NEWER SYNTHETIC METHODS VIA α - OXOKETENE S, S - AND S, N - ACETALS

BY

Kethiri Raghava Reddy

Department of Chemistry
School of Physical Sciences

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To

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Dedicated

To

My Beloved Late Uncle

पूर्वोत्तर पर्वतीय विश्वविद्यालय
बिजनी परिसर, शिलांग - 793003 (मेघालय)
North-Eastern Hill University
Bijni Complex, Shillong - 793003 (Meghalaya)
Phone :
Gram : NEHU

Professor (Mrs.) H. Ila
Dean
School of Physical Sciences
Department of Chemistry

CERTIFICATE

I hereby certify that the entire work embodied in this thesis has been carried out by Mr. Kethiri Raghava Reddy under my guidance in the Department of Chemistry, North-Eastern Hill University, Shillong.

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

[H. Ila]
Research Supervisor
2/12/94

पूर्वोत्तर पर्वतीय विश्वविद्यालय
बिजनी परिसर, शिलांग - 793003 (मेघालय)
North-Eastern Hill University
Bijni Complex, Shillong - 793003 (Meghalaya)

Phone :
Gram : NEHU

Professor M.K. Choudhuri
Head
Department of Chemistry

This is to certify that Mr. Kethiri Raghava Reddy, 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)	German Language (University level)	SPS-602
(2)	Spectroscopic Methods in Chemistry (School level)	CHEM-622
(3)	Highlights in Organic Chemistry (Departmental level)	CHEM-621
(4)	Biosynthesis and Natural Products Chemistry (Departmental level)	CHEM-630

M Choudhuri 02/12/94
[Prof. M.K. Choudhuri]

HEAD
Department of Chemistry
North Eastern Hill University
Shillong-793 003

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If the maxim "Hanging and Wiving go by destiny" were to be true "Hanging Wiving and Supervising go by destiny" should also be true from my experience under the supervision of ***Prof. (Mrs.) H. Ila****, Dean, School of Physical Sciences. I am much beholden to express my profuse gratitude to her for her excellent, inspiring, dynamic guidance, invaluable suggestions and constant encouragement throughout my research.*

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(KETHIRI RAGHAVA REDDY)

C O N T E N T S

P R E F A C E

The work described in this thesis is a part of an ongoing research programme in our laboratory on the synthetic exploitation of polarised ketene dithioacetals, which serves as versatile 3-carbon synthons with ambident 1,3-dielectrophilic centers for designing various methodologies for both carbocyclic and heterocyclic compounds. These polarised ketene acetals are conveniently prepared from any active methylene compound in one pot operation.

Our group's continued interest in the chemistry of these class of compounds have been centered around exploitation of the differential electrophilicity of 1,3-carbon centers for the chemo-, stereo-and regioselective construction of new bonds involving either 1,2- or 1,4-nucleophilic additions leading to a number of synthetic routes for a wide range of sulfur containing and sulfur free organic molecules. In the present investigation, further new interesting synthetic transformations of polarised ketene dithioacetals and their sister counterparts are described. The thesis consists of five chapters. The first chapter covers a brief account on the general reactivity profile of α-oxoketene

dithioacetals, their sister counterparts and some of the recent transforamtions reported from our group.

In the second chapter, aromatic annelation methodology was well explained for the synthesis of regiospecifically substituted amino aromatics by reacting lithio amino crotonate (binucleophile) with various α-oxoketene S,S- and S,N-acetals (dielectrophilic) are described. Third chapter of this thesis deals with a detailed investigation on the generation and reaction of hitherto unreported 3-lithiomethyl-2-methyl-1-phenyl pyrazolin-5-one with various oxoketene S,S- and S,N-acetals for the synthesis of 1,2-disubstituted indazolones and their condensed analogs.

Synthesis of a highly diastereoselective cyclopentenes by anionic [3+2] annulation strategy via α-oxoketene dithioacetals is presented in chapter four.

In the last chapter, deprotonation studies of various α-oxoketene S,N-acetals and Dimethyl N-aroyl carbimido dithiotes for the synthesis of 2-aminothiophenes and 2-methylthiothiazoles are described.

Each chapter is divided into Introduction, Results and Discussion, Conclusion and Experimental Section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The references of the published work of the present investigation are cited in the respective chapters.

CHAPTER I

POLARIZED KETENE S,S- AND S,N-ACETALS AS POTENTIAL SYNTHETIC BUILDING BLOCKS IN ORGANIC SYNTHESIS: A BRIEF REVIEW

Polarized ketene dithioacetals have been proved to be among the simplest synthetic intermediates in various synthetic transformations[1]. This class of compounds can be easily prepared from a wide variety of active methylene compounds by the condensation of the corresponding enolate with carbon disulfide or trithiocarbonate followed by alkylation of the intermediate dithiolate species often in one pot operation in moderate to good yield[2-9]. They exhibit well defined physical properties either as crystalline solids or distillable liquids and can be purified by conventional methods.

For convenience, this chapter is divided into three sections. In the first section a brief survey of polarized ketene S,S-acetals are described and the second section describes a survey of

polarized ketene S,N- and N,N-acetals. The present work has been described in the third section.

1.1 The polarized Ketene S,S-acetals

Polarized ketene S,S-acetals 1 have been recognized as useful building blocks in many synthetic operations[1]. This class of compounds can be conveniently prepared by reacting any active methylene compound with two equivalents of base and carbondisulfide followed by alkylation[2,3,5]. Various bases and reaction conditions have been employed depending on the nature of the active methylene compound. This section is devoted for the discussion on the chemistry of α-oxoketene dithioacetals in the context of the practical and potential application to organic synthesis.

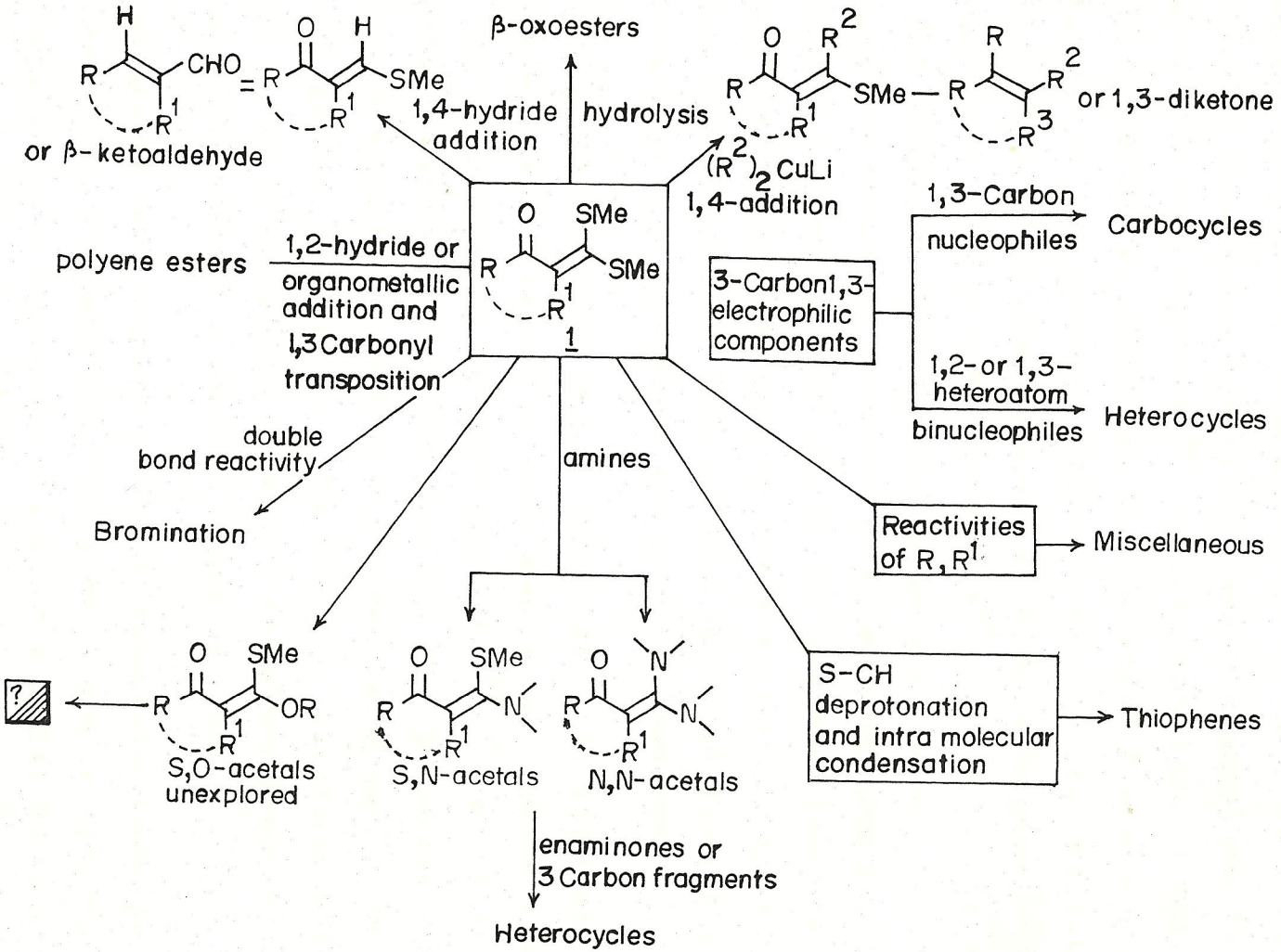
In 1910 Kelber and co-workers[10,11] reported the first synthesis of α-oxoketene dithioacetals. Much of the earlier works on oxoketene dithioacetals were confined to their preparation and properties, while little attention was paid for their synthetic utility. Hence, more than half a century the synthetic potential of these class of compounds remained unexplored. Later Thuillier and Vialle prepared these compounds in high yield in one pot reaction by reacting the active methylene ketone with carbondisulfide in the presence of sodiumamylate followed by alkylation[2,3,5]. Subsequently, these reaction conditions have been greatly improved using different bases and reaction conditions[4,6-9]. A large number of α-oxoketene dithioacetals have now been reported and they emerged as very useful synthetic

intermediates over the last two decades and their chemistry has been reviewed by Dieter[1a] and Junjappa et al[1b].

