SYNTHETIC INVESTIGATIONS ON POLARIZED KETENE DITHIOACETALS: NOVEL METHODS FOR THE SYNTHESIS OF CARBOCYCLES AND HETEROCYCLES

ABSTRACT

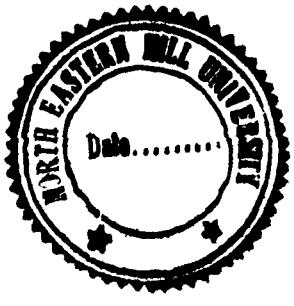
By

BALU M. P.

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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

DOCTOR OF PHILOSOPHY



To

NORTH-EASTERN HILL UNIVERSITY

SHILLONG - 793001

INDIA

1989

chemistry

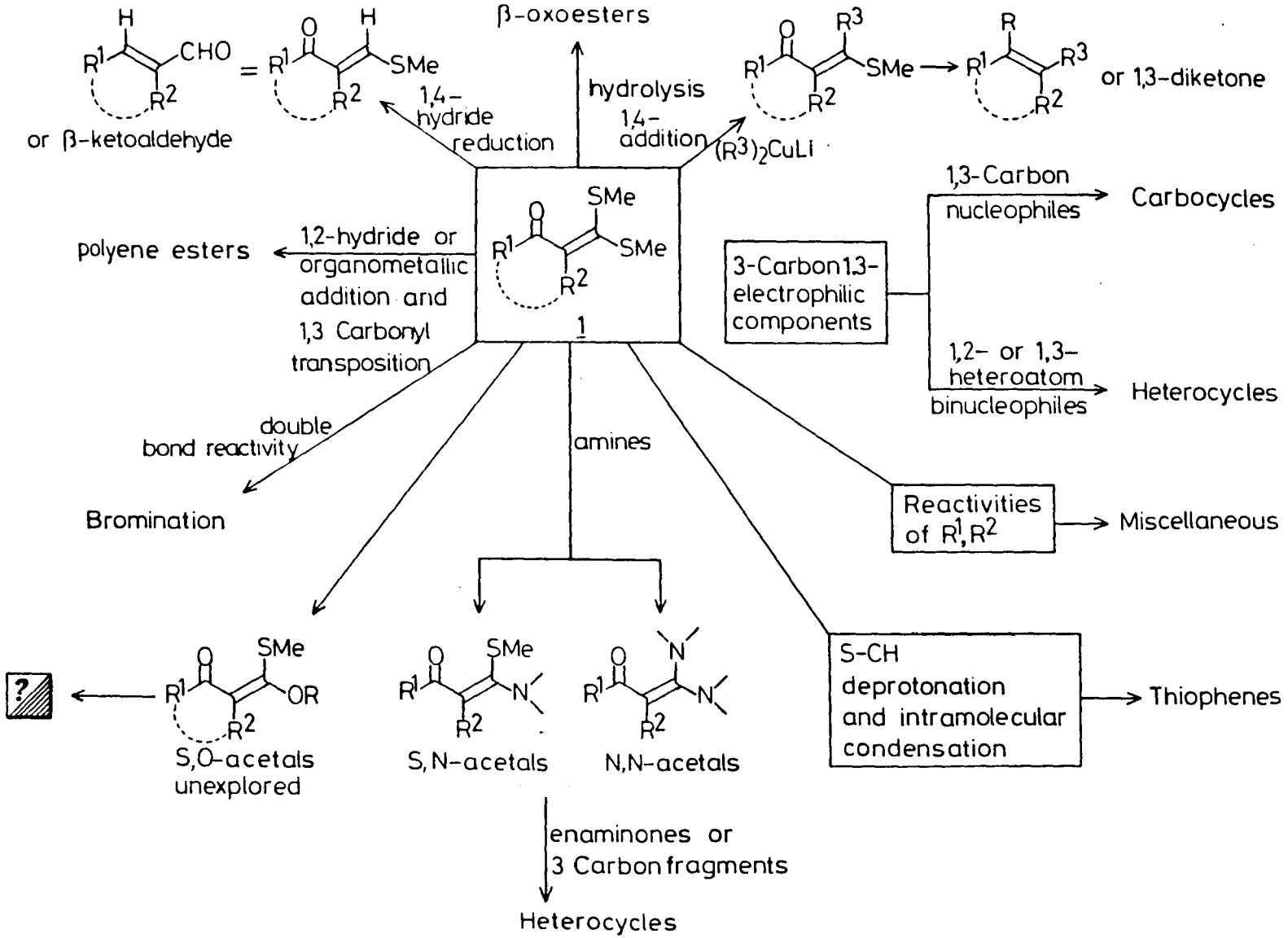
The α-oxoketene dithioacetals of the general formula 1 are among the simplest synthetic intermediates, which can be prepared by reacting any active methylene compound with two equivalents of base and carbon disulfide followed by alkylation. The first synthesis of α-oxoketene dithioacetals was reported by Kelber in 1910.[1] After the intial synthesis, for more than half a century the synthetic potential of these class of compounds remained unexplored. Later Thuillier and co-workers prepared these compounds in high yields in one pot reaction directly from ketones using sodium t-amylate as base and two equivalents of alkyl halide.[2] Subsequently these reaction conditions have been greately improved using different bases and reaction conditions.[3,4] A large number of oxoketene dithioacetals have now been reported and their chemistry has been reviewed.[5]

The α-oxoketene dithioacetals essentially is a masked β-ketoester in which the ester functionality is protected as a ketene dithioacetal. It may also be viewed as an α,β-unsaturated ketone containing a highly functionalized β-carbon atom. Thus, these intermediates possess 1,3-electrophilic centres with differing electrophilicity making them an excellent class of 3-carbon synthons. Their 1,3-electrophilic reactivity has been extensively studied for the *stereo*- and *regio*selective construction

of new carbon-carbon bonds either by a 1,2-nucleophilic addition to the carbonyl group or by a 1,4-conjugate addition to the β-carbon of the enone system.

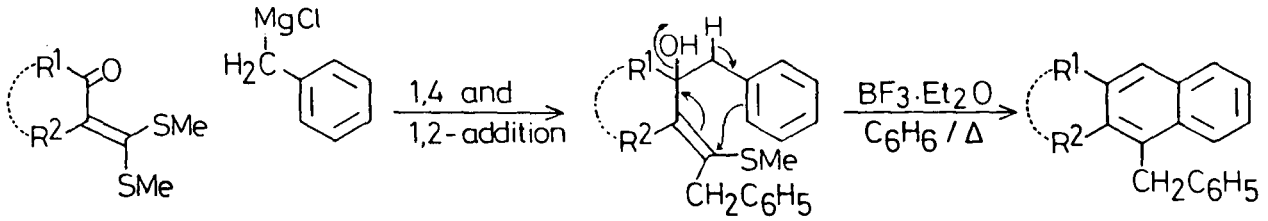
Scheme 1 outlines various reactivity profiles of α-oxoketene dithioacetals of the general formula 1. Hydrides and methylmagnesium halides have been shown to undergo 1,2-addition to yield the carbinol acetal, which under solvolytic conditions were transformed to various products.[6,7] Organocuprates, bulkier alkyl and aryl Grignard reagents add in a 1,4- or sequential 1,4- followed by 1,2-addition to α-oxoketene dithioacetals.[7,8] The α-oxoketene dithioacetals possess typical 1,3-electrophilic centres. These intermediates react with 1,2- and 1,3-heteroatom binucleophiles to give five and six membered heterocyclic compounds while 1,3-carbon binucleophiles give carbocyclic compounds.[5] Some of the other general reaction pathways are also shown in Scheme 1. Thus, it is apparent that the oxoketene dithioacetals of general formula 1 constitute an important class of synthons with reactive electrophilic and nucleophilic centres distributed at various centres of its skeleton permitting reactions of great synthetic importance.

In the present study, it was proposed to undertake some of the transformations based on α-oxoketene S,S and S,N-acetals. In the second chapter, the reaction of benzylmagnesium chloride with α-oxoketene dithioacetals 1 leading to condensed aromatic systems has been


β-oxoesters
or β-ketoaldehyde
1,4-hydride reduction
hydrolysis
1,4-addition
$(R^3)_2CuLi$
or 1,3-diketone
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
double bond reactivity
Bromination
amines
Reactivities of R^1, R^2
Miscellaneous
S,O-acetals unexplored
S,N-acetals
N,N-acetals
S-CH deprotonation and intramolecular condensation
Thiophenes
enaminones or 3 Carbon fragments
Heterocycles

Scheme-1

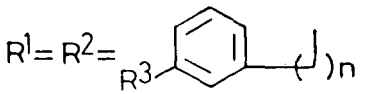
presented.[9] Thus, the carbinolacetals 3 obtained by the reaction of benzylmagnesium chloride with oxoketene dithioacetals indicated that the addition took place in a 1,4-followed by 1,2-sequence and underwent $BF_3.Et_2O$ assisted aromatic annelation to yield the corresponding naphthalenes 4 in excellent yields (Scheme 2). The generality of the method have been studied in greater details by using wide structural variants of 1. Interestingly, when these reactions were extended to 1-naphthylmethylmagnesium chloride 5, the addition with oxoketene dithioacetals 1 took place exclusively in 1,2-fashion to yield the corresponding carbinolacetals 6 in high yields.[10] These carbinolacetals could be smoothly cyclized in the presence of $BF_3.Et_2O$ to the the corresponding phenanthrenes 7 (Scheme 3) in good yields. Some of these methylthio substituted phenanthrenes 7 were desulphurized to the corresponding phenanthrenes 8 by treating with *Raney-Ni* in methanol. Similarly when 2-naphthylmethylmagnesium bromide 9 was reacted with 1,the 1,4-followed by 1,2-addition carbinolacetals 10 (Scheme 4) were formed in good yields and they afforded the corresponding phenanthrenes 11 under similar reaction conditions as described earlier. While studying the generality of this phenanthrene synthesis it was observed that only oxoketene dithioacetals derived from tetralones underwent exclusive 1,2-addition with 2-naphthylmethyl-magnesium bromide. It appears that both steric and electronic factors play an important role in the



1 2 3 4

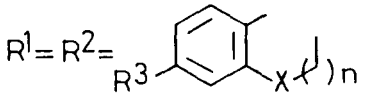
$R^1 = C_6H_5$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-naphthyl ; $R^2 = H$; 58–65 %

$R^1 = R^2 = -(CH_2)_4-$; 81 %



n=1 ; 62 %

n=2 ; 71 %

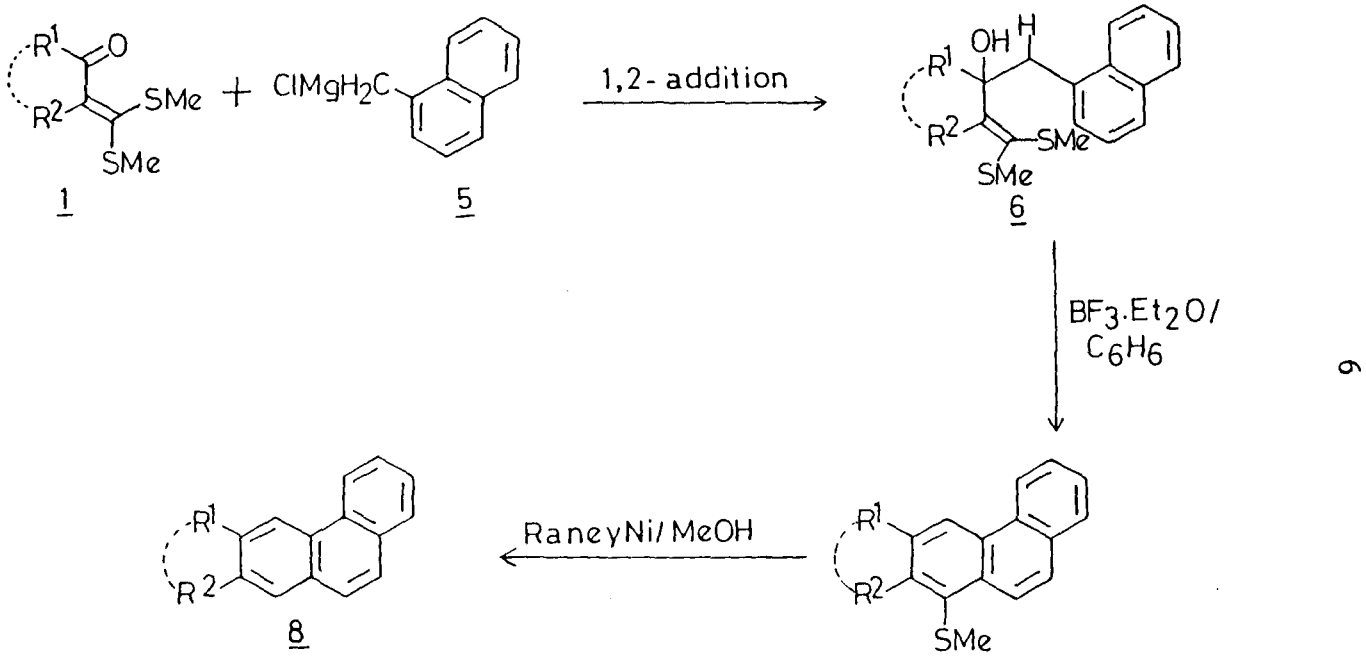


$R^3 = H$; X = S ; n = 1 ; 58 %

$R^3 = Me$ X = S ; n = 2 ; 68 %

$R^3 = H$; X = O ; n = 2 ; 67 %

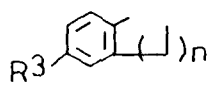
Scheme–2



1 5 6 7 8

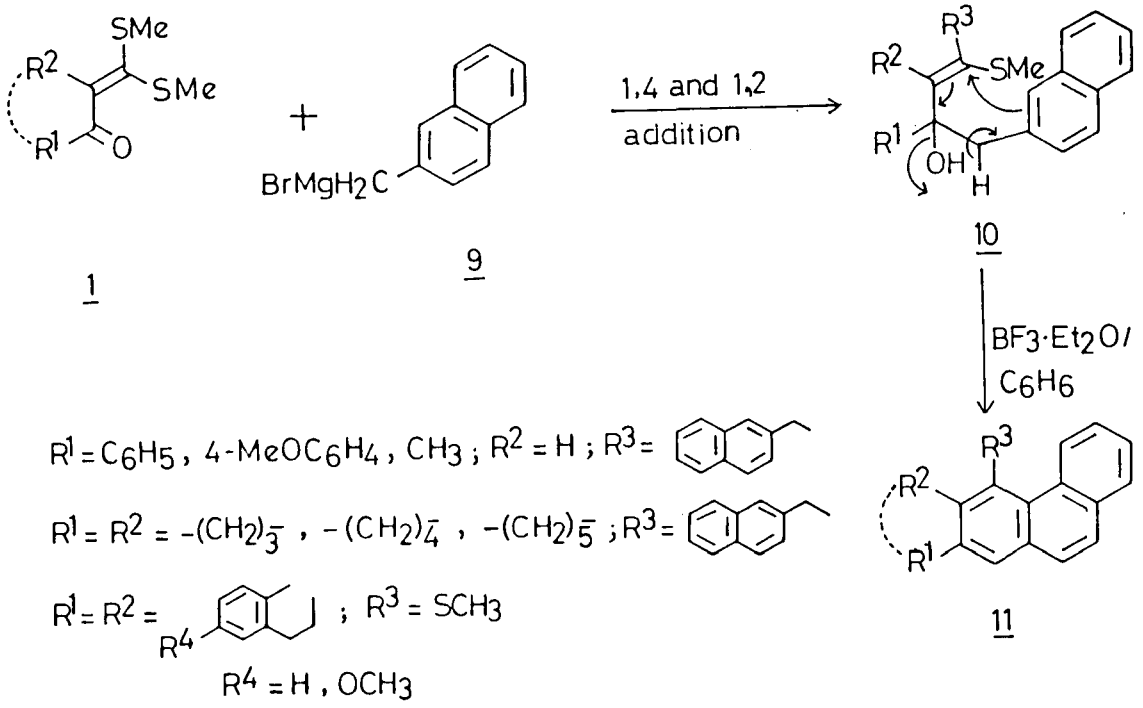
$R^1 = C_6H_6$, 4-$MeOC_6H_4$; 4-ClC_6H_4 , CH_3 ; $R^2 = H$

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

$R^1 = R^2 =$ 

$R^3 = H$; n = 1
$R^3 = H$; n = 2
$R^3 = CH_3O$; n = 2

Scheme – 3



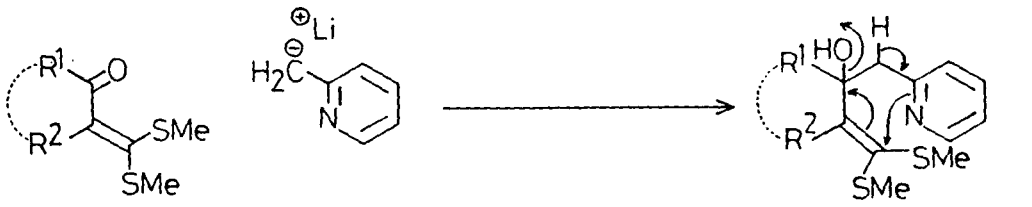
1 9 10 11

Scheme - 4

different reactivity patterns of benzyl, 1-naphthylmethyl- and 2-naphthylmethylmagnesium halides with α-oxoketene dithioacetals.

In Chapter III, the reaction of various α-oxoketene dithioacetals with 2-picolyllithium has been described. The α-oxoketene dithioacetals 1 react with 12 in an exclusive 1,2-manner to yield the corresponding carbinol acetals 13 which on $BF_3.Et_2O$ assisted cyclization afforded the corresponding quinolizinium tetrafluoroborates 14 (Scheme 5) in high yields. The generality of this method has been studied by using wide structural variants of 1. Also α-enoyl ketene dithioacetals 15 reacted with 2-picolyllithium to give the corresponding quinolizinium tetrafluoroborates 17 (Scheme 6) in high yields. The methylthio groups in few of these salts could be easily displaced by the corresponding ethoxy group in refluxing ethanol.

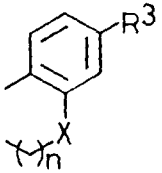
1,3-Anionic cycloaddition of 1,3-diphenyl-2-azaallyl and ethyl(benzylideneamino)acetate anions 19 and 31 with α-oxoketene dithioacetals[12] have been described in the Chapter IV. Thus, when 1,3-diphenyl-2-azaallyllithium 19 reacted with oxoketene dithioacetals 1, the corresponding pyrroles 20 (Scheme 7) were formed in good yields, apparently through [3+2] cycloaddition and subsequent elimination of methylthio group. However, with nitroketene dithioacetals 21 the corresponding pyrrole was not isolated, the fully saturated pyrrolidine 22 was



1 12 13

$R^1 = R^2 = -(CH_2)_4-$; 82 %

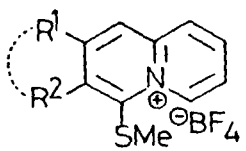
$R^1 = R^2 = -(CH_2)_5-$; 79 %



X = CH_2 ; n=1; R^1 = H, MeO, Me; 78-85 %

X = S ; n=2 ; R^1 = Me; 80 %

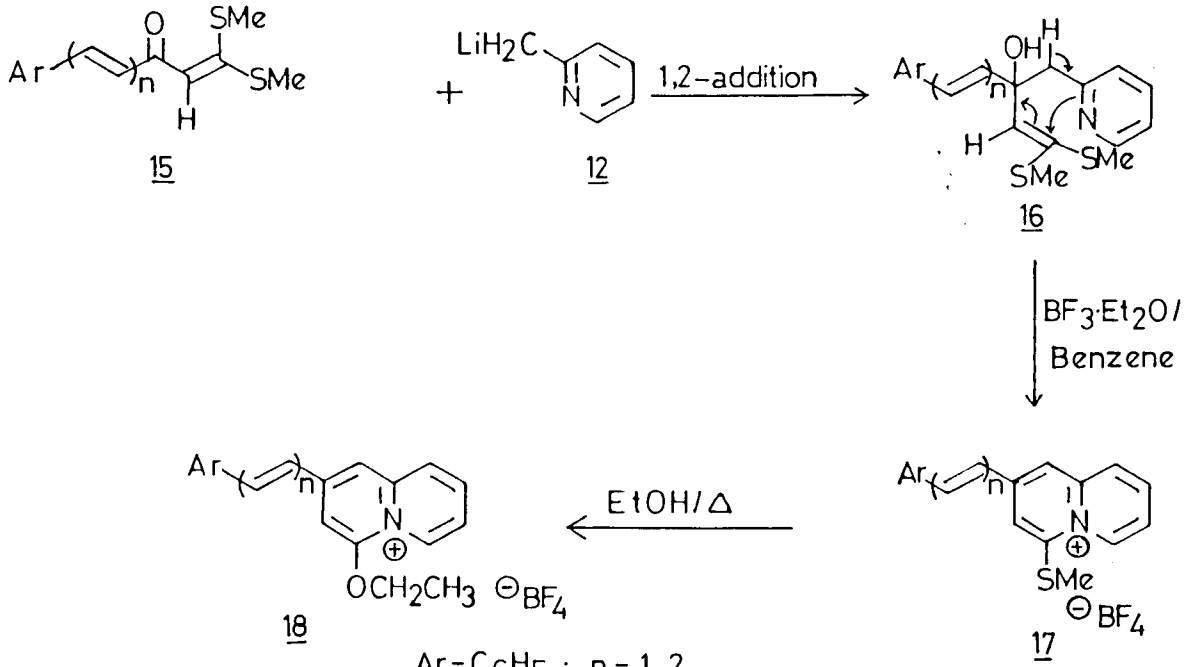
X = O ; n=2 ; R^1 = H; 81 %



14

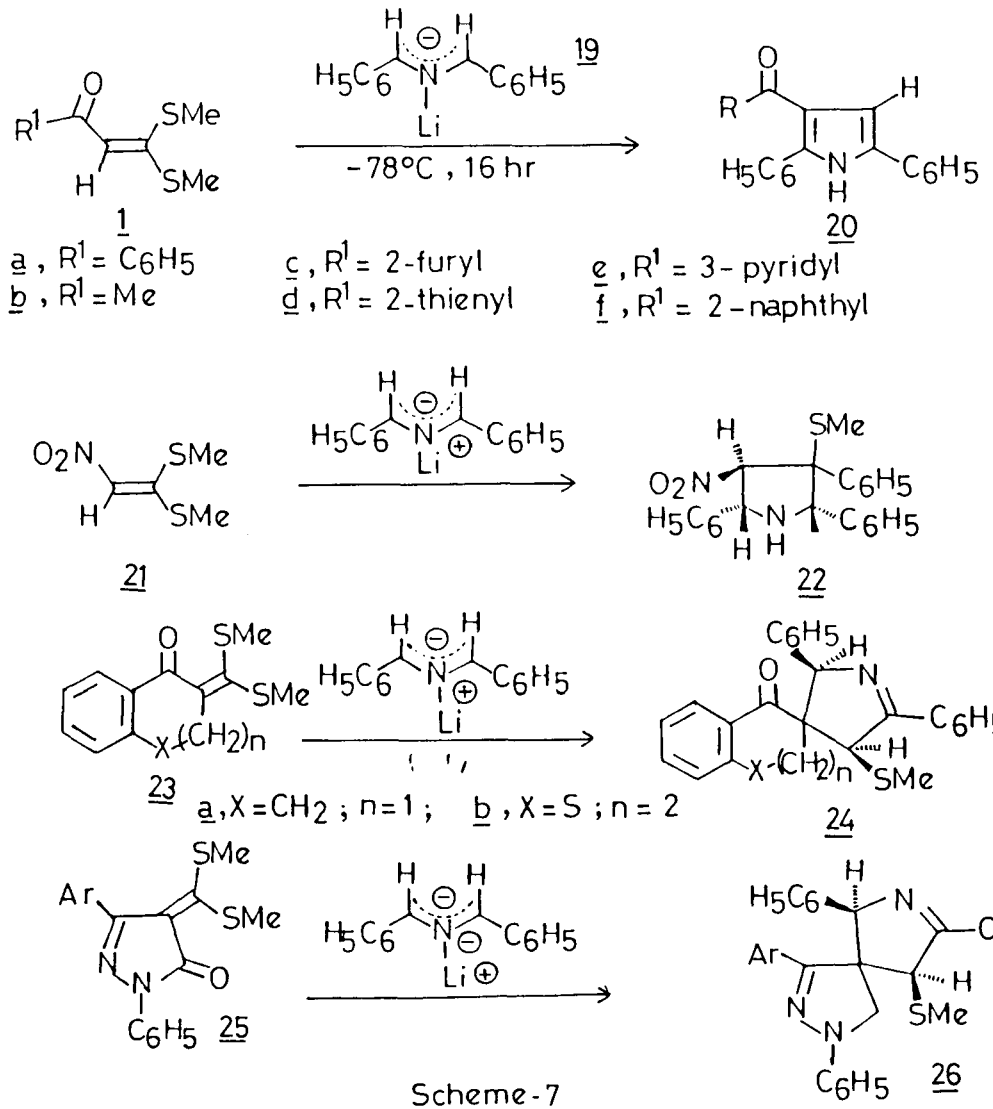
R^1 = C_6H_5 , 4-MeC_6H_4 , 4-$MeOC_6H_4$, 2-naphthyl ,
2-furyl , 2-thienyl , 2-(styryl); R^2 = H ; 73-86 %

Scheme-5



Ar = C_6H_5 ; n = 1, 2
Ar = 4-$MeOC_6H_4$; n = 1, 2
Ar = 4-ClC_6H_4 ; n = 1
Ar = 3,4-$(MeO)_2$; n = 1
Ar = 3,4 Methylenedioxy ; n = 1, 2

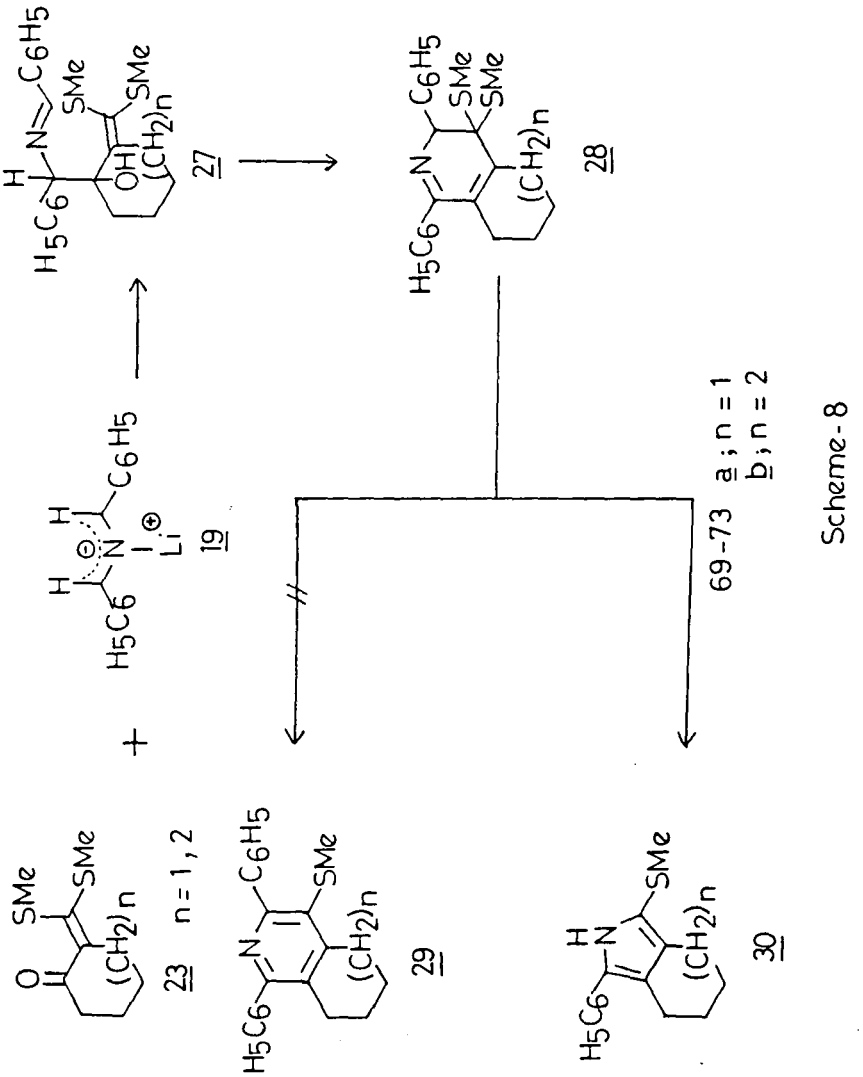
Scheme - 6


SMe
SMe
H
1
19
Li
-78°C , 16 hr
20
a , R1 = C6H5
b , R1 = Me
c , R1 = 2-furyl
d , R1 = 2-thienyl
e , R1 = 3-pyridyl
f , R1 = 2-naphthyl
21
22
23
a, X = CH2 ; n = 1 ; b , X = S ; n = 2
24
25
26

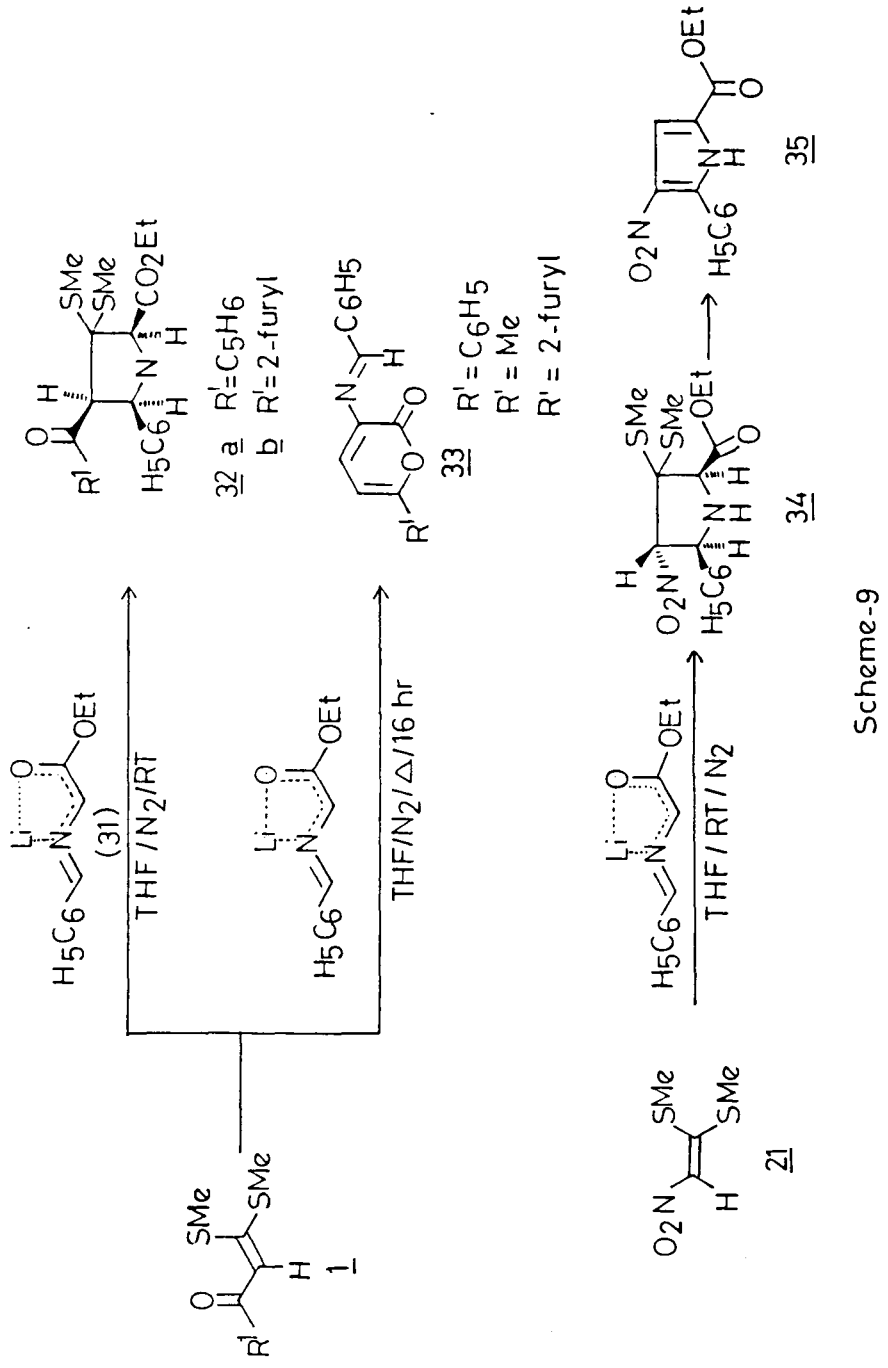
Scheme-7

the only product obtained. The spiropyrrolines 24 and 26 were obtained in good yields by the reaction of 1,3-diphenyl-2-azaallyl anion 19 with 23 and 25 (Scheme 7) respectively. However, oxoketene dithioacetals 23 derived from cyclohexanone and cycloheptanone reacted with 1,3-diphenyl-2-azaallyllithium in a 1,2-addition manner to give the fused dihydropyridines 28 which on treatment with $HgCl_2$ in THF gave the corresponding pyrroles 30 in good yields (Scheme 8). The 2-azaallyl-anion 31 derived from ethyl(benzyldeneamino)acetate by treatment with $LiBr/Et_3N$ reacted with 1 to yield the corresponding pyrrolidines 32 at room temperature, while the pyran-2-ones 33 were formed when the reaction mixture was refluxed under an efficient atmosphere of N_2. The detailed mechanistic pathways for the formation of various products and the factors governing the course of reactions are discussed in the same Chapter. Interestingly the nitroketene S,S-acetal 21 also reacted with 31 to yield the corresponding pyrrolidine 34 which underwent dethiomethylation and oxidative aromatization to yield the 4-nitropyrrole 35 (Scheme 9).

In the last Chapter the reactivity of organometallic reagents towards α-oxoketene N,S-acetals has been presented. The N,S-acetals 36, which can be considered as enaminoketones undergo exclusive 1,4-addition with Grignard reagents (1.5 eqv.) to yield the corresponding 1,3-diketones 37 (Scheme 10) and no products arising from

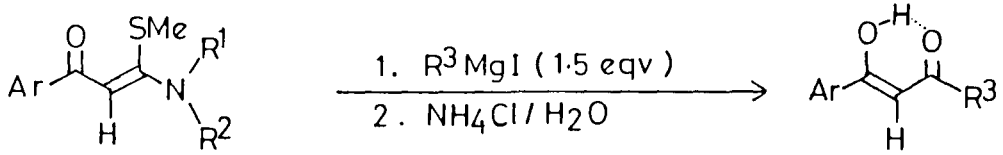


Scheme-8



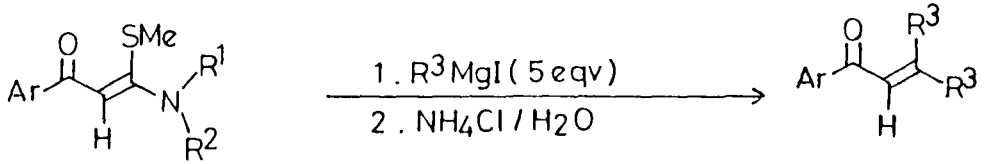
Scheme-9

1,2-addition were detected in the reaction mixture. However, when N,S-acetals 36 were reacted with excess of Grignard reagents (5 eqv.), double 1,4-addition was observed to yield the corresponding dialkylketones 38 (Scheme 10) in moderate yields. The $NaBH_4$ and $NaBH_3CN$ reductions of 36 were also investigated in the present study. Thus, N,S-acetals 36 underwent reduction with $NaBH_4$ to yield the corresponding γ-hydroxyamines 39 (Scheme 11) in good yields. Interestingly the $NaBH_3CN$ reduction of 36 yielded the corresponding β-aminoketones 40 (Scheme 11) in excellent yields arising exclusively from 1,4-addition.



36 37

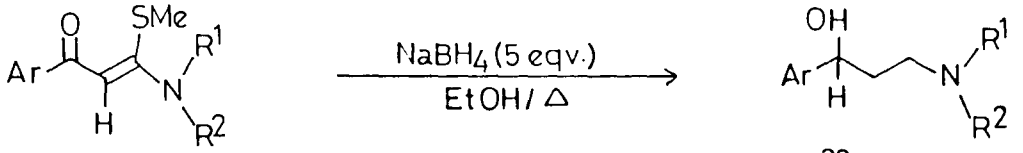
Ar = C_6H_5 , 4-$MeOC_6H_4$; $R^1 = R^2 = -(CH_2)_5-$, Me ;
R^3 = Me , Et , n-pr, C_6H_5



36 38

Ar = C_6H_5 ; 4-$MeOC_6H_4$; $R^1 = R^2 = -(CH_2)_5-$; Me
R^3 = Me , Et , n-Pr.

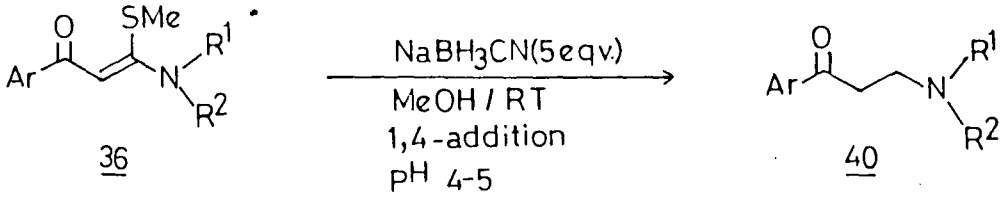
Scheme-10



36 39

Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_5$; $R^1 = C_6H_5$, $R^2 = H$

Ar = 4-$EtOC_6H_4$; $R^1 = C_6H_5$; $R^2 = H$



36 40

Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_5$; $R^1 = C_6H_5$; $R^2 = H$; R^1 = 4-ClC_6H_4 ; $R^2 = H$

Ar = 4-ClC_6H_4 ; $R^1 = C_6H_5$; $R^2 = H$

Ar = 4-$MeOC_6H_4$; $R^1 = C_6H_5$; $R^2 = H$

Scheme-11

REFERENCES

1. Kelber,C. *Chem.Ber.* 1910, *43*, 1252.
2. Thuillier,A.; Vialle,J. *Bull.Soc.Chim.Fr.*, 1962, 2182.
3. Chauhan,S.M.S; Junjappa,H. *Tetrahedron*, 1976, *32*, 1779.
4. Dieter,R.K. *J.Org.Chem.*, 1981, *46*, 5031.
5. Dieter,R.K. *Tetrahedron*, 1986, *42*, 3029.
6. Myrboh,B.; Ila,H.; Junjappa,H. *J.Org.Chem.* 1983, *48*, 5327.
7. Singh,G.; Purkayastha,M.L.; Ila,H.; Junjappa,H. *J. Chem.Soc.Perkin.Trans.I*, 1985, 1289.
8. Dieter,R.K.; Silks,L.A.; Fishpaugh,J.R.; Kstuer,M.E. *J.Am.Chem.Soc.* 1985, *107*, 4679.
9. Balu,M.P.; Singh,G.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1986, *27*, 117.
10. Balu,M.P.; Ila,H.; Junjappa,H. Unpublished results.
11. Balu,M.P.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1987, *28*, 3023.
12. Balu,M.P.; Ila,H.; Junjappa,H. Unpublished resutls.

SYNTHETIC INVESTIGATIONS ON POLARIZED KETENE DITHIOACETALS: NOVEL METHODS FOR THE SYNTHESIS OF CARBOCYCLES AND HETEROCYCLES

By

BALU M. P.

DEPARTMENT OF CHEMISTRY

SCHOOL OF PHYSICAL SCIENCES

A THESIS

SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR

THE DEGREE OF

DOCTOR OF PHILOSOPHY

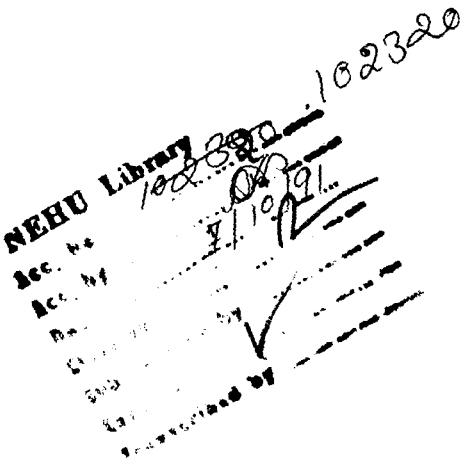
To

NORTH-EASTERN HILL UNIVERSITY

SHILLONG - 793001

INDIA

1989



Phone :
Grams : NEHU

North-Eastern Hill University

Bijni Complex
Bhagyakul. Shillong - 793003 (Meghalaya)

Professor H.Junjappa, FNA
Department of Chemistry

This is to certify that the work described in this thesis has been carried out by Mr. M.P. Balu under my supervision. He has satisfactorily completed the pre-Ph.D. courses prescribed and the minimum period of two years of investigational work for the award of Ph.D. degree in Chemistry.

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

H.JUNJAPPA
Supervisor

Phone :
Grams : NEHU

North-Eastern Hill University

Bijni Complex
Bhagyakul, Shillong - 793003 (Meghalaya)

Head
Department of Chemistry

This is to certify that Mr. M.P. Balu a Ph.D. student of the Department of Chemistry has satisfactorily completed the following courses as a part of his Ph.D programme.

Title	Course No.
1. Organomettalic Chemistry	Chem - 620
2. Biosynthesis & Natural Product Chemistry	Chem - 630
3. Medicinal Chemistry	Chem - 631
4. French Language	Chem - 601

H. Ila
Professor & Head

Head
Department of Chemistry
North-Eastern Hill University
Shillong — 793 003.

ACKNOWLEDGMENTS

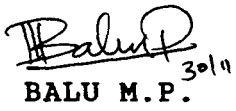
The research work described in this thesis was carried out in the Department of Chemistry, North-Eastern Hill University, Shillong under the supervision of Prof. H. Junjappa, Department of Chemistry. I would like to express my deep sense of gratitude for his excellent guidance and constant encouragement throughout the course of this investigation. I am also grateful to Prof. (Mrs) H.Ila, Head, Department of Chemistry for her invaluable advice and encouragement.

A large debt of gratitude is owed to my colleagues and friends with whom I have been associated throughout these years. I have taken the generosity of too many of them and to list them individually is impossible. I humbly say `THANK YOU'.

For providing excellent analytical and spectral facilities I thank the Directors and Technical Staffs of RSIC North-Eastern Hill University and Central Drug Research Institute, Lucknow. Quite a few spectral and analytical data were obtained from Dr. S. Apparao, Department of Chemistry and Biochemistry, Utah State University, USA and Dr. Gurdeep Singh, Institut Fur Organische Chemie, Universitat, Hamburg, West Germany, I express my sincere gratitude to them.

Special recognition and gratitude are due to Mr. Vijayan and Sivaprakashan C.V for the help extended by them in processing this thesis.

Finally, I would like to thank my parents and all my family members, they not only endured, also encouraged, assisted and inspired.



BALU M.P.

C O N T E N T S

P R E F A C E

Polarized ketene dithioacetals, which can be easily prepared from a wide 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 work described in this thesis has been carried out as a part of this ongoing research programme and highlights new transformations of oxoketene dithioacetals.

The first chapter gives an account of some of the recent transformations of oxoketene dithioacetals reported from this laboratory. The second chapter deals with a new general method for aromatic annelation by the reaction of α-oxoketene dithioacetals with benzyl-, 1-naphthylmethyl- and 2-naphthylmethylmagnesium halides, followed by cycloaromatization of the resulting carbinolacetal. In the third chapter of the thesis, synthesis of substituted and fused quinolizinium compounds via cycloaromatization of α-oxoketene dithioacetals with 2-picolyllithium has been described. 1,3-Anionic cycloadditions of 1,3-diphenyl-2-azaallyl and ethyl (benzylideneamino)acetate anions with α-oxoketene dithioacetals have been described in chapter IV. The last chapter of the thesis deals with studies on the additions of Grignard reagents and metal hydrides to oxoketene N,S-acetals.

CHAPTER I

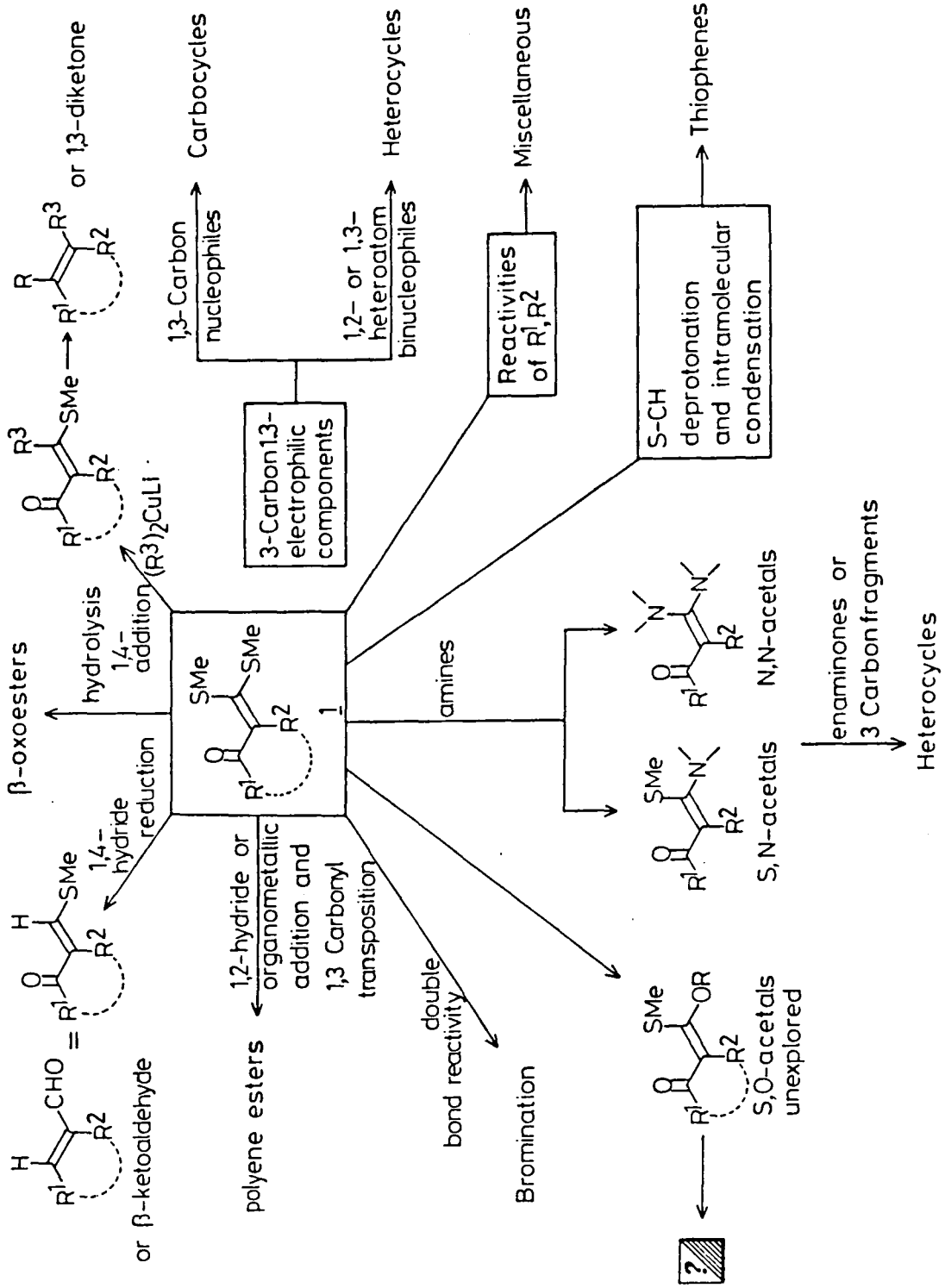
POLARIZED KETENE DITHIOACETALS: GENERAL INTRODUCTION.

The versatile synthon family of polarized ketene dithioacetals have been recognized as useful building blocks in various synthetic transformations.[1] This class of compounds can be easily prepared from a wide variety of active methylene compounds and carbon disulfide in the presence of a suitable base followed by alkylation often in one pot reaction in moderate to good yields.[2-9] The oxoketene dithioacetals exhibit well defined physical properties either as crystalline solids or as distillable liquids and can be purified by conventional methods. Kelber and co-workers reported the first synthesis of α-oxoketene dithioacetals in 1910.[10-11] After the initial synthesis, for more than half a century the synthetic potential of these class of compounds remained

unexplored. Later Thuillier and co-workers in 1962 synthesised oxoketene dithioacetals in higher yields using sodium amylate as base and this family of compounds emerged as very useful synthetic intermediates over the last two decades.[1]

The oxoketene dithioacetals which can be prepared by easier methods in one pot reaction in high yields exhibit greater stability than the corresponding O,O-acetals.[12] They can be further converted to the corresponding ketene dihalogenides,[13-14] N,S-[15] and N,N-[16] acetals making them more important as precursors for a large variety of functionalized acetals. The oxoketene dithioacetals have been shown to be excellent three carbon fragments, with 1,3-carbons possessing differential electrophilic properties, which is an important prerequisite in designing methodologies for both carbocyclic and heterocyclic synthesis. They also possess considerable synthetic potential for the regioselective construction of new bonds via 1,2-nucleophilic additions to ketone carbonyl or 1,4-conjugate addition reactions to the β-carbon of the enone system. The intermediate allylic alcohols and enones can,in turn, be exploited in additional bond forming reactions.

The general reactivity pattern of α-oxoketene dithioacetals 1 is outlined in the Scheme 1. Hydrides and organometallic reagents add to the carbonyl carbon in a 1,2-manner but this sequence can be altered to the 1,4-


β-oxoesters
hydrolysis
1,4-addition
(R3)2CuLi
or 1,3-diketone
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
3-Carbon1,3-electrophilic components
Reactivities of R1,R2
Miscellaneous
S-CH deprotonation and intramolecular condensation
Thiophenes
1,4-hydride reduction
or β-ketoaldehyde
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
polyene esters
double bond reactivity
Bromination
amines
N,N-acetals
S,N-acetals
enaminones or 3 Carbon fragments
Heterocycles
S,O-acetals unexplored
?

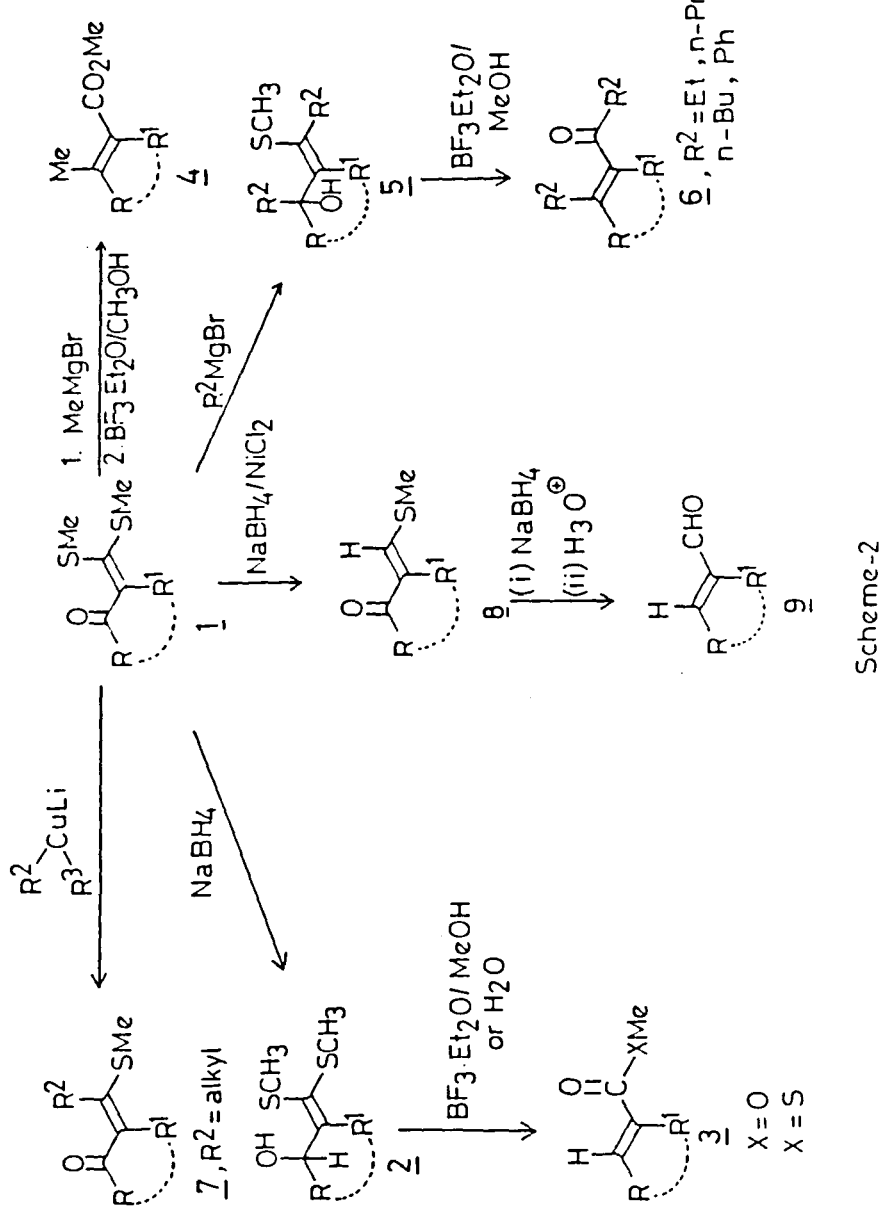
Scheme-1

path by suitably changing the reaction conditions and reagents.[17-19] Further transformations of these 1,2 or 1,4-addition products have also been investigated extensively.[17] The differential electrophilicity at 1,3-carbon of the oxoketene dithioacetals have been judiciously utilized for the synthesis of both 5- and 6-membered heterocycles by reacting with 1,2- and 1,3-heteroatom binucleophiles respectively. The 1,3-carbon binucleophiles have been similarly used in the synthesis of carbocycles. The enolate anion formed by the deprotonation (When R'=alkyl) can undergo condensation with aldehydes to give α-enoyl ketene dithioacetals.[6,20] When R^2 is a methyl group an allylic anion is generated in the presence of strong bases leading to rearranged products[21]. Deprotonation of the thiomethyl group followed by intramolecular Aldol type condensation to afford thiophenes is also reported.[22,23] These oxoketene dithioacetals can be easily converted to the corresponding O,S-, N,S- and N,N-acetals. The reactivity of the double bond has also been studied with electrophiles. Thus the bromination at α-position with N-bromosuccinimide has been carried out successfully.[24] In the following section some of the selected transformations reported from this laboratory are briefly summarized.

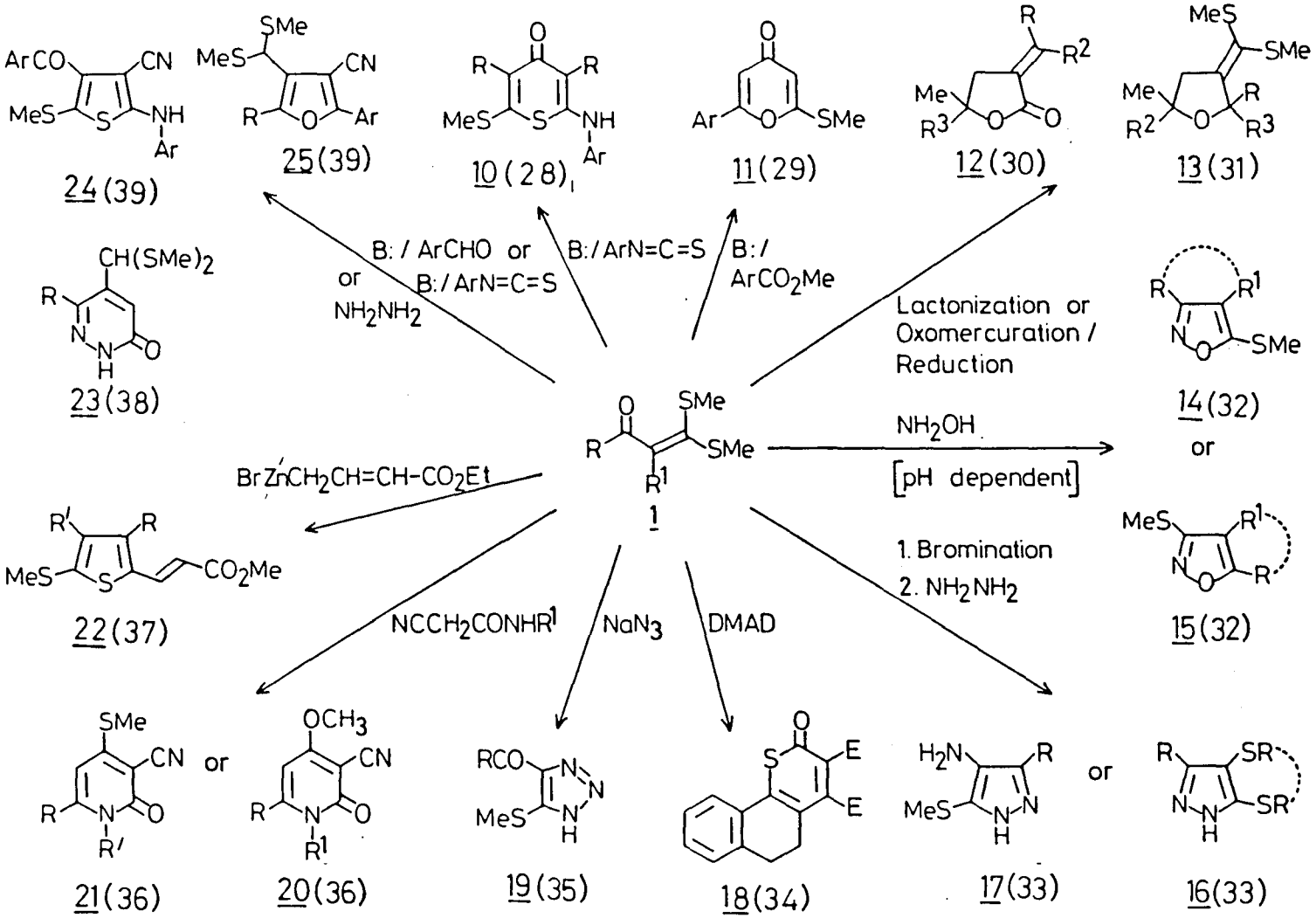
The oxoketene dithioacetals have been reported to undergo chemoselective 1,2-reduction with $NaBH_4$ to give the

corresponding carbinol acetals, 2,[25,26] which were shown to undergo smooth methanolysis in the presence of borontrifluoride etherate to afford α,β-unsaturated methyl esters 3a in high yields (Scheme 2). The overall transformation is considered as homologation of active methylene ketons involving a 1,3-carbonyl transposition. The Grignard and organolithium reagents undergo either regioselective 1,2-addition to afford the α-hydroxyketene dithioacetals or a sequential 1,4- and 1,2-addition to afford the α-hydroxyvinylsulfides.[17-19] The borontrifluoride etherate catalysed solvolysis or the hydrolysis of these carbinols yield either β-substituted α,β-unsaturated esters 4 or the corresponding ketones 6 (Scheme 2) in good yields. Dieter and co-wokers have reported the chemo and stereoselective addition of organocuprates to dithioacetals 1.[18,19] Thus organocuprates are shown to undergo conjugate addition to give β-alkylthio- β-substituted α,β-unsaturated ketones 7. The oxoketene dithioacetals were also shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthioalkenylketones 8 which are further transformed to the corresponding α,β-unsaturated aldehydes 9[27] (Scheme 2).

