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

Abstract

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A B S T R A C T

The α-oxoketene dithioacetals of general formula 1 were first reported by Kelber and co-workers in 1910. Improved mthods for the synthesis of these compounds have been subsequentely developed, and they can now be prepared, often in one pot operation by treating enolate anion with carbondisulphide followed by alkylation. They can also be converted into the corresponding S,N-, N,N- and O,S-acetals, although there are direct methods for the synthesis of S,N-acetals from active methylene compounds. The α-oxoketene dithioacetals possess 1,3-electrophilic centers with a discrete disymmetry in their electrophilic property, which makes these compounds follow regiospecific attack by nucleophiles depending on their nucleophilicity. Their 1,3-electrophilic reactivity has been extensively exploited for the chemo-, stereo- and regioselective construction of new bonds involving either 1,2- or 1,4-nucleophilic addition leading to a diverse product range[1] (scheme 1).

Similarly, the α-oxoketene S,N-acetals exhibit 1,3-electrophilicity substantially inversed so that the β-carbon becomes more electrophilic than the oxo carbon. The nucleophilic ragents therefore preferentially add in the 1,4- fashion, in these systems.

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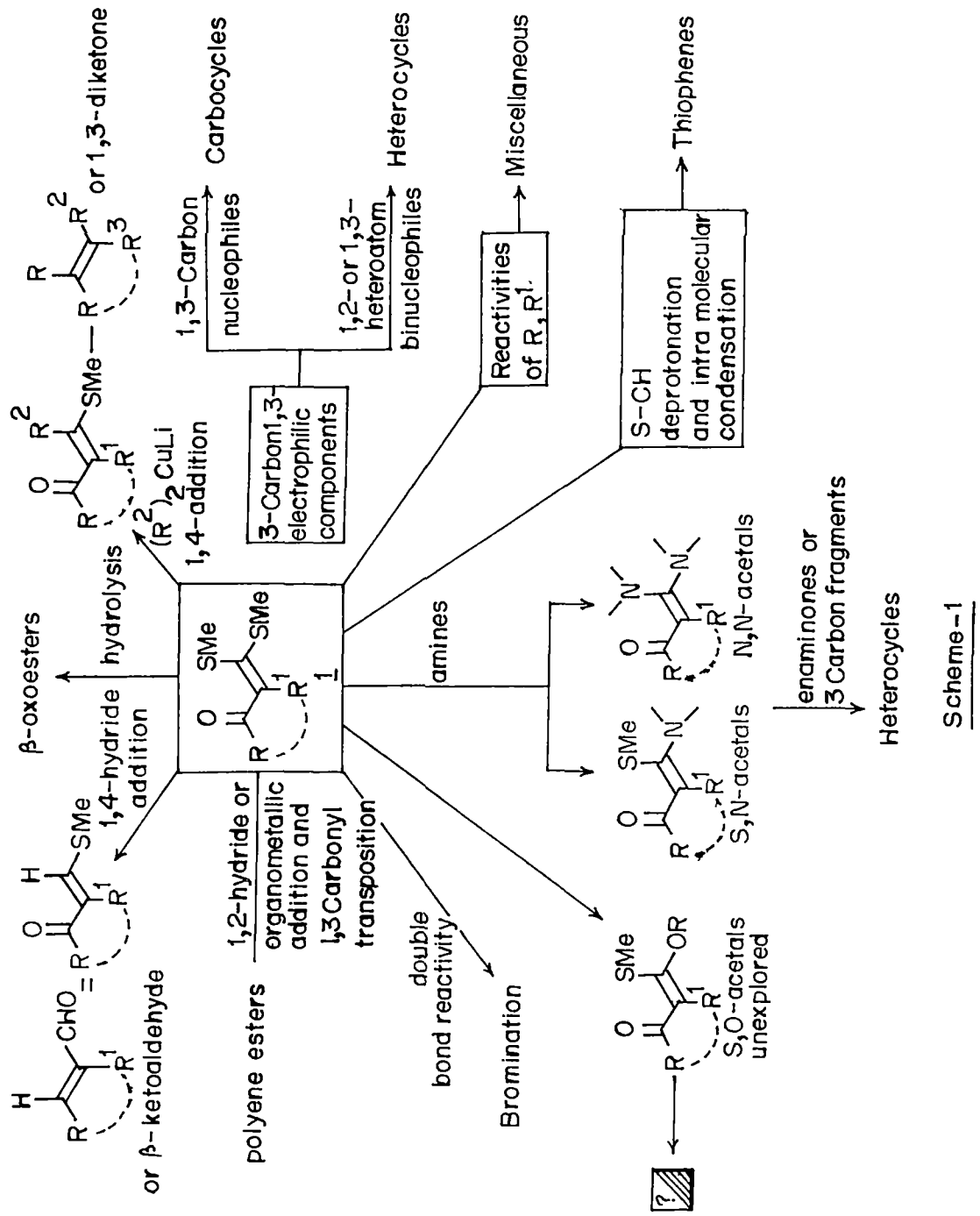
1. Review : Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron*, **1990**, *46*, 5423.