The α-oxoketene dithioacetals can be prepared by easier methods in one pot operation in high yields with well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stored indefinitely without decomposition. The corresponding α-oxoketene O,O-acetals[12] are moisture sensitive and undergo hydrolysis under mild conditions. The oxoketene dithioacetals are essentially a masked β-ketoester in which the ester functionality is protected as a ketene dithioacetal. Alternatively, it may be viewed as an α,β-unsaturated ketone containing a highly functionalized β-carbon. The oxoketene dithioacetals have been shown to be an excellent three carbon fragements, with 1,3-carbons possessing differential electrophilic properties which is an important pre-requisite in designing various methodologies for both carbocyclic and heterocyclic compounds. They also possess considerable synthetic potential for the chemo-, stereo- and regioselective construction of new bonds via 1,2-nucleophilic additions to ketone carbonyl or by 1,4-conjugate addition to the β-carbon of the enone system. The intermediate allylic alcohols and enones can, inturn, be exploited in additional bond forming reactions. Also, oxoketene dithioacetals can be further converted to the corresponding ketene dihalogenides[13,14], N,S-[15] and N,N-acetals[16] making them more important as precursors for a large variety of functionalized acetals. The preparation of N,S-acetals is accomplished through the displacement of one of the thiomethyl

groups by a suitable amine in refluxing ethanol[15,17]. Alternatively, they can be prepared directly from active methylene ketones by reacting their enolate anion with alkyl and arylisothiocyanates followed by alkylation[18]. The oxoketene N,N-acetals can be prepared in high yield by displacing both the thiomethyl groups by amines in refluxing acetic acid[17,19]. The preparation of O,S-acetal are accomplished through the displacement by an oxygen nucleophile of the sulfonium salt[20]. The oxoketene S,S-, N,S- and N,N-acetals have been extensively used in this laboratory[1] for the synthesis of both heterocyclic and carbocyclic compounds, while the chemistry of O,S-acetals remains unexplored.

Scheme 1 outlines various reactivity profiles of α-oxoketene dithioacetals of the general formula 1 Hydrides and organo metallic reagents give 1,2-addition products typical of carbonyl function reactivity[21]. These additions can be directed in a 1,4-manner by suitably manipulating the reaction condition and reagents[21-23]. Further transformations of these 1,2- or 1,4-addition products have also been investigated extensively[21]. 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-hetero atom 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[3b,24]. When R^1 is a methyl group an allylic

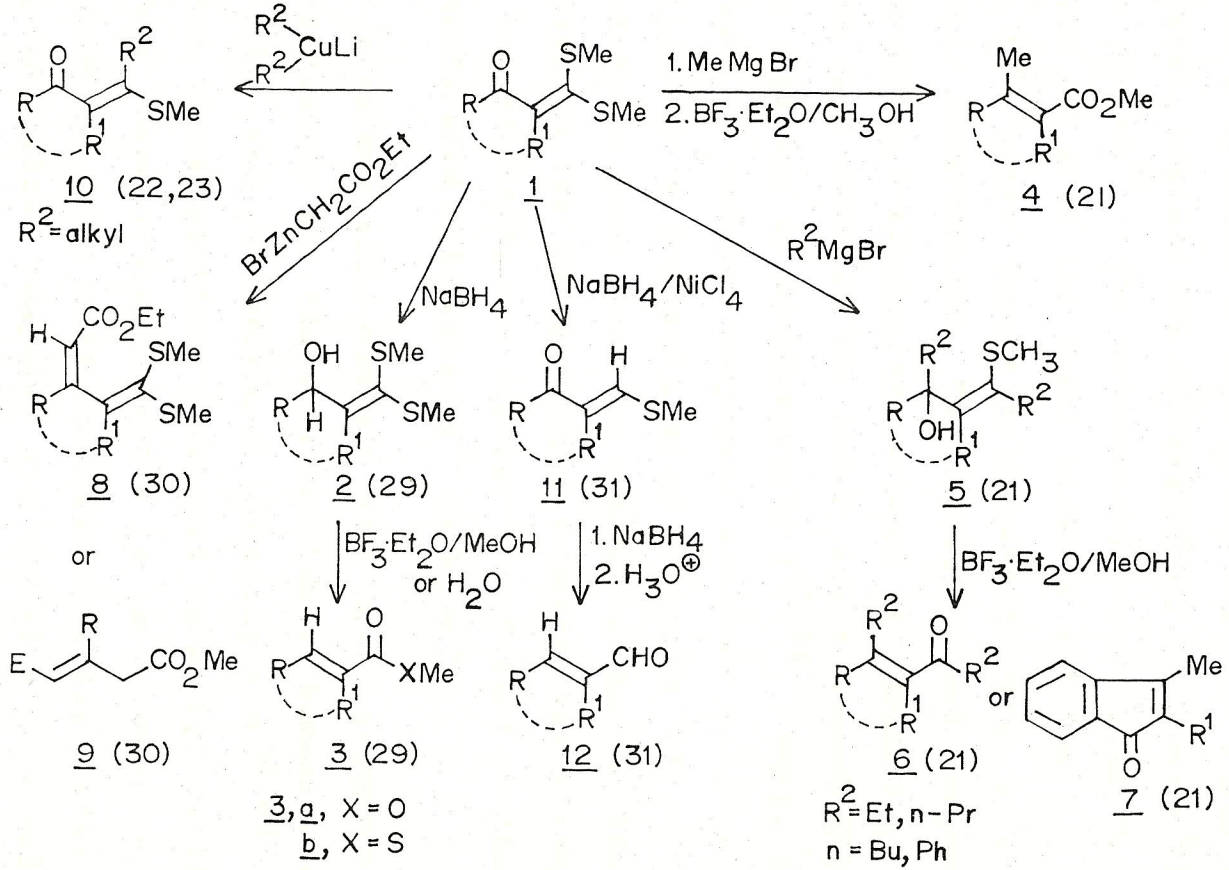

β-oxoesters
or β-ketoaldehyde
1,4-hydride addition
hydrolysis
or 1,3-diketone
(R2)2CuLi
1,4-addition
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles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

Scheme-1

anion is generated in the presence of strong bases leading to rearranged products[25]. Deprotonation of the thiomethyl group followed by intramolecular Aldol type condensation to afford thiophenes is also reported.[26] As discussed earlier they can be easily converted to oxoketene O,S- N,S-and N,N-acetals. The reactivity of the mercapto double bond is also exploited with electrophiles. Thus dithioacetals 1 (R^1=H) undergoes bromination at α-position with N-bromosuccinimide[27]. Thus, it is apparent that the oxoketene dithioacetals of general formula 1 constitute an important class of synthons with reactive electrophilic and nucleophilic centers distributed in various centers of its skeleton permitting reactions of great synthetic importance. In the following sections some of the selected transformations reported from this laboratory are briefly summarized.

The oxoketene dithioacetals 1 have been reported to undergo chemoselective 1,2-reduction with sodium borohydride ($NaBH_4$) to give the corresponding carbinol acetals 2[28,29], which were shown to undergo smooth methanolysis in the presence of boron trifluride etherate to afford α,β-unsaturated methyl esters 3[29] in high yields (scheme 2). The overall transformation can be viewed as the homologation of active methylene ketones at the α-position, involving 1,3-carbonyl transposition.

The Grignard and organo lithium reagents undergo either regioselective 1,2-addition to afford the α-hydroxy ketene dithioacetals or a sequential 1,4-and 1,2-additions to afford the β-hydroxyvinyl sulfides[21-23]. The borontrifluride etherate catalysed solvolysis or the hydrolysis of these carbinols yield

