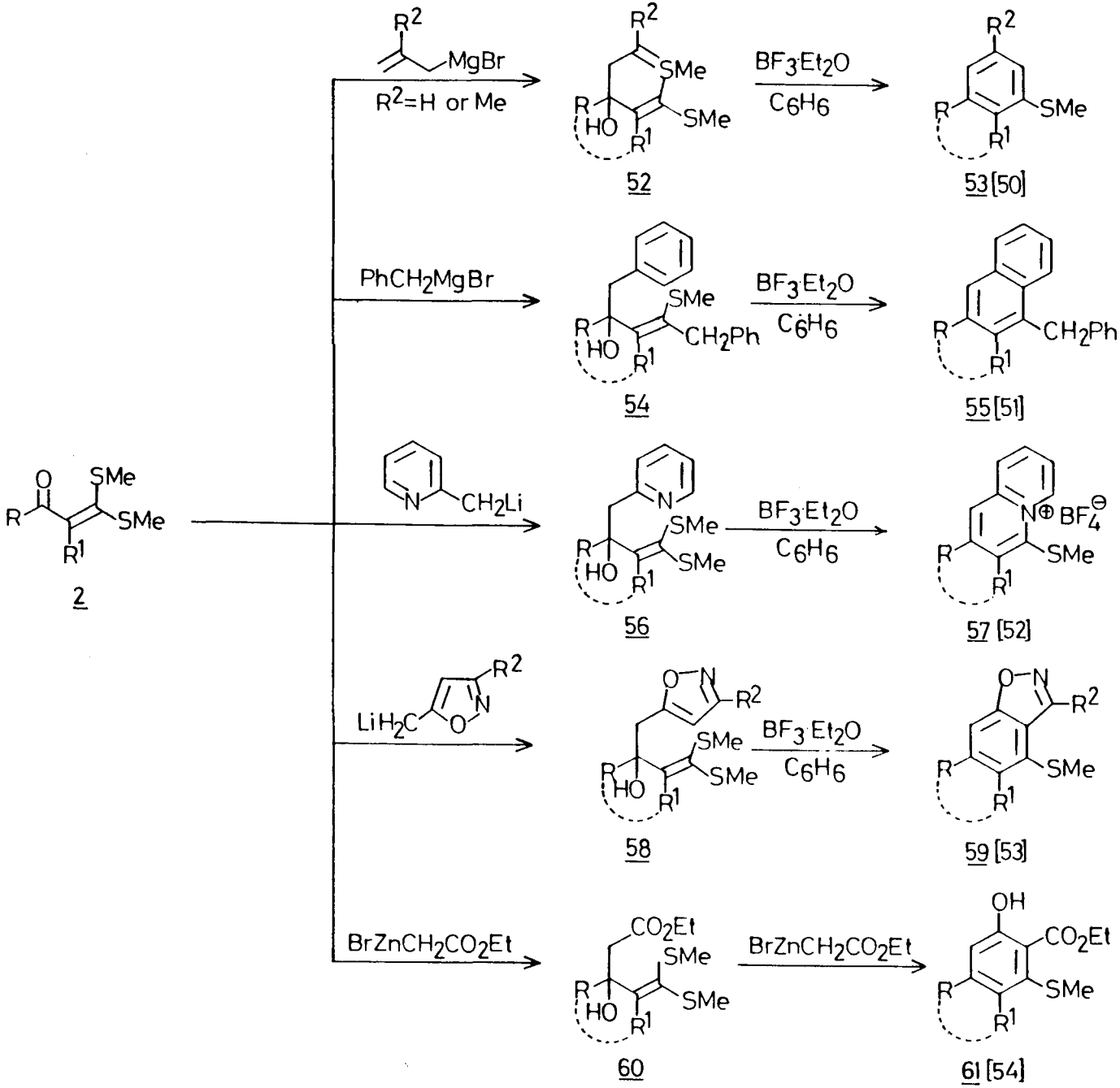
From these transformations it is apparent that the α-oxoketene dithioacetals with different functional groups would provide many new possibilities of further useful transformations of important synthetic applications.

The Scheme 4 outlines the various transformations achieved from α-cinnamoyl and 5-aryl-2,4-pentadienoylketene dithioacetals. A general method for the synthesis of polyene esters 40[43] and γ,δ-unsaturated β-ketoester 42[45] have been developed. The corresponding cyclopentenones 41 and 43 are formed when the polyenes carry substituents at 2 and 4 positions. The styryl pyrimidines and pyridones 44, 45 and 46 were also synthesized[46,47]. It has also been shown that cinnamoylketene dithioacetals 39 undergo regioselective cyclopropanation and epoxidation at the styryl double bond. These intermediates were further exploited for the synthesis of pyrones 48[48] and cyclopentanones 50[49] and 51[49] respectively.

A new general method for aromatic annelation was developed by Singh, Ila and Junjappa[50]. The α-oxoketene dithioacetals 2 were shown to react with allylmagnesium bromide in an exclusive 1,2-fashion to give the corresponding allyl carbinolacetals 52 which underwent cycloaromatization on treatment with borontrifluoride etherate in benzene to afford annelated benzenoids[50]. The method is shown to be extremely versatile and found general applications for the synthesis of other benzenoids. Benzylmagnesium halides underwent the sequential 1,4- and 1,2-conjugate addition to yield the corresponding naphthoannelated products 55[51] under similar reaction conditions. Organolithium reagents such as 2-picolyllithium and 3-methyl-5-lithiomethylisoxazole also underwent regiospecific 1,2-addition and gave the corresponding quinolizium salts 57[52] and 1,2-benzisoxazoles 59[53]. The cycloaromatization


49 [49]
50 [49]
and
51 [49]
40 [43]
41 [44]
$(CH_3)_2S^{\oplus}-\overset{O}{\overset{\|}{C}}-CH_2^{\ominus}$
1. $NaBH_4$ / MeOH
2. $BF_3{\cdot}Et_2O$ / MeOH
42 [45]
H_2O_2
NaOH
$BF_3{\cdot}Et_2O$ / $HgCl_2$
MeOH
39
47 [48]
1. $BF_3{\cdot}Et_2O$ / THF
2. AcOH / EtOH
$CNCH_2CONH_2$
$NaOPr^i$
$HN{=}C(NH_2)_2$
NaOR
43 [45]
48 [48]
46 [47]
or
45 [47]
44 [46]

Scheme 4

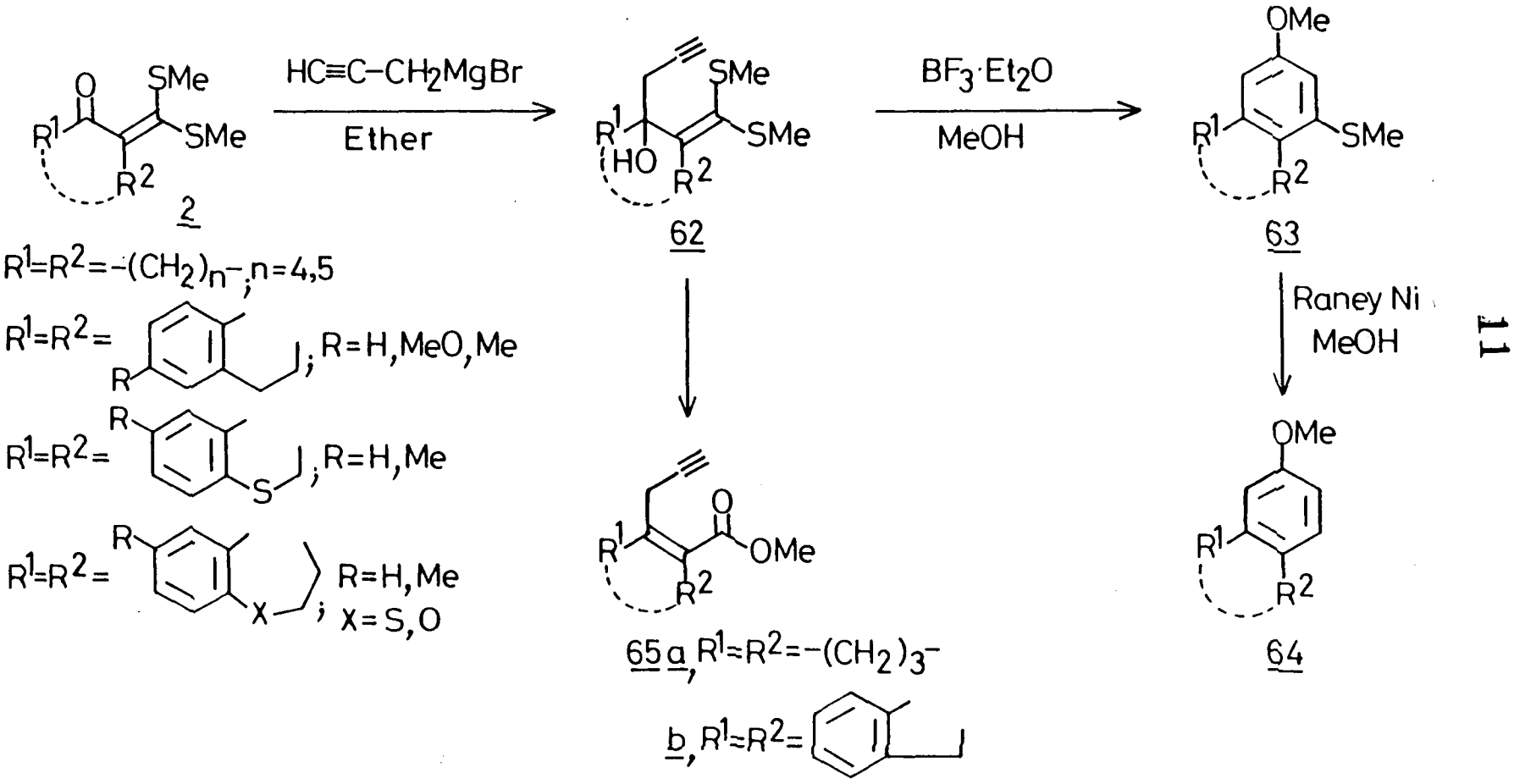

R2
MgBr
R2=H or Me
52
BF3·Et2O
C6H6
53 [50]
PhCH2MgBr
54
55 [51]
CH2Li
56
57 [52]
LiH2C
58
59 [53]
BrZnCH2CO2Et
60
61 [54]
2

Scheme 5

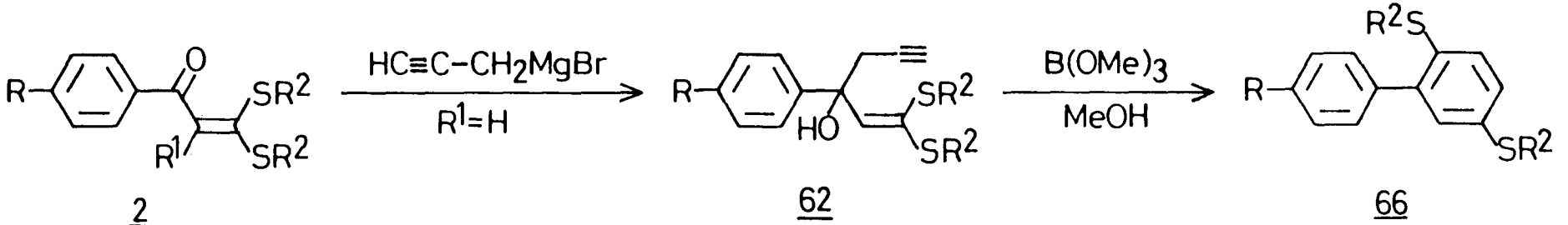
of α-oxoketene dithioacetals with Reformatsky reagent has ($BrZnCH_2CO_2Et$) also been reported to afford substituted and annelated salicylates 61[54] (Scheme 5).

In the present study, it was proposed to undertake some of the transformations based on α-oxoketene dithioacetals. The carbon-carbon bond formation is one of the important reactions in organic synthesis. It was, therefore, considered of interest to undertake the investigation of new carbon-carbon bond forming reactions on α-oxoketene dithioacetals and their further transformations to develop newer synthetic methodology for important class of organic compounds.

In the second chapter, the reaction of propargylmagnesium bromide with α-oxoketene dithioacetals have been described. The propargylmagnesium bromide undergo exclusive 1,2-addition with α-oxoketene dithioacetals 2 to give carbinolacetals 62 in high yields. These carbinolacetals 62, derived from cyclic α-oxoketene dithioacetals 2, on treatment with strong Lewis acid in methanol, underwent solvent assisted cycloaromatization to afford thioresorcinol dimethyl ethers 63[55] in high yields (Scheme 6). The carbinolacetals derived from five membered ketones failed to undergo cycloaromatization and gave only β-propargyl ene esters 65[55]. Interestingly, on the otherhand the carbinolacetals derived from acyclic ketene dithioacetals on treatment with weaker Lewis acid in methanol, yielded 2,5-bis(methylthio)biphenyls 66 in good yields (Scheme 7). Similarly, the cinnamoylketene dithioacetals, under analogous conditions, afforded stilbenes 69 in moderate to good yields (Scheme 7). The detailed mechanism of formation of biphenyls, stilbenes and thioresorcinol dimethylethers has also been discussed.


HC≡C–CH2MgBr
Ether
BF3·Et2O
MeOH
Raney Ni
MeOH
SMe
OMe
HO
2
62
63
64
65a, R1=R2=–(CH2)3–
b, R1=R2=
R1=R2=–(CH2)n–; n=4,5
R1=R2= ; R=H,MeO,Me
R1=R2= ; R=H,Me
R1=R2= ; R=H,Me
X=S,O

Scheme 6



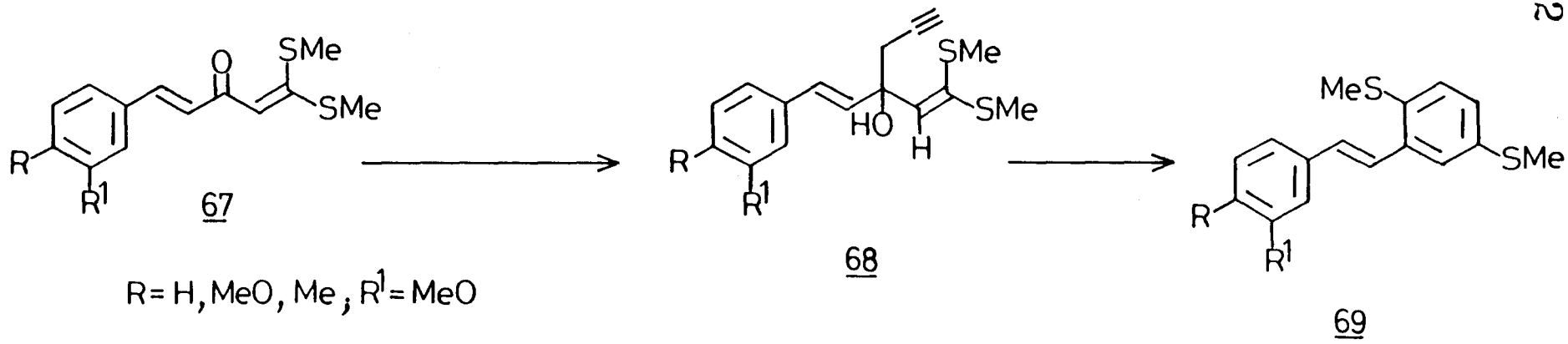
2

62

66

R=H,MeO,Me, Cl, Br

R^2 = Me, Et, n-Pr, i-Pr



67

68

69

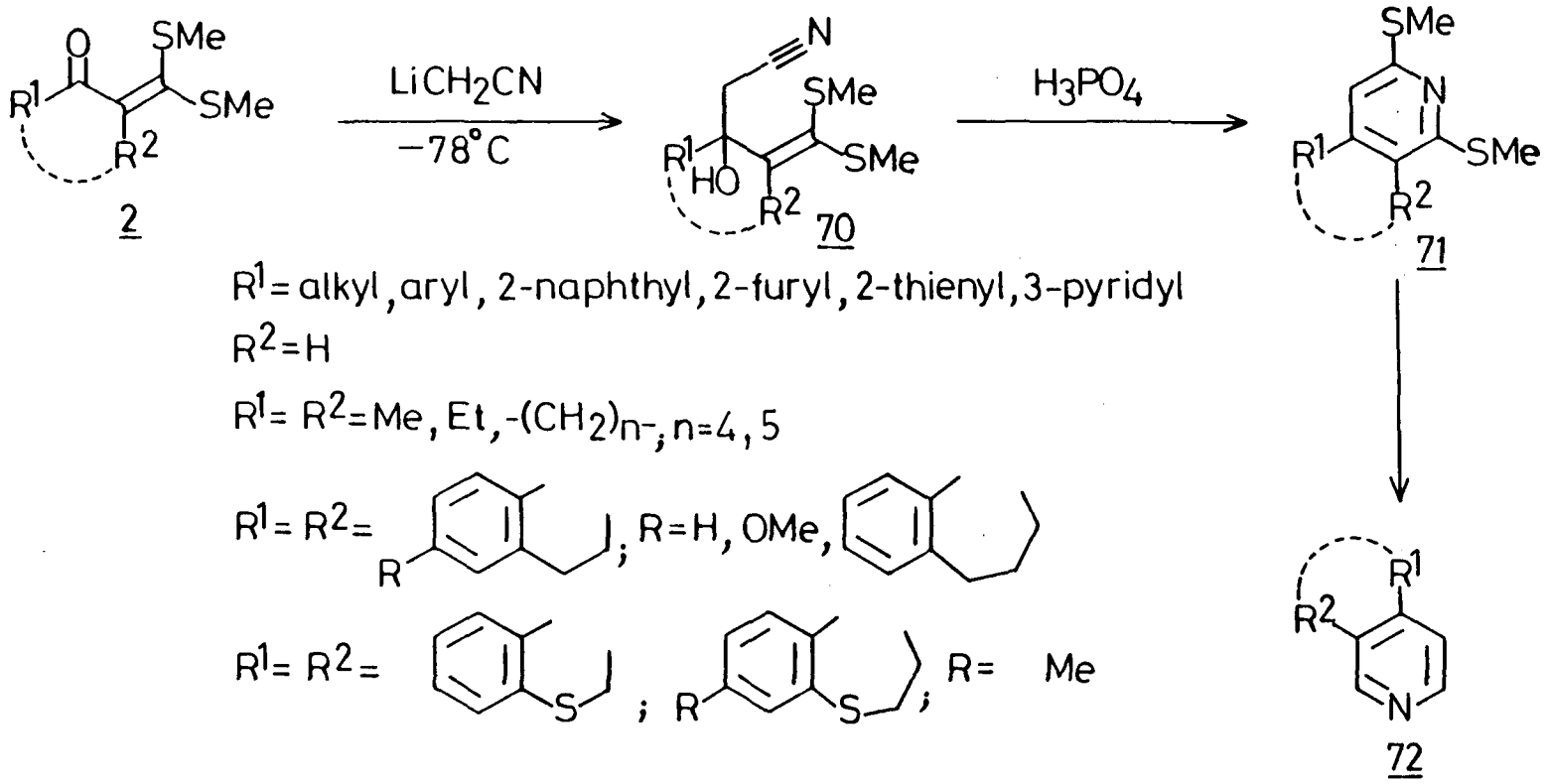
R= H, MeO, Me; R^1 = MeO

Scheme 7

In the third Chapter, the reaction of α-oxoketene dithioacetals with lithioacetonitrile has been discussed. The lithioacetonitrile adds regiospecifically 1,2-fashion to the carbonyl carbon to give the corresponding carbinolacetals 70 in excellent yields which on treatment with orthophosphoric acid to give 3,4-substituted and 4,5-annelated pyridines 71[56] in high yields (Scheme 8). The carbinolacetals 74 derived from cinnamoylketene dithioacetals 73 gave similarly styryl pyridines 75 in moderate to good yields. Anion generated from propionitrile also underwent 1,2-addition to afford carbinolacetals 76 in excellent yields which on subsequent treatment with H_3PO_4 gave, similarly 3-methyl-4-substituted and 4,5-annelated pyridines 77 in high yields (Scheme 9).

Furthermore, the carbinolacetals 70 have been used to synthesize substituted and annelated 2-bromopyridines 78 which were obtained in excellent yields. The 2,6-bis(methylthio) groups of pyridines 71 have been replaced by Nickel induced Grignard reactions to give 2,6-disubstituted pyridines 79 in good yields (Scheme 10).

In the second part of the same Chapter, the reaction of α-oxoketene dithioacetals with β-substituted-β-lithioaminoacrylonitrile have been discussed. The anion, β-lithioaminocrotononitrile adds to α-oxoketene dithioacetals 2 in 1,4-manner and under the experimental condition affords substituted and annelated nicotinonitriles 80 in excellent yields (Scheme 11). Similarly, when the reaction was extended to cinnamoylketene dithioacetals and 5-aryl-2,4-pentadienoylketene dithioacetals, the regiospecific 1,4-addition took place on the styryl double bond rather than the bis(methylthio) carbon to give nicotinonitriles 81 (Scheme 12). The detailed mechanism of formation of these substituted and annelated nicotinonitriles have been discussed in



R^1 = alkyl, aryl, 2-naphthyl, 2-furyl, 2-thienyl, 3-pyridyl

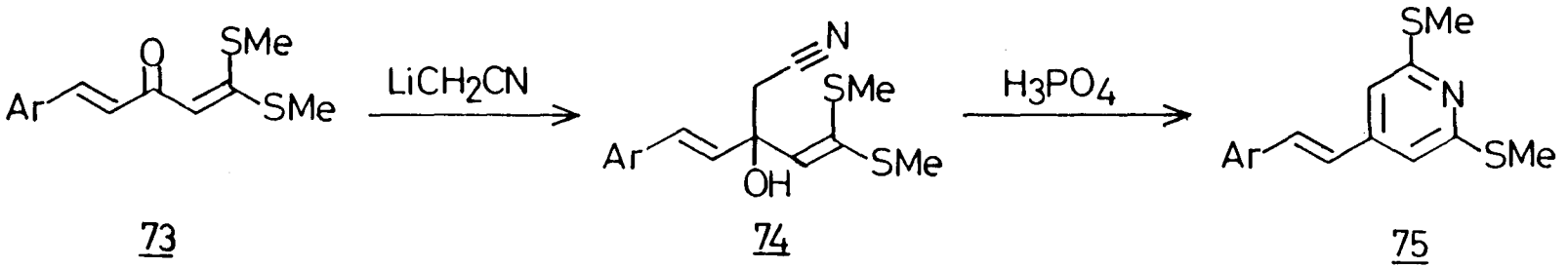
R^2 = H

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

$R^1 = R^2$ = ; R = H, OMe,

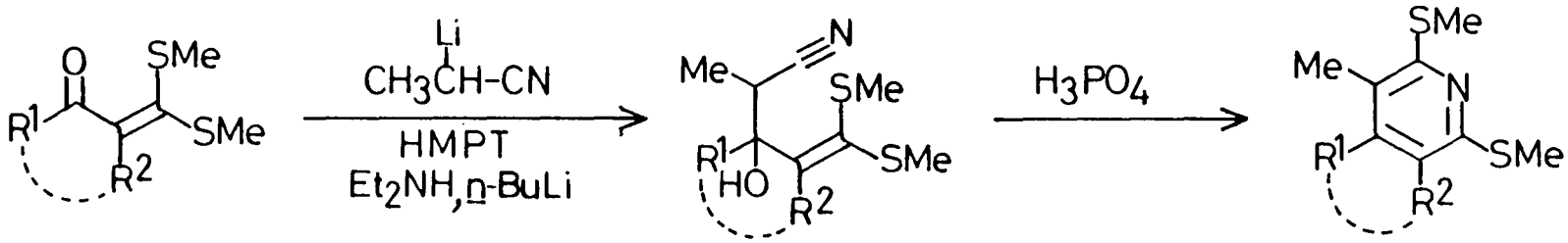
$R^1 = R^2$ = ; R = Me

Scheme 8



73 74 75

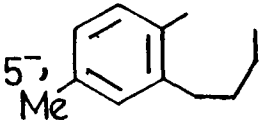
Ar = C_6H_5, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-ClC_6H_4



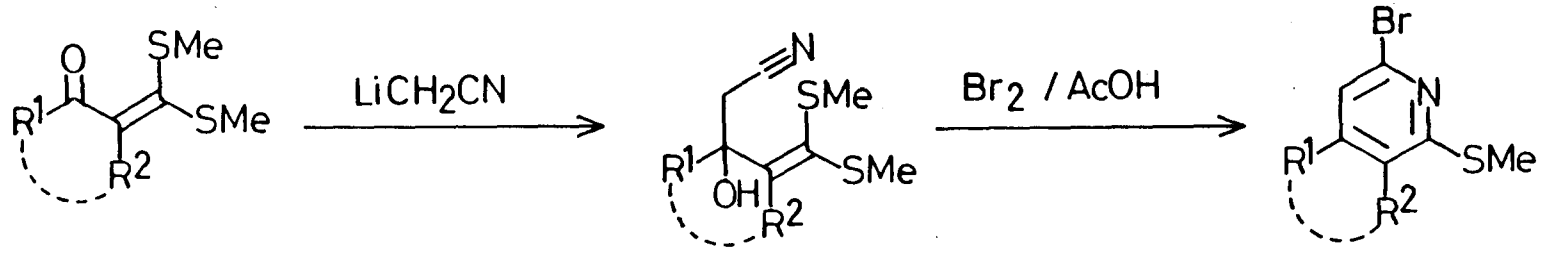
2 76 77

R^1 = C_6H_5, 2-furyl ; R^2 = H

$R^1 = R^2$ = -$(CH_2)_4$-, -$(CH_2)_5$-,



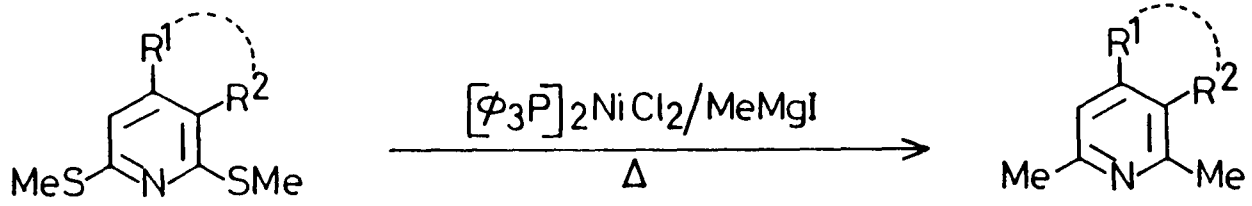
Scheme 9



2 70 78

$R^1 = C_6H_5$, 3-pyridyl; $R^2 = H$

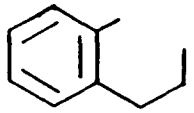
$R^1 = R^2 = (CH_2)_4$;



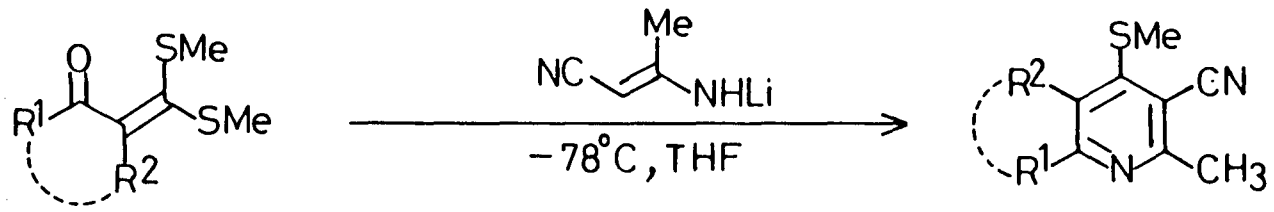
71 79

a, $R^1 = C_6H_5$; $R^2 = H$

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

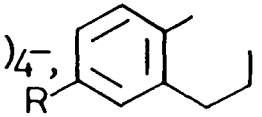


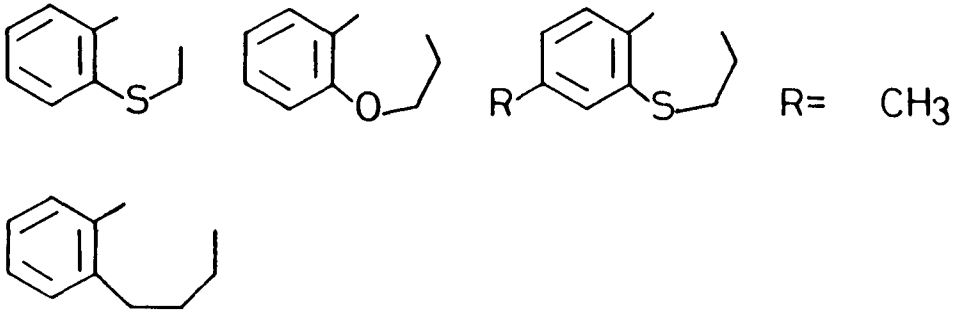
Scheme 10



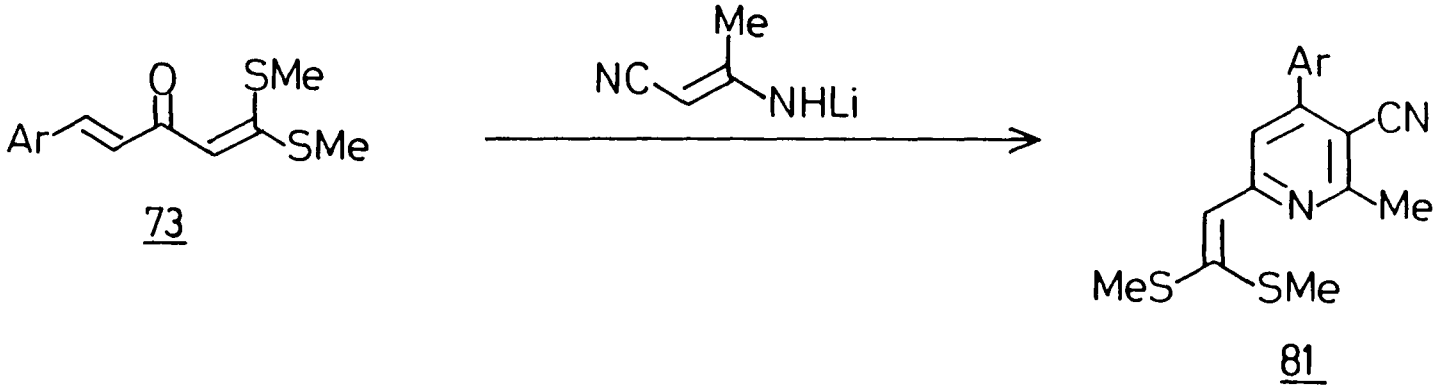
2 80

R^1 = alkyl, aryl, 2-furyl, 2-thienyl, 2-naphthyl, 3-pyridyl; R^2 = H

$R^1 = R^2 = -(CH_2)_3-, (CH_2)_4-,$  , R = H, OCH_3



Scheme 11



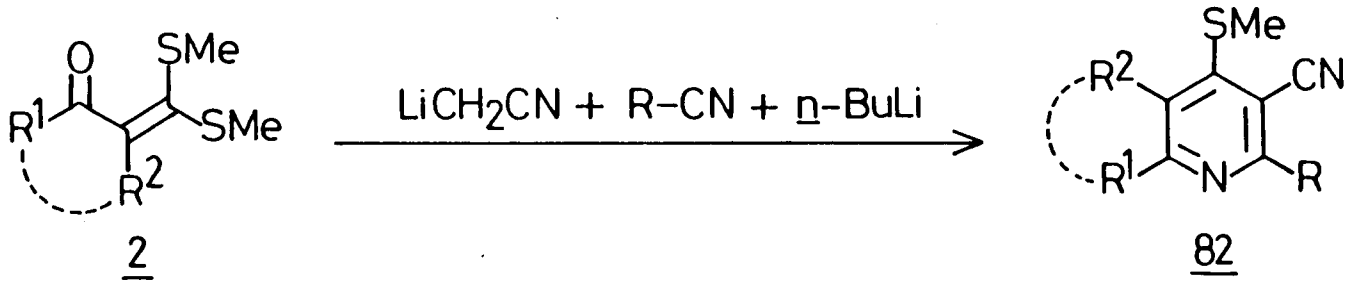
73 81

Ar= C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4HC{=}CH$

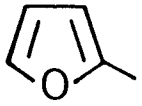
Scheme 12

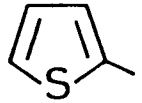
this Chapter. β-Substituted β-lithioaminoacrylonitrile anions have also been generated and added to the α-oxoketene dithioacetals 2 which under the analogous experimental condition, gave 2,6-disubstituted and 2,3-annelated nicotinonitriles 82 in excellent yields (Scheme 13). The reduction studies of these product pyridines have also been described.

In the fourth Chapter, the studies on Diels-Alder cycloaddition of vinylketene dithioacetals have been discussed. The diene vinylketene dithioacetals 83 have been conveniently prepared from the corresponding α-oxoketene dithioacetals 2, and are shown to react with doubly activated dienophiles, such as maleic anhydride to give cycloadducts phthalic anhydrides 84[57] in good yields. When vinylketene dithioacetals with R^1=R^2=Me and R^1=Et,R^2=Me, were reacted with maleic anhydride under analogous conditions, the bicyclic adducts 85a and 85b were obtained in high yields (Scheme 14). The mechanism of formation of these bicyclic adducts have also been discussed. The vinylketene dithioacetals with DMAD afforded substituted phthalates 86[57] (Scheme 15). Attempted preparation of vinylketene dithioacetal derived from indanone 87 by either of the methods (dehydration or Wittig) gave only dimeric adduct 88. Adduct 89 was also obtained when the crude diene was reacted with maleic anhydride (Scheme 15).

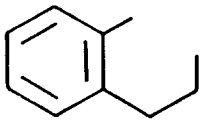


2 82

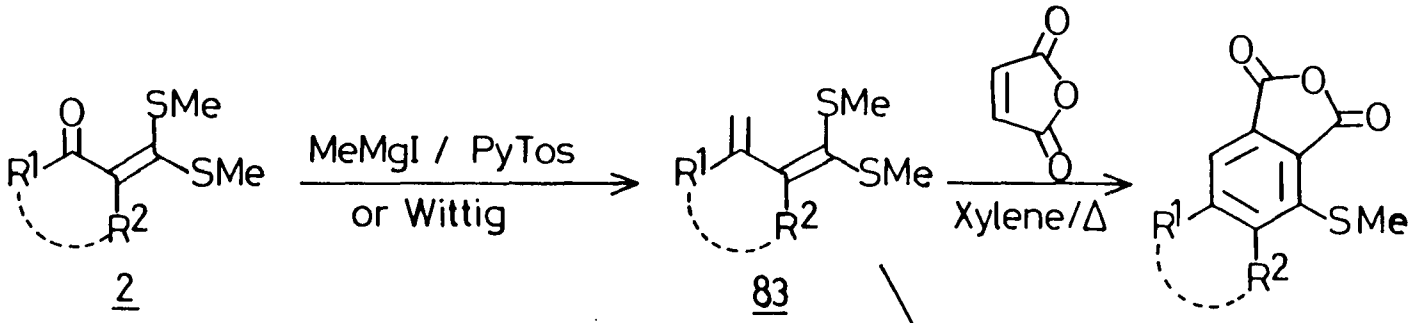
R =  ; $R^1 = C_6H_5$, 2-thienyl, 2-furyl, $R^2 = H$

R =  ; $R^1 = C_6H_5$, 2-thienyl, 2-furyl; $R^2 = H$

R = C_6H_5; R^1 = Me, C_6H_5; 2-furyl

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

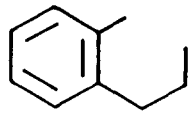
Scheme 13

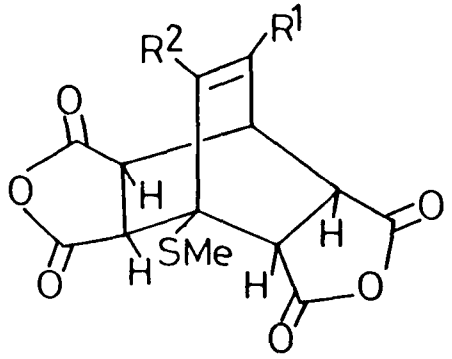


2 83 84

R^1 = Me, C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4

R^2 = H

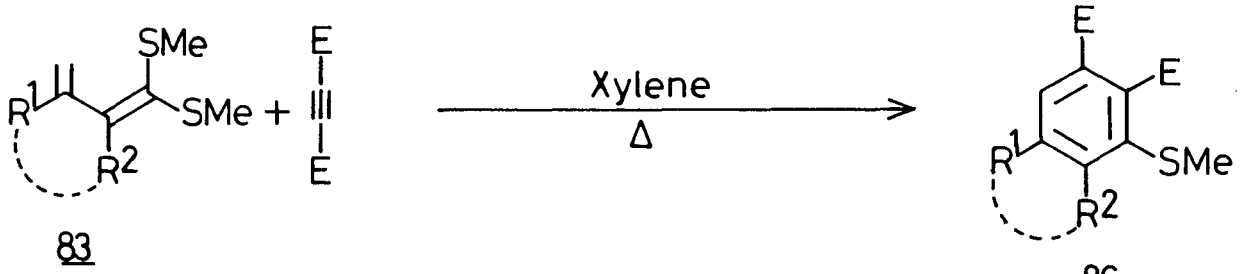
$R^1 = R^2 = -(CH_2)_4-$, 



85 a, $R^1 = R^2$ = Me

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

Scheme 14

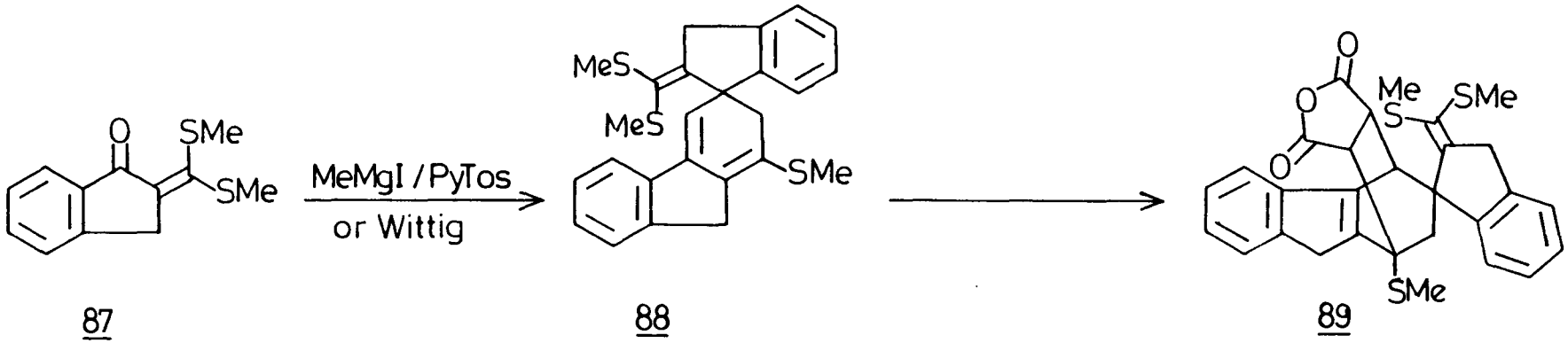


83 86

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

b, R^1=R^2=Me

E = CO_2Me



87 88 89

Scheme 15

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CHAPTER II

REACTION OF α-OXOKETENE DITHIOACETALS WITH PROPARGYLMAGNESIUM BROMIDE: A NOVEL AROMATIC ANNELATION REACTION*

II.1 INTRODUCTION

Although, the synthesis of many five and six membered heterocycles with one or two heteroatoms have been reported from appropriate acyclic precursors, similar approaches for the synthesis of aromatics have been less extensively investigated. The availability of benzene and its family including many important fused aromatics from coal tar did not warrant the development of

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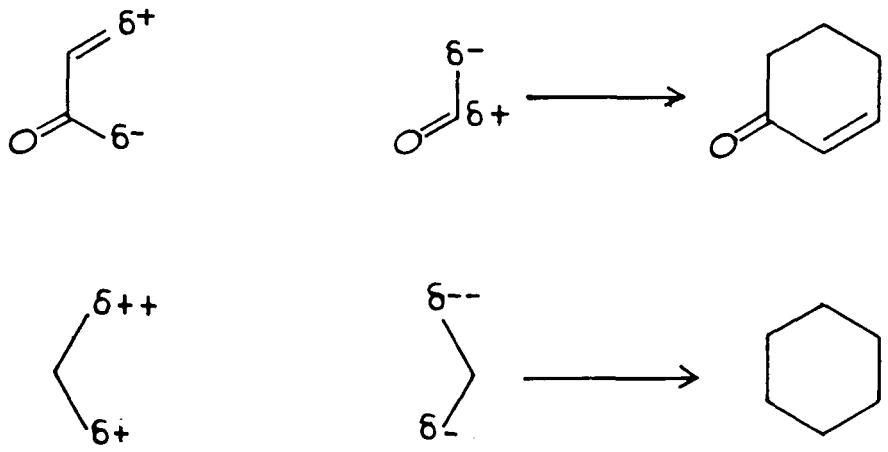
* Arun K. Gupta, H. Ila and H. Junjappa, Tetrahedron Lett. 28, 1459 (1987).

efficient synthetic methods in the early part of the century. Much of the work in the past, in this area, has been centered around the study of aromatic substitution rather than their synthesis. Consequently, extensive literature is now available regarding both nucleophilic and electrophilic substitution at the benzene ring. Thus the ring functionalization is the most important approach for preparing the substituted benzenoids. The introduction of one or two substituents in the benzene ring generally poses difficulties due to frequent formation of ortho, meta and para isomeric mixtures which not only results in overall lower yields of the desired regioisomer but also causes difficulties in their separation in the pure form.

The strategy to construct benzenoid ring systems and other fused ring cyclic aromatics with appropriate substituents can also be achieved from suitably substituted open-chain precursors. Such an approach would give overall high yields of the desired aromatic compound which may be otherwise not so easily accessible from the preconstructed benzene ring through conventional reported chemistry. The ring synthesis from open-chain precursors also permits introduction of labelled carbon such as ^{13}C and ^{14}C since the corresponding labelled open-chain precursors can more easily be synthesized. Many methods have already been developed to construct highly substituted aromatics from open-chain precursors. These methods have been already reviewed[1].

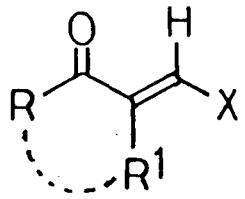
One of the important approaches for the construction of six membered rings, involves coupling of two fragments, one with two carbon atoms and other with four carbon atoms (Diels-Alder[2] and Robinson annelation[3]).

The regiochemistry in these reactions is essentially controlled by the direction of polarization within each fragments as represented schematically for the Robinson annelation (Scheme 1). The other commonly employed approach involves the combination of two three carbon fragments one with two 1,3-electrophilic sites and other with 1,3-nucleophilic sites. The regiochemistry of the product formation in these reactions is controlled by the differential reactivities of these sites (Scheme 1). In recent years, a number of 1,3-electrophilic

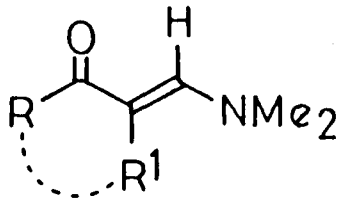


Scheme 1

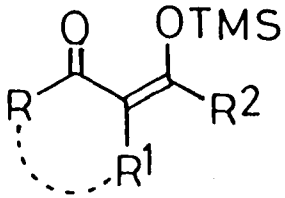
3-carbon components derived from β-dicarbonyl compounds have been developed[1]. These intermediates undergo cycloaromatization on reaction with 1,3-binucleophilic 3-carbon components to give aromatic compounds with desired regiochemistry. Some of these systems with 1,3-electrophilic sites employed in cycloaromatization reactions are shown in the Scheme 2. Thus β-dimethylaminoenone 6 has been condensed with dimethyl 3-oxoglutarate 7 to yield the substituted phenol derivatives 8 (Scheme 3). Similarly, the styrylenaminone 9 has been successfully



1



2



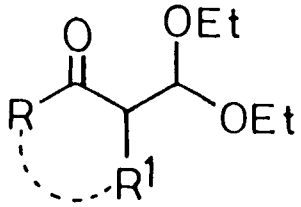
3

a X= Cl

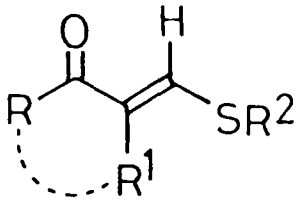
b X= OH

c X= OMe/OEt

R^2=H, alkyl



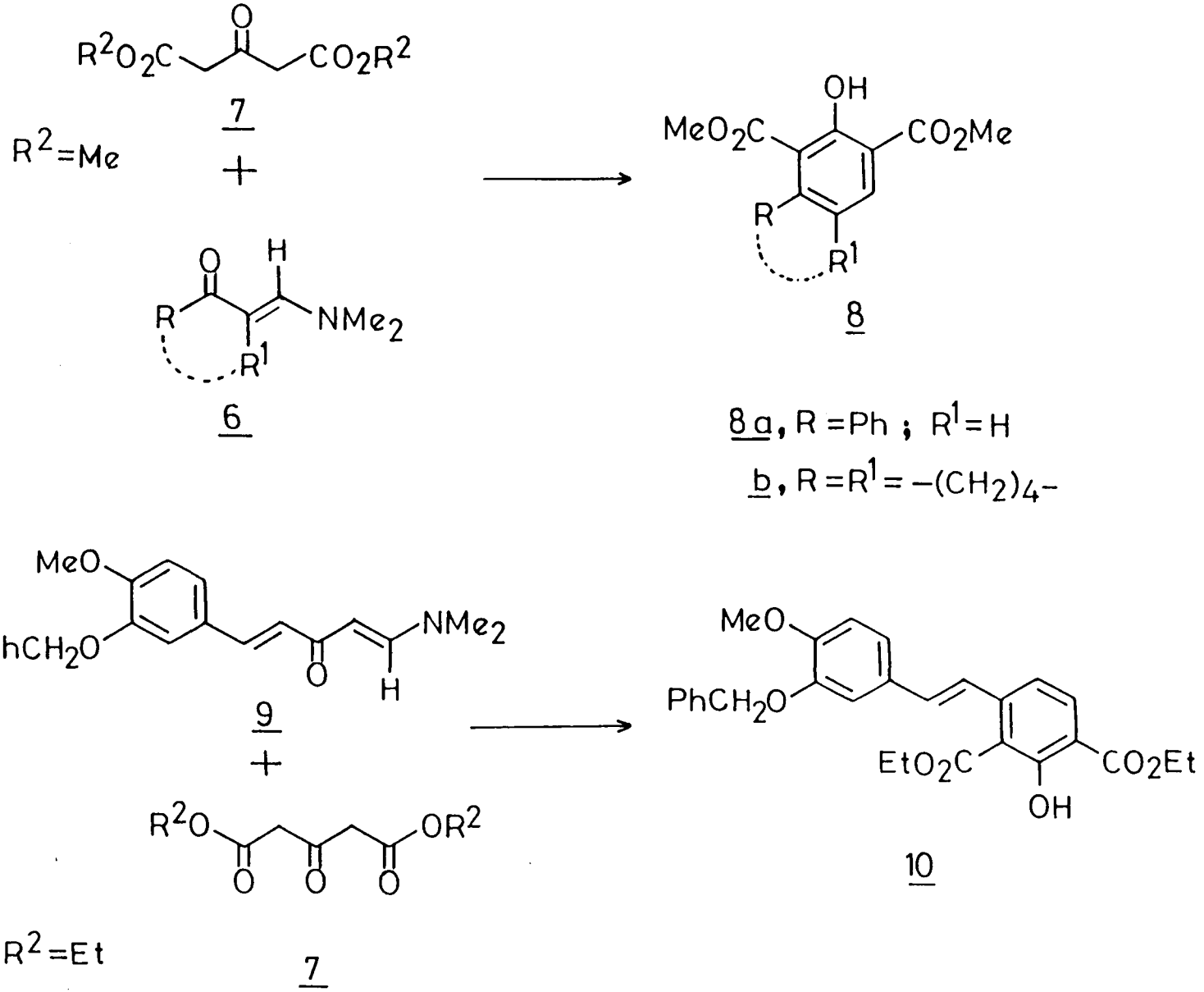
4



5

R^2= alkyl

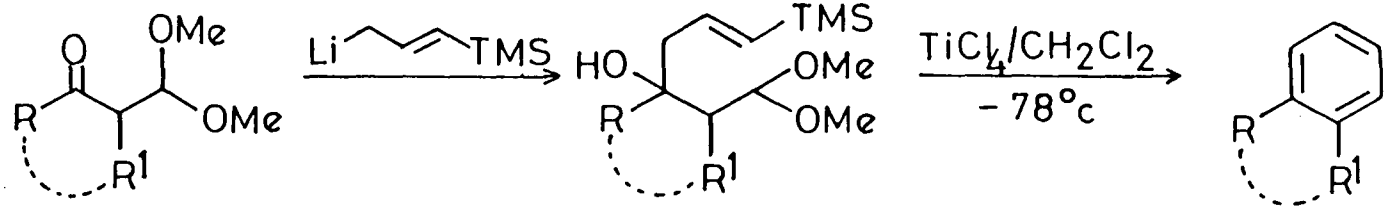
Scheme 2


R2O2C
CO2R2
7
R2=Me
+
H
NMe2
R
R1
6
MeO2C
OH
CO2Me
8
8a, R=Ph ; R1=H
b, R=R1=-(CH2)4-
MeO
PhCH2O
NMe2
9
R2O
OR2
7
R2=Et
EtO2C
CO2Et
10

Scheme 3

employed in a novel cycloaromatization step in the total synthesis of Phyllodulcin 10[4] in good yield (Scheme 3).

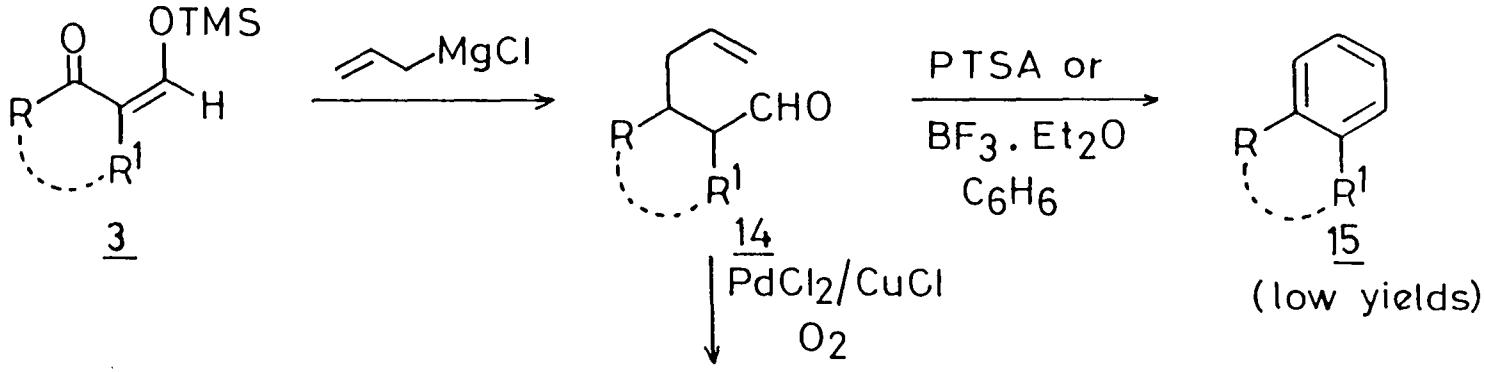
A novel general approach for benzoannelation of active methylene ketones has been described recently by Tius and co-workers[5-9]. The transformation involves either intramolecular cationic or anionic cyclization of open-chain ene-acetals or ene-aldehydes. Thus a number of substituted benzene and biphenyl derivatives 13 have been synthesized in good yields by subjecting the intermediate enolacetals 12 to cationic cyclization in the presence of Titanium tetrachloride at -78°C. The intermediate vinylsilane acetals 12 were prepared in high yields by the addition of allyltrimethylsilyllithium to the β-ketoacetals 11[5]. Similarly the β-silyloxyenones 3 were shown to react with allylmagnesium chloride to yield the corresponding ene-aldehydes 14 which underwent cycloaromatization to afford benzoannelated products 15 in low yields[6]. The ene-aldehydes 14 could also be oxidized through palladium catalyzed oxygenation to the corresponding keto – aldehyde 16 which were subsequently cycloaromatized to yield either phenols 17[8a] or the pyridines 18[8b] (Scheme 4). Alternatively the ene-aldehydes 22 (R = Me) obtained from similar transformations could be cycloaromatized to the various benzoannelated products 23 thus providing a general route for benzoannelation of active methylene ketones through β-silyloxyenones (Scheme 5)[6]. The same authors have also extended aromatic annelation methodology for the synthesis of catechol monoethers 27 through 1,2-addition of alkoxyallyl anion to 3 in the presence of zinc chloride followed by a series of transformations involving intermediates 24-26 shown in the Scheme 6[9].