Numerous substituted and fused five and six membered heterocyclics have been synthesised using oxoketene dithioacetals.[28-29] Some of the selected transformations are shown in Scheme 3. Some of the important transformations developed based on α-cinnamoyl and 5-aryl-2,4-



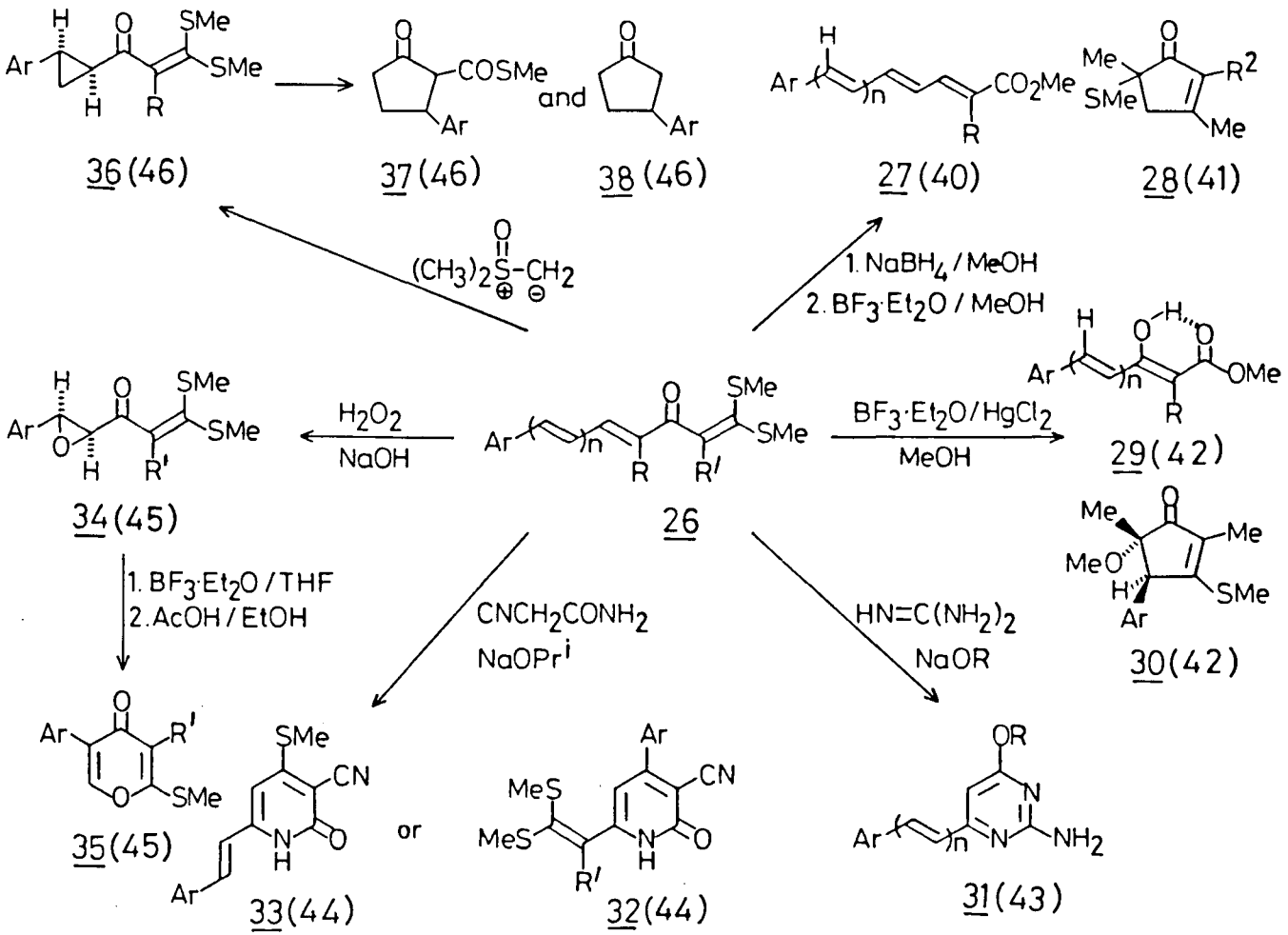
Scheme-2


24 (39)
25 (39)
10 (28)
11 (29)
12 (30)
13 (31)
23 (38)
B: / ArCHO or
or B:/ ArN=C=S
NH2NH2
B:/ ArN=C=S
B:/ ArCO2Me
Lactonization or
Oxomercuration /
Reduction
14 (32)
or
NH2OH
[pH dependent]
1
BrZnCH2CH=CH-CO2Et
22 (37)
1. Bromination
2. NH2NH2
15 (32)
NCCH2CONHR1
NaN3
DMAD
21 (36)
20 (36)
19 (35)
18 (34)
17 (33)
or
16 (33)

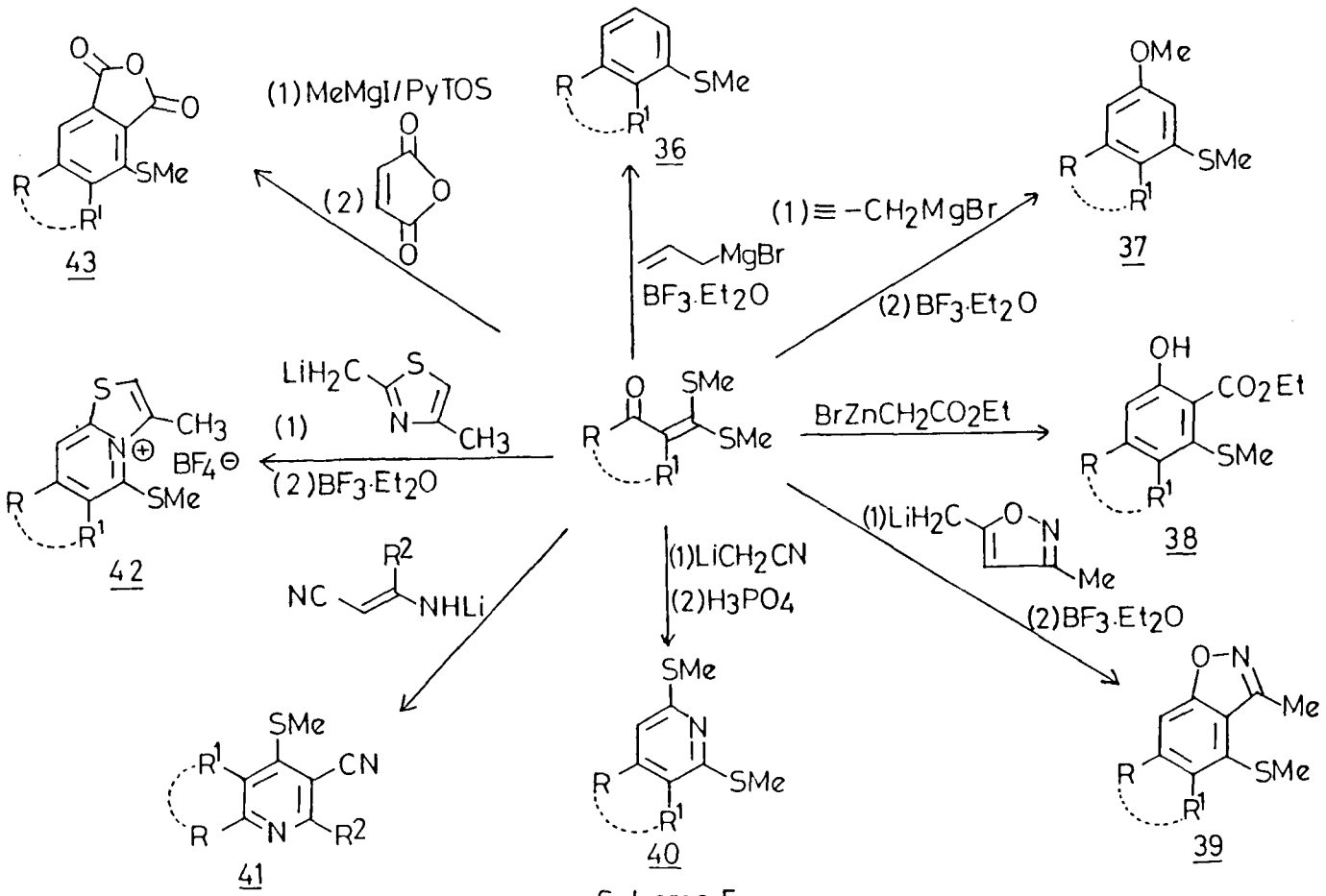
Scheme-3

pentadienoylketene dithioacetals are outlined in Scheme 4. A general method for the synthesis of polyene esters 27[40] has been reported by 1,2-reduction of 26 followed by methanolysis in the presence of borontrifluoride etherate. In Hg(II) assisted hydrolysis the corresponding α,β-unsaturated -β-keto esters 29 are formed,[42] while in the case of 2,4-disubstituted systems (R=R'=CH_3) the corresponding cyclopentenones 28 and 30 are obtained under similar reaction conditions.[41,42] Synthesis of styrylpyrimidines 31, pyridones 32 and 33 were also achieved using these intermediates.[43,44] The cinnamoyl ketene dithioacetals 26 have been reported to undergo regioselective cyclopropanation and epoxidation at the styryl double bond.[45,46] These intermediates 34 and 36 were further exploited for the synthesis of pyrones 35 and cyclopentanones 37 and 38 respectively[45,46] (Scheme 4).

Aromatic annelation via α-oxoketene dithioacetals, developed from this laboratory has emerged as an area of great synthetic potential. Some of the important synthetic outcome of this aromatic annelation methodology is depicted in Scheme 5. The reaction of allylmagnesium bromide with α-oxoketene dithioacetals has been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetals in high yields, which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives 6.[47] The approach is extended for the synthesis of other benzenoids 37[48] and 38[49]. The


36(46)
37(46)
and
38(46)
27(40)
28(41)
(CH3)2S-CH2
1. NaBH4 / MeOH
2. BF3·Et2O / MeOH
H2O2
NaOH
BF3·Et2O/HgCl2
MeOH
29(42)
34(45)
26
1. BF3·Et2O / THF
2. AcOH / EtOH
CNCH2CONH2
NaOPri
HN=C(NH2)2
NaOR
30(42)
35(45)
or
33(44)
32(44)
31(43)

Scheme-4

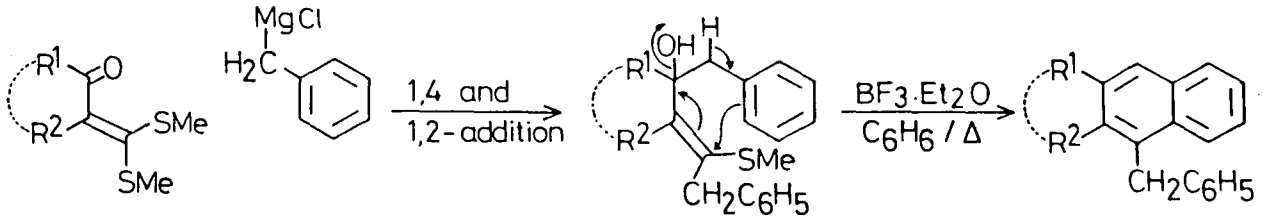

(1) MeMgI / PyTOS
(2)
BF3·Et2O
(1) ≡ –CH2MgBr
(2) BF3·Et2O
BrZnCH2CO2Et
(1) LiH2C
(2) BF3·Et2O
(1) LiCH2CN
(2) H3PO4
NC
NHLi
SMe
OMe
OH
CO2Et
CN
Me
R
R1
R2
36
37
38
39
40
41
42
43

Scheme-5

method is further shown to be extremely versatile and found general application for the synthesis of 1,2-benzisoxazoles 39,[50] pyridines 40[51] and 41,[52] thiazolopyridinium salts 42 [53]. The Diels-Alder cycloadditions of vinylketene dithioacetals derived from the corresponding oxoketene dithioacetals 1 with maleic anhydride afforded the phthalic anhydrides 43 in good yields.[54]

The α-oxoketene dithioacetals with a wide ranging functional group variation and many easily accessible reagents and reactive intermediates manifestly hold many new synthetic possibilities leading to diverse product range, including both carbocyclic and heterocyclic systems.

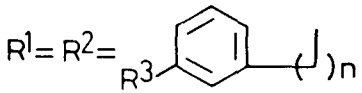
In continuation of these studies, further investigations of some selected reactions with α-oxoketene dithioacetals have been carried out as a part of the present programme. In the second chapter, the reaction of benzylmagnesium chloride with α-oxoketene dithioacetals 1 leading to condensed aromatic systems has been presented.[55] Thus, the carbinol acetal 45 obtained by the reaction of benzylmagnesium chloride with oxoketene dithioacetal 1 indicated that the addition took place in a 1,4- followed by 1,2-sequence and underwent $BF_3.Et_2O$ assisted aromatic annelation to yield the corresponding naphthalenes 46 in excellent yields (Scheme 6). The generality of the method have been studied in greater details by using



1 44 45 46

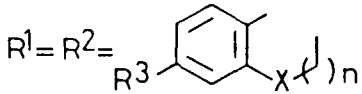
$R^1 = C_6H_5$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-naphthyl ; $R^2 = H$; 58–65 %

$R^1 = R^2 = -(CH_2)_4-$; 81 %



n=1 ; 62 %

n=2 ; 71 %



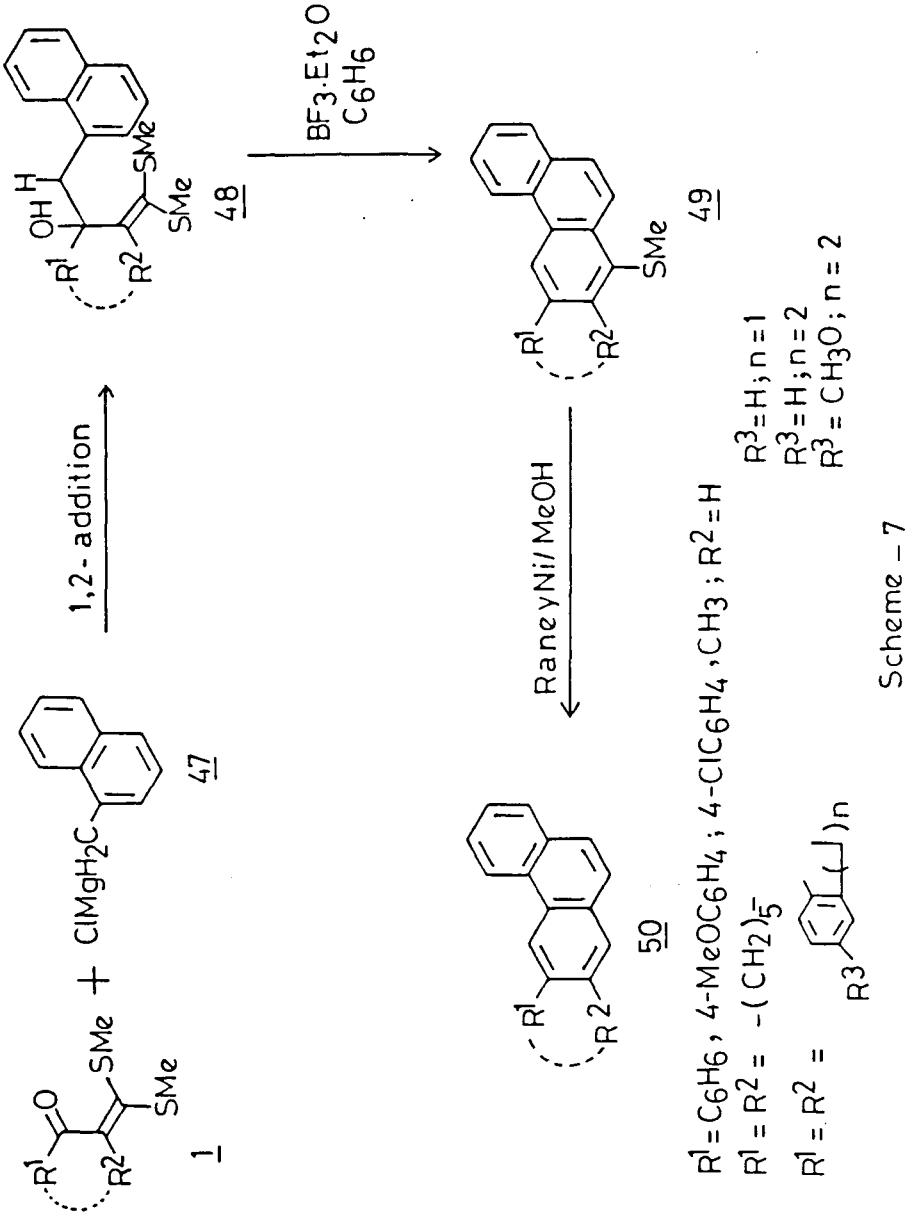
R^3= H ; X = S ; n = 1 ; 58 %

R^3= Me X = S ; n = 2 ; 68 %

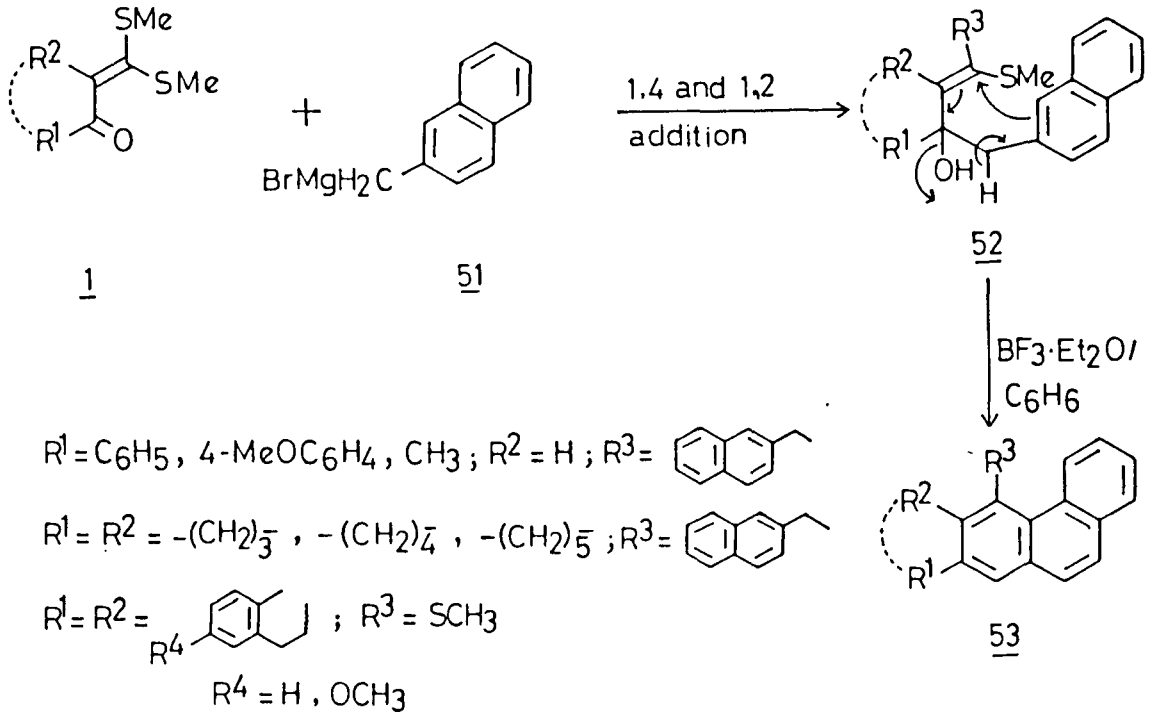
R^3= H ; X = O ; n = 2 ; 67 %

Scheme–6

wide structural variants of 1. The merits and demerits of the method are included in the discussion. Interestingly when these reactions were extended to 1-naphthylmethylmagnesium chloride 47, the addition with oxoketene dithioacetal 1 took place exclusively in 1,2-fashion to yield the corresponding carbinolacetals 48 in high yields. These carbinolacetals could be smoothly cyclised in the presence of $BF_3.Et_2O$ to the corresponding phenanthrenes 49 in good yields. Some of the phenanthrenes 50 which were known in the literature were prepared by subjecting 49 to *Raney-Ni* desulphurisation. It is pertinent to note that the present phenathrene synthesis is applicable to wide structural variants of 1 (Scheme 7) as well as constitutes perhaps the best synthetic approach to various substituted and fused phenathrenes.[56] Similarly when 2-naphthylmethylmagnesium bromide was reacted with 1, the 1,4- followed by 1,2-addition carbinolacetals 52 were formed in good yields and they afforded the corresponding phenathrenes 53 under similar reaction conditions as described earlier. While studying the generality of this phenathrene synthesis it was observed that only oxoketene dithioacetals derived from tetralones underwent exclusive 1,2-addition with 2-naphthylmethylmagnesium bromide. It appears that both steric and electronic factors play an important role in the different reactivity patterns of benzyl, 1-naphthylmethyl and 2-naphthylmethylmagnesium halides with α-oxoketene dithioacetals.


1,2-addition
BF3.Et2O/
C6H6
RaneyNi/MeOH
1
47
48
49
50
R1=C6H6, 4-MeOC6H4 ; 4-ClC6H4 ,CH3 ; R2=H
R1 = R2 = -(CH2)5-
R1 = R2 =
R3=H; n=1
R3=H; n=2
R3 = CH3O; n=2

Scheme – 7



1 51 52 53

Scheme - 8

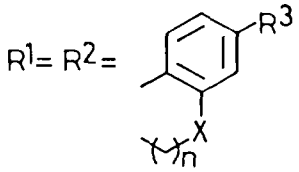
In chapter 3, the reaction of various α-oxoketne dithioacetals with 2-picolyllithium has been described. The α-oxoketene dithioacetals 1 react with 54 in an exclusive 1,2- manner to yield the corresponding carbinol acetals 55 which on $BF_3.Et_2O$ assisted cyclization afforded the corresponding quinolizinium tetrafluoroborates 56 in high yields. The generality of this method has been studied by using wide structural variants of 1 (Scheme 9). Also when α-enoyl ketene dithioacetals 57 (Scheme 10) reacted with 2-picolyllithium to give the corresponding quinolizinium tetrafluoroborates 59 in high yields. The methylthio group in few of these salts 59 could be easily displaced by the corresponding ethoxy group in refluxing ethanol.

1,3-Anionic cycloaddition of 1,3-diphenyl-2-azaallyl and ethyl(benzylideneamino)acetate anions 61 and 73 with α-oxoketene dithioacetals have been described in the Chapter IV. Thus, when 1,3-diphenyl-2-azaallyllithium 61 reacted with oxoketene dithioacetals 1, the corresponding pyrroles 62 (Scheme 11) were formed in good yields, apparently through [3+2] cycloaddition and subsequent elimination of methylthio group. However with nitroketene dithioacetal 63 the corresponding pyrrole was not isolated, the fully saturated pyrrolidine 64 was the only product obtained. The spiropyrrolines 66 and 68 were obtained in good yields by the reaction of 1,3-diphenyl-2-azaallyl anion 61 with 65 and 67 (Scheme 11)

1 54 55

$R^1 = R^2 = -(CH_2)_4-$; 82 %

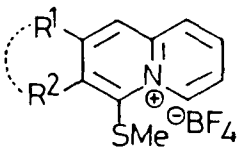
$R^1 = R^2 = -(CH_2)_5-$; 79 %



X = CH_2 ; n=1; R^1 = H, MeO, Me; 78-85 %

X = S ; n=2 ; R^1 = Me; 80 %

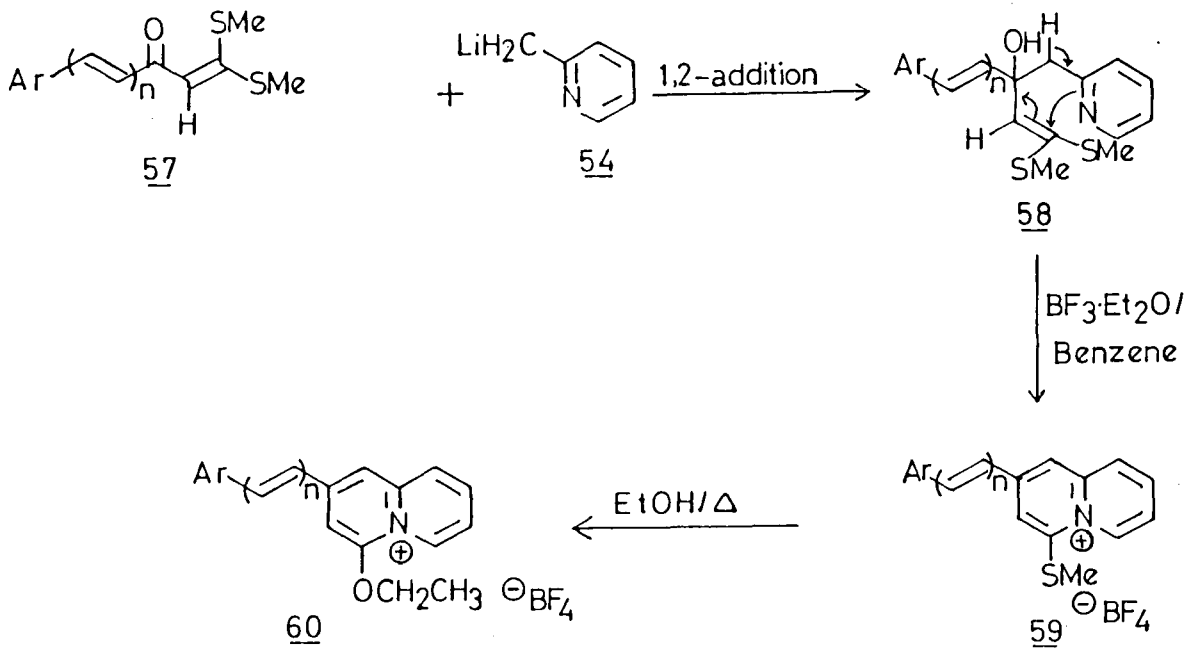
X = O ; n=2 ; R^1 = H; 81 %



56

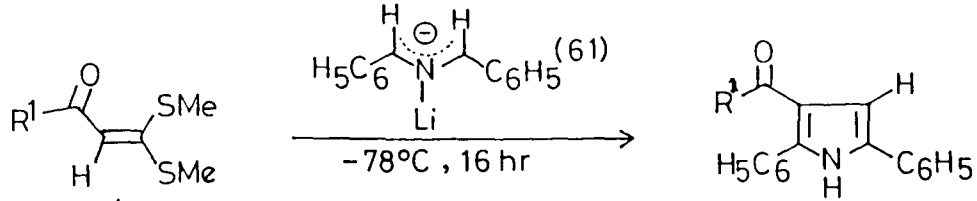
$R^1 = C_6H_5$, 4-MeC_6H_4 , 4-$MeOC_6H_4$, 2-naphthyl ,
2-furyl , 2-thienyl , 2-(styryl); R^2 = H ; 73-86 %

Scheme- 9



Ar = C_6H_5 ; n = 1, 2
Ar = 4-$MeOC_6H_4$; n = 1, 2
Ar = 4-ClC_6H_4 ; n = 1
Ar = 3,4-$(MeO)_2$; n = 1
Ar = 3,4 Methylenedioxy ; n = 1, 2

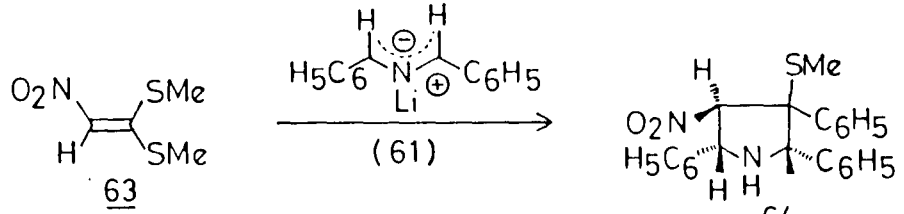
Scheme-10



1

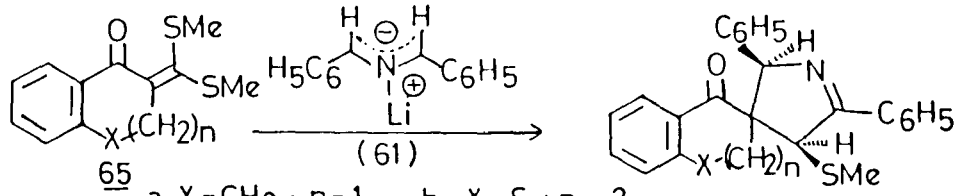
62

a , R^1 = C_6H_5 c , R^1 = 2-furyl e , R^1 = 3-pyridyl
b , R^1 = Me d , R^1 = 2-thienyl f , R^1 = 2-naphthyl



63

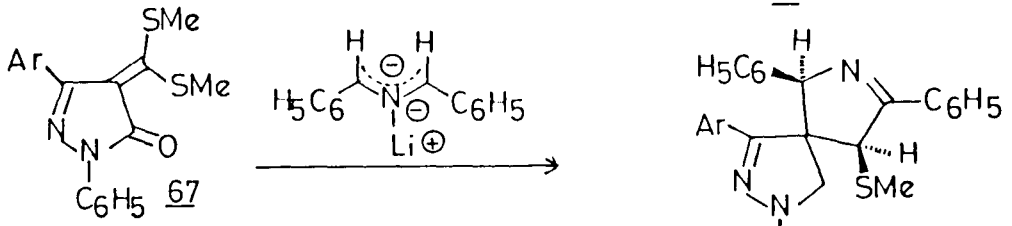
64



65

a, X = CH_2 ; n = 1 ; b , X = S ; n = 2

66



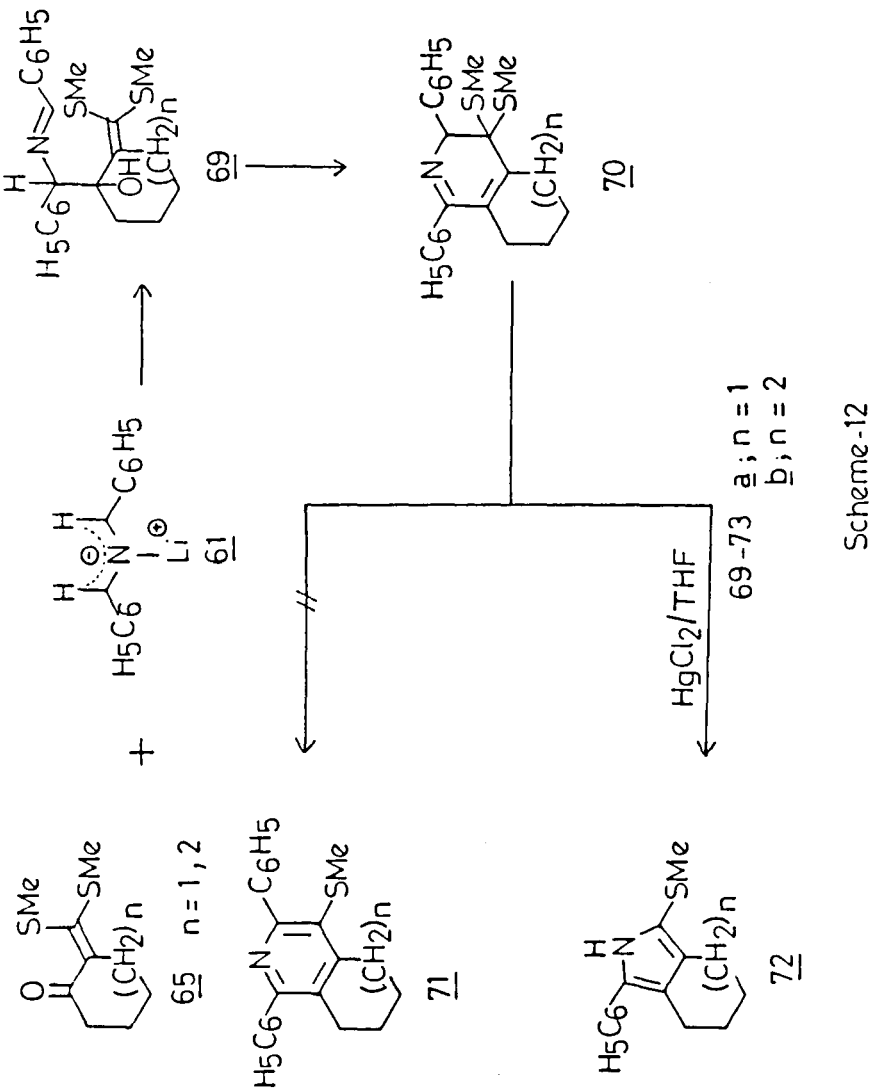
67

68

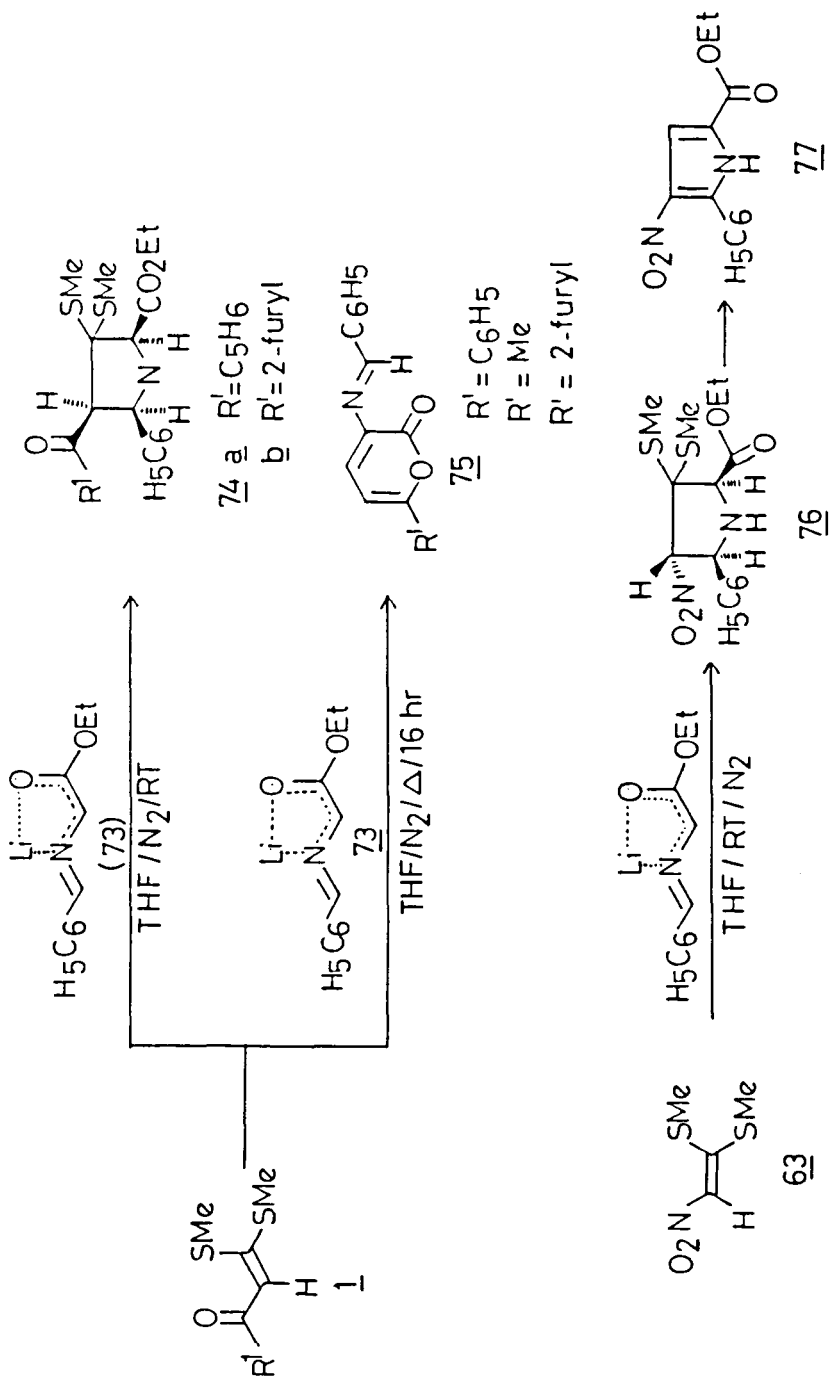
Scheme-11

respectively. However, oxoketene dithioacetals 65 derived from cyclohexanone and cycloheptanone reacted with 1,3-diphenyl-2-azaallyllithium 61 in a 1,2-addition manner to give the fused dihydro pyridines 70 which on treatment with $HgCl_2$ in THF gave the corresponding pyrroles 72 in good yields (Scheme 12). The 2-azaallyl-anion 73 derived from ethyl(benzylideneamino)acetate by treatment with $LiBr/Et_3N$ reacted with 1 to yield corresponding pyrrolidines 74 at room temperature, while the pyran-2-ones 75 were formed when the reaction mixture was refluxed under an efficient atmosphere of N_2. The detailed mechanistic pathways for the formation of various products and the factors governing the course of reaction are discussed in the same chapter. Interestingly the nitroketene S,S-acetal 63 also reacted with 73 to yield the corresponding pyrrolidine 76 which underwent dethiomethylation and oxidative aromatization to yield the 4-nitropyrrole 77 (Scheme 13).

In the last chapter the reactivity of organometallic reagents towards α-oxoketene N,S-acetals has been presented. The N,S-acetals 78, which can be considered as enaminoketones undergo exclusive 1,4-addition with Grignard reagents (1.5 eqv.) to yield the corresponding 1,3-diketones 79 (Scheme 14) and no products arising from 1,2-addition were detected in the reaction mixture. However, when N,S-acetals 78 were reacted with excess of Grignard reagents (5 eqv.), double 1,4-addition was

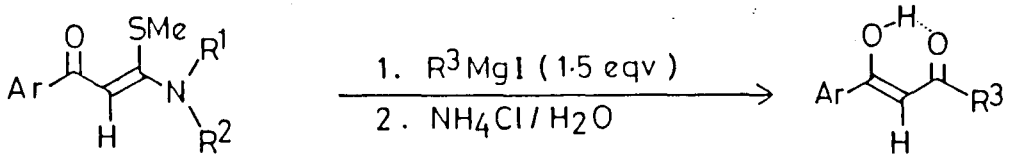


Scheme-12



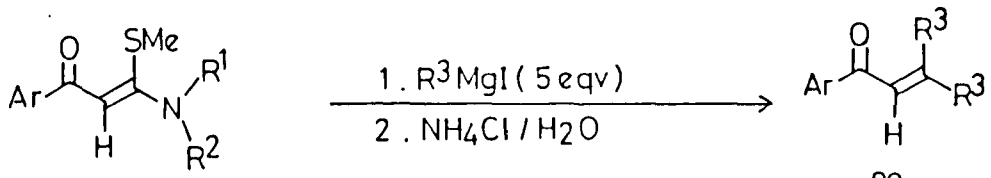
Scheme-13

observed to yield the corresponding dialkylketones 80 (Scheme 14) in moderate yields. The $NaBH_4$ and $NaBH_3CN$ reductions of 78 were also investigated in the present study. Thus, N,S-acetals 78 underwent reduction with $NaBH_4$ to yield the corresponding γ-hydroxyamines 81 (Scheme 15) in good yields. Interestingly the $NaBH_3CN$ reduction of 78 yielded the corresponding β-aminoketones 82 (Scheme 15) in excellent yields arising exclusively from 1,4-addition.



78 79

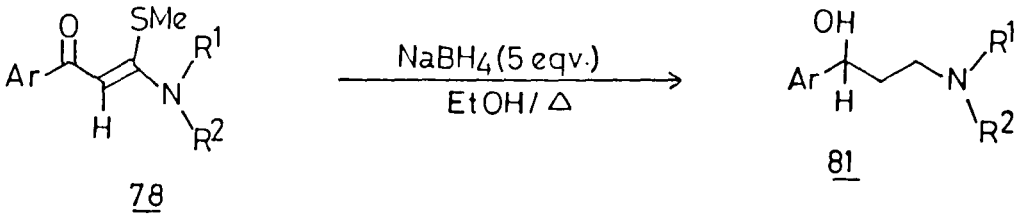
Ar = C_6H_5 , 4-$MeOC_6H_4$; $R^1 = R^2 = -(CH_2)_5-$, Me ;
R^3 = Me , Et , n-pr, C_6H_5



78 80

Ar = C_6H_5 ; 4-$MeOC_6H_4$; $R^1 = R^2 = -(CH_2)_5-$; Me
R^3 = Me , Et , n-Pr.

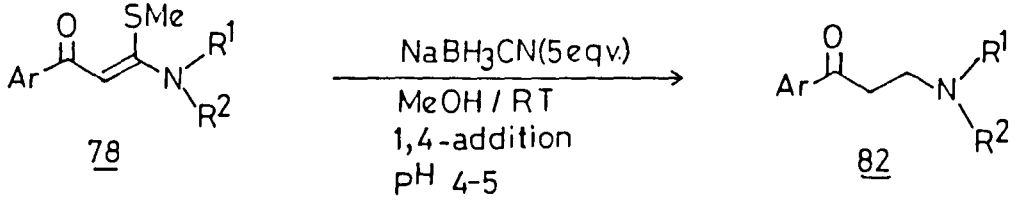
Scheme-14



78 81

Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_5$; $R^1 = C_6H_5$, $R^2 = H$

Ar = 4-$EtOC_6H_4$; $R^1 = C_6H_5$; $R^2 = H$



78 82

Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_5$; $R^1 = C_6H_5$; $R^2 = H$; R^1 = 4-ClC_6H_4 ; $R^2 = H$

Ar = 4-ClC_6H_4 ; $R^1 = C_6H_5$; $R^2 = H$

Ar = 4-$MeOC_6H_4$; $R^1 = C_6H_5$; $R^2 = H$

Scheme-15

REFERENCES

1. For a review see Dieter,R.K. *Tetrahedron,*, 1986,*42*, 3029.
2. Thuillier,A; Vialle,J.; *Bull.Soc.Chim.Fr.* 1959, 1398.
3. Chauhan,S.M.S.; Junjappa,H. *Tetrahedron,* 1976, *32*, 1779.
4. Saquet,M.; Thuillier,A. *Bull.Soc.Chim.Fr.* 1966, 1582.
5. Gompper,R.; Schmidt,R.R.; Kutter,E. *Leibigs Ann. Chem.* 1965, *37*, 684.
6. Thuillier,A.; Vialle,J. *Bull.Soc. Chim.Fr.* 1962, 2194.
7. Corey,E.J.; Chen,R.H.K. *Tetrahedron Lett.* 1973, 3817.
8. Shahak,I.; Sarson,Y. *Tetrahedron Lett.* 1973, 4207.
9. Dieter,R.K. *J.Org.Chem.* 1981, *46*,5031.
10. Kelber,C. *Chem.Ber.* 1910, *43*, 1252.
11. Kelber,C.; Schwarz,A. *Chem.Ber.* 1912 *44*, 137.
12. McElvain,S.M. *Chem.Rev.* 1949, *45*, 453.
13. Borman,D. in*Houben-Weyl, Methoden Der Organischen Chemie B.VII/4 pp.442,* Georg Themie Verlag Stuttgart 1968.
14. Pohland,A.E.; Benson,W.R. *Chem.Rev.* 1966, *66*, 161.
15. Gompper,R.; Shaefer, *Chem.Ber.* 1967, *100*, 591.
16. Ref. 13, pp. 391.
17. Singh,G.; Purkayastha,M.L.; Ila,H.; Junjappa,H. *J.Chem.Soc.Perkin Trans.I.* 1985, 1289.

18. Dieter,R.K.; Silks,L.A.; Fishpaugh,J.R.,Kastner,M.E. *J.Amer.Chem.Soc.* 1985, *107*, 4679.

19. Dieter,R.K.; Fishpaugh,J.R.; Silks, L.A.*Tetrahedron Lett.* 1982 *23*, 3751.

20. Myrboh,B.; Asokan,C.V.; Ila,H.; Junjappa,H.*Synthesis* 1984, 50.

21. Apparao,S.;Rahman,A.;Ila,H.;Junjappa,H.*Tetrahedron Lett.* 1982, *23* 971.

22. Marino,J.P.; Kostuysk,J.L. *Tetrahedron Lett.* 1979, *20*, 2489.

23. Marino,J.P.; Kostusyk,J.L. *Tetrahedron Lett.* 1979, *20*, 2493.

24. Singh,G.; Ila,H.; Junjappa,H. *Synthesis*, 1985, 165.

25. Saquet,M; Thuillier,A. *Bull.Soc.Chim. Fr.* 1966, 3969.

26. Myrboh,B.; Ila,H.; Junjappa, H. *J.Org.Chem.* 1983, *48* 5327.

27. Myrboh,B.; Singh,L.W.; Ila,H.; Junjappa,H. *Synthesis* 1982, 307.

28. Singh,L.W.; Ila,H.; Junjappa, H. *Synthesis* 1985, 531.

29. Singh,L.W.; Ila, H.; Junjappa,H. *Synthesis* 1987,873.

30. Dutta,A.; Ila,H.; Junjappa,H. *Tetrahdron* 1987, *43*, 5367.

31. Dutta,A.; Bhattacharjee,S.; Ila, H.; Junjappa, H. *Synthesis* 1988, 728.

32. Purkayastha,M.L.; Ila,H.; Junjappa,H. *Synthesis*, 1989, 20.

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

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

35. Chakrasali,R.T.; Ila,H.; Junjappa,H. *Synthesis*, **1988**, 453.

36. (a) Rastogi,R.R.; Ila,H.; Junjappa,H. *J.Chem. Soc. Chem. Comm.*, **1975**, 645 (b) Rastogi,R.R.; Kumar,A.; Ila,H.; Junjappa,H. *J.Chem.Soc.Perkin Trans.I.* **1978**, 549.

37. Dutta,A.; Ila,H.; Junjappa, H.; *Synthesis*, **1988**, 556.

38. Singh,L.W.; Ila,H.; Junjappa, H. *Synthesis*, **1988**,89.

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

40. Asokan,C.V.; Ila,H.; Junjappa, H. *Synthesis*, **1985**, 163.

41. Asokan,C.V.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1985**, *26*, 1087.

42. Asokan,C.V.; Bhattacharjee,S.; Ila, H.; Junjappa,H. *Synthesis* **1988**, 281.

43. Singh,L.W.;Gupta,A.K.;Ila,H.;Junjappa,H.; *Synthesis* **1984**, 516.

44. Singh,L.W.; Ila,H.; Junjappa,H.; *Indian J. of Chem.* **1987**, *26B*, 607.

45. Deb.B.; Asokan,C.V.; Ila, H.; Junjappa,H. *Synthesis*, **1987**, 893.

46. Deb.B; Asokan,C.V.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1988, *29*, 2111.

47. Singh,G.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1984, *25*, 5095.

48. Gupta,A.K.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1987, *28* 1459.

49. Dutta,A.; Ila,H. Junjappa,H. *Tetrahedron Lett.* 1988, *29* 497.

50. Balu,M.P.; Pooranchand,D.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1988, *29*, 501.

51. Gupta,A.K.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1988, *29* 6633.

52. Gupta,A.K.; Ila,H.; Junjappa,H. Unpublished Results.

53. Thomas,A.; Ila,H.; Junjappa,H. Unpublished Results.

54. Gupta,A.K.; Ila, H.; Junjappa, H. *Tetrahedron*, 1989 *45*, 1509.

55. Balu,M.P.; Singh,G.;Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1986, *27*,117.

56. Finar,I.L. in *Organic Chemistry*, Vol.1., ELBS Pages 817-823.

57. Balu,M.P.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1987,*28*, 3023.

CHAPTER II

REACTIONS OF α-OXOKETENE DITHIOACETALS WITH BENZYL-,1-NAPHTHYLMETHYL- AND 2-NAPHTHYLMETHYLMAGNESIUM HALIDES: A NEW GENERAL METHOD FOR AROMATIC ANNELATION*

II.1. INTRODUCTION

Construction of aromatic rings from non-aromatic precursors is an area of current research interest in synthetic organic chemistry[1]. Such a strategy of construction of aromatic rings from appropriate open chain precursors leads to regiospecifically substituted benzenoids and other condensed aromatics which are often prepared in low yields through multiple steps involving electrophilic substitution. Thus direct introduction of

---

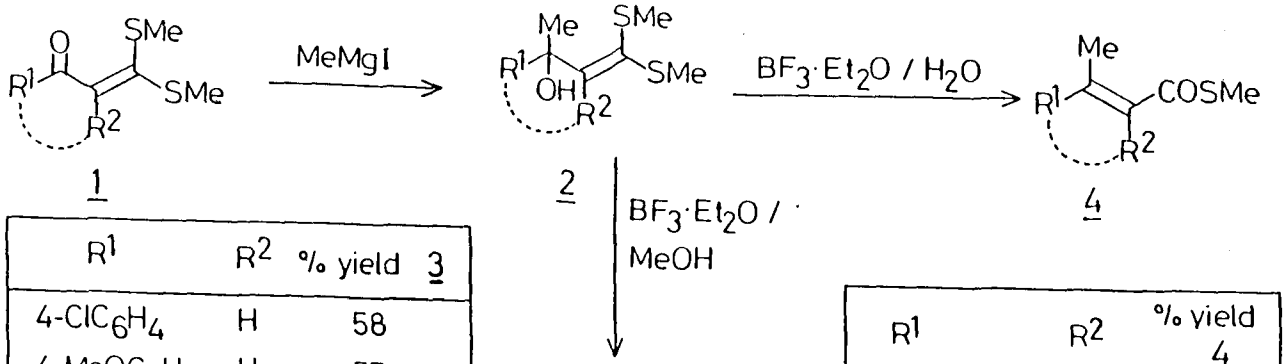
*Balu,M.P.; Singh,G.; Ila,H.;Junjappa,H. *Tetrahedron Lett.* 1986, *27*, 117.

substituents in aromatic ring system suffers limitations making it sometimes experimentally difficult operation in the total synthesis of target molecule. On the other hand, an approach involving the construction of aromatic ring from appropriately functionalized open chain precursors would yield aromatic compounds with built in substituents of the precursors. Such an approach has been in practice for the synthesis of a large number of heterocyclic compounds while it has not been extensively investigated for the construction of aromatic systems. An attempt has been made in this investigation to develop a methodology for the synthesis of condensed aromatics from α-oxoketene dithioacetals. A number of methods have been developed in the recent years to construct aromatic rings from open chain precursors and these methods have been reviewed[2]. The most recent and relevant approaches to the present investigation, from this laboratory and by others have been briefly summarized in the following discussion.

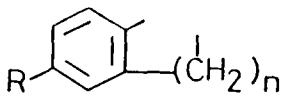
New carbon-carbon bond formation using organometallic reagents is one of the most important processes for elaboration of carbon skeletons ("backbone of organic synthesis")[3]. The reactivity profile of α-oxoketene dithioacetals towards various organometallic reagents has been extensively investigated in this laboratory. Thus, methylmagnesium iodide was shown to react with oxoketene dithioacetals 1 in an exclusive 1,2-addition manner to

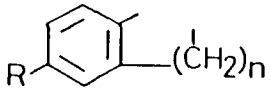
yield the corresponding enol acetals 2 (Scheme 1) which on borontrifluoride etherate assisted methanolysis and hydrolysis yielded the corresponding eneesters 3 and the thioesters 4 respectively[4]. The generality of the method was established by choosing different dithioacetals as shown in Scheme 1. When the bulkier organomagnesium reagents were used the reaction generally proceeded in a 1,4-manner followed by 1,2-addition path to yield the carbinol acetals 6, which afforded the corresponding α,β-unsaturated ketones 7 under methanolysis conditions (Scheme 2). When the carbinol acetal 8 derived from the reaction of phenylmagnesium bromide with 1, were refluxed in benzene in the presence of catalytic amounts of borontrifluoride etherate, the incipient electrophilic species generated *in situ* were found to attack the aromatic ring to give the corresponding indenes 9 in good yields[5]. The sulphur free indenes 10 were also prepared by *Raney-Ni* desulphurization of 9 (Scheme 3).

Interestingly, when allylmagnesium bromide was reacted with 1 (Scheme 4), the carbinolacetals 11, from an exclusive 1,2-addition were obtained in nearly quantitative yields. These carbinolacetals on treatment with borontrifluoride etherate in benzene underwent smooth cycloaromatization to yield the corresponding benzene derivatives 12[6]. Thus a new general method for the synthesis of substituted and annelated benzenoids was

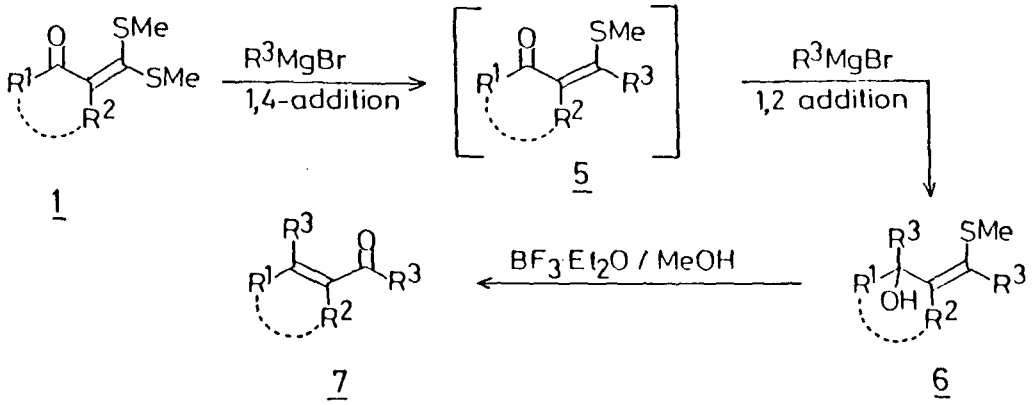


1 2 3 4

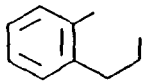
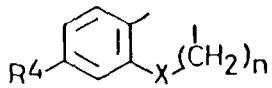
R^1	R^2	% yield 3
4-ClC_6H_4	H	58
4-$MeOC_6H_4$	H	57
Et	Me	69
Me	Bu	50
$-(CH_2)_3-$		66
$-(CH_2)_4-$		69
		
	R= H; n=1	65
	R= H; n=2	70
	R= MeO; n=2	75

R^1	R^2	% yield 4
Ph	H	41
		
	R= H; n=1	55
	R= H; n=2	60
	R= MeO; n=2	58

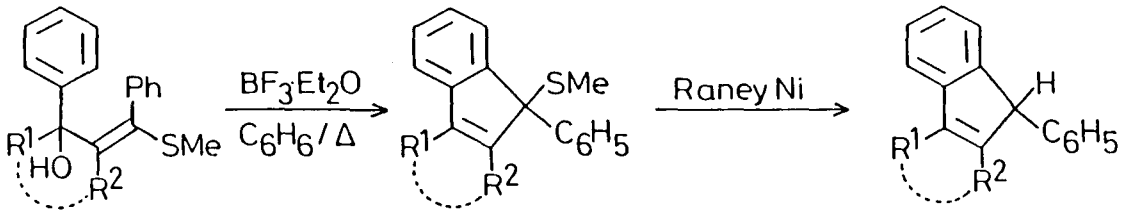
Scheme-1



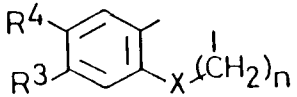
1 5 6 7

R^1	R^2	R^3	% yield 7
$-(CH_2)_4-$		Et	48
$-(CH_2)_4-$		n-Pr	50
$-(CH_2)_4-$		n-Bu	55
$-(CH_2)_3-$		n-Bu	53
		n-Pr	50
		n-Bu	55
C_6H_5	H	C_6H_5	71
4-MeC_6H_4	H	C_6H_5	64
4-$MeOC_6H_4$	H	C_6H_5	61
$-(CH_2)_4-$		C_6H_5	53
			
$R^4=H; X=CH_2; n=1$		C_6H_5	65
$R^4=H; X=S, n=1$		C_6H_5	62
$R^4=Me, X=S, n=1$		C_6H_5	67
$R^4=Me; X=S; n=2$		C_6H_5	62
$R^4=H, X=O; n=2$		C_6H_5	57

Scheme-2

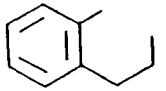


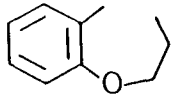
8 9 10

R^1	R^2	% yield 9
C_6H_5	H	67
C_6H_5	CH_3	71
		
X=CH_2; n=1; R^3=R^4=H		54
X=S; n=1; R^3=R^4=H		72
X=S; n=2; R^3=Me; R^4=H		76
X=S; n=2; R^3=H; R^4=Me		71
X=O; n=2; R^3=R^4=H		68

R^1=Ph R^2=H 48%

R^1=Ph R^2=Me 56 %

R^1=R^2=  29 %

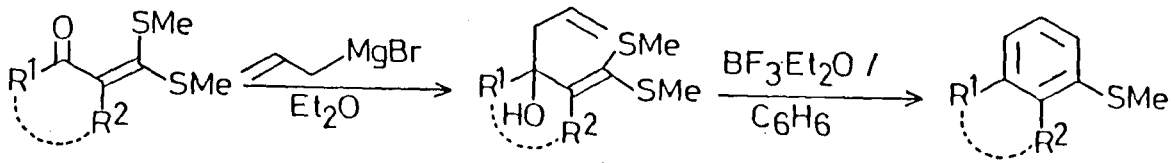
R^1=R^2=  51 %

Scheme 3

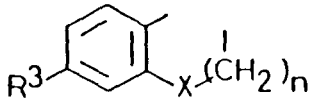
developed through oxoketene dithioacetals 1 *via* their allylcarbinol acetals 11. The method was found to be of general synthetic application though in few cases, yields were moderate (Scheme 4).

When the allyl and crotylmagnesium halides were reacted with cinnamoylketene dithioacetals 13, the carbinol-acetals 14 thus formed underwent facile cycloaromatization in the presence of Lewis acid ($BF_3.Et_2O$) to yield the corresponding *trans* stilbenes 15[7]. Some of these stilbenes were desulphurized using Nickel boride in refluxing ethanol. The method was found to be of general synthetic application with moderate to good yields with different cinnamoyl ketene dithioacetals and allyl anions as described in Scheme 5. The importance of this methodology lies in the fact that this is the only method reported for the synthesis of stilbenes involving construction of one of the phenyl rings from acyclic precursors.[8]

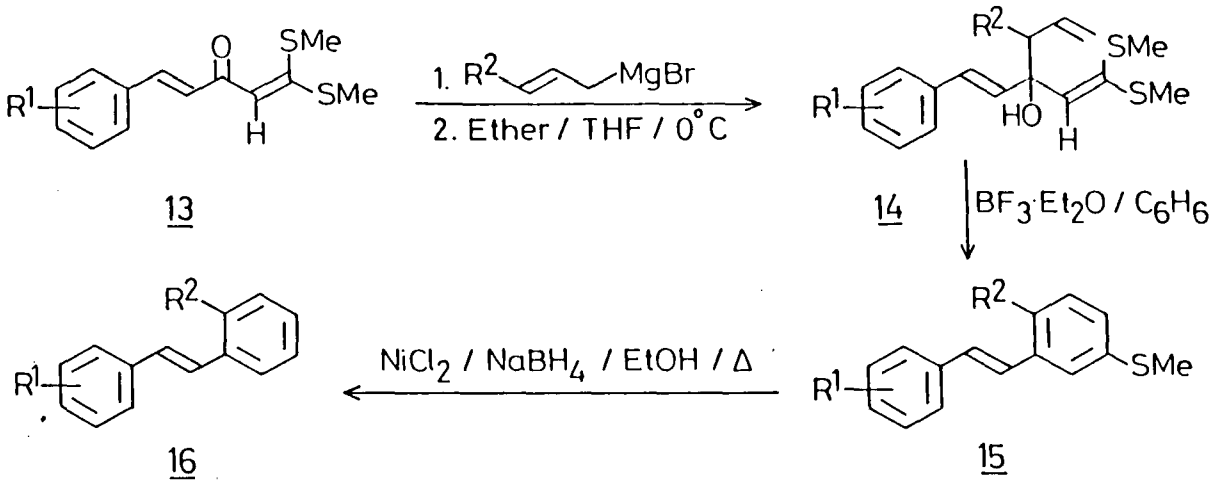
It was considered of interest, that propargyl magnesium bromide should also react with 1 to yield the corresponding alcohols 17 with the terminal acetylenic functionality instead of double bond as in the case of allyl alcohols. These alcohols should undergo cycloaromatization with the participation of an external nucleophile to yield the corresponding functionalized aromatic compounds. This goal was achieved when carbinolacetals 17 were prepared in high yields and



1 11 12

R^1	R^2	% yield 12
$-(CH_2)_4-$		74
$-(CH_2)_3-$		64
		
R^3=H; X=CH_2; n=0		54
R^3=H; X=CH_2, n=1		68
R^3=MeO, X=CH_2; n=1		67
R^3=H, X=S; n=1		59
R^3=H, X=S, n=2		67
R^3=H; X=O; n=2		64
C_6H_5	H	45
4-$MeOC_6H_4$	H	39
4-ClC_6H_4	H	40
Et	Me	40

Scheme-4



13 14 15 16

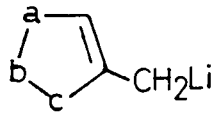
R^1	R^2	% yield 16
H	H	59
4-Me	H	61
4-Cl	H	62
H	Me	60

R^1	R^2	% yield 15	R^1	R^2	% yield
H	H	68	2,6-Cl_2	H	52
4-Me	H	62	3,4-Cl_2	H	53
4-Cl	H	68	H	Me	52
3-MeO	H	57	4-Me	Me	51
2-Cl	H	61	4-Cl	Me	51

Scheme -5

subjected to cycloaromatization in the presence of borontrifluoride etherate in methanol to afford the corresponding methoxy substituted aromatics 18 in good yields (Scheme 6)[9]. Some of these compounds were desulphurized (*Raney Ni/EtOH*) to yield the corresponding sulphur free anisole derivatives 19.