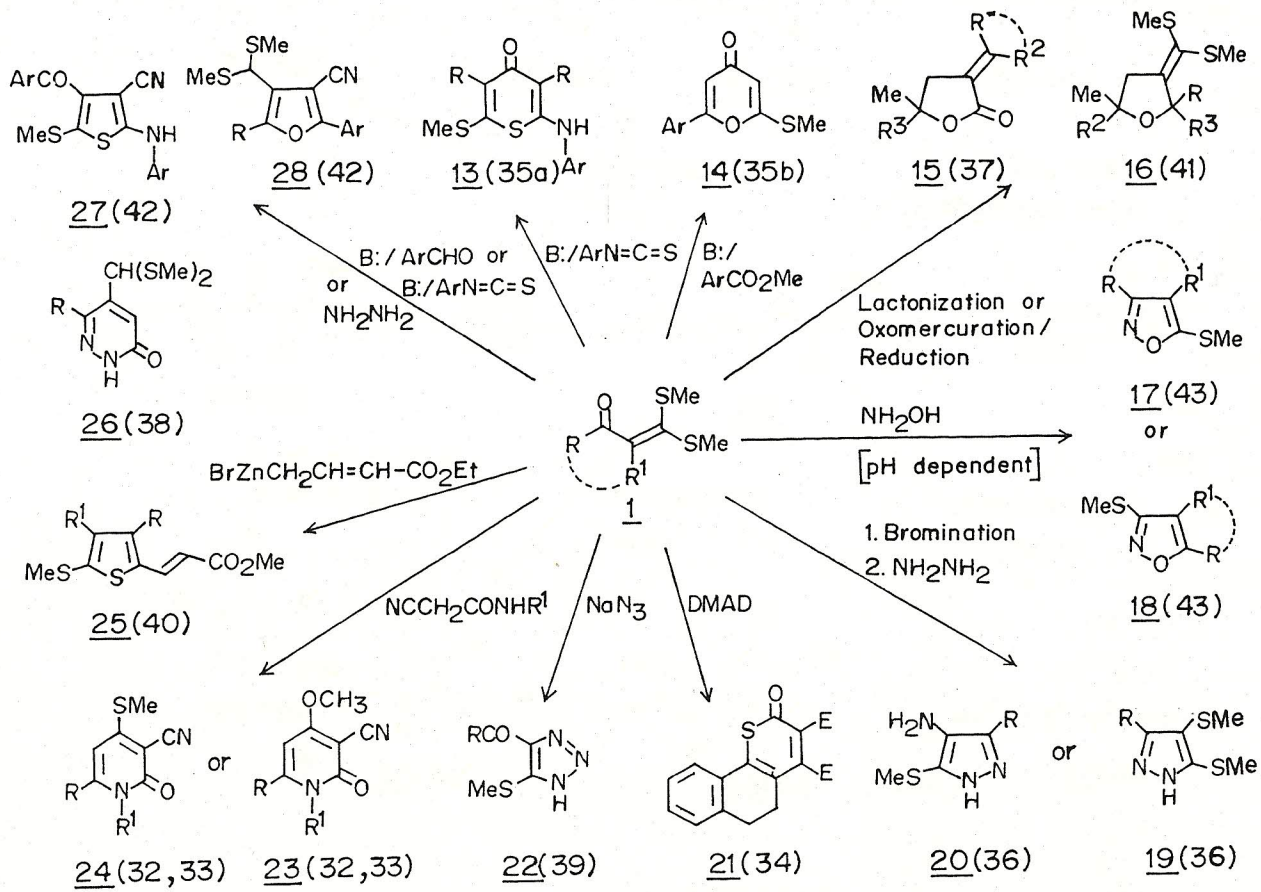

R2CuLi
R2CuLi
10 (22,23)
R2 = alkyl
1. Me Mg Br
2. BF3·Et2O/CH3OH
4 (21)
BrZnCH2CO2Et
NaBH4
NaBH4/NiCl4
R2MgBr
1
8 (30)
or
9 (30)
2 (29)
11 (31)
5 (21)
BF3·Et2O/MeOH
or H2O
1. NaBH4
2. H3O⊕
BF3·Et2O/MeOH
3 (29)
3, a, X = O
b, X = S
12 (31)
6 (21)
R2 = Et, n-Pr
n = Bu, Ph
or
7 (21)

Scheme-2

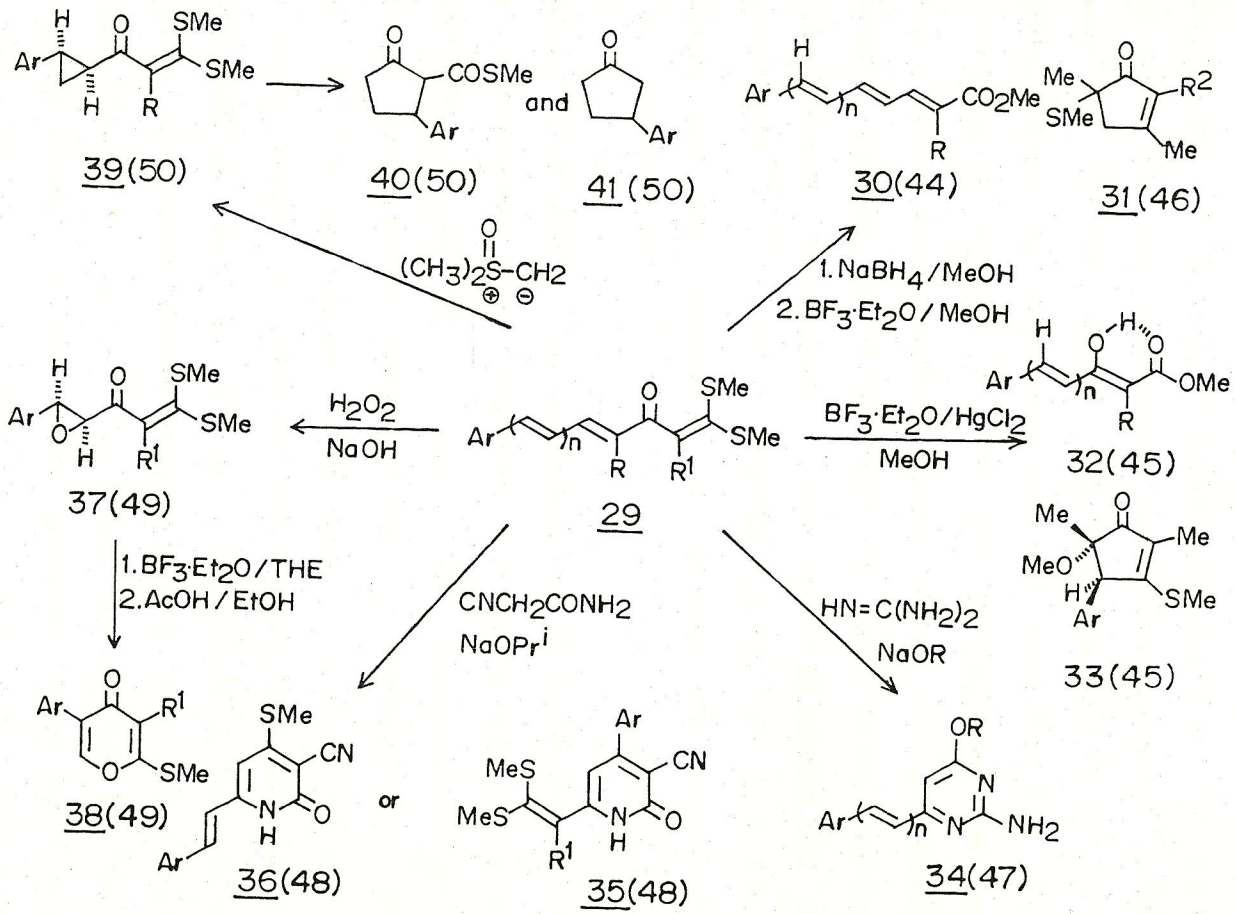
either β-substituted α,β-unsaturated esters **4** or the corresponding ketene **6**[21] (scheme 2) in good yields. However, when the R is alkyl or aryl group the open chain cinnamates were not formed, instead the corresponding 2,3-disubstituted indenones **7** were formed[21]. The Reformatsky reaction on dithioacetal **1** is reported to give the diene ester **8** and the β, γ -unsaturated ester **9**[30], these dienes hold considerable promise as useful synthetic intermediates. The overall transformation is considered as a double 1,3-alkylative carbonyl transposition. Dieter and co-workers have reported the chemo- and stereoselective addition of organo cuprates to dithioacetals **1**[22,23]. Thus, organo cuprates are shown to undergo conjugate addition to give β-alkylthio β-substituted α,β-unsaturated ketones **10**. The oxoketene dithioacetals were shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthio alkenyl ketones **11**. These intermediates are further transformed to the corresponding α,β-unsaturated aldehydes **12**[31] (scheme 2).

The α-oxoketene dithioacetals have been extensively explored in this laboratory for the construction of numerous substituted and fused five and six membered heterocycles[32-43]. Some of the selected transformations developed recently are shown in scheme 3. From these transformations it is apparent that α-oxoketene dithioacetals with wide functional group variation and many easily accessible reagents and reaction intermediates manifest various possibilities leading to diverse product range.

Various transformations developed on α-cinnamoyl and 5-aryl-2,4-pentadienyl ketene dithioacetals **29** are outlined in scheme 4. A


27(42)
28(42)
13(35a)
14(35b)
15(37)
16(41)
26(38)
17(43)
or
18(43)
25(40)
1
24(32,33)
23(32,33)
22(39)
21(34)
20(36)
19(36)
B:/ ArCHO or
or B:/ArN=C=S
NH2NH2
B:/ArN=C=S
B:/
ArCO2Me
Lactonization or
Oxomercuration /
Reduction
NH2OH
[pH dependent]
BrZnCH2CH=CH-CO2Et
1. Bromination
2. NH2NH2
NCCH2CONHR1
NaN3
DMAD
or
or