11 12 13

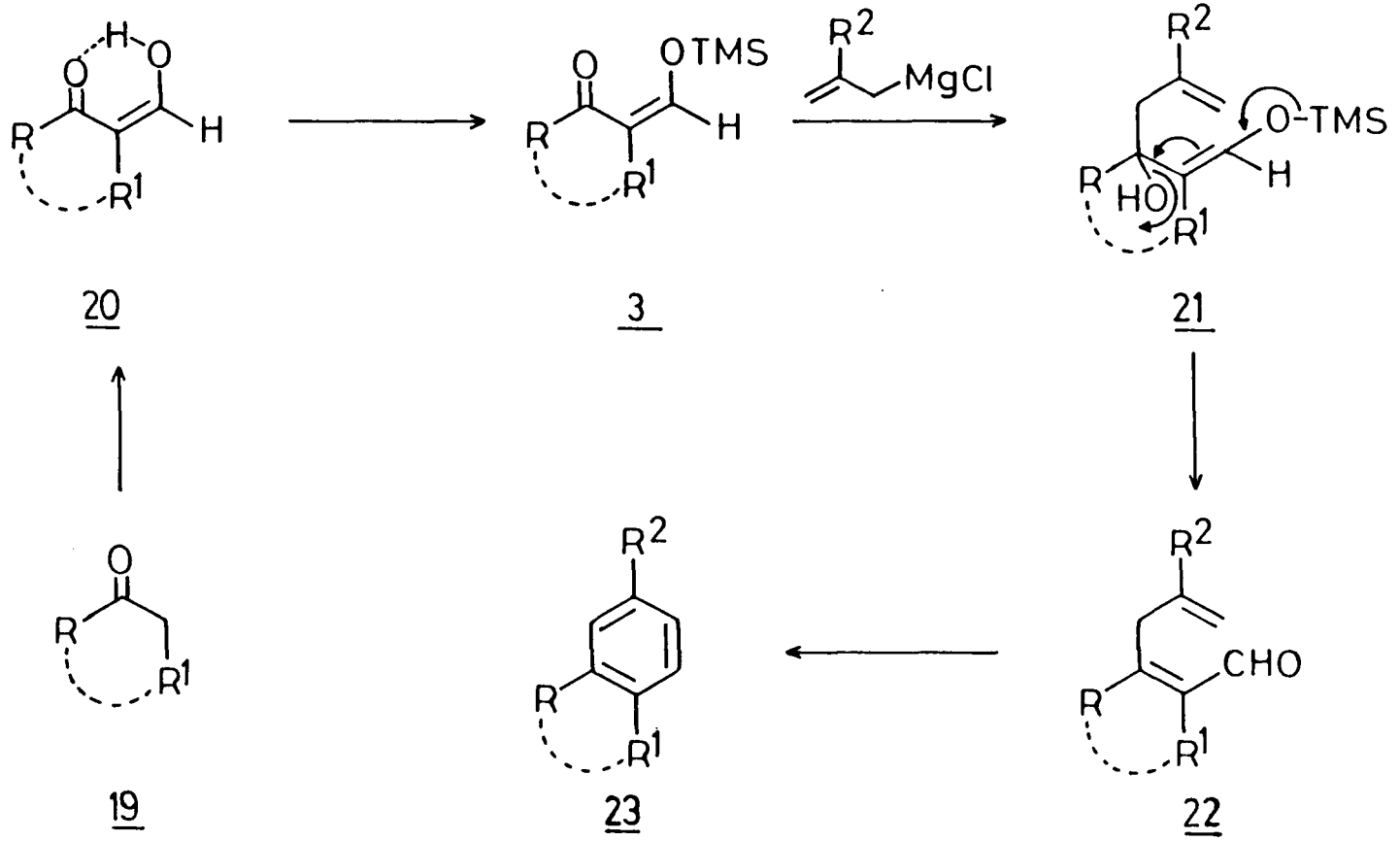
11-13, R = aryl, naphthyl

R^1 = H, Me

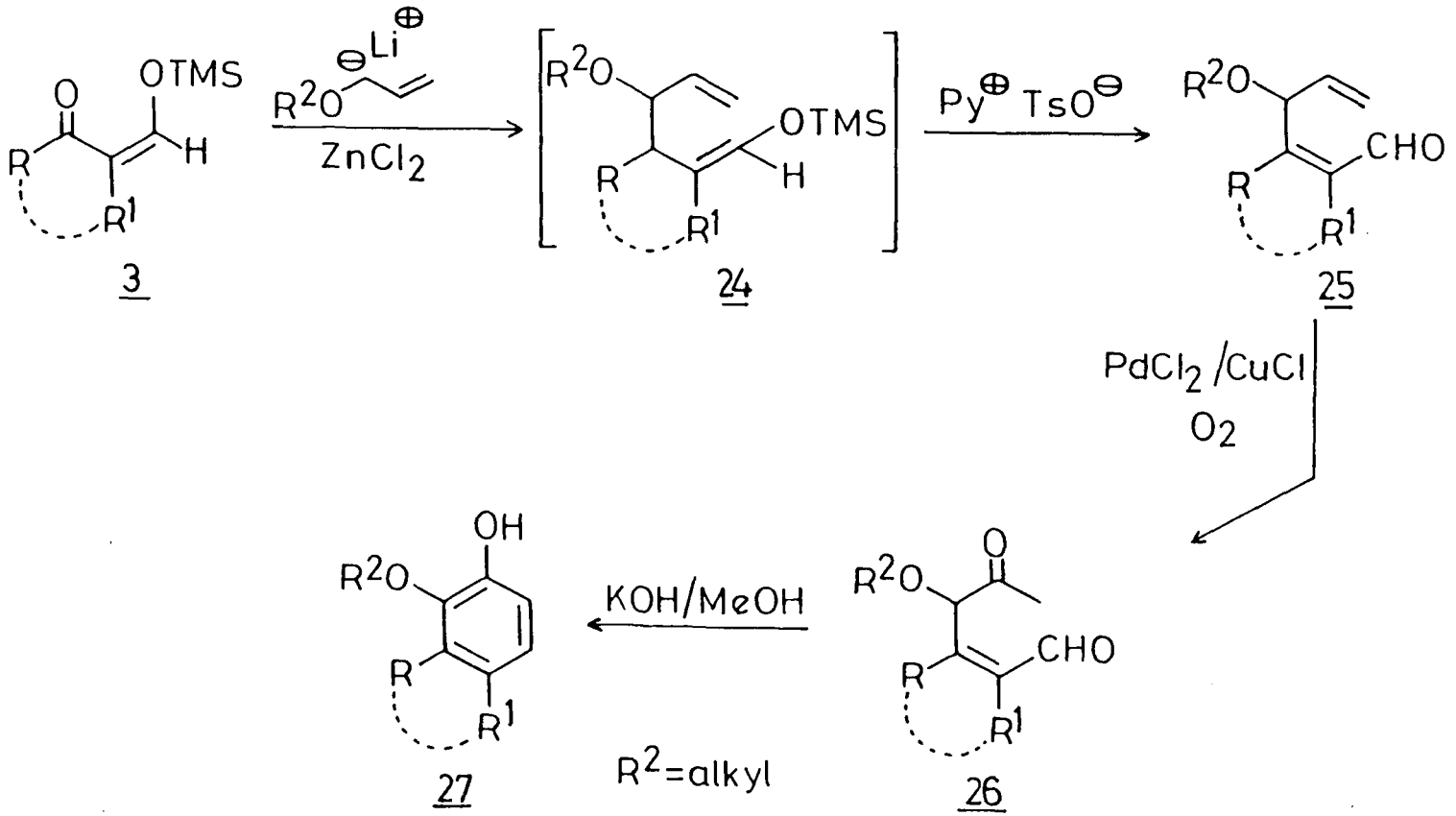


3 14 15 (low yields) 16 17 18

Scheme 4



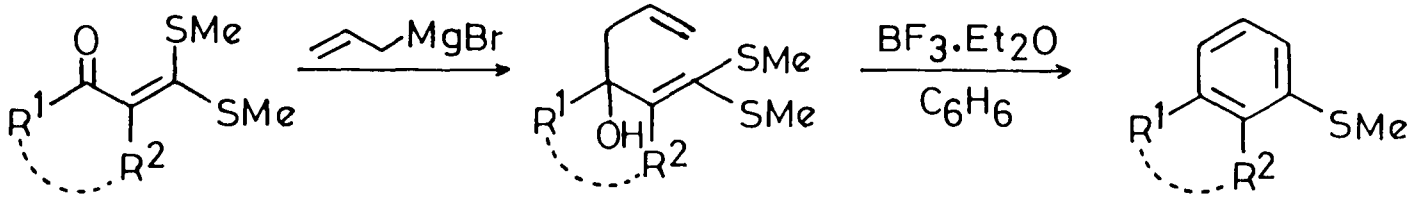
Scheme 5


OTMS
O
R
R1
H
3
R2O
Li⊕
⊖
ZnCl2
[
]
OTMS
H
24
Py⊕ TsO⊖
CHO
25
PdCl2 /CuCl
O2
O
CHO
26
KOH/MeOH
OH
27
R2=alkyl

Scheme 6

Singh, Ila and Junjappa first reported[10] a novel cycloaromatization sequence starting from α-oxoketene dithioacetals 28 which are easily accessible from the corresponding active methylene ketones in high yields in one pot reaction. Thus 28 reacted smoothly with allylmagnesium halides to yield the corresponding allyl alcohols 29 in quantitative yields. These alcohols were found to be unstable and were subjected to Lewis acid catalyzed cycloaromatization in the presence of boron-trifluoride etherate in benzene to yield the corresponding cycloaromatized benzenoids 30 in high yields. The reaction was extensively investigated and found to be of general synthetic application. Soon after the publication of this paper, Dieter and co-workers also reported[11] aromatic annelation essentially involving identical reaction sequence. Subsequently, the method developed in this laboratory was extended for the synthesis of substituted stilbenes (Scheme 7). Thus, cinnamoylketene dithioacetals 31 underwent facile 1,2-addition with allyl- and crotyl-magnesium chloride in highly regioselective manner followed by treatment with borontrifluoride etherate to afford the stilbene thiomethyl ethers 32 in good yields[12] (Scheme 7). This was the first report of stilbene synthesis involving the construction of one of the aromatic rings from the open-chain precursors. The method also possesses specific advantages since it can be used to synthesize unsymmetrical stilbenes with desired regiochemistry (Scheme 7)[12].

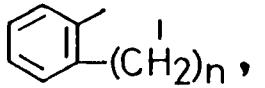
The α-oxoketene dithioacetals have therefore, manifested useful reactivity towards allylmagnesium halides leading to the corresponding aromatic systems. It was, therefore, considered of interest to study the reaction of these intermediates with propargylmagnesium bromide. Such a reaction

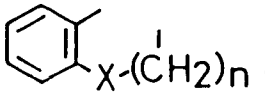


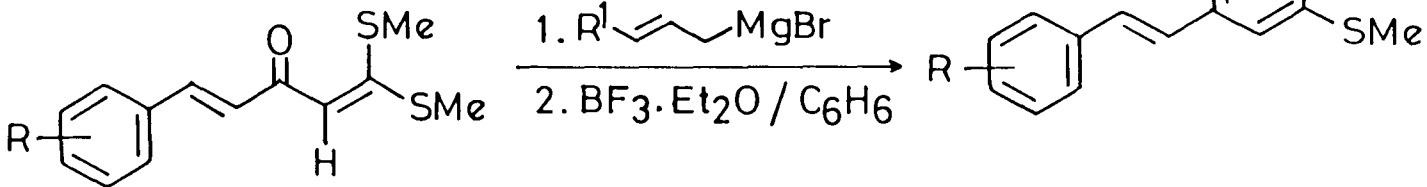
28 29 30

R^1 = aryl, alkyl ; R^2 = H

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

$R^1 = R^2 =$  , n = 1, 2

$R^1 = R^2 =$  , n = 1 2 ; X = S, O



31 32

R = Cl, MeO, H

R^1 = H, Me

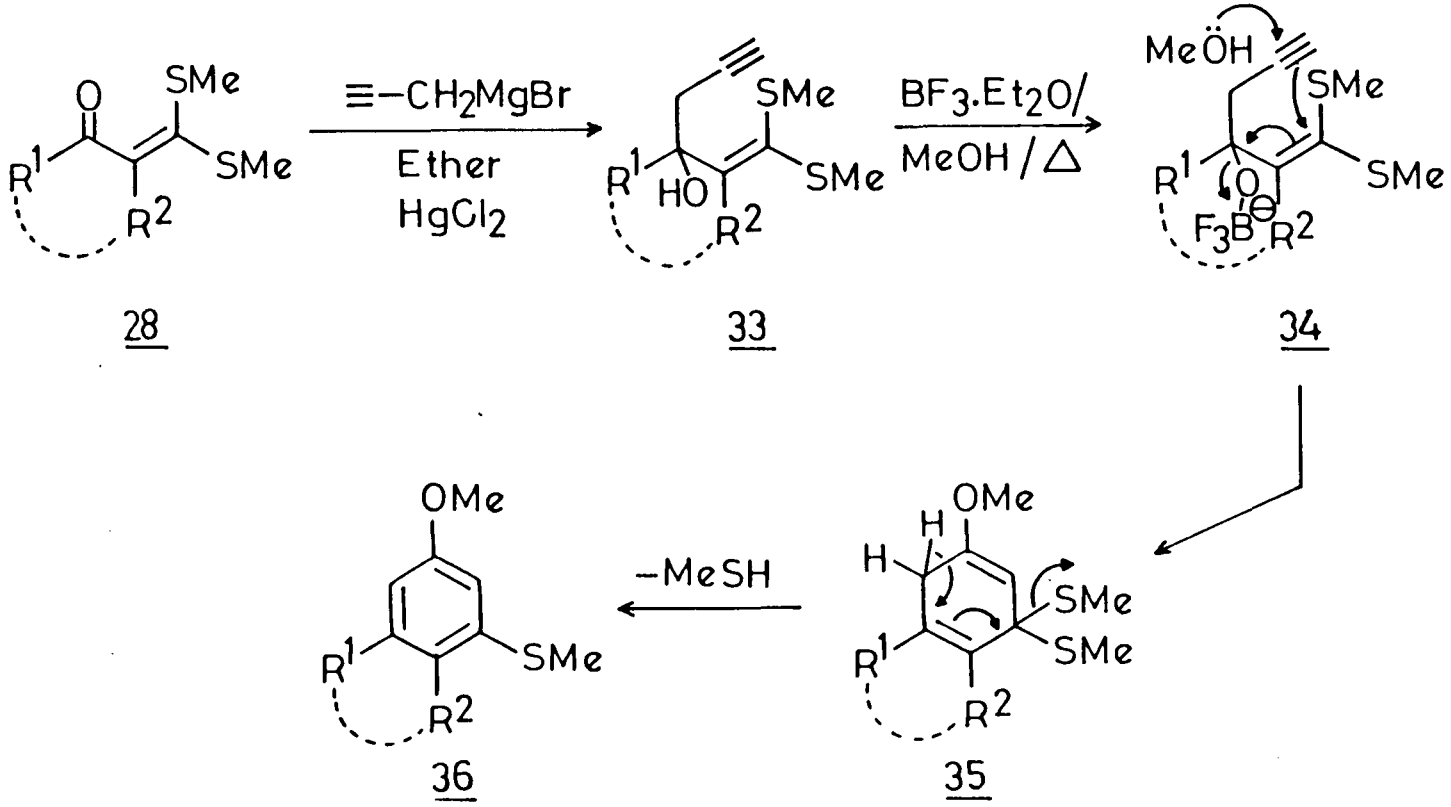
Scheme 7

will give the carbinolacetals 33 with a terminal acetylenic functionality that can participate intramolecularly with concomitant attack of external nucleophile on incipient vinyl cation during cycloaromatization to yield the corresponding benzenoids and other derivatives. A general sequence of these transformations involving the cycloaromatization of 33 in the presence of borontrifluoride and methanol as a nucleophile and as a solvent to yield the corresponding thioresorcinol dimethyl ethers 36 as shown in the Scheme 8. The scope and limitations of these reactions have been thoroughly investigated and results are described here.

II.2 RESULTS AND DISCUSSION

II.2A The Reaction of Cyclic α-Oxoketene Dithioacetals with Propargylmagnesium Bromide: A New General Synthesis of Annelated Thioresorcinal Dimethyl Ethers

When 2-[bis(methylthio)methylene]cyclohexanone (28a) was reacted with propargylmagnesium bromide, the intermediate carbinolacetal, formed exclusively in 1,2-manner in nearly quantitative yield, was directly subjected to borontrifluoride etherate catalyzed methanolysis. The reaction mixture after work-up, afforded a colourless oil (76%), which was characterized as 6-methoxy-8-methylthio-1,2,3,4-tetrahydronaphthalene (36a) (Scheme 9) on the basis of spectral and analytical data. Its mass spectrum exhibited molecular ion peak at m/z 208(M^+,100%) and was analyzed for $C_{12}H_{16}OS$ while its IR(neat) spectrum showed the peaks at 1590, 1575 and 1460 cm^{-1}. The structure of 36a was further confirmed from its ^1H NMR(CCl_4) spectrum. Thus, the multiplet at δ 1.62-1.98(4H) was assigned to the ring methylene protons, while the signal due to methylthio protons appeared at δ 2.33(s,3H). An another multiplet appeared at δ 2.40-2.91(4H)



28 33 34 35 36

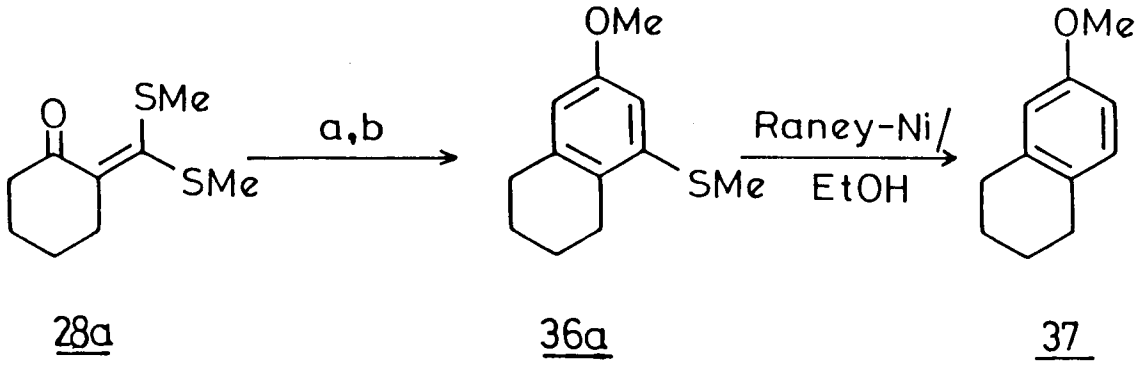
Scheme 8

due to ring methylene protons while a singlet at δ 3.66(3H) corresponded to the methoxy group. The two aromatic protons were present as sharp doublet (J=2.5Hz) at δ 6.25(1H,H-7) and δ 6.42(1H,H-5) respectively. The structure of 36a was further confirmed by subjecting it to Raney Nickel desulphurization to yield the known 6-methoxy tetralin 37[13] (Scheme 9).

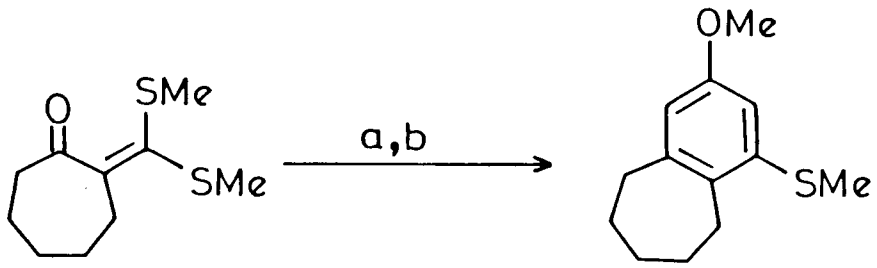
The probable mechanism for the formation of thioresorcinol derivative is shown in the Scheme 8. The cyclization proceeds as expected through intramolecular participation of propargyl triple bond with concomitant attack of methanol on the incipient vinyl cation 34, to give 35, followed by elimination of methylmercaptan to give benzoannelated products 36 (Scheme 8).

In order to explore the scope and generality of this transformation, other cyclic dithioacetals were also subjected to reaction with propargyl-magnesium bromide. Thus, 7-methylthio-9-methoxybenzosuberane (36b) was obtained in 71% yield, when 2-[bis(methylthio)methylene]cycloheptanone (28b) was subjected to similar reaction sequence as described for 28a (Scheme 9).

Interestingly, when 2-[bis(methylthio)methylene]cyclopentanone (28c) was subjected to similar reaction sequence, the expected cycloaromatized product 36c was not formed. Instead, the product isolated was characterized as β-propargyl ene ester 38 in 78% yield (Scheme 10). The structure of 38 was confirmed on the basis of its spectral and analytical data. Its mass spectrum exhibited a molecular ion peak at m/z 164 (M^+,44%) and it was analyzed for $C_{10}H_{12}O_2$ while its IR spectrum exhibited characteristic peaks at 2105 and 1704 cm^{-1} due to triple bond and ester carbonyl groups



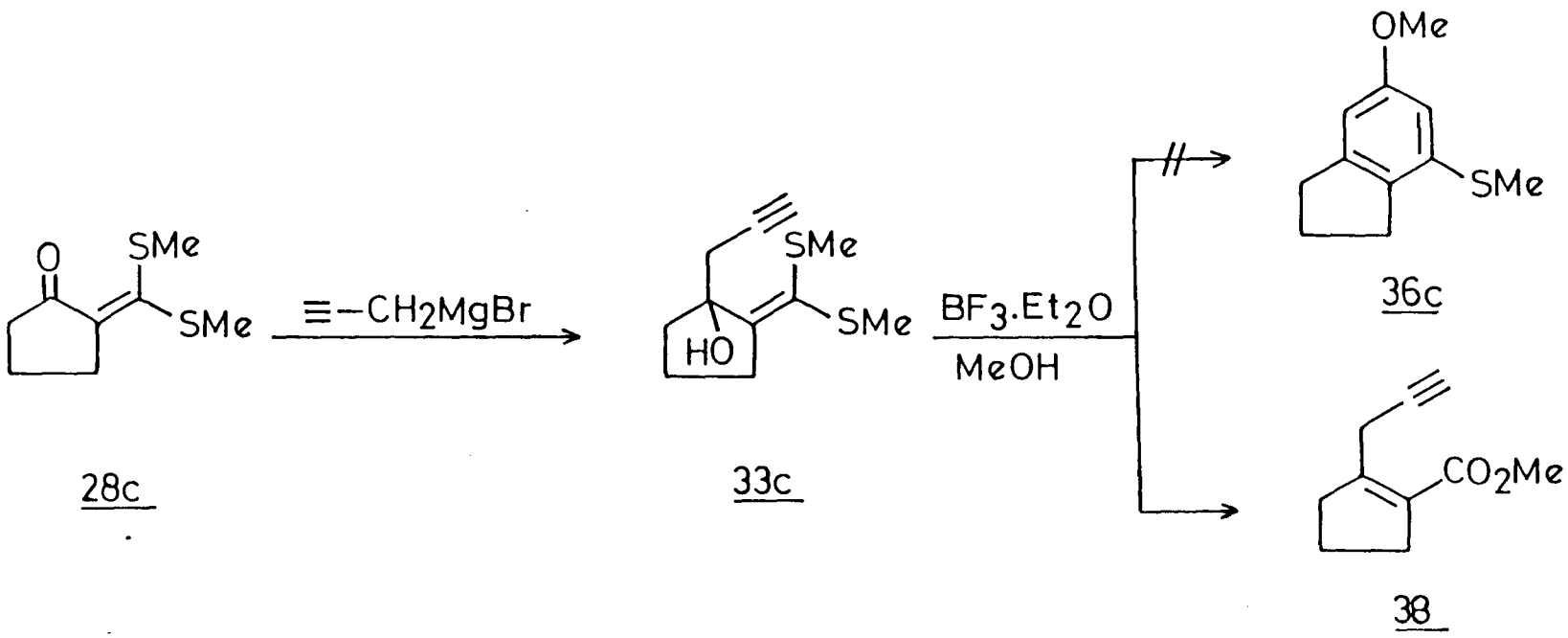
28a 36a 37



28b 36b

a=HC≡−CH_2MgBr ; b = $BF_3.Et_2O$ /MeOH

Scheme 9

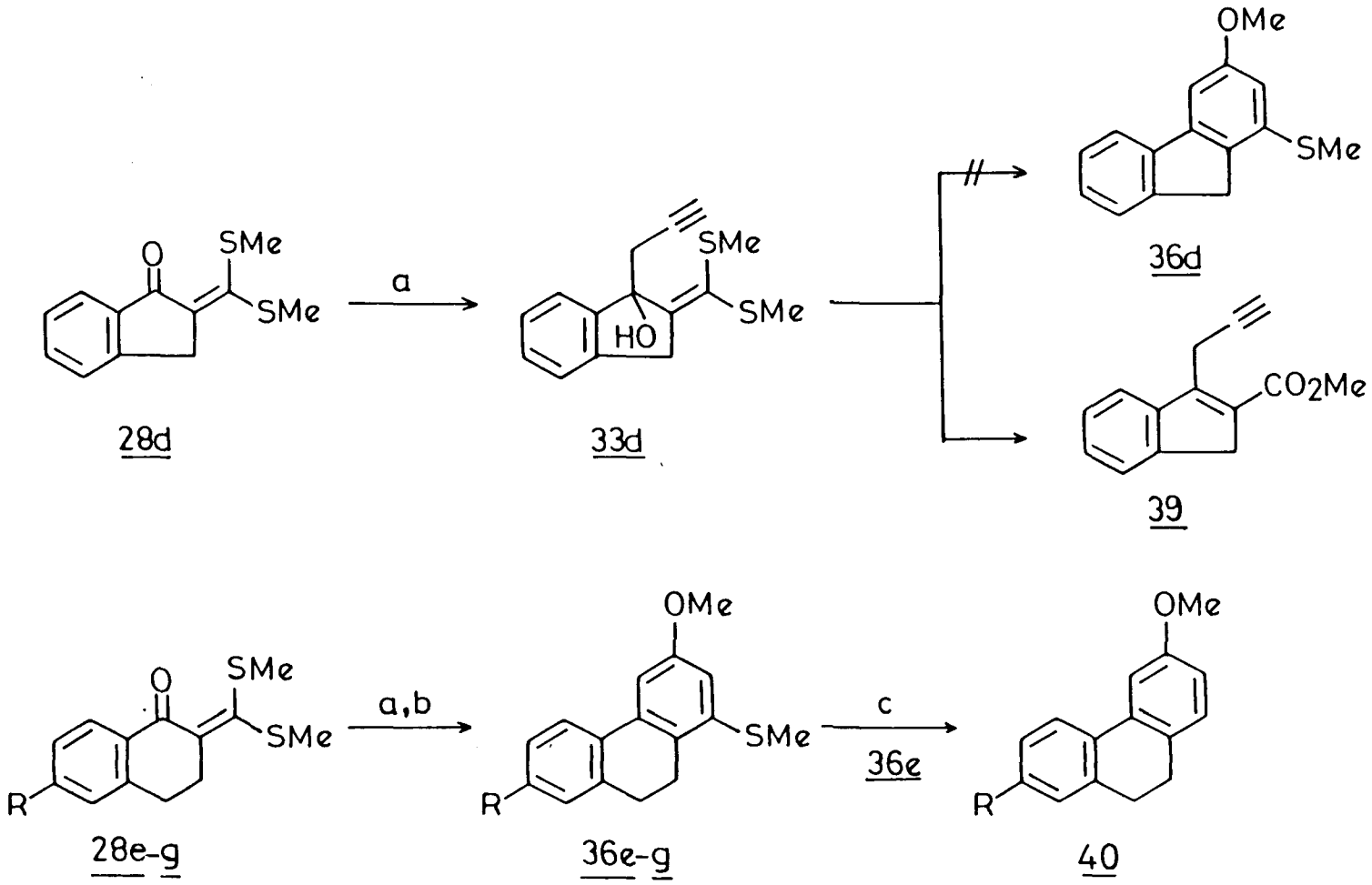


28c 33c 36c 38

Scheme 10

respectively. The structure of 38 was further confirmed from its ^{1}H NMR spectrum (CCl_4). Thus, the triplet at δ 1.79(1H,J=2.5Hz) was assigned to the acetylenic proton while the multiplets at δ 2.10-2.44 (2H) and δ 2.48-2.78(4H) were assigned to ring methylene protons. The propargyl CH_2 protons appeared as a broad singlet at δ 3.53(2H). The carbmethoxy protons appeared as a singlet at δ 3.60(3H). Thus, the formation of 36c was ruled out and structural assignment of 38 was fully confirmed. The failure of 33c to undergo cycloaromatization to yield 36c appears to be due to unfavourable geometry of 5-membered carbocyclic ring (Scheme 10). Similarly, the oxoketene dithioacetal 28d derived from indanone, though yielded the corresponding carbinolacetal 33d in high yield but failed to undergo cycloaromatization to 36d and the product isolated, on analysis, was characterized as β-propargyl ene ester 39. The spectral and analytical data of 39 were in agreement with the proposed structure and are described in the experimental section. Here, again the failure of 33d to undergo cyclization appeared to be due to difficulties in bringing both the 3-carbon atoms in coplanarity in the transition state (Scheme 11).

The method was further extended to other cyclic ketene dithioacetals derived from tetralones 28e-g when the corresponding dihydrophenanthrene derivatives 36e-g were obtained in 66-78% overall yields. One of them (36e) underwent facile desulphurization with W-4 Raney Nickel to afford the known 5,6-dihydro-2-methoxyphenanthrene (40)[14] (Scheme 11). The analytical and spectral data of 36e-g are described in the experimental section.



28, 36e, R=H

28, 36f, R= OMe

28, 36g, R= Me

a= HC≡C−CH2MgBr /Et2O

b= BF3.Et2O/ MeOH/ △

c = Raney-Ni/EtOH/ △

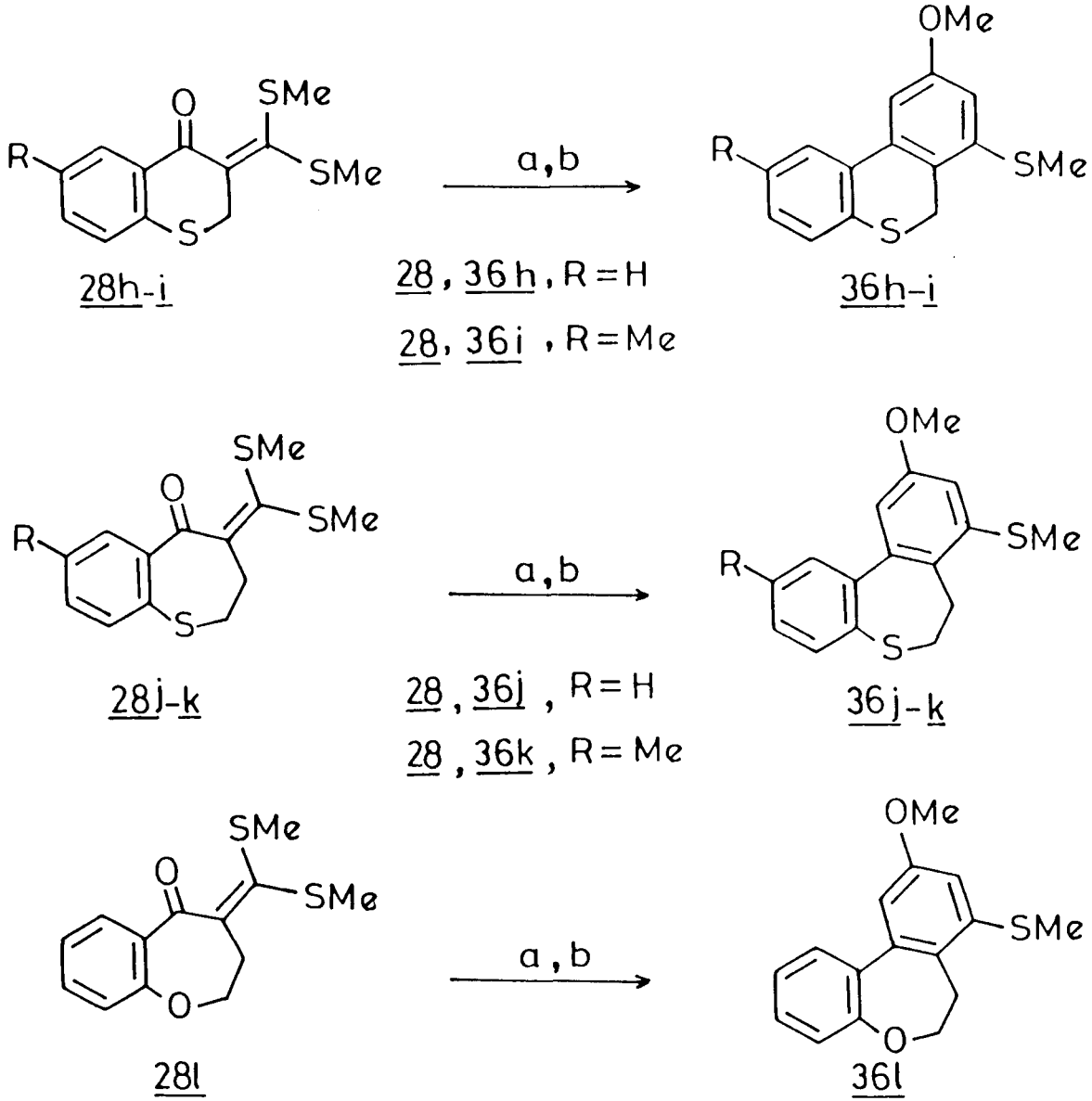
Scheme 11

The cycloaromatization transformations were also extended to the synthesis of novel fused polycyclic sulphur and oxygen heterocycles. Thus, the dithioacetals 28h-k derived from the corresponding benzothiapyran-4-one and benzthiepenone underwent 1,2-addition with propargylmagnesium bromide followed by the solvent assisted cycloaromatization of the resulting carbinolacetals to afford the corresponding dibenzothiapyrans 36h-i and dibenzothiepins 36j-k in 68-81% overall yields. Similarly, 4-[bis(methylthio)methylene]-2,3-dihydrobenzoxepin-5-(2H)-one (281) afforded 361 in 75% yield (Scheme 12). The spectral and analytical data of these products are given in the experimental section.

II.2B Reaction of Acyclic α-Oxoketene Dithioacetals with Propargylmagnesium Bromide: A New General Synthesis of Bis(alkylthio)biphenyls and Stilbenes

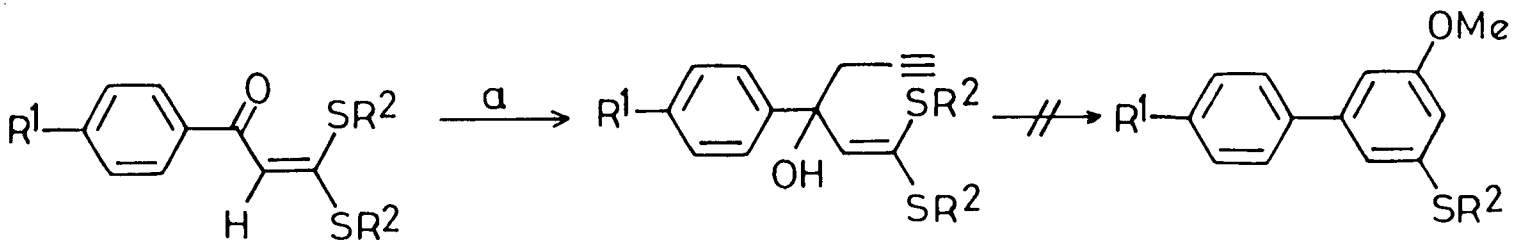
The reaction of propargylmagnesium bromide with α-oxoketene dithioacetals 41 derived from acetophenones has been extensively investigated and the results are described here.

The oxoketene dithioacetal 41a underwent smooth 1,2-addition with propargylmagnesium bromide to afford the corresponding carbinolacetal 42a in nearly quantitative yield. The crude carbinolacetal was then treated with borontrifluoride etherate in methanol as described above, the expected biphenyl 43a could not be detected and the reaction mixture was found to be an intractable tar (Scheme 13). However, when 42a was refluxed with milder Lewis acid like trimethyl borate [$B(OMe)_3$] in methanol for 20 hr, the product isolated was a colourless solid (m.p. 89-90°) (65%) and analyzed for $C_{15}H_{16}OS_2$. The product exhibited its mass spectrum, a molecular ion peak at m/z 276(M^+,100%) while its IR spectrum (KBr) exhibited medium intensity bands at 1610, 1582 and 1520 cm^{-1}. Its 90 MHz



a, $HC{\equiv}C{-}CH_2MgBr$ / Et_2O ; b , $BF_3.Et_2O$ /MeOH

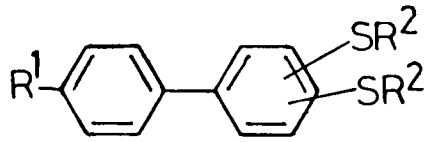
Scheme 12



41a-h 42a-h 43

a ≡ $-CH_2MgBr$

$B(OMe)_3$/ MeOH/Δ, 12-24h



44a-h

41-44a, R^1=OMe ; R^2=Me

b, R^1=H ; R^2=Me

c, R^1=Cl ; R^2=Me

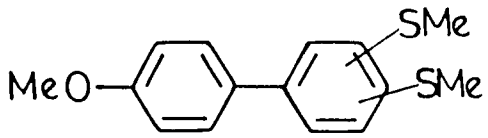
d, R^1=Br ; R^2=Me

e, R^1=R^2=Me

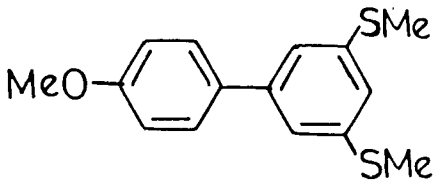
f, R^1=H ; R^2=Et

g, R^1=H ; R^2=n-pr

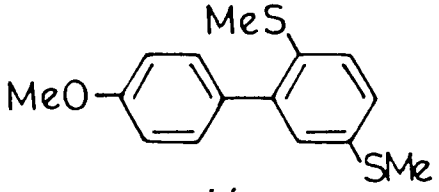
h, R^1=OMe ; R^2=i-pr



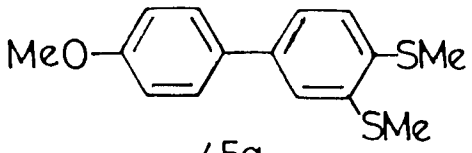
44A



44B



44a

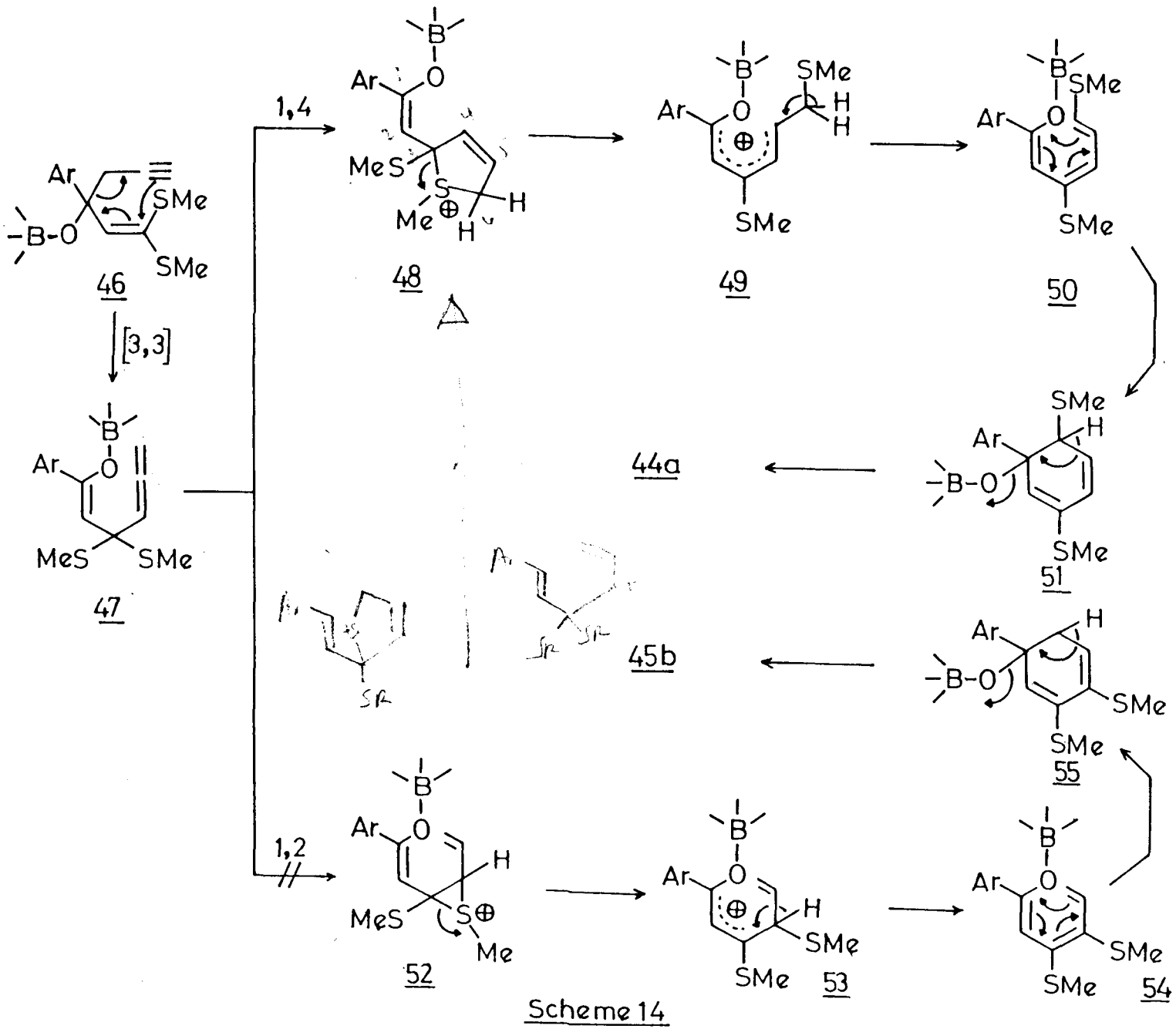


45a

Scheme 13

^{1}H NMR spectrum ($CDCl_3$) exhibited two peaks at δ 2.49(3H) and δ 2.52(3H) which were assigned to two methylthio groups besides a three proton singlet at δ 3.85 due to methoxy group. Also the ^{1}H NMR spectrum of the product showed absence of signals due to olefinic and propargyl protons, on the otherhand it exhibited a seven proton multiplet between δ 6.90-7.50 due to aromatic protons which apparently demonstrated that the cyclo-aromatization of the carbinol 42a has taken place in the presence of trimethyl borate to give bis(methylthio) biphenyl (44A) without incorporation of methanol. However, the problem to assign the correct positions of the methylthio groups in 44A became intricate and possibly an intramolecular methylthio shift took place as it was evident by the appearance of two peaks for two methylthio groups in the ^{1}H NMR spectrum which also indicates that these two methylthio groups are not symmetrically placed in the newly formed aromatic ring and rules out the possibility of 1,3-methylthio shift which will afford symmetrical bismethylthio biphenyl 44B. The remaining two possibilities of methylthio shift either 1,4- or 1,2- would give the structure 44a or 45a for the product (Scheme 13)

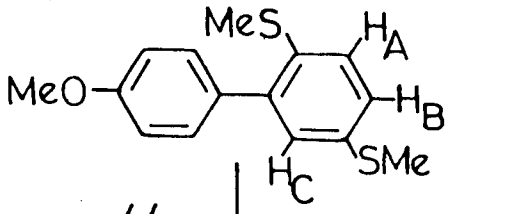
The probable mechanism of the formation of bis(methylthio)biphenyl (44a and 45a) is depicted in the Scheme 14. The borate complex of the carbinolacetal 46 first undergo a [3,3] sigmatropic shift to give an allene intermediate 47 in which two possibilities exist for migration of methylthio group. If the migration involves a 1,2-methylthio shift, it will form 3,4-bis(methylthio) biphenyl 45a while a 1,4-methylthio shift would afford the corresponding 2,5-bis(methylthio)derivative 44a (Scheme 14). The formation of 44a appears to be more favourable than that of 45a because the resulting pentadienyl carbocation 49 formed



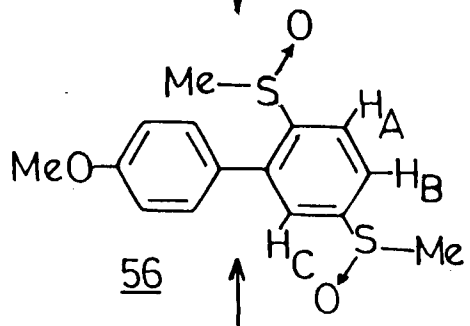
Scheme 14

through five membered intermediate 48 is more stable than the allyl carbocation 53 formed through episulfonium intermediate 52 (Scheme 14). Subsequent deprotonation and electrocyclization of resulting trienes (50 or 54) affords the intermediates 51 or 55 which on loss of $(MeO)_3B$-OH yields either 44a or 45a.

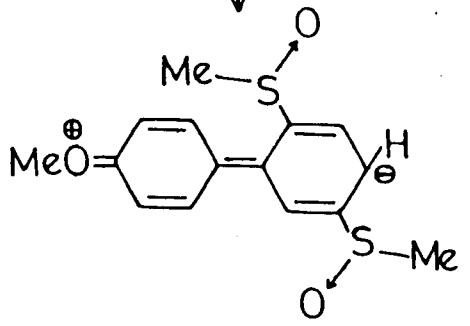
In order to differentiate between regioisomer 44a and 45a, the product was oxidized with m-chloroperbenzoic acid (MCPBA)[15] to give the corresponding sulfoxides (56 or 57). A comparison of ^1H NMR chemical shifts of aromatic protons in the biphenyl (44a or 45a) and the corresponding sulfoxides (56 or 57) also favors structure 44a formed by 1,4-methylthio migration, over 45a. Thus, the high resolution ^1H NMR (400 MHz) (CCl_4) spectrum of the product biphenyl clearly showed two singlets for methylthio groups at δ 2.49 and 2.52 respectively, while methoxy protons appeared at δ 3.85 as singlet. The aromatic protons of the methoxy substituted benzene ring appeared as A_2B_2 pattern at δ 6.97(2H) and 7.50(2H) respectively. The doublet at δ 7.26, which was integrated for one proton showed the coupling constant of 7.96Hz, characteristic of ortho coupling, was assigned for H_A proton. While a double doublet at δ 7.33(1H) with coupling constants of 7.96 and 1.87Hz respectively, was assigned for H_B proton. The H_C proton of the newly formed ring appeared as doublet at δ 7.38 with coupling constant J=1.87Hz which indicates the coupling with meta proton (H_B) (Scheme 15). The ^1H NMR ($CDCl_3$) of the corresponding sulphoxide 56 showed two singlets (3H each) for the methyl groups of the sulphoxide at δ 2.91 and 2.93 respectively while methoxy protons appeared at δ 3.87. The A_2B_2 pattern of aromatic protons of the methoxy substituted ring appears at δ 7.02(2H) and 7.65(2H) respectively. The



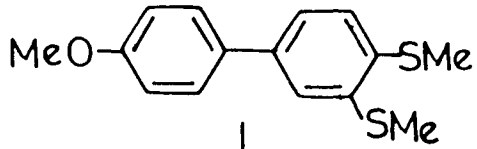
44a



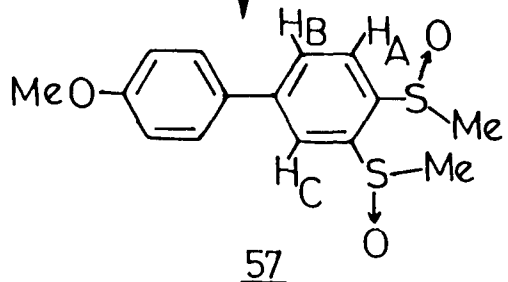
56



56A



45a



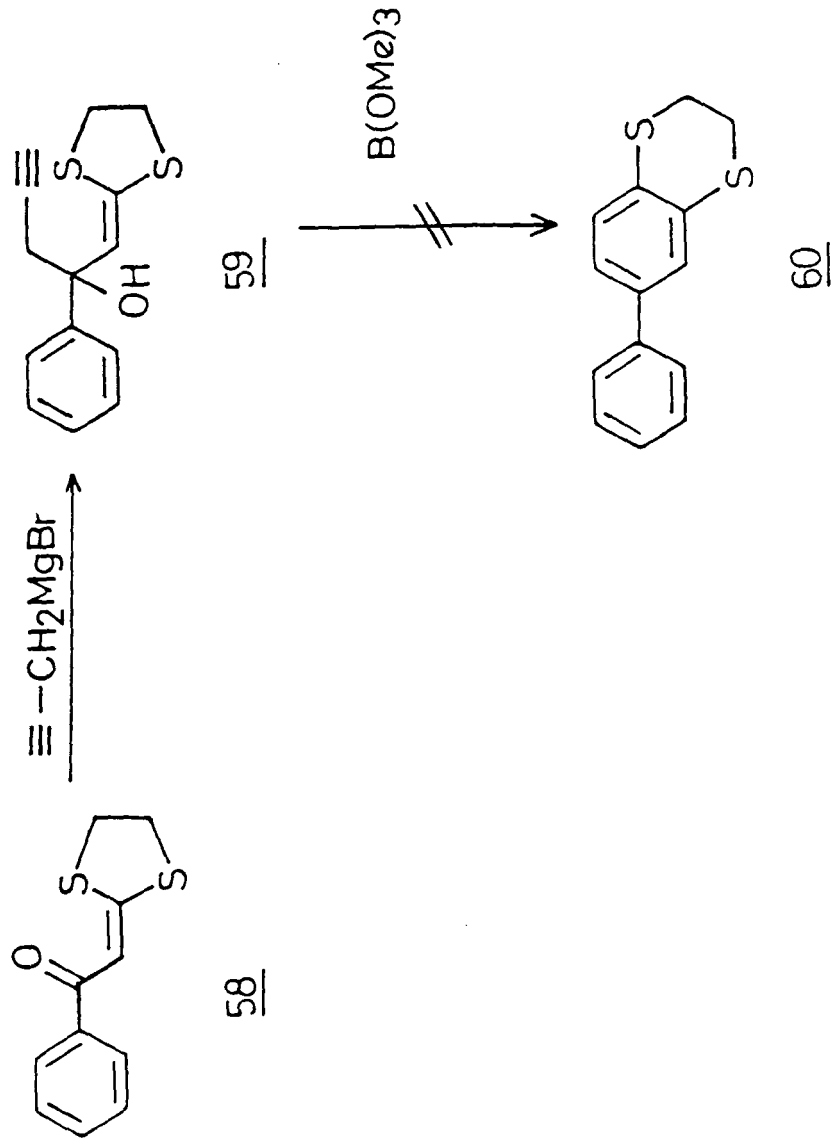
57

Table

Proton	44a(ppm)	J(Hz)	56(ppm)	J(Hz)	Δ ν(ppm)
H_A	7·26(d)	7·96	8·09(d)	8·11	0·83
H_B	7·33(dd)	7·96 1·87	7·91(dd)	8·11 1·72	0·58
H_C	7·38(d)	1·87	8·25(d)	1·72	0·87
H-3′ & H-5′	6·97(d)	9·0	7·02(d)	8·8	0·15
H-2′ & H-6′	7·50(d)	9·0	7·65(d)	8·8	0·15

Scheme 15

H_A proton appeared as a doublet at δ 8.09(J_{ortho}=8.11Hz) while H_B proton was present as double doublet at δ 7.91(J_{ortho}=8.11 and J_{meta}=1.72Hz) respectively. The signal due H_C proton appeared at δ 8.25 as doublet (J_{meta}=1.72Hz). From the above data (Table in Scheme 15), it is evident that there exists a considerable downfield deshielding effect on the chemical shifts of each proton i.e. H_A,H_B and H_C caused by adjacent sulphoxide groups in 56 as compared with 44a. The less downfield shift (Δν=0.58ppm) for H_B proton in 56 as compared to shifts of H_A and H_C protons (Δν=0.83 and 0.87ppm) is probably due to shielding of H_B proton to some extent caused by electron donating effect of methoxy group (resonance structure 56A). The downfield deshielding effect would have been observed only for adjacent protons (H_A and H_C ortho to sulfoxide group) for the regioisomer sulfoxide 57 which would be formed by oxidation of 45a. Thus, on the basis of carbonium ion stability in the transition state and oxidation studies, the structure 44a was preferred over 45a. Further support for the formation of 44a became apparent on the basis of cycloaromatization studies of the carbinolacetal 59 (Scheme 16) in which the structure is prepositioned for 1,2-shift under analogous reaction conditions. However, 59 failed to undergo cycloaromatization to give expected 60 on refluxing in presence of trimethylborate. The implication of this reaction also rules out the possibility of involvement of 1,2-shift for the formation of product 45a. Thus, on the basis of these arguments, the structure of the product isolated was assigned 2,5-bis(methylthio)-4'-methoxy biphenyl (44a) (Scheme 13). However, final confirmation of the structure will be obtained from its X-ray diffraction studies, the results of which are still awaited.



58 59 60

Scheme 16

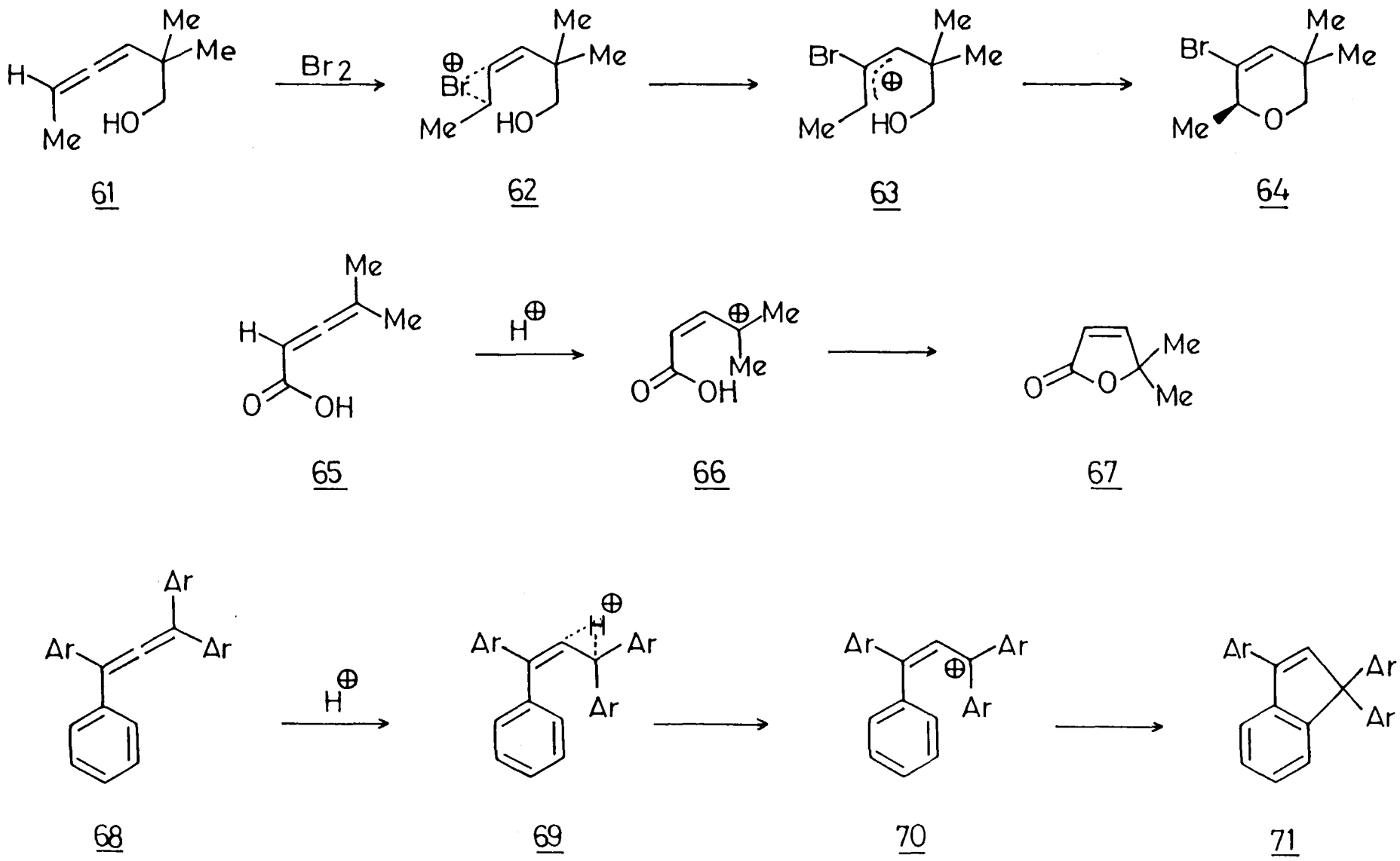
There are some parallel examples reported[16-19] in the literature of allenic systems where the five membered transition state as proposed in the Scheme 14 can be supported , though the stability of carbonium ions may not be necessarily the same under identical environment. Some of these literature examples are shown in the Scheme 17.