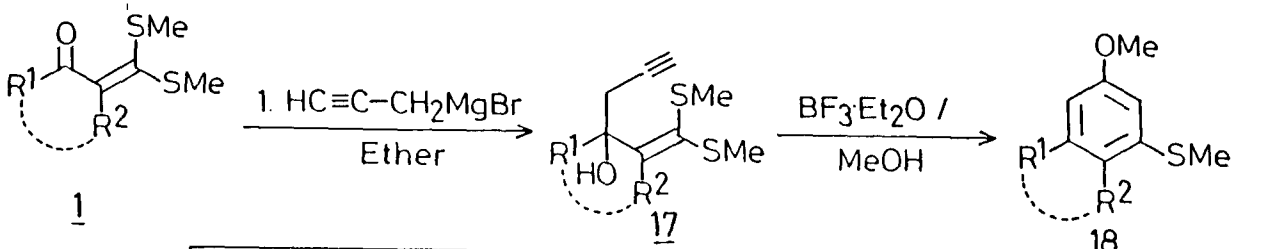
In continuation of these studies yet another broad based plan, to explore the possibilities of annelalting aromatic rings over preconstructed five membered heterocycles by condensing α-oxoketene dithioacetals 1 with the appropriate lithioallyl system of the general formula 20A was envisaged. As a part of this programme,

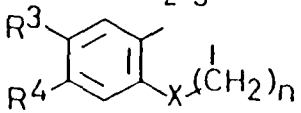


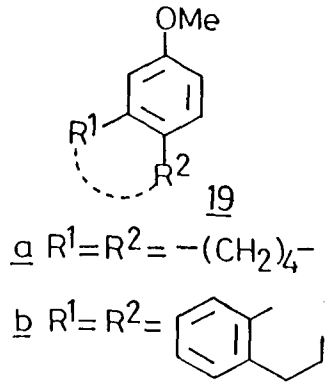
20A

3-methyl-5-lithiomethylisoxazole 20 was reacted with 1 to yield the corresponding 1,2-benzisoxazoles 22 via carbinolacetal 21, under the described conditions[10]. The method was of considerable synthetic importance since it could be extended to a large number of structural variants of 1 giving rise to different substituted and annelated 1,2-benzisoxazoles in high yields (Scheme 7).

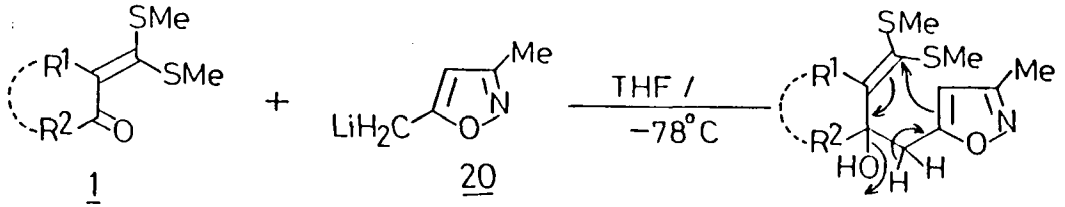
It is pertinent to note that recently, a few synthetic approaches to prepare condensed aromatics involving combination of 1,3-electrophilic and 1,3-nucleophilic

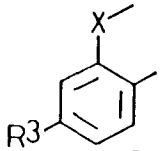


R^1	R^2	% yield 18
	$-(CH_2)_4-$	76
	$-(CH_2)_5-$	71
		
$R^3=R^4=H; X=CH_2; n=1$		78
$R^3=H, R^4=MeO; X=CH_2; n=1$		66
$R^3=H; R^4=Me; X=CH_2; n=1$		77
$R^3=R^4=H; X=S; n=1$		72
$R^3=Me; R^4=H; X=S; n=1$		68
$R^3=R^4=H; X=S; n=2$		69
$R^3=Me; R^4=H; X=S; n=2$		81
$R^3=R^4=H; X=O; n=2$		75



Scheme-6

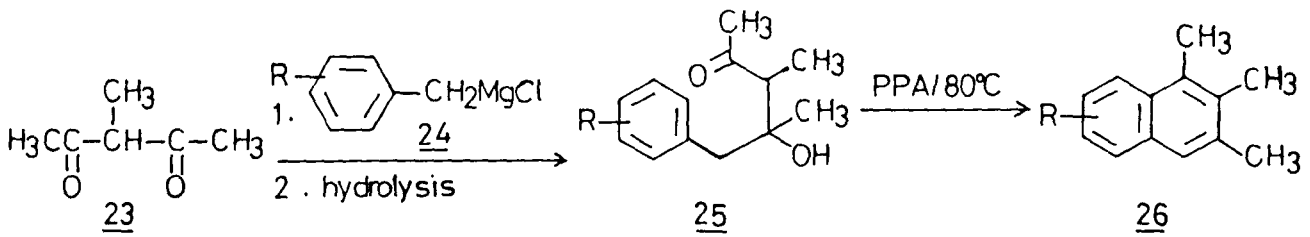


R^1	R^2	% yield 22
C_6H_5	H	73
4-ClC_6H_4	H	66
4-$MeOC_6H_4$	H	68
ß-naphthyl	H	64
Me	H	54
2-furyl	H	59
2-thienyl	H	61
$-(CH_2)_4-$	H	65
$-(CH_2)_5-$	H	67
		
R^3=H X= CH_2		57
R^3=H X= $-(CH_2)_2-$		76
R^3=Me X= $-S(CH_2)_2-$		81

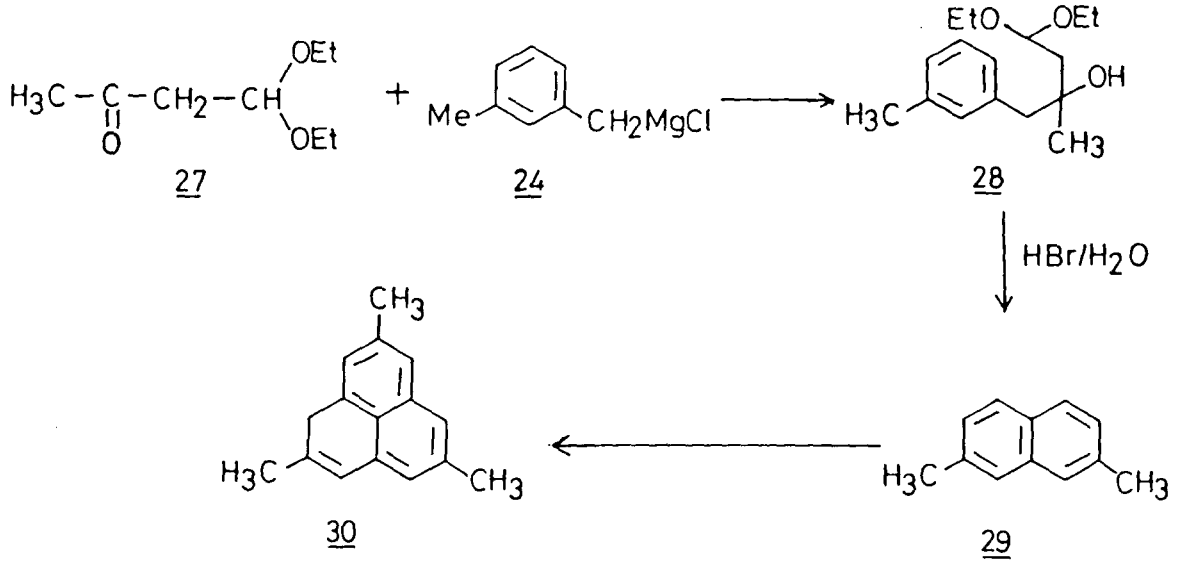
Scheme-7

fragements have been developed[11-13]. In the present investigation it was planned to study the cycloaromatization of α-oxoketene dithioacetals with benzyl, 1-naphthylmethyl and 2-naphthylmethylmagnesium halides with a view to develop a general approach for condensed aromatic compounds. Our literature survey at this stage revealed that Leitch and co-workers have reacted substituted benzylmagnesium chloride with symmetrical β-diketone 23 to yield the corresponding β-hydroxyketone 25 followed by cyclodehydration in the presence of polyphosphoric acid to afford polymethyl substituted naphthalenes 26 in 19-67% overal yields[11,12]. The same authors have also reported a similar synthetic methodology for the preparation of 2,7-dimethyl naphthalenes 29 which are useful intermediates for the synthesis of substituted phenalenes 30 with three fold rotational symmetry capable of forming symmetrical radicals or cations[13]. Thus, the reaction of substituted benzylmagnesium chloride 24 with β-oxoacetal 27 afforded the corresponding carbinolacetal 28, which underwent cycloaromatization in the presence of hydrobromic acid to yield the corresponding 2,7-dimethyl naphthalene 29 (Scheme 8).

A novel approach for aromatic annelation of active methylene ketones through β-silyloxyenones has been described recently in a series of papers by Tius and co-workers[14-18]. In continuation of these studies, after our publication appeared on napththoannelation[19], Tius



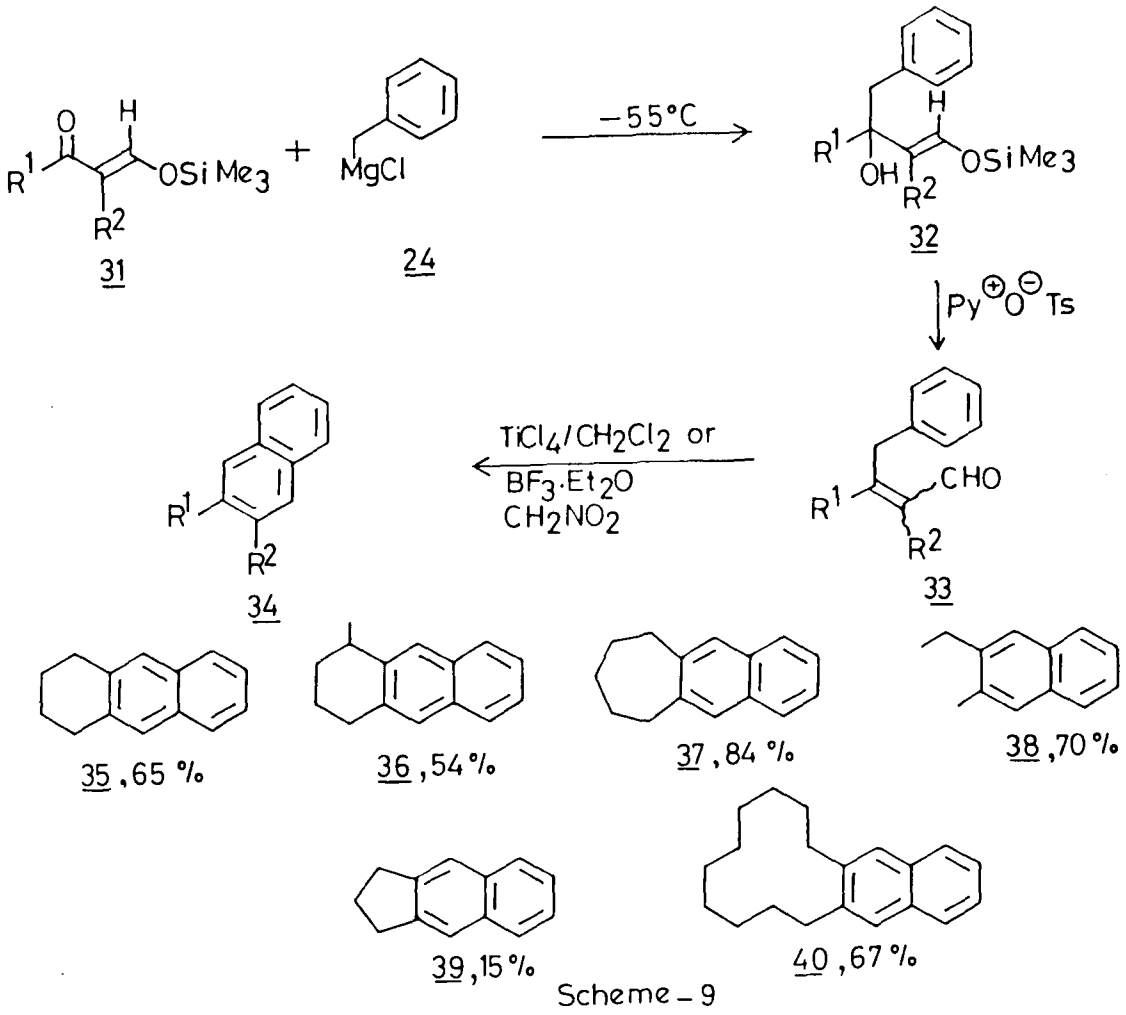
R = H ; 4 - Me ; 2,3,4 -(Me)3 ; 5,6,7 -(Me)3 – 19-67 %



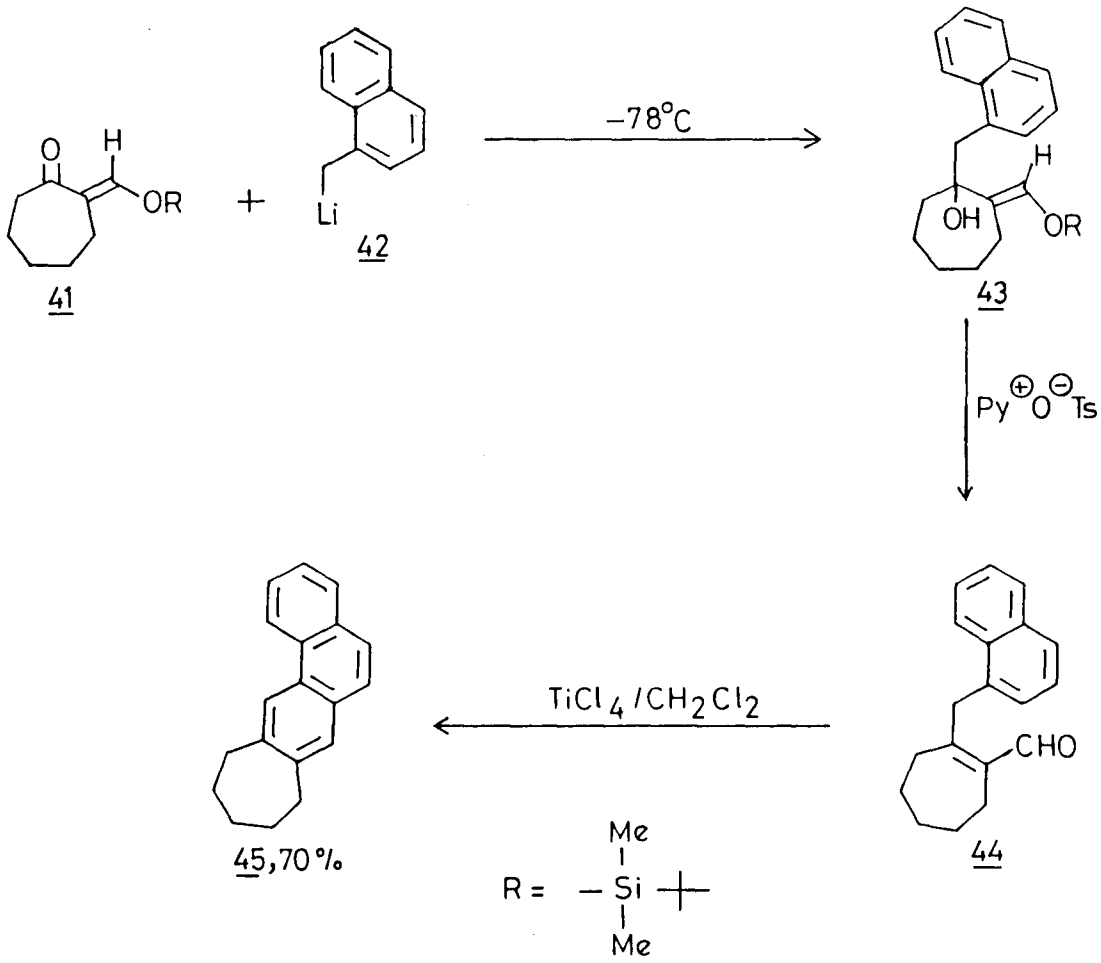
Scheme – 8

and Gomez-Galeno reported a cationic cyclization for the synthesis of naphthalenes[20]. They reacted benzylmagnesium chloride with trimethylsilyl vinylogous ester 31 to give the corresponding tertiary alcohols 32 which were converted to the α,β-unsaturated aldehydes 33 by treatment with pyridinium tosylate. The enealdehydes 33 underwent intramolecular cyclization in the presence of either $TiCl_4/CH_2Cl_2$ or $BF_3.Et_2O/CH_3NO_2$ to afford the corresponding naphthalenes 34. Thus a series of annelated naphthalenes 35-40 (Scheme 9) were prepared in 15-84% overall yield using this methodology. The same authors have also reported the reaction of tertiarybutylsilyloxy vinylogous ether 41 with 1-naphthylmethyllithium to give the corresponding annelated phenathrene 45 in 70% yield under identical reaction conditions (Scheme 10). However the generality of this reaction has not been studied.

Another approach for naphthoannelation leading to polycyclic aromatic hydrocarbons,using Vilsmeier reaction pathway has been reported by Krishna Rao and co-workers[21] (Scheme 11). Reaction of 6-methoxytetralone with benzylmagnesium chloride yielded the alcohol 47, which under Vilsmeier reaction conditions gave the corresponding aldehyde 48, and aromatization in the presence of polyposphoric acid to afford the corresponding dihydrobenzanthracene 49a which on dehydrogenation with DDQ yielded the fully aromatic polycyclic hydrocarbon 49b

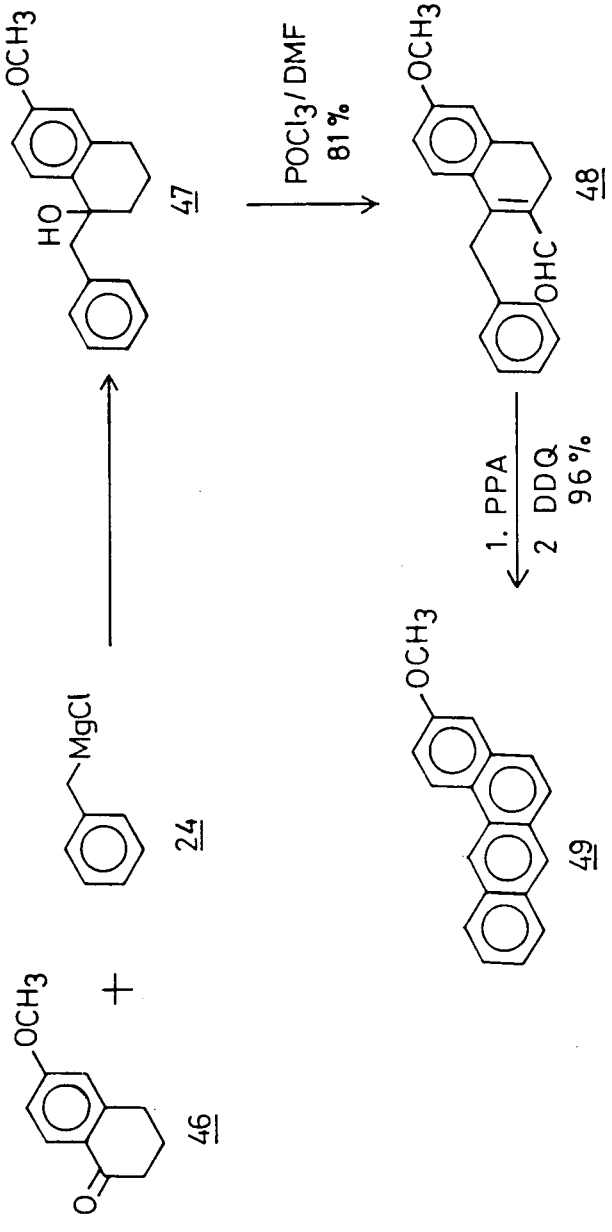

R1
O
H
OSiMe3
R2
31
+
MgCl
24
−55°C
OH
32
Py⊕O⊖Ts
CHO
33
TiCl4/CH2Cl2 or
BF3·Et2O
CH2NO2
34
35, 65 %
36, 54 %
37, 84 %
38, 70 %
39, 15 %
40, 67 %

Scheme – 9



41 + 42 → 43 → 44 → 45, 70%

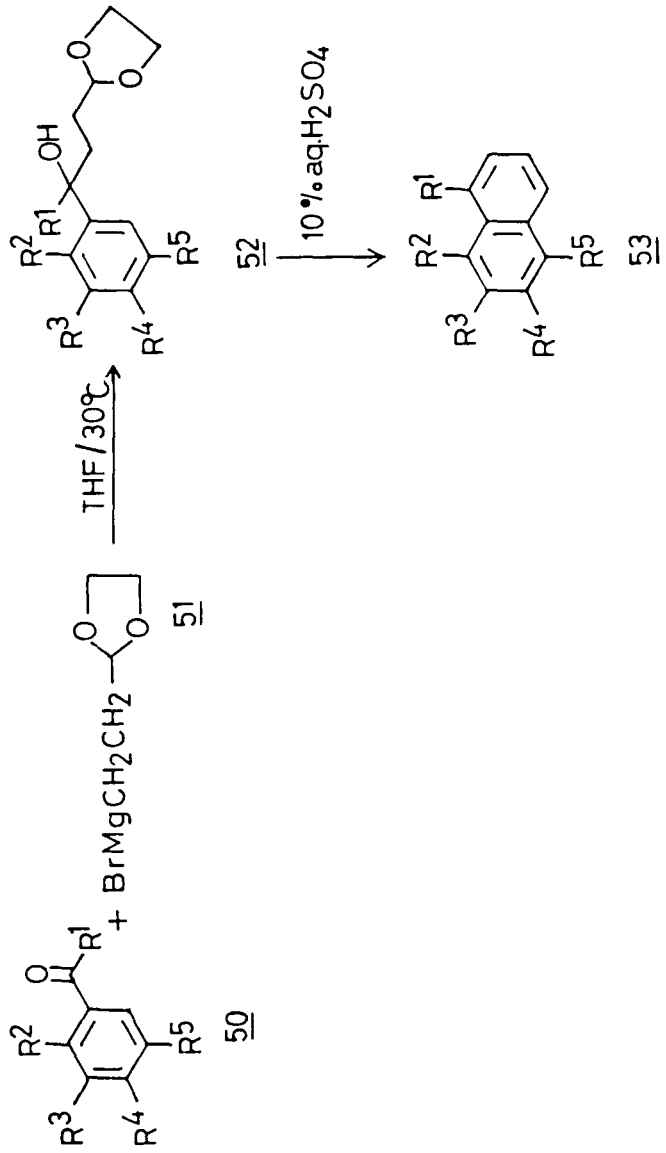
Scheme–10


OCH3
O
46
+
MgCl
24
HO
47
POCl3/DMF
81 %
OCH3
OHC
48
1. PPA
2 DDQ
96 %
OCH3
49

Scheme_11

in good yield (Scheme 11). In an another approach, substituted aromatic aldehydes 50 were reacted with functionalized Grignard reagent 51 to yield the corresponding alcohol 52 which upon treatment with 10% aqueous sulfuric acid underwent smooth cyclodehydration to yield the substituted naphthalenes 53 in moderate to good yields (Scheme 12)[22].

In the light of these developments it was considered of interest to undertake a systematic investigation to study the reaction of benzylmagnesium chlrode with α-oxoketene dithioacetals. Such a study would lead to intermediate alcohols that might undergo cycloaromatization through the participation of the aromatic ring, so that a methodology would be formulated for the synthesis of a wide variety of naphthoannelated products depending on the structural characteristics of the oxoketene dithioacetals. The reactions of 1-naphthylmethylmagnesium chloride and 2-naphthylmethylmagnesium bromide with oxoketene dithioacetals and their subsequent transformations to condensed polycyclic hydrocarbons have also been investigated. The following section describes the successful application of the aromatic annelation approach for the synthesis of substituted and annelated naphthalenes, phenanthrenes and other polycyclic aromatic hydrocarbons.



Scheme–12

II.2 RESULTS AND DISCUSSION

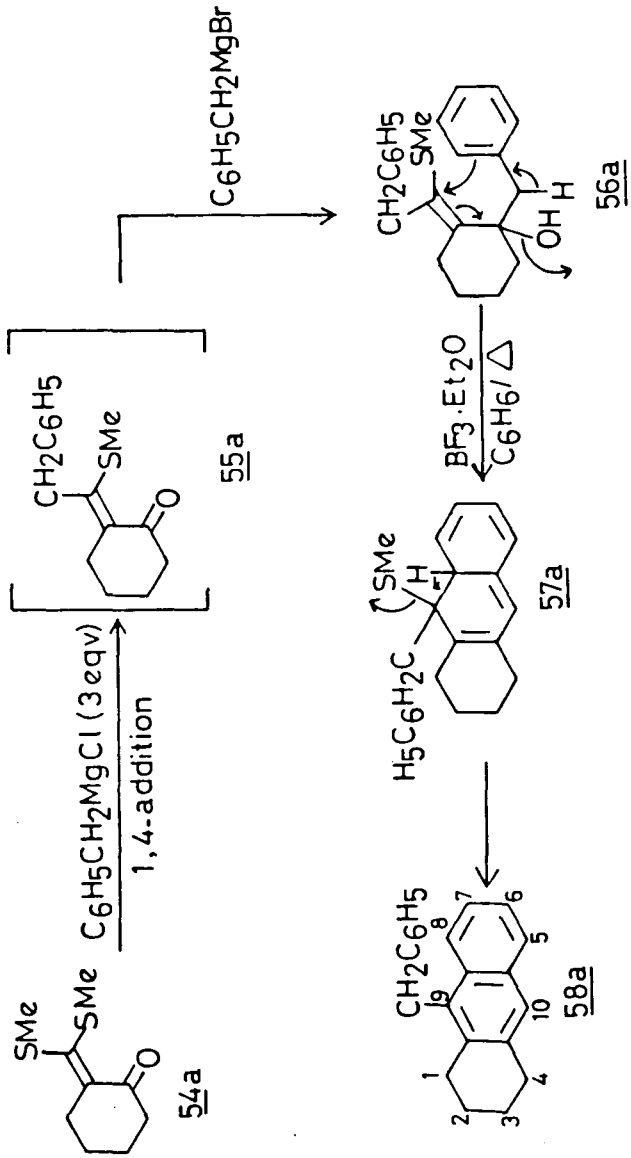
II.2.1 Cycloaromatization of α-Oxoketene Dithioacetals with Benzylmagnesium Chloride: A Novel Naphthalene Annelation Reaction.

The selected α-oxoketene dithioacetals 1a-i and 54a-f required for the present investigation were prepared according to the known procedure[23-25] by reacting the respective active methylene ketones with two equivalents of base and carbon disulfide followed by alkylation. Authenticity of these compounds were confirmed by comparision of their spectral and anlytical data with those of the reported values.

When the α-oxoketene dithioacetals 54a was reacted with benzylmagnesium chloride(1.25 eqv), the reaction mixture after work up and subsequent treatment with $BF_3.Et_2O$ in refluxing benzene yielded after purification a colourless solid, m.p. 106°C, along with the unreacted starting material 54a(35%). The product was characterized as 9-benzyl-1,2,3,4-tetrahydroanthracene 58a from its analytical and spectral data. Thus it exhibited in its mass spectrum a peak at m/z 272(M^+,100%) and was analyzed for $C_{21}H_{20}$. The prominent absorbtion bands in the IR spectrum (KBr) are observed at ν_{max}1610 and 1500 cm^{-1}. The structure was further confirmed from its ^1H NMR spectrum (CCl_4). The signals at δ 1.45-1.90 (4H) and δ 2.50-3.00 (4H) as multiplets and integrating

for 8 protons were assigned to the ring methylene protons, a sharp singlet at δ4.32 (2H) was assigned to the two benzylic protons and the aromatic protons appeared as multiplet (10H) between δ 6.60-7.85. From the structure of 58a, it was apparent that two equivalents of benzylmagnesium chloride have been used for each mole of 54a. Therefore, in a separate experiment 54a was reacted with excess of benzylmagnesium chloride (3 equivalent) when the yield of 58a was raised to 81% and no trace of unreacted starting material 54a was detected in the reaction mixture (Scheme 13).

After this preliminary reaction, various oxoketene dithioacetals were reacted with benzylmagnesium chloride to study the general applicability of the reaction. Thus, when 54b derived from cyclopentanone was reacted with 24 the corresponding carbinolacetal 55b was obtained in high yield but it failed to undergo cycloaromatization to the corresponding cyclopentanaphthalene derivative 58b in the presence of $BF_3.Et_2O$. On the other hand when the oxoketene dithioacetal derived from indanone 54c was reacted with benzylmagnesium chloride under similar reaction conditions followed by cycloaromatization, the corresponding naphthoannelated product 58c was obtained in 62% yield. Similarly the oxoketene dithioacetal 54d derived from α-tetralone afforded the corresponding dihydrobenzanthracene derivative 58c in 71% yield under identical

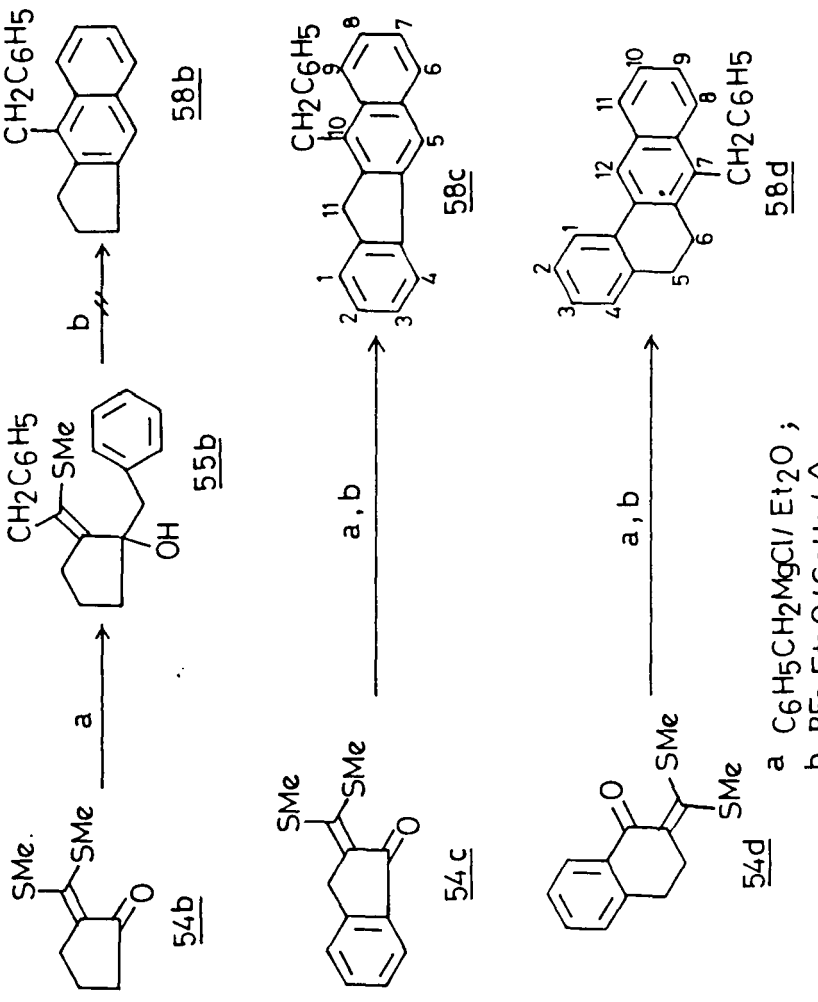

SMe
SMe
O
54a
C6H5CH2MgCl (3eqv)
1,4-addition
CH2C6H5
SMe
O
55a
C6H5CH2MgBr
CH2C6H5
SMe
OH
H
56a
BF3·Et2O
C6H6/Δ
SMe
H
H5C6H2C
57a
CH2C6H5
58a

Scheme-13

reaction conditions (Scheme 14). The structures of these compounds were confirmed from their analytical and spectral data which are described in the experimental section. The other oxoketene dithioacetals from 54e,54f and 54g derived from benzoheterocyclic ketones also reacted with benzylmagnesium chloride and followed the described cycloaromatization sequence to yield the corresponding naphthoannelated products 58e-g in 58-68% overall yields (Scheme 15).

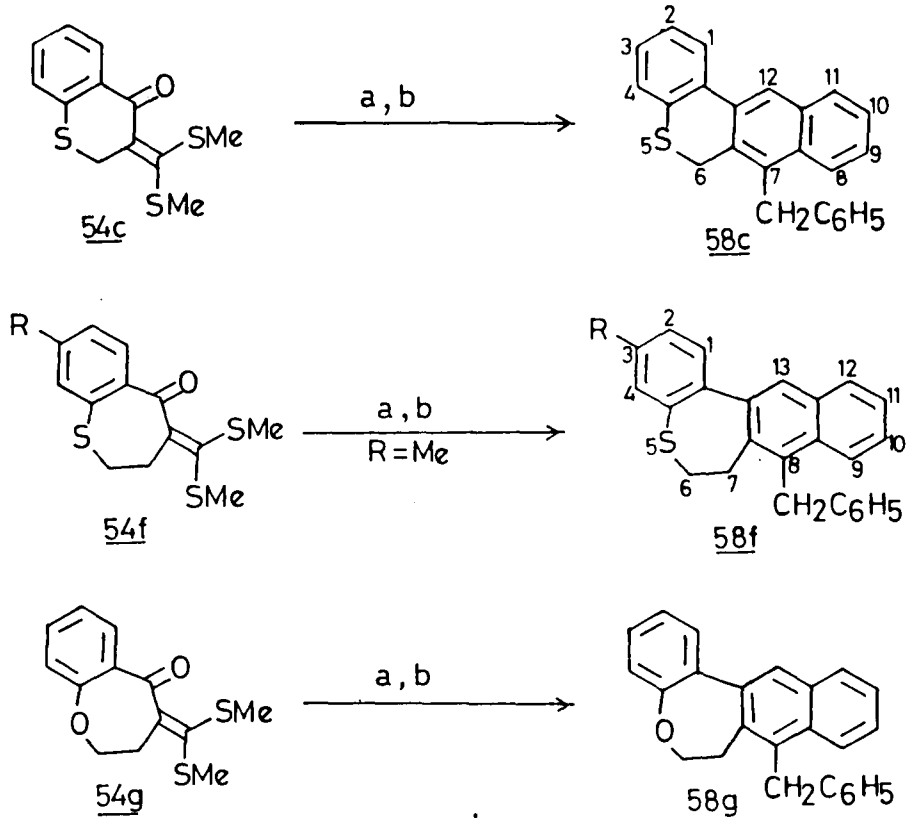
The probable mechanism for the formation of 63 from 1 is shown in Scheme 16. Apparently, the benzylmagnesium chloride undergoes initial 1,4-conjugate addition to give β-benzyl-β-methylthioalkenylketones 60, which compete with 1 to react with benzylmagnesium chloride *via* preferential 1,2-addition yielding the corresponding carbinols 61 in the overall reaction sequence. Subsequent $BF_3.Et_2O$ catalyzed cyclodehydration of the carbinols 61 affords 63 in good yields. It is important to note that the attempts to isolate either the carbinol 60 or the β-methylthioalkenyl ketones 59 in these reactions were unsuccessful.

When this methodology was extended to open chain oxoketene dithioacetals 1a-e, the corresponding 1-benzyl-4-arylnaphthalene derivatives were formed in good yields (Scheme 17). Thus the carbinolacetal 61a obtained by the reaction of 1a with benzylmagnesium chloride underwent smooth cycloaromatization in the presence of



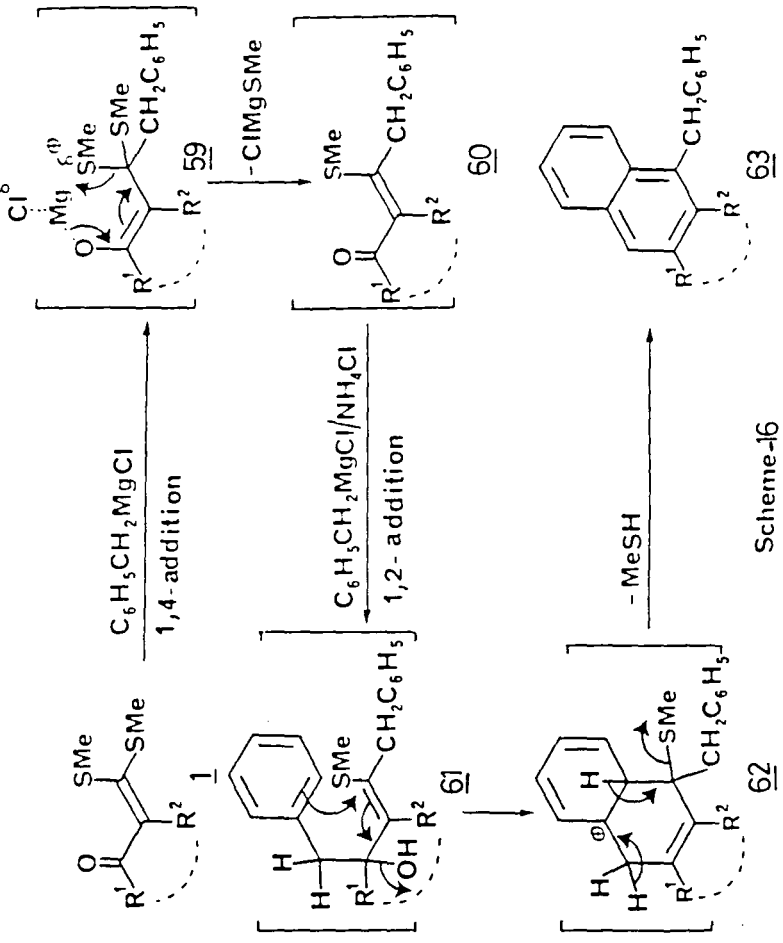
a $C_6H_5CH_2MgCl$ / Et_2O ;
b $BF_3.Et_2O$ / C_6H_6 / Δ

Scheme-14

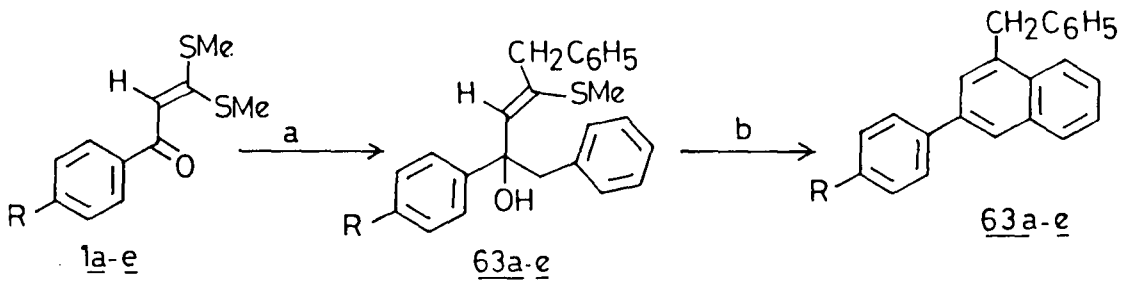


a $C_6H_5CH_2MgCl$ (3 eqv)/ Et_2O b $BF_3.Et_2O$ / C_6H_6 / △

Scheme–15


C6H5CH2MgCl
1,4-addition
-ClMgSMe
C6H5CH2MgCl/NH4Cl
1,2-addition
-MeSH
1
59
60
61
62
63

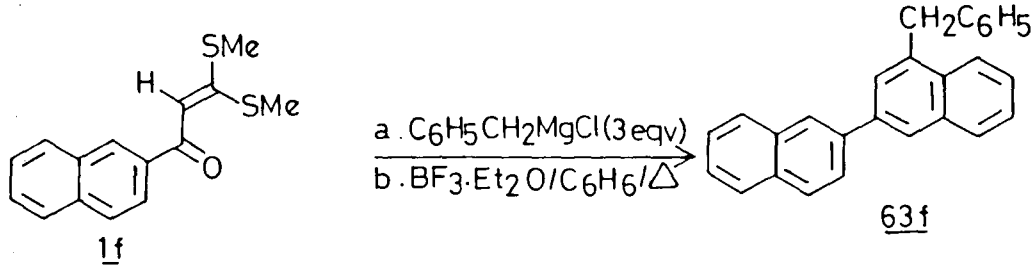
Scheme-16



1a-e 63a-e 63a-e

a, $C_6H_5CH_2MgCl$(3eqv) / Et_2O b, $BF_3.Et_2O/C_6H_6/\triangle$

a, R = H, b, R = Cl, c, R = Br, d, R = MeO, e, R = Me

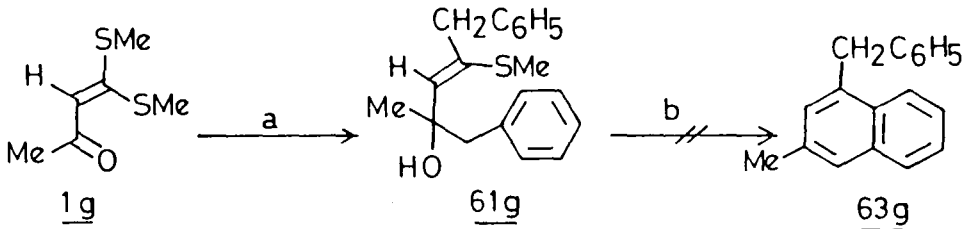


1f 63f

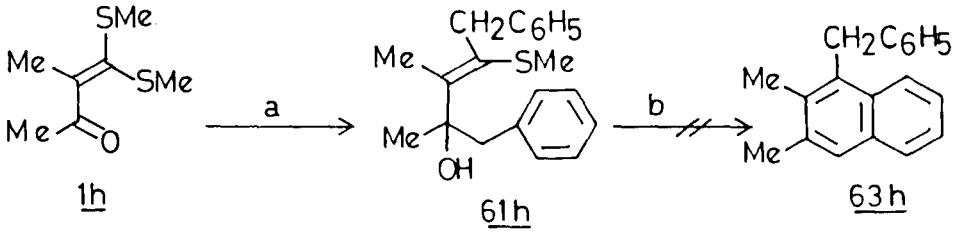
Scheme—17

borontrifluoride etherate to yield the corresponding naphthalene 63a in 59% yield. Similarly the other ketene dithioacetals 1b-e also gave the corresponding naphthalene derivatives 63b-e in good yields. The analytical and spectral data of these compounds which are in agreement with the assigned structures are described in the experimental section. Also the binaphthyl derivative 63f was obtained in 58% yield from the corresponding oxoketene dithioacetal 1f under similar reaction conditions (Scheme 17). Notable exceptions which failed to undergo the cycloaromatization transformation, were the carbinolacetals 61g and 61h derived from the corresponding oxoketene dithioacetals 1g and 1h under similar reaction conditions. In refluxing borontrifluoride etherate and benzene, these carbinolacetals became intractable and the naphthalene derivatives 64a and 64b could not be isolated (Scheme 18).

Interestingly, the carbinolacetal 61i derived from α-methyl β-benzoyl ketene dithioacetal 1i underwent intramolecular electrophilic substitution to afford the corresponding 1,3-dibenzyl-2-methyl-1-(methylthio)indene 65, and the cycloaromatization product 63i was not formed as observed in other cases (Scheme 19). These results are in line with our earlier observation[4]. Thus, in the case of alcohols 61a-e (Scheme 17) derived from acetophenones, the bulkier aryl group occupies the *quasiequatorial* position (64A), which leads to cycloaromatization of the



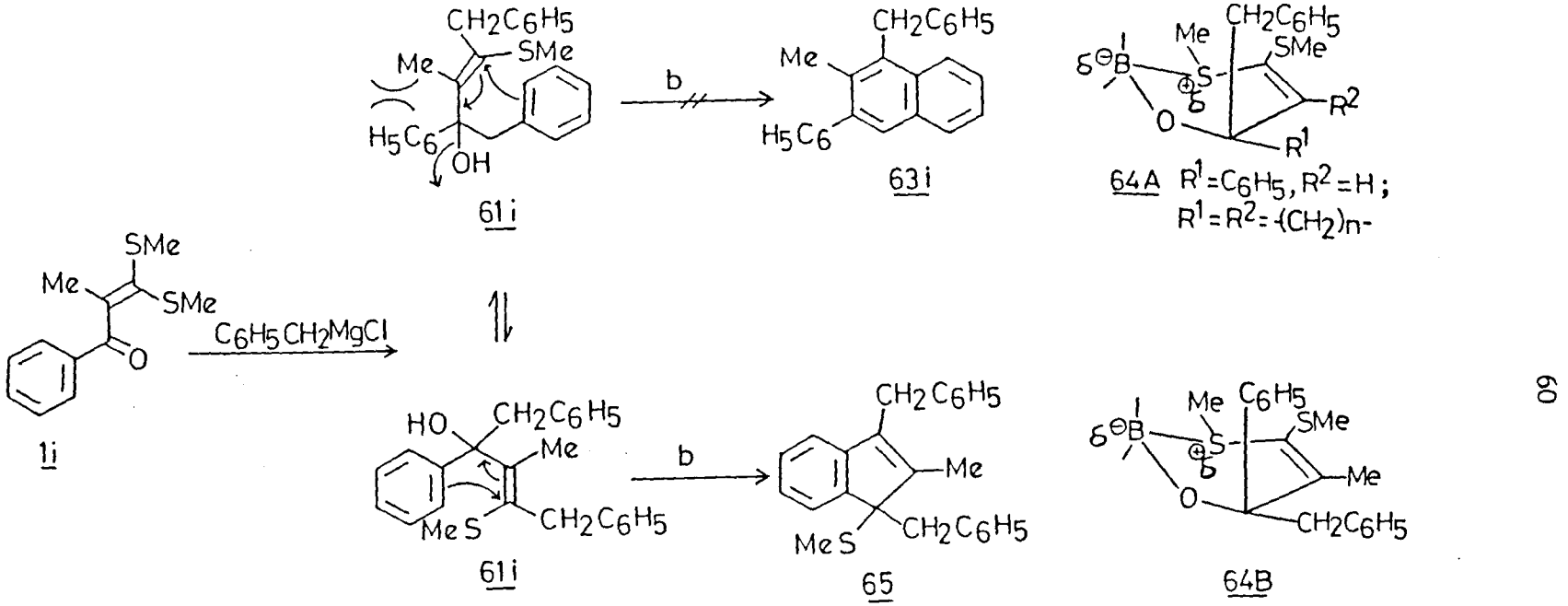
1g 61g 63g



1h 61h 63h

a $C_6H_5CH_2MgCl/Et_2O$ b $BF_3.Et_2O/C_6H_6/\Delta$

Scheme–18


CH2C6H5
SMe
Me
H5C6
OH
61i
b
63i
64A R1=C6H5, R2=H;
R1=R2=-(CH2)n-
1i
C6H5CH2MgCl
HO
65
64B
b BF3.Et2O / C6H6 / △

Scheme–19

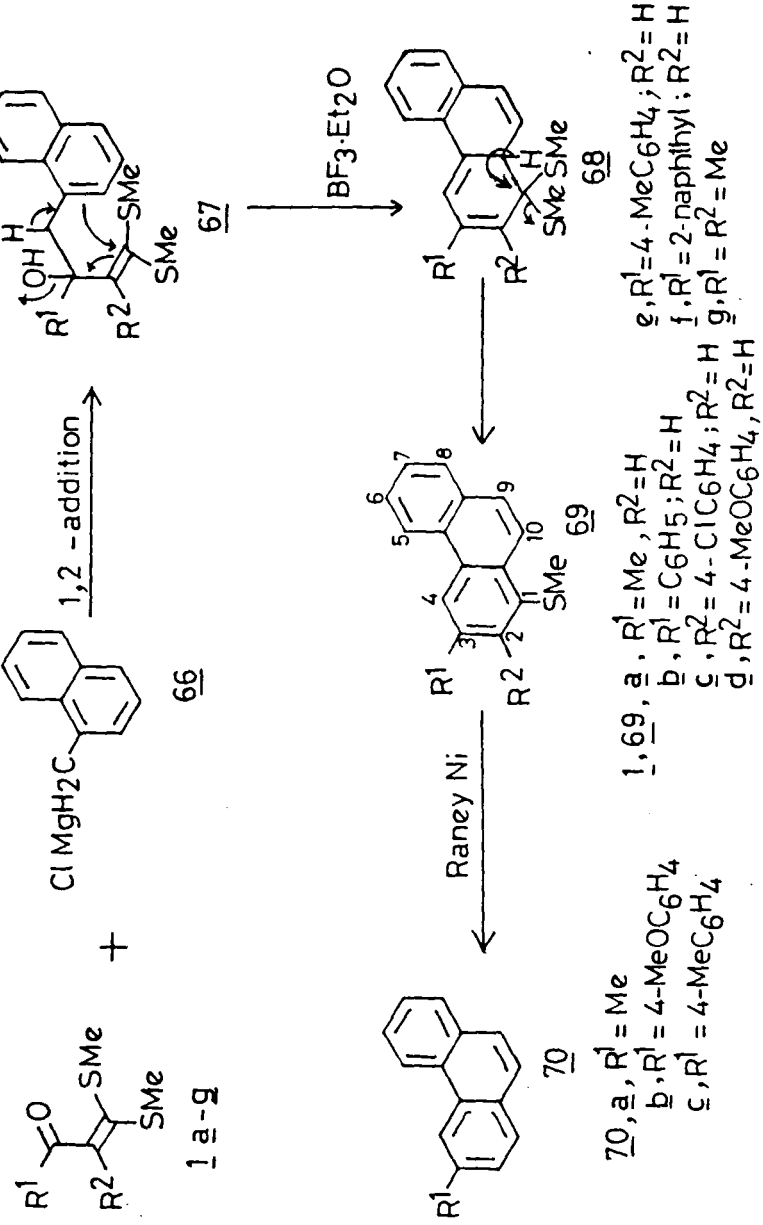
alcohols 61a-e in the presence of $BF_3.Et_2O$ to afford the naphthalene derivatives 63a-e. However, when there is a bulkier methyl substituent on the α-carbon as in the carbinolacetal 61i (Scheme 19), the benzyl group occupies the *quasiequatorial* position (64B) to minimize the steric interaction, leading to the formation of the indene derivative 65.

From the aforesaid examples it is clear that the naphtho-annelation appears to be of general synthetic application for the preparation of various condensed aromatics which are otherwise difficult to obtain from the reported methods. It was further contemplated that any aromatic system carrying a halomethyl group as reactive terminal that forms the corresponding Grignard reagent, should in principle react with 1 to give the enol acetal, which will undergo cycloaromatization with the participation of the aromatic ring to yield polycyclic aromatic hydro-carbon depending on the nature of the Grignard reagent and/or of the oxoketene dithioacetal used. As a part of this general synthetic approach two aromatic systems, 1-naphthylmethylmagnesium chloride and 2-naphthylmethyl-magnesium bromide have been examined to explore the possibilities of enhancing the importance of aromatic annelation methodology for the synthesis of polycyclic aromatic hydrocarbons.

II.2.2 Cycloaromatization of α-Oxoketene Dithioacetals with 1-Naphthylmethylmagnesium Chloride and 2-Naphthylmethylmagnesium Bromide: Novel Phenanthrene annelation Reaction

When the oxoketene dithioacetal 1a was reacted with 1-naphthylmethylmagnesium chloride 66 the corresponding carbinolacetal 67 was obtained in high yields. It was then subjected to borontrifluoride etherate treatment followed by usual work-up and column chromatography to give a single product which was characterized as 3-methyl -1-(methylthio)phenanthrene 69a (69%) on the basis of its analytical and spectral data. The product 69a exhibited molecular ion peak at m/z 238 (M^+,100%) in its mass spectrum and was analyzed for $C_{16}H_{14}S$. The ^1H NMR spectrum of 69a showed singlets at δ 2.54(3H)and 2.62(3H) which were assigned to CH_3 and SCH_3 protons respectively. The aromatic protons appeared at the following δ values 7.29 (s,1H,H-2); 7.45-7.90 (m,5H); 8.36 (s,1H,H-4); 8.61 (m,1H,H-5). The structure of 9a was further confirmed by dethiomethylation with *Raney-Nickel* to afford the known 3-methylphenanthrene 70a (m.p. 63-64°C[26]) in 73% yield. From the structure of 69a it is apparent that 1-naphthylmethylmagnesium chloride 66 has undergone regioselective 1,2-addition with 1. The exclusive 1,2-addition of 66 with oxoketene dithioacetals appears to be influenced by steric factors (Scheme 20).

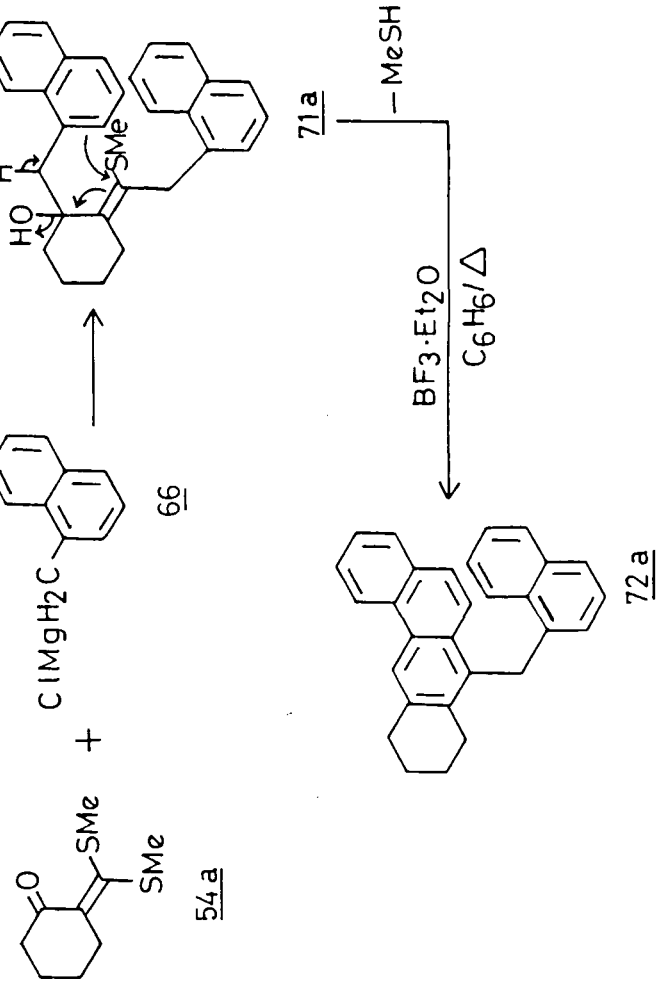
The efficacy of this method for the synthesis of other substituted and fused phenathrenes has been established


1,2 -addition
BF3·Et2O
Raney Ni
1 a-g
66
67
68
69
70
1,69, a, R1=Me, R2=H
b, R1=C6H5; R2=H
c, R2=4-ClC6H4; R2=H
d, R2=4-MeOC6H4, R2=H
e, R1=4-MeC6H4; R2=H
f, R1=2-naphthyl; R2=H
g, R1=R2=Me
70, a, R1=Me
b, R1=4-MeOC6H4
c, R1=4-MeC6H4

Scheme-20

by reacting 66 with various oxoketene dithioacetals.Thus, the phenanthrenes 69b-g were similarly prepared from the corresponding acyclic ketene dithioacetals (Scheme 20) in good yields. The structures of all these compounds were established on the basis of their analytical and spectral data which are described in the experimental section. Two of the methylthio substituted phenanthrenes 69d and 69e were desulphurized by *Raney-Ni* to yield the corresponding sulphur free phenanthrenes 69d and 69e (Scheme 20). Their spectral and analytical data are described in the experimental section.

When the oxoketene dithioacetal 54a derived from cyclohexanone was reacted with 66(1.25 eqv.), the carbinol-acetal 71a thus formed after cycloaromatization gave 72a, alongwith unreacted starting material 54a (35%). The structure of 72a was fully established from its analytical and spectral data (experimental). Apparently the regioselectivity of 66 with 54a again follows sequential 1,4-followed by 1,2-addition to yield 72a (Scheme 21). Thus in another experiment, when 54a was reacted with three equivalents of 1-naphthylmethylmagnesium chloride 66, the yield of 72a was increased upto 68%, with no trace of unreacted starting material. Similar results were obtained when 66 was reacted with oxoketene dithioacetal derived from cyclopentanone 54b to give the cycloaromatized product 72b in 58% yield

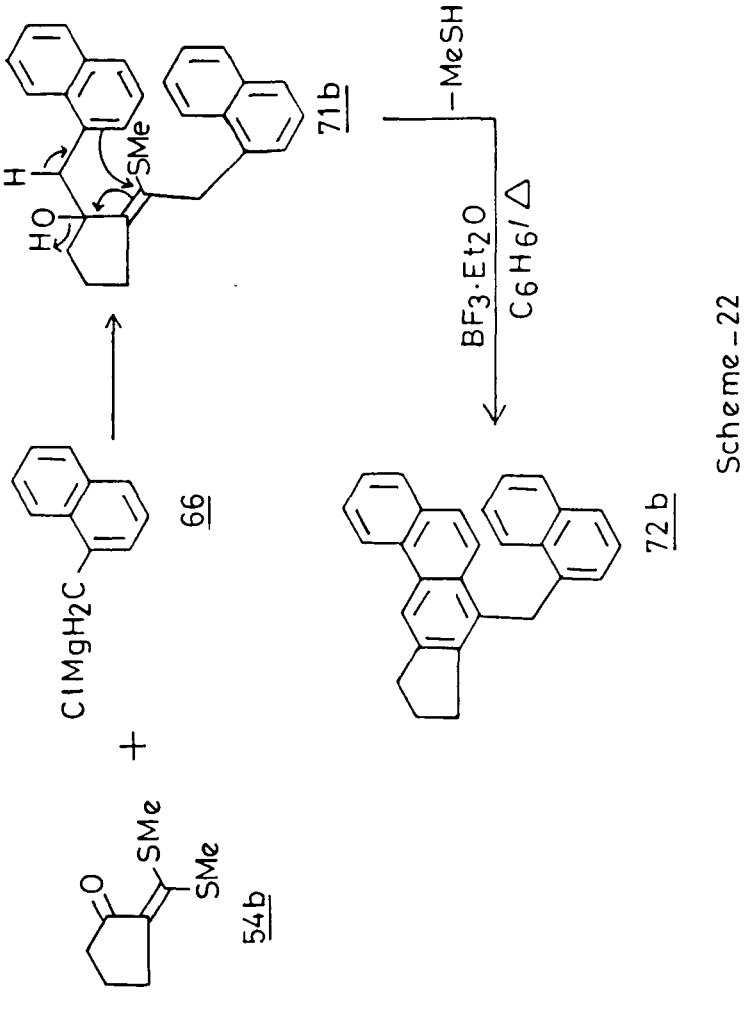


Scheme – 21

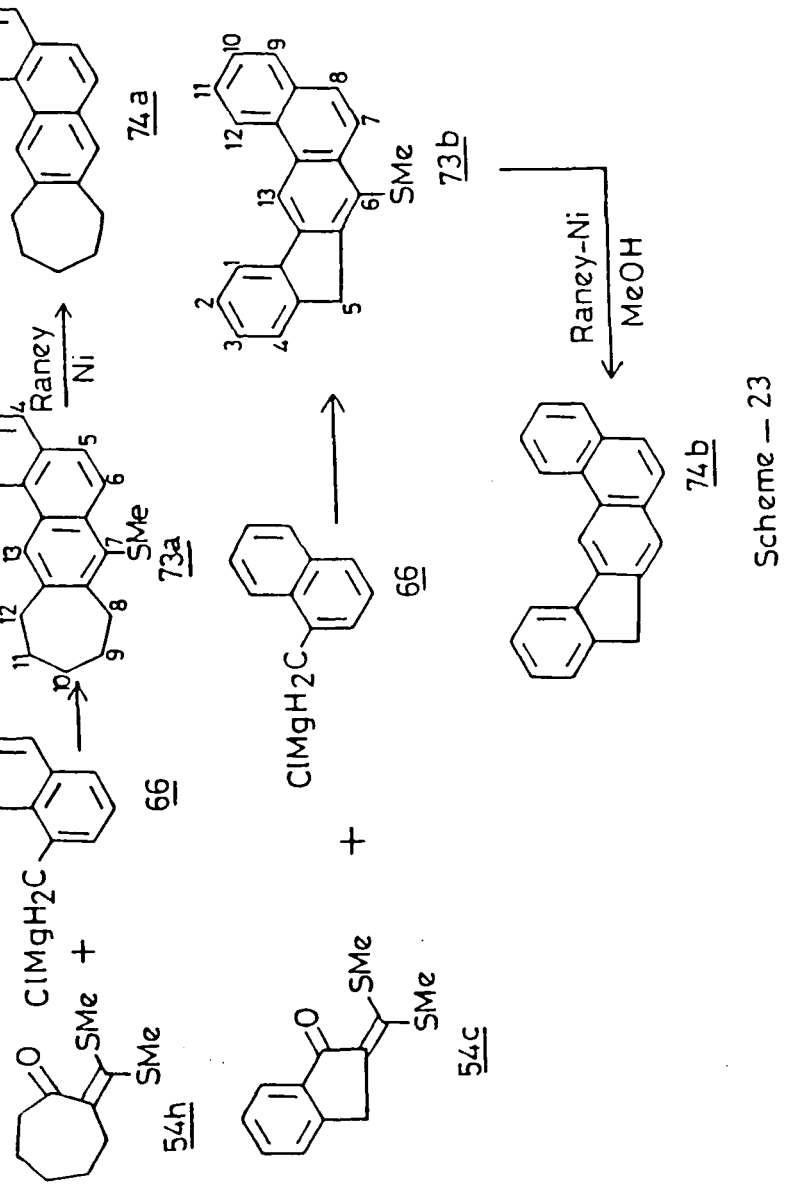
(Scheme 22). The structure of 72b was fully established from its analytical and spectral data (experimental section).