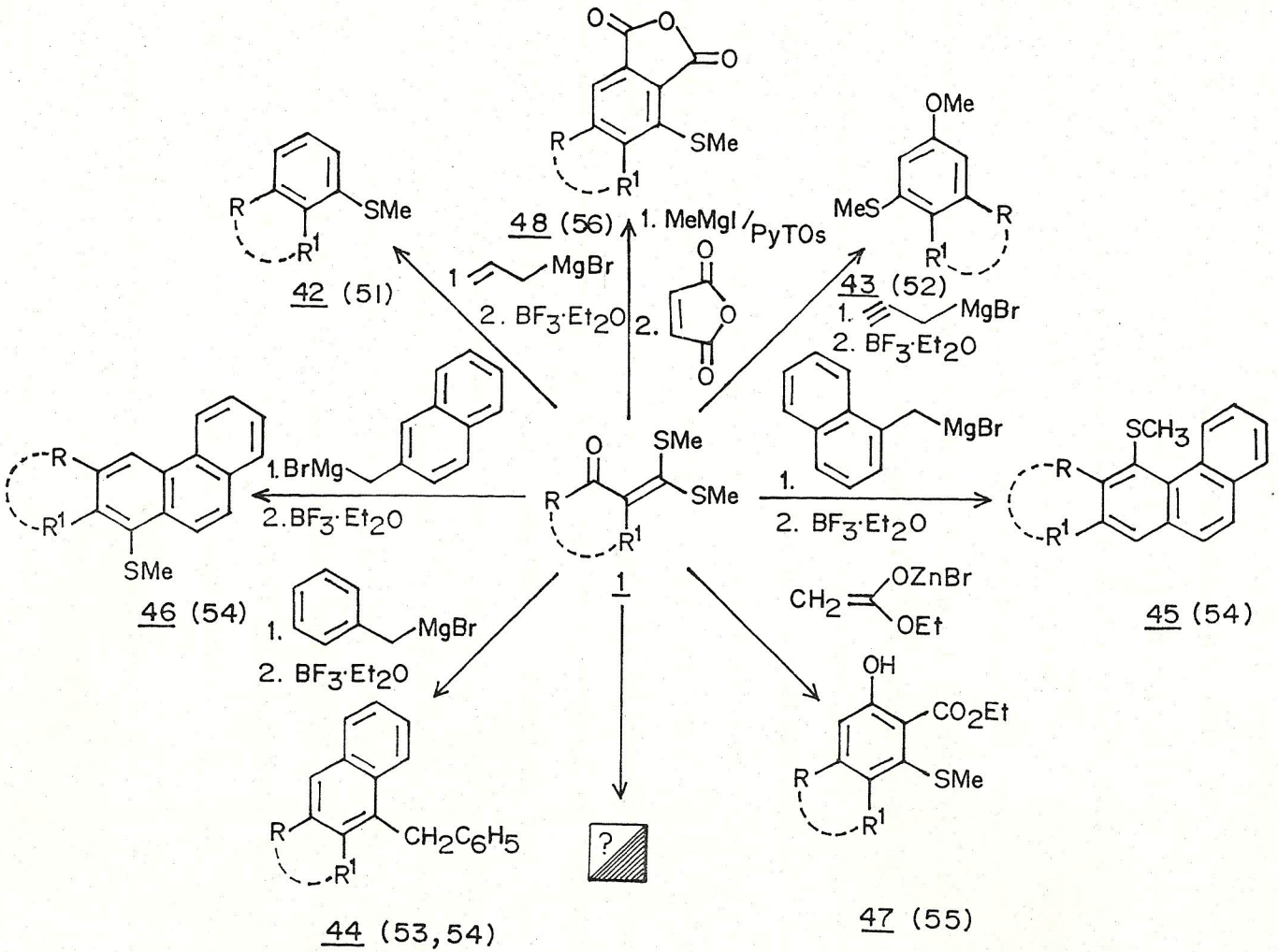
Scheme-3


39(50)
40(50)
and
41(50)
30(44)
31(46)
1. NaBH4/MeOH
2. BF3·Et2O/MeOH
(CH3)2S-CH2
H2O2
NaOH
BF3·Et2O/HgCl2
MeOH
32(45)
37(49)
29
1. BF3·Et2O/THF
2. AcOH/EtOH
CNCH2CONH2
NaOPr^i
HN=C(NH2)2
NaOR
33(45)
38(49)
or
36(48)
35(48)
34(47)

Scheme - 4

general method for the synthesis of polyene esters 30[24,44] have been reported by 1,2-reduction followed by methanolysis in the presence of boron trifluride etherate. In Hg(II) assisted hydrolysis the corresponding γ -δ-unsaturated β-keto esters are formed[45]. In the case of 2,4-disubstituted ($R=R^1=CH_3$), the corresponding cyclopentanones 40 and 41 are formed in both reaction conditions[45,46]. Styryl pyrimidines 34 pyridones 35 and 36 were also synthesised using these intermediates[47,48]. The cinnamoyl ketene dithioacetals 29 have been reported to undergo regioselective epoxidation and cyclopropanation at the styryl double bond[49,50]. The intermediates 37 and 39 were further explored for the synthesis of pyrones 38 and cyclopentanones 40 and 41 respectively[49,50].

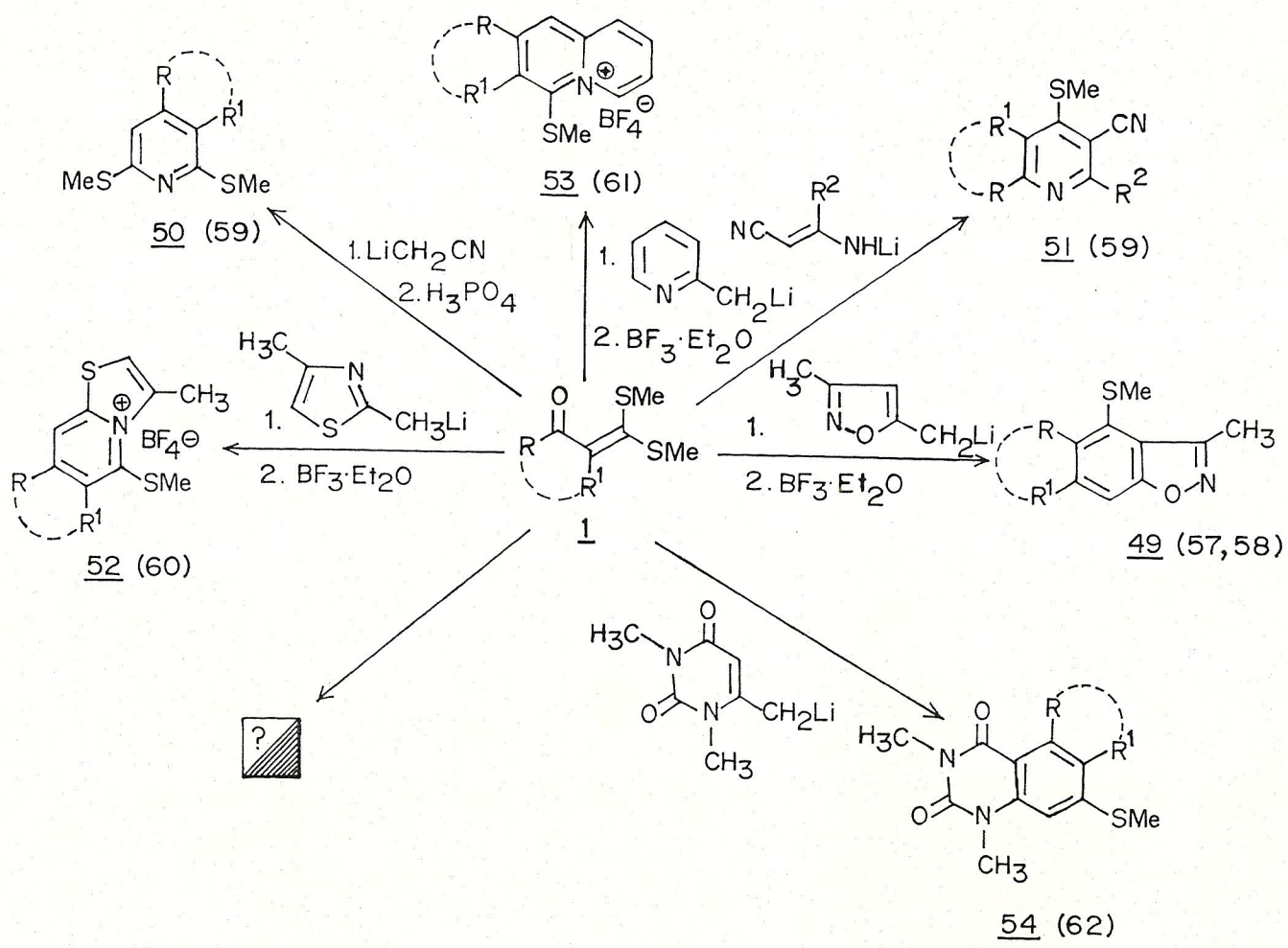
Aromatic annelation via α-oxoketene dithioacetals, developed from this laboratory has emerged as an area of great synthetic potential. Some of the important synthetic outcome of this aromatic annelation methodology is outlined in scheme 5. The reaction of allylmagnesium bromide with α-oxoketene dithioacetals have been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetal in high yields, which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives 42[51]. This method is further shown to be extremely versatile and found general, when extended to propargyl magnesium bromide to afford methoxy substituted benzoannelated products 43[52]. Subsequentely, this method of aromatic annelation was extended to naphtho annelation. When benzyl magnesium chloride was reacted with α-oxoketene dithioacetals, which on treatment with $BF_3.Et_2O$ gave the corresponding naphthalene


48 (56)
1. MeMgI / PyTOs
42 (51)
43 (52)
1. MgBr
2. BF3·Et2O
2.
1. BrMg
2. BF3·Et2O
1.
2. BF3·Et2O
46 (54)
45 (54)
1
1. MgBr
2. BF3·Et2O
CH2 OZnBr OEt
44 (53,54)
47 (55)
?

Scheme — 5

derivatives 44[53,54] through benzene ring participation. This naphtho annelation methodology was extended to α-naphthyl methyl magnesium chloride and β-naphthyl methyl magnesium chloride to yield the corresponding phenanthrenes 45 and 46[54]. With ethyl zinc bromoacetate α-oxoketene dithioacetals yielded the corresponding regiospecifically substituted and annelated 6-methylthio benzoates 47 in good yields[55]. The Diels-Alder cycloadditions of vinyl ketene dithioacetals derived from the corresponding oxoketene dithioacetals 1 with maleic anhydride afforded the phthalic anhydrides 48 in good yields[56]. With a view to enhance the scope of aromatic annelation methodology for the synthesis of benzoheterocycles, heteroaromatic annelation methodology was developed in this laboratory by reacting appropriately substituted heteroallyl systems with α-oxoketene dithioacetals. Thus, the reaction of lithiomethylisoxazole with α-oxoketene dithioacetal yielded the corresponding benzisoxazoles 49 in excellent yield[57,58] (scheme 6). This method was further shown to be extremely versatile and general when extended for the synthesis of pyridines 50 and 51[59], thiazolopyridinium salts 52[60], quinolizinium salts 53[61] and quinazolines 54[62]. This methodology developed as considerable synthetic importance due to the fact that, a large number of azallyl anions could be used to construct various heteroaromatic compounds.

The α-oxoketene dithioacetals therefore with a wide ranging functional group variation and many easily accessible reagents and reactive intermediates manifestly hold many new synthetic


50 (59)
53 (61)
51 (59)
52 (60)
1
49 (57,58)
54 (62)
1. LiCH2CN
2. H3PO4
1.
2. BF3·Et2O
1.
2. BF3·Et2O
1.
2. BF3·Et2O
?

Scheme — 6

possibilities leading to diverse product range, including carbocyclic, heterocyclic and benzoheterocyclic systems.