After confirming the structure of 44a where preferred 1,4-methylthio group migration was suggested to take place,further scope of these reactions was investigated. Thus, the α-oxoketene dithioacetals 41b-h under similar reaction condition employed for 41a, underwent smooth cycloaromatization to yield the corresponding 2,5-alkylthio-4'-substituted biphenyls 44b-h in 48-68% overall yields (Scheme 13). The analytical and spectral data of these biphenyls have been described in the experimental section.

The methodology, was further extended to examine its applicability on cinnamoylketene dithioacetals 72a-d to yield the corresponding stilbenes under analogous condition. Thus, cinnamoylketene dithioacetal 72a also underwent smooth 1,2-addition to yield the corresponding carbinol-acetal 73a which under analogous conditions afforded the 2,5-bis(methylthio) stilbene (74a) in 58% yield. The structure of 74a was in agreement with its analytical and spectral data. Similarly, other cinnamoylketene dithioacetal 72b-d also yielded the corresponding stilbenes 74b-d in 51-54% overall yields (Scheme 18). The spectral and analytical data of these stilbenes are described in the experimental section.

II.3 CONCLUSION

From the aforesaid results of the present investigation it is evident that the α-oxoketene dithioacetals are useful synthetic intermediates


Me
Me
H
HO
Me
61
Br 2
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HO
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62
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Me
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HO
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Me
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H⊕
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Me
Me
O
O
67
Ar
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H
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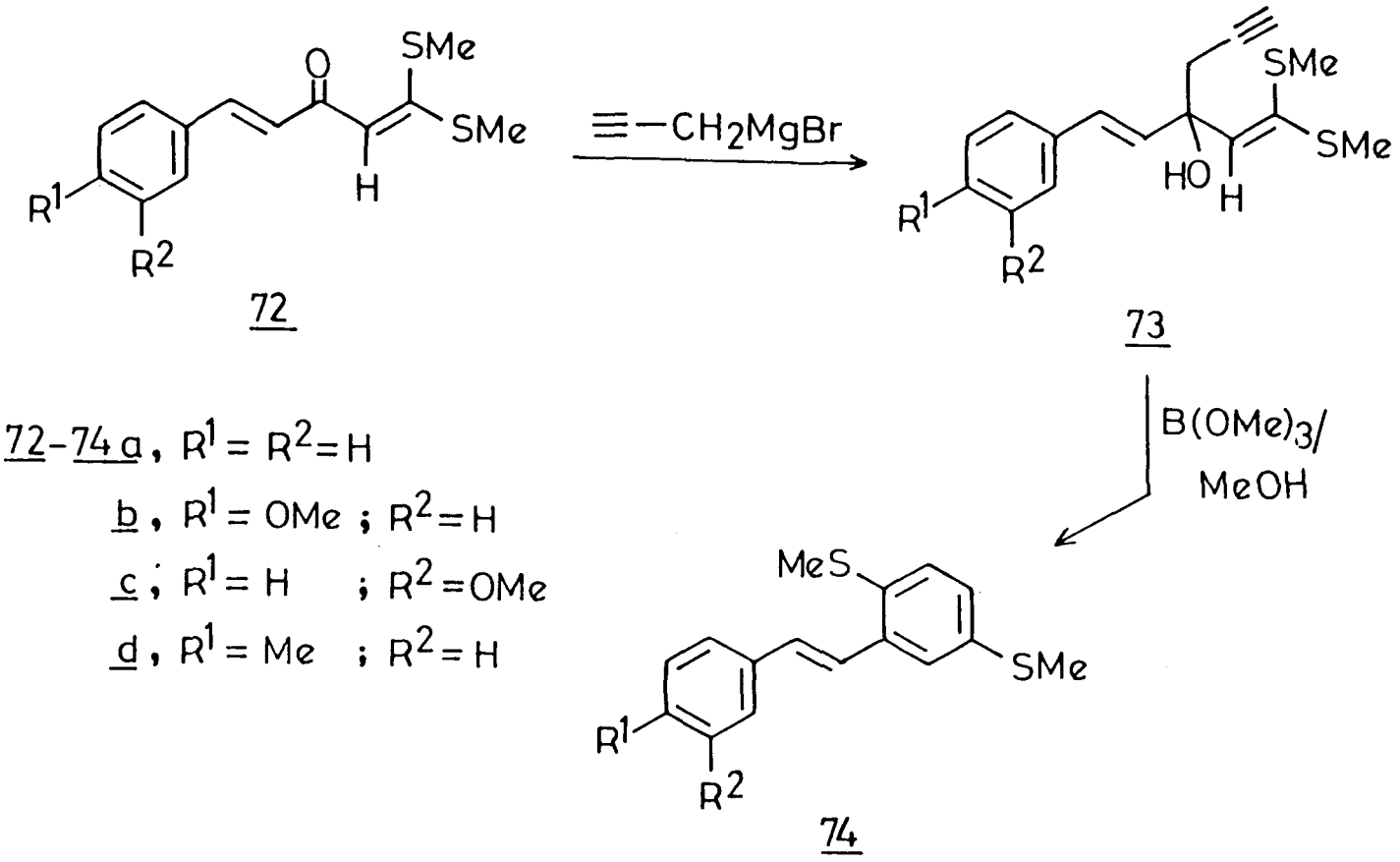
Ar
Ar
71

Scheme 17



72-74 a, $R^1 = R^2 = H$

b, $R^1 = OMe$; $R^2 = H$

c; $R^1 = H$; $R^2 = OMe$

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

Scheme 18

for the aromatic annelation sequence and constitutes a novel general methodology for cycloaromatization to yield the corresponding alkoxy benzenoids, biphenyl and stilbene derivatives. In the case of cyclic oxoketene dithioacetals, the external nucleophile participates in the ring closure whereas acyclic ketene dithioacetals prefer to undergo intramolecular reorganisation to yield the benzenoids. The migration of alkylthio group is of mechanistic interest and appears to involve the most preferred pathways due to both steric and electronic considerations. Thus, the methodology developed is of considerable synthetic importance and provides a simple two step route to substituted and annelated benzenoids from a wide variety of commercially available active methylene ketones.

II.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390, 90 MHz spectrometer, until otherwise stated and the chemical shift values are expressed as δ(ppm) downfield from Me_4Si as internal standard. ^{13}C NMR were recorded on Brucker WH-400 spectrometer. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. Elemental analysis were carried out on a Heraus CHN-O-RAPID instrument.

Starting Materials

The propargyl bromide (solution in toluene and stabilized with 0.3% magnesium oxide) was purchased (Aldrich) and was used after distillation. The commercial sample of acetophenone, 4-methylacetophenone, 4-methoxyacetophenone, 4-chloroacetophenone, 4-bromoacetophenone,

cyclopentanone, cyclohexanone, cycloheptanone, 1-tetralone, 6-methyl-tetralone, 6-methoxytetralone, methyl iodide, ethyl iodide, n-propyl bromide, 1,2-dibromopropane and i-propyl bromide were purified and dried before use whenever necessary. The cyclic ketones, 1-indanone[20] benzothiapyran-4-one[21], benzthiepenone[22] and 1-benzoxepin-5-(2H)one[23] were prepared according to reported procedures.

Grignard grade magnesium turnings (SISCO) were used for all Grignard reactions, which were carried out under nitrogen atmosphere. Boron-trifluoride etherate was distilled (125-26°C) before use while trimethylborate (99%) was purchased (Aldrich) and used as such. Diethyl ehter and benzene were dried over sodium wire and distilled prior to use.

W-4 Raney Nickel was prepared according to the reported procedure[24]. The previously reported[25-32] α-oxoketene dithioacetals were prepared by the general method described below.

General Procedure for the preparation of α-Oxoketene Dithioacetals (28a-l, 41a-h and 58):

A mixture of ketone (20 mmol) and carbondisulphide (20 mmol) was added dropwise to an ice cold and well stirred suspension of sodium t-butoxide (40 mmol) in dry benzene (200 ml) and the reaction mixture was allowed to stir at room temperature for 5-6 hrs. Acid free dimethyl sulphate (or required alkylhalide) (20 mmol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stir at room temperature for 6-10 hr. The reaction mixture was poured over ammonium chloride solution (250 ml) and the layers were separated. The aqueous layer was extracted with benzene (100 ml) and the combined benzene

extracts were washed with water (4x500 ml), dried (Na_2SO_4) and evaporated. Trituration of the oily residue with hexane gave the dithioacetals as yellow crystalline solids except in the case of 28a-c and 41f-g which were obtained as viscous oil in good yields. The physical and spectral data were compared with that of reported values.

Condensation of α-acylketene dithioacetals with aldehydes; General Procedure for the preparation of compounds 72a-d:

To a cooled and stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (60 mmol) in ethanol (30 ml), a solution of the α-acylketene dithioacetal (30 mmol) and the aldehyde (30 mmol) in minimum ethanol was added dropwise over a period of 5 minutes. The reaction mixture was brought to room temperature over a period of 20 minutes and further stirred at room temperature for 4-5 hrs. The mixture was diluted with cold water (100 ml) and solid separated was filtered, washed with water (4x100 ml) and dried. The physical and spectral data were found to be in confirmity with that of reported values,

General Procedure for the Reaction of Propargylmagnesium Bromide with α-Oxoketene Dithioacetals 28a-l, 41a-h and 58:

Magnesium (0.03g atom) activated with a catalytic amount of mercuric chloride was suspended in dry ether (25 ml) and propargyl bromide (3.57g, 30 mmol) was added dropwise at room temperature under nitrogen atmosphere. After completion of addition, the mixture was stirred further for 5 minutes then it was cooled and a solution of corresponding α-oxoketene dithioacetals (10 mmol) in dry benzene (25 ml) was added, dropwise and allowed the reaction mixture, to stir further for

1 hr. The reaction mixture was quenched with saturated ammonium chloride solution (100 ml) extracted with ether (2x100 ml). The combined ether extracts were washed with water and dried (Na_2SO_4) and distilled under reduced pressure to afford the crude carbinolacetals as a viscous liquid, which however, decomposed on attempted purification by silica gel column chromatography.

General Procedure for Borontrifluoride Etherate Catalyzed Benzoannelation of Carbinolacetals 33a-l:

To a solution of crude carbinolacetals (10 mmol) in superdry methanol (30 ml), borontrifluoride etherate (4 ml) was added and the reaction mixture was refluxed with stirring for 1 hr. The reaction mixture was cooled and poured into saturated sodium bicarbonate solution (100 ml), extracted with chloroform (2x100 ml). The organic layer was washed with water, dried (Na_2SO_4). Evaporation of solvent gave crude products which were purified by a column chromatography over silica gel to afford pure products using hexane as eluent.

The spectral and analytical data for benzoannelated products 36a-b, 36e-l and β-propargyl ene esters 38 and 39 are given below.

6-Methoxy-8-methylthio-1,2,3,4-tetrahydronaphthalene(36a); was isolated as colourless viscous oil; yield 76%; spectral data described in text. (Found: C,69.02; H,7.69; Calc. for $C_{12}H_{16}OS$: C,69.18; H,7.74%); m/z 208(M^+,100%), 193(84), 160(71).

7-Methoxy-9-methylthio-benzosuberane(36b); was isolated as colourless viscous liquid; yield 71%; IR ν_{max}(neat) 1592, 1571, 1461, 1452 cm^{-1}; ^1H NMR(CCl_4): 1.34-1.93(m,6H,$C\underline{H}_2$); 2.33(s,3H,$SC\underline{H}_3$); 2.60-2.98(m,4H, $C\underline{H}_2$); 3.69(s,3H,$OC\underline{H}_3$); 6.38(d,1H,J=2.5Hz,$\underline{H}$-8); 6.50(d,1H,J=2.5Hz,$\underline{H}$-6).

(Found: C,70.14; H,7.96; Calc. for $C_{13}H_{18}OS$: C,70.22; H,8.15%); m/z 222 (M^+,100%), 207(35), 174(27).

Methyl 4,5-dihydro-2-(1-propyne)-3H-cyclopent-1-ene-1-carboxylate (38); was isolated as colourless liquid (hexane); yield 78%; spectral data described in text. (Found: C,72.99; H,7.25; Calc. for $C_{10}H_{12}O_2$: C,73.14; H,7.37%); m/z 164(M^+,44%),

Methyl-1-(1-propyne)-3H-ind-1-ene-2-carboxylate (39); was isolated as colourless crystals (hexane); yield 82%; m.p. 118-119°C; IR ν_{max}(KBr) 2107, 1697, 1608 cm^{-1}; ^1H NMR($CDCl_3$): 1.85(t,1H,J=2.5Hz,-C≡C-H); 3.60 (brs,2H,CH_2-C≡C); 3.80(s,3H,CH_3O); 4.00(brs,2H,CH_2); 7.15-7.50(m,3H, ArH); 7.62-7.78(m,1H,ArH). (Found: C,79.15; H,5.68; Calc. for $C_{14}H_{12}O_2$: C,79.22; H,5.70%; m/z 212(M^+,98%), 152(100).

5,6-Dihydro-2-methoxy-4-(methylthio)phenanthrene (36e); was isolated as colourless crystals (hexane); yield 78%; m.p. 39-40°C; IR ν_{max}(KBr) 1600, 1581, 1560 cm^{-1}; ^1H NMR($CDCl_3$): 2.32(s,3H,SCH_3); 2.75(s,4H,CH_2); 3.72(s,3H,OCH_3); 6.60(d,1H,J=2.5Hz,H-3); 6.95(d,1H,J=2.5Hz,H-1); 7.03-7.45(m,3H,ArH); 7.45-7.73(m,1H,ArH). (Found: C,74.89; H,6.31; Calc. for $C_{16}H_{16}OS$: C,74.96; H,6.29%); m/z 256(M^+,90%), 241(29), 208(100), 193(20), 165(62).

5,6-Dihydro-2,8-dimethoxy-4-(methylthio)phenanthrene (36f); was isolated as colourless crystals (hexane); yield 66%; m.p. 45-46%; IR ν_{max}(KBr) 1595, 1560, 1500 cm^{-1}; ^1H NMR(CCl_4): 2.27(s,3H,SCH_3); 2.64(s,4H,CH_2); 3.29(s,3H,OCH_3); 3.32(s,3H,OCH_3); 6.36-6.68(m,3H,ArH); 6.80(d,1H,J=2.5Hz, H-1); 7.24-7.46(brd,1H,H-10). (Found: C,71.16; H,6.23; Calc. for $C_{17}H_{18}O_2S$: C,71.29; H,6.33%); m/z 286(M^+,100%), 271(16), 239(83), 226(22).

5,6-Dihydro-2-methoxy-8-methyl-4-(methylthio)phenanthrene (36g); was isolated as thick liquid; yield 77%; IR ν_{max}(neat) 1590, 1550, 1495 cm^{-1}; ^1H NMR(CCl_3): 2.24(s,3H,$C\underline{H}_3$); 2.37(s,3H,$SC\underline{H}_3$); 2.72(s,4H,$C\underline{H}_2$); 3.78(s,3H,$OC\underline{H}_3$); 6.60-6.72(m,1H,Ar$\underline{H}$); 6.90-7.72(m,3H,Ar$\underline{H}$); 7.35-7.61(m, 1H,Ar$\underline{H}$). (Found: C,75.45; H,6.73; Calc. for $C_{17}H_{18}OS$: C,75.51; H,6.71%); m/z 270(M^+,98%); 255(24); 222(100), 207(18).

9-Methoxy-1-(methylthio)-2H-benzothiapyrano[3,4-b][1]benzene (36h); was isolated as colourless crystals (hexane); yield 72%; m.p. 89-90°C; IR ν_{max}(KBr) 1588, 1533 cm^{-1}; ^1H NMR($CDCl_3$): 2.41(s,3H,$SC\underline{H}_3$); 3.80(s,3H, $OC\underline{H}_3$); 3.80(s,2H,S-$C\underline{H}_2$); 6.75(d,1H,J=2.0Hz,$\underline{H}$-10); 6.95(d,1H,J=2.0Hz, $\underline{H}$-8); 7.00-7.45(m,3H,Ar$\underline{H}$); 7.58-7.71(m,1H,Ar$\underline{H}$). (Found: C,65.52; H,4.98; Calc. for $C_{15}H_{14}OS_2$: C,65.66; H,5.14%); m/z 274(M^+,80%), 259(100), 226(53).

9-Methoxy-6-methyl-1-(methylthio)-2H-benzothiapyrano[3,4-b][1]benzene (36i); was isolated as colourless solid (hexane); m.p. 58-59°C; yield 68%; IR ν_{max}(KBr) 1585, 1572, 1550 cm^{-1}; ^1H NMR(CCl_4): 2.29(s,3H,$C\underline{H}_3$); 2.36(s,3H,$SC\underline{H}_3$); 3.75(s,3H,$OC\underline{H}_3$); 3.82(s,2H,$C\underline{H}_2$); 6.66-7.24(m,4H,Ar$\underline{H}$); 7.38(s,1H,$\underline{H}$-8). (Found: C,67.91; H,5.47; Calc. for $C_{16}H_{16}OS_2$: C,68.01; H,5.59%); m/z 288(M^+,78%), 273(100).

2,3-Dihydro-10-methoxy-1-(methylthio)benzothiepino[4,5-b][1]benzene(36j); was isolated as colourless crystals (hexane); m.p. 98-99°C; yield 69%; IR ν_{max}(KBr) 1595, 1570, 1558 cm^{-1}; ^1H NMR(CCl_4): 2.46(s,3H,$SC\underline{H}_3$); 2.79-3.28(m,2H,$C\underline{H}_2$); 3.32-3.64(m,2H,$C\underline{H}_2$); 3.74(s,3H,$OC\underline{H}_3$); 6.54(d,1H, J=2.0Hz,$\underline{H}$-11); 6.72(d,1H,J=2.0Hz,$\underline{H}$-9); 7.08-7.60(m,4H,Ar$\underline{H}$). (Found: C,66.57; H,5.62; Calc. for $C_{16}H_{16}OS_2$: C,66.63; H,5.59%); m/z 288(M^+, 100%), 276(15), 260(66), 241(10).

2,3-Dihydro-10-methoxy-7-methyl-1-(methylthio)-benzothiepino[4,5-b] benzene (36k); was isolated as colourless crystals (hexane); m.p. 125-126°C; yield 81%; IR ν_{max}(KBr) 1588, 1572, 1458 cm^{-1}; ^1H NMR (CCl_4): 2.31(s,3H,$C\underline{H}_3$); 2.42(s,3H,$SC\underline{H}_3$); 2.78-3.25(m,2H,$C\underline{H}_2$); 3.25-3.50(m,2H,$C\underline{H}_2$); 3.65(s,3H,$OC\underline{H}_3$); 6.53(d,1H,J=2.0Hz,$\underline{H}$-11); 6.68(d, 1H,J=2.0Hz,$\underline{H}$-9); 7.02-7.30(m,2H,$\underline{H}$-5 and $\underline{H}$-7); 7.36(brd,1H,J=2.0Hz, $\underline{H}$-8). (Found: C,67.42; H,5.88; Calc. for $C_{17}H_{18}OS_2$: C,67.51; H,6.00%); m/z 302(M^+,100%), 287(29), 274(92), 254(13).

2,3-Dihydro-10-methoxy-1-(methylthio)-benzoxepino[4,5-b][1]benzene(361); was isolated as colourless crystals (hexane); m.p. 68-69°C; yield 75%; IR ν_{max}(KBr) 1594, 1563, 1489, 1466, 1427 cm^{-1}; ^1H NMR(CCl_4): 2.28(s, 3H,$SC\underline{H}_3$); 2.78(t,2H,J=7.5Hz,$C\underline{H}_2$); 3.60(s,3H,$OC\underline{H}_3$); 4.32(t,2H,J=7.5Hz, $C\underline{H}_2$); 6.50-6.72(m,2H,$\underline{H}$-9 and $\underline{H}$-11); 6.84-7.34(m,4H,Ar$\underline{H}$). (Found: C,70.61; H,6.04; Calc. for $C_{16}H_{16}O_2S$: C,70.56; H,5.92%); m/z 272(M^+,100%), 257(74), 224(16).

General Procedure for Reductive Dethiomethylation of Thioresorcinol dimethyl ethers 36a and 36e:

A solution of the corresponding thioresorcinol dimethyl ether (0.5 mmol) in methanol (75 ml) was stirred at room temperature with W-4 Raney Nickel (ca.15-20 times by weight) for 3 hr. (monitored by t.l.c.). The Nickel was separated by filtration and residue was washed with methanol. The methanol was evaporated and the product was extracted with chloroform (50 ml), washed with water (50 ml), dried (Na_2SO_4), evaporated and purified by passing through silica gel column.

6-Methoxy-1,2,3,4-tetrahydronaphthalene (37); was isolated as colourless oil; yield 66%; IR ν_{max}(neat) 1610, 1575, 1500 cm^{-1}; ^1H NMR(CCl_4):

1.68-1.98(m,4H,$C\underline{H}_2$); 2.53-2.84(m,4H,$C\underline{H}_2$); 3.69(s,3H,$OC\underline{H}_3$); 6.57(s, 1H,$\underline{H}$-5); 6.63(d,1H,J=2.0Hz,$\underline{H}$-7); 6.95(d,1H,J=9.0Hz,$\underline{H}$-8). (Found: C,81.37; H,8.59; Calc. for $C_{11}H_{14}O$: C,81.44; H,8.70%).

5,6-Dihydro-2-methoxy-phenanthrene (40); was isolated as colourless solid (hexane); m.p. 55-56°C; yield 69%; IR ν_{max}(KBr) 1610, 1564, 1500 cm^{-1}; ^1H NMR(CCl_4): 2.73(s,4H,$C\underline{H}_2$); 3.73(s,3H,$OC\underline{H}_3$); 6.63(dd,1H, J=9.0Hz and 2.0 Hz, $\underline{H}$-3); 6.90-7.40(m,5H,Ar$\underline{H}$); 7.49-7.78(m,1H,$\underline{H}$-10). (Found: C ,85.48; H,6.59; Calc. for $C_{15}H_{14}O$: C,85.68; H,6.71%).

General Procedure for Trimethylborate Catalyzed Cyclization of the Carbinolacetals 42a-h, 59, 73a-d; Synthesis of 2,5-Bis(alkylthio) Biphenyls 44a-h and Stilbenes 74a-d:

The crude carbinolacetals (10 mmol) were refluxed with trimethylborate (99% , 15 ml) in dry methanol (75 ml) for 24-30 hrs(monitored by t.l.c.). The reaction mixture was then cooled, poured into saturated sodium bicarbonate solution (100 ml) extracted with chloroform (2x100 ml). Organic layer was washed with water and dried (Na_2SO_4). Evaporation of solvent yielded crude products. Analytically pure products were obtained by passing the crude product through a column of neutral alumina using hexane as eluent.

Spectral and analytical data for the cycloaromatized products 44a-h and 74a-d are described below.

2,5-Bis(methylthio)-4'-methoxybiphenyl(44a); was isolated as colourless needles (hexane); m.p. 89-90°C; yield 65%; spectral data described in text. (Found: C,65.02; H,5.89; Calc. for $C_{15}H_{16}OS_2$: C,65.18; H,5.84%); m/z 276(M^+,100%), 261(13), 228(20), 213(5), 197(32).

2,5-Bis(methylsulphonyl)-4'-methoxybiphenyl (56):

A solution of 2,5-bis(methylthio)-4'-methoxybiphenyl (44a) (1.38g, 5 mmol) in dichloromethane (15 ml) was cooled in ice bath and m-chloroperbenzoic acid (3.13g of 55% MCPBA, 10 mmol) was added. The solution was allowed to warm to room temperature over the next hour, diluted with chloroform (50 ml), washed twice with 10% of sodium bicarbonate solution and once with water, and dried (Na_2SO_4). Removal of solvent followed by recrystallization of residue from ether gave colourless crystals; m.p.147-148°C; yield 84%; IR ν_{max}(KBr) 1602, 1575, 1510, 1060 (ν_{SO}) cm^{-1}; ^1H NMR data described in text; ^{13}C NMR (17.0 MHz) ($CDCl_3$): 43.00, 43.12($SO\underline{C}H_3$); 54.96($O\underline{C}H_3$); 114.18, 120.60, 123.74, 127.97, 129.70(aromatic $\underline{C}H$); 130.37, 140.00, 143.26, 144.89, 159.93 (quaternary, $\underline{C}$). (Found: C,58.33; H,5.20; Calc. for $C_{15}H_{16}O_3S_2$: C,58.42; H,5.23%); m/z 308(M^+,100%), 293(23), 276(20), 260(53).

2,5-Bis(methylthio)biphenyl (44b); was isolated as colourless needles (hexane); m.p. 55-56°C; yield 62%: IR ν_{max}(KBr) 1595, 1575, 1540 cm^{-1}; ^1H NMR(400 MHz) ($CDCl_3$): 2.51(s,3H,$SC\underline{H}_3$); 2.53(s,3H,$SC\underline{H}_3$); 7.28(d,1H, $J_{3,4}$=7.9Hz,$\underline{H}$-3); 7.35(dt,1H,$J_{3',4'}$=7.3Hz,$J_{2',4'}$=1.4Hz,$\underline{H}$-4'); 7.38(dd,1H, $J_{3,4}$=7.9Hz,$J_{4,6}$=1.96Hz,$\underline{H}$-4); 7.43(d,1H,$J_{4,6}$=1.96Hz,$\underline{H}$-6); 7.44(d,2H, J=7.3Hz,$\underline{H}$-3' and $\underline{H}$-5'); 7.57(d,2H,J=7.3Hz,$\underline{H}$-2' and $\underline{H}$-6'); ^{13}C NMR (62.97 MHz) ($CDCl_3$): 16.54, 16.61($SC\underline{H}_3$); 124.82, 126.25, 126.85, 127.33, 127.66, 128.72 (arom, $\underline{C}H$); 137.25, 138.36, 139.28, 140.45(quat.$\underline{C}$). (Found: C,68.15; H,5.61; Calc. for $C_{14}H_{14}S_2$: C, 68.25; H,5.73%); m/z 246(M^+,100%), 198(27), 167(34), 152(12).

2,5-Bis(methylthio)-4'-chlorobiphenyl (44c); was isolated as colourless needles (hexane); m.p. 115-116°C; yield 68%; IR ν_{max}(KBr) 1491, 1453,

1431 cm^{-1}; ^1H NMR($CDCl_3$): 2.44(s,3H,SCH_3); 2.46(s,3H,SCH_3); 7.10-7.44(m,7H,ArH). (Found: C,59.69; H,4.76; Calc. for $C_{14}H_{13}ClS_2$: C,59.88; H,4.67%); m/z 282(M^+,44%), 280(M^+,100), 234(9), 232(22), 203(11), 201(33), 197(8).

2,5-Bis(methylthio)-4'-bromobiphenyl (44d); was isolated as colourless needles (hexane); m.p. 132-133°C; yield 66%; IR ν_{max}(KBr) 1483, 1440, 1420 cm^{-1}; ^1H NMR(CCl_4): 2.22(s,6H,SCH_3); 6.92-7.24(m,7H,ArH); ^{13}C NMR (67.89 MHz) ($CDCl_3$): 16.29, 16.49(SCH_3); 124.60, 125.62, 127.09, 128.50 (arom CH); 132.00; 132.44, 137.62, 137.77, 138.35, 139.37(quaternary,C). (Found: C,51.76; H,4.22; Calc. for $C_{14}H_{13}BrS_2$: C,51.65; H,4.02%); m/z 327(M^+,98%), 325(M^+,100), 247(27), 245(29), 230(40).

2,5-Bis(methylthio)-4'-methylbiphenyl (44e); was isolated as colourless needles (hexane); m.p. 75-76°C; yield 48%; IR ν_{max}(KBr) 1503, 1445, 1425 cm^{-1}; ^1H NMR(CCl_4): 2.32(s,3H,CH_3); 2.40(s,3H,SCH_3); 2.42(s,3H, SCH_3); 6.88-7.45(m,7H,ArH). (Found: C,68.99; H,6.32; Calc. for $C_{15}H_{16}S_2$: C,69.18; H,6.19%); m/z 260(M^+,100%), 212(27), 181(36), 165(16).

2,5-Bis(ethylthio)biphenyl (44f); was isolated as colourless liquid; yield 61%; IR ν_{max}(neat) 1600, 1580, 1535 cm^{-1}; ^1H NMR(CCl_4): 1.25(t, 6H,J=7.5Hz,CH_3); 2.78(q,2H,J=7.5Hz,CH_2); 2.82(q,2H,J=7.5Hz,CH_2); 7.06-7.55(m,8H,ArH). (Found:C,70.19; H,6.68; Calc. for $C_{16}H_{18}S_2$: C,70.02; H,6.61%); m/z 274(M^+,100%), 246(38), 212(20).

2,5-Bis(n-propylthio)biphenyl (44g); was isolated as yellow oil; yield 63%; IR ν_{max}(neat) 1600, 1580, 1445 cm^{-1}; ^1H NMR(CCl_4): 1.01(t,6H,J=7.5 Hz,CH_3); 1.70(sext,4H,J=7.5Hz,CH_2); 2.81(t,2H,J=6.0Hz,CH_2); 2.84(t,2H, J=6.0Hz,CH_2); 7.18-7.56(m,8H,ArH). (Found: C,71.52; H,7.27; Calc. for

$C_{18}H_{22}S_2$: C,71.47; H,7.33%); m/z 302(M^+,100%), 260(97), 218(53), 184(88), 152(33).

2,5-Bis(isopropylthio)-4'-methoxybiphenyl (44h); was isolated as colourless needles (hexane); m.p. 95-96°C; yield 64%; IR ν_{max}(KBr) 1604, 1518, 1458, 1440 cm^{-1}; ^1H NMR(250 MHz) ($CDCl_3$): 1.35(d,6H, J=6.71Hz,C<u>H</u>$_3$); 1.36(d,6H,J=6.71Hz,C<u>H</u>$_3$); 3.48-3.54(m,2H,C-<u>H</u>); 3.84(s, 3H,OC<u>H</u>$_3$); 6.98(d,2H,A_2B_2,J=8.85Hz,,Ar<u>H</u>); 7.32(dd,1H,$J_{3,4}$=7.93Hz,$J_{4,6}$= 1.83Hz,<u>H</u>-4); 7.38(d,1H,$J_{3,4}$=7.93Hz,<u>H</u>-3); 7.50(d,2H,A_2B_2,J=8.85Hz, Ar<u>H</u>); 7.52(d,1H,$J_{4,6}$=1.83Hz,<u>H</u>-6); ^{13}C NMR(22.6 MHz)($CDCl_3$): 22.98 (<u>C</u>H$_3$); 37.14(<u>C</u>-H); 55.36(O<u>C</u>H$_3$); 114.29, 124.74, 127.88, 135.84, 139.18(aromatic, <u>C</u>H); 128.93, 131.14, 132.71, 137.93, 159.28(quaternary, <u>C</u>). (Found: C,68.51; H,7.36; Calc. for $C_{19}H_{24}OS_2$: C,68.63; H,7.28%); m/z 333(M^+_{+1},100%), 290(35), 248(85), 214(25).

2,5-Bis(methylthio)stilbene (74a); was isolated as colourless crystals (hexane); m.p. 114-115°C; yield 58%: IR ν_{max}(KBr) 1580, 1488, 1455, 1436 cm^{-1}; ^1H NMR($CDCl_3$): 2.45(s,3H,SC<u>H</u>$_3$); 2.48(s,3H,SC<u>H</u>$_3$); 6.99(s, 1H,olefinic). 7.13-7.50(m,9H,Ar<u>H</u>+olefinic). (Found: C,70.39; H,5.88; Calc. for $C_{16}H_{16}S_2$: C,70.54; H,5.92%); m/z 272(M^+,100%); 224(10), 193 (18), 178(19), 160(10).

2,5-Bis(methylthio)-4'-methoxystilbene (74b); was isolated as colourless crystals (hexane); m.p. 89-90°C; yield 54%; IR ν_{max}(KBr) 1600, 1507, 1460 cm^{-1}; ^1H NMR($CDCl_3$): 2.36(s,3H,SC<u>H</u>$_3$); 2.41(s,3H,SC<u>H</u>$_3$); 3.76(s, 3H,OC<u>H</u>$_3$); 6.70-7.43(m,9H,Ar<u>H</u>); ^{13}C NMR(67.89 MHz)($CDCl_3$): 16.54(S<u>C</u>H$_3$), 55.39(O<u>C</u>H$_3$), 114.38, 127.85(vinylic); 124.04, 125.29, 125.89, 127.38, 128.51(arom,<u>C</u>H); 130.22, 135.92, 136.80, 137.97, 159.66(quaternary,<u>C</u>).

(Found: C,67.38; H,5.95; Calc. for $C_{17}H_{18}OS_2$: C,67.51; H,6.00%); m/z 302(M^+,100%), 200(17), 121(15).

2,5-Bis(methylthio)-3'-methoxystilbene (74c); was isolated as colourless crystals (hexane); m.p. 82-83°C; yield 51%; IR ν_{max}(KBr) 1604, 1572, 1488, 1427 cm^{-1}; ^1H NMR($CDCl_3$): 2.48(s,3H,S$\underline{CH}_3$); 2.52(s,3H,S$\underline{CH}_3$); 3.82(s,3H,O$\underline{CH}_3$); 6.70-7.41(m,9H,Ar$\underline{H}$). (Found: C,67.54; H,6.07; Calc. for $C_{17}H_{18}OS_2$: C,67.51; H,6.00%); m/z 302(M^+,100%), 272(3), 254(8), 224(4), 208(16).

2,5-Bis(methylthio)-4'-methylstilbene (74d); was isolated colourless crystals (hexane); m.p. 78-79°C; yield 52%; IR ν_{max}(KBr) 1580, 1560, 1506, 1480 cm^{-1}; ^1H NMR($CDCl_3$): 1.25(s,3H,C$\underline{H}_3$); 2.34(s,3H,S$\underline{CH}_3$); 2.49(s,3H, S$\underline{CH}_3$); 6.95-7.51(m,9H,Ar$\underline{H}$). (Found: C,71.35; H,6.42; Calc. for $C_{17}H_{18}S_2$: C,71.28; H,6.33%); m/z 286(M^+,100%); 238(10), 224(5), 207(17).

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CHAPTER III

III.1 REACTIONS OF α-OXOKETENE DITHIOACETALS WITH LITHIOACETONITRILES: A NEW GENERAL METHOD FOR THE SYNTHESIS OF 3,4-SUBSTITUTED AND 4,5-ANNELATED PYRIDINES*.

III.2 REACTIONS OF α-OXOKETENE DITHIOACETALS WITH β-SUBSTITUTED-β-LITHIOAMINOACRYLONITRILES: A NOVEL GENERAL METHOD FOR SYNTHESIS OF 2,6-DISUBSTITUTED AND 2,3-ANNELATED PYRIDINES.

III.1.1 INTRODUCTION

The reactions of allyl[1,2] and benzyl[3] anions with α-oxoketene dithioacetals to yield the corresponding aromatic compounds has been well investigated in this laboratory. The overall process involves the construction of aromatic and fused aromatic systems from open-chain precursors involving α-oxoketene dithioacetals as one of the three carbon fragments. As a part of this programme

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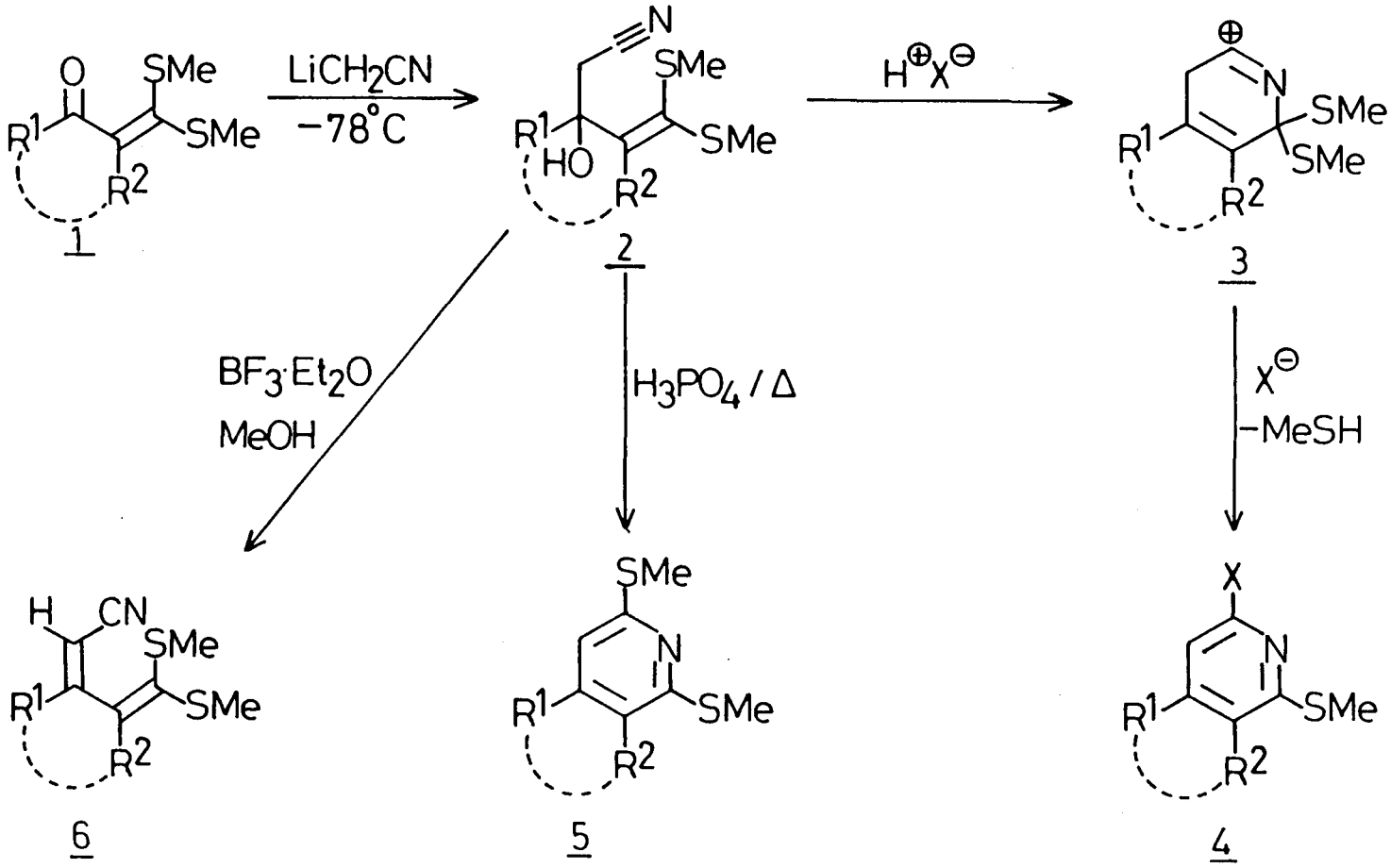
*Arun K. Gupta, H. Ila and H. Junjappa, Tetrahedron Lett. 29, 6633 (1988).

the reaction of propargylmagneisum halide[4] with α-oxoketene dithioacetal has been well investigated and the results have been described in the Chapter II. The terminal triple bond in these cases participates in the aromatic annelation and the incorporation of a solvent nucleophile which is finally carried to the products. It was further considered of interest that the addition of lithioacetonitrile to α-oxoketene dithioacetals 1 should yield the corresponding carbinolacetals 2 in which nitrogen atom is so positioned that it can participate in the new C-N bond formation so that the ring closure should yield the corresponding pyridine derivatives instead of aromatic systems under analogous conditions. The proposed transformations from 1 have been described in Scheme 1. The present chapter describes the reaction of α-oxoketene dithioacetals with lithioacetonitriles leading to a new general method for the synthesis of substituted and annelated pyridines.

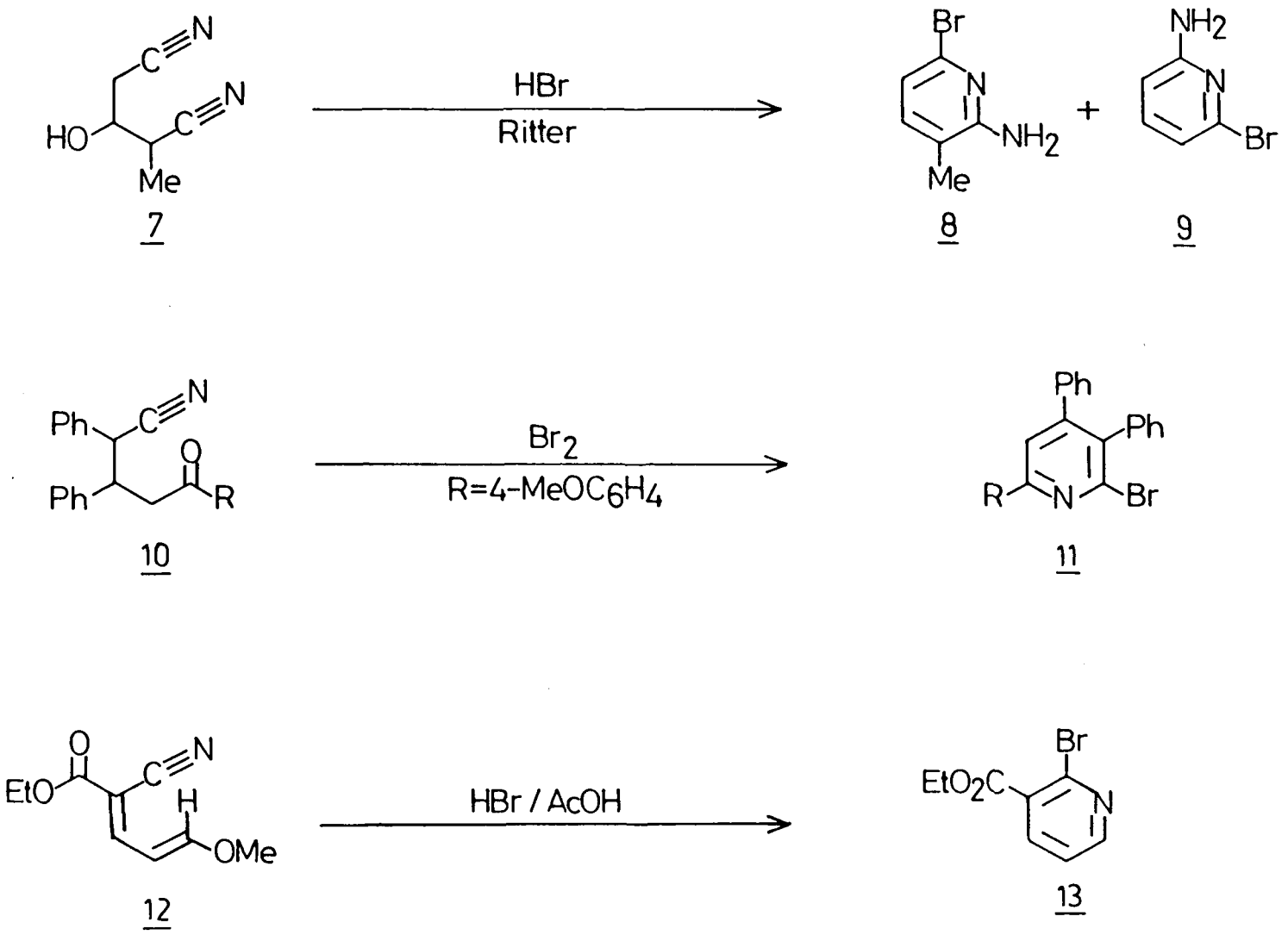
Abundant literature[5,6] is available on the synthesis of pyridine compounds involving principally either modification of the preconstructed pyridine nucleus or through the construction of the pyridine ring from appropriately substituted open-chain precursors. One of the oldest and most useful methods in the latter approach involves the condensation of two three atom fragments (C-C-C and C-C-N), variously designed and employed to realize the ring synthesis. Some of the related references on the construction of pyridine derivatives involving open-chain precursors have been briefly described in the following paragraphs.



Scheme 1

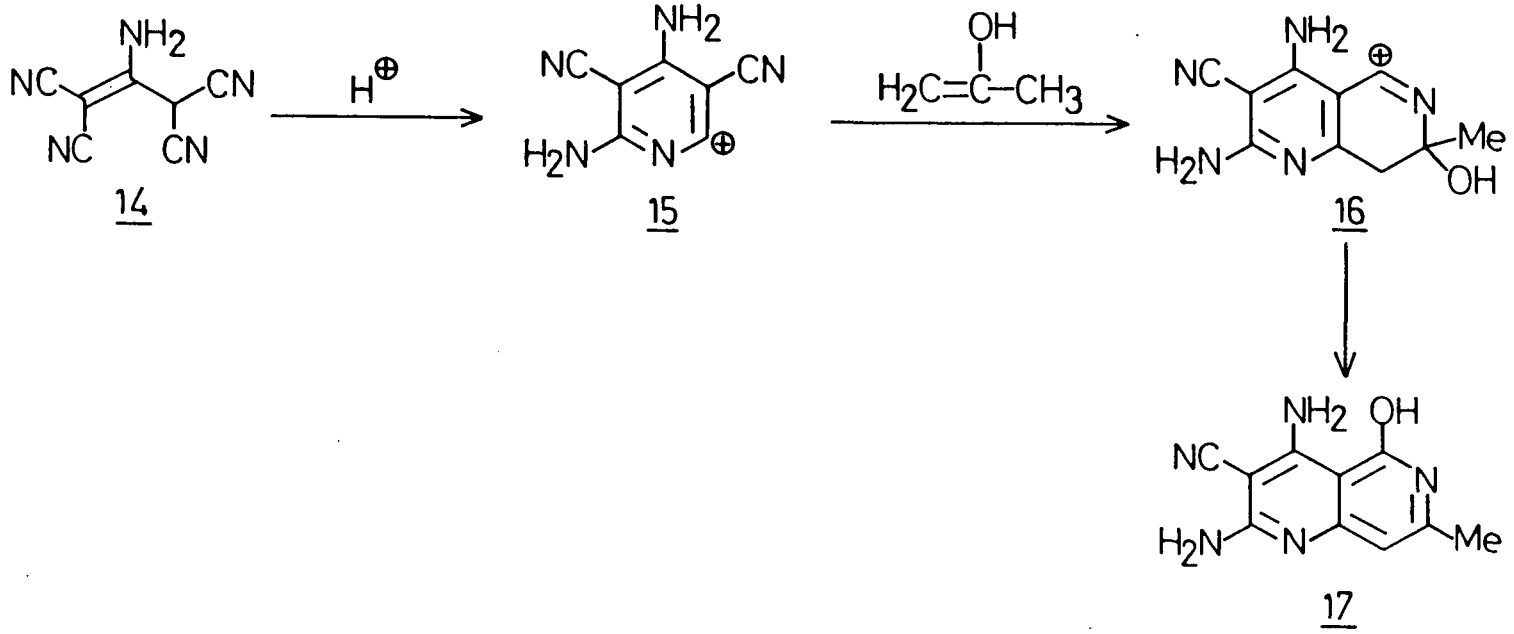
Johnson and co-workers[7] have studied the preparation of pyridine compounds from α,ω-dinitrile systems. The 3-hydroxyglutaronitrile 7 reacts readily with anhydrous hydrogen bromide or iodide under Ritter reaction pathway to yield a mixture of substituted pyridines 8 and 9 in which the entry of bromine is probably taking place from both the nitrile group resulting in a mixture. Similarly, the corresponding δ-ketonitrile 10[8] on treatment with bromine in acetic acid yielded the corresponding 2-bromo-3,4-diphenyl-6-substituted pyridine 11. Recently, Bryson and co-workers[9] have developed a novel method for the synthesis of ethyl 2-bromopyridine-3-carboxylate (13) via Ritter reaction on ethyl 1-cyano-4-methoxy-1,3-butadiene-1-carboxylate (12) (Scheme 2). Similarly, the tetracyanopropenes 14 underwent intramolecular C-N bond formation when treated with halogen acids to yield a transient pyridinium cation 15, which was subsequently trapped by acetone in the reaction medium to yield the highly substituted naphthyridine derivative 17[10] (Scheme 3). Similar approach has also been used to synthesize isoquinoline 20 when imino thioether 18 was heated in acetic acid either with or without sodium acetate[11] (Scheme 3).

Potts and co-workers[12,13] have developed a new and versatile synthesis of 2,6-disubstituted pyridines from α-oxoketene dithioacetals. The approach involved the regioselective conjugate addition of methyl-ketone carbanion 22 to the α-oxoketene dithioacetal 21 to yield quantitatively the intermediate 1,5-enediones 23. The reaction of these enediones with ammonium acetate in hot acetic acid gave the

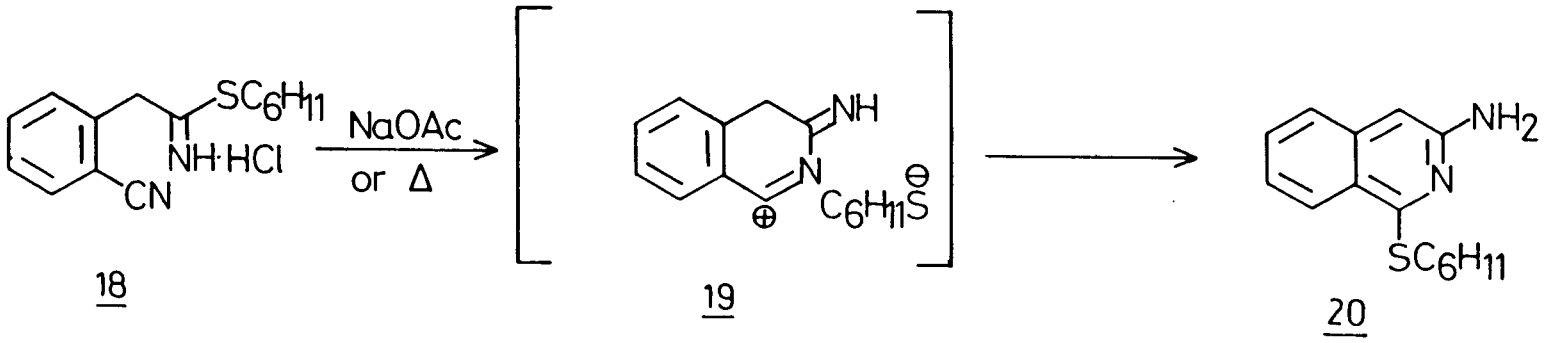


7 8 9 10 11 12 13

Scheme 2



14 15 16 17

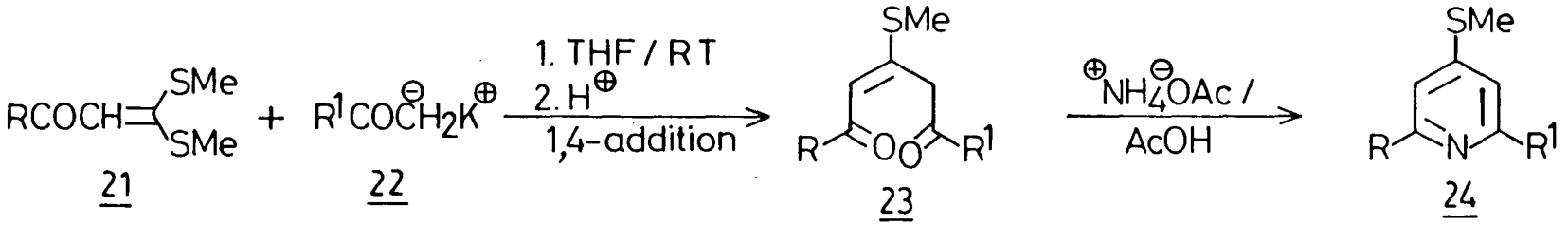


18 19 20

Scheme 3

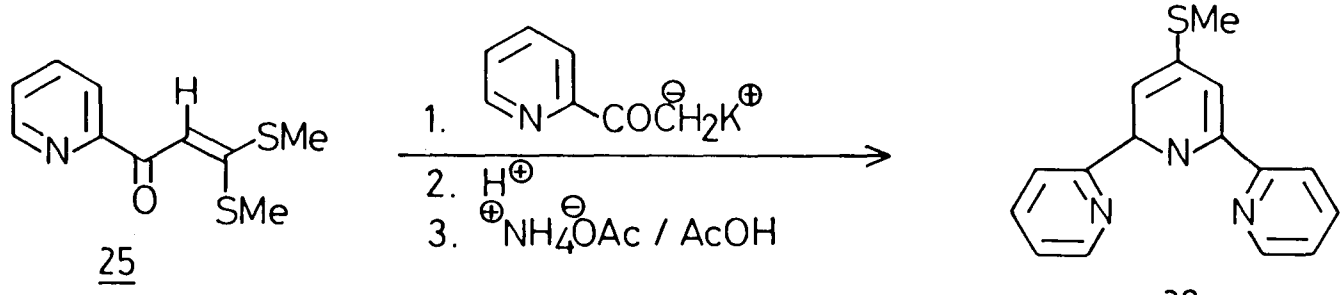
corresponding 2,6-disubstituted-4-(methylthio)pyridines 24 (Scheme 4) in good yields. The method was shown to be of general synthetic utility and a number of 2,6-disubstituted pyridines and polypyridinyls were synthesized. Thus, 2,6-bis(2-pyridinyl)-4-(methylthio) pyridine (26)[14] was synthesized through conjugate addition of enolate anion from 2-acetylpyridine to α-oxoketene dithioacetal 25 derived from 2-acetylpyridine. In the similar sequence of reactions the 2-(5-acetyl-2-thienyl)-4-(methylthio)-6-(2-thienyl)pyridine (28)[14] was synthesized starting from the corresponding oxoketene dithioacetal 27 (Scheme 4). The corresponding furyl derivative was also prepared in a similar manner. The oxoketene dithioacetals 29 and 31 derived from the 2,6-diacetylpyridine and 2,5-diacetylthiophene respectively, reacted similarly, with carbanion of 2-acetylpyridine to yield the corresponding polypyridinyl derivatives 30[13] and 32[14] (Scheme 5). The chemistry of these polypyridinyls is of particular importance since they can be good ligands for metal cations. Following same procedure the tetrahydroquinoline 34[14] (Scheme 5) and benzo[h]dihydroquinoline derivative 36[14] (Scheme 6) were obtained in low yields from the corresponding dithioacetals 33 and 35 respectively.