Interestingly again, when 66 was reacted with oxoketene dithioacetals 54h and 54c derived from cycloheptanone and indanone respectively, after cycloaromatization of the resulting carbinolacetal yielded the corresponding polycyclic hydrocarbons 73a and 73b in high yields. These hydrocarbons 73a and 73b have obviously been formed by an exclusive 1,2-addition of 66 with the oxoketene dithioacetals 54h and 54c (Scheme 23). The spectral and analytical data of these compounds were in confirmity with the assigned structures (experimental). The compounds 73a and 73b were desulphurized to the corresponding polycyclic hydrocarbons 74a and 74b by *Raney-Ni* hydrogenation, and their spectral and analytical data are described in the experimental section.

When the reaction of 66 was extended to the oxoketene dithioacetals 54d and 54i derived from tetralones, the products isolated were characterized as the 7-methylthio substituted 8,9-dihydrobenzanthracene 73c and the methoxy analogue 73d, respectively. The product 73c was aromatized by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give aromatized dibenzanthracene 75 in excellent yields. Removal of the methylthio group of 75 was smoothly effected by *Raney-Ni* hydrogenation in methanol to yield the known polycyclic hydrocarbon dibenz



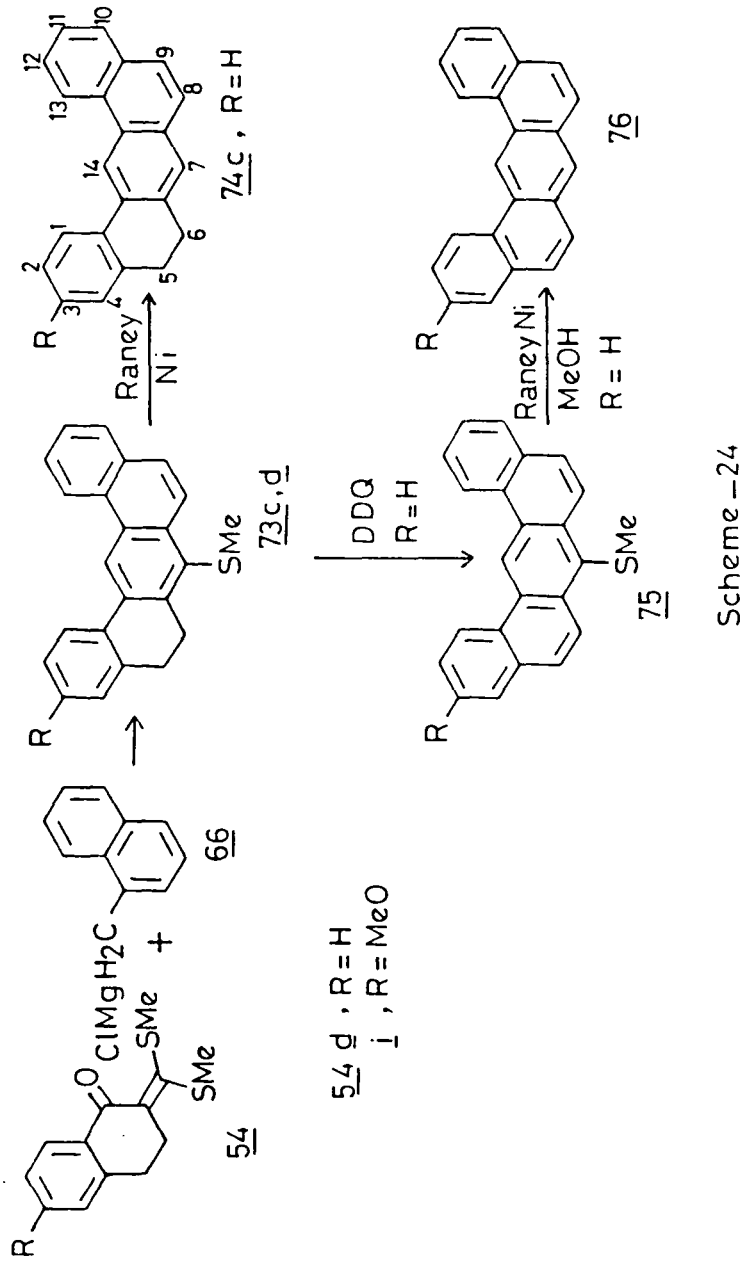
Scheme-22


ClMgH2C
SMe
SMe
54h
66
Raney Ni
73a
74a
ClMgH2C
66
SMe
SMe
54c
73b
Raney-Ni
MeOH
74b

Scheme – 23

[a,j]anthracene 76 (m.p.210°-211°C,reported 212°)[26]. The dihydrobenzanthracene 3c was also desulphurized under similar reaction conditions *(Raney-Ni/MeOH)* to yield 74c (Scheme 24). The structures of all these products were fully established from their spectral and analytical data which are given in the experimental section.

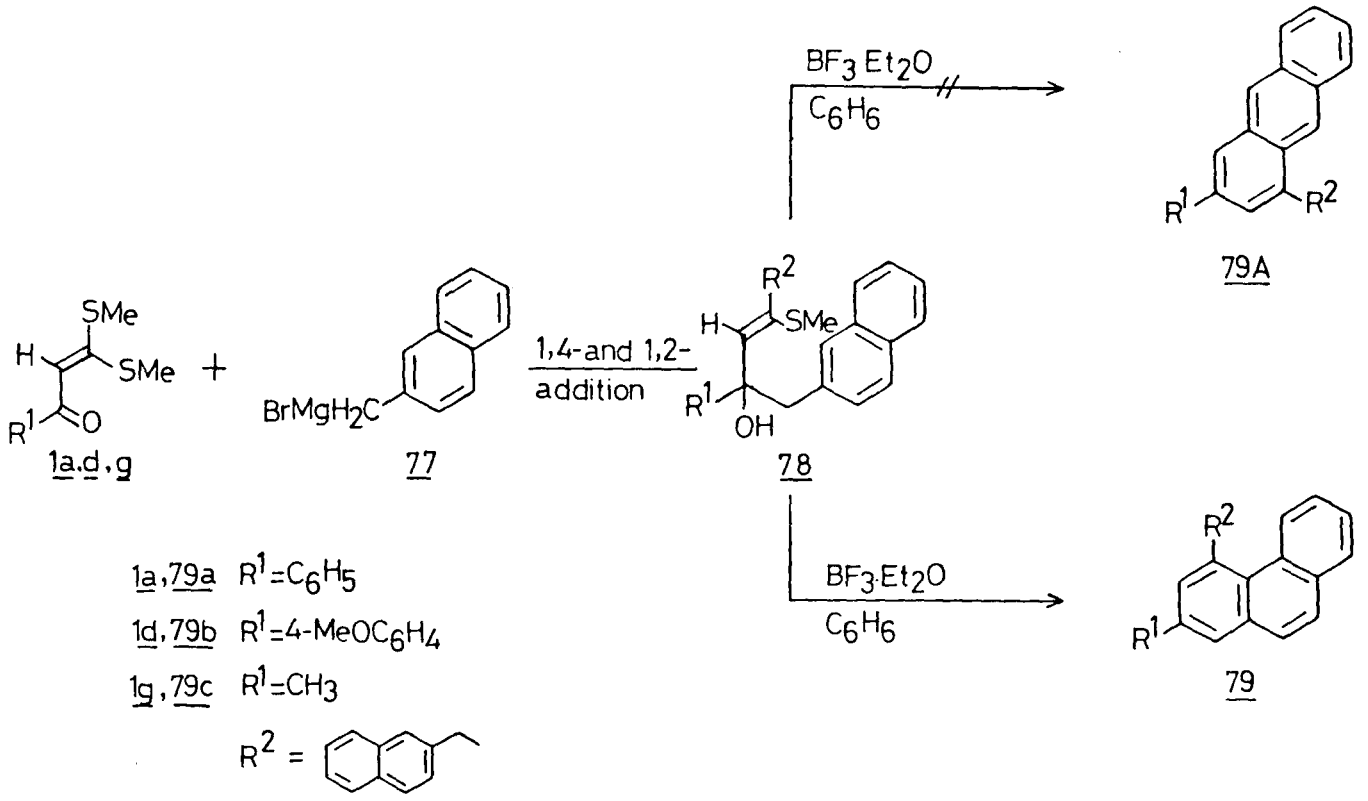
The reaction of 2-naphthylmethylmagnesium bromide 77 with α-oxoketene dithioacetals was next examined. When 1a was reacted with 1.25 equivalents of 77, the reaction mixture after work up and subsequent treatment with $BF_3.Et_2O$ yielded after purification a colourless solid, m.p. 149°C, alongwith the unreacted starting material 1a. The product was characterized as 4-(2-naphthylmethyl)-3-phenylphenanthrene 79a from its analytical and spectral data. Thus it exhibited molecular ion peak at m/z 394 (M^+),36% and was analyzed for $C_{31}H_{22}$. The IR spectrum (KBr) of 79a showed prominent absorbtion bands at ν_{max}1595, 1555, 1490 cm^{-1}. The structure of 79a was further confirmed from its ^1H NMR spectrum in $CDCl_3$ which exhibited a singlet at δ 4.79(2H) due to the benzylic protons while the aromatic protons appeared as multiplet between δ 7.28-8.28(18H) and as singlets at δ 8.49(1H) and 8.59(1H) which were assigned to H-3 and H-1 protons respectively. From the structure of 79a, it is aparent that 2-naphthylmethylmagnesium bromide 77 reacted with 1a in a 1,4 followed by 1,2-addition manner to give the intermediate carbinol acetal 78a which on cycloaromatiza-


R
O
ClMgH2C
SMe
SMe
54
66
73c,d
SMe
Raney Ni
74c , R=H
DDQ
R=H
54 d , R=H
i , R=MeO
75
SMe
Raney Ni
MeOH
R = H
76

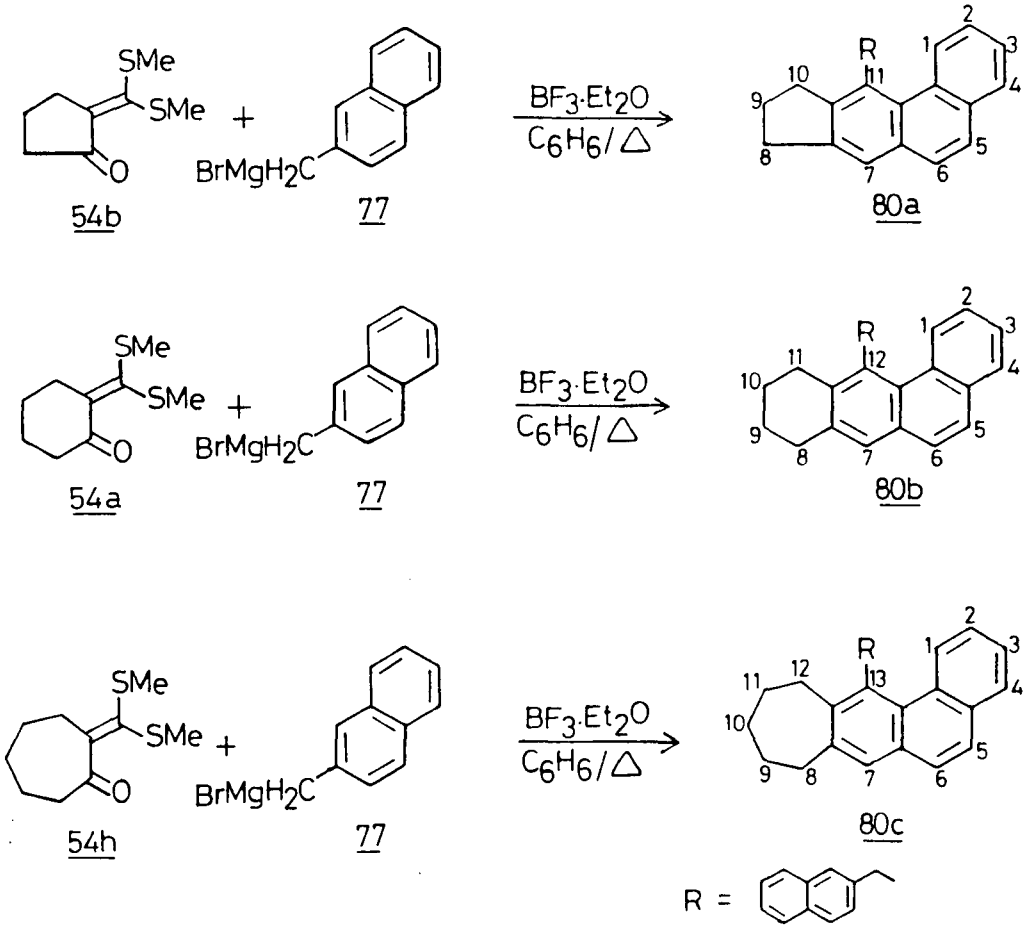
Scheme–24

tion in the presence of $BF_3.Et_2O$ afforded 79a. Therefore, in a separate experiment when 1a was reacted with excess (3 eqv.) of 2-naphthylmethylmagnesium chloride, the yield of 79a was raised to 61%. The structure of 79a has been assigned on the basis of the reactivities of naphthalenes, where the side chain at 2-position invariably interact through α-carbon to give the angularly substistuted phenanthrenes. The other possibility of 78 cyclizing through C-3 of naphthalene to afford the corresponding anthracene derivative 79A is ruled out. Similarly 2-naphthylmethylmagnesium bromide reacted with oxoketene dithioacetals 1d and 1g to afford the corresponding phenanthrenes 79b and 79c in 63 and 58% yields respectively. The spectral and analytical data of 79b and 79c are described in the experimental section (Scheme 25).

The reactivity of cyclic oxoketene dithioacetals 54a,b and 54h with 2-naphthylmethylmagnesium bromide followed sequential 1,4 and 1,2-addition under described reaction conditions to yield the corresponding annelated phenanthrenes 80a-c (Scheme 26) in 50-60% overall yields. The analytical and spectral data of these phenanthrenes 80a-c are in agreement with the assigned structures (experimental). However, α-oxoketene dithioacetals 54d and 54i derived from tetralones reacted with 77 in an exclusive 1,2-fashion to yield the corresponding methylthio substituted dibenzanthracenes 82a and 82b in 53 and 56% yields respectively. The product 82a was


SMe
H
SMe
R1
O
1a,d,g
+
BrMgH2C
77
1,4-and 1,2-
addition
R2
H
SMe
R1
OH
78
BF3 Et2O
C6H6
R1
R2
79A
BF3·Et2O
C6H6
R2
R1
79
1a,79a R1=C6H5
1d,79b R1=4-MeOC6H4
1g,79c R1=CH3
R2 =

Scheme-25

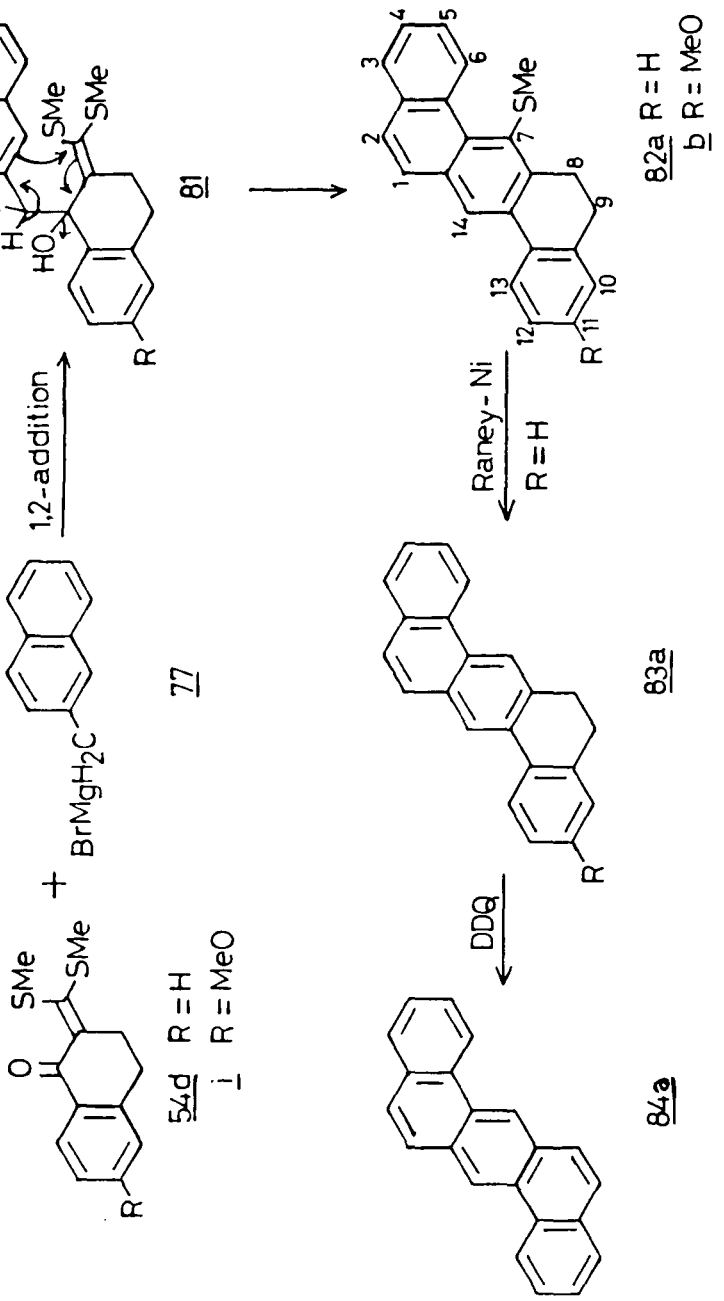


Scheme – 26

dethiomethylated in the presence of *Raney-Nickel* to give 8,9-dihydrodibenz[a,h]anthracene 83a which on dehydrogenation with DDQ afforded the parent dibenz[a,h]anthracene 84a in 68% yield. The physical and spectral data of dibenz[a,h]anthracene 84a was in agreement with that of reported values.[44]

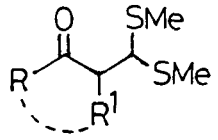
CONCLUSION

The α-oxoketene dithioacetals have been shown to be useful intermediates for the synthesis of naphthalenes, phenanthrenes and other fused aromatic systems by reacting them with benzyl-,1-naphthylmethyl- and 2-naphthylmethylmagnesium halides followed by cycloaromatization. Benzylmagnesium chloride reacts with α-oxoketene dithioacetals in a sequential 1,2- followed by 1,4-addition, leading to the corresponding naphthoannelated compounds. The reaction was found to be very general for the synthesis of various substituted and fused naphthalene derivatives with a few exceptions. The oxoketene dithioacetals derived from cyclopentanone and acetone although gave the corresponding carbinolacetals on reaction with benzylmagnesium chloride but failed to give the cycloaromatized naphthalenes. Also the oxoketenedithioacetals with an α-methyl substitution failed to give the expected naphthalene and afforded instead the corresponding indene derivative. However, 1-naphthylmethylmagnesium chloride underwent an exclusive 1,2-addition with oxoketene dithi-


SMe
SMe
O
R
54d R=H
i R=MeO
+
BrMgH2C
77
1,2-addition
SMe
SMe
H
H
HO
R
81
SMe
R
82a R=H
b R=MeO
Raney-Ni
R=H
R
83a
DDQ
84a

Scheme - 27

oacetals to yield the corresponding phenathrenes in high yields. It is pertinent to note that the 1,2-regioselectivity of 1-naphthylmethylmagnesium chloride is lost in the reaction of oxoketene dithioacetals derived from cyclopentanone and cyclohexanone, where the reaction took a 1,4- followed by 1,2-adition sequence to afford the corresponding phenathrenes. Again, the reaction of 2-naphthylmethylmagnesium bromide underwent a 1,4-addition followed by 1,2-addition path to yield the corresponding phenanthrenes. One exception was noted in the reaction of 2-naphthylmethylmagnesium bromide with the oxoketene dithioacetal derived from tetralone, where exclusive 1,2-addition was observed. The 1,2-regioselectivity observed for 1-naphthylmethylmagnesium chloride in these investigations appears to be due to both steric and electronic factors, since the highly delocalized anions behave like soft nucleophiles and undergo preferential frontier orbital controlled 1,4-addition[27] in the initial step. Efforts to achieve 1,2-addition only, by reacting these anions with β-ketothioacetals 85 derived



85

from α-oxoketene dithioacetals, thereby avoiding benzyl and naphthylmethyl substitutions in the cycloaromatized products are being attempted.

II.4 EXPERIMENTAL SECTION

General

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 90 MHz on a Varian EM-390 spectrometer and the chemical shift values are expressed as δ(ppm) down field from tetramethyl silane (TMS), as internal standard. IR spectra were run on Perkin-Elmer model 297 spectrometer and the mass spectra were recorded on Jeol JMS D 300 instrument. Carbon and Hydrogen elemental analysis were done on a Heraeus CHN-O-RAPID instrument.

Grignard grade magnesium turnings (SISCO) were used for all the Grignard reactions, which were carried out under an atmosphere of oxygen free dry nitrogen gas. Benzylchloride and 1-chloromethylnaphthalene were purchased (Aldrich) and used as supplied. Borontrifluoride etherate was distilled (125-26°C) before use. TLC (silica gel BDH) was used for monitoring the reactions.

Starting Materials

The commercial samples of acetophenone, 4-chloroacetophenone, 4-methylacetophenone, 4-methoxyacetophenone, acetone, cyclopentanone, cyclohexanone and cycloheptanone were purified by distillation under reduced pressure before use.

2-Bromomethylnaphthalene was prepared by reported procedure[28]. 1-Tetralone, b.p. 140-150°C (10 mm)[29], 1-indanone, m.p. 39-40°C[30], propiophenone, b.p. 105-10°C (8 mm)[31], 2,3-dihydro-1-benzothiopyran-4-one, b.p. 154°C (12 mm)[32] 3,4-dihydro-8-methyl-1-benzothiepin-5(2H)-one, b.p. 138-42°C (0.7 mm)[33], 3,4-dihydro-1-benzoxepin-5(2H)-one, b.p. 106°C (2 mm)[34] were prepared acording to the reported procedures.

The following previously reported oxoketene dithioacetals; 3,3-bis(methylthio)-1-phenyl-2-propen-1-one 1a, m.p. 93°C[35]; 3,3-bis(methylthio)-1-(4-chlorophenyl)-2-propen-1-one 1b, m.p. 109-10°C[35], 3,3-bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one 1d m.p.100°C[35], 2-[bis(methylthio)methylene]cyclohexanone 54b b.p. 118°C (1 mm)[36], 2-[bis(methylthio)methylene]-1-indanone54c m.p. 70-71°C[37]; 2-[bis(methylthio)methylene]-1-tetralone 54d m.p. 58°C[38]; 2-[bis(methylthio)methylene]-6-methoxy-1-tetralone 54i, m.p. 78°C[39]; 3,3-bis(methylthio)-2-methyl-1-phenyl-2-propen-1-one 1i b.p. 168-70°C (13 mm)[40], 3-[bis(methylthio)methylene]-2,3-dihydro-1-benzothiopyran-4-one 54e m.p. 80-81°C[41]; 4-[bis(methylthio)methylene]-2,3-dihydro-1-benzothiopyran-4-one 54e m.p. 80-81°C[41]; 4-[bis(methylthio)methylene]-3,4-dihydro-8-methyl-1-benzothiepin-5(2H)-one 54f, m.p. 136°C[41]; 4-[bis(methylthio)-methylene]-3,4-dihydro-8-methyl-1-benzothiepin-5(2H)-one 54g m.p. 78°C[41]; were prepared according to general procedure described in the following section. *W4-Raney*

Nickel was prepared according to the reported procedure[42].

General method for the preparation of Oxoketene Dithioacetals 1a-i and 54a-g using Sodium-t-butoxide.

A mixture of the ketone (0.5 mol) and carbon disulphide (0.5 mol) in dry benzene (100 ml) was added dropwise to an ice cooled and well stirred suspension of sodium-t-butoxide (1.0 mol and the reaction mixture was stirred for 4-5 hr. Methyliodide (1.1 mol) was then gradually added with cooling and the reaction mixture was further stirred for 6 hr and then refluxed for 1 hr, cooled and poured into ice cooled water. The benzene layer was separated and the aqueous phase was extracted with benzene (200 ml), the combined benzene extracts were washed with water (200 ml), dried (Na_2SO_4) and evaporated to give the crude dithioacetals 1 which were further purified either by crystallization or by distillation under reduced pressure.

General procedure for the Reaction of Benzylmagnesium Chloride with Oxoketene Dithioacetals

To an ice cooled solution (0.5°C) of benzylmagnesium chloride [0.03 mol, prepared from magnesium turnings (1.0g) and benzyl chloride (3.60g)] in dry ether (60 ml), oxoketene dithioacetal (0.015 mol) in dry benzene (25 ml) was added dropwise (2-3 min) under an efficient

atmosphere of nitrogen. The reaction mixture after stirring for 45 min, was decomposed by pouring over saturated aqueous NH_4Cl solution (50 ml) and then extracted with ether (2x50 ml). The combined ether extracts were washed with water (50 ml), dried (Na_2SO_4) and evaporated give the crude alcohol which were used as such for the cycloaromatization step.

General procedure for Borontrifluoride Etherate catalysed Cycloaromatisation of Carbinolacetals 55a,55c-g,61a-g: Synthesis of Naphthoannelated products 58a, 58c-g, 63a-f.

To a solution of the carbinolacetal (0.01 mol) in dry benzene (50 ml), borontrifluoride etherate (2 ml) was added and the reaction mixture was refluxed for 45 min. It was then cooled, poured into saturated $NaHCO_3$ solution (50 ml), extracted with chloroform (2x100 ml), washed with water (50 ml) dried (Na_2SO_4) and evaporated to give a viscous residue, which upon column chromatography over silica gel (hexane as eluent) afforded analytically pure products.

9-Benzyl-1,2,3,4-tetrahydroanthracene (58a): was isolated as colourless crystals (hexane); yield 81%;IR and NMR data given in the text. (Found: C, 92.51; H, 7.38; Calc. for $C_{21}H_{20}$: C,92.60; H, 7.40%); m/z 272 (M^+,22%);181(10).

10-Benzylbenzo[b]fluorene (58c): was isolated as colourless crystals (hexane); yield (62%); m.p.187^oC; IR ν_{max}

(KBr) 1600,1580,1498 cm^{-1}; ^1H NMR (CCl_4); 3.91 (s, 2H, CH_2); 4.50 (s, 2H,benzylic CH_2); 6.98-7.51 (m,9H,arom); 7.70-8.19 (m,5H,arom); (Found: C,93.94; H,5.90; Calc. for $C_{24}H_{18}$: C,94.08; H,5.92%); m/z 307 (M^+,34%); 228(12).

7-Benzyl-5,6-dihydrobenz[a]anthracene (58d): was isolated as colourless crystals (hexane); yield (71%); m.p. 108°C; IRν_{max}(KBr) 1600,1580,1488 cm^{-1}; ^1H NMR (CCl_4); 2.78-3.22 (m,4H,CH_2); 4.49 (s,2H,benzylic CH_2); 6.88-7.61 (m,8H,arom); 7.61-8.03 (m,5H,arom); 8.19 (s,1H,H-12) (Found: C, 93.78; H,6.19; Calc. for $C_{23}H_{20}$: C,93.71; H, 6.29%); m/z 320 (M^+,100%); 242(20).

7-Benzyl-6H-[1]benzothiapyrano[3,4-b]naphthalene (58e): was isolated as yellow crystals (hexane); yield 58%; m.p. 93-94P°C; IRν_{max}(KBr) 1598,1495,1461 cm^{-1}; ^1H NMR (CCl_4); 3.95 (s,2H,SCH_2);4.41 (s,5H,arom);7.85 (s,1H,H-12)(Found: C, 85.12; H,5.30; Calc. for $C_{24}H_{18}S$:C,85.17; H, 5.36%) m/z 338 (M^+,8%);21(20).

8-Benzyl-6,7-dihydro-3-methyl[1]benzothiapeno[4,5-b]naphthalene (58f): was isolated as yellow crystals (hexane); yield 68%; m.p. 110°C; IRν_{max}(KBr) 1600,1499,1458 cm^{-1}; ^1H NMR (CCl_4); 2.21 (s,3H,CH_3);2.41-3.02 (m,2H,CH_2);3.18 (s,2H, benzylic CH_2);3.21-3.75 (m,2H,SCH_2);6.40-6.68 (m,3H, arom);6.79-7.81 (m,9H,arom); (Found: C,85.28; H,6.19;Calc. for $C_{26}H_{22}S$: C,85.20; H,6.05%);m/z 366 (M^+,100%)289(7).

8-Benzyl-6,7-dihydro[1]benzoxepino[4,5-b]naphthalene (58g): was isolated as colourless crystals (hexane);

yield 67%; m.p. 155°C, IR ν_{max}(KBr) 1601,1580,1498 cm^{-1}; ^1H NMR (CCl_4)2.90 (t,J=7 Hz,2H,CH_2);4.18 (t,J=8 Hz,OCH_2); 4.48 (s,2H,CH_2); 6.80-7.45 (m,10H,arom);7.61-8.04(m,4H, arom); (Found: C,92.78; H,5.91;Calc. for $C_{25}H_{20}O$: C, 92.82; H, 5.99%); m/z 336 (M^+,100%);302(6).

1-Benzyl-3-phenylnaphthalene (63a): was isolated as pale yellow crystals (hexane); yield 59%; m.p. 119°C; IR ν_{max}(KBr) 1600,1548,1495 cm^{-1};^1H NMR (CCl_4);3.92(s,2H, benzylic CH_2); 6.65 (s,1H,arom);7.01-7.71 (m,15H,arom); (Found: C,93.81;H,6.01;Calc. for $C_{23}H_{18}$:C,93.84:H,6.16%); m/z 294(M^+,26%);217(25).

1-Benzyl-3-(4-chlorophenyl)naphthalene (63b): was isolated as colourless crystals (hexane); yield 68%; m.p. 95°C; IR ν_{max}(KBr) 1600,1498,1450 cm^{-1};^1H NMR (CCl_4); 4.26 (s,2H,benzylic CH_2); 6.96-7.41 (m,11H,arom); 7.48-8.09 (m,4H,arom); (Found: C,83.92; H,5.41; Calc. for $C_{23}H_{17}Cl$: C, 84.01;H,5.21%); m/z 328 (M^+,100%) 215(50).

1-Benzyl-3-(4-bromophenyl)naphthalene (63c): was isolated as colourless crystals (hexane); yield 69%; m.p. 80-81°C; IR ν_{max}(KBr) 1600,1490,1448 cm^{-1}; ^1H NMR (CCl_4); 4.35 (s, 2H,benzylic CH_2); 7.05-7.58 (m,10H ,arom); 7.66-8.49 (m, 5H,arom) (Found: C, 73.92; H,4.51; Calc. for $C_{23}H_{17}Br$: C, 74.00; H,4.59%); m/z 373 (M^+,25%); 292(17).

1-Benzyl-3-(4-methoxyphenyl)naphthalene (63d): was isolated as yellow crystals (hexane); yield 61%; m.p. 115°C;

IRν_{max}(KBr) 1605,1520,1498 cm^{-1}; ^1H NMR (CCl_4) 3.75 (s, 3H,OCH_3); 4.41 (s,2H,benzylic CH_2); 6.80 (d,J=9Hz,2H, A_2B_2,arom);7.05-8.01 (m,13H,arom) (Found: C,88.79; H,6.08; Calc. for $C_{24}H_{20}O$: C, 88.85; H, 6.21%); m/z 324(M^+,100%); 309(10).

1-Benzyl-3-(4-methylphenyl)naphthalene (63e): was isolated as yellow crystals (hexane); yield 65%; m.p. 112°C; IRν_{max}(KBr) 1600,1498,1458 cm^{-1}; ^1H NMR (CCl_4); 2.21 (s, 3H,CH_3); 3.91 (s,2H,benzylic CH_2); 6.79-7.81 (m,15H, arom); (Found: C, 93.49; H,6.48;Calc. for $C_{24}H_{20}$: C, 93.46; H,6.54%); m/z 308 (M^+,37%); 264(100).

1-Benzyl-3,2'-binaphthyl (63f): was isolated as pale yellow crystals (hexane); yield (58%); m.p. 190°C; IR ν_{max}(KBr) 1605,1565,1495 cm^{-1}; ^1H NMR (CCl_4); 4.39 (s, 2H, benzylic CH_2); 6.42-6.61 (m,2H,arom); 7.01-8.06 (m,16H, arom); (Found: C,94.01; H,5.79; Calc. for $C_{27}H_{20}$: C, 94.15; H, 5.85%) m/z 344 (M^+,100%);267(22).

1,3-Dibenzyl-2-methyl-1-(methylthio)indene (65): was isolated as colourless crystals (hexane); yield (57%); m.p. 82°C; IRν_{max}(KBr) 1601,1553,1494 cm^{-1}; ^1H NMR (CCl_4); 1.25 (s,3H, SCH_3);1.80 (s,3H,SCH_3); 3.21 (q,J=2 Hz,2H,benzylic CH_2);3.59(brs,2H,benzylic CH_2);6.39-7.09 (m,13H,arom); 7.39 (m,1H,arom);(Found: C,84.18;H,6.71; Calc. for $C_{25}H_{24}S$: C,84.22;H,6.78%);m/z 356 (M^+,8%) 341(3) 309(5). (? 100%)

General procedure for the Reaction of 1-Naphthylmethyl-magnesium chloride 66 with Oxoketene dithioacetals:

To a cooled solution (0-5°C) of 1-naphthylmethylmagnesium chloride [0.015 mol,prepared from magnesium turnings (1.0g) and 1-(chloromethyl)naphthalene (2.64g),(0.03 mol case of 54a and 54b)] in dry ether (60 ml) oxoketene dithioacetal (0.01 mol) in dry benzene (25 ml) was added dropwise (2-3 min) and after stirring for 45 min, the reaction mixture was decomposed by pouring into saturated aqueous NH_4Cl solution (50 ml) and then extracted with ether (2x50 ml). The combined ether extracts were washed with water (50 ml), dried (Na_2SO_4) and evaporated to give the crude carbinol acetal (90%) as a viscous liquid, which however decomposed on attempted purification through silica gel column.

General Procedure for Borontrifluoride etherate catalysed cycloaromatisation of carbinol acetals: Synthesis of 69a-g,72a,b,73a-d. To a solution of the carbinol (0.01 mol) in dry benzene (50 ml), borontrifluoride etherate (2 ml) was added and the reaction mixture was refluxed for 45 min. It was then cooled,poured into saturated $NaHCO_3$ solution (50 ml) extracted with chloroform (2x100 ml), washed with water (50 ml) dried (Na_2SO_4) and evaporated to give viscous residue, which upon column chromatography over silica gel (hexane as eluent) afforded analytical pure products.

3-Methyl-1-(methylthio)phenanthrene (69a) was isolated as colourless crystals (hexane); yield 69%; m.p. 79°C; IR ν_{max}(KBr) 1598,1560,1505 cm^{-1}; ^1H NMR ($CDCl_3$); 2.54 (s, 3H,CH_3); 2.62 (s,3H,SCH_3); 7.29 (s,1H,arom); 7.45-7.90 (m,5H, arom); 8.36 (s,1H,arom); 8.61 (m,1H,arom);(Found: C,80.52; H,5.98; Calc. for $C_{16}H_{14}S$:C,80.63; H,5.92%); m/z (M^+,100%);208(10).

1-(Methylthio)-3-phenylphenathrene (69b): was isolated as colourless crystals; yield 74% m.p. 101°C; IRν_{max}(KBr) 1590.1560,1505 cm^{-1}; ^1H NMR ($CDCl_3$); 2.58 (s,3H,SCH_3); 7.40-7.98 (m,10H,arom); 8.24 (d,J=9 Hz,1H, arom); 8.73 (m,2H,arom); (Found: C,83.82; H,5.31; Calc. for $C_{21}H_{16}S$: C, 83.96; H,5.40%); m/z 300 (M^+,100%); 285(17); 252(20).

3-(4-Chlorophenyl)-1-(methylthio)phenathrene (69c): was isolated as colourless crystals; yield 72%; m.p. 127°C; IRν_{max}(KBr) 1598,1570,1560 cm^{-1}; ^1H NMR ($CDCl_3$); 2.59 (s, 3H,SCH_3); 7.35-7.98 (m,9H,arom); 8.26 (d,J=8 Hz,1H,arom); 8.49-8.61 (m,2H,arom); (Found: C,75.21; H,4.58; Calc.for $C_{21}H_{15}ClS$: C, 75.32; H,4.52%); m/z 334 (M^+,100%); 284(20).

3-(4-Methoxyphenyl)-1-(methylthio)phenathrene (69d): was isolated as colourless crystals; yield 81%; m.p. 125°C; IRν_{max}(KBr) 1620, 1598,1516 cm^{-1};^1H NMR ($CDCl_3$); 2.56 (s,3H,SCH_3); 3.78 (s,3H,OCH_3); 6.88 (d,J=9Hz, 2H,A_2B_2 arom);7.31-7.82 (m,7H,arom); 8.21 (d,J=9Hz,2H,A_2B_2 arom); 8.49-8.81 (m,2H, arom); (Found: C, 79.82; H,5.51; Calc.

for $C_{22}H_{18}OS$: C,79.96; H, 5.49%); m/z 330 (M^+,100%); 315(20).

3-(4-Methylphenyl)-1-(methylthio)phenathrene (69e) was isolated as light yellow crystals (hexane); yield 79%; m.p. 109°C; IR ν_{max}(KBr) 1590,1588,1500 cm^{-1}; ^1H NMR ($CDCl_3$); 2.42 (s,3H,CH_3); 2.62 (s,3H,SCH_3); 7.25 (d, J=9Hz, 2H,A_2B_2 arom); 7.49-7.86 (m,7H,arom); 8.21 (d, J=9Hz, 1H, arom); 8.62 (m,2H,arom); (Found: C,83.92; H, 5.68; Calc.for $C_{22}H_{18}S$: C,84.03; H,5.77%); m/z 314 (M^+,100%); 299(11).

3-(2-Naphthyl)-1-(methylthio)phenanthrene 69f):was isolated as colourless crystals (hexane); yield 66%; m.p. 182-183°C. IR ν_{max}(KBr) 1598.1501,1460 cm^{-1}; ^1H NMR ($CDCl_3$); 3.01 (s,3H,SCH_3); 6.71-7.15 (m,8H,arom); 7.21-7.78 (m,7H, arom); (Found: C,86.81; H,4.84; Calc.for $C_{27}H_{18}S$: C,86.59; H,4.84%).

2,3-Dimethyl-1-(methylthio)phenathrene(69g): was isolated as light yellow crystals(hexane); yield 68%; m.p. 92-93°C IR ν_{max}(KBr) 1585,1510,1440 cm^{-1}; ^1H NMR ($CDCl_3$) 2.42 (s, 3H, CH_3)2.55 (s,3H,CH_3); 2.61 (s,3H,SCH_3); 7.42-7.98 (m, 5H,arom); 8.32 (s,1H,H-4);8.55 (brd,1H,arom); (Found: C, 81.12; H,6.41; Calc. for $C_{17}H_{16}S$: C, 80.90; H,6.39%).

7-(1-Naphthylmethyl)8,9,10,11-tetrahydrobenz[a]anthracene (72a): was isolated as colourless crystals (hexane); yield 68%;m.p. 178°C IR ν_{max}(KBr) 1596,1506 cm^{-1}; ^1H NMR ($CDCl_3$); 1.68-1.98 (m,4H,CH_2), 2.54-2.86 (m,2H,CH_2); 2.98-3.25 (m,2H,CH_2);4.73 (s,2H, benzylic CH_2); 6.51 (d,

J=7Hz,1H,arom); 6.98-7.91 (m,10H,arom); 8.15 (m,1H,arom); 8.45 (s,1H,H-12); 8.78 (d,J=9 Hz,1H,H-1); (Found: C, 93.49; H,6.32; Calc. for $C_{29}H_{24}$: C,93.51; H,6.49%);m/z 372 (M^+,100%); 244(74).

9,10-Dihydro-[8H]-7-(1-naphthylmethyl)cyclopenta[b]phenathrene (72b): was isolated as colourless crystals (hexane);yield 58%;m.p. 141°C;IR ν_{max}(KBr)1598,1501 cm^{-1}; ^1H NMR ($CDCl_3$); 2.12 (m,2H,CH_2); 2.98 (t,J=7Hz,2H,CH_2); 4.91 (s,2H,benzylic CH_2); 6.68 (d,J=7Hz; 1H,arom);7.05-8.20 (m,10H,arom); 8.45 (dd,J=7 and 2.5Hz,1H,arom); 8.72 (s,1H,H-11); 8.89 (d,J=7Hz,1H,H-10); (Found:C, 93.71; H, 6.09; Calc. for $C_{28}H_{22}$: C,93.81; H,6.19%); m/z 358 (M^+, 100%); 231(96).

7-Methylthio-9,10,11,12-tetrahydro[8H]cyclohepta[b]phenathrene (73a): was isolated as colourless crystals (hexane); yield 68% m.p. 114°C; IR ν_{max}(KBr)1580,1505, 1490 cm^{-1};^1H NMR ($CDCl_3$); 1.58-2.02 (m,4H,CH_2); 7.54-8.25 (m,5H,arom); 8.56 (s,1H,H-13); 8.79 (m,1H,arom);(Found: C,82.01; H,6.81; Calc.for $C_{20}H_{20}S$; C,82.14; H,6.89%); m/z 292 (M^+,100%); 215(62).

6-Methylthio[5H]indane[2,1-b]phenathrene (73b): was isolated as colourless crystals (hexane); yield 66%; m.p. 146°; IR ν_{max}(KBr) 1598,1565,1515 cm^{-1};^1H NMR($CDCl_3$); 2.52 (s,3H,SCH_3);4.35 (s,2H,CH_2); 7.49-8.31 (m,8H,arom); 8.85-9.18 (m,2H,arom); 9.32 (s,1H,H-13);(Found:C,84.42;H,5.19; Calc. for $C_{22}H_{16}S$:C,84.57; H,5.16%);m/z 312 (M^+,50%); 265(100).

5,6-Dihydro-7-(methylthio)dibenz[a,j]anthracene(73c): was isolated as colourless crystals (hexane); yield 67%; m.p. 85°C IRν_{max}(KBr) 1595,1511,1482 cm^{-1}; ^1H NMR ($CDCl_3$); 2.15 (s,3H,SCH_3); 2.78 (m,2H,CH_2);3.36 (m,2H,CH_2); 7.02-7.89 (m,8H,arom); 8.54 (m,2H,arom);8.86 (s,1H,H-13); (Found:C,84.51; H,5.61; Calc. for $C_{23}H_{18}S$: C, 84.62; H, 5.56%); m/z 326 (M^+,81%); 279(3); 278(100).

5,6-Dihydro-3-methoxy-7-(methylthio)dibenz[a,j]anthracene (73d): was isolated as light yellow crystals (hexane); yield 74%; m.p.144-145°C;IRν_{max}(KBr);1602,1585,1575 cm^{-1}; ^1H NMR ($CDCl_3$); 2.29 (s,3H,SCH_3);2.75-3.02 (m,2H,CH_2); 3.34-4.42 (m,2H,CH_2);3.85 (s,3H,OCH_3); 6.78 (m,2H,arom); 7.25 (s,1H,H-4); 7.54-8.08 (m,4H,arom); 8.65-8.89 (m,2H, arom);9.02 (s,1H,H-14);(Found:C,87.92; H,5.58; Calc.for $C_{24}H_{20}OS$: C, 88.08; H,5.65%);m/z 356 (M^+,100%); 309(22).

Dehydrogenation of 73c with DDQ: A solution of 73c (100mg) and DDQ (100 mg) in dioxane (20 ml) was refluxed for 24 hr under a N_2 blanket. The precipitated hydroquinone was filtered off and the filtrate was chromatographed over silica gel using hexane as eluent to yield **7-(Methylthio)dibenz[a,j]anthracene (75):** as colourless crystals (hexane); yield 96%; m.p.193°C; IRν_{max} (KBr) 1600,1580,1510 cm^{-1}; ^1H NMR ($CDCl_3$); 2.38 (s, 3H, SCH_3); 7.55-8.02 (m,8H,arom); 8.69-9.04 (m,4H,arom); 10.00 (s,1H,H-14);(Found: C,85.18; H,4.71; Calc. for $C_{23}H_{16}S$: C,85.15; H, 4.97%).

General Procedure for Raney-Nickel Desulphurization of the Cycloaromatized Products 69a,69d,69e,73a-c and 75
To a solution of methylthiophenanthrene (200 mg) in methanol (20 ml) was added Raney-Nickel (W-4) (Ca.2g) and the mixture was stirred at room temperature for 5-6 hr (monitored by t.l.c.). It was then filtered and the residue washed with hot methanol (3x10 ml). The bulk of the methanol was removed under reduced pressure and the residue diluted with chloroform (30 ml), washed with water (2x25 ml), dried and evaporated to give crude desulphurized products. Analyticlly pure compounds were obtained by column chromatography of the product over silica gel using hexane as eluent.

3-Methylphenanthrene (70a): was isolated as colourless crystals (hexane); yield 73%; m.p. 60-61°C (lit.[43],m.p. 62°C) IR ν_{max}(KBr) 1598,1460,1440 cm^{-1}; ^1H NMR ($CDCl_3$); 2.69 (s,3H,CH_3); 7.35-7.98 (m,7H,arom); 8.41-8.71 (m,2H, arom); (Found: C,93.68; H,6.18; Calc.for $C_{15}H_{12}$:C,93.75; H, 6.25%).

3-(4-Methoxyphenyl)phenathrene (70b): was isolated as colourless crystals (hexane); yield 89%; m.p. 72°C IR ν_{max} 1600,1575,1496 cm^{-1}; ^1H NMR ($CDCl_3$); 3.91 (s, 3H, OCH_3); 7.06-7.38 (m,3H,arom); 7.61-8.12 (m,8H,arom); 8.85-9.05 (m,2H,arom); (Found: C,88.68; H,5.71; Calc. for $C_{21}H_{16}O$: C, 88.70; H,5.67%).

3-(4-Methylphenyl)phenathrene (70c): was isolated as colourless crystals (hexane); yield 91%; m.p. 68°C. IR ν_{max}(KBr)1600,1560,1500 $^{-1}$; ^{1}H NMR ($CDCl_3$); 2.32 (s, 3H, CH_3); 7.23-8.18 (m,11H,arom); 8.68-8.98 (m,2H,arom) (Found: C,93.82; H,5.98; Calc. for $C_{21}H_{16}$: C,93.99; H,6.01%).

2,3-Cycloheptaphenathrene (74a): was isolated as colourless crystals (hexane); yield 89%; m.p. 78°C IR ν_{max}(KBr) 1605,1560 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.38-2.02 (m,6H,CH_2); 2.91-3.12 (m,2H,CH_2); 3.22-3.48 (m,2H,CH_2); 7.18-8.18 (m, 6H,CH_2); 7.18-8.18 (m,6H,arom); 8.45-8.85 (m,2H,arom); (Found: C,92.58; H,7.28; Calc. for $C_{19}H_{18}$: C, 92.64; H,7.36%).

5H-Indane[2,1-b]phenanthrene (74b): was isolated as colourless crystals (hexane); yield (82%); m.p. 101-102°C IR ν_{max}(KBr) 1604,1550 cm^{-1}; ^{1}H NMR ($CDCl_3$); 4.02 (s,2H, CH_2); 7.21-8.05 (m,10H,arom); 8.75 (brd, 1H,arom); 9.01 (s,1H,H-13); (Found: C,94.58; H,5.21; Calc.for $C_{21}H_{14}$; C, 94.69; H,6.89%).

5,6-Dihydrodibenz[a,j]anthracene (74c): was isolated as colourless crystals (hexane); yield 81%; m.p. 134°C; IR ν_{max}(KBr) 1598,1502,1440 cm^{-1}; ^{1}H NMR ($CDCl_3$); 2.81-3.21 (m,4H,CH_2); 7.18-8.34 (m,10H,arom); 8.64 (brd,1H, arom); 9.11 (s,1H,H-14); (Found:C,94.18; H,5.71; Calc.for $C_{22}H_{16}$: C,94.25; H,5.75%).

Dibenz[a,j]anthracene (75): was isolated as colourless crystals (hexane); yield 78%; m.p. 210-211°C. (lit.[44]; m.p.212 °C); IR ν_{max} 1600,1510,1485 cm^{-1}; ^1H NMR ($CDCl_3$); 7.38-7.95 (m,10H,arom); 8.25 (s,1H,H-7); 8.71-9.08 (m,2H, arom); 9.95 (s,1H,H-14); (Found: C,94.83; H,5.01; Calc. for $C_{22}H_{14}$: C,94.93; H,5.07%).

General Procedure for the Reaction of 2-Naphthylmethylmagnesium Bromide 77 with α-Oxoketene Dithioacetals: The α-oxoketene dithioacetals (0.01 mol) were reacted with 2-naphthylmethylmagnesium bromide 77 (0.03 mol) for 1a,d,g,54a,b,h and 0.015 mol for 54d and 54i) in the same manner as described for 1-naphthylmethylmagnesium chloride and the resulting carbinol acetals were cycloaromatized with borontrifluoride etherate and worked-up according to the method described earlier. The spectral and analytical data of cycloaromatized products is given below.

4(2-Naphthylmethyl)-2-phenylphenanthrene (79a) was isolated as colourless crystals(hexane);yield 71%;m.p.149°C. IR and NMR data given in text. (Found: C, 94.27; H,5.68; Calc. for $C_{31}H_{22}$: C,94.38; H,5.62%); m/z 394 (M^+, 36%)); 279(20).

2-(4-Methoxyphenyl)-4-(2-Naphthylmethyl)phenanthrene(79b) was isolated as colourless crystals (hexane); yield 73%; m.p. 163-164°C IR ν_{max}(KBr) 1600,1575,1510 cm^{-1}; ^1H NMR ($CDCl_3$): 3.81 (s, 3H,OCH_3); 5.02 (s,2H,benzylic CH_2); 6.89-8.08 (m,17H,arom); 8.52 (m,2H,arom); (Found:

C,90.43; H,5.62; Calc. for $C_{32}H_{24}O$: C,90.53; H,5.70%); m/z 424 (M^+,100%); 295(8).

2-Methyl-4-(2-naphthylmethyl)phenanthrene (79c) was isolated as colourless crystals (hexane); yield 71%; m.p.122°C; IR ν_{max}(KBr) 1590,1460,1440 cm^{-1}; ^1H NMR ($CDCl_3$): 2.68 (s,3H,CH_3); 4.25 (s,2H,benzylic CH_2); 7.04-8.12 (m,13H,arom); 8.31 (s,1H,arom); 8.49 (s,1H, arom); (Found: C,93.82; H,6.01; Calc. for $C_{26}H_{20}$: C,93.94; H,6.06%); m/z 332 (M^+, 100%); 317(19).

9,10-Dihydro-[8H]-11-(2-naphthylmethyl)cyclopenta[b]phenanthrene (80a) was isolated as colourless crystals (hexane); yield 56%; m.p. 142°C; IR ν_{max}(KBr) 1620,1598, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): 2.08 (m,2H,CH_2); 3.05 (m, 4H, CH_2); 4.64 (s,2H,benzylic CH_2); 7.09-8.02 (m,12H,arom); 8.24-8.45 (m,2H,arom); (Found: C,93.73; H,6.17; Calc. for $C_{28}H_{22}$: C,93.81; H,6.19%); m/z 359 (M^+, 100%); 282(18).

12-(2-Naphthylmethyl)8,9,10,11-tetrahydrobenz[a]anthracene(80b) was isolated as colourless crystals (hexane); yield 63%; m.p. 141°C; IR ν_{max}(KBr) 1620,1595,1498 cm^{-1}; ^1H NMR ($CDCl_3$): 1.61-2.02 (m,4H,CH_2); 2.58-3.21 (m, 4H, CH_2); 4.51 (s,2H,benzylic CH_2); 7.25-8.05 (m,12H,arom); 8.18-8.52 (m,2H,arom); (Found: C,93.48; H,6.38; Calc.for $C_{29}H_{24}$: C,93.51; H,6.49%); m/z 373 (M^+,22%);329(3).

(—,100%) ?

13-(2-Naphthylmethyl)9,10,11,12-tetrahydro[8H]cyclohepta-[b]phenathrene (80c) was isolated as colourless crystals (hexane); yield 68%; m.p. 151-152°C; IR ν_{max}(KBr) 1620,

1598,1500 cm^{-1}; ^1H NMR ($CDCl_3$); 1.35-1.89 (m,6H,CH_2); 2.75-3.10 (m,4H,CH_2); 4.72 (s,2H,benzylic CH_2); 7.18-7.98 (m,12H,arom); 8.29-8.46 (m,2H,arom); (Found: C,92.81; H,7.08; Calc. for $C_{30}H_{27}$: C,92.98; H,7.02%); m/z 388 (M^+, 100%); 316(8).

8,9-Dihydro-7(methylthio)dibenz[a,h]anthracene (82a) was isolated as colourless crystals (hexane); yield 53%; m.p. 93-94°C; IR ν_{max}(KBr) 1600,1490 cm^{-1}; ^1H NMR ($CDCl_3$): 2.18 (s,3H,SCH_3); 2.58-2.98 (m,2H,CH_2); 3.21-3.51 (m,2H, CH_2); 7.09-8.22 (m,10H,arom); 9.09 (brs,1H,arom); (Found: 84.58; H,5.36; Calc. for $C_{23}H_{18}S$: C,84.62; H,5.56%); m/z 327 (M^+,64%); 279(100).

8,9-Dihydro-11-methoxy-14-(methylthio)dibenz[a,h]anthracene (82b) was isolated as colourless crystals (hexane); yield 55%; m.p. 122-123°C; IR ν_{max}(KBr) 1605,1505 cm^{-1}; ^1H NMR ($CDCl_3$); 2.18 (s,3H,SCH_3); 2.81 (m,2H,CH_2); 3.45 (m, 2H,CH_2); 3.81 (s,3H,OCH_3); 6.69-6.98 (m,2H,arom); 7.23-8.40 (m,7H,arom); 9.18 (s,1H,arom); (Found: C,88.01; H,5.58; Calc. for $C_{24}H_{20}OS$: C,88.08; 5.65%); m/z 356 ($M^{\oplus}$, 100%); 309(18).

Raney Nickel Desulphurization of 82a**: Synthesis of 8,9-Dihydrodibenz[a,h]anthracene** (83a) was done as described earlier; work-up of the reaction mixture afforded colourless crystals (hexane); yield 68%; m.p.189-190°C; IR ν_{max} (KBr) 1598,1560 cm^{-1}; ^1H NMR ($CDCl_3$); 2.82-3.25 (m,4H,CH_2); 7.11-8.05 (m,9H,arom); 8.25 (s,1H,arom); 8.50

(s,1H,arom); 8.72 (m,1H,arom); (Found: C,94.19; H,5.48; Calc. for $C_{22}H_{16}$: C,94.25; H,5.75%).

Dehydrogenation of 83a with DDQ: Synthesis of Dibenz[a,h] anthracene (84): Dehydrogenation was carried out by same procedure as described for 73c; work-up of the reaction mixture as described afforded 84 as colourless crystals; yield 72%; m.p. 264-265°C (lit.[44] 266°C); IR ν_{max}(KBr) 1610,1503 cm^{-1}; ^1H NMR ($CDCl_3$): 7.31-8.00 (m,10H,arom); 8.81 (m,2H,arom); 9.10 (s,2H,arom); (Found: C,94.90; H,5.01; Calc. for $C_{22}H_{14}$: C,94.93; H,5.07%).

REFERENCES

1. (a) Smith,A.B.; Kilenyi,S.N. *Tetrahedron Lett.* 1985 *26*, 4419; (b) Sivavec,T.M.; Katz.T.J.*Tetrahedron Lett.* 1985, *26*, 2159; (c) Dieter,R.K.;Lin,Y.J. *Tetrahedron Lett.*. 1985, *26*, 39; (d) Kelly, T.R.; Lin,H.*J.Am.Chem.Soc.* 1985,*107*,4998; (e) Wulff,W.D.; Kaesler,R.W.; Peterson G.A.;Tang,C. *J.Chem.Soc.* 1985, *107*,1060; (f) Freskas,J.N; Swenton,J.S. *J.Chem.Soc. Chem. Comm.* 1985, 658; (g) Sivavec,T.M.; Katz,T.J.*J.Am.Chem.Soc.*1985,*107*,737; (h) Boger,D.L.; Mullican,M.D.*J.Org.Chem.* 1984,*49*,4033; (i) Gee,S.K.; Danheiser,R.L.*J.Org.Chem.*. 1984,*49*, 1672.
2. Bamfield,P.;Gordon,P.F.*Chem.Soc.Rev.* 1984, *13*,441.
3. Seebach,D. *Angew.Chem.Int.Ed.Engl.* 1988, *27*, 1624.
4. Singh,G.; Purkayastha,M.L.; Ila,H.; Junjappa,H.; *J.Chem. Soc.Perkin Trans.I.* 1985, 1289.
5. Singh,G.; Ila,H.; Junjappa,H. *Synthesis*,1985, 165.
6. Singh,G; Ila,H; Junjappa,H. *Tetrahedron Lett.* 1984,*25*, 5095.
7. Asokan,C.V.; Ila.H.; Junjappa.H. *Synthesis*,1987,284.
8. Becker, K.B. *Synthesis*, 1983, 341.
9. Gupta,A.K.; Ila.H.; Junjappa,H. *Tetrahedron Lett.* 1987,*28*, 1459.
10. Balu.M.P.; Pooranchand,D.; Ila.H.; Junjappa.H. *Tetrahedron Lett*. 1988,*29* 501.
11. Chen,T.S.; Canonne,P.; Leitch, L.C. *Synthesis*, 1973, 621.