I.2 Polarized ketene S,N- and N,N-acetals

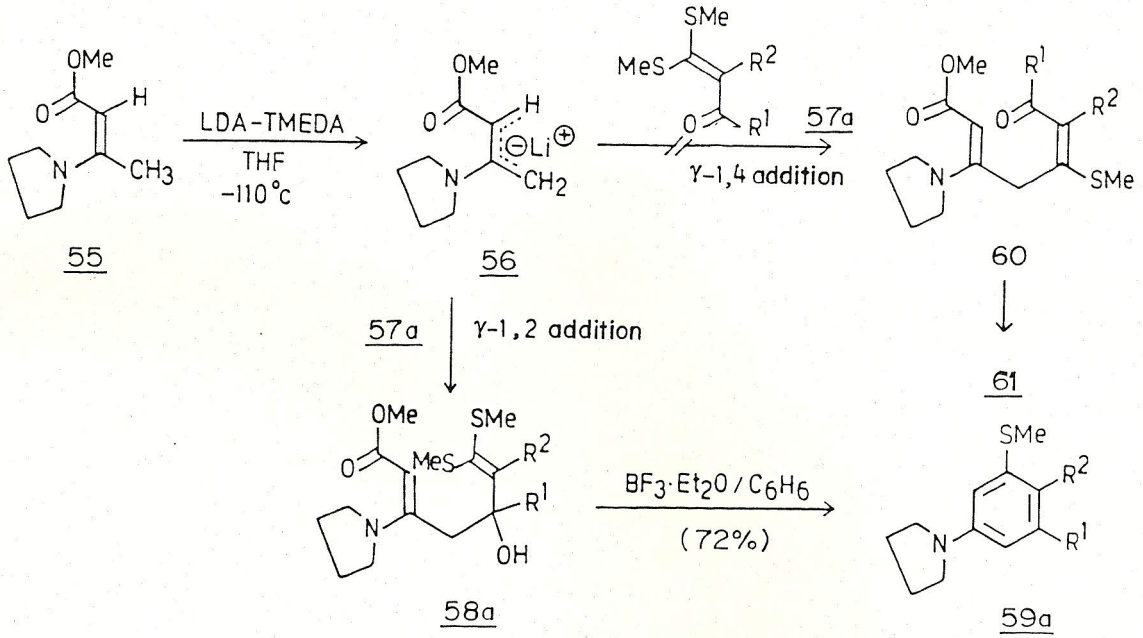
Like oxoketene S,S-acetals, the S,N- and N,N-acetals also possess 1,3-electrophilic centers and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. As stated in the preceding section, they can be prepared by displacement of one or both the thiomethyl groups on oxoketene S,S-acetals which are controlled by the stoichiometry of the used amine and reaction conditions[63-65]. The S,N-acetals can alternatively be prepared directly from any active methylene ketones by reacting their enolate anion with alkyl and aryl isothiocyanates followed by alkylation[18].

The α-oxoketene S,N- and N,N-acetals like oxoketene S,S-acetals, are well defined compounds which can be preserved without apparent decomposition. They can be considered as vinylogous amides if they are derived from ketones and as vinylogous amines if they are derived from other methylene compounds. The chemistry of enamines derived from various ketones and primary or secondary amines is well documented. They have been extensively used as synthetic intermediates to react with various electrophiles making use of α-carbon. However, these enaminones are found to be more sensitive to moisture and undergo ready hydrolytic cleavage to the starting materials. On the other hand, the ketene S,N- and N,N-acetals are more stable and exhibit properties identical to enamines. They can undergo nucleophilic

displacement with various binuclephiles[63-79] followed by intramolecular cyclization with α-oxo functionality. Like enamines the α-carbon in the ketene S,N- and N,N-acetals is nucleophilic enough to react with various electrophilic species so that these reactions can be utilized to construct heterocycles of different structural features. In α-oxoketene S,N-acetals, the reduced electrophilicity of carbonyl carbon can be attributed to the hard-soft affinity inversion. Hence, the hard nucleophiles generally attack at the β-carbon (HE) atom. The chemistry and synthetic application of the α-oxoketene S,N- and N,N-acetals have been reviewed[1b] and a number of synthetic methods have been developed in this laboratory[63-79].

I.3 The work presented in this thesis

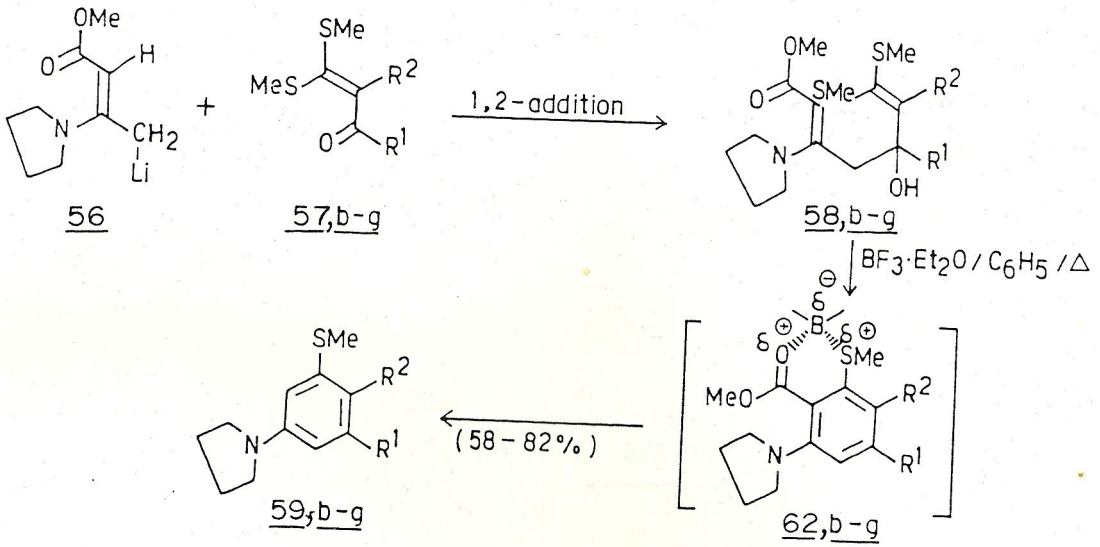
In continuation of these studies and as a part of the present research programme on α-oxoketene S,S- and S,N-acetals, it was proposed to undertake some of the transformations of these synthons. In the second chapter, aromatic annelation methodology was well explained for the synthesis of regiospecifically substituted amino aromatics. The initial γ -1,2-adduct **58** formed by the reaction of lithioaminocrotanate **56** with α-oxoketene dithioacetals **57a-i** have been shown to undergo cycloaromatization in presence of $BF_3.Et_2O$ in refluxing benzene to yield the corresponding amino benzenes **59a-i** in good yields[62] (scheme 7,8 & 9). Interestingly, the cyclic variant of oxoketene dithioacetal **57j** derived from α-tetralone reacted with **56** not in the same manner to yield the corresponding methyl (5,6-dihydro-4-