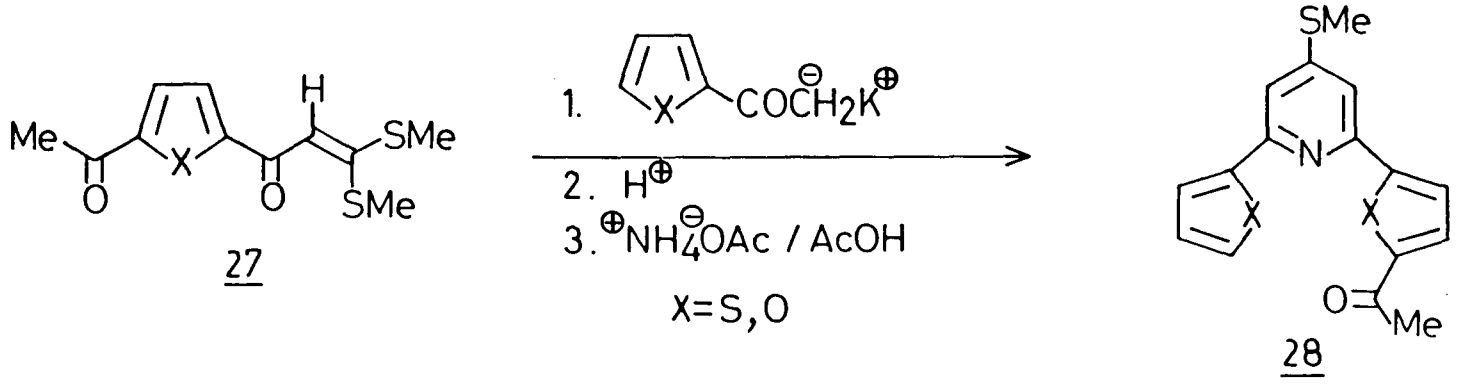
The same authors[15] extended this pyridine synthesis carrying tert-butyl groups at 2,6-positions. Thus, the α-oxoketene dithioacetals 37 when reacted with the potassium enolate of tert-butyl ketone, the corresponding 1,5-dione 38 was obtained in good yield. The intermediate 38 gave pyridine 39 under identical conditions while the corresponding pyrylium tetrafluoroborate 40 was obtained by treating



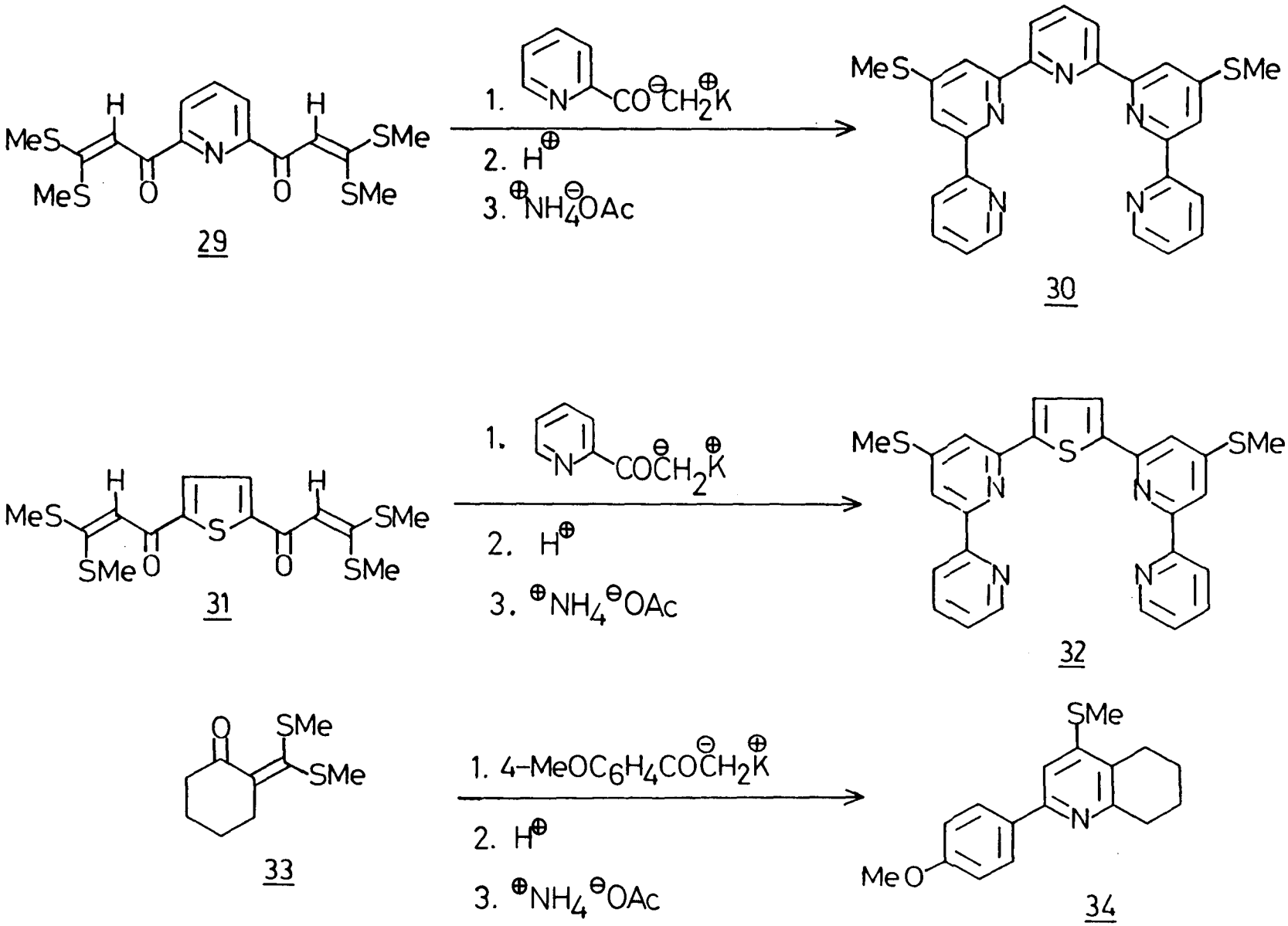
R=R^1=C_6H_5, 4-MeOC_6H_4, 4-BrC_6H_4, 2-Thienyl, 2-Furyl, 2-Pyridyl

R=2-Pyridyl; R^1=2-Thienyl, 2-Furyl, t-Butyl





Scheme 4

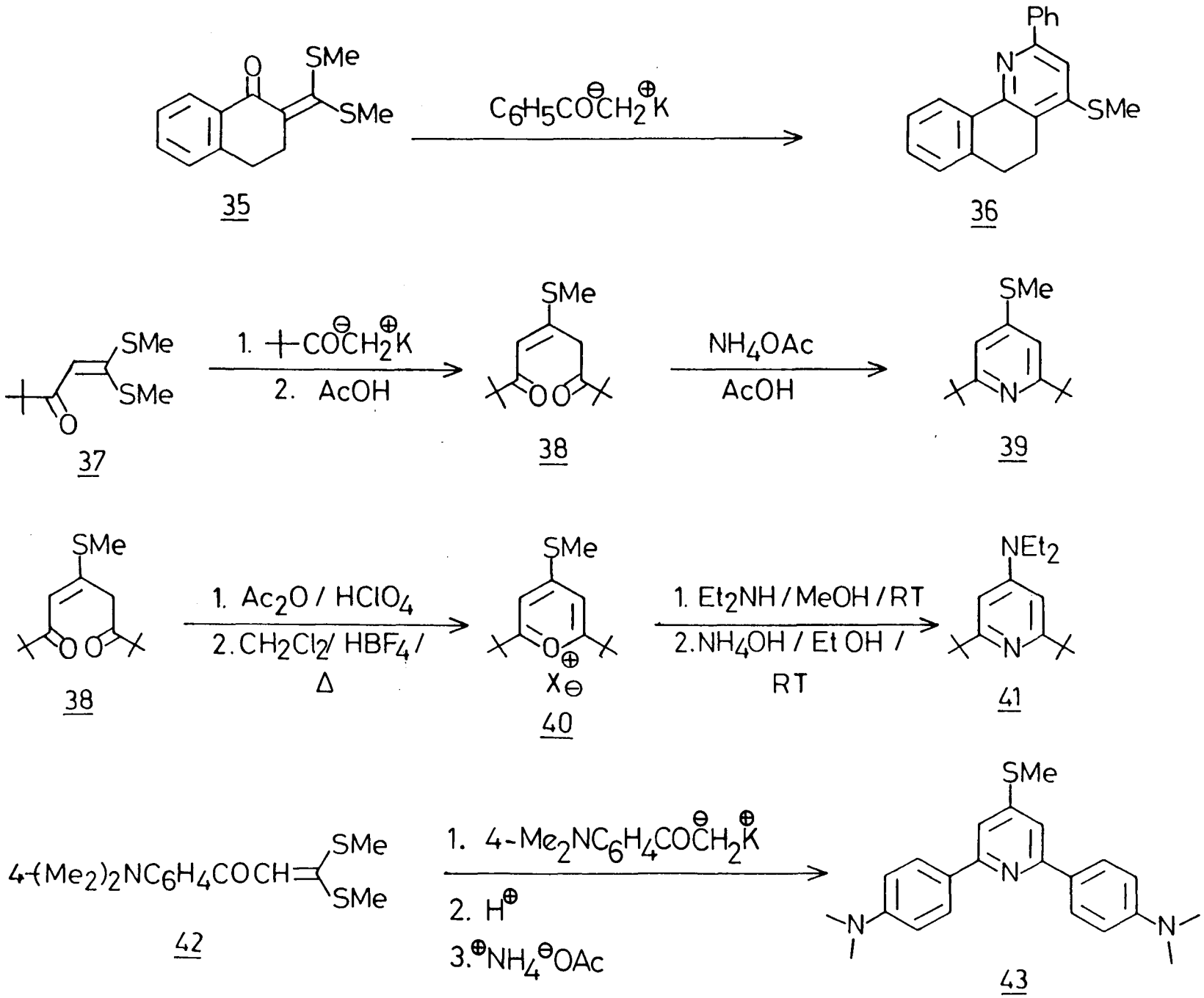

MeS
SMe
MeS
SMe
H
H
O
O
N
29
1.
2. H⊕
3. ⊕NH4⊖OAc
MeS
SMe
N
30
31
32
33
34
1. 4-MeOC6H4CO⊖CH2⊕K
MeO

Scheme 5

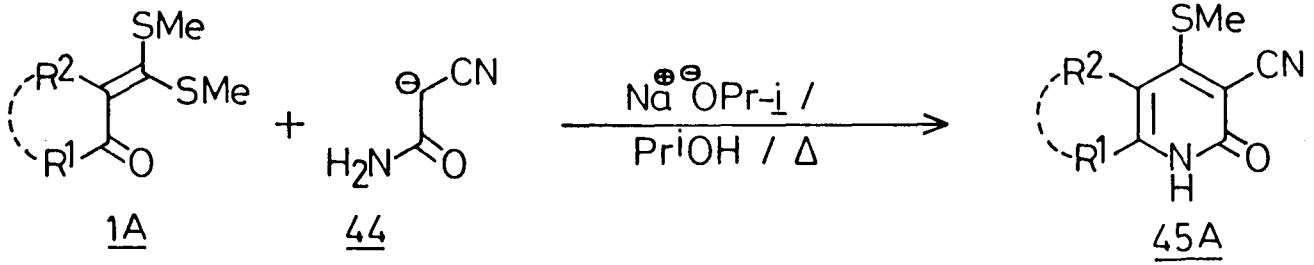
38 with perchloric acid and acetic anhydride followed by fluoroboric acid. The pyrilium salt 40 on treatment with diethylamine underwent facile displacement of methylthio group and on subsequent treatment with aqueous ammonia yielded the corresponding 4-diethylamino-2,6-di-tert-butylpyridine (41) (Scheme 6). Similarly, 2,6-di-(4-dimethylaminophenyl)pyridine (43) was obtained from the corresponding oxoketene dithioacetal 42[15] (Scheme 6).

The reaction of α-oxoketene dithioacetals 1 with enolate anion of cyanoacetamide 44 in the presence of sodium isopropoxide in boiling propan-2-ol to yield the 3-cyano-4-methylthio-2(1H) pyridones 45 was developed and reported[16,17] from this laboratory. The method was shown to be of general synthetic utility for the synthesis of substituted and fused pyridone derivatives 45 (Scheme 7). Interestingly, when N-substituted cyanoacetamide anion 46 was reacted with α-oxoketene dithioacetals 1 under analogous conditions, the corresponding N-alkyl substituted pyridones 45 could not be isolated and products isolated were characterized as 2,7-naphthyridine derivatives 47[18] (Scheme 8). The cyclic ketene-S,S-acetals also yielded the respective fused naphthyridines 47B and 47C in excellent yields (Scheme 8).

In the present study, the reactions of lithioacetonitrile and lithiopropionitrile with α-oxoketene dithioacetals 1 have been extensively studied and found to provide a new general method for the synthesis of various substituted and annelated pyridines in high yields and the results are described in the following section.

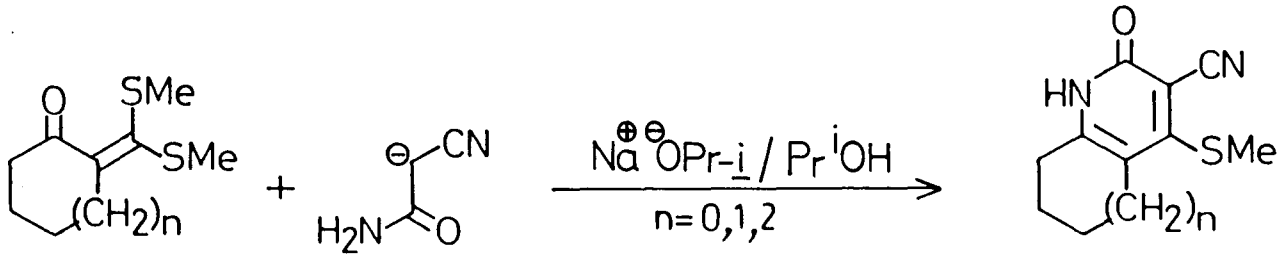

SMe
SMe
O
$C_6H_5COCH_2^{\ominus}K^{\oplus}$
Ph
N
SMe
35
36
SMe
SMe
O
1. $+COCH_2^{\ominus}K^{\oplus}$
2. AcOH
SMe
O O
NH_4OAc
AcOH
SMe
N
37
38
39
SMe
O O
1. Ac_2O / $HClO_4$
2. CH_2Cl_2/ HBF_4 /
Δ
SMe
O
$X^{\ominus}$
1. Et_2NH / MeOH / RT
2. NH_4OH / Et OH /
RT
NEt_2
N
38
40
41
4-$(Me_2)_2NC_6H_4COCH$
SMe
SMe
42
1. 4-$Me_2NC_6H_4COCH_2^{\ominus}K^{\oplus}$
2. $H^{\oplus}$
3. $^{\oplus}NH_4{}^{\ominus}OAc$
SMe
N
N
N
43

Scheme 6

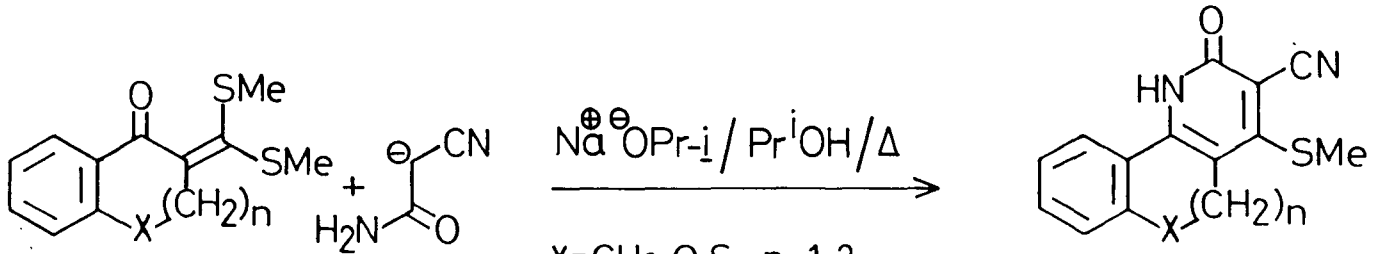


1A 44 45A

R^1 = Me, Substituted aryl; R^2 = H; R^1 = R^2 = aryl

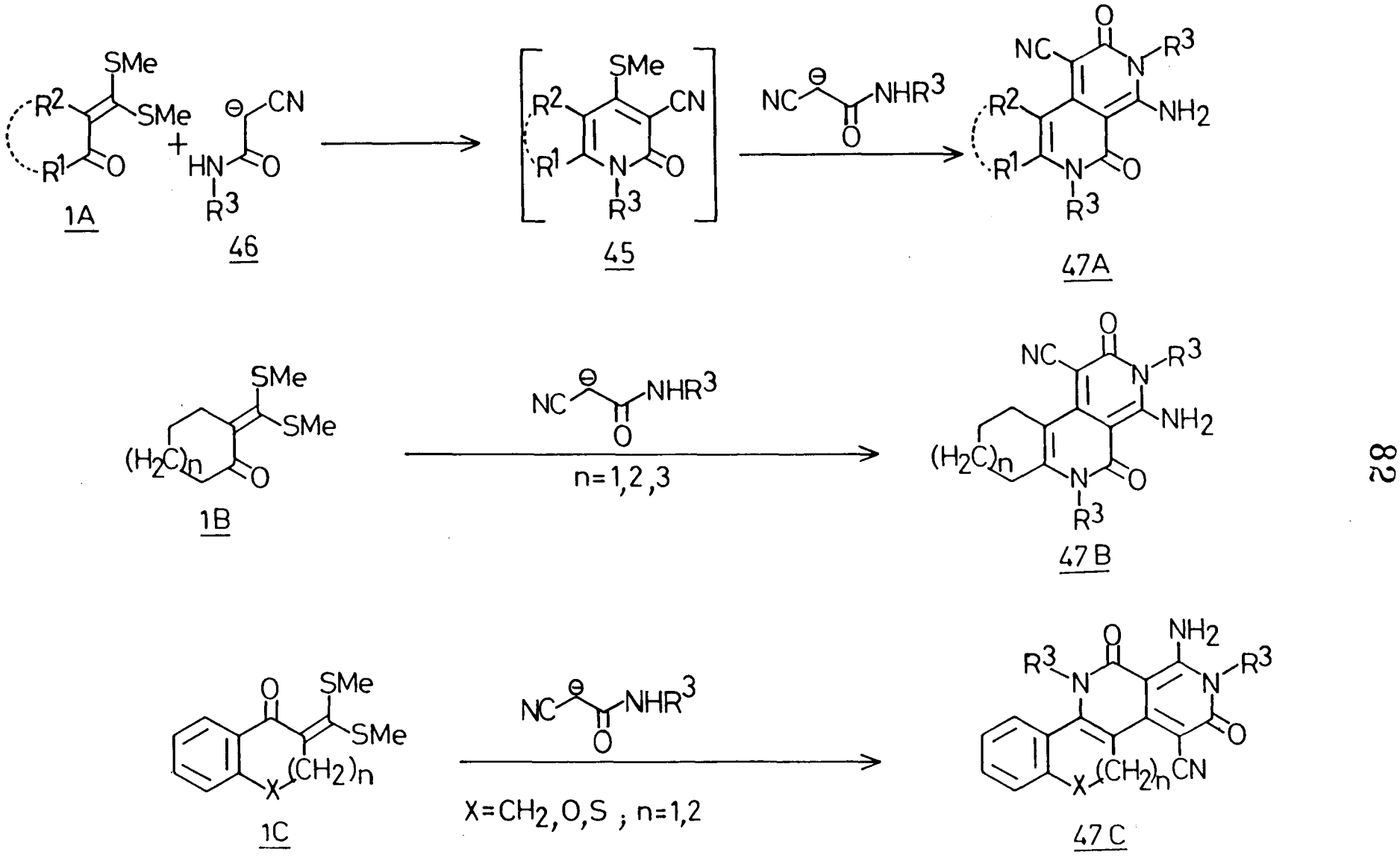


1B 44 45B



1C 44 45C

Scheme 7


SMe
SMe
R2
R1
O
CN
HN
R3
1A
46
45
NC
NHR3
NC
R3
NH2
47A
1B
n=1,2,3
(H2C)n
47B
1C
X=CH2,O,S ; n=1,2
X
(CH2)n
CN
47C

Scheme 8

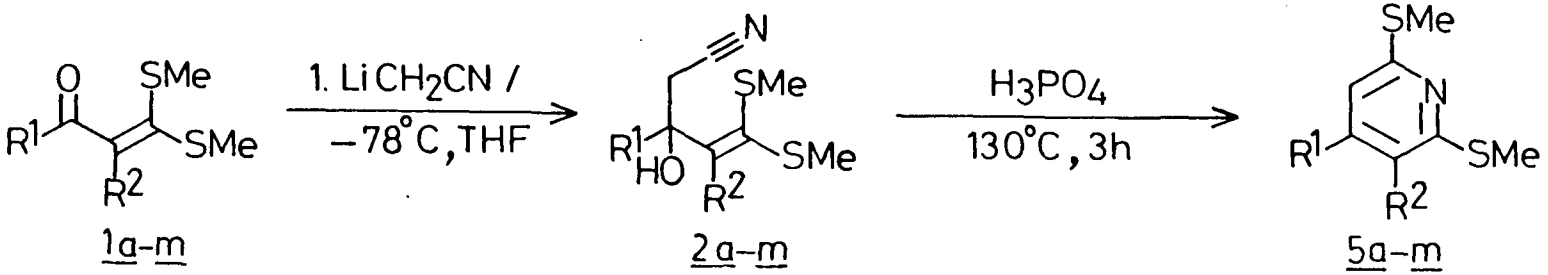
III.1.2 RESULTS AND DISCUSSION

For the present study a wide range of representative α-oxoketene dithioacetals 1 were prepared from a variety of active methylene ketones by the general procedure as described in Chapter II. All these dithioacetals were known earlier and were characterized by comparison of their physical and spectral data with those of authentic samples.

When the α-oxoketene dithioacetal 1a derived from acetophenone, was reacted with lithioacetonitrile[19] (1.25 eqv.), the corresponding carbinolacetal 2a was obtained, which was found to be formed by 1,2-addition, in nearly quantitative yield. The carbinolacetal 2a was characterized by its spectral data. The crude carbinolacetal was purified by column chromatography over neutral alumina and isolated as a colourless solid (m.p. 60-61°C) and its IR and NMR data confirmed that the carbinolacetal 2a has formed by 1,2-addition of lithioacetonitrile to α-oxoketene dithioacetal. Thus, IR spectrum (KBr) of 2a showed absorption bands at 3415(OH), 2260(CN), 1567 cm^{-1} respectively while its ^1H NMR spectrum (CCl_4) showed two singlet peaks at δ 2.15 and 2.31 (3H each) for two methylthio protons. The methylene protons appeared as a singlet at δ 2.78(2H) and the hydroxy proton was present at δ 4.73(1H) (exchangeable with D_2O). The olefinic proton appeared at δ 6.30(1H) while a multiplet between δ 7.18-7.53 which was integrating for five protons was assigned to the aromatic protons. The carbinolacetal 2a gave only the corresponding diene 6a in 68% yield (Scheme 1) when it was subjected to cycloaromatization in the presence of borontrifluoride etherate in refluxing methanol. However, when 2a was heated with orthophosphoric acid(88%)

for 3 hrs, the reaction mixture after work-up and purification (column chromatography over silica gel) gave a colourless crystalline product (m.p. 86-87°C) which was characterized as 2,6-bis(methylthio)-4-phenylpyridine (5a) in 82% yield (Scheme 9). The structure of 5a was fully established by its analytical and spectral data. It was analyzed for $C_{13}H_{13}NS_2$ and its mass spectrum exhibited the molecular ion peak at m/z 247(M^+,100%). The structure of 5a was further confirmed from its IR and NMR spectral data. The IR spectrum(KBr) of 5a exhibited bands at 1580, 1525, 1365 cm^{-1} while its ^1H NMR spectrum (CCl_4) displayed two singlets at δ 2.56(6H) and δ 7.00(2H) due to methylthio and H-3 and H-5 ring protons thus showing symmetrical disposition of methylthio groups. The remaining five aromatic protons of the phenyl group appeared as multiplet between δ 7.25-7.62. The structure assigned to 5a was further confirmed by subjecting it to Raney Nickel desulphurization to yield the known 4-phenylpyridine (48a)[20] in 65% yield (Scheme 9) (superimposable IR and NMR spectra).

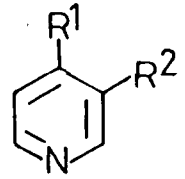
Apparently, the ring closure of carbinolacetal 2a has taken place involving an intramolecular migration of methylthio group. The mechanism governing this ring closure is depicted in Scheme 10. The carbenium ion 49a, formed by phosphoric acid is suitably activated for intramolecular Ritter type of attack from the nitrogen lone pair to yield a transient pyridinium cation 3a which is responsible for spontaneous 1,3-methylthio shift to give better stabilized pyridinium cation 50a which on loss of proton leads to the product 5a (Scheme 10).



1a-m 2a-m 5a-m

1,2,5	R^1	R^2	% yield
a	C_6H_5	H	82
b	4-ClC_6H_4	H	72
c	4-$MeOC_6H_4$	H	68
d	4-MeC_6H_4	H	83
e	2-furyl	H	71
f	2-thienyl	H	78
g	3-pyridyl	H	77
h	2-naphthyl	H	79
i	Me	H	78
j	Et	H	61
k	Me	Me	68
l	Et	Me	58
m	Me	n-Bu	52

Raney Ni | 5a,i

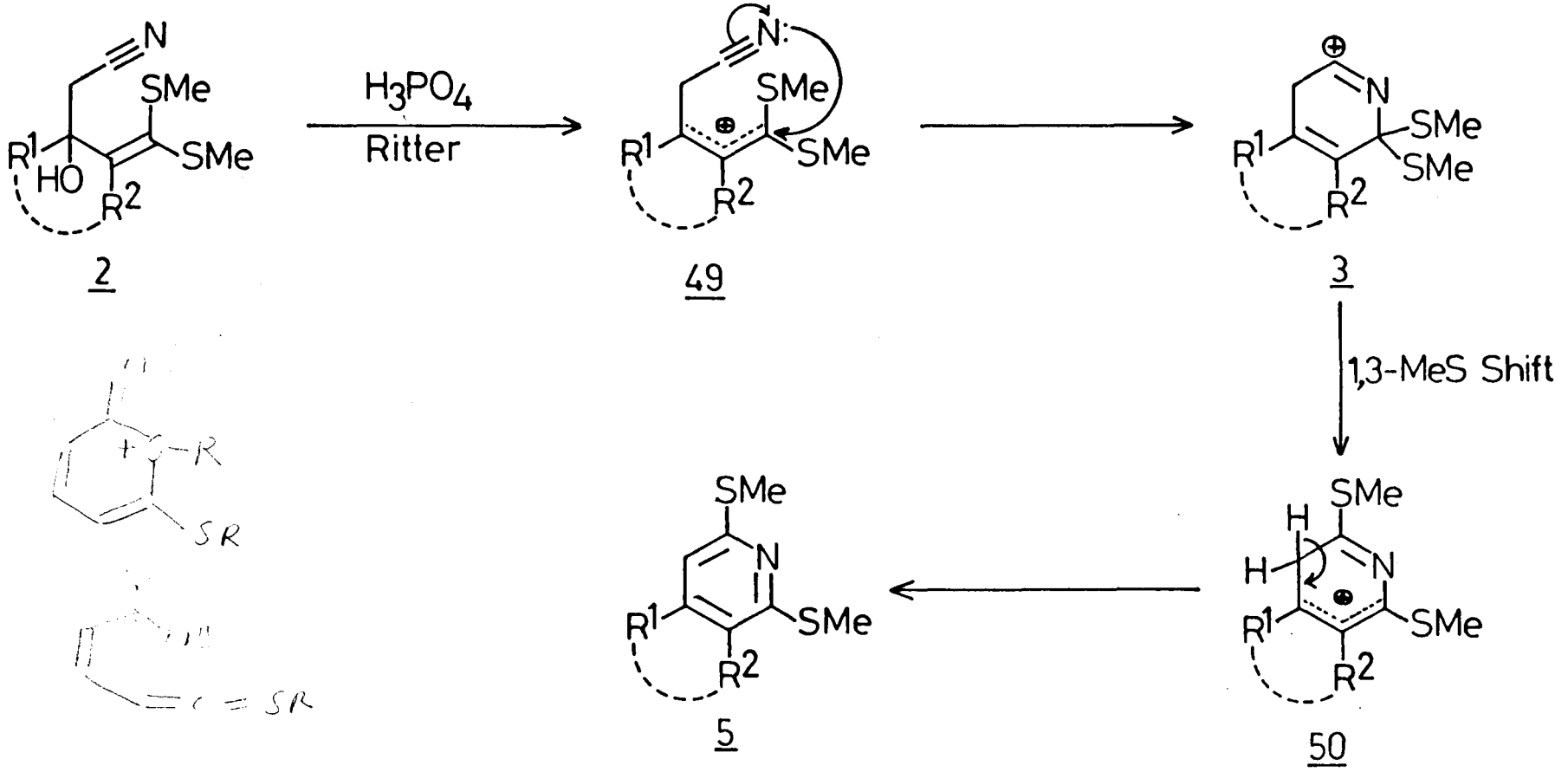


48a-b

5a, 48a, $R^1=C_6H_5$; $R^2=H$

5i, 48b, $R^1=Me$; $R^2=H$

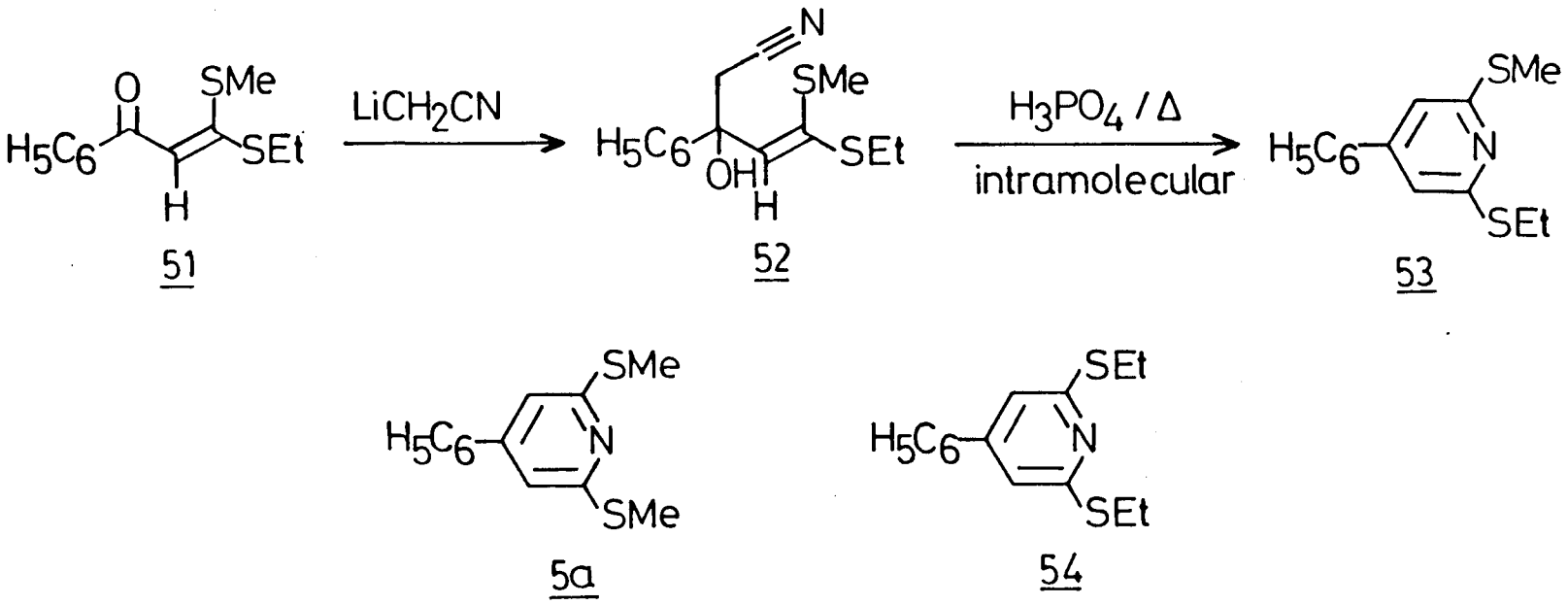
Scheme 9


N
SMe
SMe
R1
HO
R2
2
H3PO4
Ritter
N:
SMe
SMe
R1
R2
49
N
SMe
SMe
R1
R2
3
1,3-MeS Shift
SMe
H
H
N
R1
SMe
R2
50
SMe
N
SMe
R1
R2
5

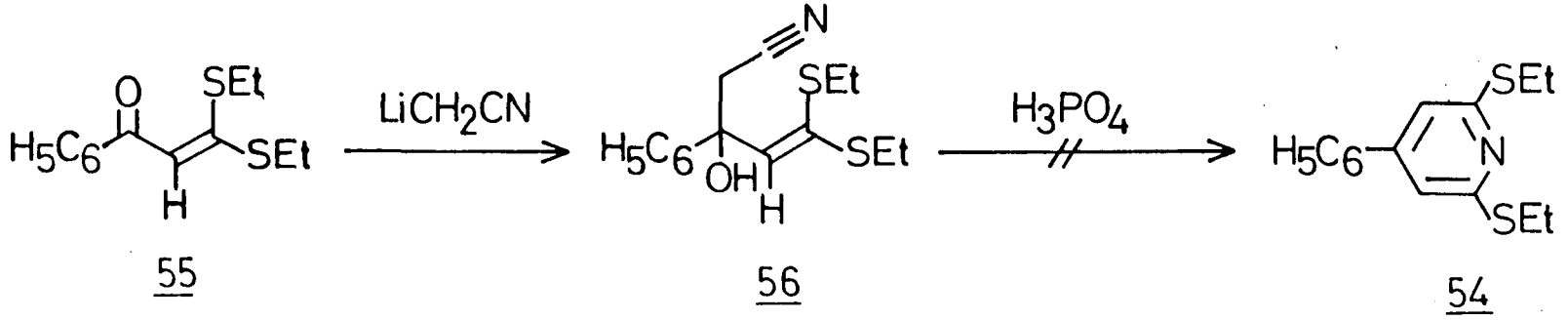
Scheme 10

The intramolecular mode of 1,3-methylthio group shift was proved by carrying out the reaction of lithioacetonitrile with unsymmetrical S-methyl-S-ethyl dithioacetal 51 under identical reaction conditions. Thus, the initial carbinolacetal 52 which was formed, underwent ring closure when treated with orthophosphoric acid, the product isolated was characterized as 2-(ethylthio)-6-(methylthio)-4-phenylpyridine (53) in 63% yield (Scheme 11). If the reactions were to follow the migration of methylthio group intermolecularly, the corresponding pyridines 5a and 54 should have also been detected in the reaction mixture. The absence of the pyridines 5a and 54 proves that the methylthio group migrates intramolecularly without permitting an extraneous nucleophile to be involved in the process of ring closure (Scheme 11). Interestingly, when the α-oxoketene dithioacetal 55 was reacted with lithioacetonitrile, although the carbinolacetal 56 was formed but it failed to undergo ring closure under identical conditions, to yield the corresponding pyridine 54 probably due to steric reasons (Scheme 11).

The method was found to be of general synthetic application when extended to other oxoketene dithioacetals derived from both acyclic and cyclic ketones. Thus, 4-substituted (5b-j) and 3,4-alkylsubstituted (5k-m) pyridines were obtained in 52-83% overall yields from the corresponding α-oxoketene dithioacetals 1b-m (Scheme 9). The structure of these pyridines have been fully confirmed from their analytical and spectral data which are described in the experimental section. However, when the oxoketene dithioacetal 1n derived from propiophenone was reacted with lithioacetonitrile, although the



51 52 53 5a 54

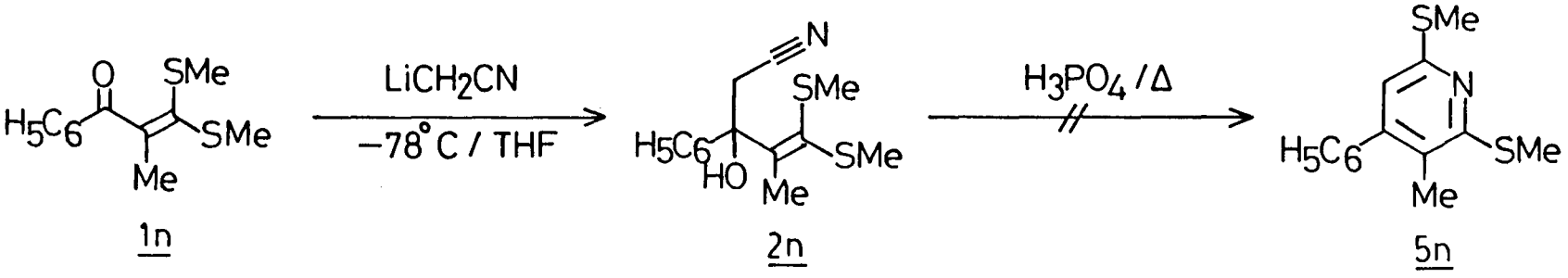


55 56 54

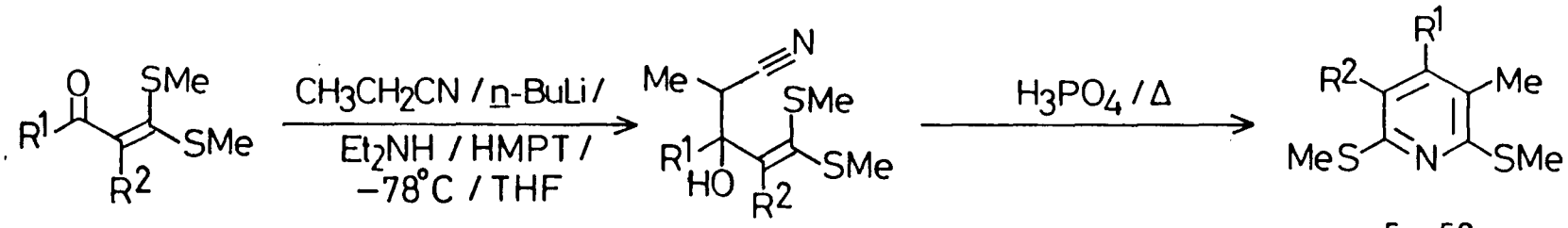
Scheme 11

corresponding carbinolacetal 2n was obtained in good yield, but it failed to undergo cyclization to afford 2,6-bis(methylthio)-3-methyl-4-phenylpyridine (5n) when reacted with phosphoric acid under analogous conditions as described. Therefore 2,6-bis(methylthio)-3-methyl-4-phenylpyridine (5n) was synthesized by an alternate route involving the reaction of α-lithiopropionitrile[21] with α-oxoketene dithioacetal (Scheme 12). Thus, the dithioacetal 1a not only reacted with α-lithiopropionitrile to yield the carbinolacetal 57a but also underwent ring closure in the presence of phosphoric acid to yield the corresponding 3-methyl-4-phenylpyridine 5n in good yield (Scheme 12). In the similar way 2,6-bis(methylthio)-4-(2-furyl)-3-methylpyridine 58 was also obtained in good yield from the corresponding α-oxoketene dithioacetal 1e. The structure of these pyridines 5n and 58 were in agreement with their analytical and spectral data and are described in the experimental section (Scheme 12).

The method was further extended to the ketene dithioacetals derived from cyclic ketones. Thus, the oxoketene dithioacetals 1o and 1p derived from cyclohexanone and cycloheptanone afforded 1,3-bis(methylthio)-5,6,7,8-tetrahydroisoquinoline (5o) and 1,3-bis(methylthio)-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridine (5p) in 76% and 71% yields respectively. The isoquinoline 5o was successfully dethiomethylated when treated with Raney Nickel to afford 5,6,7,8-tetrahydroisoquinoline (48c)[22]. However, oxoketene dithioacetal 1q derived from cyclopentanone failed to give the corresponding fused pyridine 5q (Scheme 13). The other cyclic ketene dithioacetals 1r-w derived from the corresponding ketones afforded, similarly, the fused pyridine derivatives 5r-w



1n 2n 5n



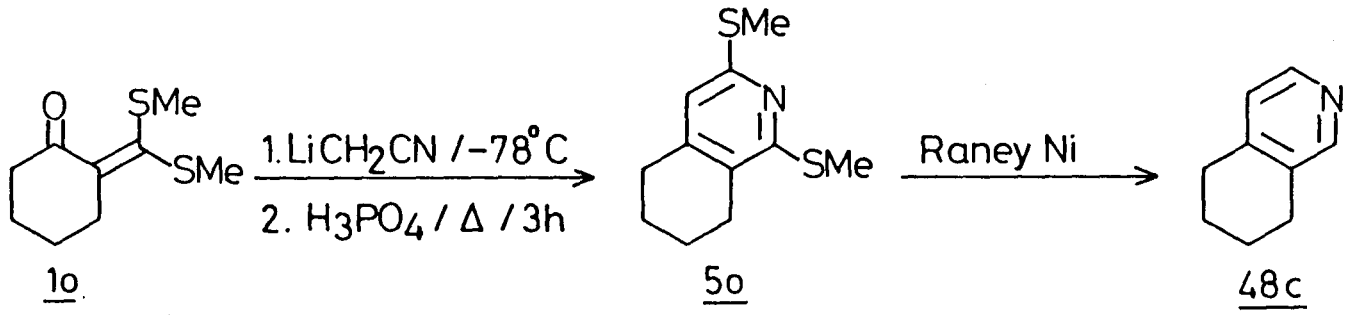
1a,e 57a-b 5n-58

$$\left[CH_3-\underset{\underset{Li}{|}}{CH}-CN\right]$$

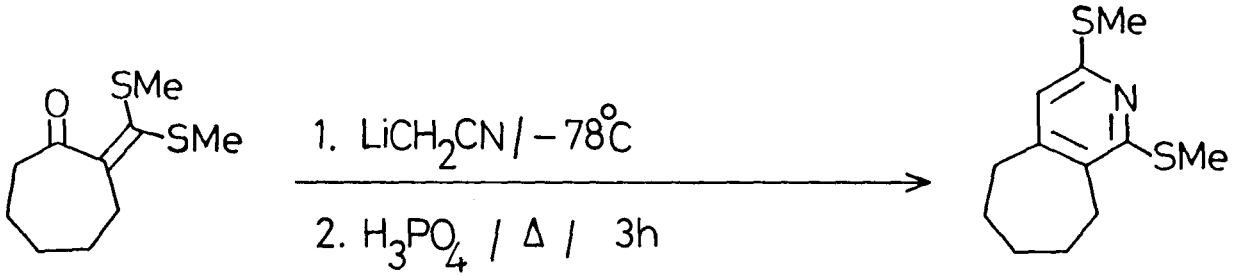
1a, 57a, 5n, $R^1=C_6H_5$; $R^2=H$

1e, 57b, 58, R^1=2 furyl; $R^2=H$

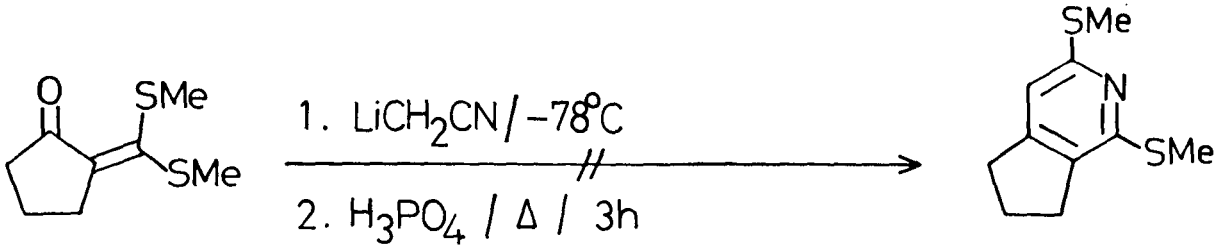
Scheme 12



1o 5o 48c



1p 5p



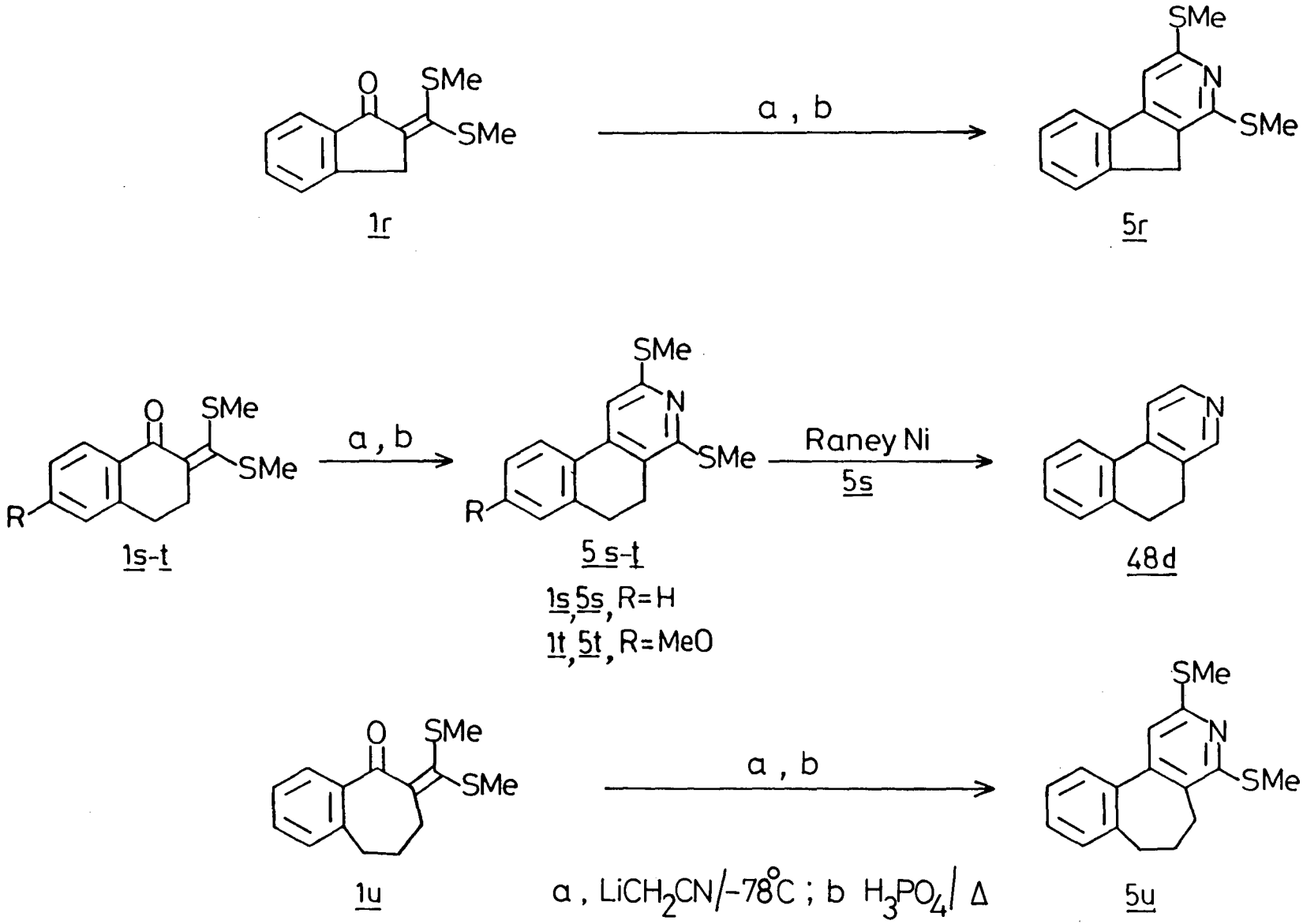
1q 5q

Scheme 13

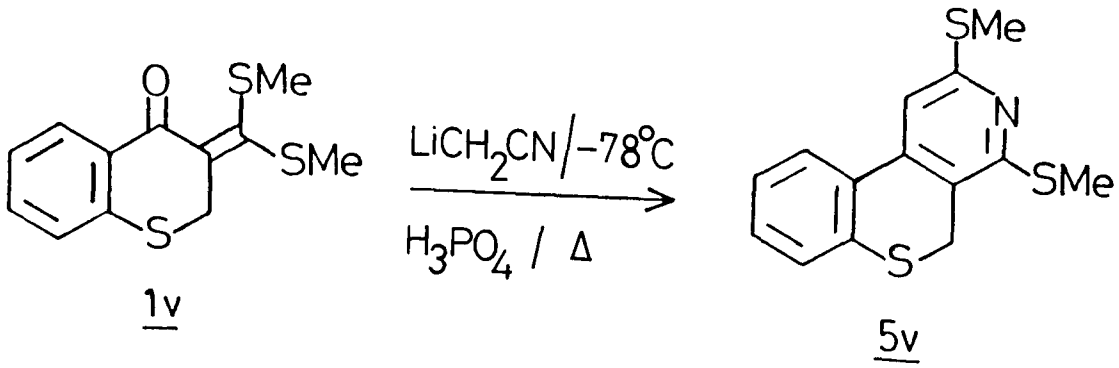
(Scheme 14 and 15). The Raney Nickel desulphurization of 5s afforded the 5, 6-dihydrobenz [f]isoquinoline (48d) in good yields (Scheme 14). The structure of these fused pyridines were fully established by their analytical and spectral data which are described in the experimental section.

The reaction of α-lithiopropionitrile with cyclic oxoketene dithioacetals were also examined and found to be successful for synthesis of fused pyridine derivatives under analogous reaction condition as described. Thus, the oxoketene dithioacetals 1o and 1p gave corresponding fused pyridines 59 and 60 in good yields while 61 was obtained from the corresponding oxoketene dithioacetal 1w (Scheme 16). The structure of 59-61 were fully confirmed from the analytical and spectral data (experimental).