12. Canonne,P.; Leitch,L.C.; *Can.J.Chem.* 1967,*45*,1761.
13. Wolinska-Mocydlarz,J.; Canonne,P.; Leitch,L.C. *Synthesis* 1974,566.
14. Tius,M.A. *Tetrahedron Lett.*,1981, *22*,3335.
15. Tius,M.A.; Ali,S. *J.Org.Chem.*, 1982, *47*, 3163.
16. Tius,M.A.; Savariar,S. *Synthesis*, 1983, 467.
17. Tius,M.A.;Thurkauf,A.;Truesdell,J.W.*Tetrahedron Lett*, 1982,*23*,2819.
18. Tius,M.A.; Thurkauf,A. *J.Org.Chem.* 1983,*48*,3839.
19. Balu,M.P.; Singh,G. Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1986,*27*, 117.
20. Tius,M.A.; Gomez-Galeno,J. *Tetrahedon Lett.* 1986, *27*, 2571.
21. Reddy,M.P.; Rao,G.S.K. *J.Org.Chem.* 1981, *46*, 5371.
22. Loozen,H.J. *J.Org.Chem.* 1975, *40*, 520.
23. Thuillier,A. Vialle, *J.Bull.Soc.Chim.Fr.* 1962 2182.
24. Apparao,S.; Bhattacharji,S.S.; Ila.H; Junjappa,H. *J.Chem.Soc.Perkin Trans.I.* 1985, 641.
25. Chauhan,S.M.S.; Junjappa,H.*Tetrahedron*, 1976, *32*, 1779.
26. Cook,J.W. *J.Chem.Soc.*,1932, 1472.
27. Howerth,R.D. *J.Chem.Soc.* 1932, 1125.
28. Chapman,N.B.; Williams,J.F.A.*J.Chem.Soc.* 1952, 5044.
29. Olsen,C.E.; Bader,A.D. *Org. Synthesis Coll.Vol.IV.* 1963, 898.
30. Koo,J. *J.Am.Chem.Soc.* 1953, *75*,1891.
31. Noller,C.R.; Adams,R. *J.Am.Chem.Soc.* 1924, *46*,1889.
32. Krollpfeiffer,F.; Schultze,H.*Ber*. 1923, *56B*, 1919.

33. Bindra,J.S.;Neyyarapally,A.T.;Gupta,R.C.;Kamboj,V.P. Anand,N. *J.Med.Chem.,* 1975,*18*, 921.

34. Fontaine,G.; *Ann.Chim.* 1968,*3*, 14179; *Chem.Abstr.* 1968,*69*, 1065364.

35. Thuillier,A.; Vialle,J. *Bull.Soc.Chim.Fr.* 1959, 1398.

36. Thuillier,A.; Vialle,J. *Bull.Soc.Chim.Fr.* 1962, 2194.

37. Apparao,S.; Datta,A; Ila,H.;Junjappa,H. *J.Chem.Soc. Perkin Trans.I.* 1984, 921.

38. Chauhan,S.M.S.; Junjappa,H.*Tetrahedron* 1976, *32*, 1779.

39. Shahak,I.; Sasson,Y. *Tetrahedron Lett.* 1973,4207.

40. Chauhan,S.M.S.; Junjappa,H. *Tetrahedron* 1976,*32*, 1911.

41. Kumar,A.; Ila,H.; Junjappa,H. *J.Chem.Res(s)* 1979, 268; *J.Chem.Res.(M)* 1979, 3001.

42. Pavlic,A.A.; Adkins,H. *J.Am.Chem.Soc.* 1946,*68*,1471.

43. Cook,J.W.; Preston,R.W.G. *J.Chem.Soc.* 1944,553.

44. Fieser,L.F.; Newman,M.S. *J.Am.Chem.Soc.* 1936, *58*, 2376.

CHAPTER III

CYCLOAROMATIZATION OF α-OXOKETENE DITHIOACETALS WITH 2-PICOLYLLITHIUM: SYNTHESIS OF SUBSTITUTED AND FUSED QUINOLIZINIUM COMPOUNDS*.

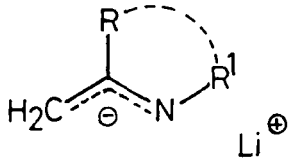
III.1 INTRODUCTION

In the preceeding chapter the studies on aromatic annelation involving the reactions of benzylmagnesium chloride and naphthylmethylmagnesium halides with oxo-ketene dithioacetals to afford the corresponding napththalenes, phenanthrenes and other polycyclic aromatic hydrocarbons have been described. The literature methods for the construction of aromatic rings from acyclic precursors have also been briefly reviewed in the introduction of the chapter. It was considered of

---

*Balu,M.P.; Ila.H.; Junjappa,H. *Tetrahedron Lett.* 1987, *28*, 3023.

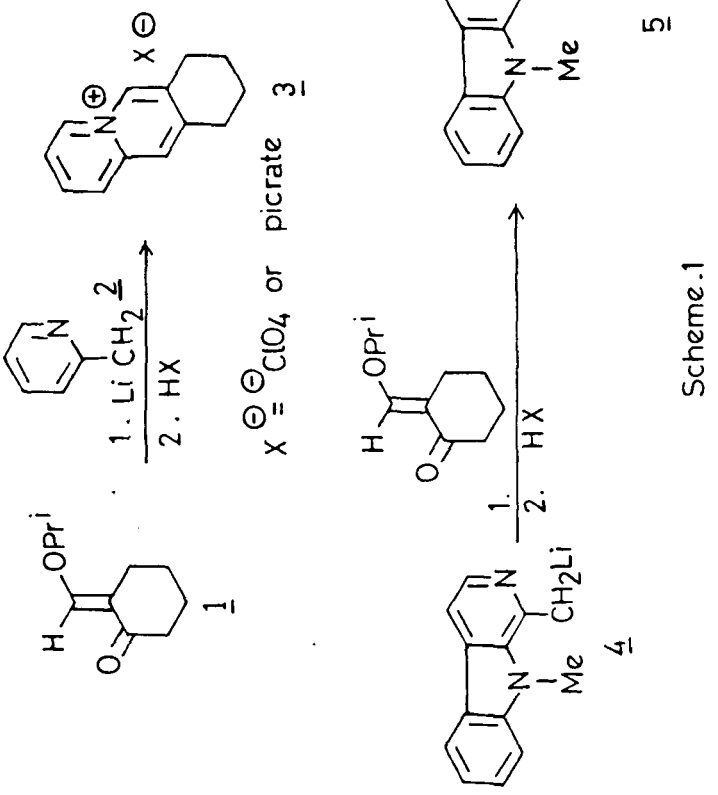
interest to extend this new methodology to construct heteroaromatic systems by reacting appropriate lithio-3-azaallyl systems[1](I) with α-oxoketene dithioacetals. As a model to examine the scope of this general synthetic



(I)

strategy, 2-picolyllithium was reacted with α-oxoketene dithioacetals to construct various quinolizinium ring systems. Our literature retrieval on this and related areas revealed that there are some interesting reports analogous to the present investigation. Some of these related approaches have been briefly discussed as an introduction to the present studies.

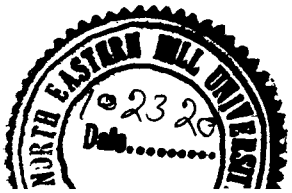
Woodward and co-workers in an elegant investigation, first reported a similar approach for the synthesis of the alkaloid sempervirine.[2] They reacted 2-picolyl-lithium 2 with isopropoxymethylenecyclohexanone 1 as a model experiment to yield the corresponding dehydro-quinolizinium cation 3 in high yield. This model was successfully extended for the smooth synthesis of salts of methylsempervirinium cation 5 by reacting the lithium derivative of N-methylharman 4 with isopropoxymethylene-cyclohexanone 1 followed by cyclization by treating with acid (Scheme 1).

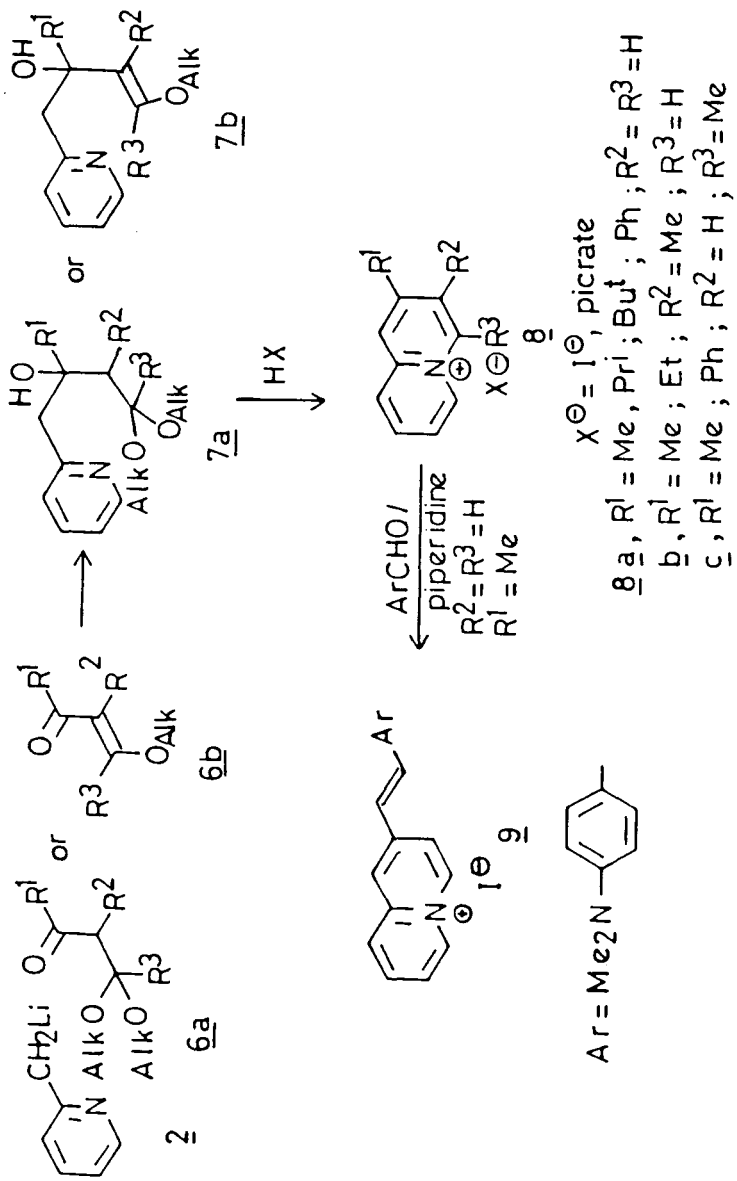


Scheme.1

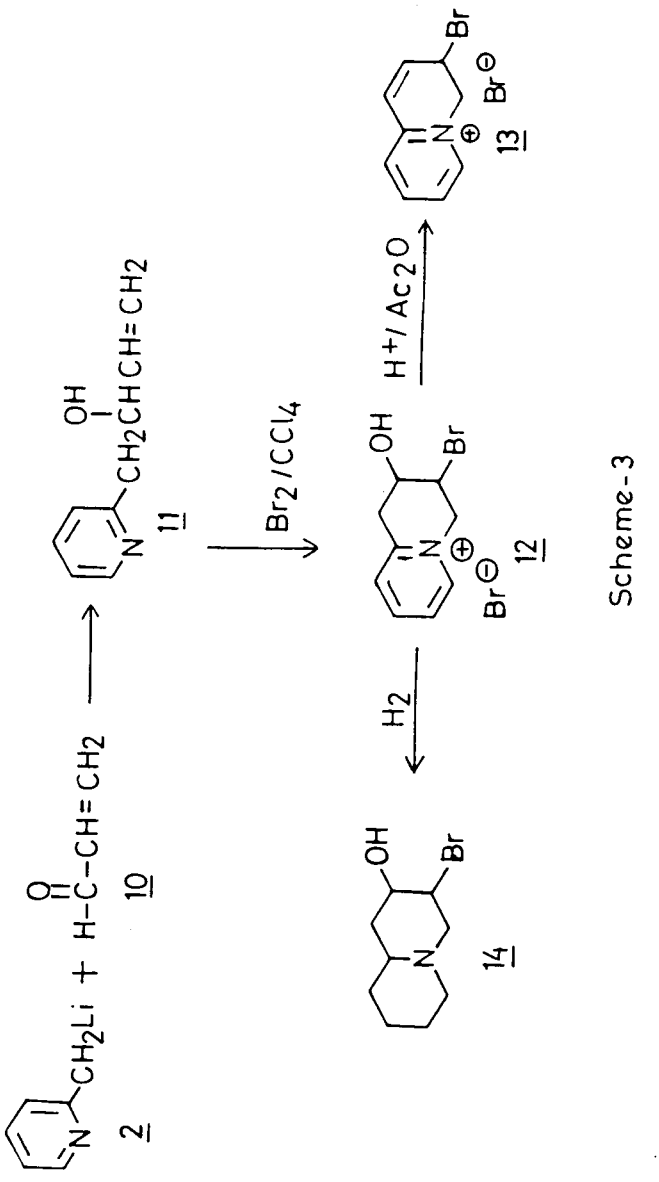
Adaptations of this synthetic method developed by Woodward was extended by later workers for the synthesis of many substituted quinolizinium ring systems.[3,4] The reaction of 2-picolyllithium 2 with β-ketoacetal of 1,3-diketone of the general formula 6 gave the corresponding carbinolacetals 7 which on acid catalyzed cyclization yielded the quinolizinium salts 8 in good yields[4] (Scheme 2). Few of these salts 8 with a methyl substitution at 2-position (R'=Me), were shown to condense with β-dimethylaminobenzaldehyde in the presence of piperidine to yield the corresponding styryl compounds 9(Scheme 2). Stuart and co-workers developed a similar methodology to construct octahydroquinolizinium ring system 14[5] which is present in a number of physiologically active alkaloids such as Lupine, Sparteine, Reserpine, Yohimbine, Veratrine etc. Thus, 2-picolyllithium 2 was reacted with acrolein 10 to yield the corresponding carbinol 11 which on bromination of the exocyclic double bond underwent intramolecular cyclization to yield the corresponding tetrahydroquinolizinium bromide 12. Subsequent hydrogenation of 12 afforded fully saturated quinolizinium compound 14 in good yield, whereas 12 underwent dehydration in the presence of acetic anhydride to give the corresponding dihydroquinolizinium salt 13 (Scheme 3).

The above approach was extended by Hansen and Amstutz for the synthesis of several 4,6-dimethylquinolizinium salts 18[6] which are precursors for the synthesis of





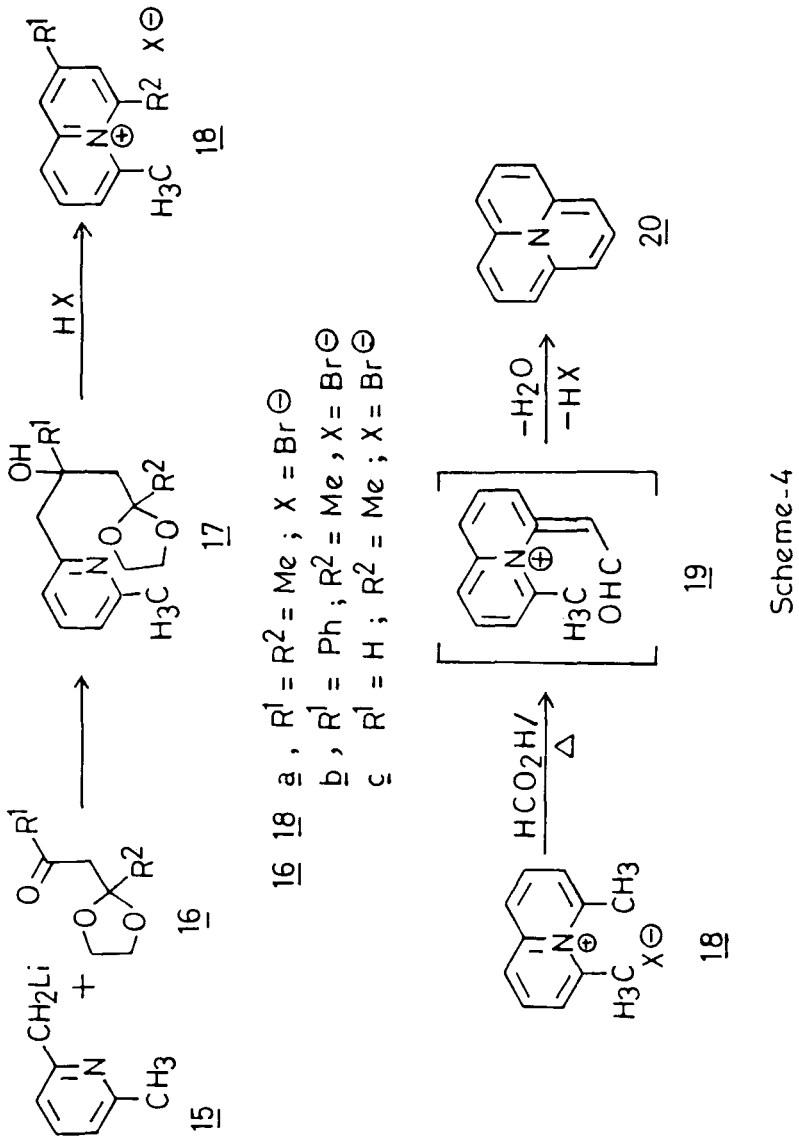
Scheme-2


CH2Li
2
O
H-C-CH=CH2
10
OH
CH2CHCH=CH2
11
Br2/CCl4
OH
Br
Br⊖
12
H+/Ac2O
Br
Br⊖
13
H2
OH
Br
14

Scheme-3

cycl[3.3.3]azine 20 (Scheme 4). Thus the reaction of 2,6-lutidyllithium 15 with the monoethylene ketal of 1,3-diketones 16 yielded the carbinols 17 which underwent smooth aromatic annelation to afford the corresponding quinolizinium salts 18. Further reaction of 4,6-dimethylquinolizinium salt 18a with formic acid yielded the adduct 19, which on cyclodehydration afforded the cycl[3.3.3]azine 20 (Scheme 4).

As an extension of aromatic annelation via α-oxoketene dithioacetals for the synthesis of heteroaromatic compounds, the reaction of lithioacetonitrile with 21 was investigated in our laboratory.[7] Thus, lithioacetonitrile underwent smooth 1,2-addition with α-oxoketene dithioacetal 21 to give the corresponding carbinolacetals 22 which on treatment with phosphoric acid yielded the corresponding 2,6-bis(methylthio)-3,4-substituted and annelated pyridines 24 in high yields. It is interesting to note that the intermediate carbinolacetal 22 arising exclusively from a 1,2-addition of lithioacetonitrile, under acidic conditions forms a carbenium ion by the loss of hydroxy group and undergoes an intramolecular Ritter reaction at the end of the chain to give cyclic cation 23 followed by 1,3-methylthio shift and proton loss to give pyridines 24. The attempts to interrupt the ring closure by external nucleophiles was succcessful in the reaction of 22 with bromine and acetic acid which afforded the corresponding 2-bromo-6-



16 18 a , $R^1 = R^2 = Me$; X = $Br^{\ominus}$

b , $R^1 = Ph$; $R^2 = Me$, X = $Br^{\ominus}$

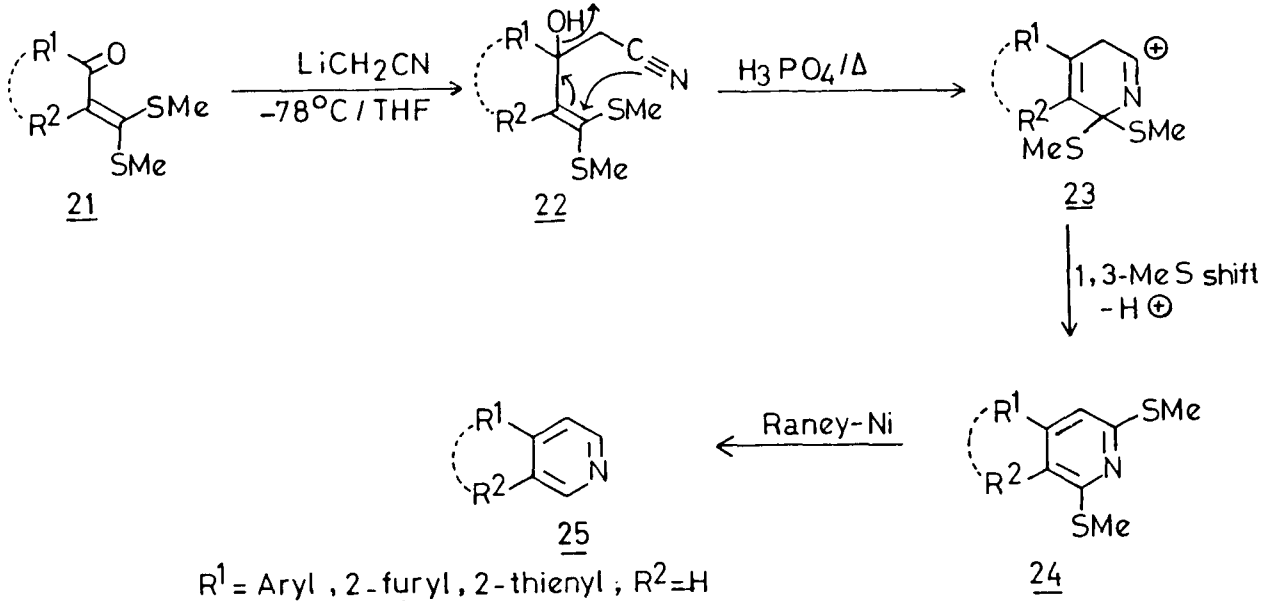
c $R^1 = H$; $R^2 = Me$; X = $Br^{\ominus}$

Scheme-4

methylthiopyridines in good yields. The method was found to be highly general and successfully extended for the synthesis of a number of pyridine derivatives in high yields as shown in the Scheme 5.

Interestingly when lithioacetonitrile was allowed to condense with acetonitrile and other nitriles an intermediate resonance stabilized anion from β-amino-crotononitrile 26 was formed in high yields. In this resonance stabilized anion, the lithium cation is generally associated with the heteroatom, while the active nucleophilic centre is the β-carbon atom. Such anions have been recognized as soft nucleophiles and generally interact with soft electrophilic centre (frontier control).[9,10] In the α-oxoketene dithioacetal 21, the β-carbon atom with an adjacent bis(methylthio)-functionality is the soft electrophilic centre and thus 26 and 21 interact through frontier orbital control (1,4-addition) to yield the corresponding 4-(methylthio) pyridines 28 in high yields.[11] This highly regio-selective reaction was extended to synthesize a large number of substituted and fused pyridines 28 (Scheme 6).

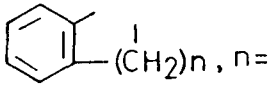
In continuation of these studies on aromatic annelation, it was further contemplated to investigate the reactions of 2-picolyllithium with α-oxoketene dithiocetals. Thus, when 2-picolyllithium 2 was reacted with oxoketene dithioacetals 21, the carbinolacetals 29 were obtained in nearly quantitative yields which on treatment with

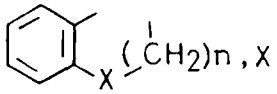


R^1 = Aryl , 2-furyl , 2-thienyl ; R^2=H

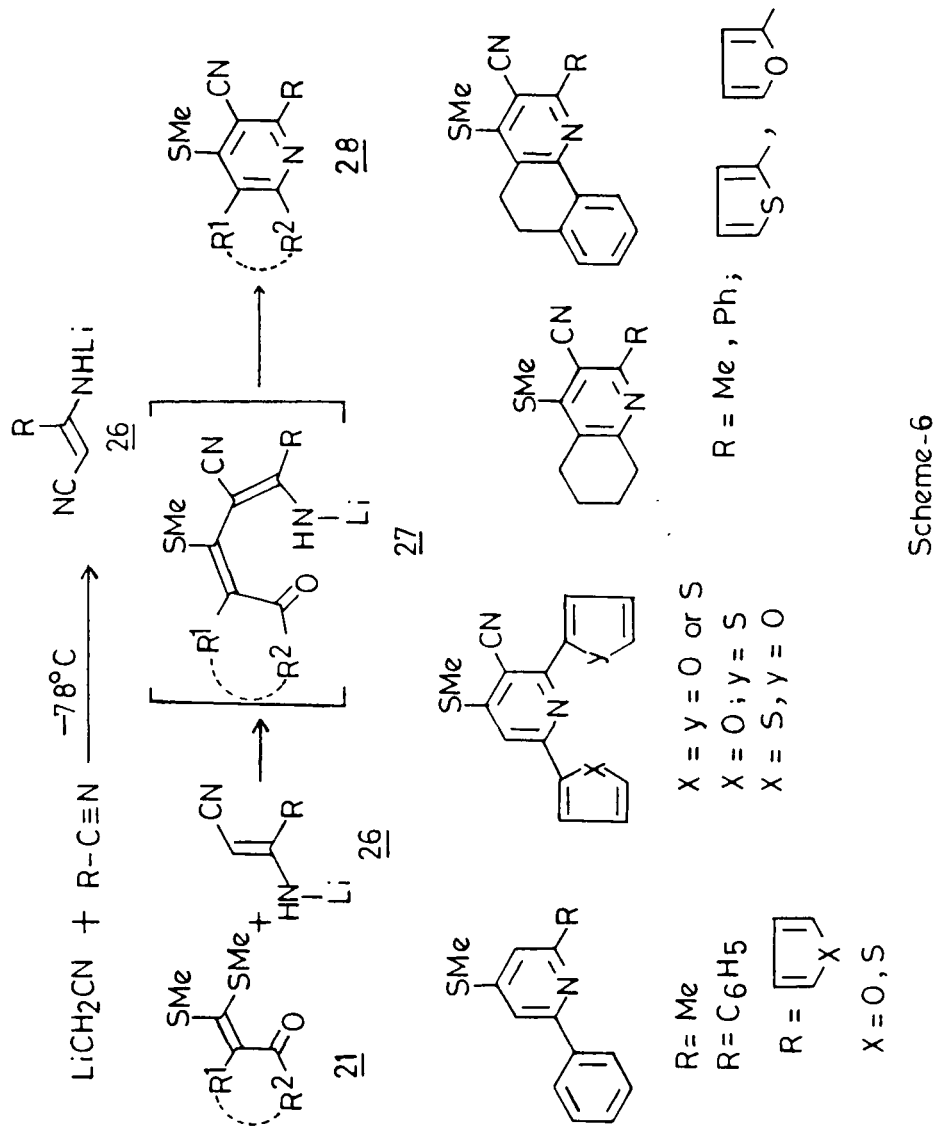
R^1 = Me , Et ; R^2 = H , Me , n-Bu

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

$R^1 = R^2$ =  , n = 1, 2, 3

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

Scheme-5


LiCH2CN + R-C≡N
−78°C
R
NC
NHLi
26
21
26
27
28
SMe
CN
R
HN
Li
O
R1
R2
R = Me , Ph ;
X = y = O or S
X = O ; y = S
X = S , y = O
R= Me
R=C6H5
X=O,S

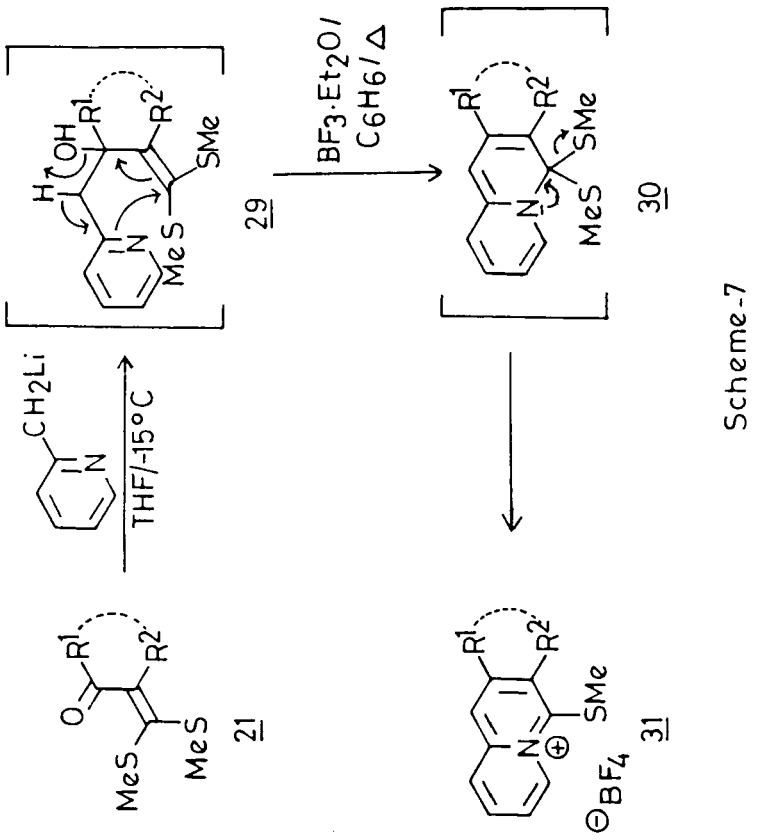
Scheme-6

borontrifluoride etherate underwent cycloarmatization to yield the corresponding quinolizinium tetrafluoroborates 31 in good yields (Scheme 7). The detailed results of this investigation is presented in the following section. Reaction of 2-picolyllithium with cyclic oxoketene dithioacetals 32 has been presented first followed by its reaction with acyclic oxoketene dithioacetals 21 and cinnamoyl ketene dithioacetals 35.

III.2 RESULTS AND DISCUSSION

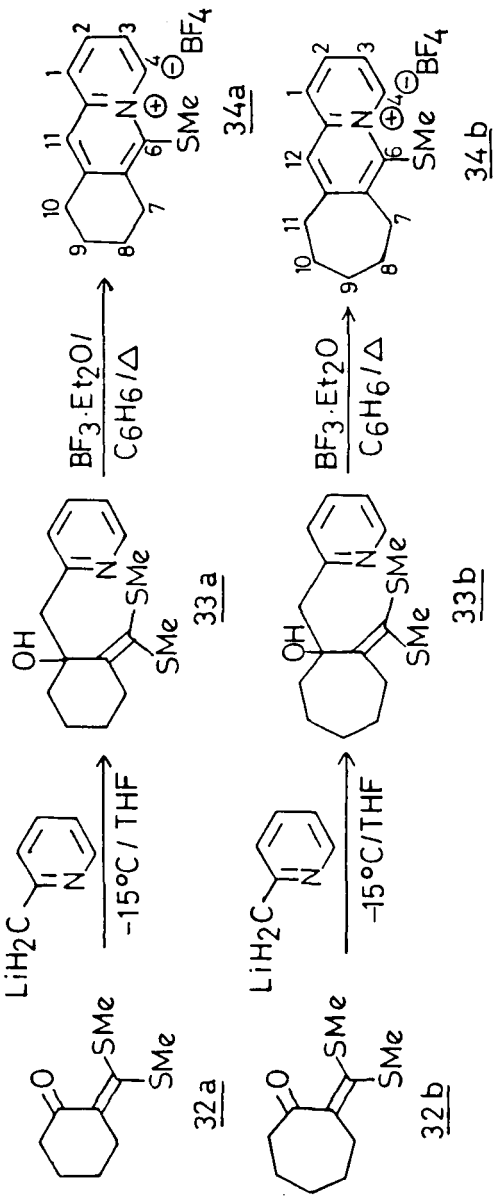
All the α-oxoketene dithioacetals 21a-i and 32a-i required for the present study were prepared according to the general procedure given in chapter II. The detailed procedure for the preparation of cinnamoylketene dithioacetals 36a-e and (5-aryl-2,4-pentadienoyl) ketene dithioacetals 40a-c is given in the experimental section. The structures of all these dithioacetals were confirmed by comparing their physical and spectral data with the reported values.[12-14]

In an optimized condition, when 2-picolyllithium 2[15] was reacted with α-oxoketene dithioacetal 32a derived from cyclohexanone, the corresponding carbinolacetal 33a was formed in quantitative yields. The carbinolacetal 33a directly subjected to borontrifluoride etherate assisted cyclisation in refluxing benzene, when the colourless crystalline solid obtained was characterized as 6-methylthio-7,8,9,10-tetrahydrobenzo[b]quinolizinium tetrafluo-



Scheme-7

roborate 34a (m.p. 148°C) in 82% yield. The compound was fully characterized on the basis of its analytical and spectral data. In its mass spectrum, it exhibited peaks at m/z 230 (8%,M^+-BF_4); 215(9%) and the compound was analyzed for $C_{14}H_{16}BF_4NS$. The IR spectrum(KBr) of this product showed bands at ν_{max} 1640 (C=N),1610,1568 and the characteristic tetrafluoroborate salt absorbtion band between 1030-1150 cm^{-1}. The structure was further confirmed from its ^1H NMR (250MHz) spectrum in $CDCl_3$. The multiplet at δ1.94 (4H) and the triplets at δ3.15(2H) and 3.32(2H) were assigned to the methylene protons, while the methylthio group appeared as sharp singlet at δ2.48 (3H). The aromatic protons appeared at δ8.04 (t,J=7Hz,1H, H-3);8.16 (t,J=7Hz,1H,H-2);8.26 (s, 1H, H-11); 8.36 (d, J=7Hz, 1H, H-1); and 10.03 (d, J=7Hz, 1H, H-4). The structure was further confirmed from its ^{13}C NMR spectrum ($CDCl_3$) which was in full agreement with the assigned structure (experimental). Similarly 2-picolyllithium 2 reacted with oxoketene dithioacetal 32b derived from cycloheptanone to yield the corresponding annelated quinolizinium tetrafluoroborate 34b through the carbinol-acetal 33b under the described conditions (Scheme 8). The analytical and spectral data of the quinolizinium salt 34b was in full agreement with the assigned structure and is given in the experimental section. However, the oxoketene dithioacetal 32c derived from cyclopentanone did not yield the corresponding quinolizinium salt 34c although the intermediate carbinol

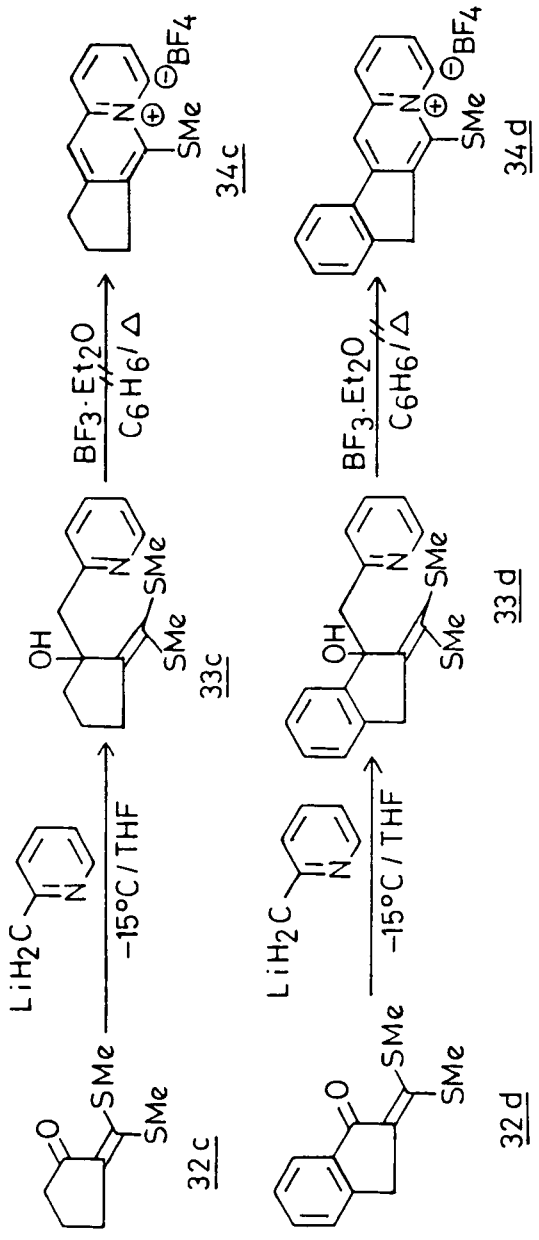


Scheme-8

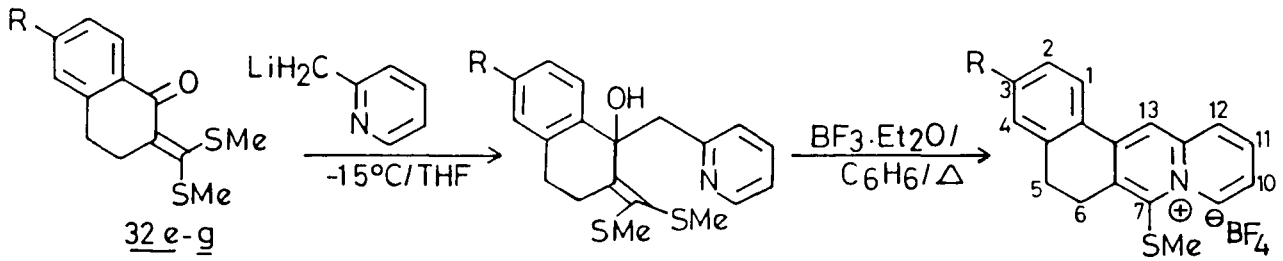
acetal 33c was obtained in high yields. Similarly 32d derived from indanone although smoothly reacted with 2-piclolyllithium to give the carbinolacetal 33d, but failed to give the corresponding fused quinolizinium tetrafluoroborate 34d (Scheme 9) on treatment with $BF_3.Et_2O$ in benzene.

The reaction of 2-picolyllithium 2 with oxoketene dithioacetals 32e-g derived from α-tetralones, yielded the corresponding carbinolacetals 32e-g in high yields which underwent smooth cycloaromatization in the presence of borontrifluoride etherate to give the corresponding fused quinolizinium salts 34e-g in 85,78 and 83% yields respectively (Scheme 10). The spectral and analytical data of all these compounds are given in the experimental section and they are in full agreement with the assigned structures. The cyclic oxoketene dithioacetals 32h and 32i derived from benzothiepinone and benzoxepinone, reacted with 2-picolyllithium to give the corresponding condensed quinolizinium salts 34h and 34i (Scheme 11) in 80 and 81% yields, respectively. The analytical and spectral data of both 34h and 34i are in agreement with the assigned structures (experimental).

Various acyclic oxoketene dithioacetals were also shown to react with 2-picolyllithium to afford the corresponding substituted quinolizinium tetrafluoroborates. Thus, oxoketene dithioacetals 21a-d reacted with 2-picolyllithium to yield the corresponding carbinolacetals 29a-



Scheme-9



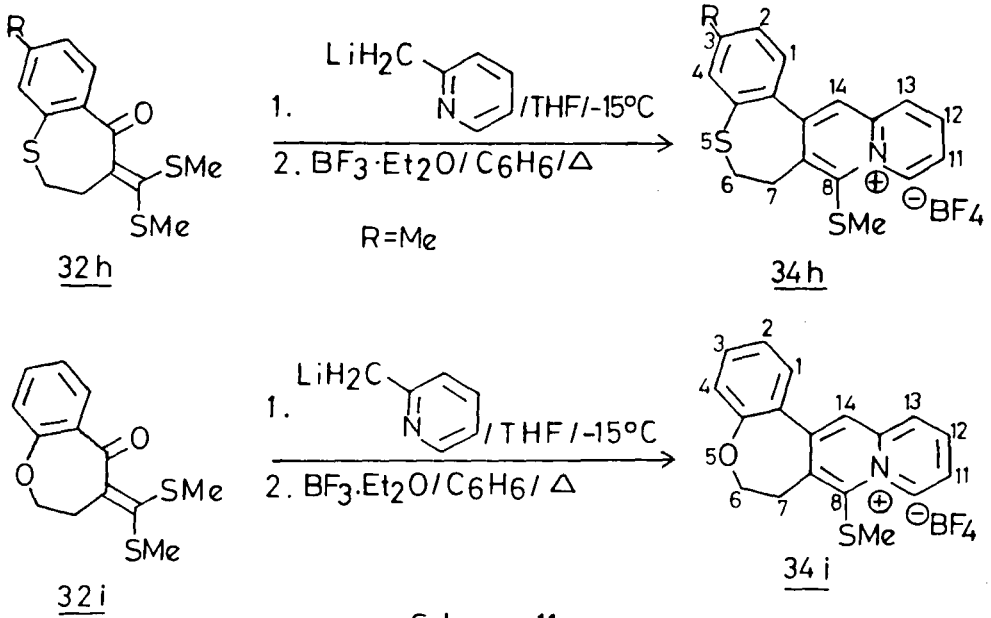
32 e-g

33 e-g

34 e-g

32-33 e , R = H
f , R = Me
g , R = MeO

Scheme-10

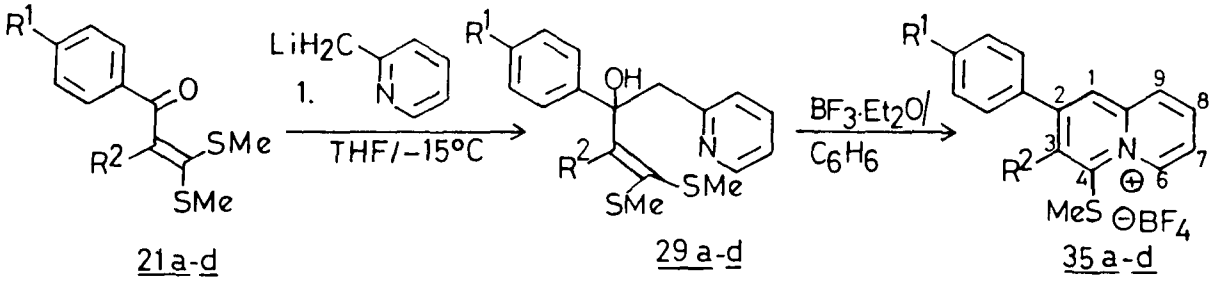

R
O
S
SMe
SMe
32h
LiH2C
N
1.
/THF/-15°C
2. BF3·Et2O/C6H6/Δ
R=Me
R
2
3
1
4
14
13
12
5S
N
11
6
7
8
⊕
⊖BF4
SMe
34h
3
2
1
4
14
13
12
5O
N
11
6
7
8
⊕
⊖BF4
SMe
34i
LiH2C
N
1.
/THF/-15°C
2. BF3·Et2O/C6H6/Δ
O
O
SMe
SMe
32i

Scheme-11

d which were directly subjected to borontrifluoride etherate assisted cycloaromatization to give the 2-aryl quinolizinium tetrafluoroborates 35a-d in 80-84% overall yields (Scheme 12). The analytical and spectral data of 35a-d are described in the experimental section, which are in full agreement with the assigned structures. Similarly quinolizinium salt 35e was obtained in 73% yield by reacting 2-picolyllithium 2 with the oxoketene dithioacetal 21e, derived from 2-acetylnaphthalene (Scheme 12).

The method was found to be equally efficient when extended to oxoketene dithioacetals 21f and 21g derived from 2-acetylthiophene and 2-acetylfuran. Thus, quinolizinium tetrafluoroborate salts 35f and 35g were obtained in 78 and 76% yields respectively from the corresponding ketene dithioacetals 21f and 21g (Scheme 13). The analytical and spectral data of these products are given in the experimental section. However, the reaction of 2-picolyllithium with the ketene dithioacetals 21h and 21i derived from acetone and ethylmethylketone failed to yield the corresponding quinolizinium salts 35h and 35i respectively (Scheme 13).

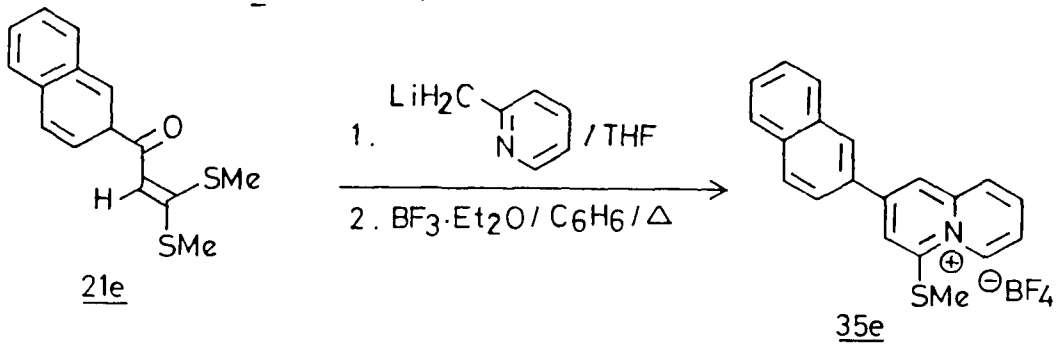
The efficacy of this reaction was further established by reacting α-cinnamoyl and α-(5-aryl-2,4-pentadienoyl)-ketene dithioacetals with 2-picolyllithium. The α-cinnamoyl ketene dithioacetals 36a-e reacted smoothly with 2-picolyllithium to yield the corresponding carbinol-



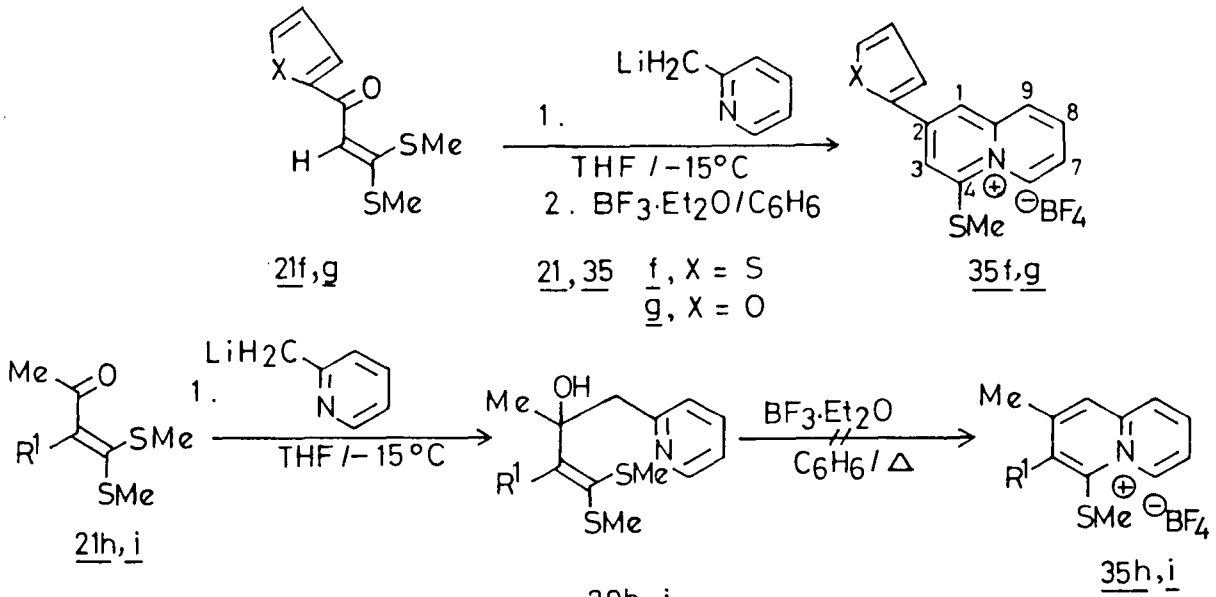
a, $R^1 = R^2 = H$; d, $R^1 = Cl$; $R^2 = H$

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

c, $R^1 = MeO$; $R^2 = H$;



Scheme-12



21f,g

21, 35 f, X = S
g, X = O

35f,g

21h, i

29h. i

35h,i

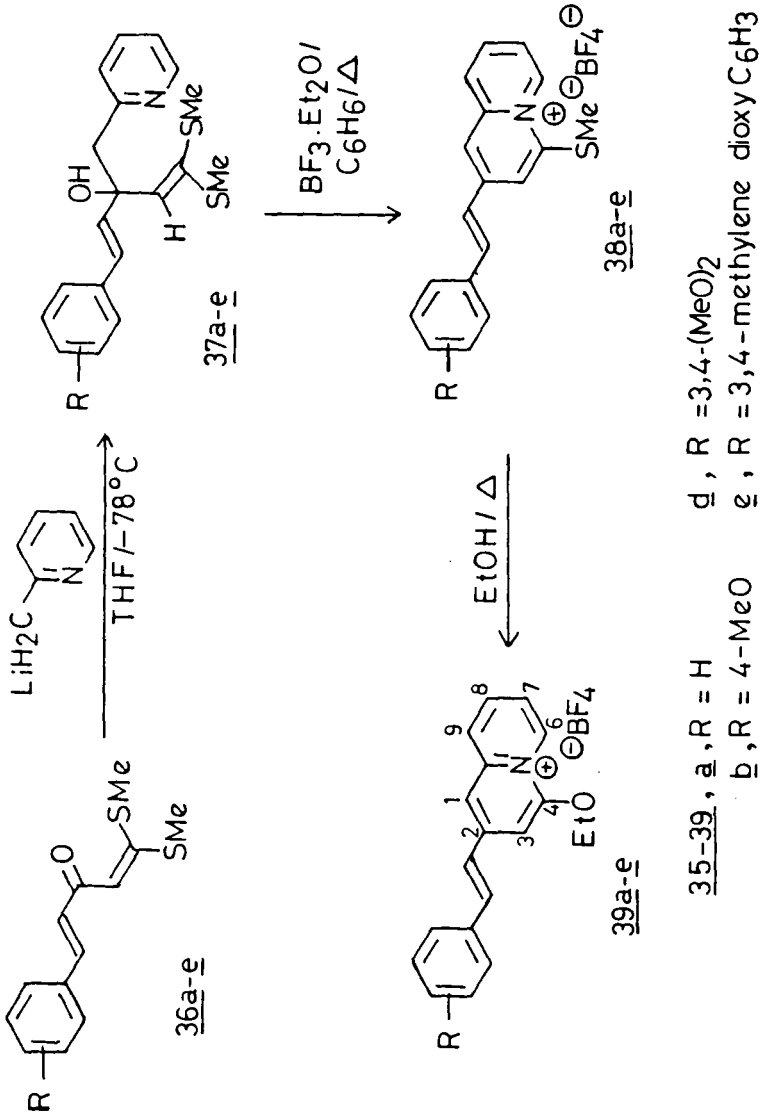
21, 29, 35, h R' = H
i R' = Me

Scheme - 13

acetals 37a-e in quantitative yields, which on subsequent treatment with $BF_3.Et_2O$ in benzene yielded the 2-styryl quinolizinium salts 38a-e in 68-74% overall yields. Interestingly the methylthio group in 38a-e was replaced by ethoxy group to give the corresponding 4-ethoxy quinolizinium salts 39a-e when these salts were refluxed in ethanol for prolonged time (20-24 hr) (Scheme 14). Similarly the dienoyl ketene dithioacetals 40a-c reacted with 2-picolyllithium to yield the corresponding dienyl quinolizinium tetrafluoroborate salts 42a-c in high yields. The salt 42c afforded the corresponding 2-ethoxy quinolizinium derivative 43c when refluxed in ethanol for longer period (24 hr). The analytical and spectral data of all the products were in agreement with the assigned structures and are given in the experimental section.

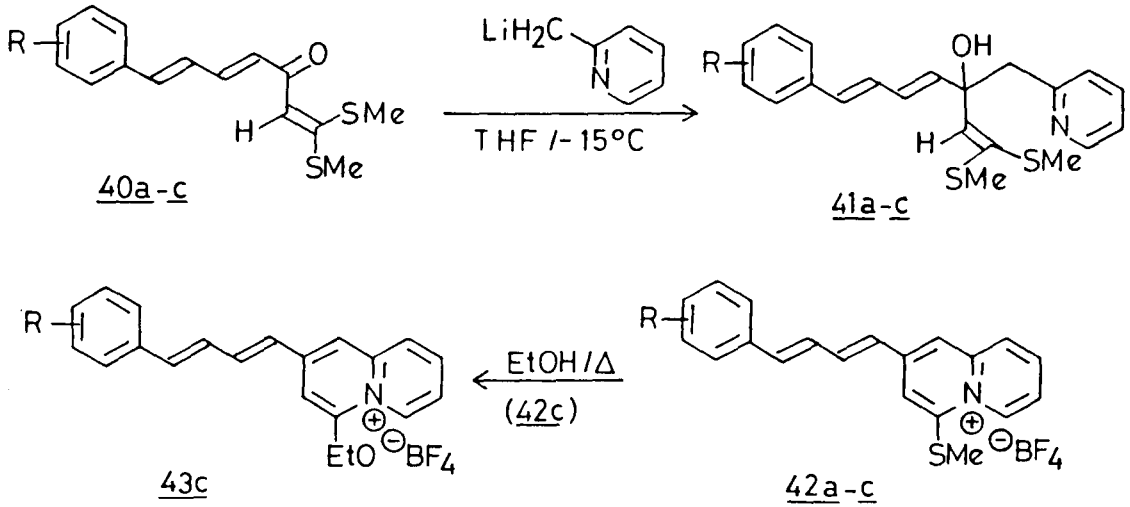
III.3 CONCLUSION

A general methodology for the synthesis of quinolizinium salts with diverse structural features is formulated via oxoketene dithioacetals through their reaction with 2-picolyllithium. The methodology developed is of considerable synthetic importance because of the fact that a large number of azaallyl anions could be used to construct various heteroaromatic compounds. Also the Woodward approach of alkaloid synthesis could be greatly and efficiently extended for the synthesis of a large



35-39 , a , R = H d , R = 3,4-$(MeO)_2$
b , R = 4-MeO e , R = 3,4-methylene dioxy C_6H_3
c , R = 2,6-Cl_2

Scheme-14



42 a , R = H
b , R = 4-MeO
c , R = 3,4-methylenedioxy

Scheme-15

number of naturally occuring compounds, which are in progress in our laboratory.

III.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run as KBr discs on a Perkin-Elmer 297 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Brucker WM-400 spectrometer in DMSO-d_6 with tetramethylsilane as internal standard unless otherwise stated. Chemical shifts are given in δ units down field from TMS. Mass spectra were obtained on a Jeol JMS D-300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-RAPID instrument.

Starting materials

2-Picoline and n-butyl bromide were purchased (Aldrich) and distilled prior to use. Lithium ingot (Aldrich) were cut into smaller pieces and washed with dry ether twice. n-Butyllithium was prepared according to the reported procedure.[16] The oxoketene dithioacetals 21a-i and 32a-i used in this study were prepared according to the general procedure described in Chapter II. The α-cinnamoylketene dithioacetals 36a-f and α-(5-aryl-2,4-pentadineoyl)ketene dithioacetals 40a-c were prepared as given below.

Condensation of α-Acylketene Dithioacetals with Aldehydes: General procedure for the Preparation of Ketene Dithioacetals 36a-f and 40a-c

To a cooled and stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (6 mmol) in ethanol (10 ml), a solution of the α-acyl ketenedithioacetal (3 mmol) and the aldehyde (3 mmol) in minimum quantity of ethanol(10ml) was added dropwise over a period of 5 minutes. The reaction mixture was brought to room temperature over a period of 30 minutes and further stirred at room temperature for 4-5 hrs. The mixture was diluted with water (50 ml) and the solid separated was filtered, washed with water (4x25 ml) and dried. The compounds 36a-f and 40a-c were previously reported [17,18] and the physical and analytical data of these compounds were found to be in conformity with that of reported values.

General procedure for the Reaction of 2-Picolyllithium with Oxoketene Dithioacetals

A solution of oxoketene dithioacetal (10 mmol) in dry tetrahydrofuran (25 ml) was added to a solution of 2-picolyllithium [15] [15 mmol, prepared from 2-picoline (1.39 gm, 15 mmol) and n-BuLi (15 mmol)] in 25 ml of THF at -20°C under N_2 atmosphere. The reaction mixture was further stirred at the same temperature for 2 hr, worked up by pouring into saturated aqueous NH_4Cl solution (50 ml),extracted with ether (2x50ml) and the combined

extracts were washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give the crude carbinols 29a-i and 33a-i in quantitative yields, which decomposed on attempted purification and were used as such in the cycloaromatization step.

General procedure for the Cycloaromatization of Carbinol Dithioacetals 29a-i and 33a-i: Synthesis of Substituted and Fused Quinolizinium tetrafluoroborates 34a-i, 35a-i 38a-e, 42a-c

To a solution of crude carbinol dithioacetal (Ca.10 mmol) obtained from above reaction, in dry benzene (50 ml), borontrifluoride etherate (3 ml) was added and the reaction mixture was refluxed with stirring for 45 min. It was then cooled and the benzene layer was removed by decantation. The remaining residue was dissolved in minimum amount of acetone, neutralized with saturated sodium bicarbonate solution and the solid separated was collected by filtration, washed with water (3x50 ml) and diethyl ether (2x10 ml). Analytically pure products were obtained by recrystallisation from glacial acetic acid.

In the case of carbinols 33a and 33b,the reaction mixture after refluxing with $BF_3.Et_2O$ in benzene for 45 minutes, was cooled, poured over saturated $NaHCO_3$ solution and extracted with chloroform (2x50 ml). The combined extracts were washed with water (50 ml) dried (Na_2SO_4) and evaporated to give a viscous residue,which were

purified by passing through silica gel column using hexane-ethylacetate (5:1) as eluent to give analytically pure products 34a and 34b. The spectral and analytical data of all quinolizinium salts are given below.

6-(Methylthio)-7,8,9,10-tetrahydrobenzo[b]quinolizinium tetrafluoroborate (34a) was isolated as light yellow crystals (EtOAc-hexane); yield 82%; m.p. 148°C;IR and ^{1}H NMR data are described in the text. ^{13}C NMR($CDCl_3$): 16.20 (SCH_3); 20.51,21.67 (*CH_2*,C-8,C-9); 29.40,29.72 (*CH_2*, C-7, C-10); 123.90, 126.92, 128.00,132.86,135.46 (*CH*,C-1,C-2, C-3,C-4, C-11); 140.59,142.49,143.34 (C-6a,C-10a); 150.09 (C-6); (Found:C,52.87;H,5.01;N,4.44;Calc.for $C_{14}H_{16}BF_4NS$: C,53.00; H,5.05; N,4.42%); m/z 230 (M^+-BF_4,8%); 215(9).

(100 ?)

6-(Methylthio)-8,9,10,11-tetrahydro-7H-cyclohepta[b]-quinolizinium tetrafluoroborate (34b) was isolated as light yellow crystals (EtOAc-hexane);yield 79%;m.p. 181°C; IRν_{max}(KBr) 1640,1612,1570,1020-1130(br) cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.77-1.98 (m,6H,*CH_2*);2.48 (S,3H,SCH_3);3.19 (m,2H,*CH_2*); 3.58 (m,2H,*CH_2*); 8.12 (t,J=8Hz,1H,H-3);8.35-8.51 (m,3H,H-1,H-2,H-12);10.12 (d,J=7Hz,1H,H-4);(Found: C, 54.12;H,5.32;N,4.33; Calc. for $C_{15}H_{18}BF_4NS$: C,54.39; H,5.48; N,4.23; m/z 244 (M^+-BF_4,6%); 229(100).

5,6-Dihydro-7-(methylthio)naphtho[1,2-b]quinolizinium tetrafluoroborate (34e) was isolated as yellow crystals (AcOH); yield 85%; m.p. 225°C; IRν_{max}(KBr) 1630,1610, 1598,980-1140(br) cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.53 (s,3H,

SCH_3); 3.06 (t,J=8Hz,2H,CH_2); 3.53 (t,J=8Hz,2H,H_2); 7.50-7.56 (m,3H,H-2,H-3,H-4); 8.10 (t,J=7Hz,1H,H-10); 8.20 (d,J=6.5Hz,1H,H-1); 8.41 (t,J=7Hz,1H,H-11); 8.58 (d, J=7Hz,H-12); 9.12 (s,1H,H-13); 10.10 (d,J=7Hz,1H,H-9); ^{13}C NMR (DMSO-d_6); 16.71 (SCH_3); 26.69,27.79 (CH_2, C-5, C-6); 120.97,124.04,126.11,127.73,128.46,128.56,131.70, 134.55, 136.33 (CH, C-1,C-2,C-3,C-4,C-9,C-10, C-11,C-12, C-13); 129.46,138.48,140.25,140.60,141.44,143.64 (C-4a, C-6a,C-7,C-12a,C-13a,C-13b); (Found: C,59.01; H,4.50; N, 3.86; Calc. for $C_{18}H_{16}BF_4NS$: C,59.10;H,4.42;N,3.84%); m/z 278 (M^+-BF_4,11%); 263(27).

5,6-Dihydro-3-methyl-7(methylthio)naphtho[1,2-b]quinolizinium tetrafluoroborate (34f) was isolated as yellow crystals (AcOH); yield 78%; m.p. 240°C; IRν_{max}(KBr) 1637, 1598,1560,1020-1138(br) cm^{-1}; ^1H NMR (DMSO-d_6) 2.43 (s,3H,CH_3); 2.53 (s,3H,SCH_3); 3.01 (t,J=8Hz,2H,CH_2) 3.53 (t,J=8Hz,2H,CH_2); 7.29 (s and d overlapped, 2H,H-2, H-4); 8.06 (d and t overlapped,2H,H-1 and H-10); 8.37 (t,J=7Hz,1H,H-11); 8.53(d,J=7Hz,1H,H-12); 9.02(s,1H,H-13) 10.05 (d,J=7Hz,H-9): (Found:C,59.97; H,4.76; N,3.72;Calc. for $C_{19}H_{18}BF_4NS$: C,60.18; H,4.78; N,3.69%) m/z 292 (M^+-BF_4, 51%); 277(54).