55 56 60 61 58a 59a

57, 58, 59, a , $R^1 = C_6H_5$; $R^2 = H$

Scheme - 7



57, 58, 62, 59, b, R^1 = 4-ClC_6H_4 ; R^2 = H

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

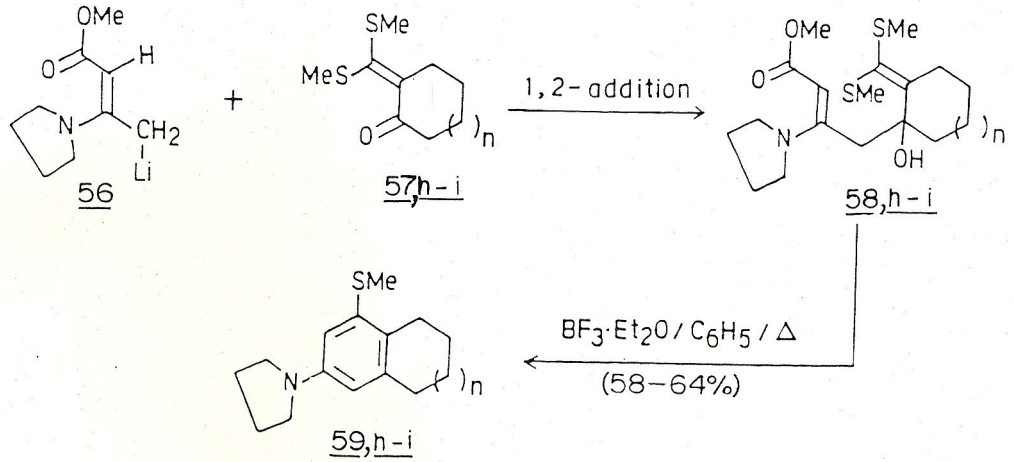
d, R^1 = 2-naphthyl ; R^2 = H

e, R^1 = 2-Furyl ; R^2 = H

f, R^1 = 2-Thienyl ; R^2 = H

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

Scheme - 8



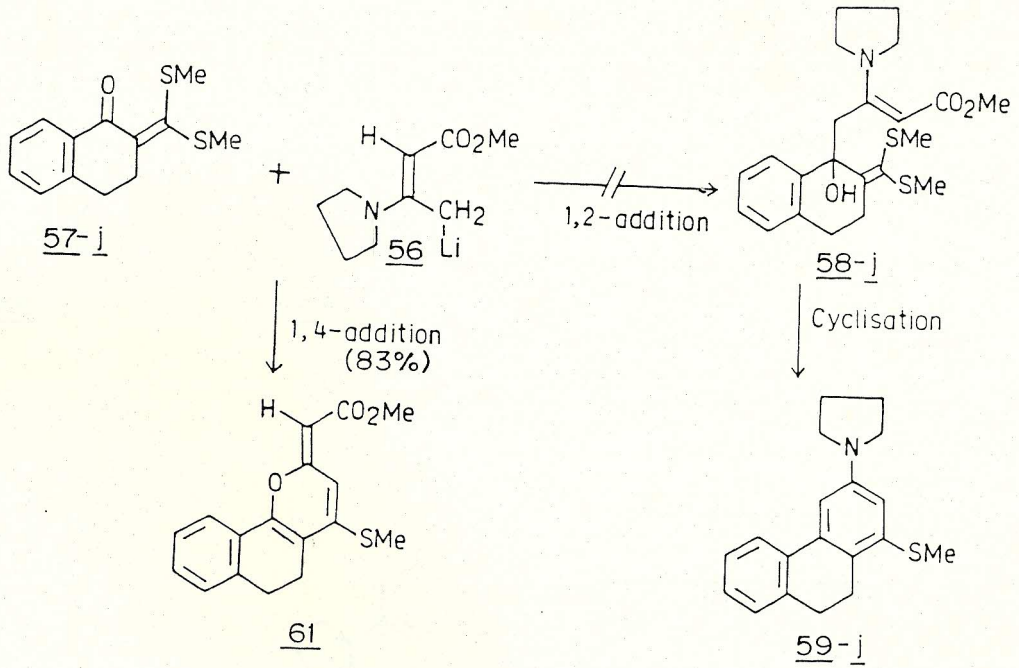
57, 58, 59 , h , n = 1
i , n = 2

Scheme - 9

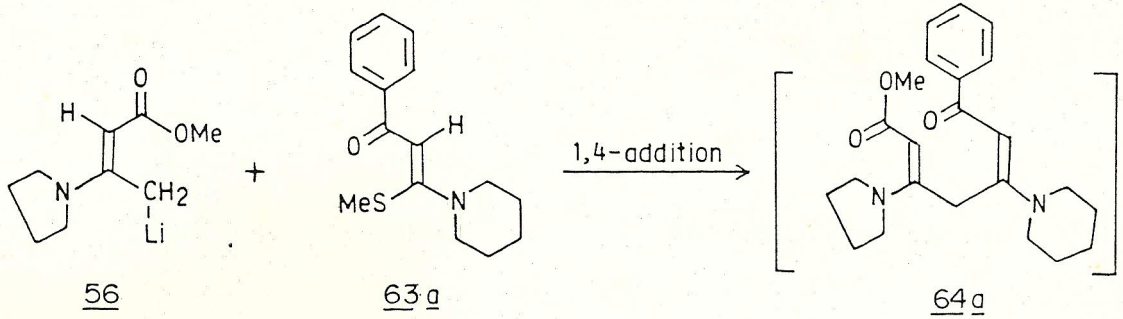
methylthio-2H-naphtho[1,2-b]pyran-2-ylidene) acetate 61 in 83% yield (scheme 10). To show further generality for the synthesis of electron rich aromatic compounds carrying two regiospecifically substituted dicycloalkylamino groups, this methodology was extended to α-oxoketene S,N-acetals. The diverse reaction mode of lithioaminocrotonate 56 with various α-oxoketene S,S- and S,N-acetals 63, the detailed mechanistic pathways for the formation of various products 65 & 67 and the factors governing the course of reaction are discussed in detail (scheme 11 to 13).

In chapter III, the heteroaromatic annelation methodology is well explained for the synthesis of hitherto unreported 1,2-disubstituted indazolones and their condensed analogs by reaction of 1,3-binucleophilic hitherto unreported 3-lithiomethyl-2-methyl-1-phenyl pyrazolin-5-one with 1,3-electrophilic α-oxoketene dithioacetals. Although, two regioisomers (linearly and angularly fused indazolones) are possible with cyclic α-oxoketene dithioacetals only one regioisomer (angularly fused indazolone) are formed in all cases. The regioisomers were assigned on the basis of ^{1}H and ^{13}C NMR data. The preliminary study on the lithioation of the 2,3-dimethyl-1-phenyl pyrazolin-5-one (Antipyrine) and the scope of this new approach developed, is discussed in detail in this chapter (scheme 14 to 17).

In chapter IV, the reactivity of various activated olefins with the anion derived from bifunctional ketene S,S-acetal, which functions as 1,3-dipole are described in detail. In principle such anionic cycloadditions should follow one of the following


O
SMe
SMe
57-j
+
H
CO2Me
N
CH2
Li
56
1,2-addition
N
CO2Me
SMe
OH
SMe
58-j
1,4-addition
(83%)
Cyclisation
H
CO2Me
O
SMe
61
N
SMe
59-j

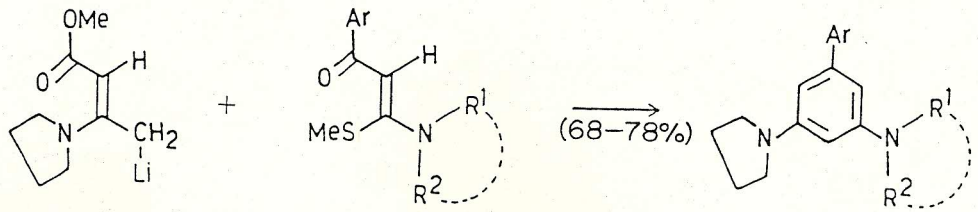
Scheme -10



56 63 a 64 a

65 a

Scheme-11

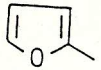


56 + 63 b-e → 65 b-e

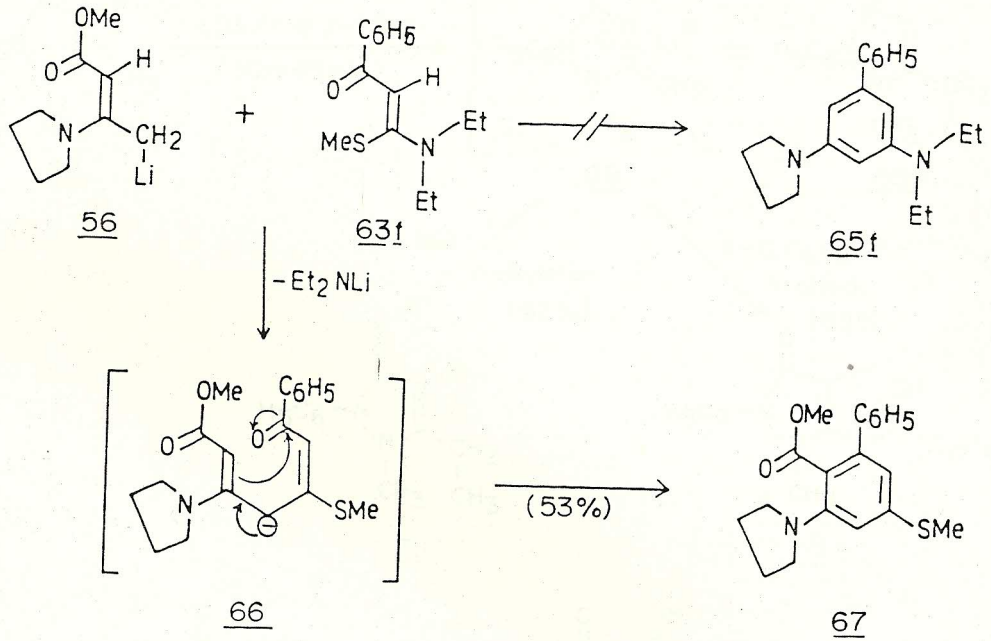
63, 65, b, Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_4-$

c, Ar = 4-Cl C_6H_4 ; $R^1 = R^2 = -(CH_2)_5-$

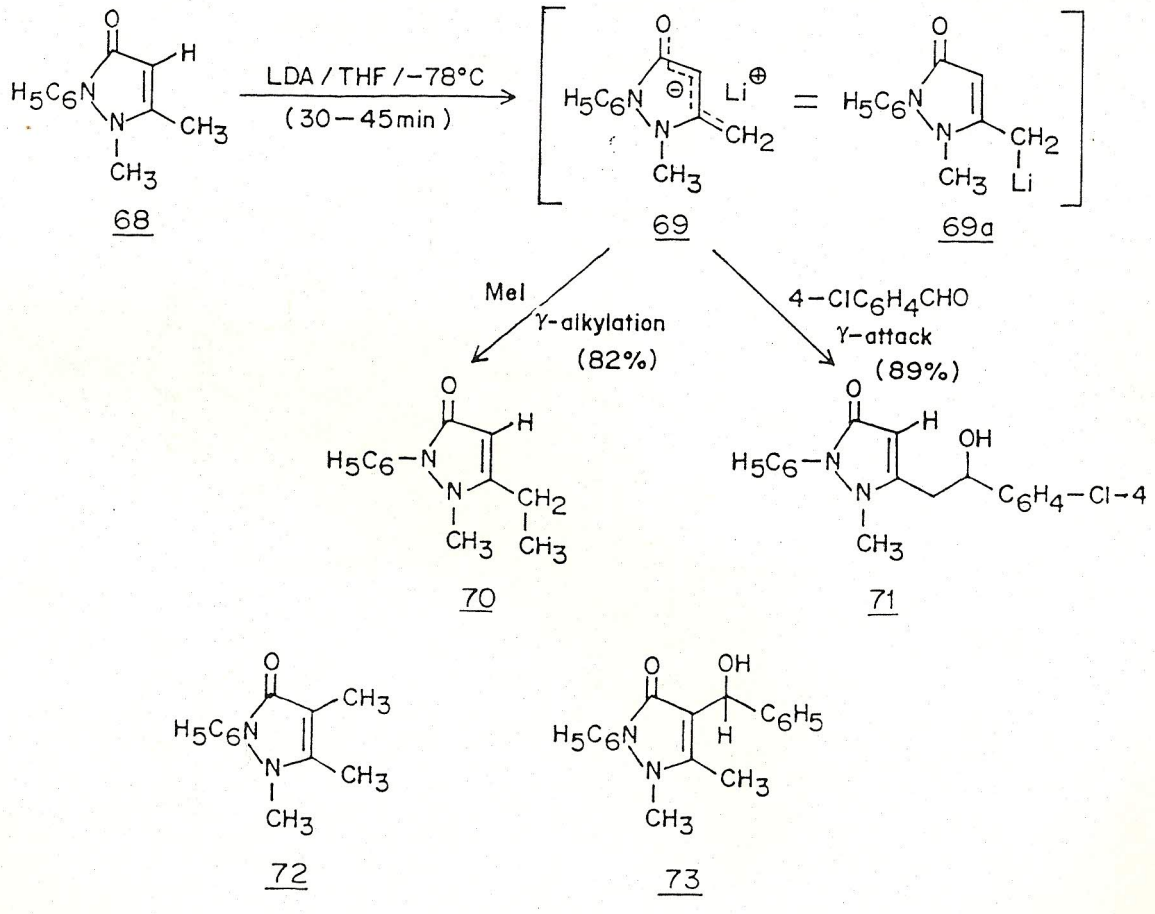
d, Ar = 4-MeO C_6H_4 ; $R^1 = R^2 = -(CH_2)_5-$