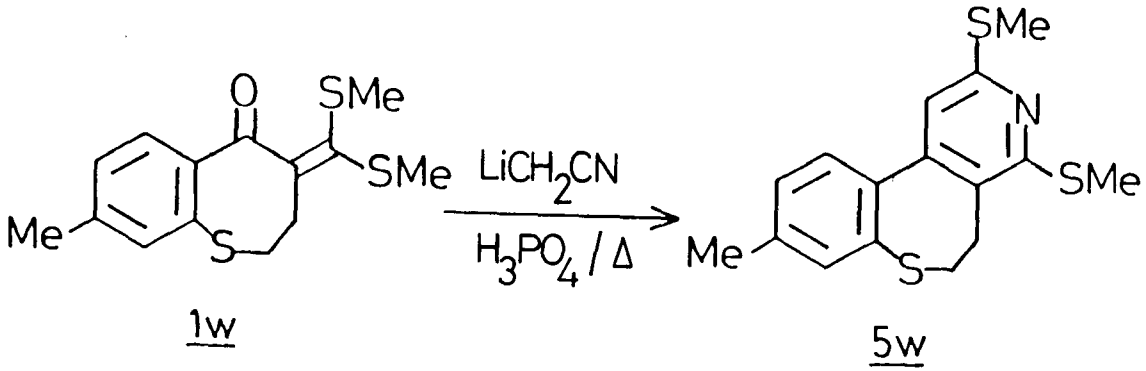
Interestingly, a successful attempt was made to incorporate external nucleophile by creating an appropriate reaction condition during ring closure. Thus, when the carbinolacetal 2a derived from 1a was treated with bromine in acetic acid, the product isolated was characterized as 2-bromo-6-(methylthio)-4-phenylpyridine (62) (Scheme 17). Similarly carbinolacetal 2g also afforded the corresponding 2-bromopyridine derivative 63 in good yields under identical conditions. Similarly, the corresponding fused bromopyridines 64 and 65 were also obtained in excellent yields when the respective carbinolacetals 2o and 2s derived from cyclic ketones were reacted with bromine under identical reaction conditions. The analytical and spectral data of these bromopyridines 62-65 were fully in agreement with their assigned structures (experimental) (Scheme 17). The formation of 2-bromopyridines 62-65


SMe
O
SMe
SMe
a , b
SMe
N
SMe
1r
5r
O
SMe
SMe
R
a , b
SMe
N
SMe
R
Raney Ni
5s
N
1s-t
5 s-t
1s,5s, R=H
1t,5t, R=MeO
48d
O
SMe
SMe
a , b
SMe
N
SMe
1u
a , LiCH2CN/-78°C ; b H3PO4/ Δ
5u

Scheme 14

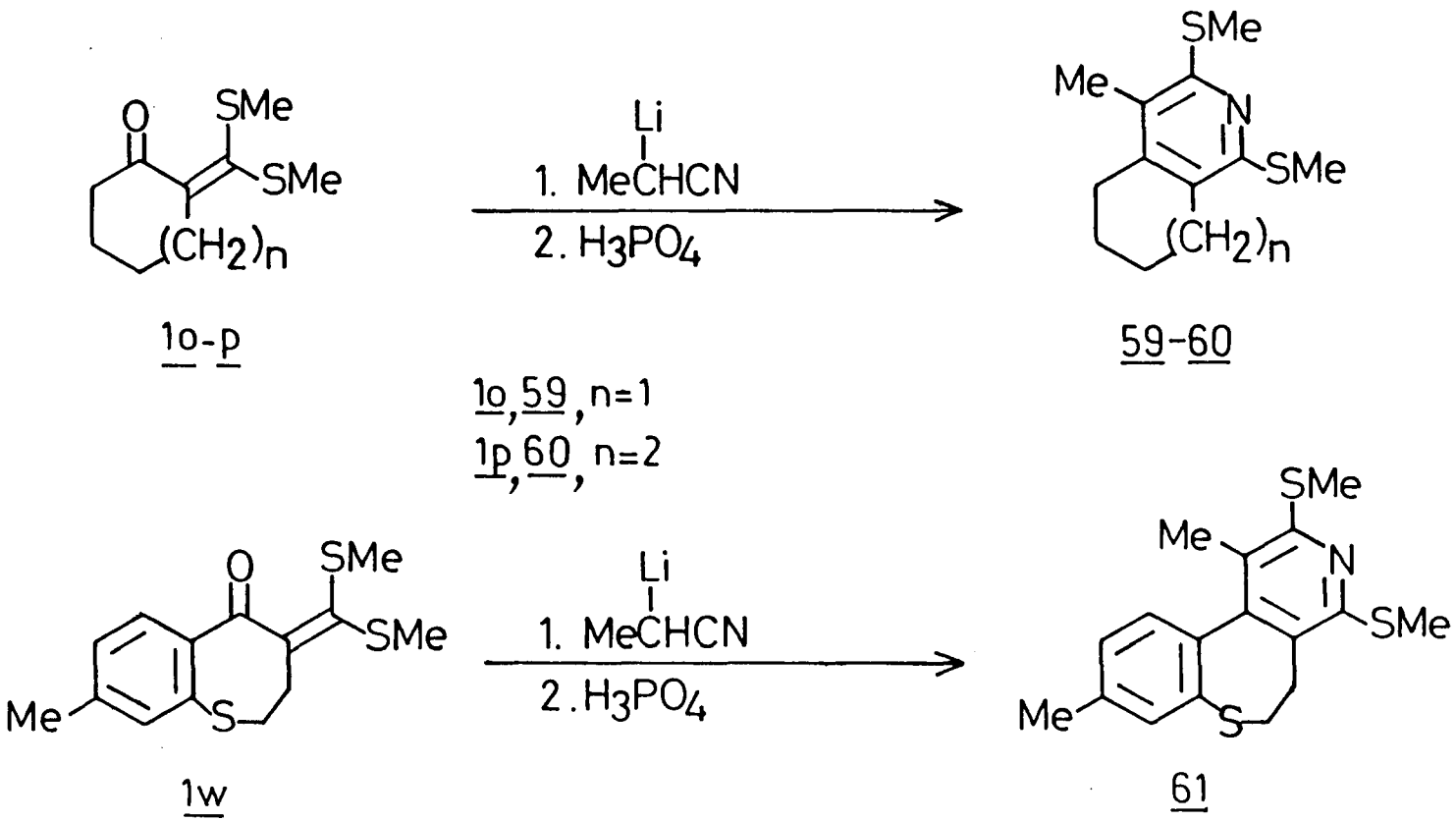


1v 5v



1w 5w

Scheme 15

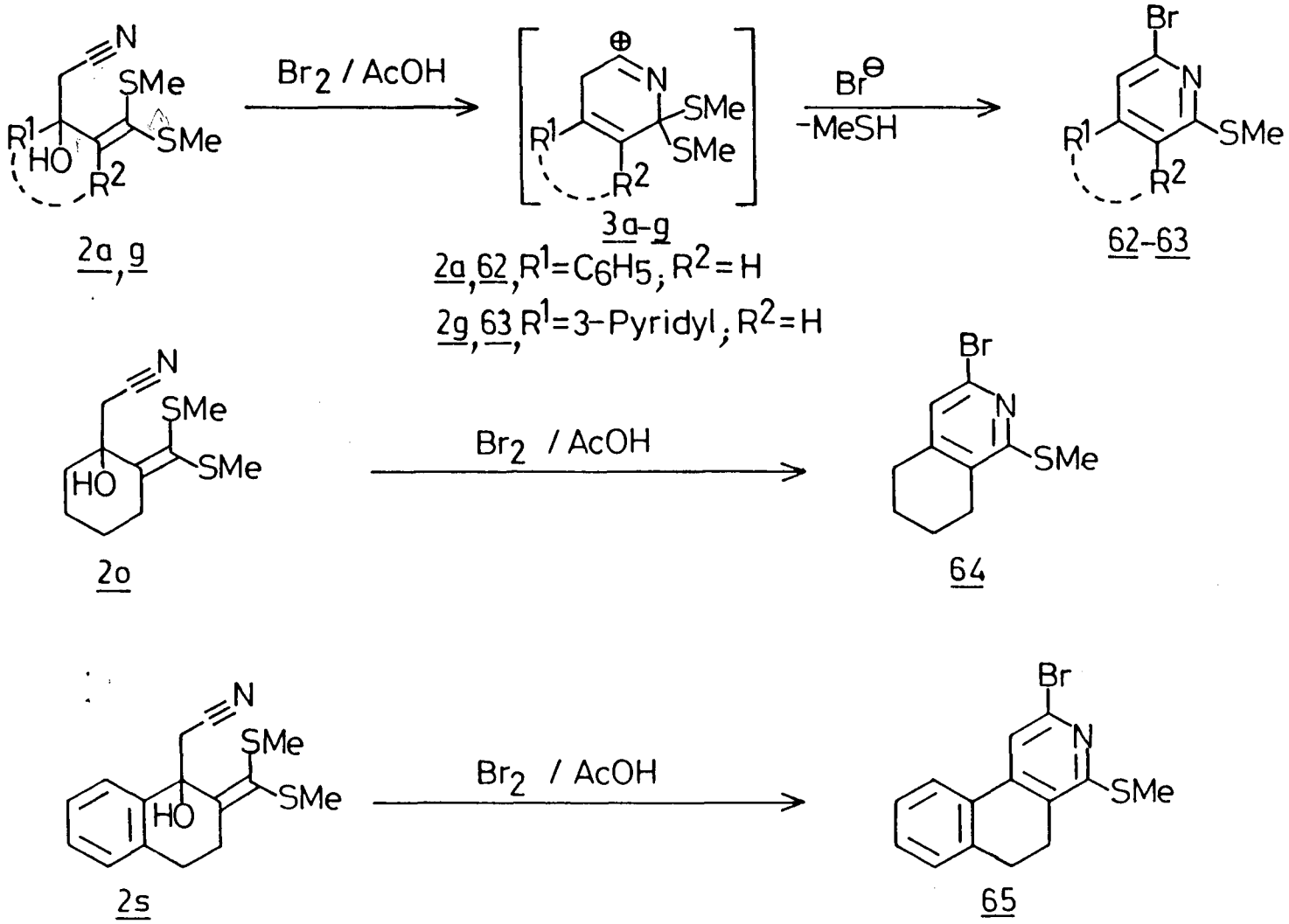

SMe
O
SMe
(CH2)n
Li
1. MeCHCN
2. H3PO4
SMe
Me
N
SMe
(CH2)n
1o-p
59-60
1o, 59, n=1
1p, 60, n=2
O
SMe
SMe
Me
S
Li
1. MeCHCN
2. H3PO4
SMe
Me
N
SMe
Me
S
1w
61

Scheme 16

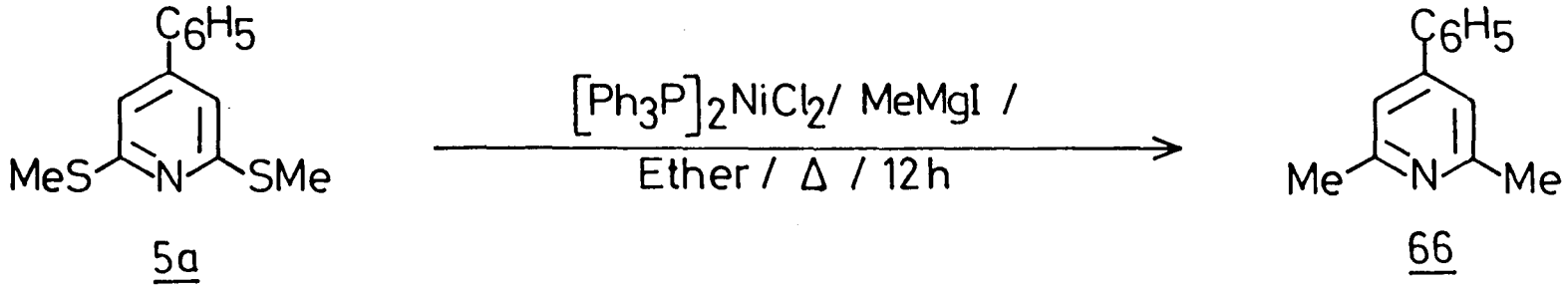
further supports the intermediacy of carbenium ion 3 which in the presence of external nucleophile undergoes addition and elimination of methylmercaptan group competetively in preference to methylthio migration (Scheme 17).

The presence of two methylthio groups at 2,6-positions of the pyridine ring could be of considerable synthetic importance, since they can be replaced by various carbon nucleophiles[23]. Only the most important carbon nucleophiles have been attempted for replacement of methylthio group which demonstrate that the methodology can be extended to synthesize variously 2,6-substituted pyridines by using appropriate carbon nucleophiles. Thus, when 2,6-bis(methylthio)-4-phenylpyridine (5a) was treated with methylmagnesium iodide in the presence of bis(triphenylphosphino) nickel dichloride $[(C_6H_5)_3P]_2NiCl_2$ complex[23], the corresponding 4-phenyl-2,6-lutidine (66) was obtained in excellent yield. Similarly, 5,6-dihydro-2,4-dimethyl-benz [f]isoquinoline (67) was obtained from the corresponding 1,3-bis(methylthio)benz-isoquinoline derivative 5s. The analytical and spectral data of 66 and 67 have been described in the experimental section (Scheme 18).

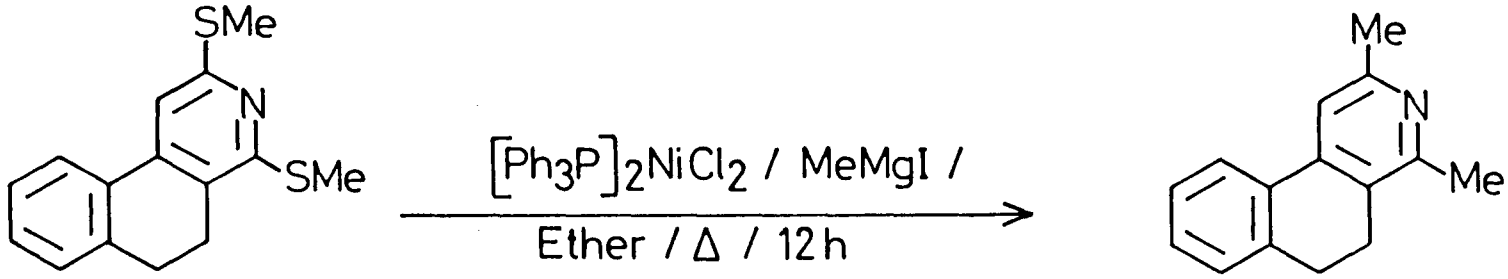
The reaction of lithioacetonitrile with cinnamoyl oxoketene dithioacetals 68a-d were next examined. When 68a was reacted with lithioacetonitrile, the corresponding carbinolacetal 69a thus formed, underwent ring closure in the presence of orthophosphoric acid to yield the corresponding 2,6-bis(methylthio)-4-styrylpyridine (70a) in 65% yield (Scheme 19). The reaction was found to be successful when other cinnamoylketene dithioacetals 68b-d were subjected to analogous reaction condition, afforded the corresponding pyridines 70b-d in good yields.


N
SMe
SMe
R1
HO
R2
Br2 / AcOH
⊕
N
SMe
SMe
R1
R2
Br⊖
-MeSH
Br
N
SMe
R1
R2
2a, g
3a-g
2a, 62, R1=C6H5; R2=H
2g, 63, R1=3-Pyridyl; R2=H
62-63
N
SMe
SMe
HO
Br2 / AcOH
Br
N
SMe
2o
64
N
SMe
SMe
HO
Br2 / AcOH
Br
N
SMe
2s
65

Scheme 17

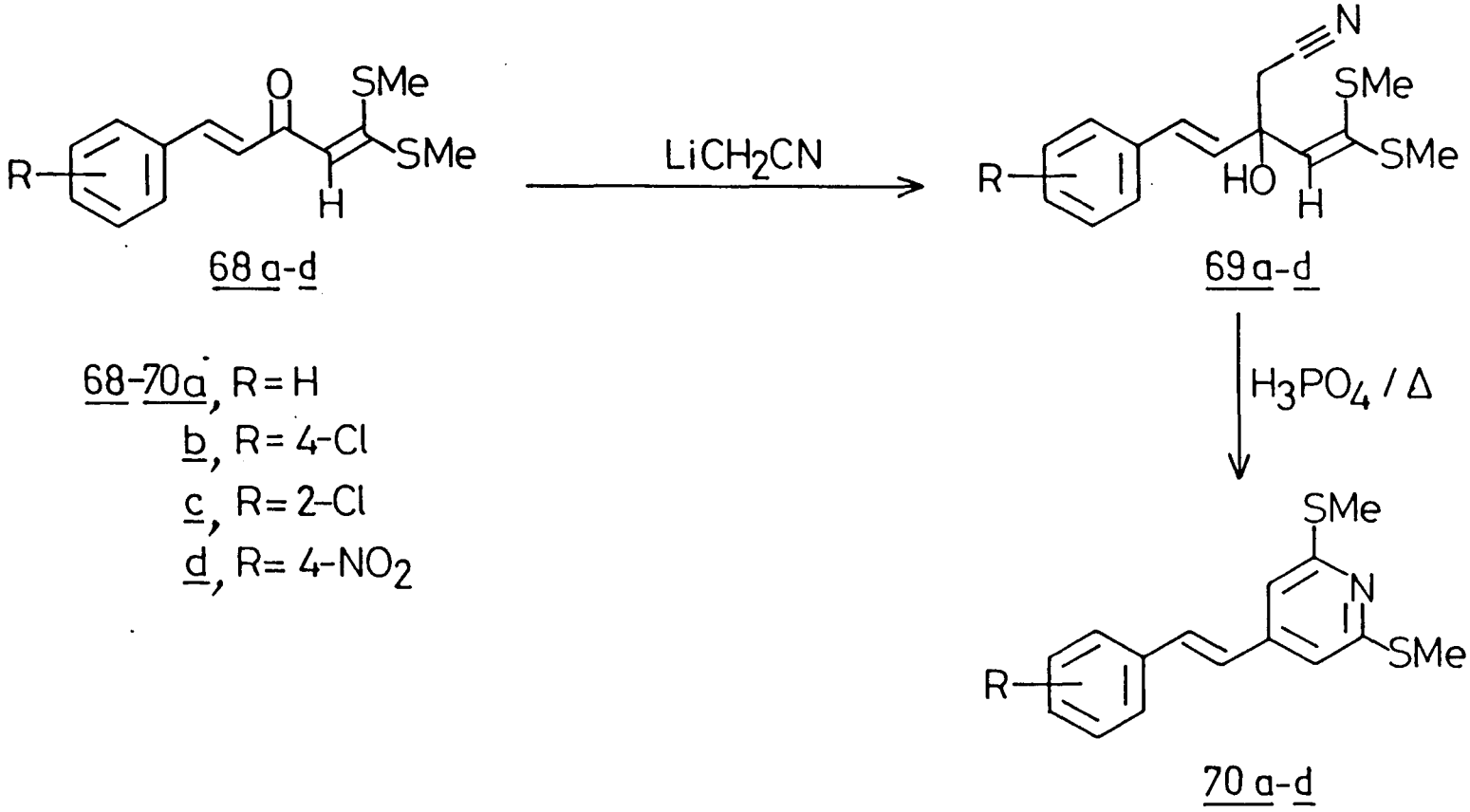


5a 66



5s 67

Scheme 18



68 a-d

69 a-d

70 a-d

68-70a, R = H
b, R = 4-Cl
c, R = 2-Cl
d, R = 4-NO_2

Scheme 19

The analytical and spectral data of these styrylpyridines 70a-d are given in experimental section (Scheme 19).

When the anion generated from phenylacetonitrile[24] was reacted with α-oxoketene dithioacetal 1a, the corresponding carbinolacetal 71 was obtained in quantitative yield however 71 afforded only the thioester 73 instead of 72 on heating with phosphoric acid. The failure of the carbinolacetal 71 to undergo cycloaromatization to afford 72 may be probably due to steric crowding in the planar transition state 74 for cyclization (Scheme 20).

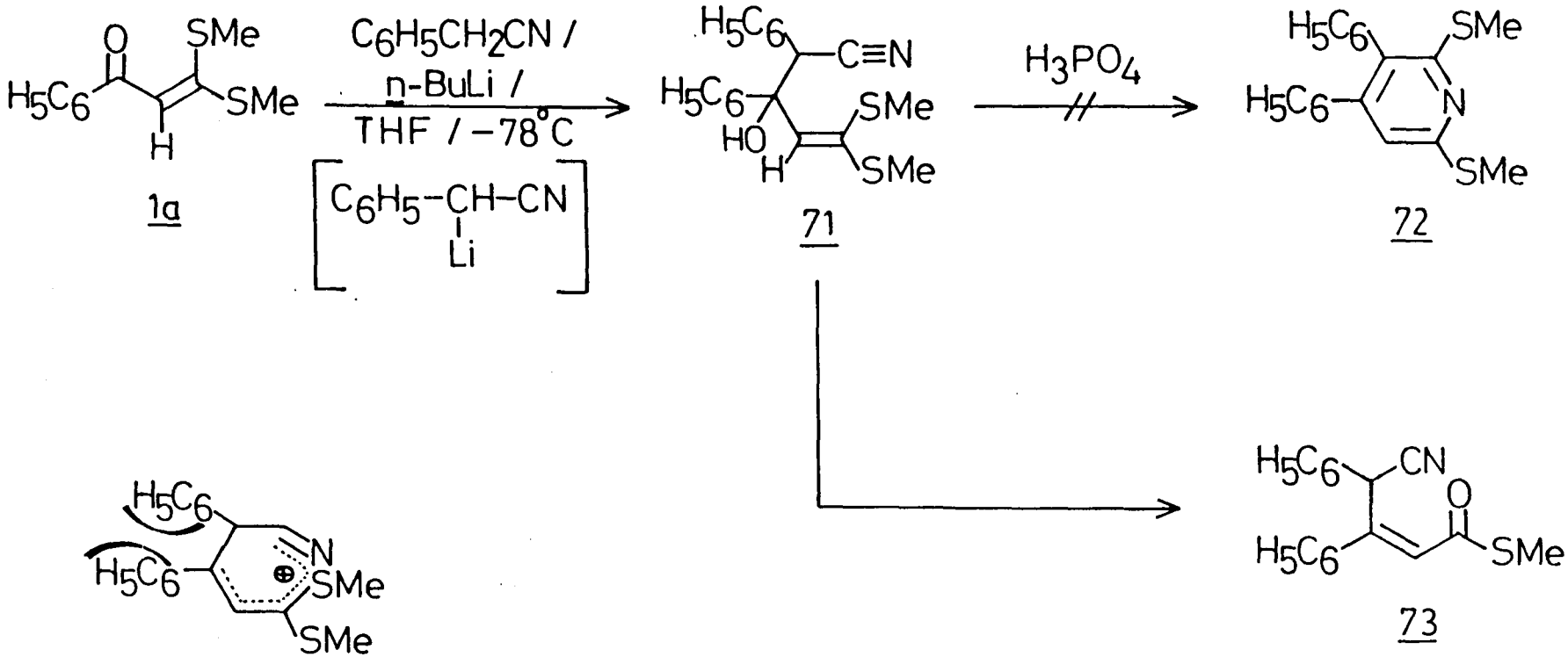
III.1.3 CONCLUSION

The lithioacetonitrile and lithiopropionitrile anion undergo exclusive 1,2-addition to α-oxoketene dithioacetals to yield the corresponding carbinolacetals in quantitative yields. These carbinolacetals underwent only dehydration rather than cycloaromatization, when treated with borontrifluoride in refluxing methanol. However, carbinolacetals underwent facile cycloaromatization which follows intramolecular Ritter reaction involving 1,3-methylthio shift, when treated with phosphoric acid. Thus, the present new approach provides a two step efficient high yield method for substituted and annelated pyridines with greater synthetic flexibility.

III.2 Reaction of α-Oxoketene Dithioacetals with β-Substituted-β-lithioaminoacrylonitriles: Synthesis of 2,6-Disubstituted and 2,3-Annelated Pyridines

III.2.1 INTRODUCTION

In the preceding section, the reaction of lithioacetonitrile, generated under controlled conditions, was shown to undergo regiospecific 1,2-

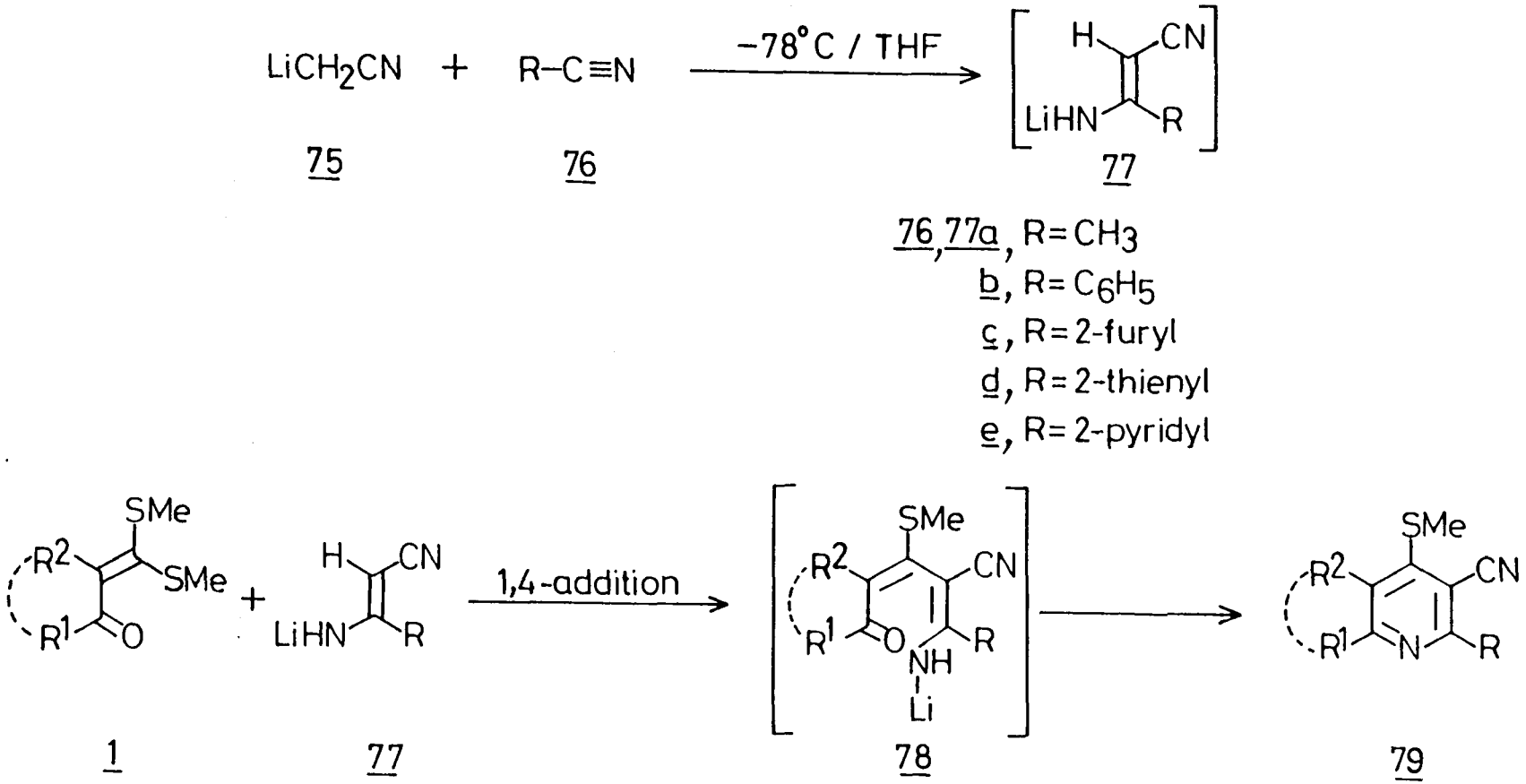


Scheme 20

addition to α-oxoketene dithioacetals and the corresponding carbinol-acetals thus obtained underwent Ritter type of intramolecular ring closure with concomitant methylthio group migration to yield the corresponding substituted and annelated 2,6-bis(methylthio)pyridines in high yields. The reaction was further successfully manipulated to incorporate external nucleophile to the developing carbocation to afford the corresponding bromopyridines. The lithioacetonitrile anion(75)can be made to undergo self condensation to give the β-lithio-aminocrotononitrile anion (77a) which is an ambidient nucleophile and it should undergo regioselective 1,4-addition to α-oxoketene dithio-acetals 1 to yield the corresponding substituted pyridines (Scheme 21). It was, therefore, considered of interest that the lithioacetonitrile can be made similarly, to react with alkyl and aryl nitriles to generate the appropriately substituted anions 77b-e which on reaction with oxo-ketene dithioacetals will yield various substituted pyridines. Such a strategy would enhance the scope of pyridines synthesis, since it is possible to manipulate the substituents at 2,6-positions.

In the present section, the results of this investigation are described. The general approach planned for the present investigation is described in Scheme 21.

A few analogous transformations, involving the reaction of functiona-lized 3-carbon 1,3-electrophilic fragments with enaminoesters and nitriles to yield the corresponding pyridine derivatives have been reported[5]. Thus acyl and benzoyl acetylenes 80 condensed with enamine 81 (R = CN,CO_2Et) at 100°C to yield the corresponding pyridines 82[25] (Scheme 22). Similarly, ethyl ethoxymethylene oxaloacetate (83) also condensed, regiospecifically, with enamine 81 to yield the corresponding


LiCH2CN + R–C≡N
−78°C / THF
H
CN
LiHN
R
75
76
77
76, 77a, R = CH3
b, R = C6H5
c, R = 2-furyl
d, R = 2-thienyl
e, R = 2-pyridyl
SMe
R2
R1
O
1,4-addition
NH
Li
N
1
77
78
79

Scheme 21

2,3,4 and 5-substituted pyridines 85. The other possibility of the formation of regioisomeric pyridines 84 through 1,2-addition of enamine was not observed[26,27] (Scheme 22). Thus in the both cases, enamines 81 attack to electrophilic β-carbon in Michael fashion, followed by intramolecular cyclization to yield the regiospecifically substituted pyridines 82 and 85.

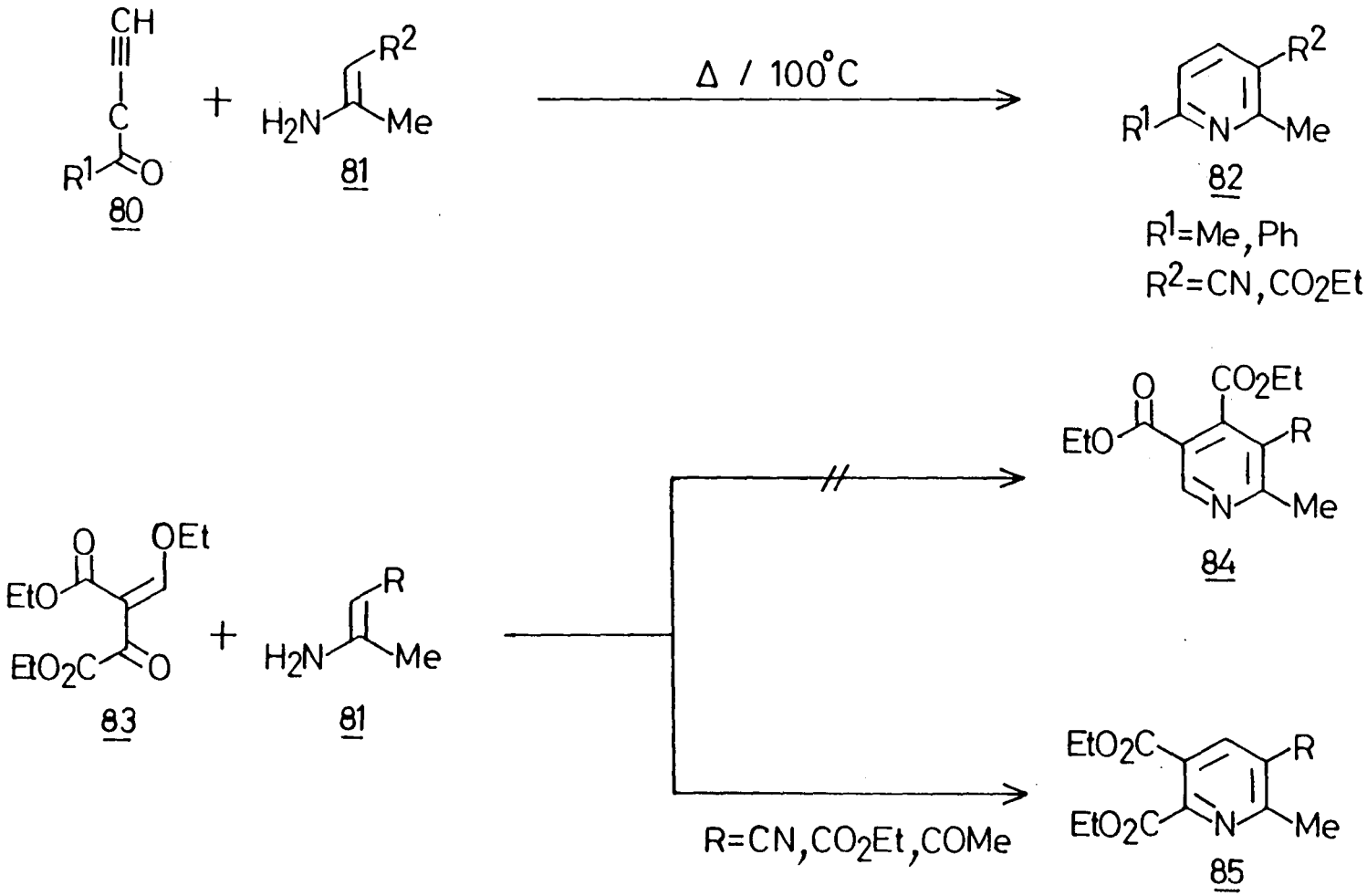
Jutz and co-workers[28] reacted the enamines 81 with vinamidinium salts 86 or 3,3-diethoxy-1-dimethylaminopropene (87) to yield the corresponding pyridines 90 (Scheme 23). The triene intermediate 88 underwent electrocyclization to give 89 which on elimination of dimethylamine afforded the products 90. The similar approach was also extended to cyclic systems. Thus, the reaction of cyclic vinamidinium salts 86 with enamine such as β-aminocrotononitrile (81) gave isomeric mixture (1:1) of fused pyridine derivatives 92 and 94 through the intermediates 91 and 93 respectively (Scheme 24).

Apparently, the aforesaid examples are condensation reactions involving neutral enamines with 1,3-electrophilic carbon fragments. It was therefore of interest to study the reactivity of enaminonitrile anions 77 with 1,3-electrophilic α-oxoketene dithioacetals (1) and results are presented in the following section.

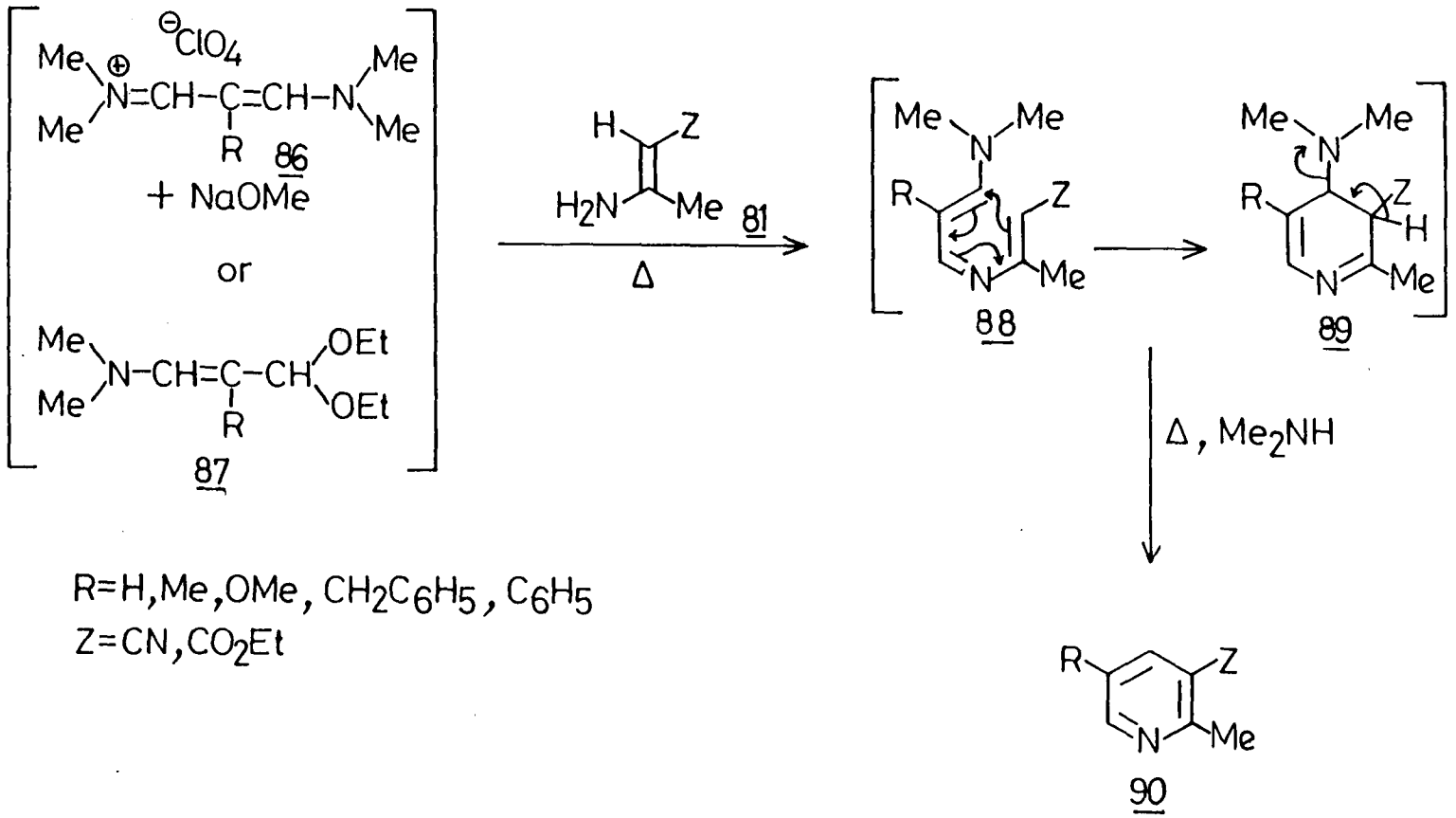
III.2.2 RESULTS AND DISCUSSION

For the present investigation, the α-oxoketene dithioacetals employed, were known and prepared according to reported procedures.

In a typical reaction, the acyclic α-oxoketene dithioacetal 1a was reacted with β-lithioaminocrotonitrile 77a (Scheme 25), generated by treating one equivalent of n-butyllithium with two equivalent of acetonitrile at -78°C, the product was isolated in 92% yield and

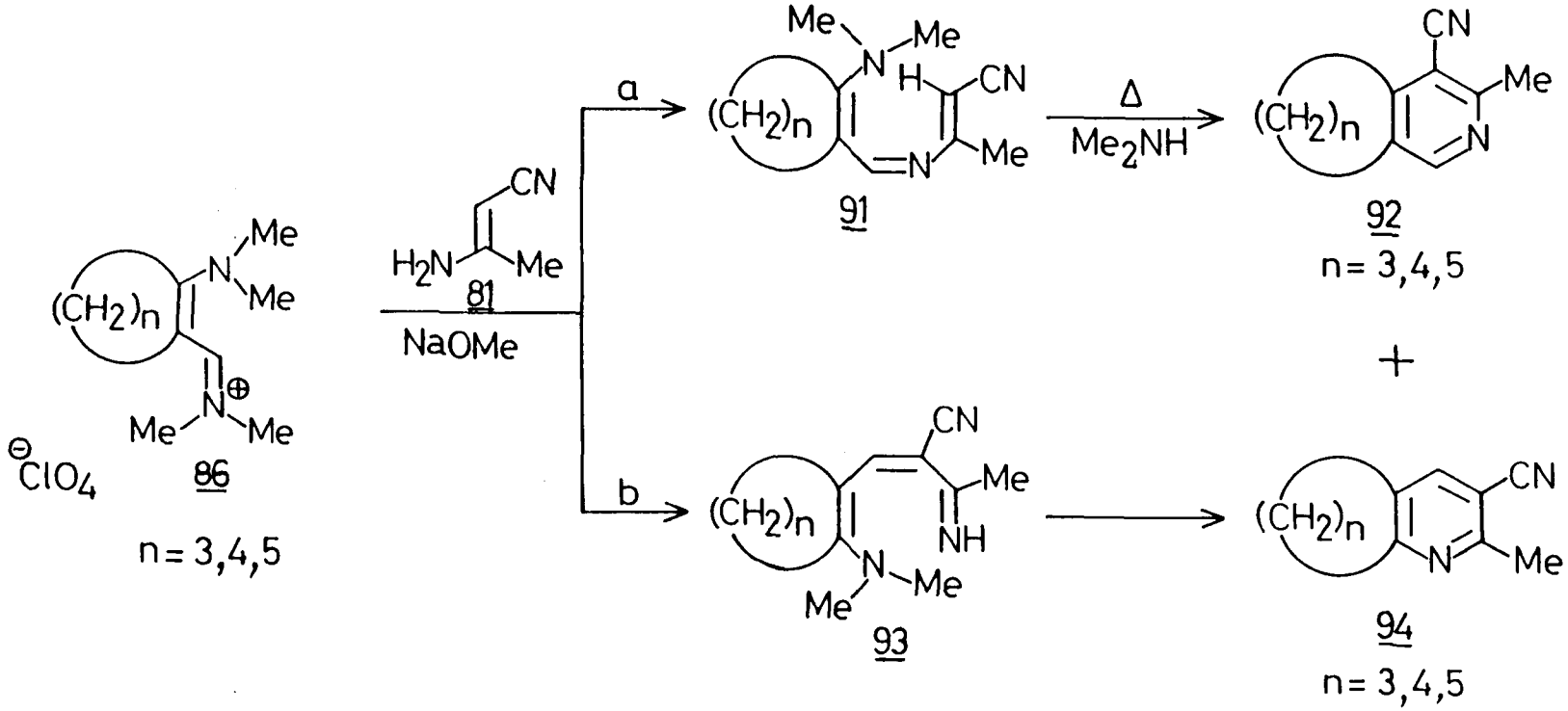

CH
C
R1
O
80
+
H2N
R2
Me
81
Δ / 100°C
R1
N
R2
Me
82
R1=Me, Ph
R2=CN, CO2Et
EtO
O
OEt
EtO2C
O
83
+
H2N
R
Me
81
CO2Et
EtO
O
R
N
Me
84
EtO2C
EtO2C
R
N
Me
85
R=CN, CO2Et, COMe

Scheme 22



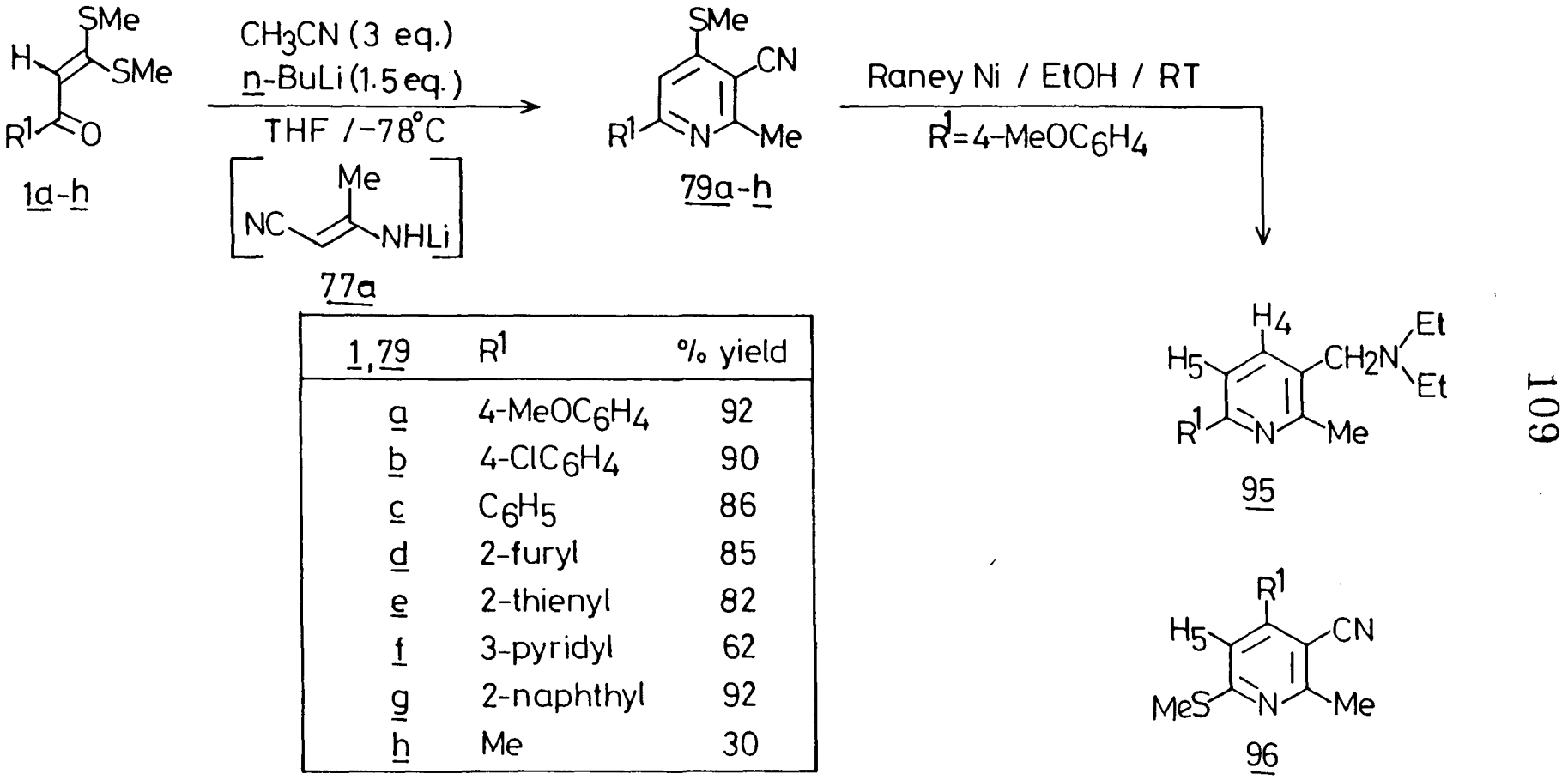
R=H,Me,OMe, $CH_2C_6H_5$, C_6H_5
Z=CN,CO_2Et

Scheme 23


Me
N
Me
(CH2)n
N⊕
Me
Me
⊖ClO4
86
n = 3,4,5
CN
H2N
Me
81
NaOMe
a
b
Me
N
Me
H
CN
(CH2)n
N
Me
91
Δ
Me2NH
CN
Me
(CH2)n
N
92
n = 3,4,5
+
CN
Me
(CH2)n
NH
N
Me
93
CN
(CH2)n
N
Me
94
n = 3,4,5

Scheme 24

characterized as 3-cyano-2-methyl-4-(methylthio)-6-(4-methoxyphenyl) pyridine (79a) (m.p. 157-158°C). The structure of 79a was confirmed from its analytical and spectral data. It was analyzed for $C_{15}H_{14}N_2OS$ and its mass spectrum showed the molecular ion peak at m/z 270(M^+,100%). It exhibited in its IR spectrum (KBr), a characteristic band at 2215 cm^{-1} which was assigned to nitrile stretching vibrations. The other prominent bands appeared at 1606, 1585 and 1556 cm^{-1}. The structure was further confirmed from its ^1H NMR spectrum ($CDCl_3$). A singlet at δ 2.60 which was integrating for 3 protons was assigned to methylthio group whereas the 2-methyl protons appeared at δ 2.74. The signal due to methoxy group was present at δ3.88(s,3H) while aromatic protons appeared as characteristic A_2B_2 doublets at δ 6.98 and 8.00 with coupling constants of 9Hz each respectively. The lone H-5 proton of the pyridine ring appeared at δ 7.28 as a singlet. The structure of 79a was further confirmed by its ^{13}C NMR spectrum and the values are as follows. The methylthio and methyl carbons appeared at δ13.96 and 23.70 respectively while methoxy carbon appeared at δ 55.24. The signals due to other atoms were present at δ 103.60(CN); 110.81(CH-5,arom), 114.09 (CH-3',arom), 115.61(C-3,arom), 128.72(CH-2',arom), 130.10(C-1',arom), 155.60(C-6,arom), 157.92(C-2,arom), 161.42(C-4',arom). The assigned structure of 79a was further supported by its reductive desulphurization. Thus, the pyridine 79a on treatment with Raney Nickel in ethanol at room temperature gave the corresponding 3-(N,N-diethylaminomethyl)-2-methyl-6-(4-methoxyphenyl)pyridine (95) in 68% yield. Apparently the pyridine 95 is formed by reductive alkylation of nitrile group of 79a in the presence of ethanol. The structure of 95 was in agreement with its analytical and spectral data (experimental). The positions of



1,79	R^1	% yield
a	4-$MeOC_6H_4$	92
b	4-ClC_6H_4	90
c	C_6H_5	86
d	2-furyl	85
e	2-thienyl	82
f	3-pyridyl	62
g	2-naphthyl	92
h	Me	30

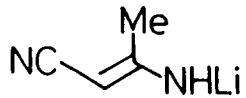
Scheme 25

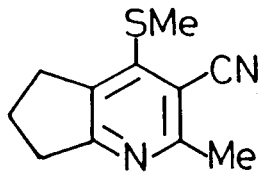
H-4 (δ 7.67,d,1H) and H-5(δ 7.44,d,1H) protons and characteristic coupling constants (J=8.0Hz) for these protons confirmed the structure assigned to 79a and it also eliminates the other possible isomeric structure 96 which could have been formed through 1,2-addition of enaminonitrile 77a to 1a (Scheme 25). The method was found to be of a general synthetic utility. Thus α-oxoketene dithioacetals 1b-h derived from the acyclic active methylene ketones similarly, yielded the corresponding pyridines 79b-h in 30-92% yield when reacted with 77a under identical condition. Though, the yields in all the cases are high, only in the case of 1h (R = Me), the corresponding pyridine 79h was obtained in low yield (30%). The probable explanation for the low yield of 1h can be attributed that in the presence of strong basic reaction conditions, the competitive deprotonation of the acyl methyl protons of 1h are responsible for lower yield of pyridine (Scheme 25). The structures of 79b-h were confirmed by its spectral and analytical data and are described in the experimental section.

The cyclic oxoketene dithioacetals 1i and 1j derived from the cyclopentanone and cyclohexanone respectively, reacted similarly with 77a under the described conditions, to yield the corresponding annelated pyridines 79i and 79j respectively in good yields (Scheme 26). In the similar way annelated pyridines 79k-m were obtained from the corresponding ketene dithioacetals 1k-m derived from tetralones and benzsuberone respectively. The analytical and spectral data confirming the structures of 79i-m have been described in the experimental section (Scheme 26).

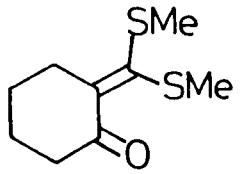
The oxoketene dithioacetals derived from benzocyclic ketones with one heteroatom such as 1n-p similarly reacted with 77a as described

1i

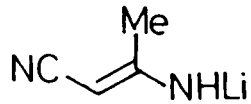


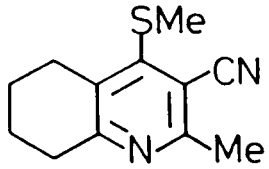


79i

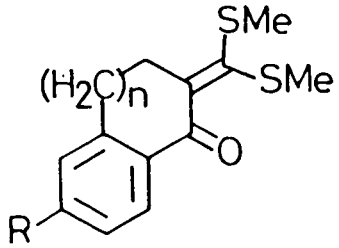


1j

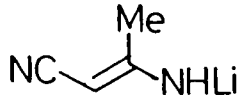


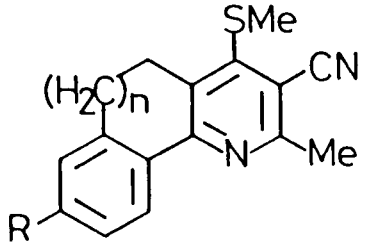


79j



1k-m





79k-m

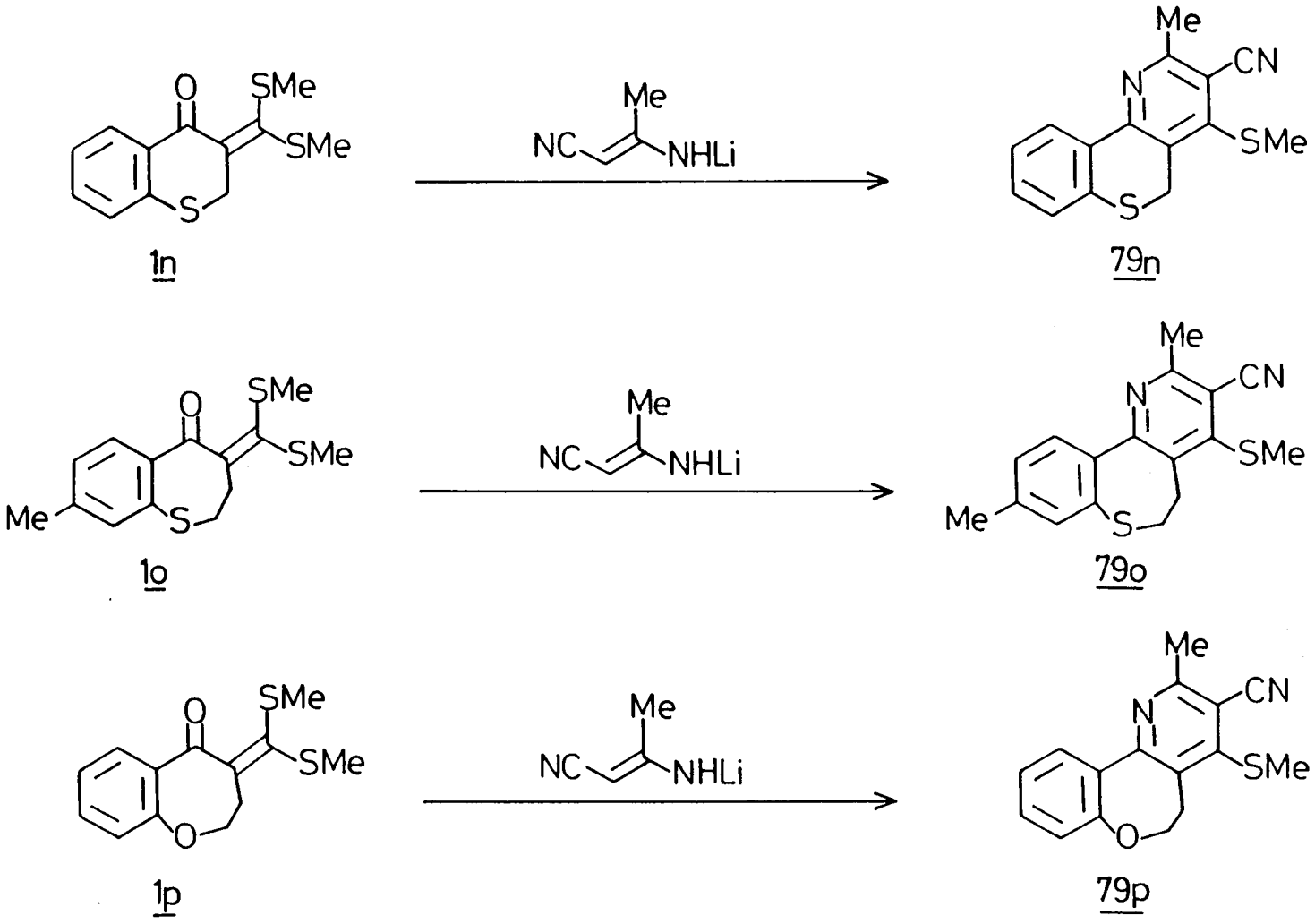
1,79k R=H,n=1
l R=MeO,n=1
m R=H,n=2

Scheme 26

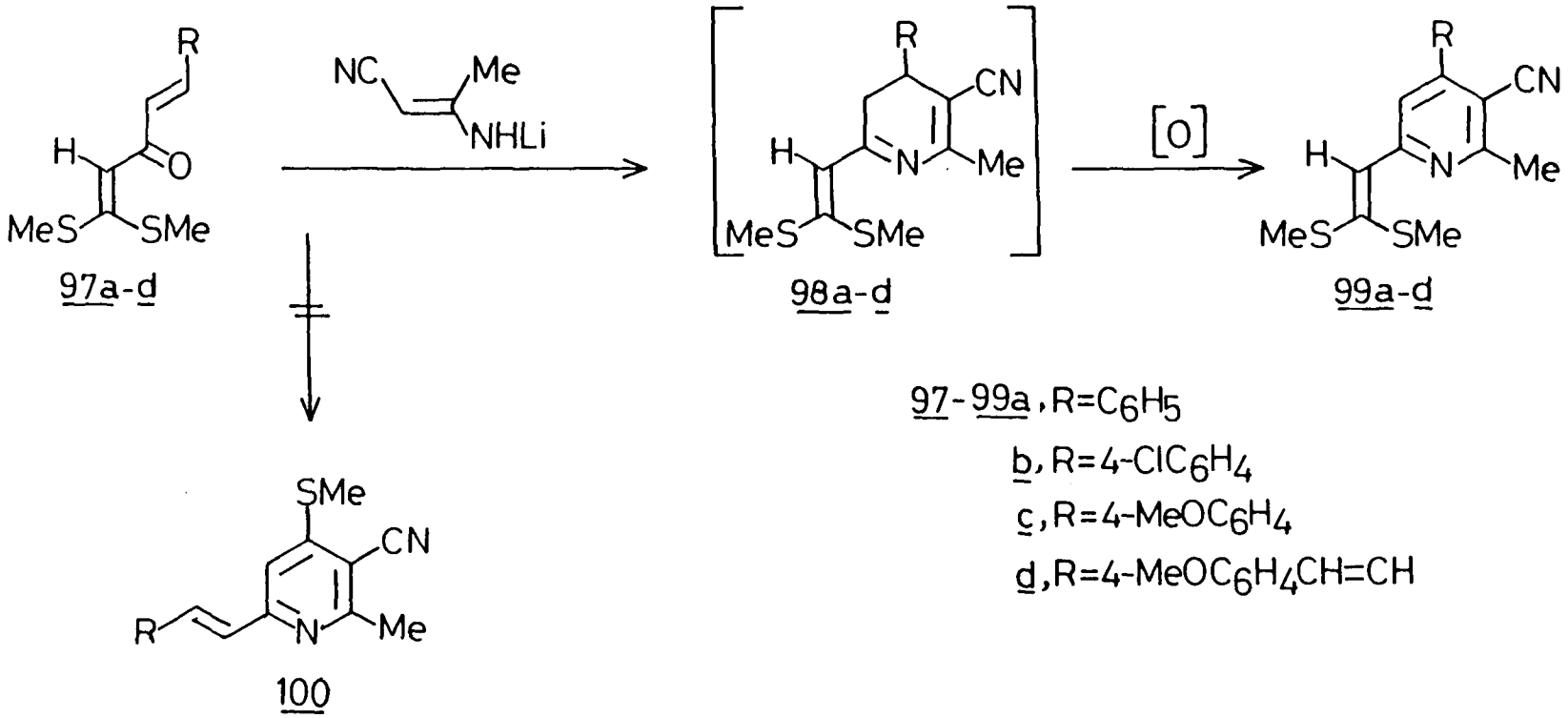
above and the corresponding fused pyridine derivatives 79n-p were obtained in 83-89% overall yields (Scheme 27). The analytical and spectral data of these fused pyridines 79n-p are described in the experimental section.