5,6-Dihydro-3-methoxy-7-(methylthio)naphtho[1,2-b]quinolizinium tetrafluoroborate (34g) was isolated as yellow crystals (AcOH); yield 83%; m.p. 228°C; IRν_{max}(KBr) 1636, 1596,1560, 1020-1100(br) cm^{-1}; ^1H NMR (DMSO-d_6): 2.50 (s,3H,SCH_3); 3.04 (t,J=8Hz,2H,CH_2); 3.54 (t,J=8Hz,2H,CH_2)

3.88 (s,3H,OCH_3); 7.04-7.10 (m,2H,H-2 and H-4);8.05 (t, J=7Hz, 1H, H-10); 8.10 (d,J=8Hz,1H,H-1); 8.33 (t,J=7Hz,1H,H-11); 8.50 (d,J=7Hz,1H,H-12);8.96 (s,1H,H-13); 10.02 (d,J=7Hz, 1H,H-9); (Found: C, 57.63; H, 4.43; N, 3.59; Calc. for $C_{19}HH_{18}BF_4NOS$: C,57.73; H, 4.59,N, 3.54%); m/z 308 (M^+-BF_4, 60%); 293(74).

6,7-Dihydro- 3-methyl-8-(methylthio)-[1]-benzothiapino-[4,5-b]quinolizinium tetrafluoroborate (34h) was isolated as colourless crystals (AcOH); yield 80%; m.p. 278°C; IR ν_{max}(KBr) 1646,1635,1607,1114-1073(br) cm^{-1}; ^1H NMR (DMSO-d_6); 2.45 (s,3H,CH_3); 2.57 (s,3H,SCH_3); 2.79-3.22 (m,2H,CH_2); 3.69-4.19 (m,2H,CH_2); 7.51 (m,2H,H-1,H-2); 7.68 (d,J=7Hz,1H,H-13); 8.24 (t,J=7Hz,1H,H-11); 8.49 (t,J=7Hz,1H,H-12); 8.70 (s,2H,H-4,H-14); 10.15 (d, J=7Hz, 1H,H-10);(Found: C,55.22, H,4.40, N,3.38, Calc. for $C_{19}H_{18}BF_4NS_2$: C,55.48; H,4.41, N,3.41%) m/z 324 (M^+-BF_4, 5%); 309(52).

6,7-Dihydro-8-(methylthio)-[1]-benzoxepino[4,5-b]quinolizinium tetrafluoroborate (34i) was isolated as colourless crystals (AcOH); yield 81%; m.p. 242°C; IR ν_{max}(KBr) 1640,1635,1607,1073-1160(br) cm^{-1}; ^1H NMR (DMSO-d_6): 2.58 (s,3H,SCH_3); 3.57 (t,J=7Hz,2H,CH_2); 4.64 (t,J=7Hz,2H,CH_2) 7.29 (d,J=7.5Hz,1H,H-4); 7.50 (t,J=7Hz,1H,H-3); 7.64 (t, J=7Hz,1H,H-2); 7.79 (d,J=7Hz,1H,H-1); 8.21 (t,J=7Hz, 1H, H-11); 8.48 (t,J=7Hz,1H,H-12); 8.67 (d,J=7.5Hz,1H,H-13);8.81 (s,1H,H-14); 10.16 (d,J=7Hz, 1H,H-10); (Found:C,

56.59; H,4.35, N,3.65,Calc. for $C_{18}H_{16}BF_4NOS$: C,56.70; H,4.23; N,3.67%); m/z 294 (M^+-BF_4,16%); 279(48).

4-(Methylthio)-2-phenyl quinolizinium tetrafluoroborate (35a) was isolated as yellow crystals (AcOH); yield 82%; m.p. 268°C; IR ν_{max}(KBr) 1638,1604, 1019-1120(br) cm^{-1}; ^1H NMR (DMSO-d_6): 3.09 (s,3H,SCH_3); 7.64-7.89 (m,3H, arom);8.14-8.31 (m,3H,arom);8.38-8.53 (m,2H,H-8 and H-3); 8.62 (d,J=7Hz,H-9);8.86 (s,1H,H-1);9.48 (d,J=7Hz,1H,H-6); (Found: C,56.25; H,4.19; N,4.09; Calc. for $C_{16}H_{14}BF_4NS$: C,56.65; H,4.16; N,4.13%); m/z 252 (M^+-BF_4, 25%); 237(66); 193(100).

2-(4-Methylphenyl)-4-(methylthio)quinolizinium tetrafluoroborate (35b) was isolated as yellow crystals (AcOH); yield 86%; m.p. 260°C; IR ν_{max}(KBr) 1624,1598,1560, 1010-1120(br) cm^{-1}; ^1H NMR (DMSO-d_6); 2.42 (s,3H,CH_3); 3.07 (s,3H,SCH_3); 7.42 (d,2H,A_2B_2arom); 8.05 (d, and t overlapped, 3H,A_2B_2 arom and H-7); 8.25 (s,1H,H-3); 8.36 (t,J=7Hz,1H,H-8); 8.55 (d,J=7Hz,1H,H-9); 8.79 (s,1H,H-1) 9.31 (d,J=7Hz,H-6); ^{13}C NMR (DMSO-d_6); 16.27 (CH_3); 20.81 (SCH_3); 119.53,119.93,123.52,127.64,128.32,129.96,135.72 (CH,C-1,C-3,C-6,C-7,C-8,C-9 and arom); 131.94,141.35, 143.94,145.29,147.58(C-2,C-9a,C-4,C-1'and C-4'of phenyl); (Found: C,57.08; H,4.51; N,3.91; Calc. for $C_{17}H_{16}BF_4NS$: C,57.18; H,4.57; N,3.97%); m/z 266 (M^+-BF_4, 24%); 251(73); 207(100).

2-(4-Methoxyphenyl)-4-(methylthio)quinolizinium tetrafluoroborate (35c) was isolated as yellow crystals (AcOH); yield 84%; m.p. 255°C; IR ν_{max}(KBr) 1638,1610,1600,1578, 1010-1110(br) cm^{-1}; ^1H NMR (DMSO-d_6); 3.06 (s,3H,SCH_3); 3.89 (s,3H,OCH_3); 7.20 (d,2H,A_2B_2 arom); 8.02 (t, J=7Hz, 1H,H-7); 8.14 (d,2H,A_2B_2 arom); 8.25 (s,1H,H-3); 8.32 (t, J=7Hz,1H,H-8); 8.51 (d,J=7Hz,1H,H-9); 8.78 (s,1H,H-1); 9.29 (d,J=7Hz,1H,H-6); ^{13}C NMR(DMSO-d_6); 16.29 (SCH_3); 55.48 (OCH_3); 114.83,118.69,119.55,123.22,128.19,129.46, 131.75,135.54 (CH,C-1,C-3,C-6,C-7,C-8,C-9 and arom); 143.93, 145.00, 147.41 (C-2,C-9a and C-4); 125.91,161.85 (C-1 and C-4' of phenyl); (Found: C,55.27; H,4.47; N,3.88; Calc. for $C_{17}H_{16}BF_4NOS$: C,55.30; H,4.36; N, 3.79%); m/z 282 (M^+-BF_4, 8%); 267(35).

2-(4-Chlorophenyl)-4-(methylthio)quinolizinium tetrafluoroborate (35d) was isolated as light yellow crystals (AcOH); yield 69%; m.p.244-245°C; IR ν_{max}(KBr) 1636, 1612. 1592, 1137-1008(br) cm^{-1}; ^1H NMR (DMSO-d_6) (90MHz): 2.98 (s,3H,SCH_3); 7.51-8.15 (m,6H,arom); 8.21-8.52 (m,3H, arom); 9.25 (d,J=7Hz,1H,H-6); (Found: C,53.24; H,3.52; N,3.81; Calc. for $C_{16}H_{13}BClF_4NS$: C,53.44; H, 3.64; N, 3.90%).

4-(Methylthio)-2-(2-naphthyl)quinolizinium tetrafluoroborate (35e) was isolated as yellow crystals (AcOH); yield 73%; m.p. 273°C; IR ν_{max}(KBr) 1639,1611,1571, 1028-1118(br) $^{-1}$; ^1H NMR (DMSO-d_6): 3.12 (s,3H,SCH_3); 7.66 (m, 2H, naphthyl); 8.01-8.29 (m,5H,H-7, naphthyl); 8.39

(t,J=7Hz, 1H,H-8); 8.46 (s,1H,H-3); 8.62 (d,J=7Hz,1H,H-9); 8.79 (s,1H,H-1' naphthyl); 9.00 (s,1H,H-1); 9.37 (d,J=7Hz,1H,H-6); (Found: C,61.52; H,4.12; N,3.54; Calc. for $C_{20}H_{16}BF_4NS$: C, 61.71; H,4.14; N,3.60%); m/z 302 (M^+-BF_4, 5%); 287(49).

4-(Methylthio)-2-(2-thienyl)quinolizinium tetrafluoroborate (35f) was isolated as yellow crystals (AcOH); yield 85%; m.p. 225°C; IR ν_{max}(KBr) 1630,1600,1560,1020-1190(br) cm^{-1}; ^1H NMR (DMSO-d_6):3.04 (s,3H,SCH_3);7.37 (dd,J=3.5 and 1.5Hz,1H,H-4'thienyl);8.01 (m,2H,H-7 and H-3' thienyl) 8.26-8.54 (m,3H,H-8,H-3 and H-5'thienyl); 8.55 (d,J=7Hz,1H,H-9);8.64 (s,1H,H-1);9.29(d,J=7Hz,H-6); (Found: C,48.52; H,3.51;N, 4.00; Calc.for $C_{14}H_{12}BF_4NS_2$: C,48.71; H,3.51; N,4.06%); m/z 258 (M^+-BF_4,2%) 243(12).

2-(2-Furyl)-4-(methylthio)quinolizinium tetrafluoroborate (35g) was isolated as yellow needles (AcOH); yield 76%; m.p. 245°C; IR ν_{max}(KBr) 1639,1618,1562,1024-1080(br) cm^{-1} ^1H NMR (DMSO-d_6); 3.01 (s,3H,SCH_3); 6.88 (dd,J=3 and 1.5Hz,1H,H-4'furyl); 7.82 (d,J=3Hz,H-3'furyl); 8.01 (t, J=7Hz, 1H,H-7); 8.14-8.18 (m,2H,H-3 and H-5'furyl); 8.32 (t,J=7Hz,1H,H-8); 8.59 (s and d overlapped, 2H,H-1 and H-9);9.28 (d,J=7Hz,1H,H-6); (Found: C,50.79; H,3.59; N,4.24; Calc. for $C_{14}H_{12}BF_4NOS$: C,51.08; H,3.68; N,4.26%); m/z 242 (M^+-BF_4, 25%); 227(100).

General procedure for the Displacement of the Methylthio group in 38a-e and 42a by Ethoxy group.

The quinolizinium salts 38a-e and 42c (5 mmol) were refluxed in ethanol (25 ml) for 24-28 hr, filtered, cooled and the crystals separated were collected by filtration to obtain the ethoxy substituted quinoliznium salts 39a-e and 43c.

4-Ethoxy-2-styryl quinolizinium tetrafluoroborate (39a) was isolated as yellow crystals (EtOH); yield 74%; m.p. 201-202°C; IR ν_{max}(KBr) 1620,1600,1582,1010-1130(br) cm^{-1} ^1H NMR (DMSO-d_6)(90MHz); 1.65 (t,J=7Hz,3H,CH_3); 4.72 (q, J=7Hz,2H,CH_2); 7.31-7.92 (m,10H,arom and olefinic); 8.15-8.45 (m,2H,arom); 9.18 (d,J=7.5Hz,1H,H-6); (Found: C,62.71; H,4.91; N,3.73; Calc. for $C_{19}H_{18}BF_4NO$: C, 62.84; H,4.99; N,3.86%); m/z 276 (M^+-BF_4,5%); 247(100).

4-Ethoxy-2-(4-methoxystyryl)quinolizinium tetrafluoroborate (39b) was isolated as yellow crystals (EtOH); yield 69%; m.p. 272°C; IR ν_{max}(KBr) 1622,1600,1505, 1010-1105(br) cm^{-1}; ^1H NMR(DMSO-d_6); 1.58(t,J=7Hz,3H,CH_3); 3.80 (s,3H,OCH_3); 4.72 (q,J=7Hz,2H,CH_2); 6.95(d,J=8.5Hz, A_2B_2 arom); 7.35 (d,J=15Hz,1H, olefinic); 7.64 (d, J=8.5Hz, 2H,A_2B_2 arom); 7.74 (s and t overlapped, 2H,H-3 and H-7);7.89 (d,J=15Hz,1H,olefinic); 8.19 (s and t overlapped,2H,H-1 and H-8); 8.35 (d,J=7Hz,1H,H-9); 9.12 (d, J=7Hz, 1H,H-6); ^{13}C NMR(DMSO-d_6); 13.72(CH_3); 55.12 (OCH_3); 68.81(CH_2); 99.93,121.44 (olefinic); 114.31, 114.64,126.38,127.55,127.83,129.07, 134.99,137.98(CH,C-

1,C-3,C-6,C-7,C-8,C-9 and phenyl); 142.09,147.44,151.49 (C-2,C-9a and C-4); 121.35,160.58 (C-1' and C-4' of phenyl); (Found: C,61.33; H,4.98; N, 3.63; Calc. for $C_{20}H_{20}BF_4NO_2$: C,61.09; H, 5.13;N,3.56%); m/z 306 (M^+-BF_4, 8%); 277(100).

2-(2,6-Dichlorostyryl)-4-ethoxyquinolizinium tetrafluoroborate (39c) was isolated as light yellow crystals (EtOH); yield 68%; m.p. 233°C; IRν_{max}(KBr) 1630,1585, 1040-1110(br) cm^{-1}; ^1H NMR (DMSO-d_6); 1.62 (t,J=7Hz, 3H, CH_3); 4.76 (q,J=7Hz,2H,CH_2); 7.36 (d,J=15Hz,1H,olefinic); 7.48 (brs,1H,arom); 7.62 (brs,1H,arom); 7.65(brs,1H, arom); 7.90 (d,J=15Hz,1H,olefinic); 7.94 (t,J=7Hz,1H,H-7) 7.98(s,1H,H-3); 8.29 (t,J=7.5Hz,1H,H-8); 8.42 (s and d overlapped , 2H,H-1 and H-9); 9.31 (d,J=7Hz,1H,H-6); (Found:C,52.69; H, 3.61; N,3.29;Calc.for $C_{19}H_{16}BCl_2F_4NO$; C,52.82; H,3.73; N,3.24%); 317 (M^+-BF_4-29,37%);252(40).

2-(3,4-Dimethoxystyryl)-4-ethoxyquinolizinium tetrafluoroborate (39d) was isolated as yellow crystals (EtOH); yield 71%; m.p. 268°C; IRν_{max}(KBr) 1620,1595,1505, 1010-1100(br) cm^{-1}; ^1H NMR(DMSO-d_6); 1.57 (t,J=7Hz, 3H,CH_3); 3.78 (s,3H,OCH_3); 3.80 (s,3H,OCH_3); 4.71 (q,J=7Hz,2H,CH_2) 7.06(d,J=7Hz,1H,arom); 7.22 (d,J=7Hz,1H,arom); 7.31(s,1H, arom); 7.38 (d,J=15Hz,1H,olefinic); 7.75 (s and t overlapped,2H,H-3 and H-7); 7.89 (d,J=15Hz,1H,olefinic); 8.14 (s and t overlapped,2H,H-1 and H-8);8.28(d,J=7Hz,1H,H-9); 9.19 (d,J=7Hz,1H,H-6); (Found: C,59.32; H,5.10; N,3.12;

Calc. for $C_{21}H_{22}BF_4NO_3$: C,59.59; H,5.24;N,3.31%); m/z 336 (M^+-BF_4, 8%); 307(100).

4-Ethoxy-2-(3,4-methylenedioxystyryl)quinolizinium tetrafluoroborate (39e) was isolated as yellow crystals(EtOH); yield 68%; m.p.271-272°C; IRγ_{max}(KBr) 1620,1600,1582, 1020-1100(br) cm^{-1}; ^1H NMR (DMSO-d_6); 1.59 (t,J=7Hz, 3H, CH_3); 4.68 (q,J=7Hz,2H,*CH_2*); 6.09 (s,2H,CH_2); 6.99 (d, J=8Hz,1H,arom);7.13 (d,J=8Hz,1H,arom);7.36 (s and d overlapped,3H,arom and olefinic); 7.74 (s,1H,H-3); 7.78-7.92 (m,2H,H-7 and olefinic); 8.05 (s,1H,H-1); 8.13 (t,J=7Hz, 1H,H-8); 8.31(d,J=7Hz,1H,H-9); 9.16 (d,J=7Hz,1H,H-6); (Found: C,59.10; H,4.28; N,3.53; Calc. for $C_{20}H_{18}BF_4NO_3$: C,58.99; H,4.46; N,3.44%); m/z 291 (M^+-BF_4-29);262(65).

4-(Methylthio)-2-(4-phenyl-1,3-butadienyl)quinolizinium tetrafluoroborate (42a) was isolated as yellow crystals (EtOAc); yield 76%; m.p. 220-221°C; IRν_{max} 1639,1600,1566 1011-1164(br) cm^{-1}; ^1H NMR (DMSO-d_6): 2.98 (s,3H,SCH_3); 6.89 (d,J=15Hz,1H,olefinic);7.04 (d,J=15Hz,1H,olefinic); 7.26(dd,J=15 and 7Hz,1H,olefinic); 7.30-7.41 (m,3H,arom); 7.15 (m,2H,arom); 7.82 (dd,J=15 and 7Hz,1H,olefinic); 7.92 (t,J=7Hz,1H,H-7); 8.21 (s,1H,H-3); 8.29 (t,J=7Hz,1H, H-8); 8.36 (s,1H,H-1); 8.90 (d,J=7Hz,1H,H-9); 9.23 (d, J=7Hz,1H,H-6); (Found: C,61.21; H,4.42; N,3.32; Calc. for $C_{20}H_{18}BF_4NS$: C, 61.40; H,4.64; N,3.58%); m/z 304 (M^+-BF_4, 4%); 289(11).

4-(Methylthio)-2-[4-(4-methoxyphenyl)1,3-butadienyl]quinolizinium tetrafluoroborate (42b) was isolated as yellow crystals (EtOAC); yield 73%; m.p. 235-236°; IR ν_{max} 1620, 1580,1510,1030-1100(br) cm^{-1}; ^1H NMR (DMSO-d_6) 2.95 (s, 3H,SCH_3); 3.69 (s,3H,OCH_3); 6.86 (d,J=15Hz,1H,olefinic); 6.92 (d,J=8Hz,2H,arom); 6.97 (d,J=15Hz,1H,olefinic); 7.12 (dd,J=15 and 7Hz,1H,olefinic); 7.53 (d,J=8Hz,2H,arom); 7.78 (dd,J=15 and 7Hz,1H,olefinic); 7.91 (t,J=7Hz,1H,H-7); 8.12 (s,1H,H-3); 8.28 (t,J=7Hz,1H,H-8); 8.37 (s,1H, H-7); 8.39 (d,J=7Hz,1H,H-9); 9.20 (d,J=8Hz,1H,H-6); ^{13}C NMR(DMSO-d_6); 16.33 (SCH_3); 55.05 (OCH_3);114.13, 119.27,122.65,125.45,125.81,127.78,128.42,128.59,131.87, 135.36,138.74,140.05(CH,C-1,C-3,C-6,C-7,C-8,C-9,olefinic and phenyl); 143.68,143.79,146.46 (C-2,C-9a,C-4) 119.69, 159.87 (C-1' and C-4'of phenyl); (Found: C,59.68; H,4.63; N,3.59; Calc. for $C_{21}H_{20}BF_4NOS$:C,59.87;H,4.79, N,3.33%); m/z 334 (M^+-BF_4, 25%); 319(7); 286(6).

4-Ethoxy-2-[4-(3,4-methylenedioxyphenyl)-1,3-butadienyl] quinolizinium tetrafluoroborate (43c) was isolated as yellow crystals (EtOH); yield 63%; m.p. 273-274°C; IR ν_{max} *(KBr) 1640,1622,1590,1022-1105(br) cm^{-1}; ^1H NMR(DMSO-d_6)* 1.56(t,J=7Hz,3H,CH_3); 4.65 (q,J=7Hz,2H,*CH_2*); 6.01 (s,2H, *CH_2*); 6.72 (d,J=15Hz,1H,olefinic); 6.84 (m,2H,arom and olefinic); 6.98 (d,J=8Hz,1H,arom); 7.08 (dd,J=15Hz and 7Hz,1H,olefinic); 7.21 (s,1H,arom); 7.66 (m,2H,H-3 and

olefinic); 7.76 (t,J=7Hz,1H,H-7); 8.02 (s,1H,H-1); 8.10 (t,J=7Hz,1H,H-8); 8.25 (d,J=7Hz,1H,H-9);9.19 (d,J=7Hz,1H, H-6);(Found:C,60.71;H,4.52;N,3.32;Calc.for $C_{22}H_{20}BF_4NO_3$: C,60.99; H,4.65; N,3.23%); m/z 346 (M^+-BF_4,4%)317(100).

REFERENCES

1. Wittig,G.; Reiff,H. *Angew.Chem.Int.Ed.Engl.* **1968**, *7*, 7.
2. Woodward,R.B.; McLamore,W.M. *J.Am.Chem.Soc.* **1949**, *71*, 380.
3. Boekelheide,V.; Gall,W.G. *J.Am.Chem.Soc.* **1954**, *76*, 1832.
4. Richards,A.; Stevens,T.S. *J.Chem.Soc.* **1958**, 3067.
5. Stuart,D.M.; Logan,V.A.; Wischmann,K.W. *J.Org.Chem.* **1961**, *26*, 2794.
6. Hansen,H.V.; Amstutz,E.D. *J.Org.Chem.* **1963**, *28*,393.
7. Gupta,A.K.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* **1988**, *29*, 6633.
8. Crouse,D.N.; Seebach,D. *Chem.Ber.* **1968** *101* 3113.
9. Sauvetre,R.; Roux-Schmit,M.C.; Seyden-Penne,J. *Tetrahedron* **1978** *34*, 2135.
10. Lefour,M.J.; Loupy,A. *Tetrahedron* **1978**, *34*, 2597.
11. Gupta,A.K.; Ila,H.; Junjappa,H. Unpublished results.
12. Thuillier,A.; Vialle,J. *Bull.Soc.Chim.Fr.* **1962**, 2182.
13. Apparao,S.; Bhattacharjee,S.S; Ila,H.; Junjappa,H. *J.Chem.Soc.Perkin Trans.I.* **1985**, 641.
14. Chauhan,S.M.S.; Junjappa,H. *Tetrahedron* **1976**, *32*, 1779.
15. Beumel,Jr.;O.F.; Smith,W.N.; Rybalka,B. *Synthesis* **1974**, 43.

16. Gilman,H.; Beel,J.A.; Brannen,C.G.; Bullock,M.W.; Dunn,G.E.; Miller,L.S. *J.Am.Chem.Soc.* 1949,*71*,1499.

17. Thuillier,A.; Vialle,J. *Bull.Soc.Chim.Fr.* 1962,2187.

18. Asokan C.V.; Ila.H.;Junjappa,H. *Synthesis*,1985, 163.

CHAPTER IV

1,3-ANIONIC CYCLOADDITIONS OF 1,3-DIPHENYL-2-AZAALLYL AND ETHYL (BENZYLIDENEAMINO)ACETATE ANIONS WITH α-OXOKETENE DITHIOACETALS.

IV.1. INTRODUCTION

The α-oxoketene dithioacetals possess 1,3-electrophilic centres with differing electrophilicity and undergo chemoselective addition-elimination reactions with various carbon and nitrogen nucleophiles. Generally the hard carbon nucleophiles undergo exclusive 1,2-addition while the bulkier and stabilized carbanions undergo 1,4-addition, sometimes followed by 1,2-addition[1-4]. On the otherhand the nitrogen nucleophiles generally undergo 1,4-addition-elimination, though 1,2-addition sequence with hydroxylamine under basic conditions has also been

reported[5]. As an extension of these studies various allyl[1,6] and 1-azaallyl[7] anions have been shown to undergo exclusive 1,2-addition followed by Lewis acid assisted cycloaromatization to yield the corresponding aromatic and heteroaromatic compounds in high yields. In the Chapter III the reactivity of 1-azaallyl anion was demonstrated by reacting 2-picolyllithium with oxoketene dithioacetals to yield the corresponding carbinol acetals in nearly quantitative yields which on borontrifluoride etherate assisted cyclization yielded the corresponding quinolizinium tetrafluoroborates in excellent yields.[7] The double bond reactivity of the oxoketene dithioacetals towards 1,3-dipolar species such as sodium azide has also been reported from this laboratory to yield triazoles.[8]

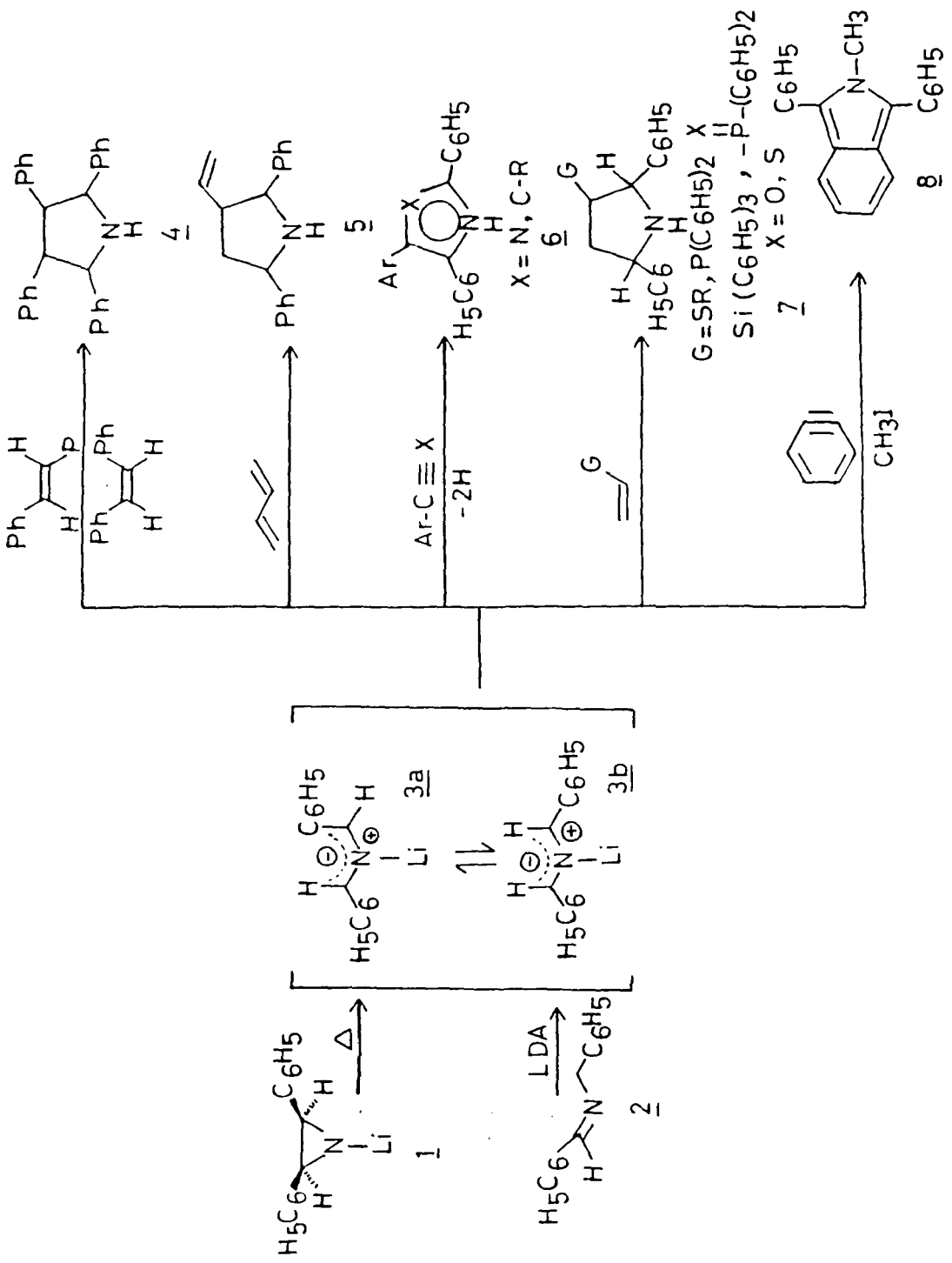
In the course of these studies it was considered of interest to examine the reactivity of 2-azaallylanions, which are known to undergo 1,3-anionic cycloaddition with activated double bonds in a concerted and stereoselective manner to give a number of five membered heterocycles[10]. The regiocontrol in these cycloaddition reactions has also shown to be remarkably selective and generally only one regioisomer is formed wherever alternative possibilities existed. The structural features of 2-azaallyl anions have been examined which are shown to exist in different configurations at different reaction conditions. Thus, 1,3-diphenyl-2-azaallyllithium in the *cis,trans* (Z,E)form can be prepared by the conrotatory

ring opening of N-lithio-cis-2,3-diphenylaziridine at 40-60°C, although it rearranges to the thermodynamically more stable *trans,trans*(E,E) form immediately[9](Scheme 1) It is therefore possible to utilize these configurational differences by carefully manipulating reaction conditions for the synthesis of stereoselective cycloadducts. In the light of these reactivity profile of 3 towards activated double bonds, it was considered to examine its reactivity with α-oxoketene dithioacetals which may lead to the corresponding pyrrolidine cycloadducts. The presence of two methylthio groups in these intermediates will further permit the elimination of methylmercaptan in the pyrrolidine adducts and the end product should result in the fully aromatized pyrroles. Such studies may qualify the α-oxoketene dithioacetals as masked acetylenic compounds. The availability of wide structural variants of α-oxoketene dithioacetals from abundantly available active methylene ketones will enhance the scope of the methodology for the synthesis of pyrroles and pyrrolidines through 1,3-anionic cycloaddition reaction. The investigations on anionic cycloadditions of 1,3-diphenyl-2-azaallyl and ethyl (benzylideneamino)acetate anions with α-oxoketene dithioacetals have been presented in this chapter.

The 1,3-anionic cycloaddition of 2-azaallyl anions have been extensively investigated and the results have been reviewed[10]. Only a selected number of key cycloaddition

reactions have been briefly discussed in this chapter as an introduction to the present investigation. 1,3-Diphenyl-2-azaallyllithium 3 was first reported by Kauffmann by reacting N-benzylidine benzylamine with lithium diisopropylamide[11]. Subsequently the same group also prepared the anion 3 from N-lithio-cis-2,3-diphenylaziridine 1 through a thermal conrotatory ring opening process[9] (Scheme 1). Most of the 1,3-anionic cycloadditions investigated have been shown to be stereospecific. The best studied reaction is that of both *cis,trans* and *trans,trans* 1,3-diphenylazaallyl-lithium 3a and 3b with *trans*- and *cis*-stilbenes[12]. The anion 3 was reacted with *trans*- and *cis*-stilbenes to yield the corresponding pyrrolidines 4 in a stereo-specific manner[12]. These observations can be most readily interpreted in terms of symmetry-allowed concerted [$\pi 4_s + \pi 2_s$] cycloaddition processes and the reaction was extended to large number of olefins with known geometry to confirm the concertedness of the reaction. The reaction of 3 with butadiene yielded the corresponding vinyl pyrrolidines 5 in high yields[13]. Also, the reaction of 3 with alkynes and nitriles yielded directly the corresponding pyrroles and imidazoles 6 respectively in good yields[14] (Scheme 1).

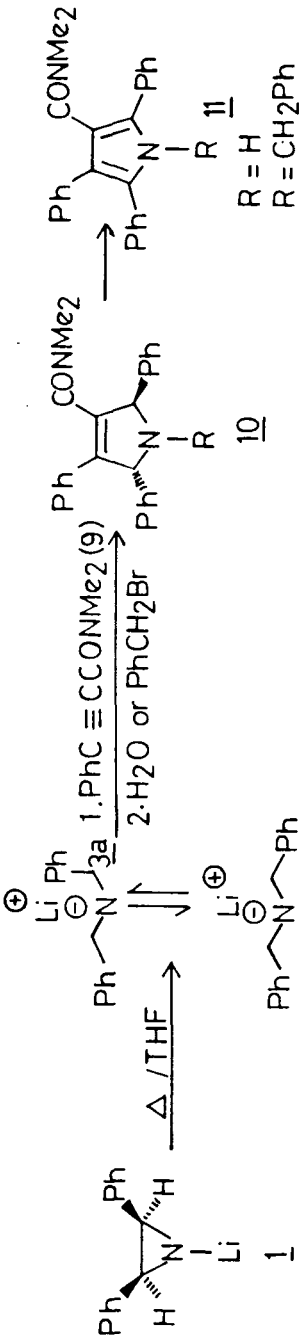
Since the activation of double bond was found to be a prerequisite for cycloaddition reactions, the double bonds activated by groups which can be cleaved



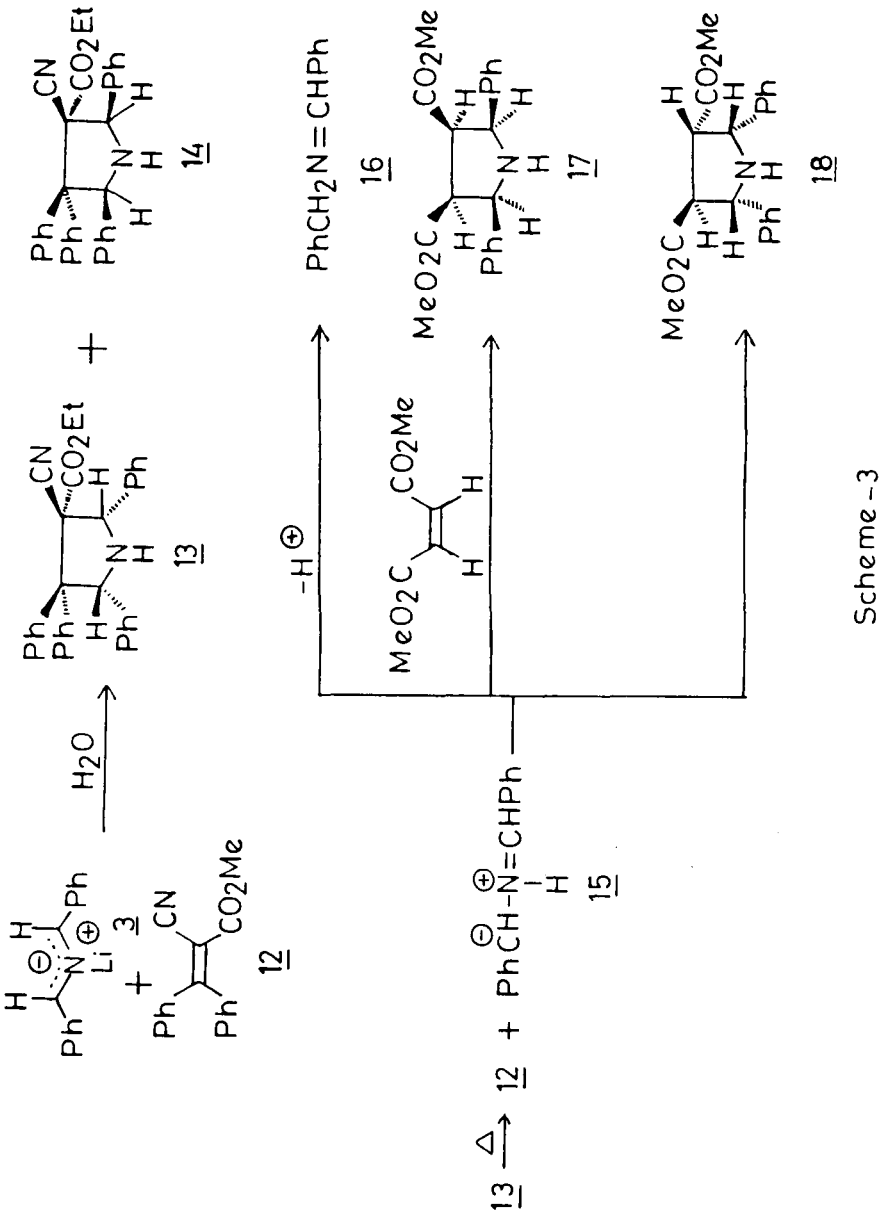
Scheme-1

subsequently using appropriate methodology have also been studied. Thus, 3 was reacted with vinyl sulphides, phosphines, selenides, triaryl silanes etc, to yield the corresponding pyrrolidines 7 in high yields and the group G could be removed using appropriate reaction conditions[15]. A few exceptions of unactivated double bond addition to 3 to yield the corresponding isoindole 8 in moderate yields (Scheme 1).

Kauffmann has reported that carbonyl groups of proven value in Diels-Alder reactions and 1,3-dipolar cycloadditions are unsuitable for anionic 1,3-cycloadditions owing to the pronounced nucleophilic character of the anionic reagents[15]. However, a few examples of this structural feature have been examined, where the carbonyl functionality does not interfere in the formation of the cycloadduct. Thus, the anion 3 when reacted with phenylpropiolic acid N,N-dimethylamide 9 affords the pyrroline 10 which is readily oxidized by air to the pyrrole 11[16] (Scheme 2). Similarly the doubly activated methyl α-cyano-β-phenylcinnamate 12 reacted with 3 to yield the corresponding pyrrolidines 13 and 14. The adduct 13 when heated in refluxing toluene under nitrogen atmosphere for 24 hours, underwent retro-cycloaddition to yield azomethine ylide 15 which on reaction with methyl maleate and methyl fumarate yielded the corresponding pyrrolidines 17 and 18 stereospecifically[17] (Scheme 3).


Ph
H
N
Li
1
Δ /THF
Li
Ph
N
Ph
3a
3b
1. PhC ≡ CCONMe2 (9)
2. H2O or PhCH2Br
CONMe2
Ph
Ph
N
R
10
11
R = H
R = CH2Ph

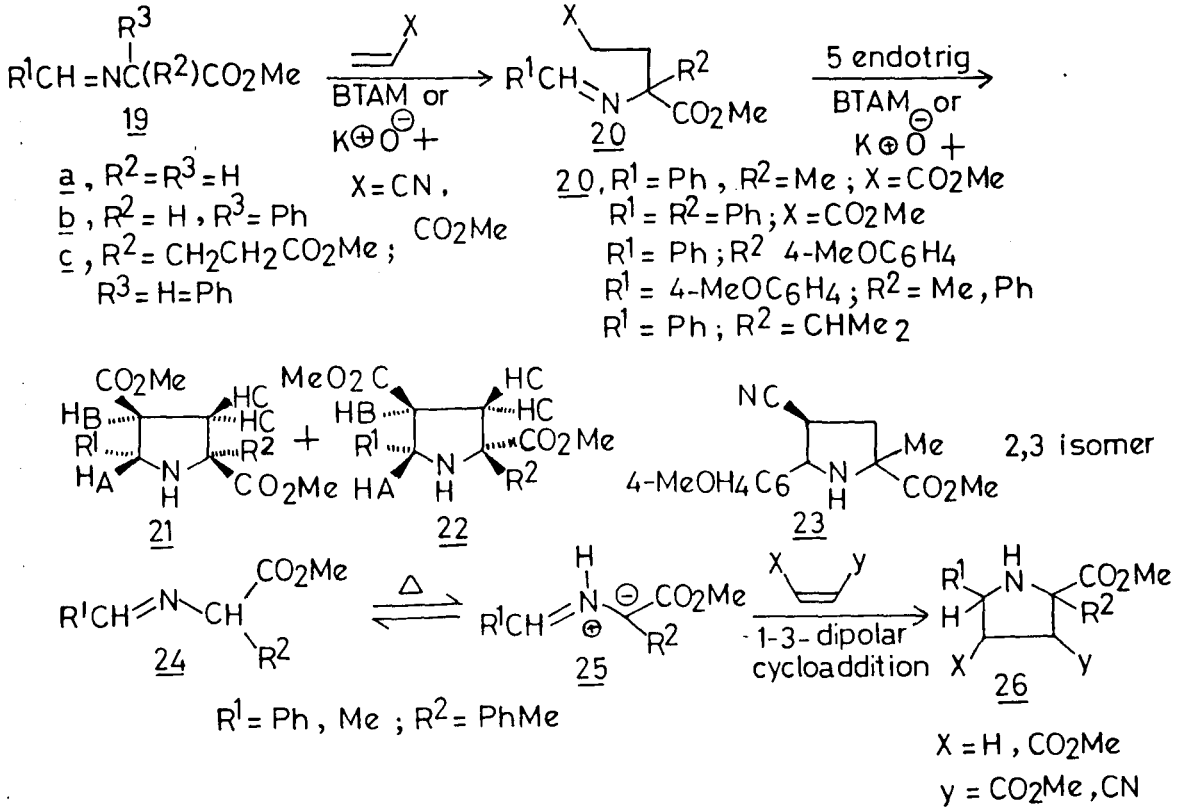
Scheme - 2



Scheme-3

An interesting example showing a two step mechanism for 1,3-anionic cycloadditions has been reported by Grigg and co-workers[18]. They have selected the potentially ambident imine anions derived from 19 which are good Michael donors and reacted them with acrylonitrile and methyl acrylate to yield the corresponding Michael adducts 20 with complete regiocontrol. These Michael adducts are of particular interest because they are structurally suitable for geometrically disfavoured *5-endo-trig* ring closure and are shown to undergo cyclisation in the presence of appropriate base and solvent to yield the pyrrolidines 21-23. However, the stereochemistry of the pyrrolidines varies with the base and solvent composition. Similarly the imines of α-amino acid esters 24 undergo cycloadditions probably via their azomethine ylides 25 to give the pyrrolidines 26 in good yields[19] (Scheme 4).

Tsuge and co-workers have described in a series of papers, the preparation of N-lithiated azomethine ylide 1,3-dipoles by reacting imines with LDA or ($LiBr/Et_3N$) and examined their reactivity towards electron deficient olefins[20,21,24]. These cycloadditions have been found to occur in an exclusively regio- and stereoselective manner. They have also offered explanation of the reactivity of 2-azaallylanions versus azomethine ylides. Although complementary in synthetic application, 2-aza-


R1CH=NC(R2)CO2Me
19
a, R2=R3=H
b, R2 = H, R3= Ph
c, R2= CH2CH2CO2Me ;
R3 = H=Ph
BTAM or
K⊕O⊖+
X=CN,
CO2Me
20
20, R1 = Ph, R2=Me ; X=CO2Me
R1 = R2=Ph; X=CO2Me
R1 = Ph; R2 4-MeOC6H4
R1 = 4-MeOC6H4; R2 = Me, Ph
R1 = Ph; R2 = CHMe2
5 endotrig
BTAM⊖or
K⊕O +
21
22
23
2,3 isomer
24
25
26
R1 = Ph, Me ; R2= PhMe
1-3-dipolar
cycloaddition
X = H, CO2Me
y = CO2Me, CN

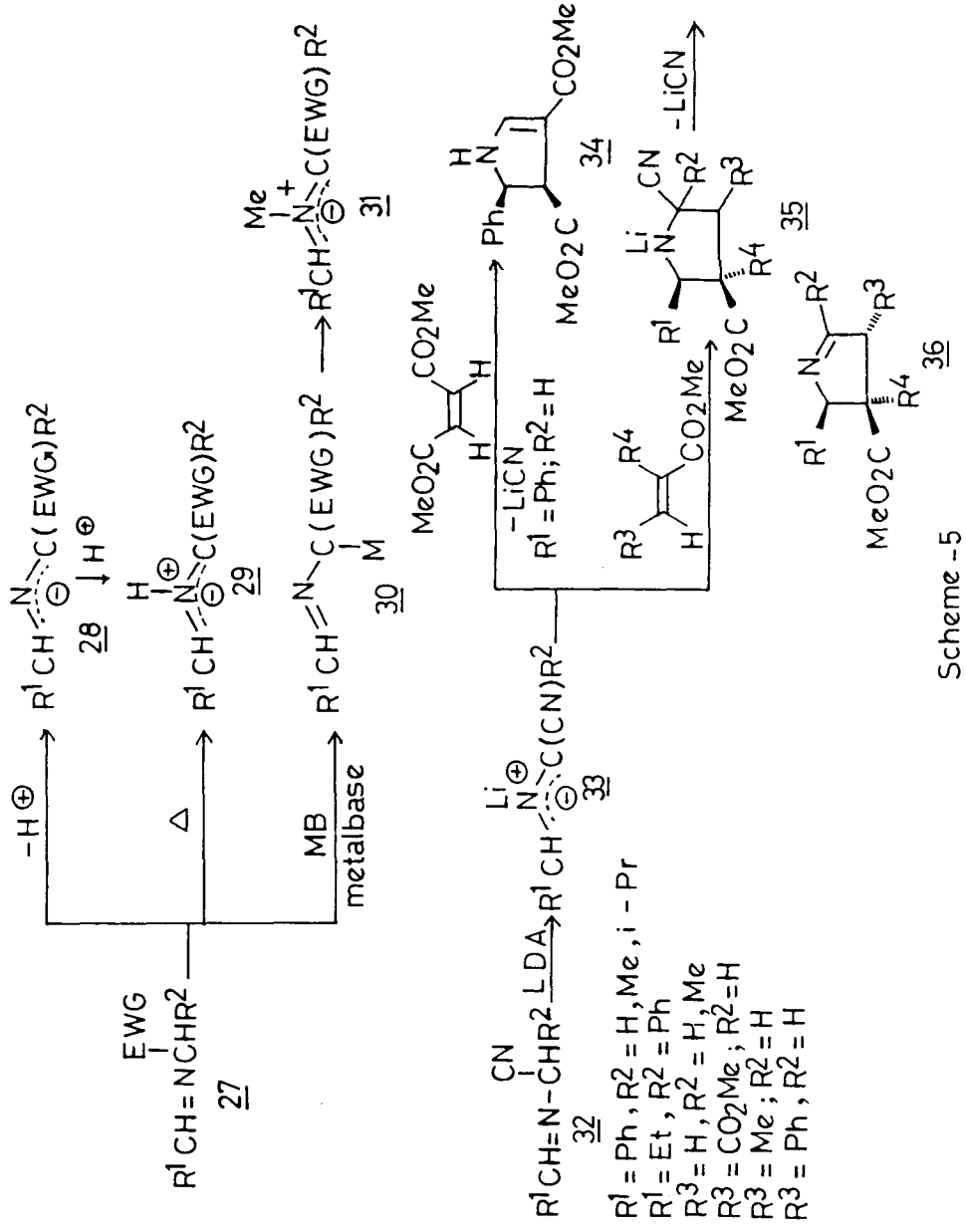
Scheme-4

allylanions and azomethine ylides are isoelectronic, both carrying 4 conjugation along a carbon-nitrogen-carbon frame work. In the case of 2-azaallyl anions, the lone pair of electrons on the nitrogen are free and consequently they should behave like a hard nucleophile rather than a 1,3-dipolar species. However, the lithium cation is known to be associated with the central nitrogen so that these anions behave like soft azomethine ylides and undergo 1,3-cycloaddition reactions. Utilizing these concepts, Tsuge and co-workers have examined the reactivity of azomethine ylides towards activated double bonds as described in the Scheme 5.

The oxoketene dithioacetals with β,β-bis(methylthio) group and an α-carbonyl functionality should behave like push-pull ethylenes and consequently their double bond activity as dipolarophile with 2-azaallylanion 3 should yield the corresponding pyrrolidines rather than the 1,2-addition products leading to pyridine 41 (Scheme 6). The results of these studies are presented in the following section.

IV.2 RESULTS AND DISCUSSION

In principle, a large structural variants of the oxo-ketene dithioacetals can be used in these cycloaddition studies, however only a selected number of these have



Scheme -5

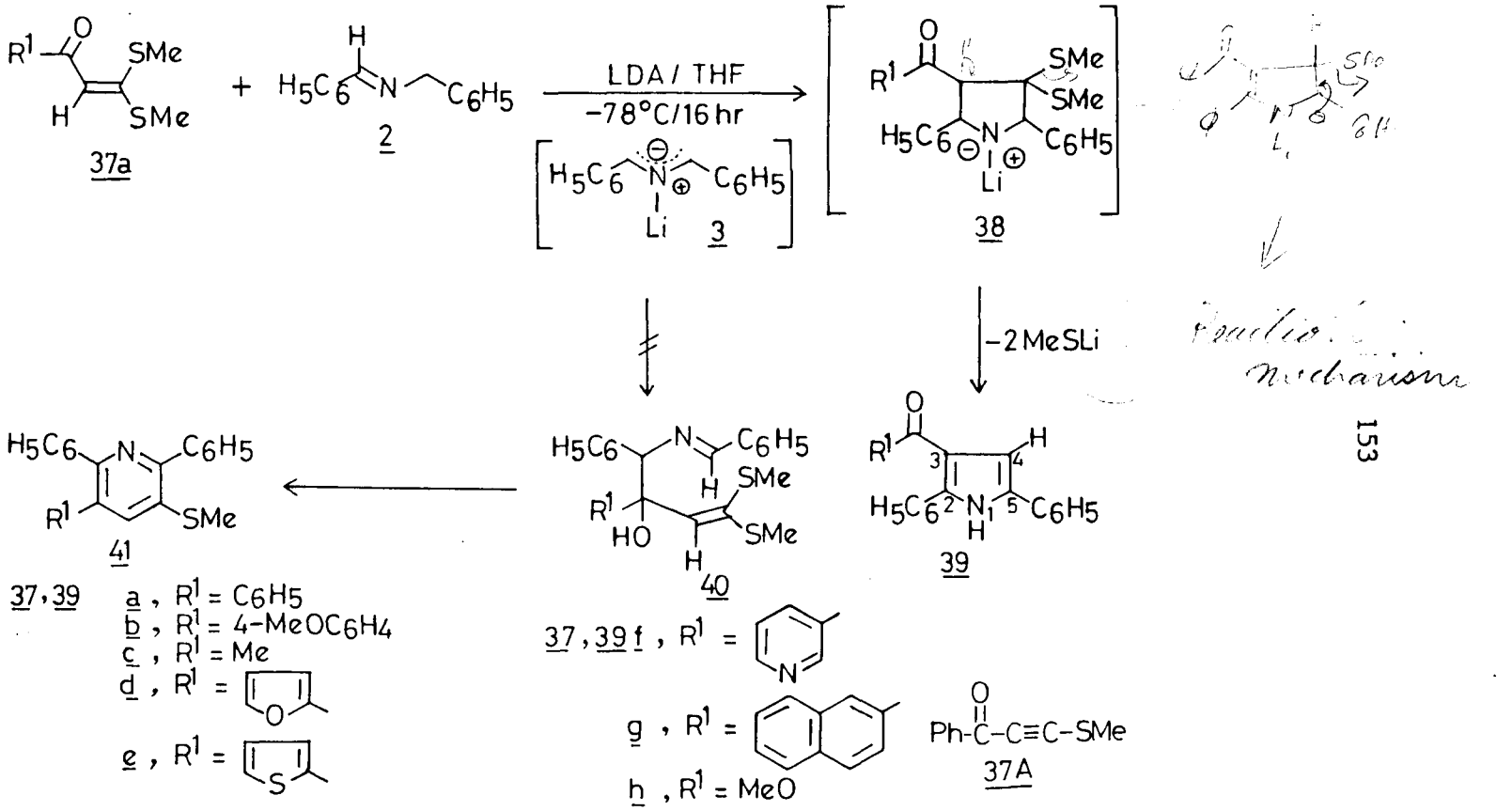
been examined in this investigation. Similarly among 2-azaallylanions, 1,3-diphenyl-2-azaallylanion has been selected as a typical example. Also the unsymmetrical azaallylanion derived from Ethyl(benzylideneamino)acetate under very mild conditions have also been used in this study to investigate the reactivity towards oxoketene dithioacetals.

IV.2.1 Reactions of 1,3-Diphenyl-2-azaallyllithium with Oxoketene Dithioacetals.

In a typical reaction, the oxoketene dithioacetal 37a was reacted with 1,3-diphenyl-2-azaallylanion 3 at -78°C derived from deprotonation of N-benzylidene benzylamine 2 using LDA as base to yield after work up the fully aromatized 3-benzoyl-2,5-diphenylpyrrole 39 in 79% yield. Apparently 39 is formed from the corresponding pyrrolidine 38 which in turn is formed via a 1,3-anionic cycloaddition of the 2-azaallylanion 3 with oxoketene dithioacetal, followed by sequential *in situ* elimination of two MeSLi groups. Thus, the oxoketene S,S-acetals as masked acetylenes are demonstrated through the formation of 39, which could have been obtained from the corresponding β-methylthiobenzoylacetylene 37A and the anion 3. Either the carbinol acetal 40, arising from a possible 1,2-addition or the corresponding cycloaromatized pyridine 41 were not detected in the reaction mixture. The structure of the pyrrole 39 was established by its analytical and spectral data. It showed in its

mass spectrum molecular ion peak at m/z 323(100%) and characteristic fragmentation patterns at m/z 246(72%) which accounted for loss of phenyl group and m/z 218(7%) due to the loss of benzoyl group. The compound was analyzed for $C_{23}H_{17}NO$ and its IR spectrum showed clearly the NH absorption as a broad band at ν_{max} 3200 cm^{-1} and two other prominent bands appeared at 1595 (C=O) and 1572 cm^{-1}. The structure of 39a was further confirmed from its ^1H NMR spectrum ($CDCl_3$). The doublet at δ6.75(1H,J=1.5Hz) was assigned to H-4 proton. The 13-aromatic protons appeared as a multiplet between δ7.00-7.58, whereas the multiplet between δ7.62-7.81 was assigned to the two ortho protons of the benzoyl group. The pyrrole NH proton appeared as broad singlet at δ11.93(1H, exchangeable with D_2O). The other oxoketene dithioacetals 37b-g similarly reacted with 3 to yield the corresponding 3-acyl pyrroles 39b-g in 71-84% overall yields (Scheme 6). Similarly α-carbomethoxyketene dithioacetal underwent facile cycloaddition with 3 to afford the corresponding 3-carbomethoxy pyrrole 39h in 71% yield. The structures of the pyrroles 39b-h thus obtained were confirmed by their analytical and spectral data which are described in the experimental section.

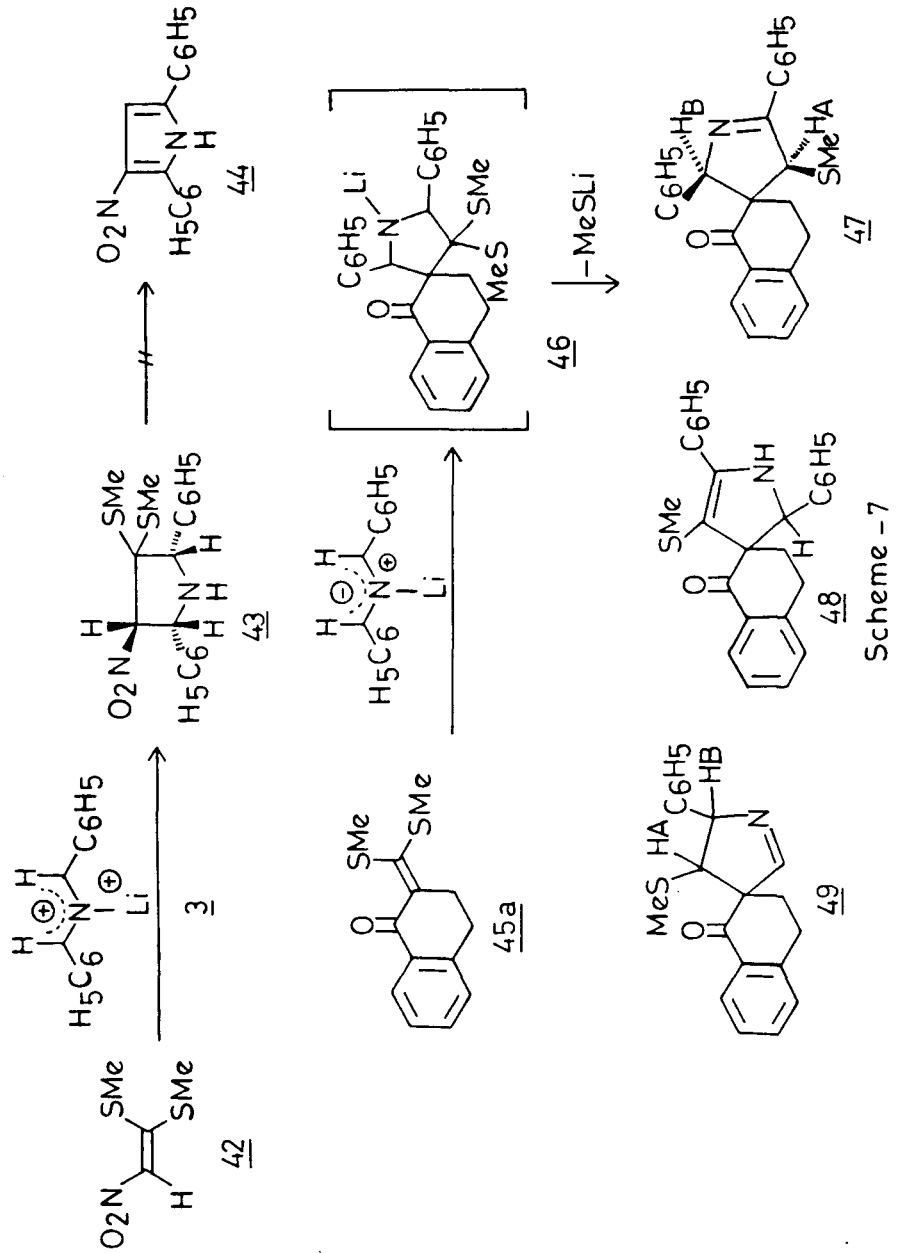
Interestingly the nitroketene S,S-acetal 42 reacted with 1,3-diphenyl-2-azaallyl anion 3 to yield the corresponding tetrahydropyrrolidine 43 in 64% yield but the fully aromatized pyrrole 44 could not be detected in


LDA / THF
−78°C/16 hr
−2 MeSLi
37a
2
3
38
39
40
41
37,39 a , R1 = C6H5
b , R1 = 4-MeOC6H4
c , R1 = Me
d , R1 =
e , R1 =
37,39 f , R1 =
g , R1 =
h , R1 = MeO
Ph-C(=O)-C≡C-SMe
37A

Scheme – 6

the reaction mixture. The structure of 43 was confirmed from its analytical and spectral data. Thus, in its mass spectrum, it exhibited a signal at m/z 360 (M^+ ,4%) and the compound was analysed for $C_{18}H_{20}N_2O_2S_2$. In its IR spectrum (KBr) the absorption band at 3342 cm^{-1} was assigned to the NH group and the strong band at 1600 cm^{-1} was assigned to the nitro group. The structure was further confirmed from its ^1H NMR spectrum ($CDCl_3$). The signals at δ1.26 (3H) and 2.08 (3H) were assigned to the two methylthio groups. The broad signal at 2.39 (1H, exchangeble with D_2O) stood for the NH proton. The broad singlet at δ4.80 was assigned to the H-2 proton while the doublet at δ4.69 (J=6Hz) accounted for the H-4 proton. The signal due to H-5 proton appeared at δ4.92 (dd,J=6 and 1.5 Hz), while the multiplet between δ7.12-7.75 was assigned to the ten aromatic protons. The stereochemical configuration of 43 was tentatively assigned as shown in Scheme 7 on the basis of known literature examples for cycloaddition of 3[10,20].