e, Ar =  ; $R^1 = R^2 = -(CH_2)-O-(CH_2)_2-$

Scheme-12

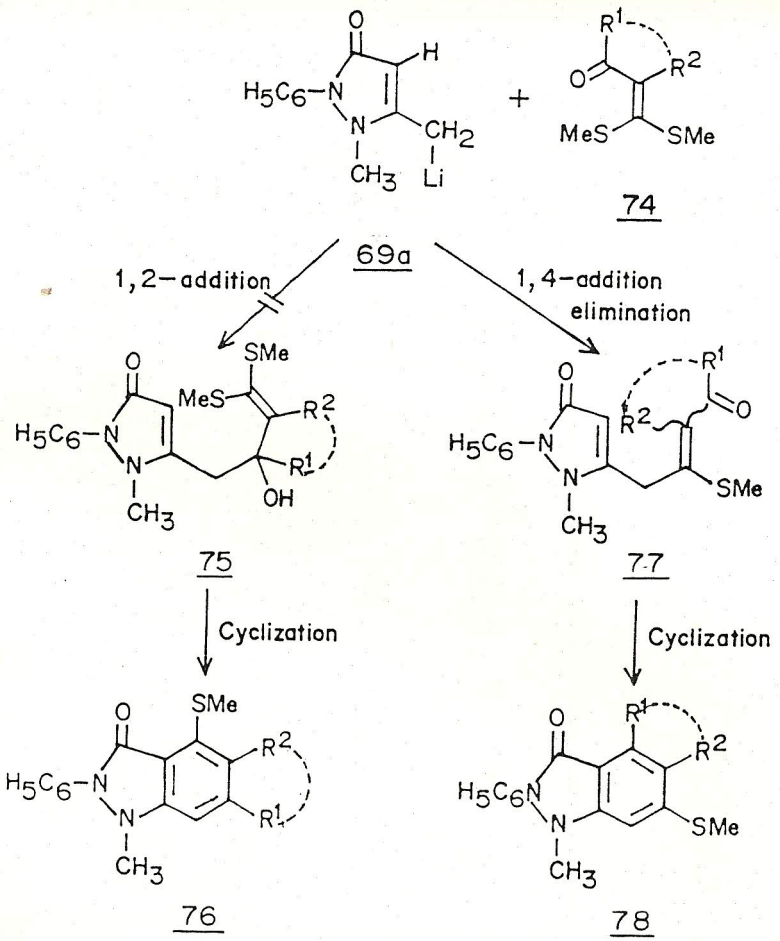

OMe
O
H
N
CH2
Li
56
+
C6H5
O
H
MeS
N
Et
Et
63f
C6H5
N
N
Et
Et
65f
-Et2 NLi
OMe
C6H5
O
O
N
SMe
66
(53%)
OMe
C6H5
O
N
SMe
67