The reactivity of anion 77a with α-cinnamoyl oxoketene dithioacetals 97a-c and the corresponding 5-aryl-2,4-pentadienoylketene dithioacetal 97d was next examined. Interestingly, 77a added, regioselectively, in 1,4-fashion to the styryl double bond to yield the unstable dihydro pyridine intermediate 98a which under the experimental condition underwent oxidation to give the aromatized pyridine 99a in excellent yields (Scheme 28). Similarly other ketene dithioacetals 97b-d afforded the corresponding pyridines in excellent yields. The structures of these pyridines (99a-d) have confirmed by its analytical and spectral data and are described in experimental section. The characteristic mercapto functionality was present without being affected as observed in their ^{1}H NMR spectra. The structure of 99a was further confirmed by its ^{13}C NMR spectra (experimental). The expected pyridines 100 which could have been formed by addition of 77a to the mercapto-β-carbon were not detected in any of these reactions confirming the high regioselectivity of the 77a in its addition to 97 (Scheme 28).

When the lithioacetonitrile (75) was coupled with benzonitrile(76b) at -78°C, the corresponding anion 77b was generated in high yield and this anion was then treated *in situ* with α-oxoketene dithioacetals 1c, the corresponding 3-cyano-2,6-diphenyl-4-(methylthio) pyridine (101a) was obtained in 91% yield. The structural assignment


O
SMe
SMe
S
1n
Me
NC
NHLi
Me
CN
N
SMe
S
79n
Me
O
SMe
SMe
S
Me
1o
Me
NC
NHLi
Me
CN
N
SMe
S
Me
79o
O
SMe
SMe
O
1p
Me
NC
NHLi
Me
CN
N
SMe
O
79p

Scheme 27



97a-d

98a-d

99a-d

100

97-99a, R=C_6H_5

b, R=4-ClC_6H_4

c, R=4-$MeOC_6H_4$

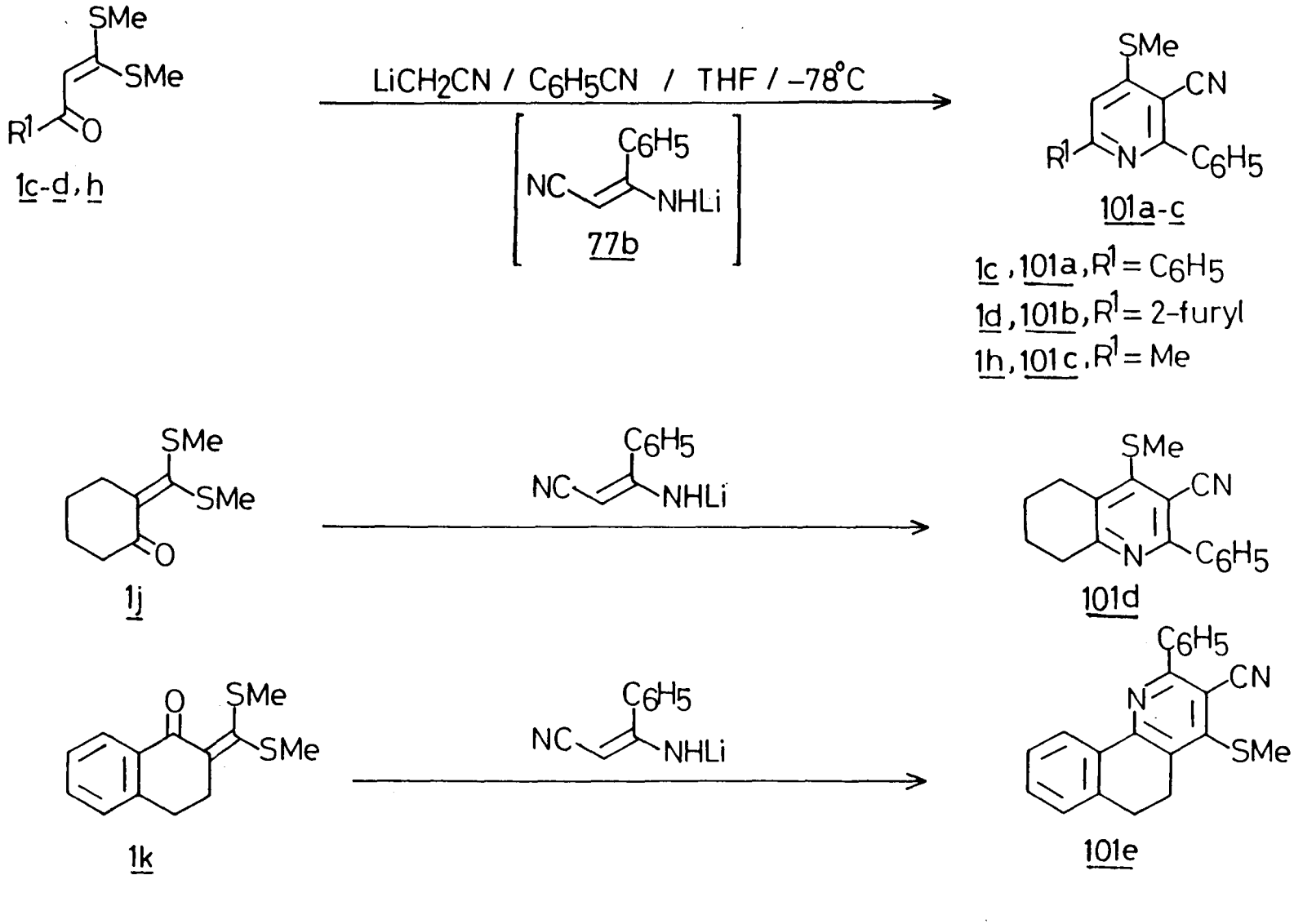
d, R=4-$MeOC_6H_4CH{=}CH$

Scheme 28

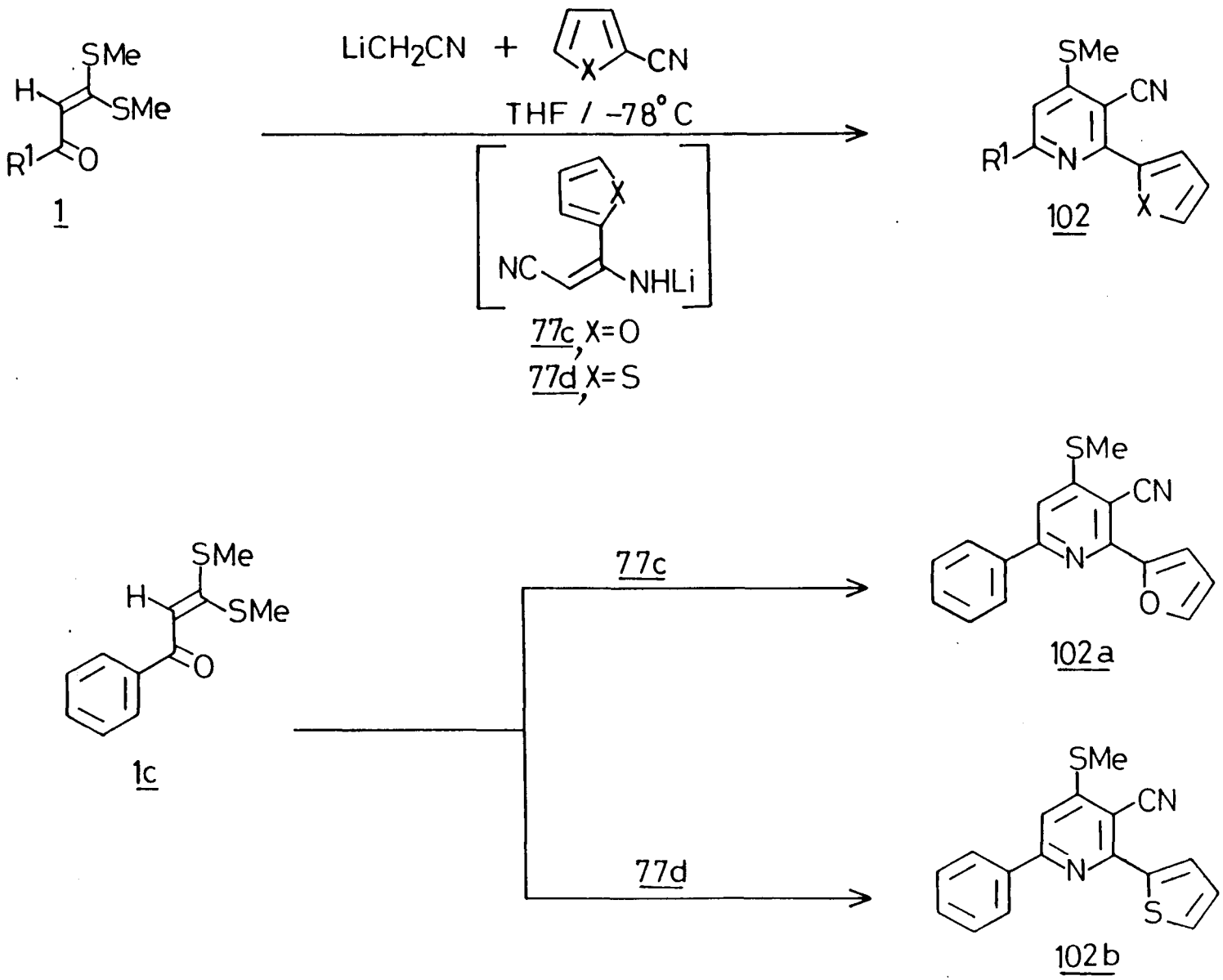
of 101a (Scheme 29) was in full agreement with its analytical and spectral data (experimental). Similarly, 101b-c were obtained from corresponding ketene dithioacetals 1d and 1h in 87% and 57% yields respectively. The anion 77b similarly, reacted with 1j and 1k to yield the corresponding 3-cyano-4-(methylthio)-2-phenyl-5,6,7,8-tetrahydroquinoline (101d) and 3-cyano-5,6-dihydro-4-(methylthio)-2-phenyl benzo[h]quinoline (101e) in excellent yields (Scheme 29). The analytical and spectral data which are in agreement with these structures are described in experimental section. Thus, the compound 2-phenylpyridines can be synthesized in one step starting from α-oxoketene dithioacetals.

When the above strategy was extended to couple lithioacetonitrile with 2-cyanofuran and 2-cyanothiophene, the corresponding anions 77c and 77d were formed in high yields and found to react smoothly with oxoketene dithioacetals in 1,4-conjugate manner followed by cyclization to yield the corresponding substituted pyridines (102 and 103) (Scheme 30 and 31). Thus, when 1c was reacted with 77c, the corresponding 3-cyano-2-(2-furyl)-4-(methylthio)-6-phenylpyridine (102a) was obtained in 76% yield. Similarly, 3-cyano-4-(methylthio)-2-(2-thienyl)-6-phenylpyridine (102b) was obtained in 65% yield when 77d was reacted with 1c. The structure of both 102a and 102b were confirmed by their analytical and spectral data (experimental) (Scheme 30).

The importance of 2,6-disubstituted pyridines particularly with 5-and 6-membered heterocycles as useful ligands have been reported[29,30]. It was considered of interest, that the present methodology can be manipulated to achieve the synthesis of these pyridines. Thus, when α-oxoketene dithioacetal derived from 2-acetylfuran 1d was reacted


SMe
SMe
R1
O
1c-d, h
LiCH2CN / C6H5CN / THF / -78°C
C6H5
NC
NHLi
77b
SMe
CN
R1
N
C6H5
101a-c
1c, 101a, R1 = C6H5
1d, 101b, R1 = 2-furyl
1h, 101c, R1 = Me
SMe
SMe
O
1j
C6H5
NC
NHLi
SMe
CN
N
C6H5
101d
O
SMe
SMe
1k
C6H5
NC
NHLi
C6H5
CN
N
SMe
101e

Scheme 29

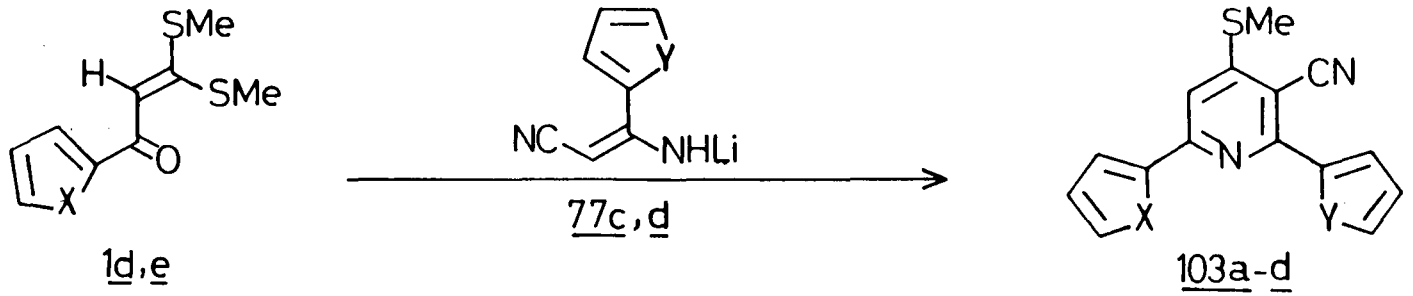

SMe
H
SMe
R1
O
1
LiCH2CN +
CN
X
THF / -78° C
NC
NHLi
77c, X=O
77d, X=S
SMe
CN
R1
N
X
102
1c
77c
77d
102a
102b
S

Scheme 30

with anion 77c the corresponding 3-cyano-2,6-bis(2-furyl)-4-(methylthio)pyridine 103a was obtained in 85% yield. Similarly, the α-oxoketene dithioacetal derived from 2-acetylthiophene 1e reacted with 77c, to yield corresponding 3-cyano-2-(2-furyl)-4-(methylthio)-6-(2-thienyl) pyridines (103b) in 78% yield. The other pyridine derivatives 103c and 103d were similarly obtained in good yields (Scheme 31). The structures of these pyridines 103a-d were in agreement with their analytical and spectral data (experimental).

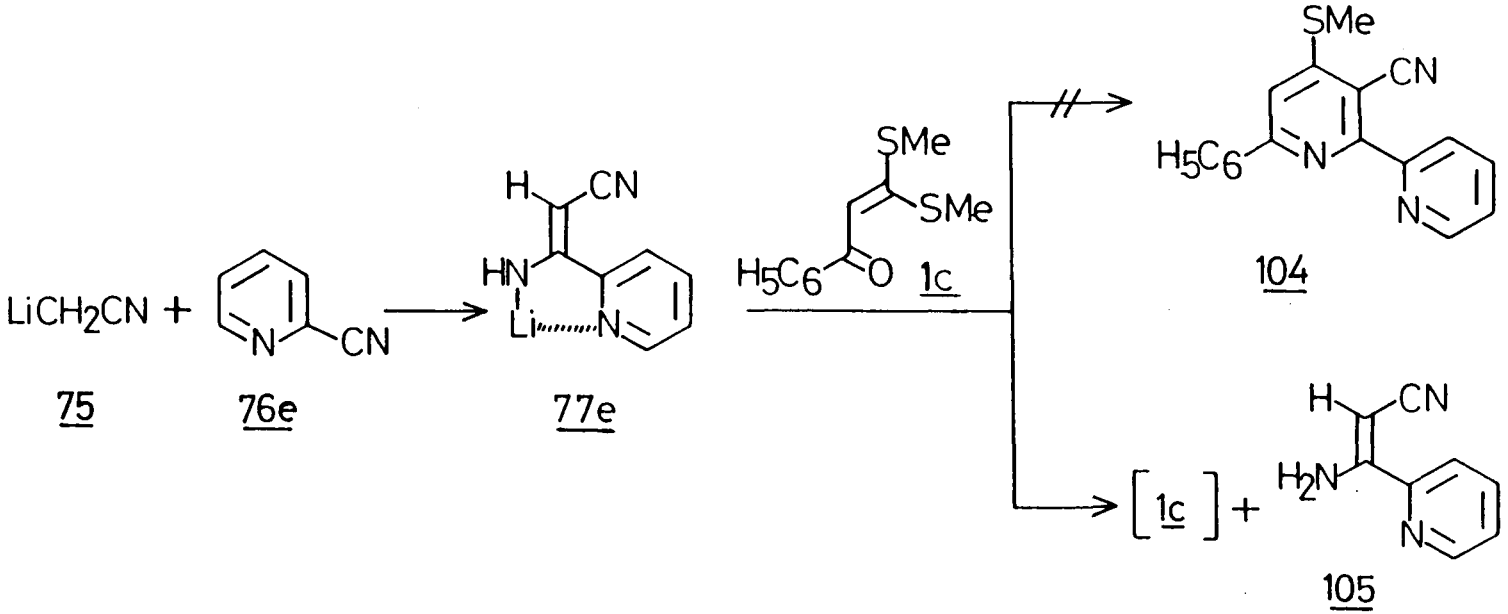
When the anion 77e, generated from lithioacetonitrile (75) and 2-cyanopyridine (76e) similarly, reacted with α-oxoketene dithioacetal 1c, the corresponding 3-cyano-4-(methylthio)-6-phenyl-2-(2-pyridinyl) pyridine (104) was not formed (Scheme 31). The product isolated was the enaminonitrile 105 along with unreacted starting material (1c). It appears that the pyridine nitrogen has a strong intramolecular chelation to the metal (77e) and which consequently reduces the nucleophilicity of the enamine carbon. Attempts to achieve the addition of 77e to 1 are still in progress.

During the course of present investigation, the pyridines were also subjected to reductive desulphurization in the presence of Raney Nickel. The nitrile group also underwent reductive alkylation with alcohols used as a reaction medium, during this operation. Thus, 79a yielded 3-(N,N-diethylaminomethyl)-2-methyl-6-(4-methoxyphenyl)pyridine (95) when reduction was carried out at room temperature in ethanol. Similarly, n-propyl analogue 106 was obtained when n-propanol was used as the reaction medium. The N,N-diethylamino derivative (95) was successfully hydrogenolysed to yield the 2,3-dimethyl-6-(4-methoxyphenyl) pyridine (107) under refluxing condition (Scheme 32). The structures



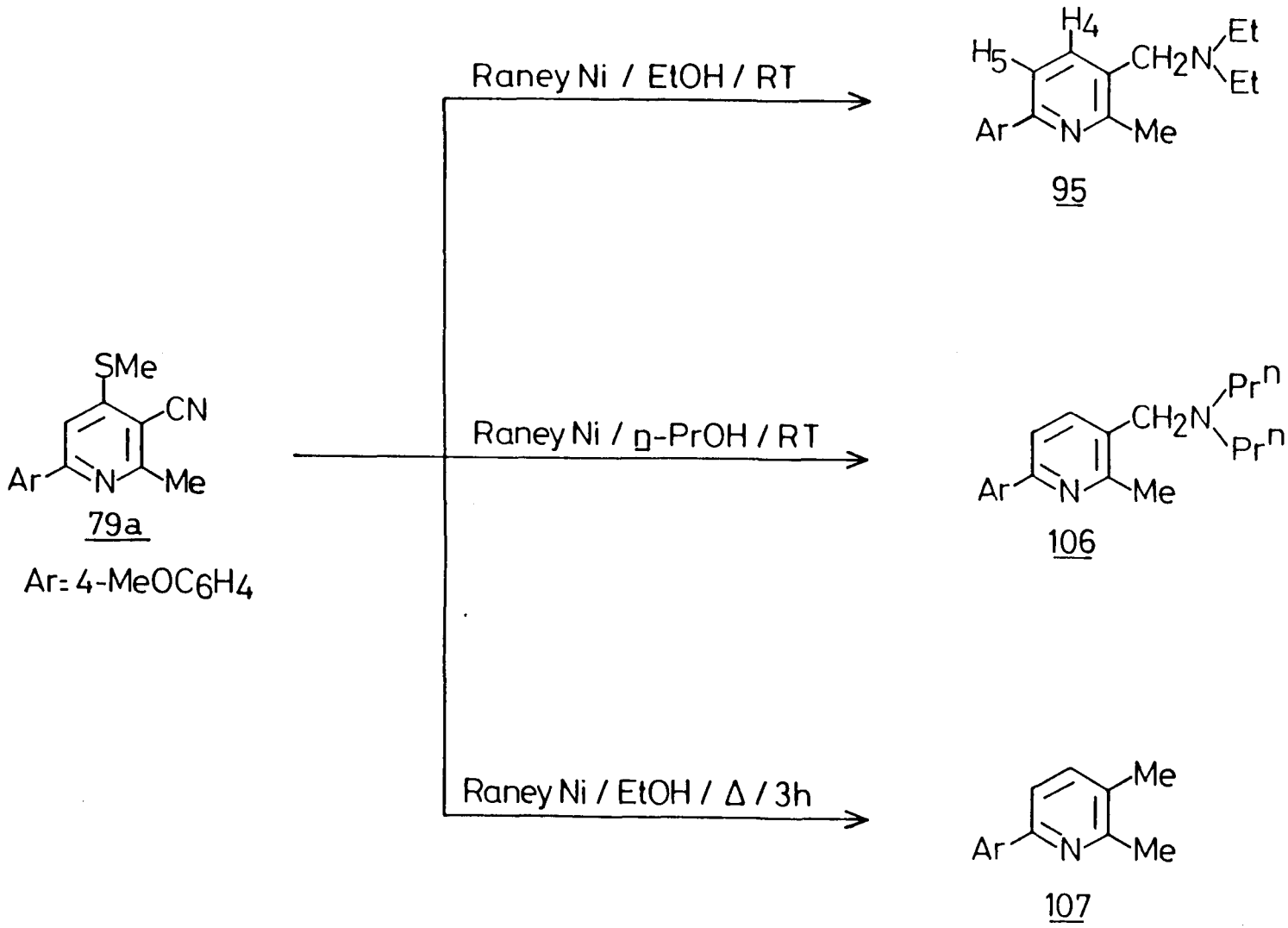
1d,e — 77c,d — 103a-d

1d, 77c, 103a, X=Y=O
1e, 77c, 103b, X=S; Y=O
1d, 77d, 103c, X=O; Y=S
1e, 77d, 103d, X=Y=S



75 — 76e — 77e — 1c — 104 — [1c] + 105

Scheme 31


SMe
CN
Ar
N
Me
79a
Ar= 4-MeOC6H4
Raney Ni / EtOH / RT
Raney Ni / n-PrOH / RT
Raney Ni / EtOH / Δ / 3h
H4
H5
CH2N
Et
Et
95
Prn
Prn
106
Me
Me
107

Scheme 32

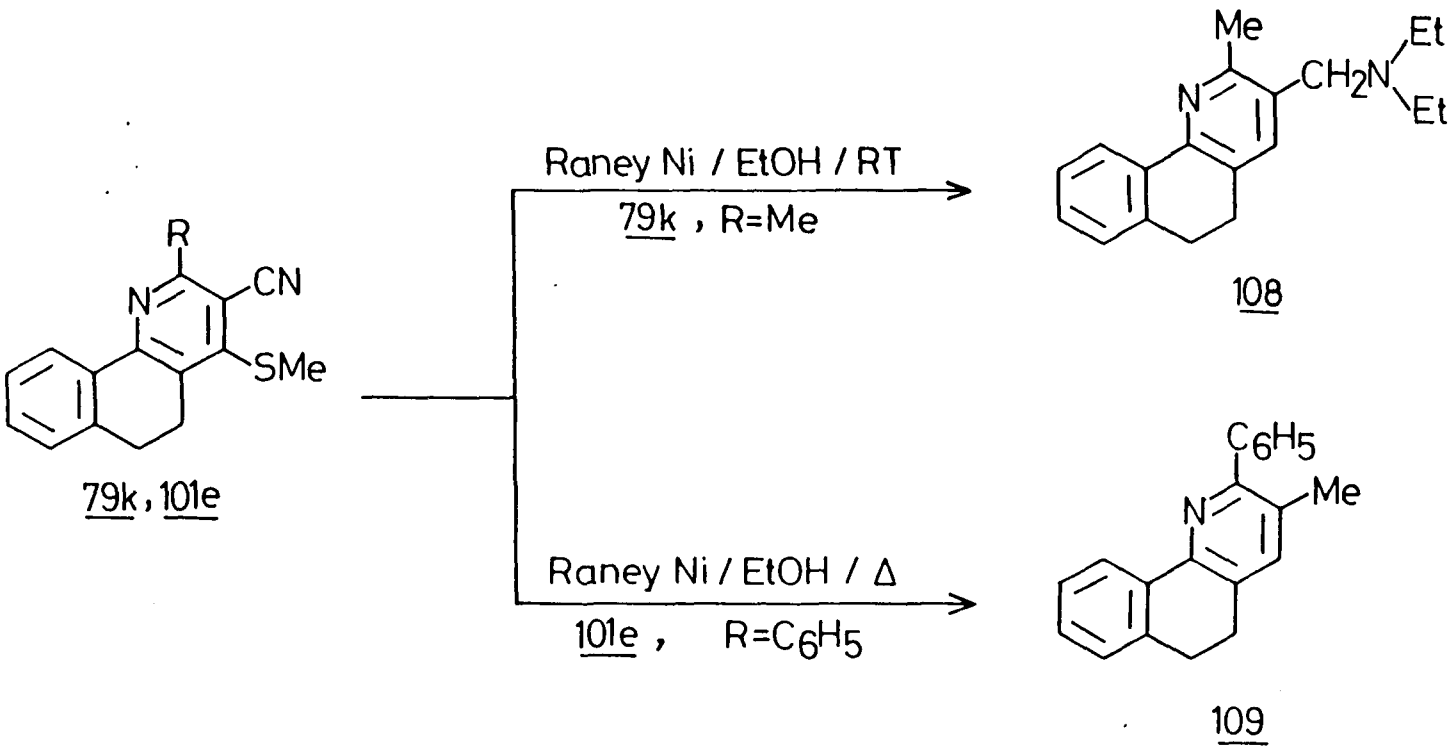
of these reduced pyridines 95, 106 and 107 were found to be in agreement with their analytical and spectral data (experimental). The similar reduction studies were extended to the pyridines derived from cyclic ketones. Thus, when 79k were subjected to Raney Nickel reductive desulphurization and alkylation at room temperature in ethanol, the corresponding 5,6-dihydro-3-(N,N-diethylaminomethyl)-2-methyl-benzo[h]quinoline (108) was obtained in good yields while under refluxing condition, 3-cyano-5,6-dihydro-4-(methylthio)-2-phenylbenzo[h]quinoline (101e) yielded the 5,6-dihydro-3-methyl-2-phenylbenzo[h]quinoline (109) in 71% yield. The spectral data for these reduced pyridine derivatives 108 and 109 are given in the experimental section (Scheme 33).

III.2.3 CONCLUSION

A new efficient general approach with provision for molecular manipulation for the synthesis of various 2,6-disubstituted and 2,3-annelated pyridines have been formulated. The method assumes particular importance since both anions (77) and the α-oxoketene dithioacetals (1) can be altered structurally as demonstrated throughout the study. It should be possible to extend this methodology for the synthesis of a number of pyridines that may possess the properties characteristic of polyligand centres.

III.3 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra refer to those run on a Varian EM-390 (90 MHz) spectrometer using TMS as


R
CN
N
SMe
79k, 101e
Raney Ni / EtOH / RT
79k , R=Me
Me
Et
CH2N
Et
N
108
Raney Ni / EtOH / Δ
101e , R=C6H5
C6H5
Me
N
109

Scheme 33

internal standard, chemical sifts are expressed as δ ppm downfield from TMS. ^{13}C NMR spectra were recorded on a Brucker WM-400 spectrometer. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. Elemental analysis were carried out on a Heraus CHN-O-RAPID instrument.

General experimental details for the preparation of α-oxoketene dithioacetals are given in Chapter II. All ketene dithioacetals employed were prepared using this procedure and were characterized by physical and spectral data. Unsymmetric ketene dithioacetal 51 (S-ethyl-S-methyl) was obtained by alkylation of the ethyl-β-hydroxy dithiocinnamate [$C_6H_5C(OH)=CHC(S)SEt$]by methyl iodide in anhydrous potassium carbonate in acetone. The preparation of α-cinnamoylketene dithioacetals were achieved by condensation of α-acylketene dithioacetals with aldehydes. 4-Methoxy-cinnamaldehyde was prepared according to the reported procedure[31].

Starting Materials

The commercial samples of acetonitrile, proprionitrile phenylacetonitrile and benzonitrile were purified by distillation before use, while 2-cyanofuran, 2-cyanothiophene and hexamethyl phosphorus triamide (HMPT) were purchased from Aldrich and used as such. 2-Cyanopyridine was prepared according to the reported procedure[32]. n-Butyllithium was prepared according to the reported procedure[33]. Tetrahydrofuran was dried over sodium wire in presence of benzophenone. W-4 Raney Nickel was prepared according to the reported procedure[34].

Generation and reaction of lithioacetonitrile with α-oxoketene dithioacetals:

To a stirred solution of freshly distilled acetonitrile (0.5125g;

12.5 mmol) in dry tetrahydrofuran (25 ml), n-butyllithium (12.5 mmol) was added under an efficient atmosphere of nitrogen, maintaining the temperature at -78°C. After stirring for 0.5 hr at -78°C, the resulting white suspension was treated during 5 min with a solution of appropriate oxoketene dithioacetals (1, 10 mmol) in 50 ml of THF. The reaction mixture was further stirred for 1 hr., slowly warming the mixture to room temperature. The reaction mixture was poured into saturated ammonium chloride and the layers were separated. The aqueous layer was extracted with ether (2x50 ml) and the combined organic layer was washed with water (100 ml), dried (Na_2SO_4) and evaporated to give crude carbinolacetals in nearly quantitative yield.

General Procedure for Cycloaromatization of Carbinolacetals; Synthesis of 2,6-Bis(alkylthio)-3,4 - substituted and 4,5-Annelated Pyridines:

The crude carbinolacetals were heated with orthophosphoric acid (25 ml, 88%) for 3 hrs. at 130°C. The reaction mixture was then cooled and poured over crushed ice-water, extracted with chloroform (3x100 ml) washed with water (150 ml) and dried (Na_2SO_4). The evaporation of the solvent gave a viscous residue, which were purified by passing through a column of silica gel (EtOAc-hexane, 1:20 as eluent) to give pure products.

2,6-Bis(methylthio)-4-phenylpyridine (5a); was isolated as light yellow crystals(hexane); m.p. 86-87°C; yield 82%; spectral data described in text. (Found: C,63.23; H,5.24; N,5.62; Calc. for $C_{13}H_{13}NS_2$: C,63.12; H,5.30; N,5.66%); m/z 247(M^+,100%), 213(24), 201(12).

2,6-Bis(methylthio)-4-(4-chlorophenyl)pyridine (5b); was isolated as light yellow crystals (hexane); m.p. 122-113°C; yield 72%; IR ν_{max} (KBr) 1576, 1512, 1488 cm^{-1}; ^1H NMR(CCl_4); 2.56(s,6H,SCH_3); 6.88(s, 2H,H-3 and H-5); 7.22-7.50(m,4H,arom). (Found: C,55.55; H,4.38; N, 4.88; Calc. for $C_{13}H_{12}ClNS_2$: C,55.40; H,4.29; N,4.97%); m/z 283(M^+, 43%), 281(M^+,100); 247(27).

2,6-Bis(methylthio)-4-(4-methoxyphenyl)pyridine (5c); was isolated as light yellow crystals (hexane); m.p. 74-75°C; yield 68%; IR ν_{max} (KBr) 1601, 1577, 1510 cm^{-1}; ^1H NMR(CCl_4): 2.58(s,6H,SCH_3); 3.80(s, 3H,OCH_3); 6.88(d,2H,J=9Hz,arom); 6.96(s,2H,H-3 and H-5); 7.50(d,2H, J=9Hz, arom). (Found: C,60.72; H,5.52; N,5.01; Calc. for $C_{14}H_{15}NOS_2$: C,60.62; H,5.45; N,5.05%); m/z 277(M^+,100%), 231(12).

2,6-Bis(methylthio)-4-(4-methylphenyl)pyridine (5d); was isolated as light yellow crystals (hexane); m.p. 78-79°C; yield 83%; IR ν_{max}(KBr) 1592, 1572, 1538, 1480 cm^{-1}; ^1H NMR(CCl_4): 2.36(s,3H,CH_3); 2.57(s, 6H,SCH_3); 6.96(s,2H,H-3 and H-5); 7.14(d,2H,J=9Hz,arom); 7.40(d,2H, J=9Hz, arom). (Found: C,64.42; H,5.65; N,5.22; Calc. for $C_{14}H_{15}NS_2$: C,64.33; H,5.78; N,5.36%); m/z 261(M^+,261%), 227(22), 215(13), 200(10), 166(11).

2,6-Bis(methylthio)-4-(2-furyl)pyridine (5e); was isolated as white crystals (hexane); m.p. 70-71°C; yield 71%; IR ν_{max}(KBr) 1601, 1564, 1530, 1485 cm^{-1}; ^1H NMR(CCl_4): 2.54(s,6H,SCH_3); 6.44(brs,1H,H-4 of furyl); 6.74(d,1H,J=3Hz,H-3); 7.02(s,2H,H-3 and H-5); 7.46(brd,1H, furyl ,H-5').(Found: C,55.76; H,4.52; N,5.82; Calc. for $C_{11}H_{11}NOS_2$: C,55.67; H,4.67; N,5.90%); m/z 237(M^+,100%), 203(16), 191(12), 162(15), 154(5).

2,6-Bis(methylthio)-4-(2-thienyl)pyridine (5f); was isolated as yellow crystals(hexane); m.p. 96-97°C; yield 75%; IR ν_{max}(KBr) 1580, 1532, 1517 cm^{-1}; ^1H NMR(CCl_4): 2.54(s,6H,SCH_3); 6.91(s,2H,H-3 and H-5); 6.92-7.06(m,1H,thienyl H); 7.20-7.36(m,2H,thienyl H).(Found: C,52.32; H,4.52; N,5.64; Calc. for $C_{11}H_{11}NS_3$: C,52.14; H,4.38; N,4.53%); m/z 253(M^+,100%), 219(11), 207(15).

2,6-Bis(methylthio)-4-(3-pyridinyl)pyridine (5g); was isolated as white crystals(EtOAc-hexane); m.p. 101-102°C; yield 77%; IR ν_{max}(KBr) 1578, 1514 cm^{-1}; ^1H NMR($CDCl_3$): 2.60(s,6H,SCH_3); 7.04(s,2H,H-3 and H-5); 7.38(brt,1H,H-5' of pyridinyl); 7.84(brd,1H,H-4' of pyridinyl); 8.66(brd,1H,H-6' of pyridinyl); 8.81(s,1H,H-2'of pyridinyl). (Found: C,58.17; H,5.02; N,11.21; Calc. for $C_{12}H_{12}N_2S_2$: C,58.03; H,4.87; N,11.13%); m/z 248(M^+,100%), 216(17), 201(12), 168(12).

2,6-Bis(methylthio)-4-(2-naphthyl)pyridine (5h); was isolated as white crystals($CHCl_3$); m.p. 118-119°C; yield 79%; IR ν_{max}(KBr) 1570, 1520 cm^{-1}; ^1H NMR($CDCl_3$); 2.60(s,3H,SCH_3); 2.62(s,3H,SCH_3); 7.11(s, 1H,H-3); 7.13(s,1H,H-5); 7.22-8.02(m,7H,arom). (Found: C,68.42; H,4.88; N,4.68; Calc. for $C_{17}H_{15}NS_2$: C,68.65; H,5.08; N,4.71%); m/z 297(M^+,100%), 281(19), 263(17), 203(22).

4-Methyl-2,6-bis(methylthio)pyridine (5i); was isolated as yellow crystals (hexane); m.p. 51-52°C; yield 78%; IR ν_{max}(KBr) 1569, 1530 cm^{-1}; ^1H NMR(CCl_4): 2.19(s,3H,CH_3); 2.54(s,6H,SCH_3); 6.61(s,2H,H-3 and H-5). (Found: C,51.72; H,5.86; N,7.68; Calc. for $C_8H_{11}NS_2$: C, 51.85; H,5.98; N,7.56%); m/z 185(M^+,100%), 151(24), 139(17), 105(20).

4-Ethyl-2,6-bis(methylthio)pyridine (5j); was isolated as yellow oil; yield 61%; IR ν_{max}(neat) 1574, 1528 cm^{-1}; ^1H NMR(CCl_4): 1.16 (t,3H,J=7.5Hz,$C\underline{H}_3$); 2.46(q,2H,J=7.5Hz,$C\underline{H}_2$); 2.50(s,6H,$SC\underline{H}_3$); 6.60 (s,2H,$\underline{H}$-3 and $\underline{H}$-5). (Found: C,54.39; H,6.42; N,6.88; Calc. for $C_9H_{13}NS_2$: C,54.23; H,6.57; N,7.03%); m/z 199(M^+,100%), 165(26), 153(16).

3,4-Dimethyl-2,6-bis(methylthio)pyridine (5k); was isolated as brown solid (hexane); m.p. 35-36°C; yield 68%; IR ν_{max}(CCl_4) 1568, 1548 cm^{-1}; ^1H NMR(CCl_4): 2.04(s,3H,$C\underline{H}_3$); 2.11(s,3H,$C\underline{H}_3$); 2.47(s, 6H,$SC\underline{H}_3$); 6.56(s,1H,$\underline{H}$-5). (Found: C,54.42; H,6.39; N,7.14; Calc. for $C_9H_{13}NS_2$: C,54.23; H,6.57; N,7.02%); m/z 199(M^+,100%), 184(15), 166(90), 153(10), 138(19), 120(14).

4-Ethyl-3-methyl-2,6-bis(methylthio)pyridine (5l); was isolated as yellow oil; yield 58%; IR ν_{max}(neat) 1568, 1530 cm^{-1}; ^1H NMR(CCl_4): 1.13(t,3H,J=7.5Hz,$C\underline{H}_3$); 2.10(s,3H,$C\underline{H}_3$); 2.51(q,2H,J=7.5Hz,$C\underline{H}_2$); 2.54 (s,6H,$SC\underline{H}_3$); 6.63(s,1H,$\underline{H}$-5). (Found: C,56.49; H,7.27; N,6.51; Calc. for $C_{10}H_{15}NS_2$: C,56.29; H,7.09; N,6.57%); m/z 213(M^+,94%), 198(14), 180(100).

2,6-Bis(methylthio)-3-(n-butyl)-4-methylpyridine (5m); was isolated as viscous yellow oil; yield 52%; IR ν_{max}(CCl_4) 1566, 1538 cm^{-1}; ^1H NMR(CCl_4): 0.90-1.20(brt,3H,$C\underline{H}_3$); 1.14-1.66(m,4H,$C\underline{H}_2$); 2.22(s,3H, CH_3); 2.56(s,6H,$SC\underline{H}_3$); 2.40-2.73(m,merged with SCH_3 signal,2H,$C\underline{H}_2$); 6.70(s,1H,$\underline{H}$-5). (Found: C,59.61; H,7.87; N,5.79; Calc. for $C_{12}H_{19}NS_2$: C,59.70; H,7.93; N,5.80%); m/z 241(M^+,36%).

1,3-Bis(methylthio)-5,6,7,8-tetrahydroisoquinoline (5o); was isolated was isolated as yellow oil; yield 76%; IR ν_{max}(neat) 1570, 1542 cm^{-1};

^{1}H NMR(CCl_4): 1.58-1.87(m,4H,$C\underline{H}_2$); 2.44(s,3H,$SC\underline{H}_3$); 2.46(s,3H,$SC\underline{H}_3$); 2.32-2.72(m,merged with SCH_3 signals, 4H,$C\underline{H}_2$); 6.51(s,1H,$\underline{H}$-4). (Found:C,58.42; H,6.68; N,6.04; Calc. for $C_{11}H_{15}NS_2$: C,58.62; H,6.71; N,6.22%);m/z 225(M^+,65%), 210(34), 192(100).

1,3-Bis(methylthio)-6,7,8,9-tetrahydro-5H-cyclohepta[c]pyridine (5p); was isolated as white crystals (hexane); m.p. 77-78°C; yield 71%; IR ν_{max}(KBr) 1560, 1530 cm^{-1}; ^{1}H NMR(CCl_4): 1.40-1.84(m,6H,$C\underline{H}_2$); 2.50(s,6H,$SC\underline{H}_3$); 2.44-2.82(m,merged with SCH_3 signal, 4H, $C\underline{H}_2$); 6.55(s,1H,$\underline{H}$-8). (Found: C,59.98; H,7.02; N,5.99; Calc. for $C_{12}H_{17}NS_2$: C,60.20; H,7.16; N,5.85%); m/z 239(M^+,79%), 206(100), 178(17).

2,4-Bis(methylthio)-indane-5H-[2,1-c]pyridine (5r); was isolated as white crystals (hexane); m.p. 125-126°C; yield 58%; IR ν_{max}(KBr) 1582, 1534 cm^{-1}; ^{1}H NMR($CDCl_3$): 2.64(s,3H,$SC\underline{H}_3$); 2.66(s,3H,$SC\underline{H}_3$); 3.68(s,2H,$C\underline{H}_2$); 7.20-7.90(m,5H,Ar$\underline{H}$). (Found: C,64.69; H,5.02; N,5.27; Calc. for $C_{14}H_{13}NS_2$: C,64.83; H,5.05; N,5.40%);m/z 259 (M^+,87%), 244(22), 226(100), 196(35).

1,4-Bis(methylthio)-5,6-dihydro-benz [f]isoquinoline (5s); was isolated as yellow crystals (hexane); m.p. 108-109°C; yield 83%; IR ν_{max}(KBr) 1560, 1524 cm^{-1}; ^{1}H NMR($CDCl_3$): 2.56(s,6H,$SC\underline{H}_3$); 2.66-2.88(m,4H,$C\underline{H}_2$); 7.09-7.24(m,4H,Ar$\underline{H}$); 7.50-7.72(m,1H,Ar$\underline{H}$). (Found: C,65.71; H,5.65; N,5.32; Calc. for $C_{15}H_{15}NS_2$: C,65.89; H,5.53; N,5.12%); m/z 273(M^+,100%), 258(23), 240(76), 228(27).

2,4-Bis(methylthio)-5,6-dihydro-8-methoxy-benz [f]isoquinoline (5t); was isolated as yellow crystals (hexane); m.p. 115-116°C; yield 77%; IR ν_{max}(KBr) 1612, 1566, 1524 cm^{-1}; ^{1}H NMR(CCl_4): 2.60(s,6H,$SC\underline{H}_3$);

2,69-2.86(m,4H,$C\underline{H}_2$); 3.80(s,3H,$OC\underline{H}_3$); 6.69(s,1H,H-1); 6.74(dd,1H, J=9.0,1.5Hz,H-9); 7.11(s,1H,H-7); 7.61(d,1H,J=9.0Hz,H-10). (Found: C,66.45; H,5.51; N,4.48; Calc. for $C_{16}H_{17}NOS_2$: C,66.33; H,5.65; N,4.62%); m/z 303(M^+,100%), 270(70), 223(29).

2,4-Bis(methylthio)-6,7-dihydro-5H-benzocyclohepta-[2,1-c] pyridine (5u); was isolated as white crystals (hexane); m.p. 87-88°C; yield 68%; IR ν_{max}(KBr) 1566, 1520 cm^{-1}; ^1H NMR($CDCl_3$): 2.02-2.57 (m,6H,$C\underline{H}_2$); 2.60(s,6H,$SC\underline{H}_3$); 6.90(s,1H,H-1); 7.17-7.39(m,4H,ArH). (Found: C,66.74; H,6.02; N,4.92; Calc. for $C_{16}H_{17}NS_2$: C,66.85; H,5.96; N,4.87%); m/z 287(M^+,100%), 272(56), 254(83).

2,4-Bis(methylthio)-benzo5H-thiopyrano[3,4-c]pyridine (5v); was isolated as yellow crystals (hexane); m.p. 118-119°C; yield 76%; IR ν_{max}(KBr) 1564, 1522 cm^{-1}; ^1H NMR($CDCl_3$): 2.59(s,3H,$SC\underline{H}_3$); 2.61 (s,3H,$SC\underline{H}_3$); 3.73(s,2H,$C\underline{H}_2$); 7.08(s,1H,H-7); 7.09-7.42(m,3H,ArH); 7.58-7.78(m,1H,ArH). (Found: C,57.46; H,4.59; N,4.94; Calc. for $C_{14}H_{13}NS_2$: C,57.69; H,4.49; N,4.81%); m/z 291(M^+,66%), 258(36), 243(16), 228(30).

2,4-Bis(Methylthio)-7-methyl-5,6-dihydrobenzothiepino[4,5-c][1] pyridine (5w); was isolated as yellow crystals (hexane-chloroform); m.p. 148-149°C; yield 79%; IR ν_{max}(KBr) 1593, 1484 cm^{-1}; ^1H NMR(CCl_4): 2.37(s,3H,$C\underline{H}_3$); 2.59(s,3H,$SC\underline{H}_3$); 2.61(s,3H,$SC\underline{H}_3$); 2.62-3.09(m,2H, $C\underline{H}_2$); 3.15-3.50(m,2H,$C\underline{H}_2$); 6.78(s,1H,H-1); 7.21(brd,1H,H-10); 7.24 (s,1H,H-8); 7.40(brd,1H,H-11). (Found: C,59.98; H,5.24; N,4.18; Calc. for $C_{16}H_{17}NS_3$: C,60.14;H,5.36; N,4.38%); m/z 319(M^+,100%), 304(84), 286(89), 272(14), 256(12), 252(13).

2-(Ethylthio)-6-(methylthio)-4-phenylpyridine (53); was isolated as yellow oil (darken on exposure to light); yield 63%; IR $\nu_{max}(CCl_4)$ 1574, 1518 cm^{-1}; ^1H NMR(CCl_4): 1.40(t,3H,J=7.5Hz,CH_3); 2.57(s,3H, SCH_3); 3.12(q,2H,J=7.5Hz,CH_2); 7.00(s,2H,H-3 and H-5); 7.30-7.64 (m,5H,ArH). (Found: C,64.18; H,5.64; N,5.12; Calc. for $C_{14}H_{15}NS_2$: C,64.33; H,5.78; N,5.36%); m/z 261(M^+,78%), 246(44), 228(42).

2,6-Bis(methylthio)-4-styrylpyridine (70a); was isolated as white crystals (hexane); m.p. 106-107°C; yield 65%; IR ν_{max}(KBr) 1574, 1522 cm^{-1}; 1H NMR(CCl_4): 2.56(s,6H,SCH_3); 7.10(s,2H,H-3 and H-5); 7.10-7.70(m,7H,ArH). (Found: C,65.87; H,5.51; N,4.98; Calc. for $C_{15}H_{15}NS_2$: C,65.89; H,5.53; N,5.12%); m/z 273(M^+,100%), 239(11),

2,6-Bis(methylthio)-4-(4-chlorostyryl)pyridine (70b); was isolated as yellow prism (hexane); m.p. 154-155°C; yield 58%; IR ν_{max}(KBr) 1570, 1521 cm^{-1}; ^1H NMR($CDCl_3$): 2.54(s,6H,SCH_3); 6.68(d,1H,J=18Hz, olefinic); 6.81(s,2H,H-3 and H-5); 7.06(d,1H,J=18Hz, olefinic); 7.11-7.42(m,4H,ArH). (Found: C,58.38; H,4.45; N,4.39; Calc. for $C_{15}H_{14}ClNS_2$: C,58.52; H,4.58; N,4.55%); m/z 309(M^+,49%), 307(100), 273(10).

2,6-Bis(methylthio)-4-(2-chlorostyryl)pyridine (70c); was isolated as yellow prism (hexane); m.p. 144-145°C; yield 61%; IR ν_{max}(KBr) 1572, 1524 cm^{-1}; ^1H NMR($CDCl_3$): 2.60(s,6H,SCH_3); 6.80(d,1H,J=18Hz, olefinic); 6.94(s,2H,H-3 and H-5); 7.12-7.70(m,4H,ArH); 7.60(d,1H, J=18Hz, olefinic). (Found: C,58.59; H,4.45; N,4.52; Calc. for $C_{15}H_{14}NS_2Cl$: C,58.52; H,4.58; N,4.55%); m/z 309(42%), 307(M^+,100).

2,6-Bis(methylthio)-4-(4-nitrostyryl)pyridine (70d); was isolated as yellow prism (chloroform); m.p. 200-201°C; yield 51%; IR ν_{max}(KBr) 1592, 1571, 1521 cm^{-1}; ^1H NMR($CDCl_3$): 2.57(s,6H,SCH_3); 6.91(s,2H, H-3 and H-5); 7.00(d,1H,J=15Hz, olefinic); 7.20(d,1H,J=15Hz, olefinic);

7.59(d,2H,A_2B_2,J=9Hz,Ar$\underline{H}$); 8.20(d,2H,A_2B_2,J=9Hz,Ar$\underline{H}$). (Found: C,56.62; H,4.50; N,8.66; Calc. for $C_{15}H_{14}N_2O_2S_2$: C,56.58; H,4.43; N,8.80%); m/z 318 (M^+,100%).

General Procedure for the reaction of α-lithiopropionitrile with α-oxoketene dithioacetals: Synthesis of 3-methyl-4-substituted and 4,5-annelated pyridines 5n, 58-61:

To a stirred solution of diethylamine (0.91g, 12.5 mmol) and hexamethylphosphorus triamide(HMPT) (2.03g, 12.5 mmol) at -15°C under nitrogen was rapidly added n-butyllithium (12.5 mmol) and stirred for 15 minutes. The reaction mixture was cooled to -78°C, and added a solution of propionitrile (0.69g, 12.5 mmol) in tetrahydrofuran (20 ml) and stirred for 10 minutes followed by addition of appropriate α-oxoketene dithioacetal (10 mmol). The mixture was kept at -78°C for 1 h and then allowed to warm upto 10°C slowly. The reaction mixture was quenched with saturated ammonium chloride solution (200 ml) extracted with ether (2x100 ml), washed with water (100 ml) and dried (Na_2SO_4). Removal of solvent gave a viscous residue which was heated with orthophosphoric acid (25 ml, 88%) for 3 hrs at 130°C. Poured over crushed ice-water, extracted with chloroform (3x100 ml), washed with water (100 ml) and dried (Na_2SO_4). The removal of solvent gave a viscous residue, which were purified by passing through a silica gel column (hexane as eluent)to give pure products.

2,6-Bis(methylthio)-3-methyl-4-phenylpyridine (5n); was isolated colourless crystals (hexane); m.p. 43-44°C; yield 67%; IR ν_{max}(KBr) 1542, 1459 cm^{-1}; ^1H NMR($CDCl_3$): 2.04(s,3H,$C\underline{H}_3$); 2.55(s,3H,$SC\underline{H}_3$); 2.59(s,3H,

$SC\underline{H}_3$); 6.70(s,1H,$\underline{H}$-5); 7.08-7.48(m,5H,Ar$\underline{H}$). (Found: C,64.21; H,5.74; N,5.34; Calc. for $C_{14}H_{15}NS_2$: C,64.33; H,5.78; N,5.36%); m/z 261(M^+, 100%);228(44); 151(32).

2,6-Bis(methylthio)-4-(2-furyl)-3-methylpyridine (58); was isolated as yellow crystals (hexane); m.p. 47-48°C; yield 54%; IR ν_{max}(KBr) 1588, 1554, 1530 cm^{-1}; ^1H NMR(CCl_4): 2.34(s,3H,$C\underline{H}_3$); 2.56(s,6H,$SC\underline{H}_3$); 6.50(brs,1H,$\underline{H}$-4 of furyl); 6.65(brd,1H,$\underline{H}$-3 of furyl); 7.14(s,1H,$\underline{H}$-5); 7.50(brs,1H,$\underline{H}$-5 of furyl). (Found: C,57.08; H,5.07; N,5.51; Calc.for $C_{12}H_{13}NOS_2$: C,57.34; H,5.21; N,5.57%); m/z 251(M^+,100%); 236(12), 218(85).

1,3-Bis(methylthio)-4-methyl-5,6,7,8-tetrahydroisoquinoline (59); was isolated as colourless crystals (hexane); m.p. 72-73°C; yield 71%; IR ν_{max}(KBr) 1544 cm^{-1}; ^1H NMR(CCl_4): 1.66-1.88(m,4H,$C\underline{H}_2$); 2.08(s,3H, $C\underline{H}_3$); 2.56(s,6H,$SC\underline{H}_3$); 2.40-2.66(m,merged with SCH_3 signal, 4H,$C\underline{H}_2$). (Found: C,59.98; H,7.06; N,6.02; Calc. for $C_{12}H_{17}NS_2$: C,60.20; H,7.16; N,5.85%); m/z 239(M^+,60%), 224(31), 206(100).