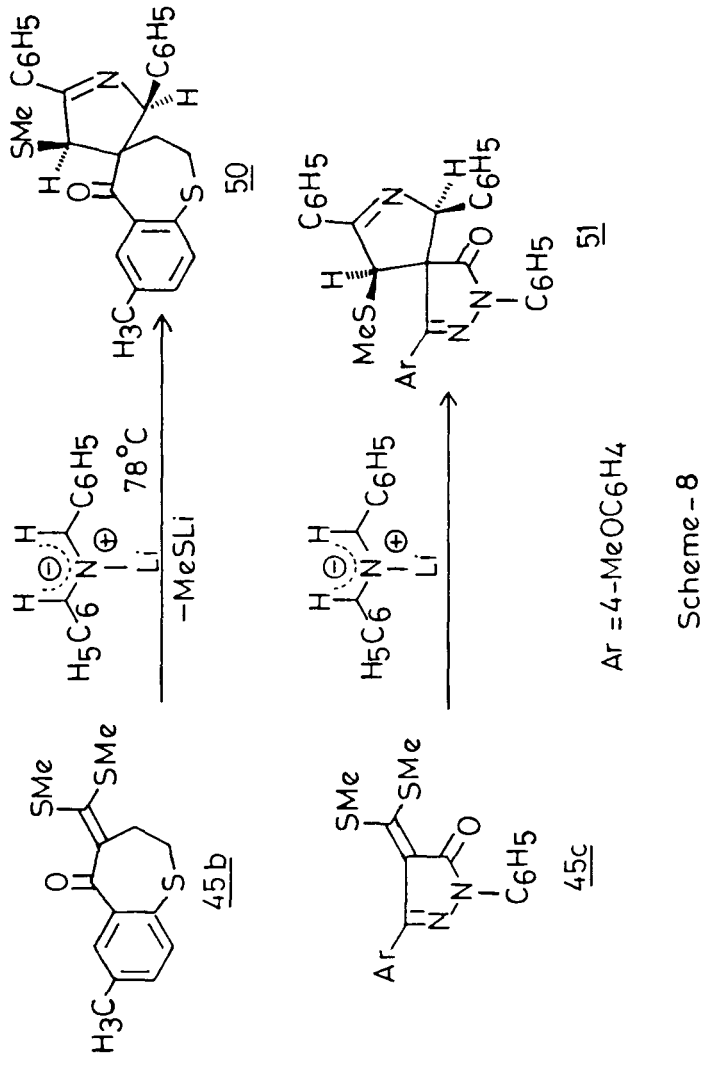
When the reaction of 3 was extended to the oxoketene dithioacetal 45a derived from tetralone, the corresponding spiropyrroline 47 was obtained in 74% yield as colourless crystalline solid. Interestingly the other possible structures 48 and 49 (Scheme 7), which might arise from prototopic shift were ruled out and the exclusive structure 47 was confirmed from its spectral data. The mass spectrum of the compound exhibited



Scheme - 7

molecular ion peak at m/z 397 (M^+,25%) and was analysed for $C_{26}H_{23}NOS$. In its IR spectrum (KBr) the absorbtion band at 1670 and 1605 cm^{-1} were assigned to C=O and C=N stretching vibrations. The clear absence of peaks due to NH group in the IR spectrum ruled out the possible structure **48**. The structure **47** was further confirmed from its ^1H NMR spectrum, which also helped to eliminate the probable structures **48** and **49**. The two multiplets (2H each) present at δ1.36-1.59 and δ2.25-2.36 were assigned to four methylene protons while the signal due to methylthio group appeared as sharp singlet (3H) at δ1.90. The aromatic protons were present as two multiplets between δ7.00-7.51 (10H) and δ8.05-8.25 (3H) respectively. The signals due to the two methine protons H_A and H_B were present at δ4.45 and δ6.22 respectively as doublets (J=2Hz). The nature of the coupling constant (J=2Hz) point to *cis* stereochemistry of H_A and H_B protons in line with the earlier reported examples in pyrroline systems.[20] Similarly the other cyclic oxoketene dithioacetals **45b** and **45c** derived from benzothiepinone and pyrazolone reacted with **3** to yield the corresponding spiropyrrolines **50** and **51** in 68 and 71% yields respectively (Scheme 8). The structure and stereochemistry of **50** and **51** were assigned with the help of their spectral and analytical data (experimental).

Interestingly, the cyclic oxoketene dithioacetals **45d** and **45e** did not react with **3** in the expected manner of the

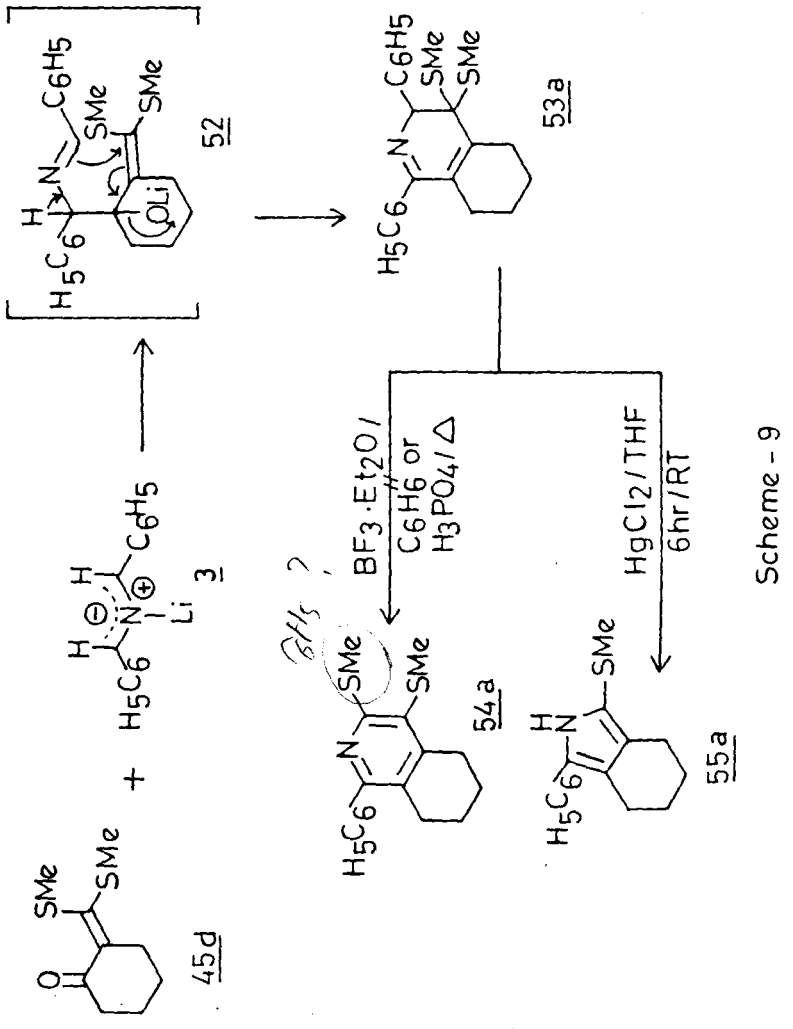


Ar =4-MeOC6H4

Scheme-8

preceeding cycloadditions. When 45d was reacted with 3 under identical reaction conditions, the product isolated in 79% yield was characterized as hexahydroisoquinoline derivative 53a and there was not trace of 1,3-anionic cycloaddition product in the reaction mixture. The structure of the compound 53a was confirmed from its analytical and spectral data. The compound exhibited in its mass spectrum a signal at m/z 379 (M^+,96%) and was analysed for $C_{23}H_{25}NS_2$. Its IR spectrum showed absorbtion bands at 1605 and 1527cm^{-1} which were assigned to C=N and C=C stretching vibrations. In its ^1H NMR spectrum the multiplet between δ1.62-1.82(4H) was assigned to methylene protons, while the two methylthio protons appeared as sharp singlets (3H each) at δ1.90 and 2.25. The other four methylene protons appeared as multiplet between δ2.50-2.74. The methine proton appeared as a sharp singlet at δ6.88 and the aromatic protons were present as multiplet (10H) between δ7.21-7.50.

The attempts to aromatize the pyridine ring in 53a by elimination of methylmercaptan under different reaction conditions to give 54a however were not successful probably due to steric crowding in 54a. On the other hand, treatment of 53a with $HgCl_2$ in THF at room temperature, gave a colourless crystalline product which was characterized as tetrahydroisoindole 55a (Scheme 9). The structure of 55a was confirmed from its analytical


SMe
SMe
O
45d
+
H
H5C6
N
Li
C6H5
3
52
C6H5
SMe
SMe
53a
BF3.Et2O/
C6H6 or
H3PO4/Δ
HgCl2/THF
6hr/RT
54a
55a

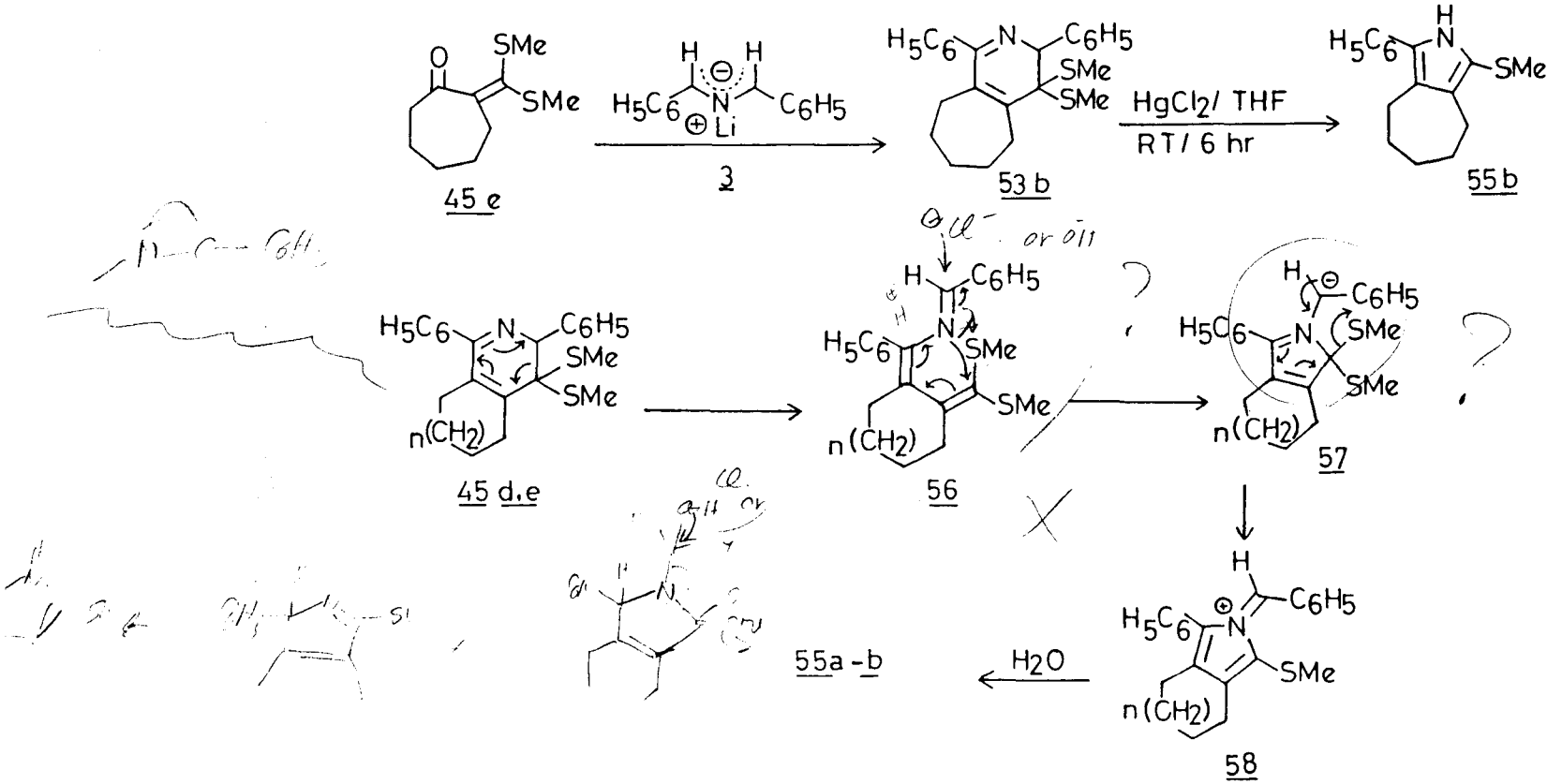
Scheme - 9

and spectral data (experimental section). Similarly 45e reacted with 3, first to yield the annelated dihydropyridine 53b in 76% yield which on treatment with $HgCl_2$ in THF at room temperature rearranged to the corresponding 3,4-annelated pyrrole 55b (Scheme 10). The structure of both 53b and 55b have been confirmed from its analytical and spectral data which are given in the experimental section.

Apparently the 1,3-diphenyl-2-azaallyl anion 3 did not undergo anionic cycloaddition with the cyclic oxoketene dithioacetals 45d and 45e to give spiropyrrolines but yielded products by sequential or concerted 1,2- and 1,4-addition-elimination to give 53 and 53b respectively. A plausible mechanism for the formation of 55a and 55b has been described in the Scheme 10. The dihydro-4,5-annelated pyridines 45 appear to suffer an electrocyclic reversion to yield the corresponding azatriene 56 which undergo intramolecular heterotriene cyclization[23] to give the intermediate 57 followed by elimination of MeSH group to yield the imminium intermediate 58 which on hydrolysis give the 3,4-annelated pyrroles 55a and 55b respectively.

IV.2.2 Lithium Bromide-Triethylamine Induced Cycloaddition Reactions of Ethyl(Benzylideneamino)acetate with Oxoketene Dithioacetals.

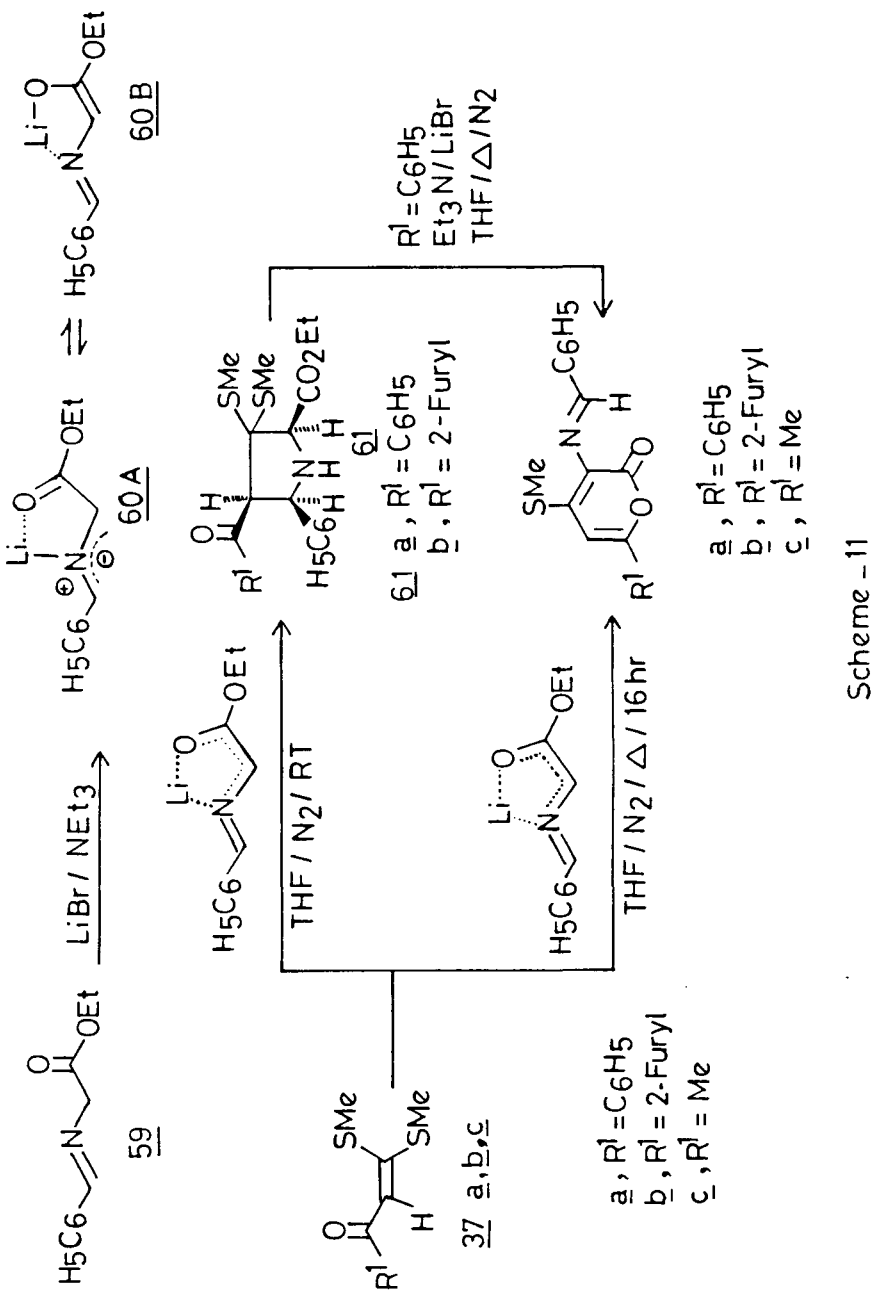
Tsuge and co-workers have extensively investigated the deprotonation of N-alkylidene-2-amino esters under



Scheme - 10

varying conditions[24]. Thus, strong bases such as LDA, n-BuLi, NaH, EtMgBr indeed yielded the corresponding anions, however these species failed to undergo cycloaddition with activated olefins. Tsuge has attributed the failure of these reactions to the facile polymerization of the activated olefins under highly basic reaction conditions. The same authors have successfully attempted the deprotonation of these esters using mild Lewis acid-base combination(LiBr-Triethylamine) to yield the corresponding N-lithiated azomethine ylides in quantitative yields which undergo neat cycloadditions with activated olefins.

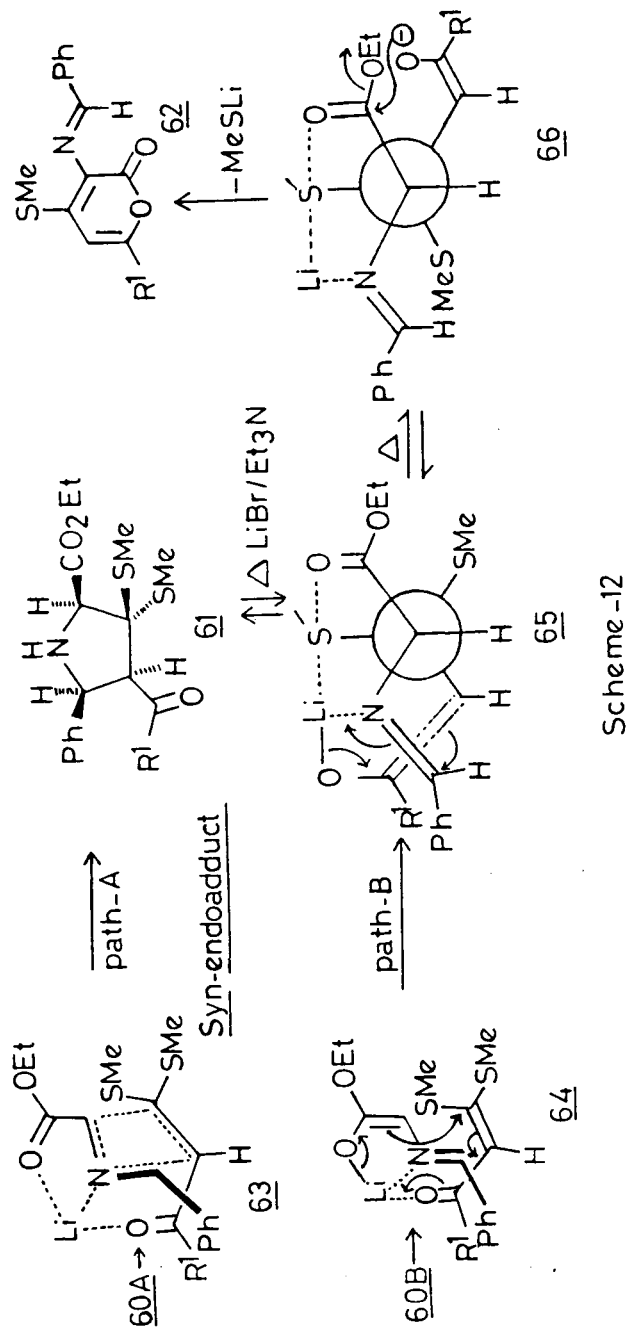
When the α-oxoketene dithioacetal 37a was reacted with N-lithiated azomethine ylide 60 generated under Tsuge's conditions (LiBr-Triethylamine) at room temperature the corresponding pyrrolidine 61a (Scheme 11) was obtained in 72% yield as a single stereoisomer. The analytical and spectral data of 61a were in confirmity with the assigned structure (experimental). Similarly the corresponding 3-furoylpyrrolidine 61b was obtained in 69% yield under identical reaction conditions. However, the α-acetyl ketene dithioacetal 37c failed to give the corresponding pyrrolidine and the bright yellow product (81%) isolated under similar reaction conditions was characterized as 6-methyl-4-(methylthio)-3-benzylidene aminopyran-2-one 62c on the basis its analytical and spectral data. Thus, in its mass spectrum, it exhibited a signal at m/z 259


59
LiBr / NEt3
60 A
60 B
37 a,b,c
THF / N2 / RT
THF / N2 / Δ / 16 hr
61 a , R1 = C6H5
b , R1 = 2-Furyl
R1 = C6H5
Et3N / LiBr
THF / Δ / N2
a , R1 = C6H5
b , R1 = 2-Furyl
c , R1 = Me

Scheme - 11

(M^+,59%) and the compound was analyzed for $C_{14}H_{13}NO_2S$. In its IR spectrum (KBr) the absorbtion band at 1690 cm^{-1} was assigned to C=O group and the strong bands at 1622 and 1598 cm^{-1} were assigned to the C=N and C=C stretching vibrations. The structure was further confirmed from its ^1H NMR spectrum ($CDCl_3$). The sharp singlets at δ2.28(3H) and δ2.43(3H) were assigned to methyl and methylthio protons respectively. The signal at δ6.12(s,1H) was assigned to the H-5 proton while the aromatic protons appeared as multiplets between δ7.31-7.56(3H) and δ7.74-8.08(2H) and the singlet at δ9.53(1H) was assigned to the benzylideneamino($C_6H_5C\underline{H}$=N-) proton. The ^{13}C NMR($CDCl_3$) spectral data was also in full agreement with the assigned structure (experimental). The pyran-2-ones 62a and 62b were also obtained when the oxoketene dithioacetal 37a and 37b were reacted with 60 under refluxing conditions (16 hr). The analytical and spectral data of the pyran-2-ones 62a and 62b were in agreement with the assigned structures and are given in the experimental section.

The possible mechanism for the formation of pyrrolidine 61 and pyran-2-one 62 from the reaction of the anion 60 with 37 is described in Scheme 12. The pyrrolidine 61 can be formed either through path A involving a concerted *endo* cycloaddition of the *syn* N-lithiated azomethine ylide 60A or through a tandem Michael-imine addition of lithium enolate 60B followed by a *5-endo-trig* cyclization



Scheme-12

of the intermediate 65. The discrimination between the two paths is not possible because of the difficulty in identifying between the two anionic intermediates 60A and 60B. The intermediate 65 at higher temperature equilibrates between the thermodynamically more stable 66 which undergo intramolecular enol lactonization and by loss of methylmercaptan to give the pyran-2-one 62. The formation of only pyran-2-one 62c from α-acetylketene dithioacetal 37c both at room temperature and under refluxing conditions can be rationalized in terms of higher stability of intermediate 66 when R^1=Me,than when R^1=Ph or furyl, probably due to steric and electronic factors. The exclusive *syn* and *endo* selectivity observed in pyrrolidine formation through both the paths presumably is a result of lithium chelation involved in the intermediates 63 and 64 (Scheme 12). Also the high *endo* selectivity may arise from the attractive secondary orbital interaction, which has many literature precedents[25,26,27].

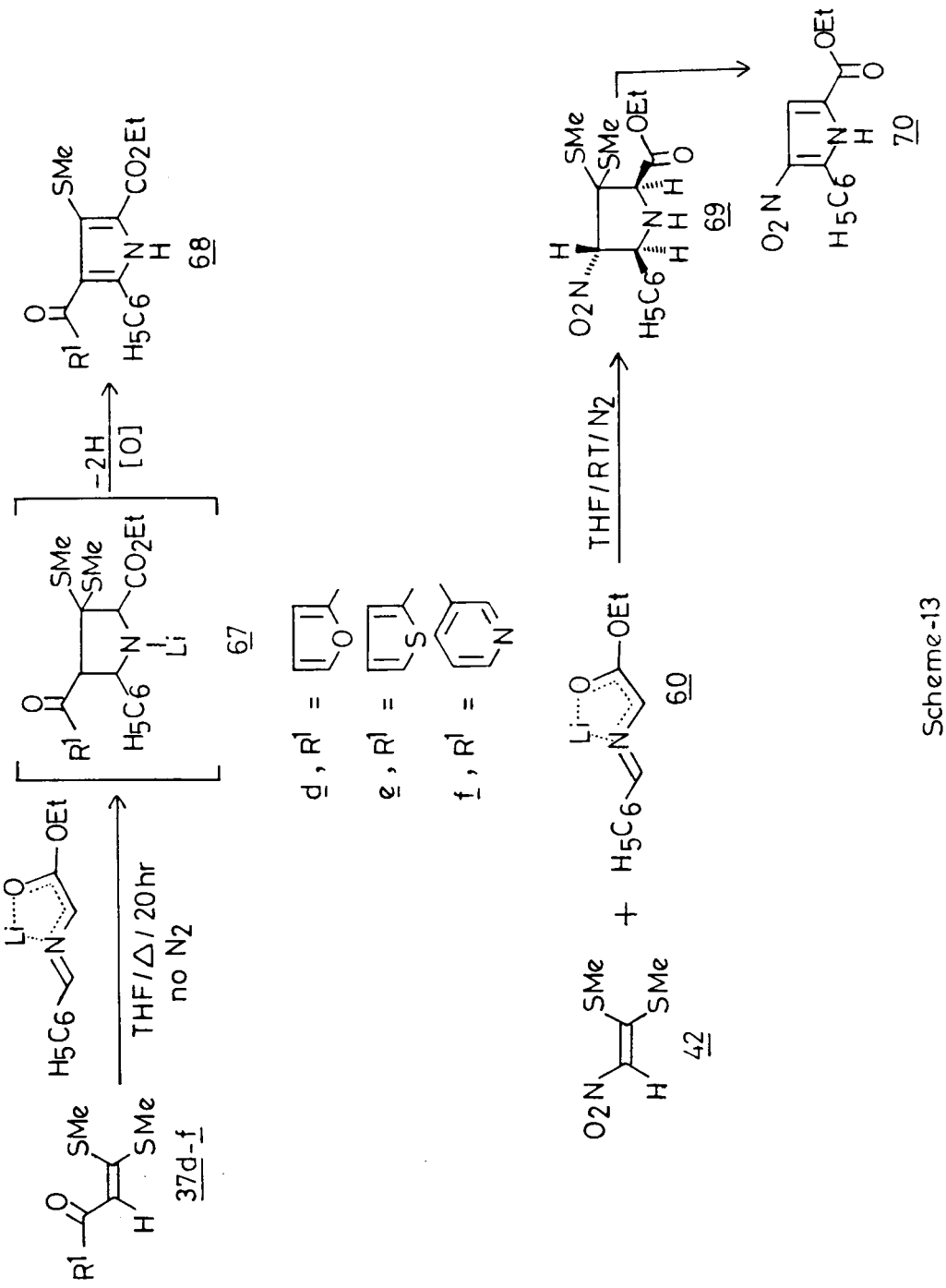
When the α-oxoketene dithioacetal derived from 2-acetyl thiophene 37e and 3-acetyl pyridine 37f were subjected to cycloaddition with 60 under identical conditions either at room temperature or under refluxing conditions, the starting ketene dithioacetal were recovered unreacted. However, when the reaction mixture was refluxed for prolonged time (30 hr) in the absence of nitrogen atmosphere, the product isolated were characterised as

pyrroles 68e and 68f respectively (Scheme 13). Similarly the 3-furoylpyrrole 68d was obtained in 61% yield when 37d was refluxed with 60 in the absence of nitrogen for 30 hr. The intermediate pyrrolidine 67 probably undergo facile dehydrogenation in the presence of oxygen to give the pyrroles 68. The analytical and spectral data of all these compounds are given in the experimental section.

The nitroketene S,S-acetal 42 similarly reacted with 60 at room temperature to give the corresponding pyrrolidine 69 in 55% yield. When the reaction mixture was refluxed for 30 hr in the absence of nitrogen atmosphere the nitropyrrole 70 was formed in 53% yield. The stereochemistry of the pyrrolidine 69 was tentatively assigned as shown in Scheme 12 with the help of its analytical and spectral data (experimental).

IV.3 CONCLUSION

The 1,3-diphenyl-2-azaallyl lithium have been shown to behave as useful 1,3-anionic species towards oxoketene dithioacetals undergoing [3+2] cycloaddition. The cycloadducts thus formed undergo double MeSH elimination to yield the corresponding pyrroles. The oxoketene dithioacetals can be considered therefore, as masked aroyl or acyl acetylenes. Two exceptions are noted in the case of cyclic oxoketene dithioacetals 45d and 45e, where the 1,2-addition predominates over the cycloaddition. Also it has been shown that ethyl(benzylideneamino)acetate in



Scheme-13

presence of lithium bromide and triethylamine undergo highly *regio* and *stereo*selective additions with oxoketene dithioacetals to give either pyrrolidine, pyran-2-one or pyrrole depending on the reaction conditions. Thus α-oxoketene dithioacetals have been proved to be acyl or benzoyl acetylene equivalent dipolarophiles as well as *push-pull* ethylenes and the present study should greatly enhance the synthetic potential of these ketene dithioacetals for the synthesis of pyrroles, spiropyrrolines, pyrrolidines etc. through a 1,3-anionic cycloaddition reaction with 2-azaallylanions.

IV.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were run as KBr discs on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal standard unless otherwise stated. Chemical shifts are expressed as δ(ppm) downfield from TMS. ^{13}C NMR spectra were recorded on a Brucker WM-400 spectrometer. Mass spectra were obtained using a Jeol JMS D-300 spectrometer. Elemental analysis were carried out on Heraeus CHN-O-RAPID instrument.

Starting Materials

Commercially available ketones were purchased (Aldrich) and were used as supplied. Benzaldehyde and benzylamine were distilled before use. Triethylamine and diisopropylamine were dried over KOH and distilled prior to the reaction. Lithium bromide (SISCO) was used as such without any further purification. Diethyl ether and tetrahydrofuran were dried over sodium wire and distilled prior to use. All α-oxoketene dithioacetals were prepared according to the general procedure described in Chapter II. n-Butyllithium was prepared by reported procedure[28] in diethyl ether. N-Benzylidenebenzylamine was prepared by the condensation of benzaldehyde with benzylamine and distilled before use[29].

Preparation of Ethyl (Benzylideneamino)acetate (59)[24]

Glycine (7.5 gm, 0.1 mol) was dissolved in 20 ml of 95% ethyl alcohol saturatred with dry HCl. This reaction mixture was refluxed (2 hr) and distilled azeotropically with dry benzene (3x50 ml), to give ethylglycinate hydrochloride which was filtered and dried, yield 9g (60%). A solution of the ethylglycinate hydrochloride (7g,0.05 mol), benzaldehyde (5.3g,0.05 mol) and triethylamine (5g, 0.05 mol) in benzene (50 ml) was refluxed for 1 hr. The reaction mixture after cooling was washed with water (3x25 ml) and the benzene layer was separated, dried (Na_2SO_4) and evaporated in vaccuo. The

residue was distilled on a Kugelrohr distilling apparatus to give pure ethyl (benzylidene amino)acetate 8.5g (90%).

General Procedure for the Generation and Reaction of 1,3-Diphenyl-2-azaallyllithium with Oxoketene Dithioacetal:

To a stirred solution of lithium diisopropylamide [(11 mmol) freshly prepared from n-butyllithium (11 mmol) and diisopropylamine (1.10gm, 11 mmol) in dry THF (20 ml)], N-benzylidenebenzylamine (1.95 gm,10 mmol) in THF (5 ml) was added slowly at -78°C under nitrogen atmosphere. The lithiation was indicated by the appearance of reddish brown colour. The solution was stirred for 1 hr at -78°C and the temperature was raised slowly to room temperature follwed by further stirring for 15hr. The reaction mixture was poured into saturated ammonium chloride solution and the organic layer was 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 viscous residue which were purifed by column chromatography over silica gel using hexane-ethylacetate as eluent (5:1) to give the corresponding 2,5 diphenyl pyrroles.

3-Benzoyl-2,5-diphenylpyrrole (39a) was isolated as colourless crystals (EtOAc-hexane), yield 79%,m.p. 168-169°C;IR and ^1H NMR data described in text. (Found: C, 85.71,H,5.21;N,4.62; Calc. for $C_{23}H_{17}NO$: C,85.42; H,5.30; N,4.36%); m/z 323 (M^+,100%); 246 (72); 218(7).

3-(4-Methoxybenzoyl)-2,5-diphenylpyrrole (39b) was isolated as light yellow crystals (EtOAc-hexane);yield 82% m.p. 183-184°C; IR ν_{max}(KBr) 3150,1605,1594,1565 cm^{-1};^1H NMR ($CDCl_3$):3.78(s,3H,OCH_3); 6.72-6.88 (m,3H,arom); 7.05-7.58 (m,10H,arom); 7.68-7.90 (m,2H,arom); 9.10 (brs,1H,NH, exchangeable with D_2O); (Found:C, 81.78;H,5.63, N,3.86 Calc. for $C_{24}H_{19}NO_2$:C,81.56; H,5.42; N,3.96%); m/z 353 (M^+,100%); 246 (24); 217(15).

3-Acetyl-2,5-diphenylpyrrole (39c)was isolated as colourless crystals (EtOAc-hexane); yield 74%; m.p. 196°C; IR ν_{max}(KBr) 3240,1605,1455 cm^{-1}. ^1H NMR ($CDCl_3$): 2.25 (s,3H,CH_3); 6.90 (d,J=1.5Hz, 1H,H-4); 7.19-7.61 (m,10H,arom); 9.08 (brs, 1H, NH, exchangeable with D_2O); (Found: C,82.54; H, 5.82; N,5.23; Calc. for $C_{18}H_{15}NO$: C, 82.73; H,5.79; N,5.36%); m/z 261 (M^+,70%); 246(100); 217(16).

2,5-Diphenyl-3-(2-~~furoyl~~)pyrrole (39d) was isolated as yellow crystals (EtOAc-hexane); yield 76%; m.p. 162-163°C. IR ν_{max}(KBr) 3240,1602,1578,1560 cm^{-1}; ^1H NMR ($CDCl_3$);6.31 (dd,J=3 and 1.5 Hz, 1H, H-4' furyl); 6.79-7.56 (m, 13H, arom); 9.60 (brs, 1H, NH, exchangeable with D_2O);(Found: C, 80.68; H, 4.58; N, 4.23; Calc. for $C_{23}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47%); m/z 313 (M^+,100%); 296(17); 284(14).

2,5-Diphenyl-3-(2-thienoyl)pyrrole (39e) was isolated as yellow crystals (EtOAc-hexane); yield 78%; m.p. 145-146°C. IR ν_{max}(KBr) 3200, 1600, 1588 cm^{-1}; ^1H NMR ($CDCl_3$):6.74-7.58 (m,14H, arom); 9.51 (brs, 1H, NH, exchangeable with D_2O); (Found: C,76.69; H, 4.38; N, 4.18; Calc. for $C_{21}H_{15}NOS$: C,76.57; H,4.59; N,4.25%); m/z 329 (M^+,100%); 246(28).

2,5-Diphenyl-3-(3-pyridoyl)pyrrole (39f) was isolated as light yellow crystals (EtOAc-hexane); yield 81%; ,m.p. 266-267°C IR ν_{max}(KBr) 3150, 1645, 1600, 1582 cm^{-1}; ^1H NMR ($CDCl_3$):6.73 (d, J=1.5Hz, 1H, H-4); 6.94-7.99 (m,12H, arom); 8.38 (d, J=6Hz, 1H, H-6' pyridyl); 8.70 (s, 1H, H-2'pyridyl); 10.61 (brs, 1H, NH, exchangeable with D_2O); (Found C, 81.23; H, 4.82, N, 8.73; Calc. for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64%); m/z 324 (M^+, 100%);247(22), 217(29).

2,5-Diphenyl-3-(2-naphthoyl)pyrrole (39g) was isolated as light yellow crystals (EtOAc-hexane); yield 84% m.p. 181°C, IR ν_{max}(KBr) 3255,1601,1570 cm^{-1}; ^1H NMR ($CDCl_3$): 6.81 (d, J=1.5Hz, 1H, H-4); 7.02-7.98 (m, 16H, arom); 8.31 (s,1H, H-1' naphthyl); 9.30 (brs, 1H, NH, exchangeable with D_2O); (Found: C, 86.58; H, 5.24; N, 3.86; Calc. for $C_{27}H_{19}NO$:C, 86.84; H, 5.13; N, 3.75%); m/z 373 (M^+,100%); 344(5).

Methyl-2,5-diphenylpyrrole-3-carboxylate (39h) was isolated colourless crystals (EtOAc-hexane); yield 71% m.p.

162°C; IR ν_{max}(KBr) 3310,1670, 1606, 1591 cm^{-1}, ^1H NMR ($CDCl_3$):3.70 (s, 3H, OCH_3); 6.96 (d, J=1.5 Hz, 1H, H-4); 7.15-7.72 (m, 10H, arom); 8.69 (brs, 1H, NH, exchangeable with D_2O); (Found: C, 77.78; H, 5.68; N,5.25; Calc. for $C_{18}H_{15}NO_2$: C,77.96; H, 5.45; N,5.05%) m/z 277(M^+,100%), 246(58); 217(15).

3,3-Bis(methylthio)-2,5-diphenyl-4-nitropyrrolidine (43) was isolated as colourless crystals (EtOAc-hexane); yield 64%; m.p. 118°C, IR and ^1H NMR data given in the text. (Found:C, 59.81; H, 5.48; N, 3.63; Calc. for $C_{18}H_{20}N_2O_2S_2$: C, 59.97,H, 5.59; N,3.89%);m/z 360 (M^+,4%) 266(37).

Spiro[(3,4-dihydronaphth-1-one)-2,3'-(2',5'-diphenyl-4'-(methylthio)-1'-pyrroline)] (47) was isolated as colourless crystals (EtOAc-hexane); yield 74%, m.p. 163°C. IR and ^1H NMR data are given in the text. (Found: C, 78.26; H, 5.89; N, 3.68; Calc. for $C_{26}H_{23}ONS$: C, 78.55; H, 5.83; N, 3.52%); m/z 397 (M^+,25%); 350(100).

Spiro[(2,3-dihydro-8-methyl-[1]-benzthiepin-5-one)-4,3'-(2',5'-diphenyl-4'(methylthio-1'-pyrroline)](50) was isolated as colourless crystals (EtOAc-hexane); yield 68%; m.p. 173-174°C. IR ν_{max} 1659,1616,1600 cm^{-1}; ^1H NMR ($CDCl_3$): 1.82 (s,3H,CH_3); 2.34 (s,3H,SCH_3); 2.48-2.95 (m,4H,$-CH_2-$); 5.05 (d, J=1.5Hz, 1H, H-4') 5.90 (d,J=1.5Hz,1H, H-2'); 7.05-7.88 (m, 12H, arom); 8.09 (d, J=9 Hz, H-6); (Found: C,72.94; H,5.74; N, 3.28; Calc. for

$C_{27}H_{25}ONS_2$ C, 73.10; H, 5.68; N,3.16%); m/z 443 (M^+, 14%); 397 (88).

Spiro[3-(4-methoxyphenyl)-1-phenyl-pyrazolo-2-one)-3,3'-(2',5'-diphenyl-4'-(methylthio)-1'-pyrroline)] (51) was isolated as yellow crystals (EtOAc-hexane); yield 71%; IR ν_{max} 1710, 1625,1608, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): 2.18 (s, 3H, SCH_3);3.69 (s,3H, OCH_3); 5.00 (d, J=1.5Hz, 1H, H-4'); 6.02 (d, J=1.5Hz, H-2'); 6.56-6.74 (m, 2H, arom); 7.02-7.65 (m, 13H, arom); 8.01-8.29 (m,4H, arom); Found: C, 74.38; H, 5.16; N, 8.32; Calc. for $C_{32}H_{27}O_2N_3S$: C, 74.25,H, 5.26; N, 8.12%).

4,4-Bis(methylthio)-1,3-diphenyl-5,6,7,8-tetrahydro-3H-isoquinoline (53a) was isolated as colourless crystals (EtOAc-hexane); yield 77%; m.p. 155°C, IRν_{max}(KBr) 1605, 1571, 1520 cm^{-1}; ^1H NMR ($CDCl_3$): 1.62-1.82 (m, 4H,-CH_2-); 1.90 (s, 3H, SCH_3); 2.15 (s, 3H, SCH_3); 2.50-2.74 (m, 4H, -CH_2-); 6.38 (s,1H, H-3); 7.21-7.50 (m,10H, arom); (Found: C, 72.53; H, 6.82; N, 3.43; Calc. for $C_{23}H_{25}NS_2$: C, 72.78; H, 6.64; N, 3.69%); m/z 379 (M^+, 96%); 332(40).

3,3-Bis(methylthio)-2,9-diphenyl-5,6,7,8-tetrahydro-4H-cyclohepta[d]pyridine (53b) was isolated as colourless crystals (EtOAc-hexane); yield 76%; m.p. 157°C; IRν_{max} (KBr) 1600,1488,1463 cm^{-1}; ^1H NMR ($CDCl_3$): 1.30-1.76 (m, 6H,CH_2); 1.87 (s,3H,SCH_3);2.07 (s,3H,SCH_3); 2.28-2.90 (m, 4H,CH_2); 6.38 (s, 1H,H-2); 7.13-7.55 (m,10H,arom); (Found: C,73.0; H,6.81; N,3.28; Calc. for $C_{24}H_{27}NS_2$: C,

73.23; H,6.92; N,3.56%); m/z 393 (M^+,100%); 346 (29); 256(17).

Mercuric Chloride Catalyzed Ring contraction of 53a and 53b: General Procedure:- A suspension of dihydropyridine 53a or 53b (1 mmol) and $HgCl_2$ (0.27g, 1 mmol) in dry THF (10 ml) was stirred at room temperature for 6 hr. The reaction mixture was filtered through a G-4 sintered funnel to remove traces of mercuric chloride and the filtrate diluted with chloroform (25 ml) washed with saturated sodium bicarbonate solution and evaporated to give the crude products which were purified by column chromatography over silica gel.Elution with hexane-ethyl acetate (20:1) gave pure products 55a and 55b respectively.

1-(Methylthio)-3-phenyl-4,5,6,7-tetrahydroisoindole (55a) was isolated as colourless crystals (EtOAc-hexane); yield 73%; m.p. 91-92°C; IR ν_{max}(KBr) 3320,1600,1585,1512 cm^{-1}; ^1H NMR ($CDCl_3$); 1.71-1.92 (m,4H,CH_2); 2.19 (s,3H,SCH_3); 2.48-2.72 (m,4H,CH_2); 7.21-7.54 (m,3H,arom); 7.61-7.82 (m,2H,arom); 8.01 (brs,1H,NH exchangeable with D_2O); (Found: C,74.12; H,7.28; N,5.54 Calc. for $C_{15}H_{17}NS$: C, 74.03, H,7.04; N,5.76%); m/z 243 (M^+,100%) 228(41).

2-(Methylthio)-8-phenyl-4,5,6,7-tetrahydro[3H]cyclohepta [c] pyrrole (55b) was isolated as colourless crystals (EtOAc-hexane); yield 68%, m.p. 90-91°C; IR

ν_{max}(KBr),3325, 1605,1598 cm^{-1},^{1}H NMR (CCl_4); 1.45-1.82 (m,6H,CH_2); 1.99 (s, 3H,SCH_3); 2.38-2.79 (m,4H,CH_2); 7.01-7.35 (m,3H, arom);7.42-7.64 (m,2H,arom);7.74 (brs,1H, NH exchangeble with D_2O); (Found: C,74.40; H,7.53; N,5.23 Calc. for $C_{16}H_{19}NS$: C,74.66; H,7.44; N,5.44%); m/z 257 (M^+,100%); 242(25).

General Procedure for the Reaction of N-Lithioethyl-(benzylideneamino)acetate with Oxoketene Dithioacetals:

To a solution of ethyl (benzylideneamino)acetate (2.10g,11 mmol) and oxoketene dithioacetal (10 mmol) in dry THF (25 ml) was added lithium bromide (1.30g,15 mmol in THF (10 ml) and then triethylamine (1.21g, 12 mmol in THF (5 ml) with the help of a syringe. The mixture was stirred at room temperature for 14-16 hr under nitrogen (checked by TLC) and poured into concentrated aqueous ammonium chloride (50 ml), extracted with chloroform (50mlx3), dried over sodium sulphate and evaporated in vaccuo. The residue was chromatographed over silica gel by using hexane-ethylacetate (5:1) as eluent to give the corresponding pyrrolidines, 61a and 61b.

Pyran-2-ones 62a and 62b were obtained when the reaction mixture after an initial 3 hr stirring at room temperature was refluxed for 16 hr at 70°C under an efficient atmosphere of nitrogen. While pyran-2-one 66c

was obtained by stirring the reaction mixture at room temperature only (16 hr).

Pyrroles **64d**, **64e** and **64f** were obtained when the same reaction mixture after an initial 3 hr stirring at room temperature was refluxed for 30 hr at 70°C in the absence of nitrogen.

Ethyl 4-benzoyl-3,3-bis(methylthio)-5-phenyl pyrrolidine-2-carboxylate (61a) was isolated as colourless crystals (EtOAc-hexane); yield 72%, m.p. 154°C; IR ν_{max}(KBr) 3300, 1750,1680,1600 cm^{-1}; ^1H NMR ($CDCl_3$); 1.39 (t,J=7Hz, 3H, CH_3); 1.98 (s,3H,SCH_3); 2.21 (s,3H,SCH_3); 2.59-2.71 (brs 1H, NH, exchangeable with D_2O) 4.31 (q,J=7Hz,2H,OCH_2); 4.68 (d, J=5Hz,1H,H-4); 4.96 (brs,1H,H-2); 5.41 (d,J=6.5 Hz, 1H, H-5); 6.98-7.69 (m, 10H, arom); ^{13}C NMR ($CDCl_3$) 12.95 (CH_3); 13.81,14.04 (SCH_3); 61.29 (OCH_2);61.78, 63.78, 70.13 (CH,C-2,C-4,C-5); 70.69, (C-3); 126.93, 127.26, 127.63, 128.21, 132.61 (CH-phenyl) 139.60, 139.61 (quaternary Ar) 170.81 (C-OEt); 197.44 (C_6H_5C-): (Found: C, 63.39; H, 6.01,N,3.22; Calc. for $C_{22}H_{25}NO_3S_2$: C, 63.58; H,6.06; N,3.37%); m/z 368 (M^+-47,100%); 225(59).

Ethyl 4-furoyl-3,3-bis(methylthio)-5-phenylpyrrolidine-2-carboxylate (61b) was isolated as colourless crystals (EtOAc-hexane); yield 69%; m.p. 135-136°C; IR ν_{max}(KBr) 3340, 1723, 1660, 1565 cm^{-1}; ^1H NMR ($CDCl_3$): 1.49 (t, J=7Hz,3H,CH_3); 2.02 (s,3H,SCH_3); 2.21 (s,3H,SCH_3); 3.05-3.20 (brs,1H,NH); 4.25 (q,J=7Hz,2H,OCH_2); 4.49 (d,

J=6.5Hz, 1H, H-4); 4.89 (s,1H,H-3); 5.38 (d, J=6.5Hz, 1H, H-5); 6.48 (dd,J=3 and 1.5Hz, H-4'furyl); 6.87-7.49 (m,7H,arom and furyl); (Found: C,59.12; H, 5.61; N,3.48; Calc. for $C_{20}H_{23}NO_4S_2$: C,59.23; H, 5.72; N, 3.45%); m/z 358 (M^+-47,14%); 312(4).

3-Benzylideneamino-4-(methylthio)-6-phenylpyran-2-one (62a) was isolated as yellow crystals (EtOAc-hexane); yield 69%; m.p.164-165°C; IRν_{max}(KBr) 1701,1618,1575 cm^{-1} ^1H NMR($CDCl_3$):2.46 (s,3H,SCH_3); 6.68 (s,1H,H-5); 7.30-7.59 (m,6H,arom);7.78-8.02 (m,4H,arom);9.49 (s,1H,CH=N-); (Found: C,71.18; H,4.79; N,4.46; Calc. for $C_{19}H_{15}NO_2S$: C,71.00; H,4.70; N,4.36%); m/z 321 (M^+,61%); 306(100).

3-Benzylideneamino-6-(2-furyl)-4-(methylthio)pyran-2-one (62b)was isolated as yellow crystals (EtOAc-hexane); yield 61%, m.p.119-120°C; IRν_{max}(KBr) 1705,1625,1562 cm^{-1} ^1H NMR ($CDCl_3$); 2.56 (s,3H,SCH_3);6.58 (dd,J=3.0 and 1.5Hz,H-4'furyl);6.73 (s,1H,H-5);7.10 (d,J=3Hz,H-3'furyl; 7.31-7.53 (m,4H,arom); 7.81-8.04 (m,2H,arom); 8.52 (s, 1H, $C_6H_5C\underline{H}$=N-); (Found: C,65.32; H, 4.38; N,4.68; Calc. for $C_{17}H_{13}NO_3s$: C, 65.58; H,4.21; N, 4.68%); m/z 311 (M^+, 3%); 296(4); 214(22).

3-Benzylideneamino-6-methyl-4-(methylthio)pyran-2-one (62c) was isolated as yellow crystals (EtOAc-hexane); yield 81%; m.p.139-140°C; IRν_{max}(KBr) 1690, 1622, 1598cm^{-1}; ^1H NMR($CDCl_3$):2.28(s,3H,CH_3); 2.43 (s,3H,SCH_3); 6.12 (s,1H,H-5); 7.31-7.56 (m,3H,arom); 7.74-8.08

(m,2H,arom); 9.53 (s,1H, $C_6H_5C\underline{H}$=N-); ^{13}C NMR ($CDCl_3$) 14.19 (CH_3); 19.78 (SCH_3); 101.22 (C-5); 122.95, (C-3) 128.68; 130.91 (CH,arom) 137.50 (quaternary Ar); 155.40 (C-4); 156.16 (C-5); 157.93 (C=O); 159.59 ($C\underline{H}$=N-); (Found: C,64.80; H,5.26; N,5.59, Calc. for $C_{14}H_{13}NO_2S$: C, 64.84; H,5.05; N,5.40%); m/z 259(M^+ 60%); 244(100), 216(22).

Ethyl 4-(2-furoyl)-3-(methylthio)-5-phenylpyrrole-2-carboxylate (68d) was isolated as colourless crystals (EtOAc-hexane); yield 73%; m.p. 117-118°C; IRν_{max}(KBr) 3310,1680, 1668,1565 cm^{-1}; ^1H NMR ($CDCl_3$); 1.38 (t,J=7Hz,3H,CH_3); 2.35 (s,3H,SCH_3); 4.30 (q, J=7Hz, 2H, OCH_2); 6.36 (dd,3 and 1.5Hz,1H,H-4'furyl); 6.91 (d,J=3Hz,1H,H-3'furyl); 7.14-7.52 (m,6H,arom and 5'furyl); 10.01 (brs,1H, NH exchangeable with D_2O); (Found: C,64.02; H,4.96;N,3.83; Calc. for $C_{19}H_{17}NO_4S$: C,64.21; H,4.82; N,3.94%); m/z 356 (M^+,100%); 309(17); 280(18).

Ethyl 3-(methylthio)-5-phenyl-4-(2-thienoyl)pyrrole-2-carboxylate (68e) was isolated as colourless crystals (EtOAc-hexane); yield 69%; m.p. 128-129°C; IRν_{max}(KBr) 3260,1680,1620, 1550 cm^{-1}; ^1H NMR ($CDCl_3$); 1.35 (t, J=7Hz,3H,CH_3); 2.45 (s,3H,SCH_3); 4.31 (q,J=7.00Hz, 2H, OCH_2); 7.05-7.49 (m,6H,arom and thienyl); 7.50-7.98 (m,2H,arom); 10.11 (brs, 1H,NH, exchangeable with D_2O) (Found: C, 61.48; H,4.58; N,3.71; Calc. for $C_{19}H_{17}NO_3S_2$: C, 61.43; H, 4.60; N,3.77%).

Ethyl-3-(methylthio)-5-phenyl-4-(3-pyridoyl)pyrrole-2-carboxylate (68f) was isolated as colourless crystals (EtOAc-hexane); yield 79%; m.p. 141-142°C; IR ν_{max}(KBr) 3410, 1718, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): 1.32 (t,J=7Hz, 3H,CH_3); 2.31 (s,3H,SCH_3); 4.31 (q,J=7Hz,2H, OCH_2); 7.21-7.49 (m,4H,arom); 8.08 (m,1H,H-4' pyridyl); 8.65(dd,J=6 and 1.5Hz,1H,H-6'pyridyl); 8.98 (d,J=1.5Hz,H-2'pyridyl); 10.61 (brs,1H,NH, exchangeable with D_2O); (Found: C,65.32; H,4.91,N,7.72; Calc.for $C_{20}H_{18}N_2O_3S$: C, 65.55; H, 4.95; N,7.65%); m/z 366 (M^+,100%); 320(34).

don't need

Ethyl-3,3-bis(methylthio)-4-nitro-5-phenylpyrrolidine-2-carboxylate (69) was isolated as colourless crystals (EtOAc-hexane); yield 58%; m.p. 160-161°c; IR ν_{max}(KBr) 3330,1728,1550,1450 cm^{-1}; ^1H NMR($CDCl_3$): 1.28 (t, J=7Hz, 3H,CH_3); 2.11 (s,3H,SCH_3);2.21 (s,3H,SCH_3); 2.60-2.65 (brs, 1H,NH exchangeable with D_2O); 4.22 (q, J=6.5Hz, 2H, OCH_2); 4.69 (brs,1H,H-2); 5.29 (m,2H,H-4 and H-5); 7.05-7.56 (m,5H,arom); (Found: C,50.50;H,5.68; N,7.72; Calc. for $C_{15}H_{20}N_2O_4S_2$: C,50.54; H,5.66; N,7.86%); m/z 262 (M^+-94, 15%); 216(6); 209(100).

Ethyl-3-nitro-2-phenylpyrrole-4-carboxylate (70) was isolated as colourless crystals (EtOAc-hexane); yield 56%; m.p. 128-129°C; IR ν_{max}(KBr) 3250,1700,1580, 1510cm^{-1} ^1H NMR($CDCl_3$); 1.22 (t,J=7Hz,3H,CH_3); 4.12 (q,J=7Hz,2H, OCH_2); 7.08-8.02 (m,6H,arom); 10.35 (brs,1H,NH, exchangeable with D_2O); (Found: C,59.10; H,4.59; N,10.78; Calc. for $C_{13}H_{12}N_2O_4$: C,59.99; H,4.65; N,10.84%).

REFERENCES

1. Singh,G.; Ila.H.; Junjappa,H. *Tetrahedron Lett.* 1984, *25* 5095.
2. Dieter,R.K.;Lin,Y.J. *Tetrahedron Lett.* 1985,*26*,39.
3. Singh,G.; Purkayastha,M.L.; Ila,H.;Junjappa,H. *J.Chem.Soc.Perkin Trans.I.* 1985, 1289.
4. Balu,M.P.; Singh,G.; Ila,H.; Junjappa,H. *Tetrahdron Lett.* 1986, *27*, 117.
5. Purkayastha,M.L.; Ila,H.; Junjappa,H.*Synthesis*, 1989, 20.
6. Balu,M.P.; Pooranchand,D.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1988, *29*, 501.
7. Balu,M.P.; Ila,H.; Junjappa,H.*Tetrahedron Lett.* 1987, *28*, 3023.
8. Chakrasali,R.T.; Ila.H.; Junjappa,H. *Synthesis,* 1988, 453.
9. Kauffmann,Th.; Habersaat,K.; Koppelmann,E.*Angew. Chem.Int.Ed.Engl.* 1972, *11*, 291.
10. Kauffmann,Th.*Angew.Chem.Int.Ed.Engl.* 1974, *13*, 627.
11. Kauffmann,Th.; Berg,H.; Koppelmann,E.*Angew.Chem. Int.Ed.Engl.* 1970,*9*,380.
12. Kauffmann,Th.; Koppelmann,E.*Angew.Chem.Int.Ed.Engl.* 1972, *11*, 290.
13. Kauffmann,Th.; Eidenschink,R.*Angew.Chem.Int.Ed.Engl.* 1971, *10* 739.
14. Kauffmann,Th.; Busch,A.; Habersaat,K.;Koppelmann,E. *Angew.Chem.Int.Ed.Engl.* 1973, *12*,569.

15. Kauffmann,Th.; Ahlers,H.; Hamsen,A.; Schulz,H.; Tilhard,H.; Vehrenhorst,A. *Angew.Chem.Int.Ed.Engl.* 1977, *16*, 119.

16. Quang,V.L.; Gaessler,H.; Quang,V.Y. *Angew.Chem.Int. Ed.Engl.* 1981, *20*, 880.

17. Sinbandhit,S.; Hamelin,J. *J.C.S.Chem.Comm.* 1977, 768.

18. Grigg,R.; Kemp.J.; Malone,J.; Tangthongkum.A.; *J.C.S. Chem.Comm.* 1980, 648.

19. Grigg,R.; Kemp,J.; Sheldrick,G.; Trotter,J. *J.C.S. Chem.Comm.* 1978, 109.

20. Tsuge,O; Ueno,K.; Kanemasa,S; Yorozu,K. *Bull.Chem. Soc.Jpn.* 1987, *60* 3347.

21. Tsuge,O.; Kanemasa,S.; Yorozu,K.; Ueno,K. *Bull.Chem. Soc. Jpn.* 1987, *60*,3359.

22. Tsuge,O.; Ueno,K. *Heterocycles,* 1982, *19*, 1411.

23. George,M.V.; Mitra,A.; Sukumaran,K.B. *Angew.Chem. Int.Ed. Engl* 1980, *19*, 973.

24. Tsuge,O.; Kanemasa,S; Yoshioka,M. *J.Org.Chem.* 1988, *53*, 1384.

25. Tsuge,O.; Kanemasa,S.; Ohe,M.; Yorozu,K.;Takenaka,S. Ueno,K. *Chem.Lett.* 1986, 1271.

26. Tsuge,O.; Kanemasa,S.; Ohe,M.; Yorozu,K.;Takenaka,; S.Ueno,K. *Bull.Chem.Soc.Jpn.* 1987, *60*,4067.

27. Grigg,R.; Donegan,G.;Gunaratne,H.Q.N.; Kennedy,D.A.; Malone,J.F.; Sridharan,V.; Thianpatanagul,S. *Tetrahedron* 1989, *45*, 1723.