Scheme-13

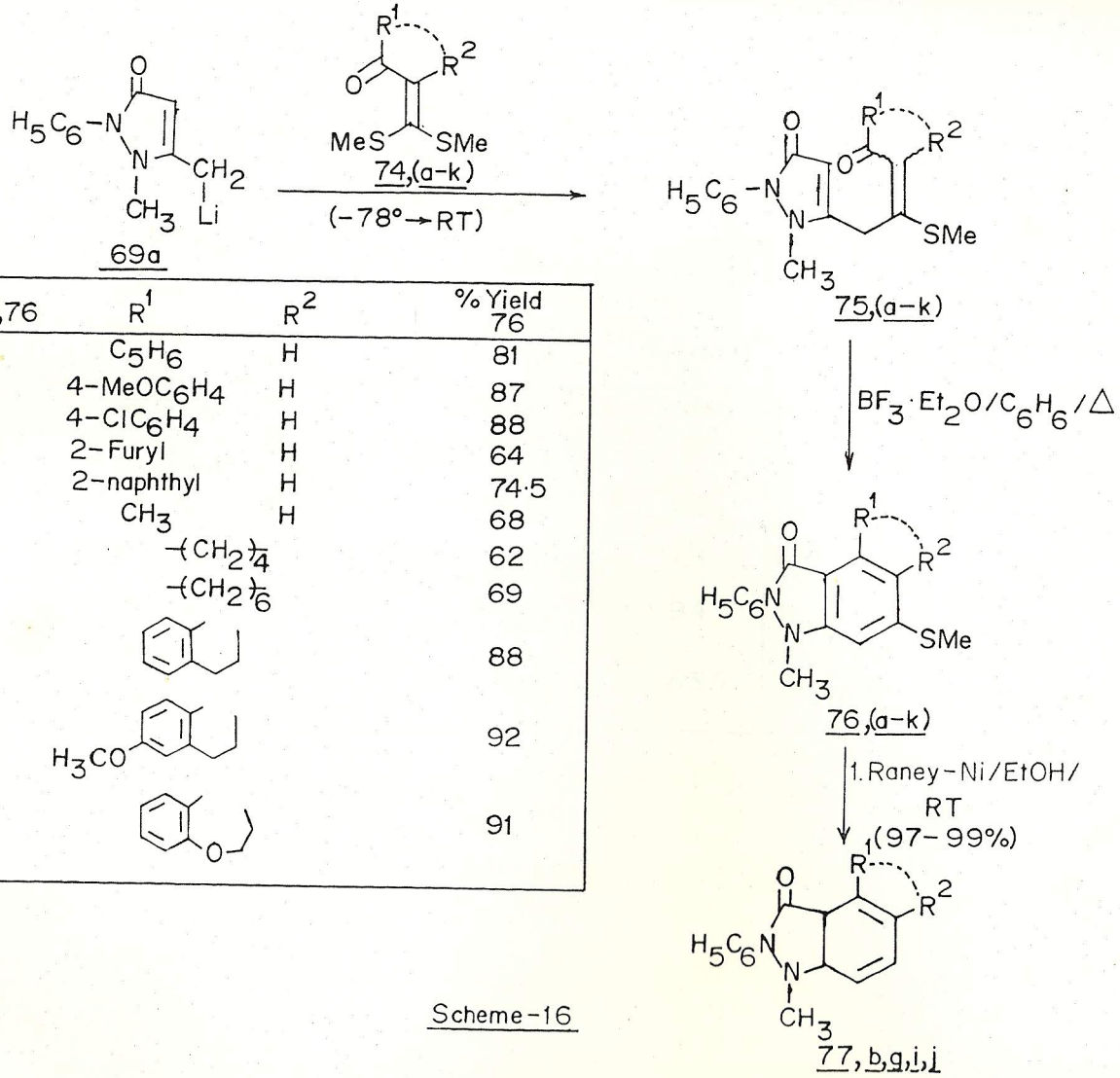


68 69 69a 70 71 72 73

Scheme —14


69a
74
1,2-addition
1,4-addition
elimination
75
77
Cyclization
Cyclization
76
78

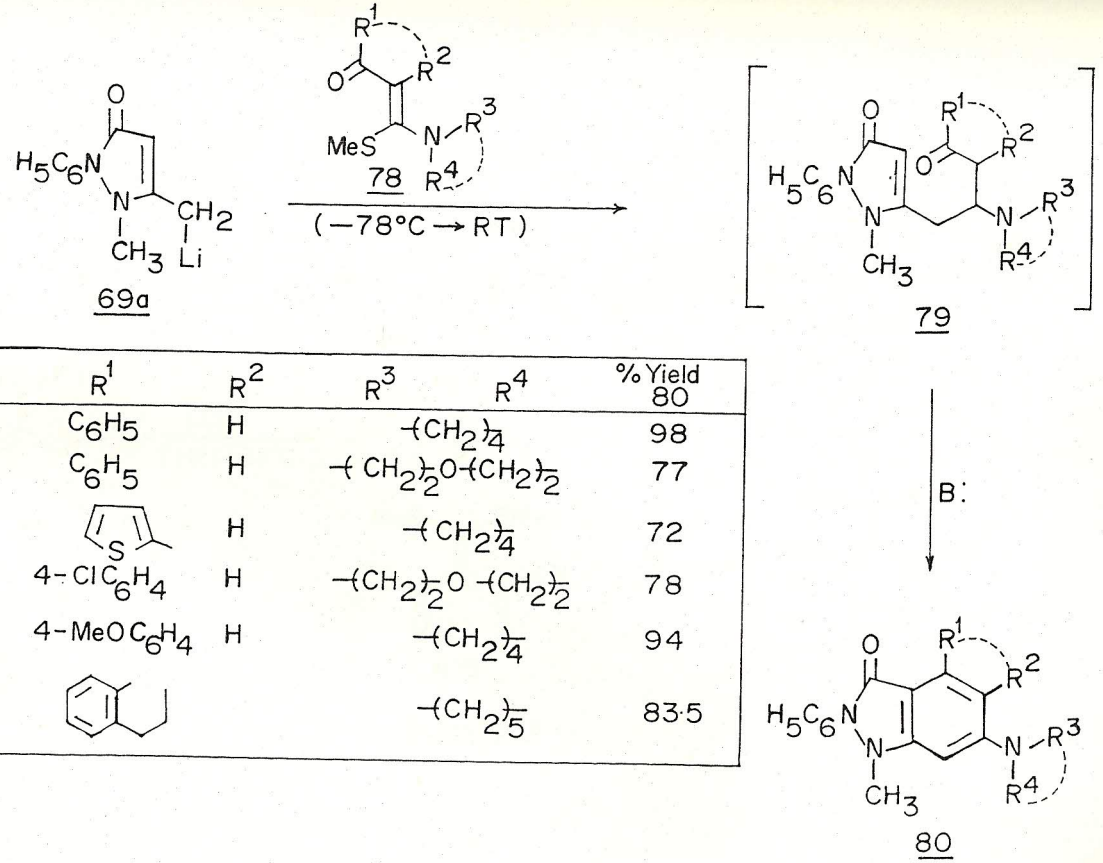
Scheme — 15



69a

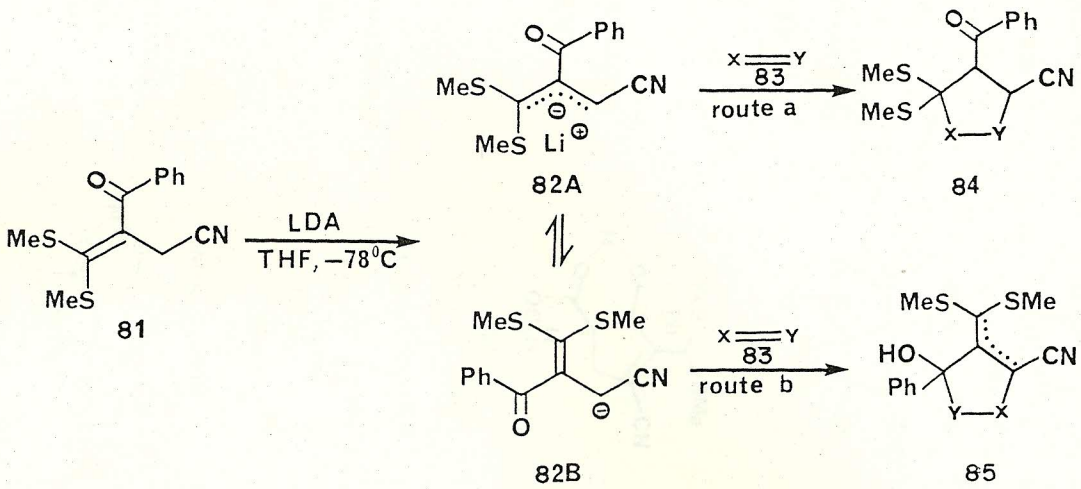
74,75,76	R^1	R^2	% Yield 76
a	C_5H_6	H	81
b	4-$MeOC_6H_4$	H	87
c	4-ClC_6H_4	H	88
d	2-Furyl	H	64
e	2-naphthyl	H	74·5
f	CH_3	H	68
g	$-(CH_2)_4-$		62
h	$-(CH_2)_6-$		69
i			88
j			92
k			91

Scheme-16



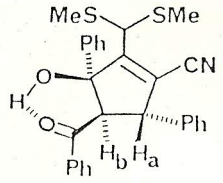
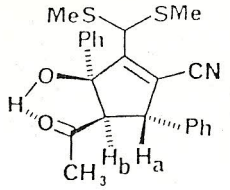
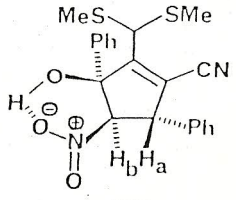
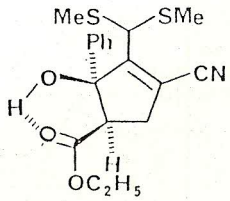
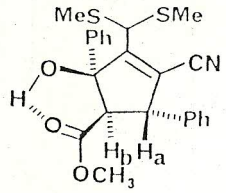
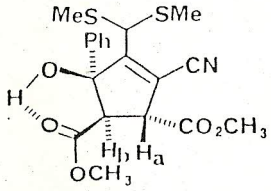
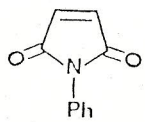
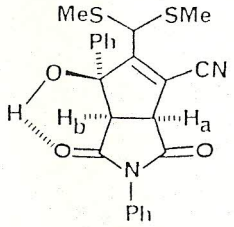
78,79,80	R^1	R^2	R^3 R^4	% Yield 80
a	C_6H_5	H	$-(CH_2)_4-$	98
b	C_6H_5	H	$-(CH_2)_2O(CH_2)_2-$	77
c		H	$-(CH_2)_4-$	72
d	4-ClC_6H_4	H	$-(CH_2)_2O(CH_2)_2-$	78
e	4-$MeOC_6H_4$	H	$-(CH_2)_4-$	94
f			$-(CH_2)_5-$	83·5

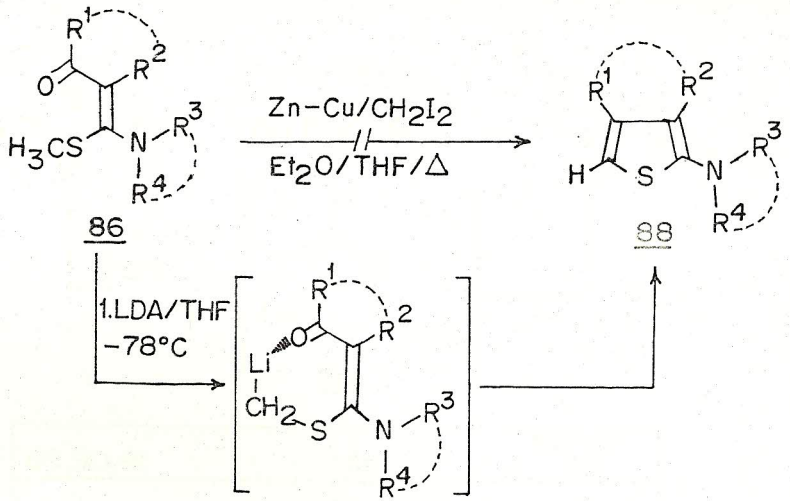
Scheme–17


Ph
MeS
CN
MeS
81
LDA
THF, −78°C
Ph
MeS
CN
MeS Li⊕
82A
X=Y
83
route a
Ph
MeS
CN
MeS
X—Y
84
MeS
SMe
Ph
CN
O
82B
X=Y
83
route b
MeS
SMe
HO
CN
Ph
Y—X
85

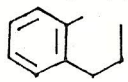
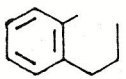
Scheme-18

Table Synthesis of Cyclopentene Derivatives

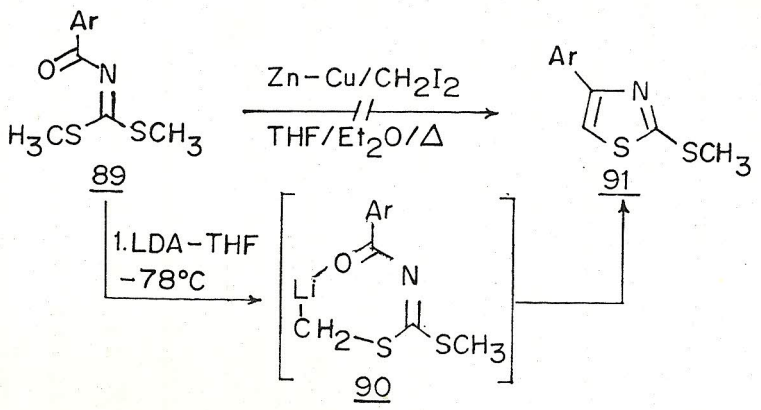
Entry	Dienophile	Product	%Yield	m.p(°C)
1.	$C_6H_5CH=CHCOC_6H_5$ **83a**	 **85a**	88	162-163
2.	$C_6H_5CH=CHCOCH_3$ **83b**	 **85b**	61	167-168
3.	$C_6H_5CH=CHNO_2$ **83c**	 **85c**	66	148-150
4.	$CH_2=CHCO_2Et$ **83d**	 **85d**	75	93-94
5.	$C_6H_5CH=CHCO_2Me$ **83e**	 **85e**	71	164-165
6. 7.	$MeO_2CCH=CHCO_2Me$ **83f**, *E* **83g**, *Z*	 **85f**	72	146-148
8.		 **85g**	65	-



86 88 87

86,87,88	R^1	R^2	R^3 R^4	%Yield 87
a	C_6H_5	H	$-(CH_2)_5-$	52
b	C_6H_5	H	$-(CH_2)_2O(CH_2)_2-$	52
c	C_6H_5	H	Et	48
d	4-$MeOC_6H_4$	H	$-(CH_2)_4-$	69
e			$-(CH_2)_4-$	71
f			$-(CH_2)_5-$	52

Scheme-19



89,90,91	Ar	% Yield 90
a	C_6H_5	74
b	4-MeC_6H_4	68
c	2-ClC_6H_4	70·5

Scheme-20

pathways: In route a, where the Michael-induced ring closure (MIRC) involving Tandem Michael addition was not considered of stereo electronically favourable route since it involved 5-*Endo Trig* ring closure which is disfavoured. However, in route b, the anion behaves as having bis(methylthio)mercapto functionality as trimethylene methane (TMM) equivalents which are excellently suited for Tandem Michael followed by aldol addition to afford the corresponding cyclopentanoids (Scheme 18). These precursors were therefore considered equivalents of trimethylene methane (TMM) and should give cyclopentanoid annelation reaction with electron withdrawing olefines. We have examined the reactivity of the anion with various activated olefins under [3+2] cycloaddition conditions and found that the reaction follows route b, in highly stereo- and regioselective manner to yield the cyclopentenes 85 in good yields[80] (Table). The results of these studies are described in this chapter.

In the last chapter, deprotonation of various α-oxoketene S,N-acetals 86 and dimethyl N-aroyl carbimidodithioates 89 were investigated, which resulted in exclusive deprotonation of thiomethyl proton involving heteroatom assisted deprotonation for the synthesis of 4-substituted/3,4-annelated 2-aminothiophenes 88 (scheme 19) and 4-substituted-2-methylthiothiazoles 91 (scheme 20) involving intramolecular aldol type addition-elimination sequence are discussed in detail.

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