1,3-Bis(methylthio)-4-methyl-6,7,8,9-tetrahydro-5H-cyclohepta[c] pyridine (60); was isolated as colourless crystals (hexane); m.p. 77-78°C; yield 73%; IR ν_{max}(KBr) 1542 cm^{-1}; ^1H NMR($CDCl_3$): 1.34-1.88(m,6H,$C\underline{H}_2$); 2.10(s,3H,$C\underline{H}_3$); 2.49(s,3H,$SC\underline{H}_3$); 2.51(s,3H,$SC\underline{H}_3$); 2.69-2.84(m,4H,$C\underline{H}_2$). (Found: C,61.59; H,7.59; N,5.51; Calc. for $C_{13}H_{19}NS_2$: C,61.61; H,7.56; N, 5.53%); m/z 253(M^+,92%), 238(52).

2,4-Bis(methylthio)-1,9-dimethyl-5,6-dihydrobenzothiepino[4,5-c] pyridine (61); was isolated as colourless crystals (hexane); m.p. 145-146°C; yield 79%; IR ν_{max}(KBr) 1599, 1540, 1528 cm^{-1}; ^1H NMR($CDCl_3$):

2.10(s,3H,C<u>H</u>$_3$); 2.38(s,3H,C<u>H</u>$_3$); 2.64(s,6H,SC<u>H</u>$_3$); 2.83-3.21(m,2H,C<u>H</u>$_2$); 3.22-3.56(m,2H,C<u>H</u>$_2$); 7.04-7.28(m,2H,Ar<u>H</u>); 7.44(brd,1H,Ar<u>H</u>). (Found: C,61.02; H,5.89; N,4.41; Calc. for $C_{17}H_{19}NS_3$: C,61.22; H,5.74; N,4.20%); m/z 333(M^+,100%); 318(40).

<u>General Procedure for Preparation of Substituted and Annelated 2-bromopyridines 62-65</u>:

To a cold solution of crude alcohols (<u>2</u>) (10 mmol) in 25 ml of glacial acetic acid, bromine (2.4g, 15 mmol) was added dropwise and reaction mixture was allowed to stir for 2 hrs. It was neutralized with a saturated solution of sodium bicarbonate and extracted with chloroform (3x100 ml), washed with water (100 ml), dried (Na_2SO_4), and solvent removed to afford the crude product, which was further purified bya column chromatography over silica gel (using hexane as eluent).

<u>2-Bromo-6-(methylthio)-4-phenylpyridine (62)</u>; was isolated as colourless crystals (hexane); m.p. 134-135°C; yield 83%; IR ν_{max}(KBr) 1550,1496 cm^{-1}; ^1H NMR($CDCl_3$): 2.52(s,3H,SC<u>H</u>$_3$); 7.04(s,2H,<u>H</u>-3 and <u>H</u>-5); 7.36-7.48 (m,5H,Ar<u>H</u>). (Found: C,51.39; H,3.54; N,4.88; Calc. for $C_{12}H_{10}BrNS$: C,51.44; H,3.60; N,5.00%); m/z 280(M^+,100%), 278(M^+,98).

<u>2-Bromo-6-(methylthio)-4-(3'-pyridinyl)pyridine (63)</u>; was isolated as isolated as colourless crystals ($CHCl_3$); m.p. 130-131°C; yield 69%; IR ν_{max}(KBr) 1602, 1586, 1479 cm^{-1}; ^1H NMR($CDCl_3$): 2.60(s,3H,SC<u>H</u>$_3$); 7.12(s,1H,<u>H</u>-5); 7.26(s,1H,<u>H</u>-3); 7.31-7.52(m,1H,<u>H</u>-5'); 7.66-7.83(brd, (1H,<u>H</u>-4'); 8.56-8.86(m,2H,<u>H</u>-2' and <u>H</u>-6'). (Found: C,46.91; H,3.32; N,10.02; Calc. for $C_{11}H_9BrN_2S$: C,46.98; H,3.23; N,9.97%); m/z 281 (M^+,9%), 279(M^+,9), 235(4), 233(3), 200(8).

3-Bromo-1-(methylthio)-5,6,7,8-tetrahydroisoquinoline (64); was isolated as colourless crystals (hexane); m.p. 49-50°C; yield 64%; IR ν_{max}(KBr) 1566, 1542 cm^{-1}; ^1H NMR(CCl_4): 1.66-2.04(m,4H,$C\underline{H}_2$); 2.54(s,3H,$SC\underline{H}_3$); 2.20-2.80(m,merged with SCH_3 signal, 4H,$C\underline{H}_2$); 6.86(s,1H,$\underline{H}$-4). (Found: C,46.45; H,4.51; N,5.38; Calc. for $C_{10}H_{12}BrNS$: C,46.52; H,4.69; N, 5.43%); m/z 259(M^++1,58%), 258(M^+,22), 257(57).

2-Bromo-5,6-dihydro-4-(methylthio)-benz [f]isoquinoline (65); was isolated as colourless crystals (hexane); m.p. 104-105°C; yield 78%; IR ν_{max}(KBr) 1606, 1582, 1553, 1530 cm^{-1}; ^1H NMR($CDCl_3$): 2.54(s,3H, $SC\underline{H}_3$); 2.68-2.88(m,4H,$C\underline{H}_2$); 7.44(s,1H,$\underline{H}$-1); 7.11-7.74(m,4H,Ar$\underline{H}$). (Found: C,54.88; H,3.92; N,4.56; Calc. for $C_{14}H_{12}BrNS$: C,54.91; H,3.95; N,4.57%); m/z 307(M^++1,100%), 306(M^+,94), 305(99), 274(53), 272(58).

Replacement of 2,6-Bis(methylthio)function of the Pyridine nucleus by Alkyl group via Nickel-Induced Grignard Reactions; General Procedure

To the suspension of methylmagnesium iodide [30 mmol, prepared from 0.72g (0.03g atom) of magnesium turnings and 4.26g (30 mmol) of methyl iodide in dry ether (25 ml)], a solution of bis(triphenylphosphino)nickel dichloride $[(C_6H_5)_3P]_2NiCl_2$(3 mmol)in 15 mL of dry benzene was dropwise added, under nitrogen at room temperature and the mixture stirred for 15 min. After this catalyst reduction, a solution of (10 mmol) appropriate thioether in 25 ml of dry benzene was added and the mixture was heated at 80°C for 12 h. It was then cooled, poured into 100 ml of saturated ammonium chloride solution, and extracted with ether (2x100 ml). The combined extract was dried (Na_2SO_4) and evaporated.

The residue was chromatographed on silica gel (elution with 20:1 hexane-ethyl acetate) to give pure 66 and 67.

2,6-Dimethyl-4-phenylpyridine (66); was isolated as colourless crystals ($CHCl_3$); m.p. 49-50°C; yield 85%; IR ν_{max}(KBr) 1606, 1553, 1494 cm^{-1}; ^1H NMR($CDCl_3$): 2.56(s,6H,CH_3); 7.15(s,2H,H-3 and H-5); 7.32-7.72(m, 5H,ArH). (Found: C,85.32; H,7.01; N,7.72; Calc. for $C_{13}H_{13}N$: C,85.20; H,7.15; N,7.64%); m/z 183(M^+,100%).

5,6-Dihydro-2,4-dimethyl-benz [f]isoquinoline (67); was isolated as colourless crystals ($CHCl_3$); m.p. 109-110°C; yield 79%; IR ν_{max}(KBr) 1590, 1549 cm^{-1}; ^1H NMR($CDCl_3$): 2.53(s,6H,CH_3); 2.68-2.92(m,4H,CH_2); 7.24-7.52(m,4H,ArH); 7.70-7.96(m,1H,H-10). (Found: C,85.98; H,7.18; N,6.52; Calc. for $C_{15}H_{15}N$: C,86.08; H,7.22; N,6.69%); m/z 209(M^+,100%), 194(53).

Desulphurization of 2,6-Bis(methylthio)pyridines (5a,i,o and s); General Procedure:

To a solution of bismethylthiopyridine (4 mmol) in ethanol (30 ml) was added Raney Nickel (W-4) (ca.10 times by weight) and the mixture was refluxed for 3 hrs. (monitored by t.l.c.). The reaction mixture was filtered and the residue was washed with hot ethanol (3x20 ml). The bulk of ethanol was removed under reduced pressure and chloroform (50 ml) was added. This solution was washed with water (2x50 ml), dried and evaporated. Analytically pure compounds (48a-d) were obtained by passing through short column of silica gel using hexane as eluent.

4-Phenylpyridine (48a); was isolated as brown solid ($CHCl_3$); m.p. 77°C (reported[20] 77-78°C); yield 65%; IR ν_{max}(KBr) 1590,1544, 1482 cm^{-1};

^{1}H NMR($CDCl_3$): 7.18-7.80(m,7H,Ar$\underline{H}$); 8.50-8.80(m,2H,Ar$\underline{H}$). (Found: C,85.09; H,5.91; N,8.97; Calc. for $C_{11}H_9N$: C,85.13; H,5.85; N,9.03%).

4-Methylpyridine (48b); was isolated as colourless oil; yield 62%; IR ν_{max}(CCl_4) 1600, 1548 cm^{-1}; ^{1}H NMR($CDCl_3$): 2.32(s,3H,$C\underline{H}_3$); 7.08 (d,2H,J=6Hz,$\underline{H}$-3 and $\underline{H}$-5); 8.48(d,2H,J=6Hz,$\underline{H}$-2 and $\underline{H}$-6). (Found: C, 77.42; H,7.57; N,15.11; Calc. for C_6H_7N: C,77.38; H,7.58; N,15.04%).

5,6,7,8-Tetrahydroisoquinoline (48c); was isolated as yellow oil, which darkens on exposure; yield 57%; IR ν_{max}(CCl_4) 1578, 1485, 1450 cm^{-1}; ^{1}H NMR(CCl_4): 1.60-1.96(m,4H,$C\underline{H}_2$); 2.40-2.94(m,4H,$C\underline{H}_2$); 6.76-7.15(m, 3H,Ar$\underline{H}$). (Found: C,81.02; H,8.11; N,10.29; Calc. for $C_9H_{11}N$: C,81.16; H,8.33; N,10.52%).

5,6-Dihydrobenz[f]isoquinoline (48d); was isolated as colourless oil; yield 58%; IR ν_{max}(CCl_4) 1600, 1580 cm^{-1}; ^{1}H NMR(CCl_4): 2.50-2.86(m, 4H,$C\underline{H}_2$); 6.84-7.25(m,5H,Ar$\underline{H}$); 7.50-8.26(m,2H,Ar$\underline{H}$). (Found: C,86.02; H,6.23; N,7.92; Calc. for $C_{13}H_{11}N$: C,86.15; H,6.12; N,7.73%).

4-Cyano-3,4-diphenyl-1-(methylthio)-but-2-ene-1-one (73): Lithiophenylacetonitrile[24] [prepared from phenylacetonitrile (1.46g,12 mmol) and n-butyllithium (12 mmol) at -78°C] was reacted with 1a (10 mmol) at -78°C and reaction mixture was stirred for 0.5 hr at same remperature. After usual work-up and treatment of resulting carbinol with H_3PO_4 as described for the reaction of lithioacetonitrile with 1a, afforded 73 as yellow crystals (hexane-$CHCl_3$); m.p. 111-112°C; yield 63%; IR ν_{max}(KBr) 3447, 2213, 1680, 1630, 1596 cm^{-1}; ^{1}H NMR($CDCl_3$): 2.62(s,3H,$SC\underline{H}_3$); 6.22(s,1H, $C\underline{H}$); 7.20-7.49(m,10H,Ar$\underline{H}$); 7.53(s,1H,olefinic). (Found: C,73.51; H,5.09; N,4.61; Calc. for $C_{18}H_{15}NOS$: C,73.69; H,5.15; N,4.77%); m/z 293(M^+,5%).

General Procedure for Synthesis of 2,6-Disubstituted and 2,3-Annelated Pyridines: The reaction of β-lithioaminocrotononitrile(77a) with 1:

To a cooled solution of freshly distilled acetonitrile (1.23g, 30 mmol) in dry THF (25 ml) at -78°C under nitrogen atmosphere, n-butyllithium (15 mmol) was added from a syringe via a rubber septum. After 30 min. of further stirring, a solution of appropriate α-oxoketene dithioacetals (10 mmol) in tetrahydrofuran (25 ml) was added. The reaction mixture was allowed to warm upto room temperature and stirred further for 20 hrs. Hydrolysis was carried out by rapid quenching of reaction mixture with saturated solution of ammonium chloride (100 ml). The organic layer was separated and aqueous layer was extracted with ether (2x50 ml). The combined organic layer was washed with water (150 ml), dried (Na_2SO_4) and the solvent evaporated. The crude product was further purified by a column chromatography over silica gel (using EtOAc-hexane, 1:20 as eluent).

3-Cyano-2-methyl-4-(methylthio)-6-(4-methoxyphenyl)pyridine (79a); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 157-158°C; yield 92%; spectral data described in text. (Found: C,66.52; H,5.29; N,10.13; Calc. for $C_{15}H_{14}N_2OS$: C,66.64; H,5.22; N,10.36%); m/z 270 (M^+,100%), 255(12), 224(18).

3-Cyano-2-methyl-4-(methylthio)-6-(4-chlorophenyl)pyridine (79b); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 162-163°C; yield 90%; IR ν_{max}(KBr) 2209, 1596, 1580, 1562 cm^{-1}; ^1H NMR($CDCl_3$): 2.62(s, 3H,S$\underline{CH_3}$); 2.74(s,3H,$\underline{CH_3}$); 7.28(s,1H,$\underline{H}$-5); 7.44(d,2H,A_2B_2,J=9.0Hz,Ar$\underline{H}$); 8.00(d,2H,A_2B_2,J=9.0Hz,Ar$\underline{H}$). (Found: C,60.98; H,3.90; N,10.02; Calc. for $C_{14}H_{11}ClN_2S$: C,61;19; H,4.04; N,10.20%); m/z 276(M^+,33%), 274(M^+, 100), 228(26).

3-Cyano-2-methyl-4-(methylthio)-6-phenylpyridine (79c); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 126-127°C; yield 86%; IR ν_{max}(KBr) 2200, 1580, 1562, 1525 cm^{-1}; ^1H NMR($CDCl_3$): 2.60(s,3H,SCH_3); 2.72(s,3H,CH_3); 7.26(s,1H,H-5); 7.34-7.52(m,3H,ArH); 7.82-8.10(m,2H, ArH). (Found: C,69.83; H,4.97; N,11.66; Calc. for $C_{14}H_{12}N_2S$: C,69.96; H,5.03; N,11.39%); m/z 240(M^+,100%), 194(31), 169(10), 152(8).

3-Cyano-2-methyl-4-(methylthio)-6-(2-furyl)pyridine (79d); was isolated as yellow crystals (hexane-$CHCl_3$); m.p. 159-160°C; yield 85%; IR ν_{max} (KBr) 2210, 1595, 1540 cm^{-1}; ^1H NMR($CDCl_3$): 2.58(s,3H,SCH_3); 2.68(s, 3H,CH_3); 6.63(brs,1H,H-4 of furyl); 7.16(d,1H,J=3.0Hz,H-3 of furyl); 7.28(s,1H,H-5); 7.51(brs,1H,H-5 of furyl). (Found: C,62.37; H,4.26; N,12.02; Calc. for $C_{12}H_{10}N_2OS$: C,62.58; H,4.38; N,12.17%); m/z 230 (M^+,100%), 202(10), 197(9).

3-Cyano-2-methyl-4-(methylthio)-6-(2-thienyl)pyridine (79e); was isolated as yellow crystals (hexane-$CHCl_3$); m.p. 155-156°C; yield 82%; IR ν_{max}(KBr) 2205, 1554, 1514 cm^{-1}; ^1H NMR($CDCl_3$): 2.47(s,3H,SCH_3); 2.66(s,3H,CH_3); 7.08-7.30(m,1H,H-4 of thienyl); 7.18(s,1H,H-5); 7.50(d, 1H,4Hz,H-3 of thienyl); 7.66(d,1H,J=4.5Hz,H-5 of thienyl). (Found: C,58.32; H,3.96; N,11.28; Calc. for $C_{12}H_{10}N_2S_2$: C,58.50; H,4.09; N, 11.37%); m/z 246(M^+,100%), 213(12), 200(8).

3-Cyano-2-methyl-4-(methylthio)-6-(3-pyridinyl)pyridine (79f); was isolated as colourless crystals ($CHCl_3$); m.p. 195-196°C; yield 62%; IR ν_{max}(KBr) 2220, 1580, 1558, 1528 cm^{-1}; ^1H NMR($CDCl_3$): 2.68(s,3H, SCH_3); 2.80(s,3H,CH_3); 7.30-7.54(m,1H,H-5 of pyridinyl); 7.40(s,1H, H-5); 8.36(m,1H,H-4 of pyridinyl); 8.70(d,1H,J=3Hz,H-6 of pyridinyl); 9.20(brd,1H,H-2 of pyridinyl). (Found: C,64.68; H,4.72; N,17.41; Calc.

for $C_{13}H_{11}N_3S$: C,64.70; H,4.60; N,17.41%); m/z 241(M^+,100%), 195(26).

3-Cyano-2-methyl-4-(methylthio)-6-(2-naphthyl)pyridine (79g); was isolated as colourless crystals ($CHCl_3$); m.p. 187-188°C; yield 92%; IR ν_{max}(KBr) 2222, 1600, 1560, 1540 cm^{-1}; ^1H NMR($CDCl_3$): 2.58(s,3H, SCH_3); 2.79(s,3H,CH_3); 7.40(s,1H,H-5); 7.42-7.60(m,2H,ArH); 7.74-8.08 (m,4H,ArH); 8.44(s,1H,ArH). (Found: C,74.36; H,4.82; N,9.61; Calc. for $C_{18}H_{14}N_2S$: C,74.45; H,4.86; N,9.65%); m/z 290(M^+,100%), 244(18).

3-Cyano-4-(methylthio)-2,6-dimethylpyridine (79h); was isolated as light brown needles (hexane); m.p. 42-43°C; yield 30%; IR ν_{max}(KBr) 2210, 1580 cm^{-1}; ^1H NMR(CCl_4): 2.42(s,3H,CH_3); 2.54(s,3H,SCH_3); 2.70 (s,3H,CH_3); 6.90(s,1H,H-5). (Found: C,60.58; H,5.69; N,15.75; Calc. for $C_9H_{10}N_2S$: C,60.64; H,5.65; N,15.72%); m/z 178(M^+,100%), 163(6), 132(62), 104(13).

3-Cyano-2-methyl-4-(methylthio)-6,7-dihydro-5H-cyclopenta[b]pyridine (79i); was isolated as viscous yellow oil; yield 57%; IR ν_{max}(CCl_4) 2200, 1590, 1545, 1525 cm^{-1}; ^1H NMR($CDCl_3$): 1.66-1.90(m,2H,CH_2); 2.36 (s,3H,SCH_3); 2.41(s,3H,CH_3); 2.62-2.97(m,4H,CH_2). (Found: C,64.59; H,5.98; N,6.74; Calc. for $C_{11}H_{12}N_2S$: C,64.67; H,5.92; N,6.86%); m/z 204(M^+,44%), 189(100).

3-Cyano-2-methyl-4-(methylthio)-5,6,7,8-tetrahydroquinoline (79j); was isolated as colourless crystals (hexane); m.p. 71-72°C; yield 62%; IR ν_{max}(KBr) 2220, 1535 cm^{-1}; ^1H NMR(CCl_4): 1.72-1.99(m,4H,CH_2); 2.62 (s,3H,SCH_3); 2.64(s,3H,CH_3); 2.70-2.98(m,4H,CH_2). (Found: C,59.95; H,6.42; N,12.90; Calc. for $C_{12}H_{14}N_2S$: C,66.01; H,6.46; N,12.83%); m/z 218(M^+,64%), 203(100).

3-Cyano-5,6-dihydro-4-(methylthio)-benzo[h]quinoline (79k); was isolated as light yellow crystals (hexane-$CHCl_3$); m.p. 131-132°C; yield 87%; IR ν_{max}(KBr) 2200, 1600, 1540, 1520 cm^{-1}; ^1H NMR($CDCl_3$): 2.62(s,3H,SCH_3); 2.76(s,3H,CH_3); 2.87-3.29(m,4H,CH_2); 7.10-7.41(m, 3H,ArH); 8.18-8.38(m,1H,H-10). (Found: C,72.09; H,5.26; N,10.51; Calc. for $C_{16}H_{14}N_2S$: C,72.14; H,5.30; N,10.52%); m/z 266(M^+,64%), 251(100),218(27).

3-Cyano-5,6-dihydro-8-methoxy-2-methyl-4-(methylthio)-benzo[h] quinoline (79l); was isolated as light yellow crystals (hexane-$CHCl_3$); m.p. 170-171°C; yield 86%; IR ν_{max}(KBr) 2209, 1611, 1575, 1540, 1515 cm^{-1}; ^1H NMR($CDCl_3$): 2.53(s,3H,SCH_3); 2.74(s,3H,CH_3); 2.81-3.29(m,4H, CH_2); 3.84(s,3H,OCH_3); 6.70-6.99(m,2H,ArH); 8.20-8.33(d,1H,J=6.0Hz, H-10). (Found: C,68.81; H,5.39; N,9.47; Calc. for $C_{17}H_{16}N_2OS$: C,68.87; H,5.44; N,9.45%); m/z 296(M^+,100%), 281(53), 246(84).

3-Cyano-6,7-dihydro-2-methyl-4-(methylthio)-5H-benzocyclohepta[1,2-b] pyridine (79m); was isolated as light yellow crystals (hexane-$CHCl_3$); m.p. 130-131°C; yield 84%; IR ν_{max}(KBr) 2217, 1543, 1518 cm^{-1}; ^1H NMR ($CDCl_3$): 2.26(brq,2H,CH_2); 2.40-2.99(m,merged with SCH_3 and CH_3 signals, 4H,CH_2); 2.66(s,3H,SCH_3); 2.85(s,3H,CH_3); 7.18-7.56(m,3H,ArH); 7.73-8.89(m,1H,H-11). (Found: C,72.76; H,5.83; N,10.12; Calc. for $C_7H_{16}N_2S$: C,72.82; H,5.75; N,9.99%); m/z 280(M^+,100%), 265(94).

3-Cyano-2-methyl-4-(methylthio)-5H-benzothiapyrano[4,3-b][1]pyridine (79n); was isolated as light yellow crystals (hexane-$CHCl_3$); m.p. 139-140°C; yield 83%; IR ν_{max}(KBr) 2205, 1585, 1544, 1520 cm^{-1}; ^1H NMR ($CDCl_3$): 2.74(s,3H,SCH_3); 2.80(s,3H,CH_3); 4.26(s,2H,CH_2); 7.18-7.39

(m,3H,ArH); 8.28-8.48(m,1H,H-10). (Found: C,63.21; H,4.29; N,9.87; Calc. for $C_{15}H_{12}N_2S_2$: C,63.35; H,4.25; N,9.85%); m/z 284(M^+,54%), 269(100), 236(46).

3-Cyano-5,6-dihydro-2,9-dimethyl-4-(methylthio)-benzothiepino[5,4-b][1]pyridine (79o); was isolated as light yellow crystals (hexane-$CHCl_3$); m.p. 182-183°C; yield 89%; IR ν_{max}(KBr) 2220, 1600, 1550, 1526 cm^{-1}; ^1H NMR($CDCl_3$): 2.40(s,3H,CH_3); 2.68(s,3H,SCH_3); 2.80(s,3H,CH_3); 2.97-3.48(m,4H,CH_2); 7.28(s,1H,H-8); 7.42(d,1H,J=9.0Hz,H-10); 7.66(d,1H, J=9.0Hz,H-11). (Found: C,65.41; H,5.04; N,8.89; Calc. for $C_{17}H_{16}N_2S_2$: C,65.35; H,5.16; N,8.97%); m/z 312(M^+,100%), 297(39), 284(54), 279(19).

3-Cyano-5,6-dihydro-2-methyl-4-(methylthio)-benzoxepino[5,4-b][1] pyridine (79p); was isolated as light yellow crystals (hexane-$CHCl_3$); m.p. 124-125°C; yield 87%; IR ν_{max}(KBr) 2222, 1604, 1552, 1530 cm^{-1}; ^1H NMR($CDCl_3$): 2.62(s,3H,SCH_3); 2.84(s,3H,CH_3); 3.20(brt,2H,CH_2); 4.52(brt,2H,CH_2); 7.02-7.51(m,3H,ArH); 7.71-7.90(m,1H,H-11). (Found: C,67.98; H,4.92; N,9.84; Calc. for $C_{16}H_{14}N_2OS$: C,68.06; H,5.00; N,9.92%); m/z 282(M^+,58%), 267(100), 253(9).

6-[2-(1,1-bismethylthio)ethylene]-3-cyano-2-methyl-4-phenylpyridine (99a); was isolated as yellow crystals (hexane-$CHCl_3$); m.p. 120-121°C; yield 89%; IR ν_{max}(KBr) 2200, 1565, 1496 cm^{-1}; ^1H NMR($CDCl_3$): 2.50(s,6H,SCH_3); 2.83(s,3H,CH_3); 6.43(s,1H, olefinic); 7.40(s,1H,H-5); 7.46-7.69(m,5H,ArH); ^{13}C NMR($CDCl_3$): 16.33(SCH_3); 17.37(SCH_3); 23.95(CH_3); 116.62(CN); 118.80 (CH, olefinic), 120.20(C-5); 128.35, 128.83, 129.59(arom C); 128.70(=C(SMe)$_2$ 137.10(C-1', quat, arom); 148.00(C-4); 155.10(C-3); 157.50(C-6); 162.50 (C-2). (Found: C,65.29; H,5.21; N,20.63; Calc. for $C_{17}H_{16}N_2S_2$: C,65.35; H,5.16; N,20.52%); m/z 312(M^+,18%), 297(100).

6-[2-(1,1-bismethylthio)ethylene-4-(4-chlorophenyl)-3-cyano-2-methyl-pyridine (99b); was isolated as yellow crystals (hexane-$CHCl_3$); m.p. 144-145°C; yield 85%; IR ν_{max}(KBR) 2200, 1595, 1575, 1562,1548 cm^{-1}; ^1H NMR($CDCl_3$): 2.50(s,6H,SCH_3); 2.70(s,3H,CH_3); 6.48(s,1H, olefinic); 7.45(s,1H,H-5); 7.50-7.64(m,4H,ArH). (Found: C,58.69; H,4.26; N,8.12; Calc. for $C_{17}H_{15}ClN_2S_2$: C,58.86; H,4.36; N,8.08%); m/z 347(M^+,16%), 333(48), 331(100).

6-[2-(1,1-bismethylthio)ethylene]-3-cyano-4-(4-methoxyphenyl)-2-methylpyridine (99c); was isolated as yellow crystals (hexane-$CHCl_3$); m.p. 155-156°C; yield 88%; IR ν_{max}(KBr) 2200, 1610, 1570, 1550, 1510 cm^{-1}; ^1H NMR($CDCl_3$): 2.50(s,6H,SCH_3); 2.81(s,3H,CH_3); 3.88(s,3H,OCH_3); 6.46 (s,1H, olefinic); 7.08(d,A_2B_2,2H,J=9.0Hz,ArH); 7.42(s,1H,H-5); 7.63(d, A_2B_2,2H,J=9.0Hz,ArH). (Found: C,62.98; H,5.22; N,8.08; Calc. for $C_{18}H_{18}N_2OS_2$: C,63.13; H,5.30; N,8.18%); m/z 342(M^+,51%), 327(100).

6-[2-(1,1-bismethylthio)ethylene]-3-cyano-4-(methoxystyryl)-2-methyl-pyridine (99d); was isolated as yellow crystals (hexane-$CHCl_3$); m.p. 139-140°C; yield 84%; IR ν_{max}(KBr) 2200, 1631, 1605, 1574, 1512, 1502 cm^{-1}; ^1H NMR($CDCl_3$): 2.50(s,6H,SCH_3); 2.72(s,3H,CH_3); 3.82(s,3H,OCH_3); 6.40(s,1H, olefinic); 6.90(d,2H,A_2B_2,J=9.0Hz,ArH); 7.21(s,1H, olefinic); 7.29(s,1H, olefinic); 7.50(d,2H,A_2B_2=J=9.0Hz,ArH); 7.58(s,1H,H-5). (Found: C,65.02; H,5.29; N,7.65; Calc. for $C_{20}H_{20}N_2OS_2$: C,65.18; H,5.47; N,7.60%); m/z 368(M^+,32%), 353(100), 335(29), 321(18).

Generation and Reaction of β-Substituted-β-Lithioaminoacrylonitrile anions (77b-e) with α-Oxoketene Dithioacetals (1); General Procedure: The reaction of β-substituted-β-lithioaminoacrylonitrile anions (77b-e) with α-oxoketene dithioacetals (1) were carried out in the similar

manner as described for reaction of β-lithioaminocrotonitrile anion (77a) with α-oxoketene dithioacetals (1) except by taking equimolar quantities of acetonitrile (0.62g, 15 mmol) and appropriate nitrile (76b-e, 15 mmol).

3-Cyano-2,6-diphenyl-4-(methylthio)pyridine (101a); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 145-146°C; yield 91%; IR ν_{max} (KBr) 2215, 1550, 1490 cm^{-1}; ^1H NMR($CDCl_3$): 2.75(s,3H,SCH_3); 7.42-7.65(m,7H,ArH); 7.84-8.20(m,4H,ArH). (Found: C,75.54; H,4.59; N,9.24; Calc. for $C_{19}H_{14}N_2S$: C,75.46; H,4.67; N,9.27%); m/z 302(M^+,100%), 269 (73), 255(31).

3-Cyano-6-(2-furyl)-4-(methylthio)-2-phenylpyridine (101b); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 176-177°C; yield 87%; IR ν_{max}(KBr) 2215, 1595, 1545 cm^{-1}; ^1H NMR($CDCl_3$): 2.65(s,3H,SCH_3); 6.51-6.61(brs,1H,H-4 of furyl); 7.19-7.30(m ,1H,H-3 of furyl); 7.40-7.62(m,5H,ArH); 7.81-8.04(m,2H,ArH). (Found: C,69.88; H,4.09; N,9.65; Calc. for $C_{17}H_{12}N_2OS$: C,69.84; H,4.14; N,9.58%); m/z 292(M^+,100%), 259(58), 248(13).

3-Cyano-6-methyl-4-(methylthio)-2-phenylpyridine (101c); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 133-134°C; yield 57%; IR ν_{max}(KBr) 2210, 1595, 1464 cm^{-1}; ^1H NMR($CDCl_3$): 2.14(s,3H,SCH_3); 2.19(s,3H,CH_3); 7.38-7.80(m,6H,ArH). (Found: C,69.81; H,5.92; N,11.68; Calc. for $C_{14}H_{12}N_2S$: C,69.96; H,5.87; N,11.66%); m/z 240(M^+,100%), 225(21).

3-Cyano-4-(methylthio)-2-phenyl-5,6,7,8-tetrahydroquinoline (101d); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 127-128°C; yield 82%; IR ν_{max}(KBr) 2210, 1579, 1550 cm^{-1}; ^1H NMR($CDCl_3$): 1.70-1.98

(m,4H,C<u>H</u>$_2$); 2.43-2.66(m,4H,C<u>H</u>$_2$); 2.60(s,3H,SC<u>H</u>$_3$); 7.32-7.58(m,3H,Ar<u>H</u>); 7.82-8.06(m,2H,Ar<u>H</u>). (Found: C,72.71; H,5.62; N,10.06; Calc. for $C_{17}H_{16}N_2S$: C,72.82; H,5.75; N,9.99%); m/z 280(M^+,80%), 247(100).

<u>3-Cyano-5,6-dihydro-4-(methylthio)-2-phenylbenzo[h]quinoline (101e)</u>; was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 174-175°C; yield 83%; IR ν_{max}(KBr) 2218, 1605, 1535, 1518 cm^{-1}; ^1H NMR($CDCl_3$): 2.64(s,3H,SC<u>H</u>$_3$); 2.64-3.09(m,2H,C<u>H</u>$_2$); 3.18-3.38(m,2H,C<u>H</u>$_2$); 7.21-7.61 (m,6H,Ar<u>H</u>); 7.90-8.09(m,2H,Ar<u>H</u>); 8.38-8.50(m,1H,<u>H</u>-10). (Found: C,76.66; H,4.88; N,8.47; Calc. for $C_{21}H_{16}N_2S$: C,76.79; H,4.91; N,8.53%); m/z 329(M^++1,100%), 328(M^+,51), 314(67).

<u>3-Cyano-2-(2-furyl)-4-(methylthio)-6-phenylpyridine (102a)</u>; was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 122-123°C; yield 76%; IR ν_{max}(KBr) 2200, 1584, 1540, 1510 cm^{-1}; ^1H NMR($CDCl_3$): 2.66(s,3H, SC<u>H</u>$_3$); 6.60-6.74(m,1H,<u>H</u>-4 of furyl); 7.40-7.84(m,6H,Ar<u>H</u>); 8.00-8.30 (m,2H,Ar<u>H</u>). (Found: C,69.66; H,3.97; N,9.49; Calc. for $C_{17}H_{12}N_2OS$: C,69.84; H,4.14; N,9.58%); m/z 292(M^+,100%), 263(24), 246(17).

<u>3-Cyano-4-(methylthio)-6-phenyl-2-(2-thienyl)pyridine (102b)</u>; was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 141-142°C; yield 65%; IR ν_{max}(KBr) 2200, 1575, 1550, 1508 cm^{-1}; ^1H NMR($CDCl_3$): 2.68(s, 3H,SC<u>H</u>$_3$); 7.11-7.40(m,2H,thienyl <u>H</u>-3 and <u>H</u>-4); 7.23(s,1H,<u>H</u>-5); 7.65 (s,5H,Ar<u>H</u>); 8.38-8.54(brd,1H,thienyl <u>H</u>-2). (Found:C,66.09; H,4.02; N,9.01; Calc. for $C_{17}H_{12}N_2S_2$: C,66.20; H,3.92; N,9.09%); m/z 308(M^+,100%

<u>3-Cyano-2,6-bis(2-furyl)-4-(methylthio)pyridine (103a)</u>; was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 151-152°C; yield 85%; IR ν_{max}(KBr) 2214, 1604, 1592, 1547, 1513, 1481 cm^{-1}; ^1H NMR($CDCl_3$):

2.59(s,3H,SC$\underline{H}_3$); 6.40-6.69(m,2H,Ar$\underline{H}$); 7.10-7.78(m,5H,Ar$\underline{H}$). (Found: C,63.77; H,3.59; N,9.98; Calc. for $C_{15}H_{10}N_2O_2S$: C,63.81; H,3.57; N,9.92%); m/z 282(M^+,100%), 254(9), 236(6).

3-Cyano-2-(2-furyl)-4-(methylthio)-6-(2-thienyl)pyridine (103b); was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 126-127°C; yield 78%; IR ν_{max}(KBr) 2200, 1549, 1505, 1480 cm^{-1}; ^1H NMR($CDCl_3$): 2.64(s, 3H,SC$\underline{H}_3$); 6.64-6.78(m,1H,$\underline{H}$-4 of furyl); 7.18-7.40(m,2H,Ar$\underline{H}$); 7.51-7.68(m,2H,Ar$\underline{H}$); 7.74-7.88(m,2H,Ar$\underline{H}$). (Found: C,60.09; H,3.32; N,9.16; Calc. for $C_{15}H_{10}N_2OS_2$: C,60.38; H,3.38; N,9.39%); m/z 298(M^+,60%).

3-Cyano-6-(2-furyl)-4-(methylthio)-2-(2-thienyl)pyridine (103c): was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 168-169°C; yield 64%; IR ν_{max}(KBr) 2200, 1588, 1550, 1510 cm^{-1}; ^1H NMR($CDCl_3$): 2.61(s, 3H,SC$\underline{H}_3$); 6.56-6.66(m,1H,$\underline{H}$-4 of furyl); 7.11-7.39(m,3H,Ar$\underline{H}$); 7.50-7.68(m,2H,Ar$\underline{H}$); 8.23-8.36(m,1H,$\underline{H}$-5 of furyl). (Found: C,60.42; H,3.24; N,9.20; Calc. for $C_{15}H_{10}N_2OS_2$: C,60.38; H,3.38; N,9.39%); m/z 298(M^+, 100%), 252(18).

3-Cyano-2,6-bis(2-thienyl)-4-(methylthio)pyridine (103d): was isolated as colourless crystals (hexane-$CHCl_3$); m.p. 149-150°C; yield 57%; IR ν_{max}(KBr) 2200, 1560, 1510 cm^{-1}; ^1H NMR($CDCl_3$): 2.70(s,3H,SC$\underline{H}_3$); 7.13-7.42(m,4H,Ar$\underline{H}$); 7.54-7.74(m,1H,Ar$\underline{H}$); 7.82-8.00(s,1H,Ar$\underline{H}$); 8.30-8.56 (s,1H,Ar$\underline{H}$). (Found: C,57.23; H,3.09; N,8.85; Calc. for $C_{15}H_{10}N_2S_3$: C,57.29; H,3.21; N,8.97%); m/z 314(M^+,100%).

3-Amino-3-(2-pyridinyl)acrylonitrile (105); was isolated as colourless crystals ($CHCl_3$); m.p. 155-156°C; yield 88%; IR ν_{max}(KBr) 3440, 3320, 2195, 1660, 1610, 1588 cm^{-1}; ^1H NMR($CDCl_3$): 4.60(s,1H,olefinic); 5.93 (brs,2H,N$\underline{H}_2$); 7.26-7.94(m,3H,Ar$\underline{H}$); 8.64(d,1H,$\underline{H}$-6). (Found: C,66.11;

H,4·65 ; H,28.79; Calc. for $C_8H_7N_3$: C,66.19; H,4·86 ; N,28.95%).

3-(N,N-diethylaminomethyl)-6- (4-methoxyphenyl)-2-methylpyridine(95); was obtained as red oil on treating 79a with Raney Nickel (W-4) in ethanol for 3 hrs. at RT; yield 58%; IR ν_{max}(neat) 1603, 1580, 1505 cm^{-1}; ^1H NMR($CDCl_3$): 1.03(t,6H,J=7.5Hz,$C\underline{H}_3$); 2.50(q,4H,J=7.5Hz,$C\underline{H}_2$); 2.62(s,3H,$C\underline{H}_3$); 3.50(s,2H,$C\underline{H}_2$); 3.80(s,3H,$OC\underline{H}_3$); 6.98(d,2H,A_2B_2,J=9.0Hz, Ar$\underline{H}$); 7.44(d,1H,J=8.0Hz,$\underline{H}$-5); 7.67(d,1H,J=8.0Hz,$\underline{H}$-4); 7.98(d,2H,A_2B_2, J=9.0Hz,Ar$\underline{H}$). (Found: C,76.11; H,8.62; N,10.02; Calc. for $C_{18}H_{24}N_2O$: C,76.02; H,8.51; N,9.85%).

3-(N,N-di-n-propylaminomethyl)-6- (4-methoxyphenyl)-2-methylpyridine (106); was obtained as red oil on treating 79a with Raney Nickel (W-4) in n-propanol for 3 hrs. at RT; yield 63%; IR ν_{max}(neat) 1604, 1580, 1503 cm^{-1}; ^1H NMR($CDCl_3$): 0.88(t,3H,J=7.0Hz,$C\underline{H}_3$); 0.92(t,3H,J=7.0Hz,$C\underline{H}_3$); 1.15-1.80(m,4H,$C\underline{H}_2$); 2.61(s,3H,$SC\underline{H}_3$); 2.24-2.85(m,merged with SCH_3 signal, 4H,$C\underline{H}_2$); 3.53(s,2H,$C\underline{H}_2$); 3.84(s,3H,$OC\underline{H}_3$); 7.06(d,2H,A_2B_2,J=9.0 Hz, Ar$\underline{H}$); 7.42-7.90(m,2H,$\underline{H}$-4 and $\underline{H}$-5); 8.04(d,2H,A_2B_2,J=9.0Hz,Ar$\underline{H}$). (Found: C,76.69; H,8.87; N,8.74; Calc. for $C_{20}H_{28}N_2O$: C,76.88; H,9.03; N,8.97%).

2,3-Dimethyl-6-(4-methoxyphenyl)pyridine (107); was obtained as colourless crystals (hexane) on refluxing 79a with Raney Nickel (W-4) in ethanol; m.p. 67-68°C; yield 65%; IR ν_{max}(KBr) 1612, 1589, 1516 cm^{-1}; ^1H NMR(CCl_4): 2.20(s,3H,$C\underline{H}_3$); 2.48(s,3H,$C\underline{H}_3$); 3.72(s,3H,$OC\underline{H}_3$); 6.84(d, 2H,A_2B_2,J=9.0Hz,Ar$\underline{H}$); 7.27(brs,2H,$\underline{H}$-4 and $\underline{H}$-5); 7.86(d,2H,A_2B_2,J=9.0Hz, Ar$\underline{H}$). (Found: C,78.66; H,7.01; N,6.62; Calc. for $C_{14}H_{15}NO$: C,78.84; H,7.09; N,6.57%); m/z 213(M^+,100%), 198(27), 183(11), 170(23).

5,6-Dihydro-3-(N,N-diethylaminomethyl)-2-methylbenzo[h]quinoline (108); was obtained as red oil on treating 79k with Raney Nickel (W-4) in ethanol at RT for 3 hrs; yield 76%; IR $\nu_{max}(CCl_4)$ 1590, 1578, 1545 cm^{-1}; ^1H NMR($CDCl_3$): 1.06(t,6H,J=6.0Hz,$C\underline{H}_3$); 2.53(q,4H,J=7.5Hz,$C\underline{H}_2$); 2.62(brs,2H,$C\underline{H}_2$); 2.90(s,3H,$C\underline{H}_3$); 3.51(brs,2H,$C\underline{H}_2$); 7.06-7.56(m,4H, Ar$\underline{H}$); 8.21-8.47(m,1H,$\underline{H}$-10). (Found: C,85.73; H,8.91; N,5.19; Calc. for $C_{19}H_{24}N$: C,85.66; H,9.08; N,5.26%).

5,6-Dihydro-3-methyl-2-phenylbenzo[h]quinoline (109); was obtained as white crystals (hexane) on refluxing 101e with Raney Nickel(W-4) in ethanol for 3 hrs.; m.p. 47-48°C; yield 71%; IR ν_{max}(KBr) 1600, 1580, 1555 cm^{-1}; ^1H NMR($CDCl_3$): 2.31(brs,2H,$C\underline{H}_2$); 2.49(s,3H,$C\underline{H}_3$); 2.88(brs,2H,$C\underline{H}_2$); 7.14-8.10(m,8H,Ar$\underline{H}$); 9.31-9.52(m,1H,$\underline{H}$-10). (Found: C,88.59; H,6.19; N,5.02; Calc. for $C_{20}H_{17}N$: C,88.52; H,6.32; N,5.16%).

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CHAPTER IV

STUDIES ON DIELS-ALDER CYCLOADDITIONS OF VINYLKETENE DITHIOACETALS*

IV. 1 INTRODUCTION

The Diels-Alder reaction is one of the most common and elegant methods for construction of six-membered ring systems[1-4]. The steric and electronic effects of the diene largely play an important role in the total regiochemical outcome of these reactions[5,6] and a variety of functionalized dienes and dienophiles have been used in recent years to achieve desired regio- and stereoselectivity in these reactions. The introduction of

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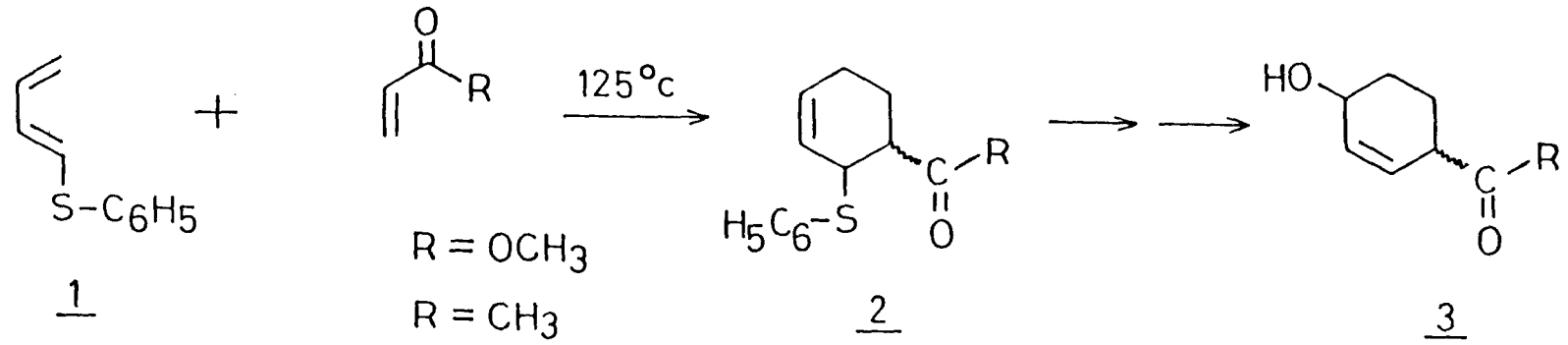
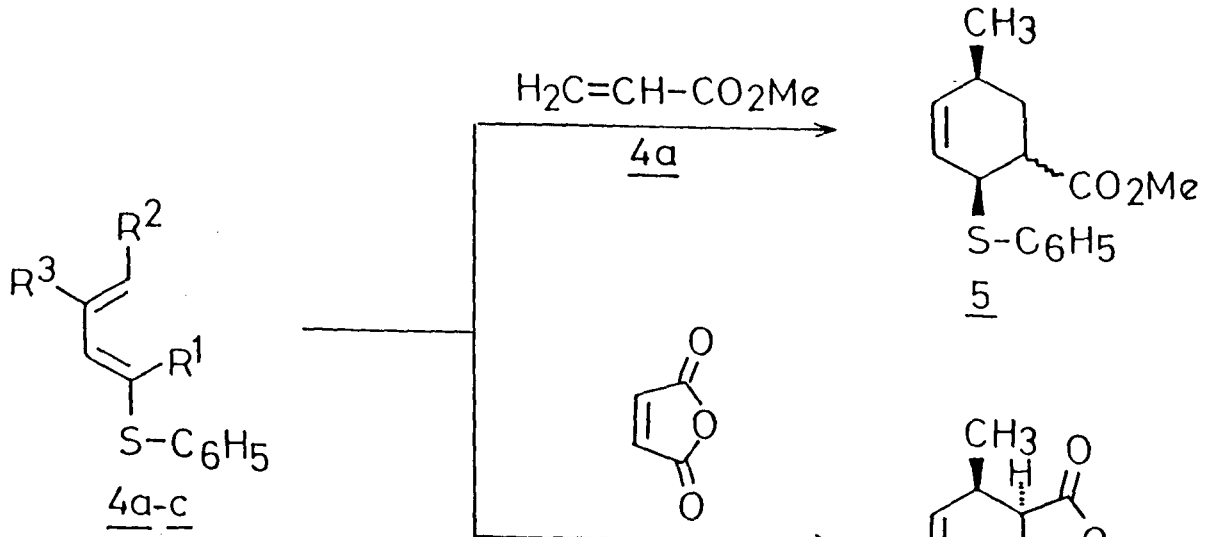
* Arun K. Gupta, H. Ila and H. Junjappa, Tetrahedron 45, 1509 (1989).

heterosubstituents on dienes invariably has a dominant effect on the regiochemistry of the cycloaddition and permits further transformations which take advantage of relationship between the heterosubstituents and the newly formed carbon-carbon bond. The utilization of such dienes has recently been an area of great synthetic activity[7].

Sulphur substituted dienes have broad synthetic potential because of the versatality of the sulphur in organic synthesis and the ease of sulphur removal through desulphurization from the product adduct. Furthermore, sulphur substituted dienes show enhanced reactivity than those of their oxygen analogues[8,9] and whenever there is a competition between oxygen and sulphur containing substituents, it is the latter group which directs the regiochemical outcome of the reaction. The acyclic dienes 1 and 4 have been synthesized by several different and complementary methods[10-12] and were shown to undergo Diels-Alder reaction. Thus, 1 reacts with unsymmetrical dienophiles to give the cycloadducts 2 with high regioselectivity while the corresponding stereoselectivity is not fully retained[10,11]. The adduct 2 subsequently undergoes [2,3] sigmatropic rearrangement to the allyl alcohol 3 (Scheme 1). Similarly the 1-phenylthiopenta-1,3-diene (R^1=H; R^2=Me) (4a) adds regiospecifically to methyl acrylate to afford the corresponding allyl sulphide 5 as a mixture of stereoisomers while its reaction with maleic anhydride affords the endo-adduct 6 (Scheme 1).





4a, R^1 = H ; R^2 = Me ; R^3 = H

b, R^1 = i-C_3H_7; R^2 = C_6H_5; R^3 = H

c, R^1 = H ; R^2 = C_6H_5; R^3 = Me

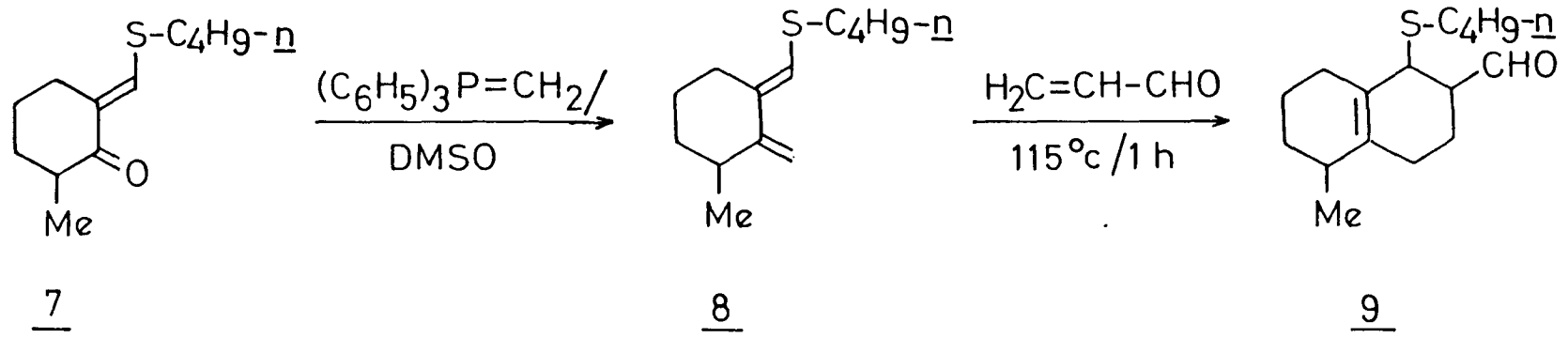
Scheme 1

The bicyclic adduct 9[13] was similarly obtained by cycloaddition of acrolein and the exocyclic diene 8 which was prepared by Wittig olefination of the ketone 7 (Scheme 2). The 2-phenylthiobutadiene 10, prepared from either methyl vinyl ketone[12] or from 3-phenylthiosulpholene[11,14] cycloadds to methyl acrylate to yield only one regioisomer 11[12,15] which on hydrolysis affords the cyclohexanone 12. Thus, the vinylthio functionality in 10 and 11 can be considered as masked keto functionality (Scheme 2).

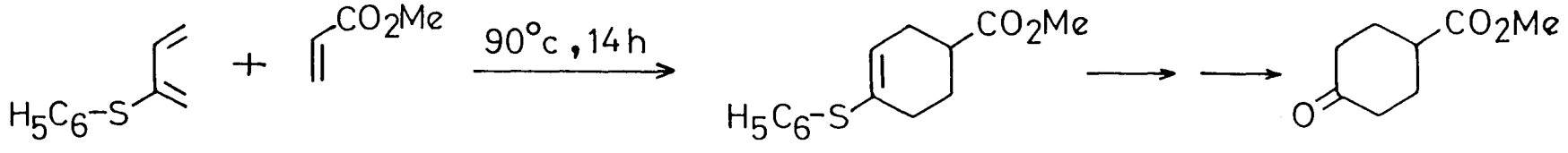
The conjugated ketene dithioacetals are synthetic reagents which can be used as diene components in Diels-Alder reaction or as synthetic equivalent of acylanion 13 with reactivity "umpolung"[16]. In Diels-Alder reaction, these intermediate could be considered as vinylketene equivalent 16, which is a latent precursor of cyclohexenone 17 (Scheme 3). However the relative unavailability of vinylketene coupled with its competitive $\pi 2s + \pi 2a$ reaction to give cyclobutanone 18 preclude its use in organic synthesis[17].

The first application of vinylketene dithioacetals as dienes in Diels-Alder reaction was studied by Carey and Court[17]. Thus the vinylketene dithioacetals 21 were easily prepared by Peterson olefination of α,β-unsaturated ketones[18] and were shown to undergo Diels-Alder reaction, with doubly activated dienophiles like maleic anhydride or tetracyanoethylene to yield cycloadducts 22a and 23 respectively (Scheme 4).