28. Gilman,H.; Beel,J.A.; Brannen,C.G.; Bullock,M.W.; Dunn,G.E.;Miller,L.S. *J.Am.Chem.Soc.* 1949, *71*,1499.

29. Kauffmann,Th.; Koppelmann,E.; Berg,H. *Angew.Chem. Int.Ed.Engl.* 1970, *9*, 163.

30. Corey,E.J.; Chaykovsky,M. *J.Am.Chem.Soc.* 1965, *87*, 1345.

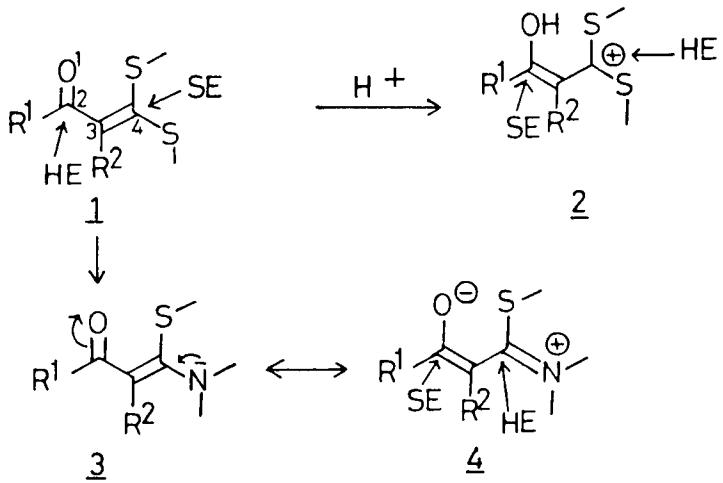
CHAPTER V

STUDIES ON THE ADDITIONS OF GRIGNARD REAGENTS AND METAL HYDRIDES TO OXOKETENE N,S-ACETALS

V.1 INTRODUCTION

In an earlier work from our laboratory[1] it has been shown that α-oxoketene dithioacetals 1 undergo highly regioselective 1,2-addition with sodium borohydride to yield the corresponding carbinolacetals which on subsequent methanolysis or partial hydrolysis afford α,β-unsaturated O-methyl and S-methyl esters respectively. It has also been shown that organolithium reagents undergo exclusive 1,2-addition with α-oxoketene dithioacetals to give the corresponding carbinolacetals.[2,3] Allyl and methylmagnesium bromides have also been found to exhibit high 1,2-regioselectivity in their additions to α-oxoketene dithioacetals.[4,5] The 1,3-electrophilic centres in 1

therefore, exhibit distinct difference in their electrophilicity. The electrophilic centres therefore, can be considered as hard (C_2) and soft (C_4) electrophiles in terms of Pearson's HSAB principle.[6] The C-4 carbon in 1 is flanked by two soft methylthio groups which renders this carbon atom soft and consequently it can be designated as soft electrophile. On the other hand the C_2-carbon attached to a hard base oxygen with a double bond can be considered as hard electrophile. This Hard-Soft dissymmetry in 1 can be advantageously used to construct new C-H,C-C and C-N bonds in a highly regioselective manner. Again, this Hard-Soft dissymetry in 1 can be reversed in two ways as shown in the Scheme 1. Thus, when oxoketene dithioacetal 1 is protonated, the proton generally associates with the hard base oxygen and the resulting positive charge is located at C-4 carbon thus rendering it hard electrophilic character (Scheme 1). The Hard-Soft affinity inversion in 1 can also be achieved by replacing one of the methylthio groups by amino group to give the corresponding N,S-acetals. The reactivities of 2 and 3 should differ markedly from that of 1 because of the Hard-Soft dissymmetry inversion, and it will be very interesting to examine the reactivities of 2 and 3 with various reagents. In the present investigation the reactivities of N,S-acetals 3 with Grignard reagents, sodium borohydride and sodium cyanoborohydride have been examined. The α-oxoketene N,S-acetals 3 can be considered as novel functionalized



Hard Soft Affinity Inversion through
α-oxoketene S,S-acetals

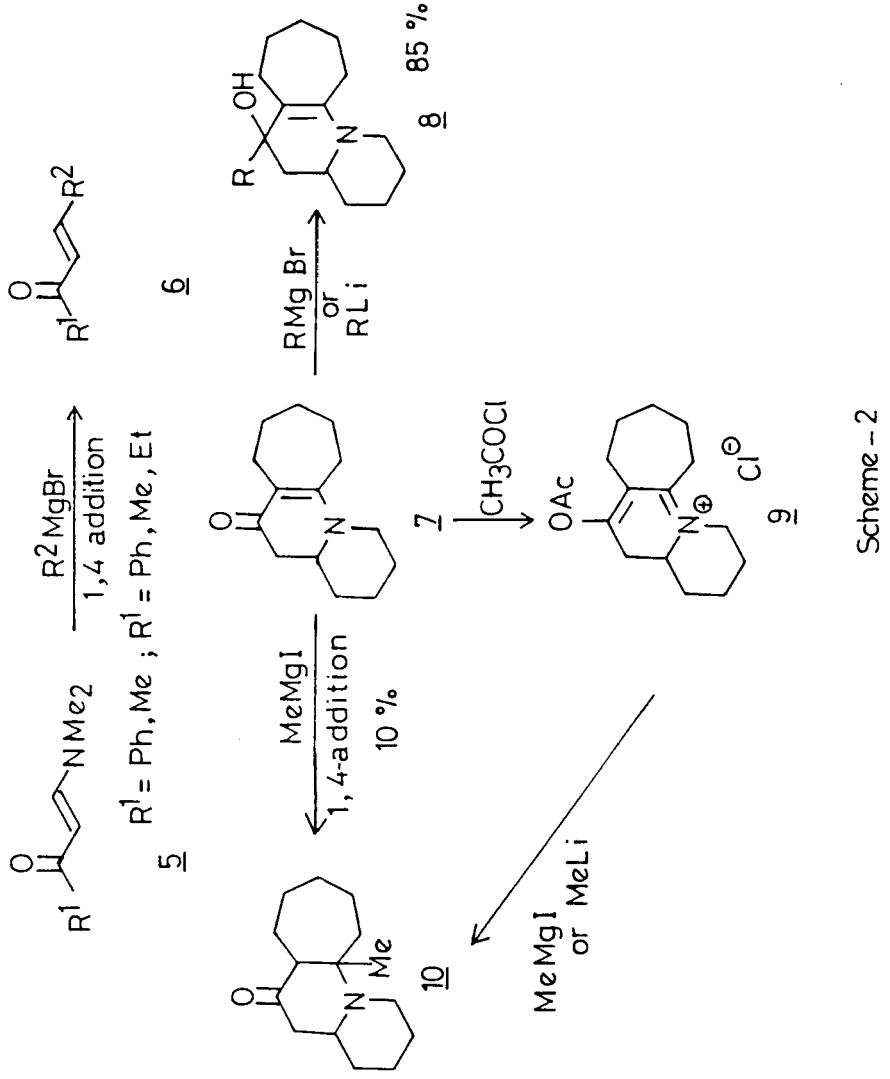
HE = Hard Electrophile ; SE= soft electrophile

Scheme-1

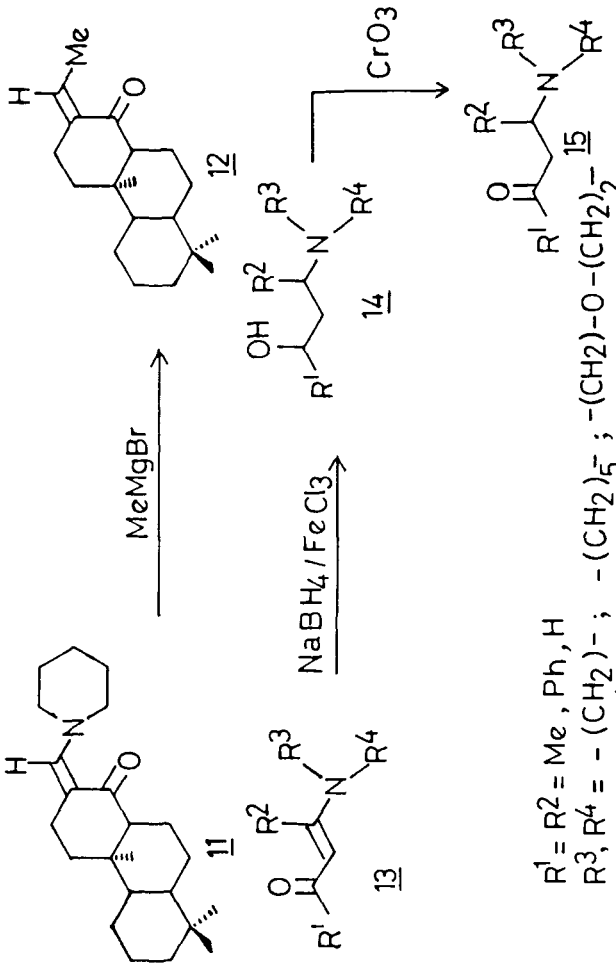
enaminones and consequently their chemical reactivity should be identical with that of enaminones described in the literature.[6] There have been some studies on the reaction of Grignard reagents and metal hydrides with enaminones which are briefly reviewed in the following discussion.

Benary has studied[8] Grignard reactions on acyclic enaminones 5 and found that they undergo exclusive 1,4-addition with Grignard reagents to afford the corresponding α,β-unsaturated ketones 6 in good yields (Scheme 2). Similarly Meyer and Singh have shown[9] that cyclic enaminone 7 reacts with Grignard or organolithium reagents to give the enamine alcohol 8 in high yield through 1,2-addition, while reaction with MeMgI gave 1,4-adduct 10 in very low yield (10%). But when the enaminone 7 was converted to its O-acetyl immonium salt 9 and reacted with methylmagnesium iodide or methyllithium, the corresponding 1,4-adduct 10 was obtained in high yields (Scheme 2).

Ireland and co-workers in the total synthesis of *dl*-sandaracopimaradiene,[10] have reacted the enaminone 11 with MeMgBr to afford the corresponding ethylidene ketone 12 in 90% yield (Scheme 3). Kashima and Yamamoto have reported[11] that β-dialkylamino conjugated enones 13 undergo reduction to the corresponding saturated γ-amino-alcohols 14 with sodium borohydride in the presence of iron(III) chloride . The resulting γ-amino alcohols 14


R1 = Ph, Me ; R1 = Ph, Me, Et
R2MgBr
1,4 addition
RMg Br
or
RLi
85 %
MeMgI
1, 4-addition
10 %
CH3COCl
MeMgI
or MeLi

Scheme – 2

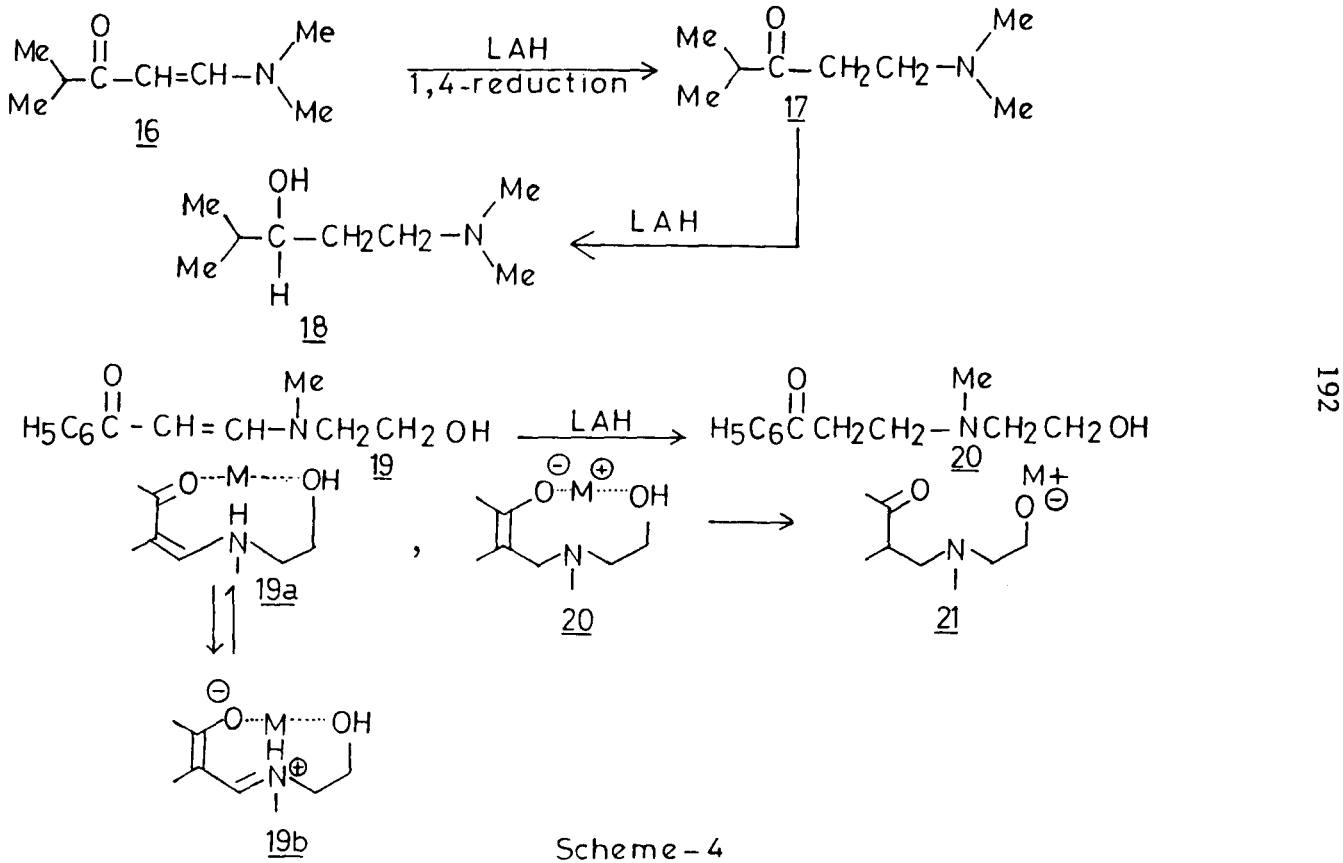

MeMgBr
NaBH4/FeCl3
CrO3
11
12
13
14
15
R1 = R2 = Me, Ph, H
R3, R4 = -(CH2)-; -(CH2)5-; -(CH2)-O-(CH2)2-
R3 = Bu ; R4 = H

Scheme-3

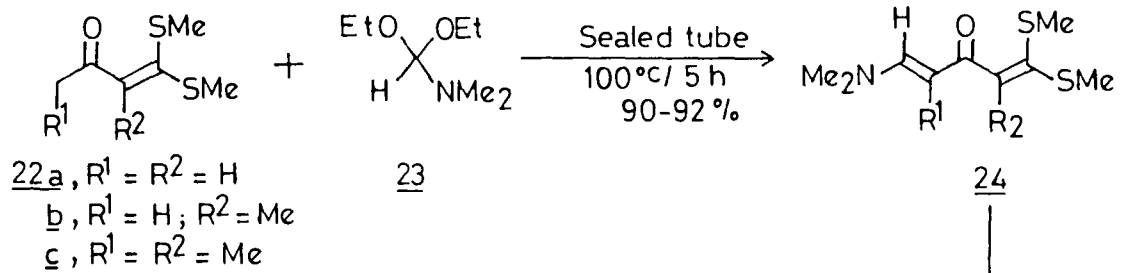
were converted into conjugated enones 15 by chromic acid oxidation and deamination (Scheme 3).

Meen and co-workers[12,13] have shown that lithium aluminium hydride reduction of enaminone 16 proceeds exclusively in 1,4-fashion to afford the corresponding saturated amino ketone 17 exclusively which on further reduction with lithium aluminium hydride affords the corresponding amino alcohol 18 (Scheme 4). Walker reported[14] that the amide vinylog 19 is reduced by lithium aluminium hydride to the saturated amino ketone 20, and he felt that the hydroxy group in 19 contributes to stopping the reduction at 20 because of the formation of "noncyclic, insoluble metallic complex salts 19-21 of this products, resulting in their precipitation ie., removal from the scene where further attack by hydride might progress."

Attempted preparation of α-enoyl ketene dithioacetals 25 by condensing the corresponding acylketene dithioacetals 22 with aliphatic aldehydes were not successful and consequently an alternative approach was developed in our laboratory.[15] Thus, the enaminones 24 were obtained in excellent yields by thermal condensation of the appropriate acylketene dithioacetals 22 with dimethyl formamide diethylacetal 23 (Scheme 5). These enaminones 24 underwent smooth 1,4-addition with alkyl Grignard reagents to afford the corresponding α-enoyl ketene



Scheme – 4



22a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = Me$
c, $R^1 = R^2 = Me$

23

24

25

$R^1 = H, Me$
$R^2 = H, Me$
$R^3 = Me, Et, n\text{-}pr, i\text{-}pr$

26

Scheme-5

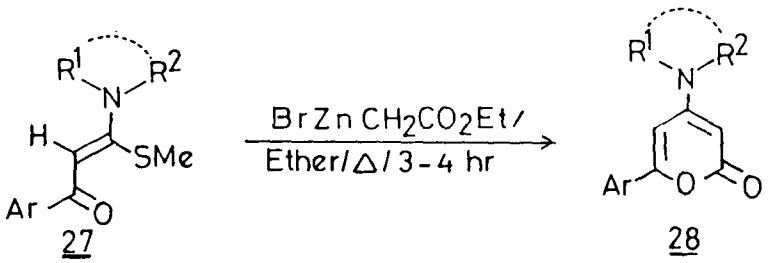
dithioacetals 25 in good yields. Preferential 1,4-attack of Grignard reagents to the enaminone moiety over acylketene dithioacetal functionality in 24 can be rationalized in terms of the enhanced electrophilic character of the 5-carbon due to delocalization of lone pair of nitrogen over enaminone system as shown in structure 26 (Scheme 5).

The reaction of Reformatsky reagent with α-oxoketene N,S-acetals was recently reported[16] from our laboratory. Thus, when the aroylketene S,N-acetals 27 were reacted with ethyl bromozincacetate, the corresponding pyran-2-ones 28 were obtained in 60-72% overall yields. Apparently, the reaction proceeds by the initial 1,4-addition of reagent followed by elimination of methylmercapto group to give the intermediate adduct 31, which on subsequent nitrogen lone pair assisted cyclization gives the product pyrone 28 (Scheme 6).

In the light of these known transformations it was considered of interest to study the reaction of α-oxoketene N,S-acetals 27 with Grignard reagents and metal hydrides. The results of these studies are described in the following section.

RESULTS AND DISCUSSION

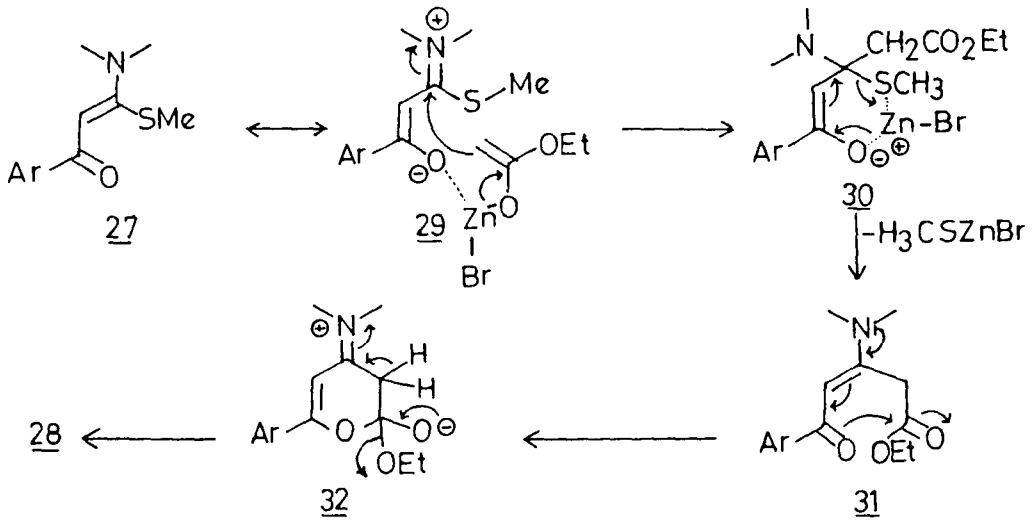
For the present study, the known oxoketene N,S-acetals 27a-c 50a-e were prepared according to the reported



27 28

Ar = C_6H_5 ; 4-MeC_6H_4 ; 4-MeOC_6H_4 ; 4-ClC_6H_4

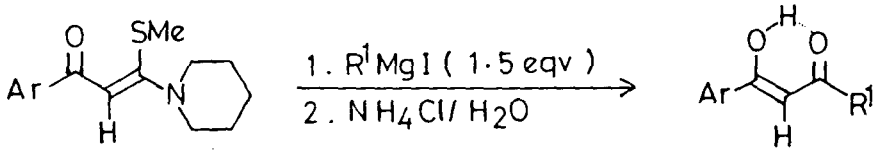
$R^1 = R^2$ = Me ; $-(CH_2)_4-$; $-(CH_2)_5-$; $-(CH_2)_2-O-(CH_2)_2-$ 60-72%



Scheme–6

procedures,[17,18] while the unknown α-oxoketene N,S-acetal 39 was prepared by reacting α-tetralone 37 with N-α-bis(methylthio)methylene piperidinium sulphate 38 (Scheme 9). The detailed experimental procedure is given in the experimental section.

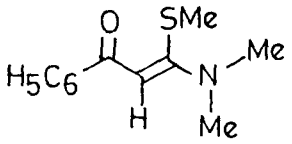
When the N,S-acetal 27a was reacted with methylmagnesium iodide (1.5 eqv.), work-up of the reaction mixture afforded a product (64%) which was characterized as α-benzoylacetone 33a m.p. 59-60°C (lit.[19] 61°C); (superimposable IR and NMR spectra). The diketone 33b was similarly obtained from the corresponding N,S-acetal 27b. The dimethylamino N,S-acetal 27c also gave the diketone 33a in 60% yield on treatment with methylmagnesium iodide under identical conditions showing that the course of reaction is unaffected by the structure of secondary amine in 27. Similarly, the reaction of ethylmagnesium bromide (1.5 eqv.) with N,S-acetal 27a and 27b gave the corresponding 1,3-diketones 33c and 33d in 61 and 64% yields respectively. The reaction of n-propylmagnesium bromide and phenylmagnesium bromide with 27a also yielded the corresponding 1,3-diketones 33e and 33f (Scheme 7). The analytical and spectral data of all the 1,3-diketones were in agreement with their assigned structures (experimental). However, when 27a was treated with excess of methylmagnesium iodide (5 eqv.), the product isolated in 52% was characterized as β,β-dimethylacrylophenone 34a. The IR and NMR spectral data



27a , Ar = C_6H_5
b , Ar = 4-$MeOC_6H_4$

33

33a , Ar = C_6H_5 ; R^1 = Me
b , Ar = 4-$MeOC_6H_4$; R^1 = Me
c , Ar = C_6H_5 ; R^1 = Et
d , Ar = 4-$MeOC_6H_4$; R^1 = Et
e , Ar = C_6H_5 ; R^1 = n-Pr
f , Ar = R^1 = C_6H_5



27c

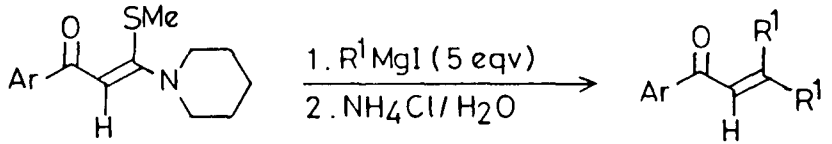
Scheme-7

of 34a was in agreement with the reported values.[20] The N,S-acetal 27b also yielded the β,β-dimethylenone 34b on treatment with excess of methylmagnesium bromide (5 eqv.). Similarly the treatment of S,N-acetals 27a and 27b with excess of ethyl or n-propylmagnesium bromide (5 eqv.) afforded the corresponding β,β-dialkylenones 34c-e in moderate to good yields (Scheme 8).

Interestingly, when 27a was reacted with isopropylmagnesium bromide (1.5 eqv.) the product isolated was identified as isobutyrophenone 35a (34%) along with the unreacted starting material 27a (Scheme 8). The yield of 35a was increased to 69% when 27a was reacted with excess (5 eqv.) of isoporpylmagnesium bromide. Similarly the reaction of 27a with t-butylmagnesium bromide (5 eqv) afforded the pivalophenone 35b in 66% yield (31% with 1.5 eqv. of t-butylmagnesium bromide).

The reaction of cyclic S,N-acetal 39 with 1.5 eqv. of methylmagensium bromide similarly afforded the corresponding 2-acetyl tetralone in 59% yield, while with excess of methylmagnesium bromide, 2-isopropylidene-1-tetralone 41 was obtained in 54% yield (Scheme 9).

The probable mechanism of the formation of various products from 27 is described in the Scheme 10. The diketones 33 are apparently formed by 1,4-addition of Grignard reagents to 27 followed by elimination of



27

27a , Ar = C_6H_5

b , Ar = 4-$MeOC_6H_4$

34

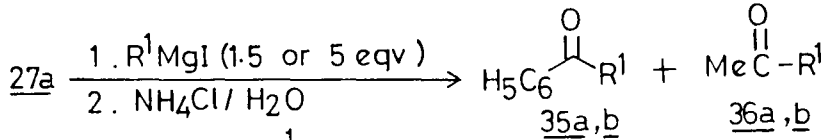
34a , Ar = C_6H_5 ; R^1 = Me

b , Ar = 4-$MeOC_6H_4$; R^1 = Me

c , Ar = C_6H_5 ; R^1 = Et

d , Ar = 4-$MeOC_6H_4$; R^1 = Et

e , Ar = C_6H_5 ; R^1 = n-Pr

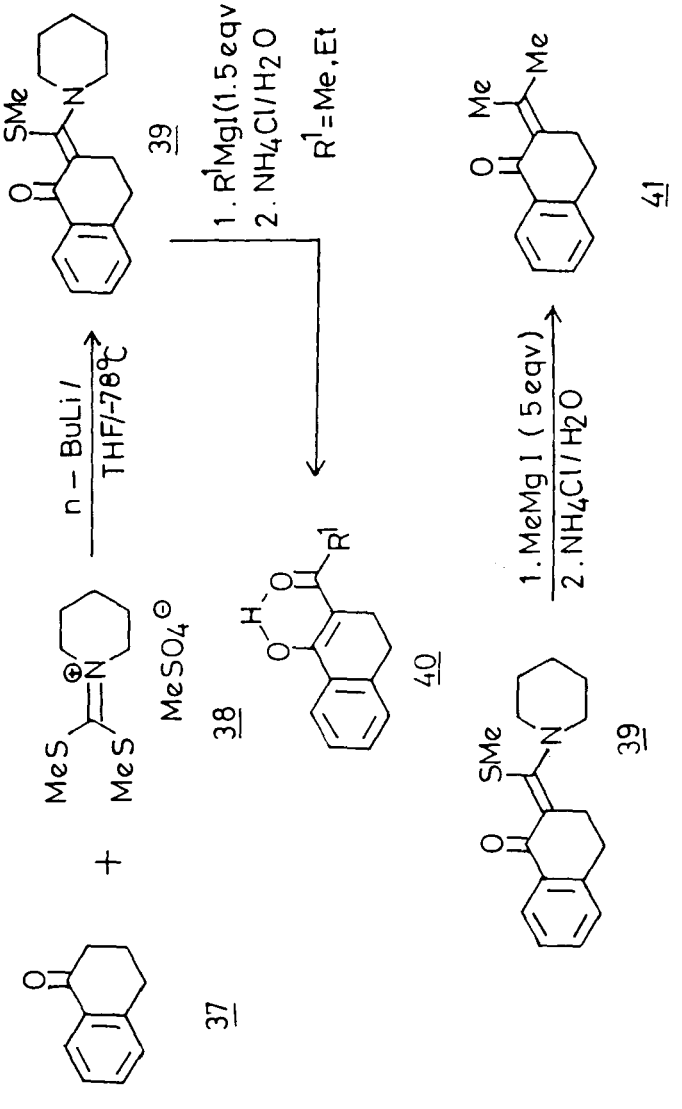


35a,b + 36a,b

a , R^1 = i-Pr

b , R^1 = t-Bu

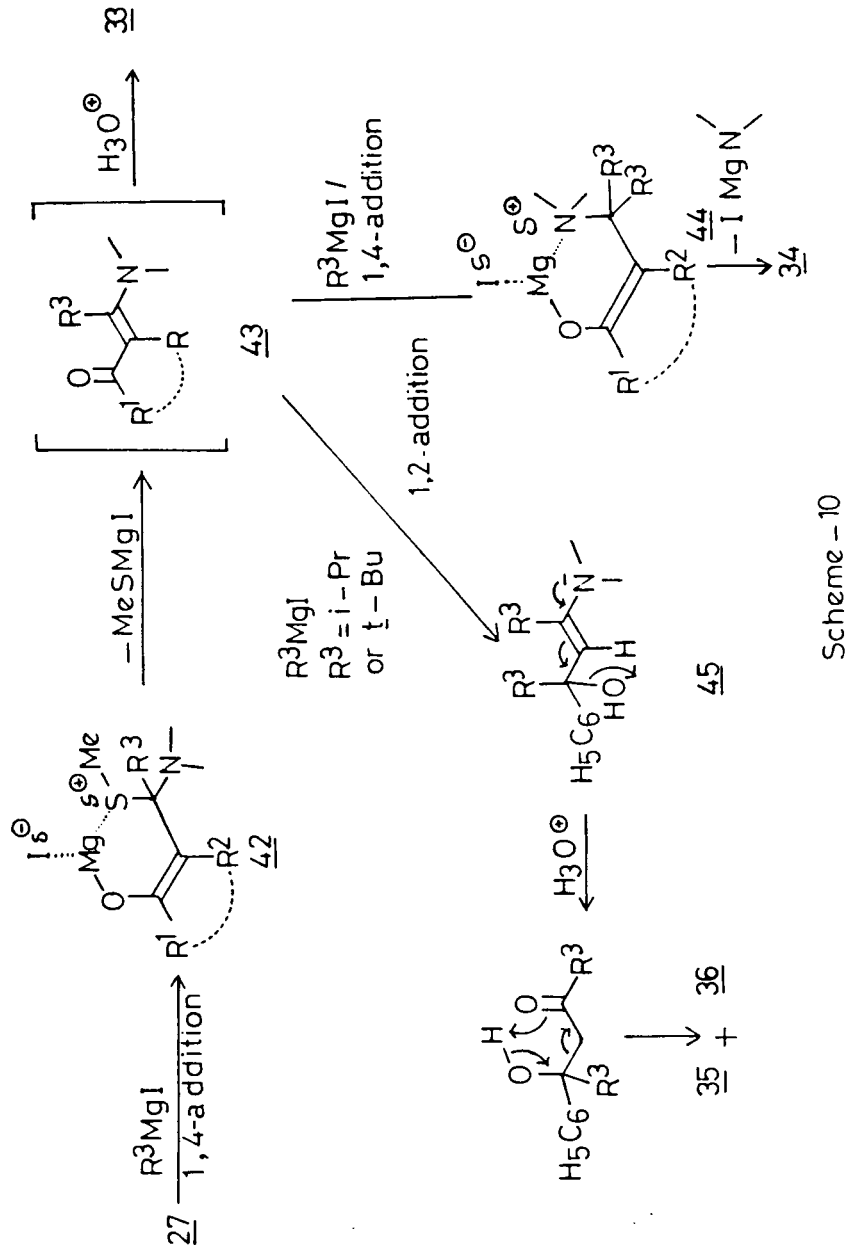
Scheme – 8


MeS
MeS
MeSO4⊖
n – BuLi /
THF/-78℃
SMe
O
N
1. R1MgI(1.5 eqv)
2. NH4Cl/H2O
R1=Me, Et
R1
O
H
O
1. MeMgI (5 eqv)
2. NH4Cl/H2O
Me
Me
37
38
39
40
41

Scheme – 9

methylmercaptomagnesium halide to give unstable enaminones 43 followed by their subsequent hydrolysis during work-up. In the presence of excess Grignard reagents, the intermediate enaminones 43 undergo further 1,4-addition of the Grignard reagents followed by elimination of piperidine to give β,β-dialkylenones 34 in moderate yields. However, the formation of ketones 35a or 35b from 27a apparently involves 1,2-additions of *i*-propyl or *t*-butyl Grignard reagents at some stage of the reaction. Increase in the yields of 35a and 35b with excess of Grignard reagents indicates that two eqv. of Grignard reagents are requdired for their formation. Thus, it appears that 27a undergoes initial 1,4-addition with either *i*-propyl or *t*-butyl Grignard reagent to give the enaminones 43 (R^3=*i*-Pr or *t*-Bu), which on subsequent 1,2-addition followed by hydrolysis and cleavage of the intermediate aldols 46 afford 35 and the corresponding aliphatic ketones 36. The presence of bulkier *i*-propyl or *t*-butyl group in 43 probably forces the benzoyl group out of plane of the planar enaminone system and thus hinders participation of lone pair of nitrogen in delocalization over carbonyl group resulting in its increased electrophilic character and ultimately resulting in 1,2-addition of Grignard reagents.

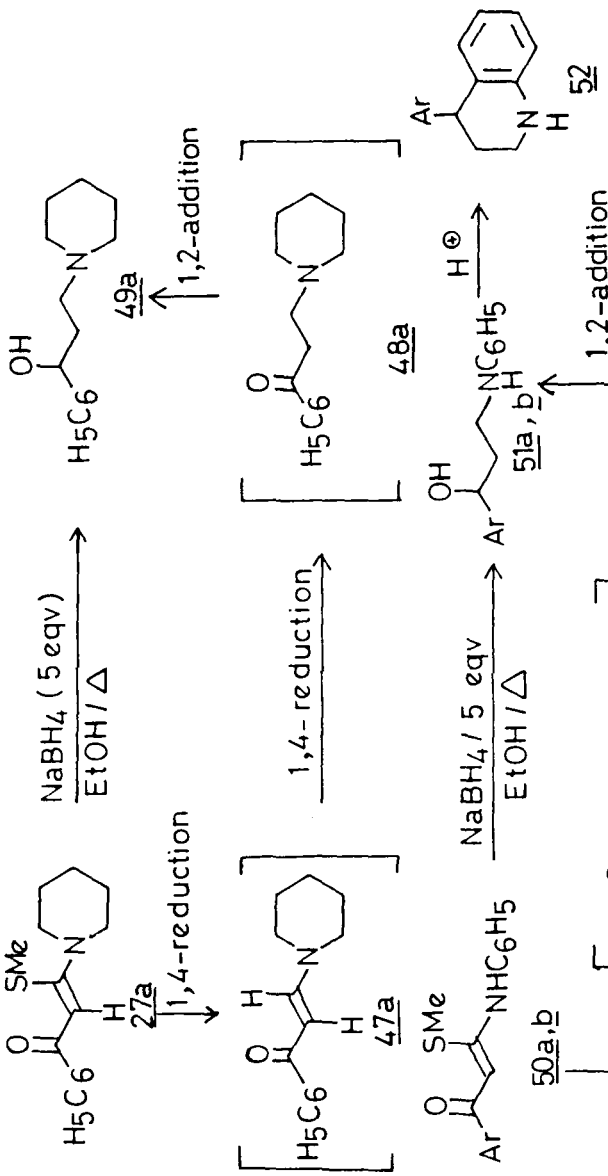
Reduction of N,S-acetals 27 and 50 with metal hydrides was next investigated. When 27a was treated with $NaBH_4$ (2 eqv.), the product isolated was characterized as



Scheme – 10

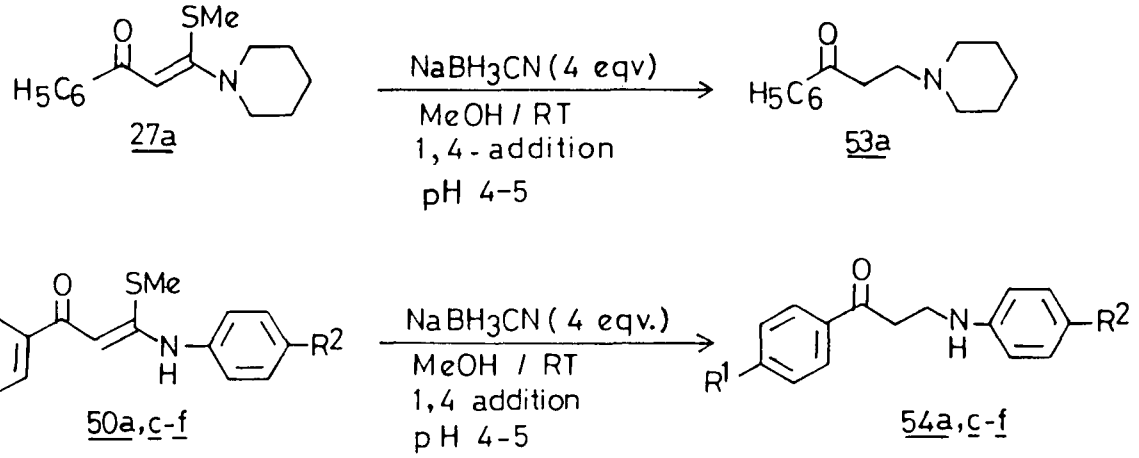
saturated amino alcohol **49a** (32%) along with unreacted starting material **27a**. However, with excess of sodium borohydride (5 eqv.), the saturated aminoalcohol **49a** was obtained in 72% yield. The alcohol **49a** is apparently derived by further reduction of intially formed saturated aminoketone **48a** through successive 1,4- reductions of **27a** (Scheme 11). Reaction of N,S-anilinoacetals **50a** and **50b** also yielded the alcohols **51a** and **51b** in good yields under identical conditions. These aminoalcohols **51** have been used for the synthesis of tetrahydroisoquinoline on treatment with 70% H_2SO_4.[22] The analytical and spectral data of all these alcohols were in confirmity with the assigned structures and are given in the experimental section.

A number of *chemo*- and *regio*selective metal hydrides have been developed in recent years for controlled reduction of substrates with sensitive functional groups. Sodium cyanoborohydride[22] with its strongly electron withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride. So we decided to investigate the reaction of sodium cyanoborohydride with N,S-acetals. When **27a** was reacted with $NaBH_3CN$ in the pH range 4-5, the corresponding aminoketone **53a** was obtained in good yield (Scheme 12). Obviously the product aminoketone **53** is formed by sequential 1,4-reduction and elimination of methylthio group of N,S-acetal **27a** and even traces of 1,2-reduction product was not detected in the reaction



a , Ar = C_6H_5
b , Ar = 4-$EtOC_6H_4$

Scheme_11



a , $R^1 = R^2 = H$
c , $R^1 = H$; $R^2 = Cl$
d , $R^1 = Cl$; $R^2 = H$
e , $R^1 = MeO$; $R^2 = H$
f , $R^1 = Me$; $R^2 = Cl$

Scheme-12

mixture. Similarly the N,S-anilinoacetals 50a,c-f also afforded the corresponding β-anilinoketones 54a,c-f in 82-86% overall yields (Scheme 12).The analylitical and spectral data of all these aminoketones 53a,54a,c-f were in agreement with their assigned structures (experimental).

V.3 CONCLUSION

The reactivity of α-oxoketene N,S-acetals towards various Grignard reagents and metal hydrides have been investigated and found to follow those of enaminones. The pronounced 1,4-selectivity of N,S-acetals towards various carbon,hydrogen and nitrogen nucleophiles will permit the regioselective construction of new C-C,C-H and C-N bonds.

V.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer and the chemical shift values are expressed as δ (ppm) downfield from TMS as internal standard. IR spectra were recorded on Perkin-Elmer 297 spectrometer. Mass spectra were obtained using a Jeol JMS D-300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-RAPID instrument. All the Grignard reactions were carried out under an atmosphere of dry, oxygen free nitrogen.

Starting Materials

The commercial samples of the various acetophenones and secondary amines were purified before use. Of the various oxoketene N,S-acetals used, 27a-c and 50a-f were prepared by the reported procedures,[17,18] and their structures were confirmed by comparing their analytical and spectral data with the reported ones. The cyclic oxoketene N,S-acetal 39 derived from tetralone was prepared by the following procedure.

2-(Methylthio-N-piperidino)methylene tetralone (39)

To a cooled (-78°C) solution of α-tetralone (1.46g, 10 mmol) and N-α-bis(methylthio)methylene piperidinium sulphate (1.57g,6 mmol) in dry THF(30 ml) under N_2 atmosphere, n-butyllithium (10 mmol) was injected slowly (5 min). The reaction mixture was stirred at -78°C for 0.5 hr and then at room temperature for 8 hr. It was then poured into aqueous saturated NH_4Cl (50ml) solution, extracted with chloroform, dried (Na_2SO_4) and evaporated to give crude 39 which was purified by column chromatography over silica gel using EtOAc:hexane (1:2) as eluent; yield 1.87g (65%) based on α-tetralone; viscous liquid;IR ν_{max}(neat) 1620 cm^{-1}; ^1H NMR(CCl_4) 1.63 (brs,6H,CH_2); 2.25 (s,3H,SMe); 2.83 (s,4H,CH_2); 3.21 (brs,4H,NCH_2); 6.97 (m,3H,arom); 7.83-8.05 (m,1H,arom) (Found: C,71.10,H,7.31; N,4.80; Calc. for $C_{17}H_{21}NOS$: C, 71.04; H,7.37; N,4.87%).

General Procedure for the Reaction of Grignard Reagents with Oxoketene N,S-acetals 27 and 39

α-Benzoylacetone(33a): To an ice cold solution (0-5°C) of methylmagnesium iodide [7.5 mmol,prepared from magnesium turnings (0.20g) and methyl iodide (1.06g) in dry ether (25 ml)], a solution of 27a (1.30g, 5 mmol) in dry THF (20 ml) was added dropwise (4-5 min). The reaction mixture was then stirred at 0°C for 30 min and then at room temperature for 4 hr. It was decomposed with saturated aqueous ammonium chloride (50 ml) and extracted with ether (3x50 ml). The combined extracts were washed with water (50 ml), dried (Na_2SO_4) and evaporated to give crude 33a; which was purified by column chromatography over silica gel using hexane as eluent to give pale yellow solid, 0.52g (64%) m.p. 59-60°C (lit.[6], 61°C) (Superimposable IR and NMR spectra).

The diketones 33b-f were similarly obtained from the respective α-oxoketene N,S-acetals 27a-c and higher alkyl and aryl Grignard reagents. The reaction of N,S-acetals 27a-c with excess of Grignard reagents (25 mml for 5 mmol of 27) were also carried out in the similar manner as described; the enones 34 were purified by column chromatography over silica gel using hexane as eluent. All the known diketones 33 and the enones 34 were characterized by comparison of their m.p. and NMR/IR spectral data with those reported. The spectral and

analytical data for unknown 33 and 34 and for those known ones, whose spectral data are not reported in the literature, are given below.

4-Methoxybenzoylacetone (33b) was isolated as pale yellow crystals (hexane) m.p. 50-51°C; yield 68%; IR ν_{max}(neat) 3420(br),1598 cm^{-1}, ^1H NMR (CCl_4) 2.09 (s,3H,CH_3); 3.80 (s,3H,OCH_3); 5.95 (s,1H,olefinic) 6.82 (d,J=9Hz,2H,arom) 7.71(d,J=9Hz,2H,arom); 16.24 (brs,1H,enolic OH exchangeable with D_2O) (Found: C,69.01; H,5.96; Calc. for $C_{11}H_{12}O_3$ C,68.75; H, 6.29%).

1-Phenylpentane-1,3-dione (33c) was isolated as pale yellow oil (lit.[23],b.p. 153-154°C/16 mm Hg);IR ν_{max}(neat): 3432(br),1663,1610 cm^{-1}; ^1H NMR (CCl_4) 1.20 (t,J=6Hz, 3H, CH_3); 2.45 (q,2H,CH_2); 6.08 (s,1H,olefinic); 7.10-7.57 (m,3H,arom); 7.70-8.00 (m,2H,arom); 16.22 (brs,1H,enolic OH exchangeable with D_2O) (Found: C,75.29; H,6.61; calc. for $C_{11}H_{12}O_2$: C,75.00; H,6.81%).

1-(4-Methoxyphenyl)pentane-1,3-dione (33d) was isolated as pale yellow oil; yield 64%;IR ν_{max}(neat) 3400(br),1655 and 1600 cm^{-1}; ^1H NMR (CCl_4) 1.56 (t,J=6Hz,3H,CH_3); 2.47 (q,2H,CH_2); 3.80 (s,3H,OCH_3); 5.99 (s,1H,olefinic); 7.82 (d,J=8.5Hz,2H,arom); 7..79 (d,J=8.5Hz,2H,arom); 16.31 (brs,1H,enolic OH exchangeable with D_2O) (Found:C,70.19; H,7.01; Calc. for $C_{12}H_{14}O_3$: C,69.90; H,6.79%).

1-Phenylhexane-1,3-dione (33e) was isolated as pale yellow viscous oil (lit.[23], b.p. 165-166°C/63 mm Hg) yield 58%; IR ν_{max}(neat) 3400(br),1661,1606 cm^{-1}; ^1H NMR (CCl_4); 0.97 (t,3H,CH_3); 1.70 (sext,2H,CH_2); 2.32 (t, 2H, CH_2); 6.04 (s,1H,olefinic); 7.28-7.52 (m,3H,arom); 7.75-8.00 (m,2H,arom);(Found:C,75.58; H,7.51;Calc.for $C_{12}H_{14}O_2$ C,75.78; H,7.36%).

Dibenzoylmethane (33f) was isolated as pale yellow solid (hexane); m.p. 77-78°C(lit.[24],77°C); yield 58% (superimposable IR and ^1H NMR spectra).

3-Methyl-but-2-enophenone (34a) was isolated as pale yellow viscous oil, yield 52%, IR and NMR data as reported.[20]

4'-Methoxy-3-methyl-but-2-enophenone (34b) was isolated as yellow viscous oil (lit.[25], b.p.160°C/10 mm Hg); yield 54%; IR and NMR data as reported.[25]

3-Ethyl-phenyl-2-pentene-1-one (34c) was isolated as pale yellow viscous liquid (lit[31],b.p. 138°C/8 mm Hg); yield 52%; IR ν_{max} (neat) 1660,1606 cm^{-1}; ^1H NMR (CCl_4) 0.90 (t, J=7Hz, 3H, CH_3); 1.02 (t, J=7Hz, 3H, CH_3); 2.18 (q,J=7Hz,2H,CH_2); 2.51 (q,J=7Hz,2H,CH_2); 6.60 (brs,1H, olefinic); 7.16-7.50 (m,3H,arom); 7.70-8.80 (m,2H,arom); (Found:C,83.10; H,8.81; Calc. for $C_{13}H_{16}O$: C,82.97; H,8.51%).

3-Ethyl-1-(4-methoxyphenyl)-2-pentene-1-one (34d) was isolated as pale yellow viscous liquid; yield 55%; IR ν_{max} (neat) 1658,1600 cm^{-1}; ^1H NMR (CCl_4) 1.04 (t,J=6.5Hz, 3H,CH_3); 1.08 (t,J=6.5Hz,3H,CH_3); 2.21(q,J=6.5Hz,2H,CH_2); 2.56 (q,J=6.5Hz,2H,CH_2); 3.72 (s,3H,OCH_3); 6.54 (s,1H,olefinic); 6.80 (d,J=9Hz,2H,arom); 7.80 (d,J=9Hz,2H,arom) (Found:C,77.22; H,8.51; Calc.for $C_{14}H_{18}O_2$: C,77.06. H,8.25%).

2-Acetyltetralone (40a) was isolated as pale yellow crystals (hexane) m.p.56^{0}C (lit.[30],55-57^{0}C); yield 59%; IR ν_{max}(KBr) 3400(br),1615 cm^{-1}; ^1H NMR (CCl_4) 2.12 (s, 3H,CH_3); 2.47-2.91 (m,4H,CH_2); 7.03-7.41 (m,3H,arom); 7.82-8.00 (m,1H,arom); 16.23 (s,1H,enolic OH exchangeable with D_2O): (Found: C,76.71; H,6.19; Calc. for $C_{12}H_{12}O_2$: C,76.59; H,6.38%).

2-Propionyltetralone (40b) was isolated as pale yellow crystals (hexane) m.p. 44-45^{o}C; yield 57%; IR ν_{max} (KBr) 3440 (br), 1620, 1590, 1560 cm^{-1}; ^1H NMR (CCl_4) 1.04 (t,J=6.5Hz,3H,CH_3); 2.39 (q,2H,CH_2); 2.42-2.81(m,4H,CH_2); 6.98-7.30 (m,3H,arom); 7.73-7.90 (m,1H,arom); 16.09 (s, 1H,enolic OH exchangeable with D_2O) (Found: C,77.41; H,6.75; Calc. for $C_{13}H_{14}O_2$: C,77.22; H,6.93%).

2-Bis(methyl)methylenetetralone (41) was isolated as pale yellow viscous liquid; yield 54%; IR ν_{max}(neat) 1660, 1613 cm^{-1}; ^1H NMR (CCl_4) 1.90(s,3H,CH_3); 2.15(s,3H,Ch_3); 2.58 (m,4H,CH_2); 6.98-7.40 (m,3H,arom); 7.90-8.13 (m,1H,arom)

(Found: C,83.65; H,7.72; Calc. for $C_{13}H_{14}O$: C,83.87; H,7.52%).

Reaction of 27a with *i*-propylmagnesium bromide was carried out as described earlier. Work-up and column chromatogrphy of the reaction mixture gave **Isobutyrophenone (35a)** as pale yellow oil (lit.[26], b.p. 102/15 mm Hg) (69% with 5 eqv. of *i*-PrMgBr); IR $_{max}$ (neat) 1679,1590 cm^{-1}; ^1H NMR(CCl_4) 1.20 (d,6H,CH_3); 3.55 (sept.,1H,CH); 7.31-7.50 (m,3H,arom); 7.81-7.99 (m,2H, arom) (superimposable IR and NMR spectra). ^1H NMR spectrum (CCl_4) of the reaction mixture after evaporation of solvent showed extra peaks at δ2.10(s,3H,CH_3CO) and 2.50 (sept.,1H, CH) due to methylisopropyl ketone 36a besides other peaks due to 35a.

Reaction of 27a with *t*-butylmagnesium bormide and work-up as described gave **Pivalophenone (35b)** as pale yellow oil (lit.[26], b.p. 219-221°C/70 mm Hg) yield 66% (with 5 eqv. of *t*-butylmagnesium bromide); IRν_{max}(neat) 1680,1600 cm^{-1} ^1H NMR (CCl_4) 1.28 (s,9H,CH_3); 7.21-7.38 (m,3H,arom); 7.51-7.70 (m,2H,arom) (Found: C,81.28, H,8.81; Calc. for $C_{11}H_{14}O$: C,81.48; H,8.64%); ^1H NMR spectrum (CCl_4) of the reaction mixture after evaporation of solvent showed extra peaks at δ0.98 (s,9H,CH_3) and 2.20 (s,3H,CH_3) due to pinacolone 36b besides other peaks due to 35b.

General Procedure for Sodium Borohydride Reduction of 27a and 50a,b.: To a stirred solution of 27a (1.30g,5 mmol)

in absolute ethanol (25 ml) was added in portions 0.95g (25 mmol) of sodium borohydride at room temperature and the reaction mixture was further stirred for 5 minutes. After refluxing for 45 min, reaction mixture was cooled, poured into ice and extracted with ether (3x50 ml). The combined extracts were washed with water (50 ml), dried (Na_2SO_4) and evaporated to give crude 49a, which was purified by column chromatography over silica gel using hexane-EtOAc (9:1) as eluent, pale yellow viscous oil (72%); IR $_{max}$(neat) 3310,1480 cm^{-1}; ^1H NMR($CDCl_3$) 1.22-1.90 (m,8H,piperidine CH_2 and CH_2); 2.07-2.61 (m,6H,NCH_2); 4.62 (t,1H,CH); 5.90 (s,1H,OH exchangeable with D_2O);7.00-7.41 (m,5H,arom) (Found: C,76.92; H,9.80; N,6.52 Calc. for $C_{14}H_2NO$: 76.71; H,9.58; N,6.39%).

3-Anilino-1-phenylpropan-1-ol (51a) was also obtained similarly as pale yellow crystals m.p. 61-62°C (lit.[27], m.p.62-63°C);yield 74%;IRν_{max}(KBr)3300,3170(br),1600 cm^{-1} ^1H NMR (CCl_4) 1.77 (q,J=6Hz,2H,CH_2); 3.01 (t,J=6Hz,2H, CH_2);3.51 (s,1H,NH,exchangeable with D_2O);4.55 (t,6Hz,1H, CH); 6.32-7.31 (m,11H,arom and OH); (Found: C,79.10; H,7.63; N,5.94; Calc. for $C_{15}H_{17}NO$:79.29,H,7.48;N,6.16%)

3-(4-Ethoxyphenylamino)-1-phenylpropan-1-ol (51b) was isolated as colourless crystals m.p. 91-92°C; yield 71%; IRν_{max} (KBr) 3250,3160(br),1598 cm^{-1}; ^1H NMR (CCl_4); 1.12 (t,J=7Hz,CH_3); 1.78 (q,J=6Hz,2H,CH_2); 2.21 (brs,1H, exchangeble with D_2O); 2.99 (t,J=6Hz,2H,CH_2); 3.68

(q,J=6Hz,2H,CH_2); 4.51 (t,J=6Hz,1H,CH); 6.21-7.30 (m,10H, arom and OH); (Found: C,74.81;H,8.10; N,5.11; Calc. for $C_{17}H_{22}NO_2$: C,74.97; N,8.14; H,5.14%).

General Procedure for Reduction of 27a,50a-e with Sodium Cyanoborohydride: To an ice cooled solution (0-5°) of 50a (1.35g, 5 mmol) in methanol (15 mol), a trace of bromocresol green was added followed by addition of methanolic HCl (2N) until the solution turned yellow. Sodium cyanoborohydride (0.63g, 10 mmol) was then added in portions followed by addition of methanolic HCl (2N) (to maintain pH at 4) till solution became yellow. The reaction mixture was further stirred for 2 hr at 26°C. The reaction mixture was then poured into aqueous NaOH (50ml, 0.1N), saturated with sodium chloride, extracted with ether (3x50 mol) and the combined extracts were washed with water (2x50 ml),dried (Na_2SO_4) and evaporated to give crude **β-Anilinopropiophenone (54a)** which was purified by recrystallization from hexane:EtOAC (4:1) pale yellow crystals, m.p. 110-111°C (lit.[28] m.p. 111-112°C) yield 82%. IR ν_{max}(KBr) 3400,1678 cm^{-1} ^1H NMR ($CDCl_3$) 3.20 (t,J=6Hz,2H,CH_2); 3.56 (t,J=6Hz,2H,CH_2); 3.91 (brs,1H, NH, exchangeable with D_2O); 6.38-8.07 (m,10H,arom); (Found: C,79.81; H,6.81; N,6.51 Calc.for $C_{15}H_{15}NO$; C,80.01; H,6.82; N,6.49.

β-(4-Chlorophenylamino)propiophenone (54c) was isolated as pale yellow crystals (EtOAc-hexane) m.p. 137-138°C

(lit.[28] m.p. 136-138°C) yield 83%; IR ν_{max}(KBr) 3390; 1670 cm^{-1}; ^1H NMR (CCl_4) 3.21 (t,J=6Hz,2H,CH_2); 3.52 (t, J=6Hz,2H,CH_2); 4.10 (brs,1H,NH,exchangeable with D_2O); 6.48-7.98 (m,9H,arom): (Found: C,69.10; H,5.52; N,5.14; Calc. for $C_{15}H_{14}ClNO$: C,69.36; H,5.39; N,5.39%).

β-Anilino-4-chloropropiophenone (54d) was isolated as colourless crystals (EtOAc-hexane); m.p.121°C; yield 86%; IR ν_{max} (KBr) 3380, 1670, 1603 cm^{-1}; ^1H NMR($CDCl_3$): 3.21 (t,J=6.5Hz,2H,CH_2);3.54(t,J=6.5Hz,2H,CH_2);3.90(brs,1H,NH, exchangeable with D_2O); 6.52-8.02 (m,9H,arom); (Found: C,69.12, H,5.50; N,5.12; Calc. for $C_{15}H_{14}ClNO$: C,69.36; H,5.39;N,5.39%).

β-Anilino-4-methoxypropiophenone (54e) was isolated as colourless crystals (EtOAc-hexane); m.p. 131°C; yield 84%; IR ν_{max}(KBr) 3385, 1670,1610 cm^{-1}; ^1H NMR ($CDCl_3$); 3.15 (t,J=6Hz,2H,CH_2); 3.45 (t,J=6Hz,2H,CH_2); 3.72 (brs, 1H,NH,exchangeable with D_2O); 3.81 (s,3H,OCH_3); 6.48-7.25 (m,7H,arom); 7.88 (d,J=9Hz,2H,arom); (Found: C,75.05; H,6.68; N,5.40; Calc. for $C_{16}H_{17}O_2N$: C, 75.25; H,6.71; N, 5.49%).

β-4-(Chlorophenylamino)-4-methylpropiophenone (54f) was isolated as colourless crystals (EtOAc-hexane); m.p. 134°C; yield 86%; IR ν_{max}(KBr) 3388,1665,1600 cm^{-1}; ^1H NMR

($CDCl_3$): 2.49 (s,1H,CH_3); 3.18 (t,J=6Hz,2H,CH_2); 3.49 (t,6Hz,2H, CH_2); 4.05 (brs,1H,exchangeable with D_2O); 6.48 (d,J=9Hz, 2H,arom); 6.86-7.38 (m,4H,arom); 7.72 (d,J=9Hz,2H,arom); (Found: C,70.21; H,5.79; N,5.01; Calc. for $C_{16}H_{16}ClNO$: C, 70.27; H,5.90; N,5.12%).

REFERENCES

1. Myrboh,B.; Ila,H.; Junjappa,H. *J.Org.Chem.* 1983, *48*, 5327.
2. Balu,M.P.; Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1987, *28*, 3023.
3. Balu,M.P.; Pooranchand,D; Ila,H.;Junjappa,H. *Tetrahedron Lett.* 1984, *25* 5095.
4. Singh,G.;Ila,H.; Junjappa,H. *Tetrahedron Lett.* 1984, *25*, 5095.
5. Singh,G.; Purkayastha,M.L.; Ila,H.; Junjappa,H. *J. Chem.Soc.Perkin.Trans.I.* 1985, 1289.
6. Tse-Lok Ho.; *Chem.Rev.* 1975, *75*, 1.
7. Greenhill,J.V. *Chem.Soc.Rev.* 1977, *6*,277.
8. Benary,E. *Chem.Ber.* 1931, *64*, 2543.
9. Meyers,A.I.; Singh,S. *Tetrahedron Lett.* 1967, 5319.
10. Ireland,R.E.;Schiess,W.P. *Tetrahedron Lett.* 1960,*25* 37.
11. Kashima,C.; Yamamoto,Y. *Chemistry Lett.* 1978, 1285.
12. Martin,C.J.;Barton,K.R.;Gott,P.G.;Meen,R.H. *J.Org. Chem.* 1966, *31*, 943.
13. de Stevens,G.; Halmandaris,A. *J.Org.Chem.* 1961, *26*, 1614.
14. Walker,N.G. *J.Org.Chem.* 1962, *27*, 4227.
15. Asokan,C.V.; Balu,M.P.; Ila,H.; Junjappa,H. *Synthesis*, 1988, 727.
16. Dutta,A.; Ila,H.; Junjappa,H. *Synthesis*, 1988, 248.

17. Viswakarma,J.N.; Apparao,S.; Ila,H.; Junjappa,H. *Ind.J.Chem.* 1985, *24B*, 466.

18. Kumar,A.;Aggarwal,V.; Ila,H.;Junjappa,H. *Synthesis*, 1980, 748.

19. Vogel,A.I. Text Book of Practical Organic Chemistry; 4th edition, *ELBS*, 1978, 445.

20. Reich,H.J.; Renga,J.M; Reich,I.L. *J.Am.Chem.Soc.* 1975, *97*, 5434.

21. Lagendries,R.F.J.; Dey Schruver,F.C.; *Tetrahedron Lett.* 1972, 4781.

22. Gogte,V.N.;Mukhedkar,V.A.;ElNamaky,H.M.;Salama,M.A.; Tilak,B.D. *Ind. J. Chem.* 1974, *12*, 1234.

23. (a) Adams,J.T.; Hauser,C.R. *J.Am.Chem.Soc.* 1945, *67*, 284. (b) Manyik,R.M.;Frostick Jr.F.C.;Sanderson,J.J. Hauser,C.R.; *J.Am.Chem.Soc.* 1953, *75* 5030.

24. Allen,C.F.H.; Abell,R.D.; Normington,J.B. *Organic Synthesis,*, Coll.Vol.I, John Wiley, 1941,205.

25. Kasturi,T.R.; Parvati,S. *J.Chem.Soc.Perkin Trans.I.* 1980,448.

26. Hudson Jr.,B.E.; Hauser,C.R. *J.Am.Chem.Soc.* 1941,*63*, 3163.

27. Dienys,G.; Cekuliene,L. *Zh.Org.Khim.* 1967,*3*, 1047.; *Chem.Abstr.* 1967 *67*, 81882x.

28. Singh,N.; Singh,S. *J.Org.Chem.* 1962 *27*, 2656.

29. Hudson,D.;Holt,G.;Wall,D.K. *J.Chem.Soc.(C)* 1970,971.

30. Burton,H.; Munday,D.A. *J.Chem.Soc.* 1957, 1718.

31. (a).Farrow,M.D.; Kon,G.A.R. *J.Chem.Soc.* 1926, 2128. (b).Broquet,C. *Terahedron*, 1973,*29*,3595.