However, the dienes 21b and 21c failed to undergo cycloaddition with maleic anhydride whereas the cycloadducts 23 were obtained in good

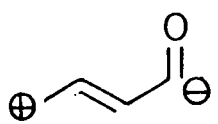


7 8 9



10 11 12

Scheme 2



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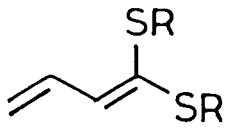

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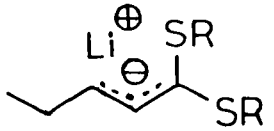

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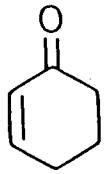

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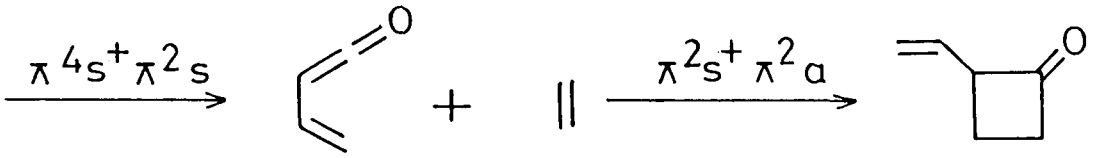
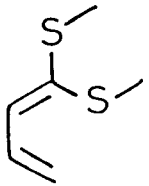


16 18



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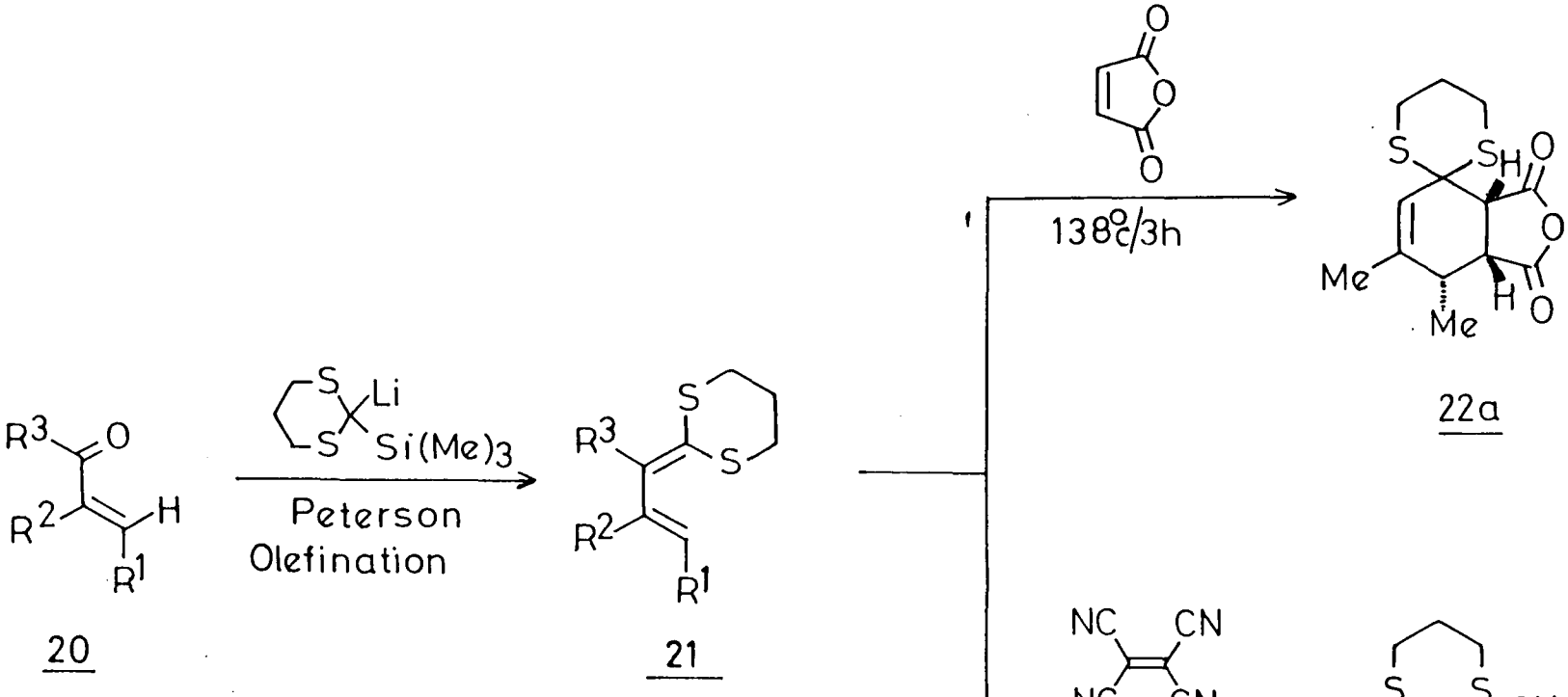
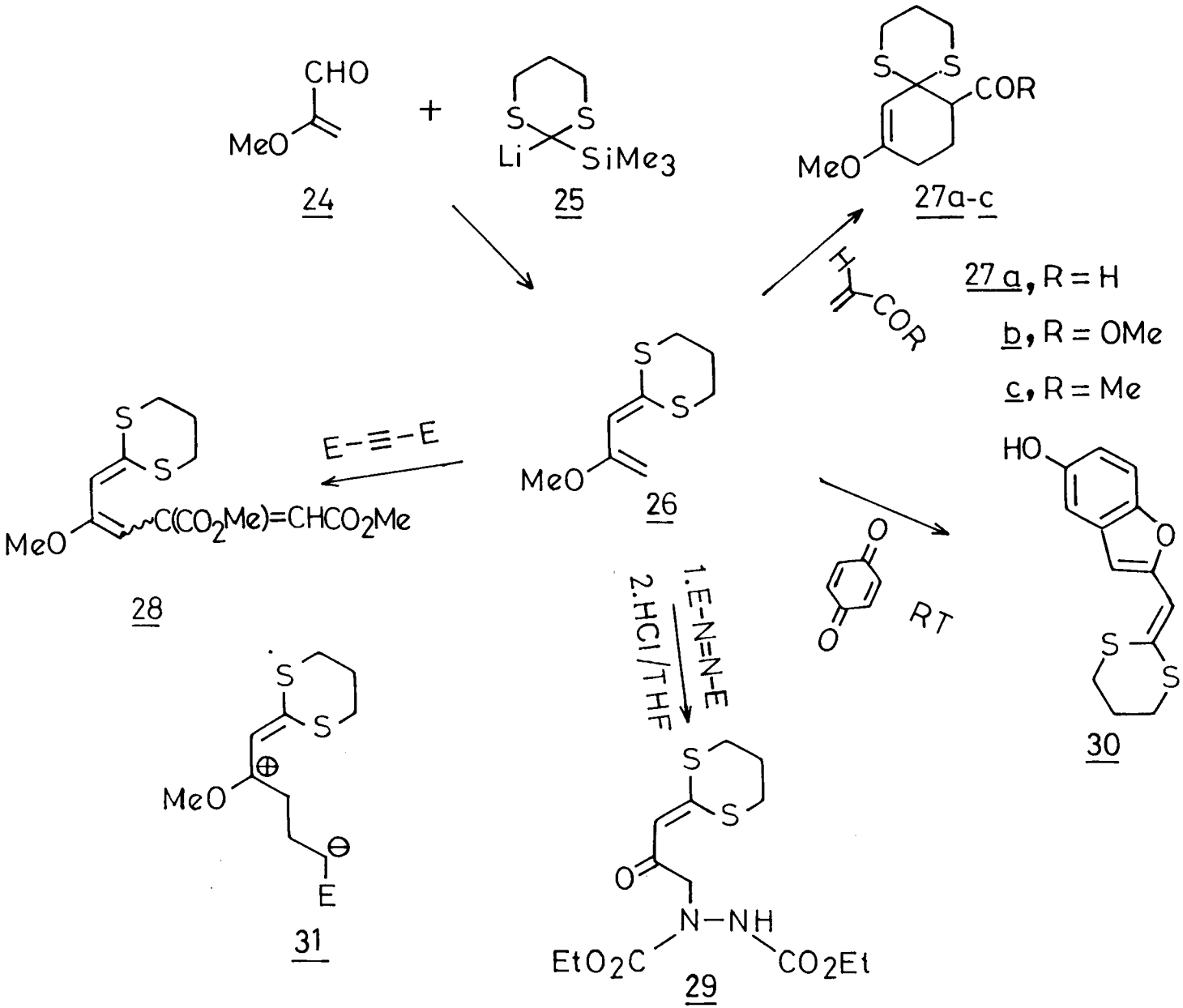
Scheme 3

yields with tetracyanoethylene (Scheme 4). Similarly these dienes were found to be inert towards dienophiles like ethyl acrylate, methyl vinyl ketone etc. The failure of these dienes to undergo cycloaddition shows that the activation by two sulphur atoms is not sufficient enough to overcome the steric hindrance involved with rigid and bulky dithiane group in 21 (Scheme 4). Subsequently, Danishefsky and co-workers[19] reinvestigated the work of Carey and Court and concluded that increased reactivity of dienes might be achieved if the terminal carbon of the allylidene group are unsubstituted and an additional electron donating group is introduced at the 3-position. Thus, the diene 26 was prepared from 2-methoxyacrolein (24) and 2-lithio-2-trimethylsilyl-1,3-dithiane (25) as shown in Scheme 5. However, the diene 26 behaved like a Michael donor with highly activated dienophiles such as dimethylacetylene dicarboxylate, diethyl azodicarboxylate and 1,4-benzoquinone to yield the corresponding Michael adducts 28, 29 and 30 respectively. On the otherhand, 26 behaved as diene with less activated dienophiles such as methyl vinyl ketone, methacrolein and methyl acrylate to afford the corresponding cycloadducts 27a-c. Thus, it appears that the highly activated dienophiles probably fail to orient themselves in a fashion to undergo concerted cycloaddition and consequently prefer the low energy pathway leading to the stepwise Michael adducts. Furthermore, the dipolar structure such as 31 which is formed by Michael addition of the diene 26 to methyl acrylate, finds other preferred pathways for charge dessipation which are of lower energy than cyclization. However, the weaker dienophiles may acquire appropriate



	R^1	R^2	R^3
21, 23a	Me	Me	H
b	Ph	H	H
c	$-(CH_2)_4-$		Me

Scheme 4


CHO
MeO
24
+
S
S
Li
SiMe3
25
S
S
COR
MeO
27a-c
27 a, R = H
b, R = OMe
c, R = Me
H
COR
S
S
MeO
26
E-≡-E
S
S
MeO
C(CO2Me)=CHCO2Me
28
1. E-N=N-E
2. HCl/THF
RT
O
O
HO
O
S
S
30
S
S
MeO
E
31
S
S
O
N–NH
EtO2C
CO2Et
29

Scheme 5

orientation due to their less reactivity leading to the observed cycloadducts 27. Thus, it appears that both steric and electronic factors are playing an important role in the reactivity of 26 either as diene or as Michael donor. The above considerations successfully led these authors to use more appropriately designed 1,3-butadienes that follow only [4+2] cycloaddition pathways. Thus, 1,1-dimethoxy-3--trimethylsilyloxy-1,3-butadiene was synthesized which proved to be an excellent diene in Diels-Alder reactions in the construction of many important aromatic and alicyclic systems bearing extensive functionality[20].

In the foregoing discussion, the vinylketene dithioacetals containing the rigid cyclic dithiane group are detrimental for smooth cycloaddition. It is quite apparent that the open-chain mercapto functionality 33 should differ in their reactivity as dienes due to their terminally unsubstituted carbon and conformationally mobile bismethylthio groups which might minimize the steric hindrance as displayed by the corresponding allylidene 1,3-dithianes. These dienes should also prove useful dienes to yield directly the dihydrobenzene derivatives, which can easily transform into fully aromatic systems, since the elimination of the methylmercaptan is imminently facile. It was, therefore, considered of interest to investigate the Diels-Alder cycloaddition reactions of vinylketene dithioacetals for their diene properties. The present chapter describes the synthesis and cycloaddition studies of these vinylketene dithioacetals.

A few of the vinylketene dithioacetals required in the present work were reported earlier by Thuillier and co-workers[16]. Thus, the

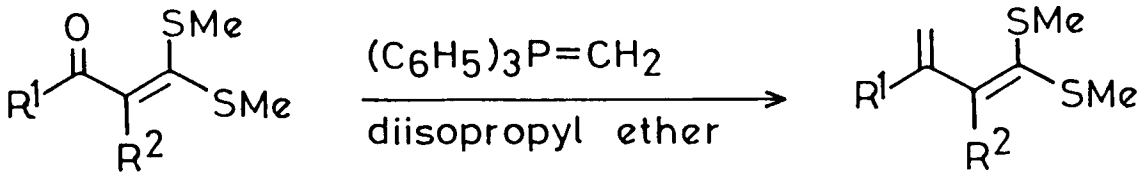
vinylketene dithioacetals 33 were obtained in excellent yields from the corresponding α-oxoketene dithioacetals 32 by Wittig olefination reaction. Similarly O-silylated α-ethylenic dithioacetals 35 were prepared by enol-silylation of the respective α-oxoketene dithioacetals 34 in the presence of zinc chloride and triethylamine (Scheme 6).

In the course of our programmed study on α-oxoketene dithioacetal, it was shown earlier[21] that methylmagnesium iodide adds smoothly to α-oxoketene dithioacetals 36 to give the corresponding carbinolacetals 37 which on borontrifluoride etherate assisted methanolysis afforded the corresponding β-methyl-α,β-ene esters. We have further shown that these carbinolacetals 37 are useful precursors for dienes 38 under appropriate dehydration conditions (Scheme 7).

In the present study we describe a new efficient method for preparation of vinylketene dithioacetals 38 and their Diels-Alder cycloaddition studies.

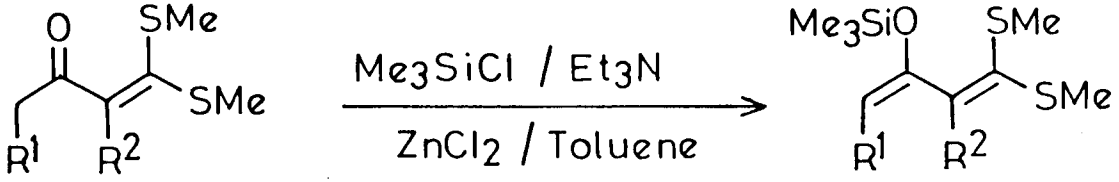
IV.2 RESULTS AND DISCUSSION

The vinylketene dithioacetals 38a-g were prepared by 1,2-addition of methylmagnesium iodide to the respective α-oxoketene dithioacetals 36a-g and subsequent dehydration of the resulting carbinolacetals 37a-g in the presence of pyridinium tosylate[22]. The dienes 38h-i were on the otherhand obtained by Wittig reaction[16], since dehydration method in these cases gave a mixture of isomeric dienes. The purified dienes 38a-i were characterized with the help of spectral data (IR and ^{1}H NMR) whereas analytically pure samples could be



32 33

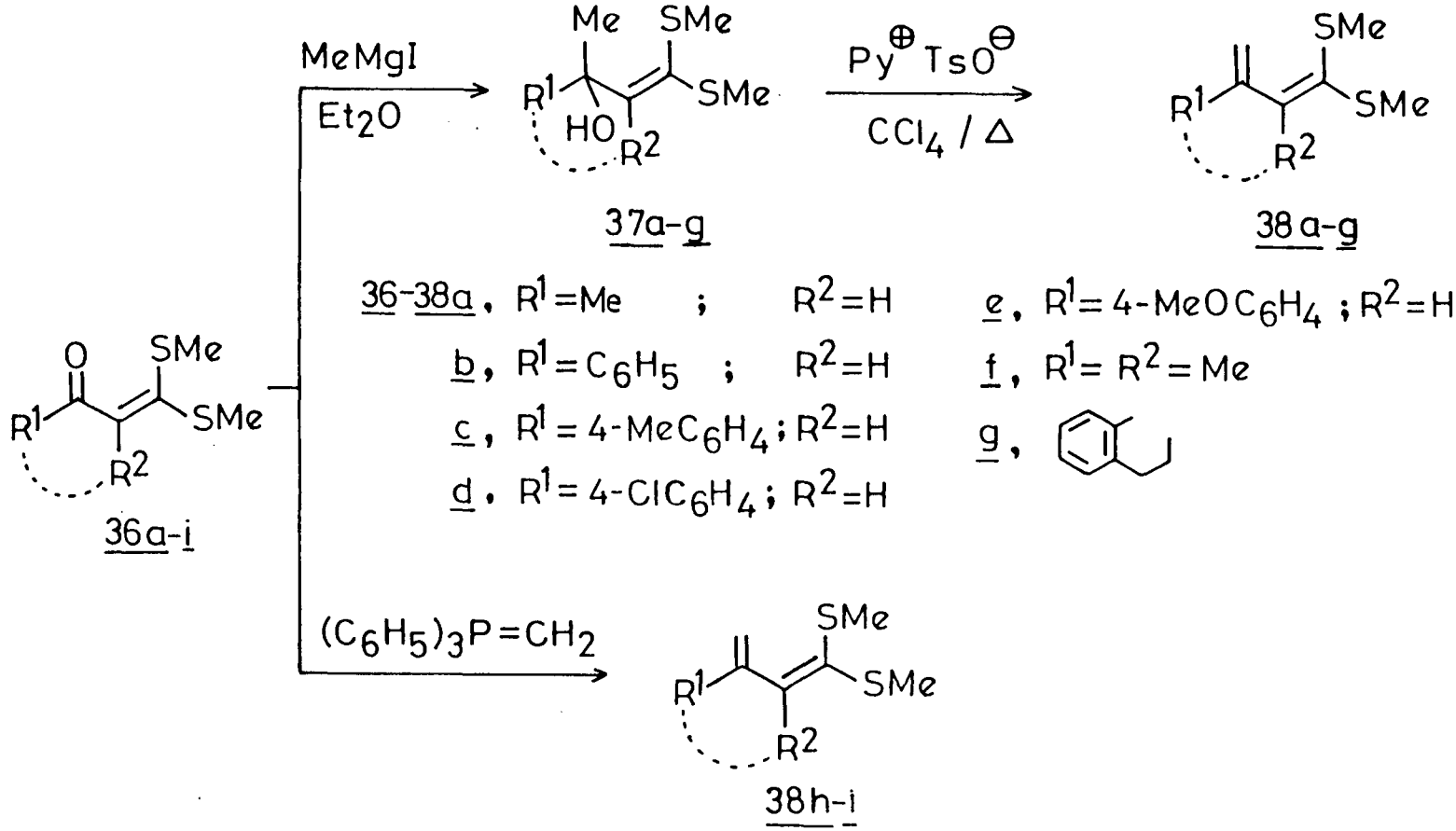
R^1	R^2	% yield
Me	H	80
Me	Me	84
C_6H_5	H	61
— $(CH_2)_3$ —		85
— $(CH_2)_4$ —		90



34 35

R^1	R^2	% yield
H	H	80
H	Me	74
— $(CH_2)_3$ —		76

Scheme 6



37a-g

38a-g

36a-i

36-38a, R^1=Me ; R^2=H

b, R^1=C_6H_5 ; R^2=H

c, R^1=4-MeC_6H_4 ; R^2=H

d, R^1=4-ClC_6H_4 ; R^2=H

e, R^1=4-MeOC_6H_4 ; R^2=H

f, R^1= R^2= Me

g,

38h-i

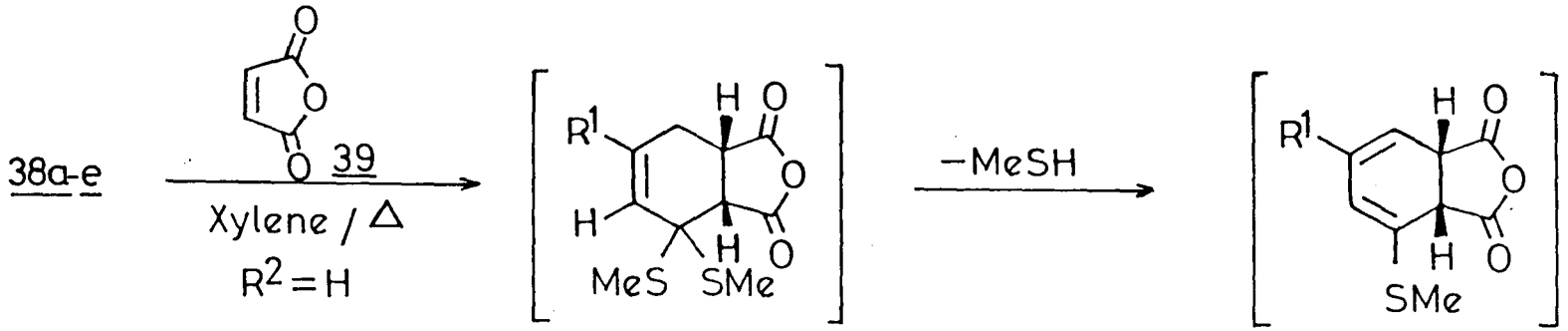
36, 38h, R^1=Et ; R^2=Me

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

Scheme 7

obtained only in the case of dienes 38a, 38f-i, since the attempted purification of 38b-e for elemental analysis resulted in their polymerization and decomposition (Scheme 7). In a typical cycloaddition study, when 38a was reacted with maleic anhydride (39) in refluxing xylene in the presence of a trace of hydroquinone, the reaction mixture after work-up yielded a light yellow crystalline compound (m.p. 201-202°C) (68%) which was characterized as 5-methyl-3-methylthiophthalic anhydride (42a) (Scheme 8). It was analyzed for $C_{10}H_8O_3S$ and its mass spectrum exhibited a molecular ion peak at m/z 208 (M^+,70%) alongwith two prominent peaks at m/z 164(70) [(M^+-44(CO_2)] and 136(100) [(M^+-44+28(CO_2+CO)]. The IR spectrum (KBr) of 42a showed characteristic anhydride carbonyl peaks at 1766 and 1830 cm^{-1} respectively. In the ^1H NMR spectrum ($CDCl_3$), the absorption due to methyl and methylthio groups appeared at δ 2.50 (s,3H) and 2.56(s,3H) respectively, while the aromatic protons appeared at δ 7.36(brs,1H) and 7.42(brs,1H) respectively. Apparently, the reaction has gone through initial 1,4-cycloaddition of 38a and 39 to give the adduct 40a, which on elimination of methylmercaptan and subsequent dehydrogenation of the resulting diene 41a under experimental conditions affords the fully aromatic 42a (Scheme 8). The methodology was found to be of general synthetic utility and other acyclic vinylketene dithioacetals 38b-e similarly, yielded the corresponding 5-aryl-3-methylthiophthalic anhydrides 42b-e in 62-72% overall yields (Scheme 8). The spectral and analytical data of these anhydrides are described in the experimental section.

Interestingly, when the vinylketene dithioacetal 38f derived from



38-42 a $R^1 = Me$

b $R^1 = C_6H_5$

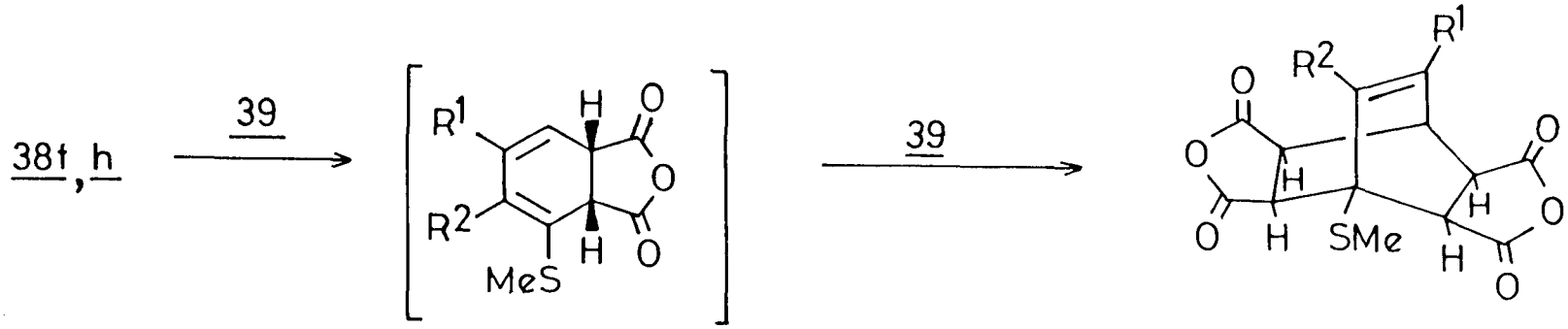
c $R^1 = 4\text{-}MeC_6H_5$

d $R^1 = 4\text{-}ClC_6H_4$

e $R^1 = 4\text{-}MeOC_6H_4$

Scheme 8

ethylmethyl ketone was reacted with 39 under identical conditions, the product isolated after work-up was characterized as bicyclic anhydride 44a (45%), which was obtained in improved yield (88%) when 38f was reacted with excess of maleic anhydride (Scheme 9). The structure of 44a was confirmed with the help of spectral and analytical data. Thus, 44a was analyzed for $C_{15}H_{14}O_6S$, while its mass spectrum exhibited molecular ion peak at m/z 322(16%) alongwith two prominent peaks at m/z 224(74) and m/z 152(100) due to the fragment ions 43a and 45 respectively (Scheme 9). The IR spectrum (KBr) of 44a showed characteristic anhydride carbonyl peaks at 1785 and 1858 cm^{-1} respectively. In the ^1H NMR spectrum (90 MHz) (DMSO-d_6) of 44a, the absorption due to two methyl and methylthio groups appeared at δ 1.60, 1.63 and 2.23 (3H each) respectively, while the signals due to bridgehead and four methine protons appeared at δ 3.30(brs,1H) and 3.60(brs, 4H) respectively. The ^{13}C NMR spectrum (75 MHz) (DMSO-d_6) of 44a confirmed its symmetrical structure and showed signals at δ 10.57 ($\underline{C}H_3$); 13.88($\underline{C}H_3$); 18.47(S$\underline{C}H_3$); 38.94(bridgehead $\underline{C}$H), 44.37, 45.57 ($\underline{C}$H); 52.85($\underline{C}$-SMe); 131.43, 132.75(olefinic $\underline{C}$) and 168.18, 171.87($\underline{C}$O) respectively. The reaction of the corresponding 2-methyl-3-ethyl derivative 38h with 39 similarly, afforded 44b in 86% yield. The analytical and spectral data of 44b are described in the experimental section. The bicyclic adducts 44a and 44b are apparently formed by further [4+2] cycloaddition of the corresponding intermediate dienes 43a and 43b with maleic anhydride(39). The dehydrogenation of 43a and 43b is not favoured probably due to steric constraints in the resulting trisubstituted phthalic anhydrides (Scheme 9).

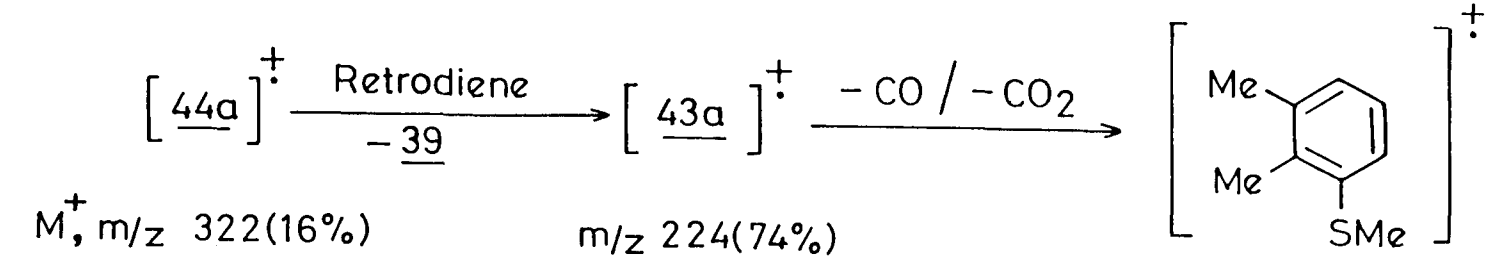


43a-b

44a-b

38f, 44a, $R^1 = R^2 = Me$

38h, 44b, $R^1 = Et$; $R^2 = Me$



M^+, m/z 322(16%)

m/z 224(74%)

45

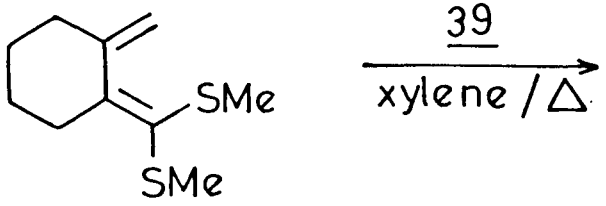
m/z 152(100%)

Scheme 9

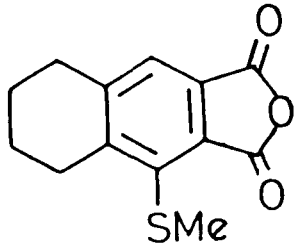
The cycloadditions of cyclic vinylketene dithioacetals 38i and 38g with 39 were next examined. Thus, when 38i was reacted with 39 under identical condition, the product isolated was characterized as 1-methylthio-5,6,7,8-tetrahydro-2,3-naphthalic anhydride (46) (71%) whereas the reaction of 38g with 39 afforded 9,10-dihydro-1-methylthio-2,3-phenanphthalic anhydride (47) in 76% yield. The structure of 46 and 47 were confirmed by their spectral and analytical data and are described in the experimental section (Scheme 10).

The attempted preparation of 38j from oxoketene dithioacetal 36j derived from indanone, by either of the methods gave only the dimeric adduct 48 (Scheme 11). When the crude diene 38j was reacted with 39 under analogous conditions, the adduct 50 was obtained which was characterized by its analytical and spectral data (experimental). The formation of adduct 50 could be explained through intermolecular Diels-Alder reaction of 38j to give the dimer 48, which on elimination of methylthio group affords diene 49. The dimeric diene 49 on [4+2] cycloaddition with maleic anhydride (39) finally yields the adduct 50 (Scheme 11).

The vinylketene dithioacetals 38a and 38f were also found to be reactive with dimethylacetylene dicarboxylate. Thus, when dienes 38a and 38f were reacted with DMAD (51) in refluxing xylene, in the presence of a trace of hydroquinone, the corresponding substituted phthalates 52a and 52b were obtained in 74% and 67% yields respectively (Scheme 12). The analytical and spectral data of these phthalates are described in the experimental section. One

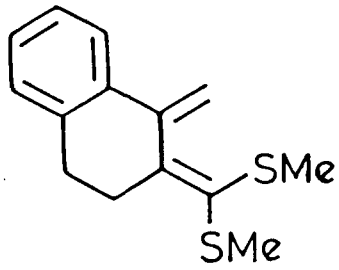


39
xylene / Δ

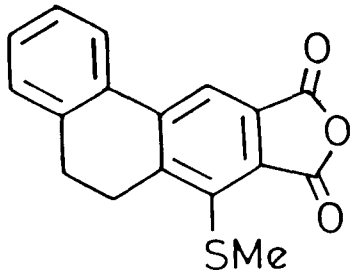


38i

46



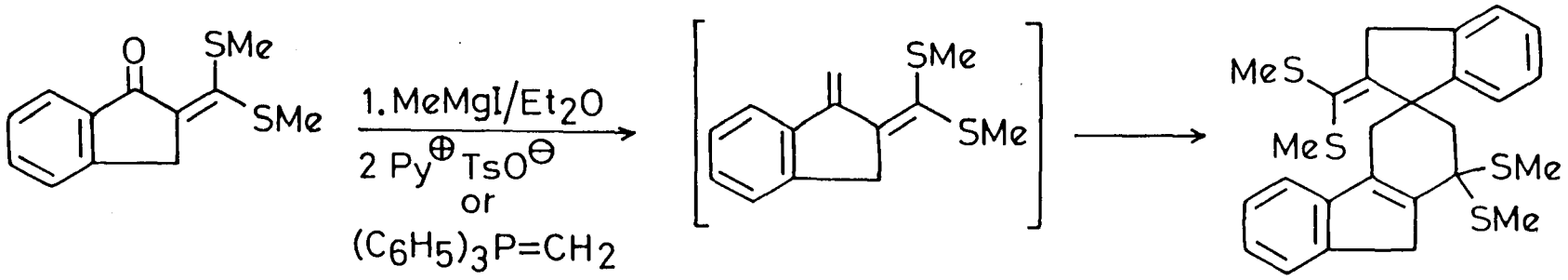
39
xylene / Δ



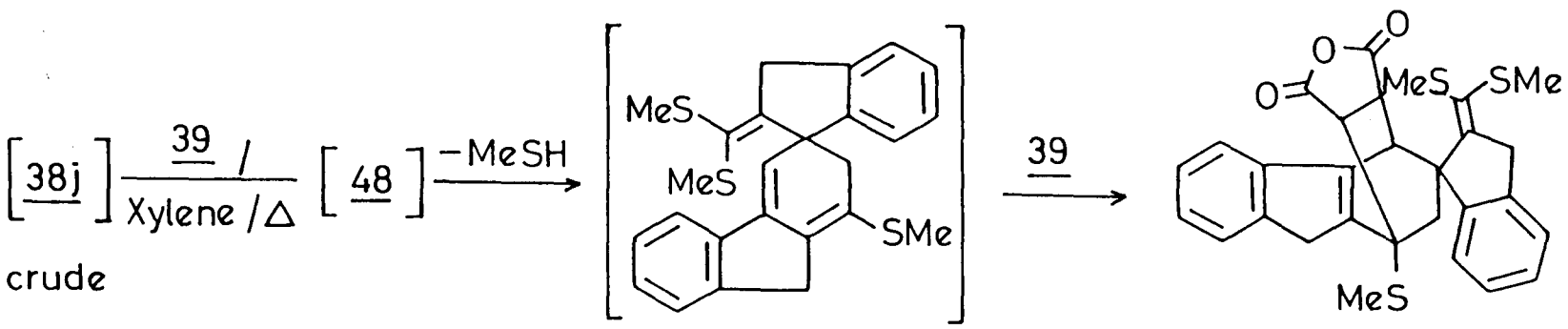
38g

47

Scheme 10



36j 38j 48



crude

49 50

Scheme 11

of them, 52a underwent facile dethiomethylation to yield sulphur free dimethyl 3-methyl-1,2-dicarboxylate (53) when treated with W-4 Raney Nickel (Scheme 12).

The dienes 38a-i however, were found to be unreactive towards weaker dienophiles like acrylonitrile, ethyl acrylate and methyl vinyl ketones.

IV. 3 CONCLUSION

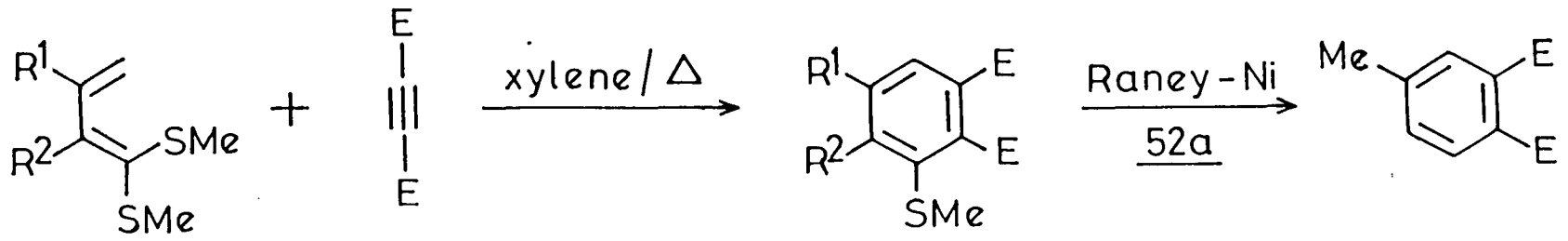
In conclusion, it may be inferred that the vinylketene dithioacetals are found to be inert towards weaker dienophiles like their 1,3-dithiano counterparts, while their reaction with activated dienophiles like maleic anhydride and DMAD provides a facile one step elaboration of benzene ring in the form of substituted phthalic anhydrides and phthalates respectively.

IV. 4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM-390, 90 MHz spectrometer while ^{13}C NMR spectra on Varian XL-300, 75 MHz spectrometer and are reported in δ units downfield from Me_4Si. Mass spectra were obtained on Jeol JMS D-300 spectrometer. Elemental analysis were carried out on a Heraus CHN-O-RAPID instrument.

Starting Materials

General experimental details for the preparation of α-oxoketene dithioacetal is given in chapter II. All ketene dithioacetal 36a-j were prepared using this procedure and were characterized by physical and spectral data.



38a, f 51 52a-b 53

38a, 52a, $R^1 = Me$; $R^2 = H$

38f, 52b, $R^1 = R^2 = Me$

Scheme 12

Pyridinium tosylate was prepared according to reported procedure[22]. Maleic anhydride and DMAD was purified prior to use. Xylene was dried over sodium wire. Triphenylphosphine and potassium tert-butoxide (97%) were purchased from Aldrich and used as such.

W-4 Raney Nickel was prepared according to the reported procedure[23].

General Procedure for the Preparation of Carbinolacetals 37a-g:

To an ice cooled (-5°C-0°C) suspension of methylmagnesium iodide [15 mmol, prepared from 0.36g(0.015g atom) of magnesium turnings and 2.10g (15 mmol) of methyl iodide] in dry ether (50 ml), a solution of corresponding α-oxoketene dithioacetal (10 mmol) in dry benzene (25 ml) was gradually added (5 min.) and the reaction mixture was stirred at room temperature for 30 min. It was then poured into satd. NH_4Cl solution (100 ml), extracted with ether (3x50 ml), the combined extracts were washed with water, dried (Na_2SO_4) and evaporated to give crude carbinols 37a-g as light yellow oil.

Genral Procedure for Dehydration of Carbinolacetals 37; Preparation of Vinylketene Dithioacetals 38a-g:

A solution of carbinolacetals 37 (10 mmol) and pyridinium tosylate (2.50g, 10 mmol) in CCl_4 (150 ml) was refluxed for 15 min. and the reaction mixture after cooling was filtered, washed with water (2x100 ml), dried (Na_2SO_4) and evaporated to give crude dienes 38a-g which was further purified by passing through neutral alumina column using hexane as eluent.

1,1-Bis(methylthio)-3-methyl-1,3-butadiene (38a); was isolated as colourless viscous liquid (88%); IR ν_{max}(neat) 1605 cm^{-1}; ^1H NMR

(CCl_4): 1.98(d,3H,J=1.5Hz,$C\underline{H}_3$); 2.24(s,3H,$SC\underline{H}_3$); 2.28(s,3H,$SC\underline{H}_3$); 5.00(brs,2H,$C\underline{H}_2$); 6.30(s,1H,$\underline{H}$-2). (Found: C,52.74; H,7.82; Calc. for $C_7H_{12}S_2$: C,52.45; H,7.54%).

1,1-Bis(methylthio)-3-phenyl-1,3-butadiene (38b); was isolated as colourless liquid (86%); IR ν_{max}(neat) 1600 cm^{-1}; ^1H NMR(CCl_4): 2.26 (s,3H,$SC\underline{H}_3$); 2.36(s,3H,$SC\underline{H}_3$); 5.32(brs,1H,$\underline{H}$-4); 5.46(s,1H,$\underline{H}$-4); 6.44 (s,1H,$\underline{H}$-2); 7.15-7.44(m,5H,Ar$\underline{H}$).

1,1-Bis(methylthio)-3-(4-methylphenyl)-1,3-butadiene (38c); was isolated as yellow viscous oil (92%); IR ν_{max}(neat) 1605 cm^{-1}; ^1H NMR(CCl_4): 2.20(s,3H,$C\underline{H}_3$); 2.28(s,6H,$SC\underline{H}_3$); 5.20(brs,1H,$\underline{H}$-4); 5.46(brs,1H,$\underline{H}$-4); 6.32(s,1H,$\underline{H}$-2); 6.84-7.14(m,A_2B_2,4H,Ar$\underline{H}$).

1,1-Bis(methylthio)-3-(4-chlorophenyl)-1,3-butadiene (38d); was isolated as yellow viscous liquid (90%); IR ν_{max}(neat) 1590 cm^{-1}; ^1H NMR(CCl_4): 2.24(s,3H,$SC\underline{H}_3$); 2.32(s,3H,$SC\underline{H}_3$); 5.28(brs,1H,$\underline{H}$-4); 5.52(brs,1H,$\underline{H}$ 4); 6.35(s,1H,$\underline{H}$-2); 7.08-7.46(m,4H,Ar$\underline{H}$).

1,1-Bis(methylthio)-3-(4-methoxyphenyl)-1,3-butadiene (38e); was isolated as yellow viscous liquid (92%); IR ν_{max}(neat) 1600 cm^{-1}; ^1H NMR(CCl_4): 2.24(s,3H,$SC\underline{H}_3$); 2.32(s,3H,$SC\underline{H}_3$); 3.70(s,3H,$OC\underline{H}_3$); 5.12(brs,1H,$\underline{H}$-4); 5.48(brs,1H,$\underline{H}$-4); 6.40(s,1H,$\underline{H}$-2); 6.70(d,2H,J=9Hz, Ar$\underline{H}$); 7.26(d,2H,J=9Hz,Ar$\underline{H}$).

1,1-Bis(methylthio)-2,3-dimethyl-1,3-butadiene (38f);was obtained as yellow oil (89%); IR ν_{max}(neat) 1642 cm^{-1}; ^1H NMR(CCl_4): 1.90 (brs,3H,$C\underline{H}_3$); 2.10(s,3H,$C\underline{H}_3$); 2.21(s,3H,$SC\underline{H}_3$); 2.30(s,3H,$SC\underline{H}_3$); 4.18(brs,1H,$\underline{H}$-4); 4.91(brs,1H,$\underline{H}$-4). (Found: C,55.40; H,8.35; Calc. for $C_8H_{14}S_2$: C,55.12; H,8.09%).

2-Bis(methylthio)methylene-1-methylene-1,2,3,4-tetrahydronaphthalene (38g); was isolated as yellow viscous liquid (90%); IR ν_{max}(neat) 1645, 1698 cm^{-1}; ^1H NMR(CCl_4): 2.22(s,3H,SCH_3); 2.31(s,3H,SCH_3); 2.66-3.02(m,4H,CH_2); 5.28(s,1H,olefinic); 5.74(s,1H,olefinic); 6.98-7.30 (m,3H,ArH); 7.36-7.64(m,1H,ArH). (Found: C,67.48; H,6.78; Calc. for $C_{14}H_{16}S_2$: C,67.69; H,6.49%).

General Procedure for the Preparation of Vinylketene dithioacetals 38h-i:

To a cooled solution (~15°C) of the Wittig reagent [prepared from triphenylphosphonium iodide (6.06g, 15 mmol) and potassium tert-butoxide (1.70g, 15 mmol) in refluxing di-iso-propyl ether (50 ml)] a solution of corresponding α-oxoketene dithioacetals (10 mmol) in di-iso-propyl ether (25 ml) were dropwise added (10 min.) and stirred for 1 hr. at room temperature under N_2 atmosphere. After dilution of the reaction mixture with 150 ml of petroleum ether, most of the triphenylphosphine oxide were removed by filtration. The filtrate was washed with a solution of saturated ammonium chloride (100 ml), washed with water (100 ml) and dried (Na_2SO_4). The solvent was removed under vacuo. The residual oil was taken in pentane, ice-cooled and filtered. Evaporation of pentane yielded the crude vinylketene dithioacetals (38h-i) which were further purified by passing through a column of neutral alumina using hexane as eluent.

1,1-Bis(methylthio)-2-methyl-3-ethyl-1,3-butadiene (38h); was obtained as yellow oil (86%); IR ν_{max}(neat) 1634 cm^{-1}; ^1H NMR(CCl_4): 1.00(t, 3H,J=7Hz,CH_3CH_2); 2.03(s,3H,CH_3); 2.17(s,3H,SCH_3); 2.20(s,3H,SCH_3);

2.23(q merged with SCH_3 and CH_3 signals, 2H,$C\underline{H}_2$); 4.61(brs,1H,$\underline{H}$-4); 4.83(brs,1H,$\underline{H}$-4). (Found: C,57.64; H,8.85; Calc. for $C_9H_{16}S_2$: C,57.39; H,8.56%).

1-Bis(methylthiomethylene)-2-methylene cyclohexane (38i); was obtained as colourless oil (88%); IR ν_{max}(neat) 1635, 1440 cm^{-1}; ^1H NMR(CCl_4): 1.40-1.83(m,4H,$C\underline{H}_2$); 2.15(s,3H,$SC\underline{H}_3$); 2.22(s,3H,$SC\underline{H}_3$); 2.42-2.80(m, 4H,$C\underline{H}_2$); 4.70(brs,1H,olefinic); 4.91(brs,1H,olefinic). (Found: C,60.23; H,8.32; Calc. for $C_{10}H_{16}S_2$: C,59.95; H,8.05%).

Cycloadditions of Vinylketene Dithioacetals 38a-i with Maleic Anhydride (39); General Procedure:

A solution of corresponding vinylketene dithioacetals 38a-i (10 mmol), maleic anhydride (39) (1.0g, 10.2 mmol) and a trace of hydroquinone in dry xylene (50 ml) were refluxed for 30 hrs. (monitored by t.l.c.) till starting materials were disappeared. Xylene was removed under reduced pressure and the residue was subjected to column chromatography over silica gel using EtOAc-hexane (1:20) as eluent to give pure anhydrides 42a-e, 46 and 47. The bicyclic anhydrides 44a-b were also obtained in the similar manner.

5-Methyl-3-methylthiophthalic anhydride (42a); was isolated as light yellow crystals (EtOAc-hexane); m.p. 201-202°C; yield 68%; spectral data described in text. (Found: C,57.89; H,4.06; Calc. for $C_{10}H_8O_3S$: C,57.68; H,3.87%); m/z 208(70%), 164(70), 136(100).

3-Methylthio-5-phenylphthalic anhydride (42b); was isolated as light yellow crystals (EtOAc-hexane); m.p. 155-156°C; yield 72%; IR ν_{max}(KBr) 1843, 1762 cm^{-1}; ^1H NMR($CDCl_3$): 2.66(s,3H,$SC\underline{H}_3$); 7.45-7.68(m,5H,Ar$\underline{H}$);

7.70(brs,1H,ArH); 7.86(brs,1H,ArH). (Found: C,66.88; H,3.91; Calc. for $C_{15}H_{10}O_3S$: C,66.65; H,3.73%); m/z 270(M^+,100%), 226(100),198(100).

5-(4-Methylphenyl)-3-methylthiophthalic anhydride (42c); was isolated as light yellow crystals (EtOAc-hexane); m.p. 170-171°C; yield 66%; IR ν_{max}(KBr) 1846, 1772 cm^{-1}; ^1H NMR($CDCl_3$): 2.40(s,3H,CH_3); 2.63(s, 3H,SCH_3); 7.20-7.54(dd,A_2B_2,4H,ArH); 7.62(brs,1H,ArH); 7.78(s,1H,ArH). (Found: C,67.81; H,4.48; Calc. for $C_{16}H_{12}O_3S$: C,67.59; H,4.26%); m/z 284(M^+,100%), 240(49), 212(37).

5-(4-Chlorophenyl)-3-methylthiophthalic anhydride (42d); was isolated as light yellow crystals (EtOAc-hexane); m.p. 176-177°C; yield 69%; IR ν_{max}(KBr) 1850, 1767 cm^{-1}; ^1H NMR($CDCl_3$): 2.60(s,3H,SCH_3); 7.38 (s,4H,ArH); 7.50(brs,1H,ArH); 7.64(brs,1H,ArH). (Found: C,59.28; H,3.21; Calc. for $C_{15}H_9ClO_3S$: C,59.12; H,2.98%); m/z 306(40%), 304(M^+,100), 262(25), 260(68), 234(21), 232(57).

5-(4-Methoxyphenyl)-3-methylthiophthalic anhydride (42e); was isolated as light yellow crystals (EtOAc-hexane);m.p. 165-166°C; yield 62%; IR ν_{max}(KBr) 1842, 1766 cm^{-1}; ^1H NMR($CDCl_3$): 2.66(s,3H,SCH_3); 3.86 (s,3H,OCH_3); 7.00(d,2H,J=9Hz,ArH); 7.58(d,2H,J=9Hz,ArH); 7.64(brs, 1H,ArH); 7.78(brs,1H,ArH). (Found: C,64.27; H,4.31; Calc. for $C_{16}H_{12}O_4S$: C,63.98; H,4.02%); m/z 300(M^+,100%), 256(47), 228(31).

Endo-7,8-Dimethyl-1-methylthiobicyclo[2.2.2]oct-7-ene-2,3,5,6-tetra-carboxylic anhydride (44a); was isolated as white crystals (EtOAc-hexane); m.p. 298-299°C; yield 45%,88% with 2 eqv. of 39; spectral data described in text. (Found: C,55.67; H,4.53; Calc. for $C_{15}H_{14}O_6S$: C,55.89; H,4.38%); m/z 322(M^+,16%); 224(74), 152(100).

Endo-8-Ethyl-7-methyl-1-methylthiobicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic anhydride (44b); was isolated as white crystals (EtOAc); m.p. 306-307°C; yield 86% with 2 eqv. of 39; IR ν_{max}(KBr) 1856, 1784 cm^{-1}; ^1H NMR(DMSO-d_6): 0.82(t,3H,J=7Hz,CH_3CH_2); 1.60(s, 3H,CH_3); 2.04(q,2H,J=7Hz,CH_3CH_2); 2.28(s,3H,SCH_3); 3.45(brs,1H, bridgehead C-H); 3.67(s,4H,ring CH); ^{13}C NMR (75 MHz) (DMSO-d_6): 10.59(CH_3); 14.58(CH_3CH_2); 17.31(SCH_3); 24.30(CH_3CH_2); 37.35(bridgehead CH); 44.81, 45.35(CH); 52.59(-C-SCH_3); 131.42, 132.01 (olefinic C); 168.23, 171.81(CO). (Found: C,57.36; H,4.69; Calc. for $C_{16}H_{16}O_6S$: C,57.13; H,4.80%; m/z 336(M^+,19%), 238(96), 166(100).

1-Methylthio-5,6,7,8-tetrahydro-2,3-naphthalic anhydride (46); was isolated as white crystals (EtOAc-hexane); m.p. 110-111°C; yield 71%; IR ν_{max}(KBr) 1840, 1778 cm^{-1}; ^1H NMR($CDCl_3$): 1.57-2.11(m,4H,CH_2); 2.55(s,3H,SCH_3); 2.70-3.19(m,4H,CH_2); 7.56(s,1H,ArH). (Found: C,62.69; H,5.11; Calc. for $C_{13}H_{12}O_3S$: C,62.88; H,4.87%); m/z 248(M^+,100%), 204(44).

9,10-Dihydro-1-methylthio-2,3-phenanphthalic anhydride (47); was isolated as white crystals (EtOAc-hexane); m.p. 171-172°C; yield 76%; IR ν_{max}(KBr) 1834, 1775 cm^{-1}; ^1H NMR($CDCl_3$): 2.51(s,3H,SCH_3); 2.78-3.07(m,2H,CH_2); 3.15-3.43(m,2H,CH_2); 7.11-7.40(m,3H,ARH); 7.65-7.97 (m,1H,ArH); 8.24(s,1H,ArH). (Found: C,68.78; H,4.29; Calc. $C_{17}H_{12}O_3S$: C,68.89; H,4.08%); m/z 296(M^+,60%), 252(39).

Dehydration of carbinolacetal (37j) gave the dimer 48; was isolated as colourless solid (EtOAc-hexane); m.p. 205-206°C; yield 82%; IR ν_{max}(KBr) 1630 cm^{-1}; ^1H NMR($CDCl_3$): 1.71-2.0(m,2H,CH_2); 2.00(s,

6H,SC$\underline{H}_3$); 2.29(s,3H,SC$\underline{H}_3$); 2.43(s,3H,SC$\underline{H}_3$); 2.81-3.03(m,2H,C$\underline{H}_2$); 3.52(brt,2H,J=1.5Hz,C$\underline{H}_2$); 4.28(s,2H,C$\underline{H}_2$); 7.02-7.45(m,8H,Ar$\underline{H}$). (Found: C,66.41; H,6.27; Calc. for $C_{26}H_{28}S4$: C,66.62; H,6.02%).

Reaction of crude 38j with 39 gave bicyclic anhydride 50; as colourless solid (EtOAc-hexane); m.p. 215-216°C; yield 59%; IR ν_{max}(KBr) 1852, 1772 cm^{-1}; ^1H NMR($CDCl_3$): 1.64(s,3H,SC$\underline{H}_3$); 1.78-2.11(m,2H,C$\underline{H}_2$); 2.34 (s,3H,SC$\underline{H}_3$): 2.39(s,3H,SC$\underline{H}_3$); 2.54-2.72(m,2H,ring C$\underline{H}$); 3.90-4.08(m, 4H,C$\underline{H}_2$); 4.50-4.64(brs,1H,bridgehead C$\underline{H}$); 6.53-6.70(m,1H,Ar$\underline{H}$); 6.90-7.46(m,7H,Ar$\underline{H}$). (Found: C,66.98; H,4.95; Calc. for $C_{29}H_{26}O_3S_3$: C,67.15; H,5.05%); m/z 470(M^+-48, 100%).

Cycloaddition of Vinylketene Dithioacetals 38a and 38f with Dimethylacetylene Dicarboxylate (51); was carried out in the similar manner as described for cycloaddition of vinylketene dithioacetal with maleic anhydride by taking 10 mmol of corresponding vinylketene dithioacetal and 1.42g (10 mmol) of dimethylacetylene dicarboxylate 51 and refluxing in dry xylene (50 ml) for 24 hrs, work-up and column chromatography as described afforded pure phthalates 52a and 52b.

Dimethyl 5-methyl-3-methylthiophthalate (52a); was isolated as yellow crystals ($CHCl_3$-hexane); m.p. 62-63°C; yield 74%; IR ν_{max}(KBr) 1720, 1600 cm^{-1}; ^1H NMR($CDCl_3$): 2.38(s,3H,C$\underline{H}_3$); 2.45(s,3H,SC$\underline{H}_3$); 3.86(s,3H, OC$\underline{H}_3$); 3.92(s,3H,OC$\underline{H}_3$); 7.36(brs,1H,Ar$\underline{H}$); 7.62(brs,1H,Ar$\underline{H}$). (Found: C,56.45; H,5.78; Calc. for $C_{12}H_{14}O_4S$: C,56.68; H,5.55%); m/z 254 (M^+,89%), 223(100).

Dimethyl 4,5-dimethyl-3-methylthiophthalate (52b); was isolated as yellow crystals ($CHCl_3$-hexane); m.p. 89-90°C; yield 67%; IR ν_{max}(KBr) 1735, 1722 cm^{-1}; ^1H NMR(CCl_4): 2.24(s,3H,C$\underline{H}_3$); 2.33(s,3H,C$\underline{H}_3$); 2.56 (s,3H,SC$\underline{H}_3$); 3.85(s,3H,OC$\underline{H}_3$); 3.95(s,3H,OC$\underline{H}_3$); 7.76(s,1H,Ar$\underline{H}$). (Found: C,57.96; H,6.29; Calc. for $C_{13}H_{16}O_4S$: C,58.19; H,6.01%); m/z 268(M^+, 23%), 237(100), 205(100).

Dimethyl-4-methylphthalate (53); was obtained from 52a by W-4 Raney Nickel dethiomethylation as viscous colourless oil; yield 78%; IR ν_{max} (neat) 1734, 1720, 1609 cm^{-1}; ^1H NMR(CCl_4): 2.30(s,3H,C$\underline{H}_3$); 3.79(s, 6H,OC$\underline{H}_3$); 7.20(d,1H,J=7.0Hz,$\underline{H}$-5); 7.35(brs,1H,$\underline{H}$-3); 7.53(d,1H,J=7.0Hz, $\underline{H}$-6). (Found: C,63.52; H,5.75; Calc. for $C_{11}H_{12}O_4$: C,63.45; H,5.81%).

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