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

Scheme-1

The discriminating 1,3-electrophilicy in the α-oxoketene dithioacetals and the S,N-acetals was exploited in the present investigation as the key theme to develope novel routes for the synthesis of carbocycles, benzoheterocycles and heterocycles. Thus, the α-oxoketene S,S-acetals **3** when reacted with methylpyrolidinocrotonate **1** under the blanket of nitrogen in the presence of LDA-TMEDA complex at -110°C, crude carbinol **4** was obtained (showing γ-1,2-regioselectivity). Which on further treatment with $BF_3.Et_2O$ in refluxing benzene yielded amino aromatics **5** in moderate to good yields[2] (scheme 2, 3 & 4). Interestingly, the cyclic variant of oxoketene dithioacetal **3j** derived from α-tetralone reacted with **2** not in the same manner to yield the corresponding methyl (5,6-dihydro-4-methylthio-2H-naphtho[1,2-b] pyran-2-ylidene)acetate **7** in good yield (scheme 5) involving γ-1,4-regioselectivity.

The reaction of lithiomethyl pyrrolidino crotonate **2** with S,N-acetals **9** with excess base yielded electron rich aromatic compounds **11** carrying two regiospecifically substituted cyclo alkyl amino groups in good yields (scheme 6 & 7). However, there was one exception, when **2** was added to corresponding diethyl amino S,N-acetal **9f** under the described reaction condition yielded the corresponding carboxylate **13** in moderate yield involving the intermediacy of **12** instead of the expected diethylaminobiphenyl **11f** (scheme 8). Thus the reaction of amino crotonates with both α-oxoketene S,S-acetals and S,N-acetals

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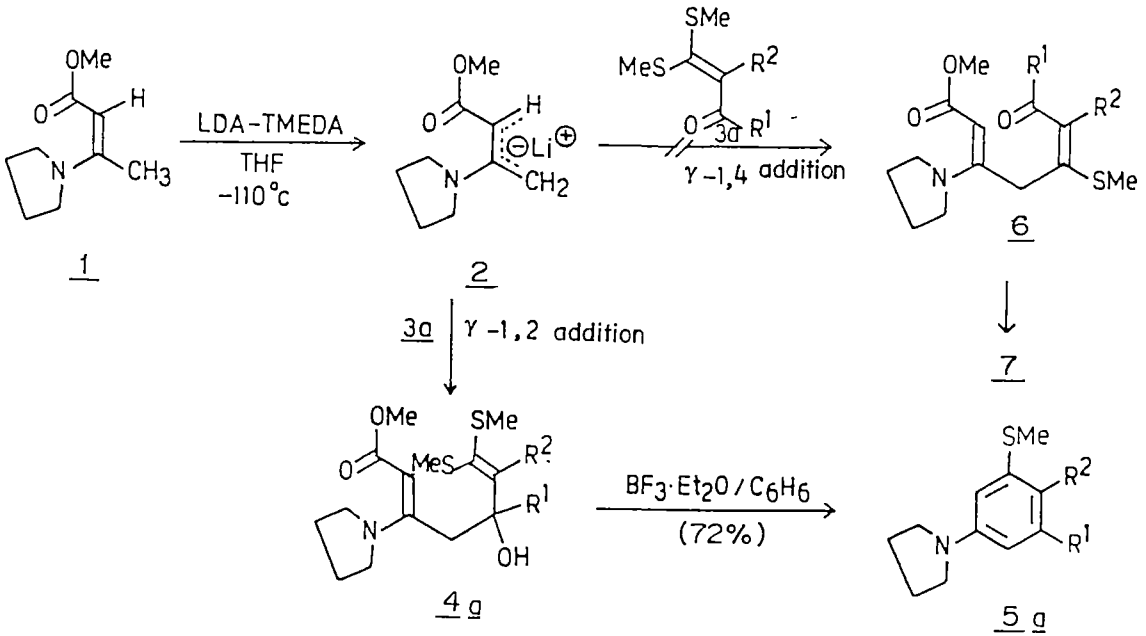
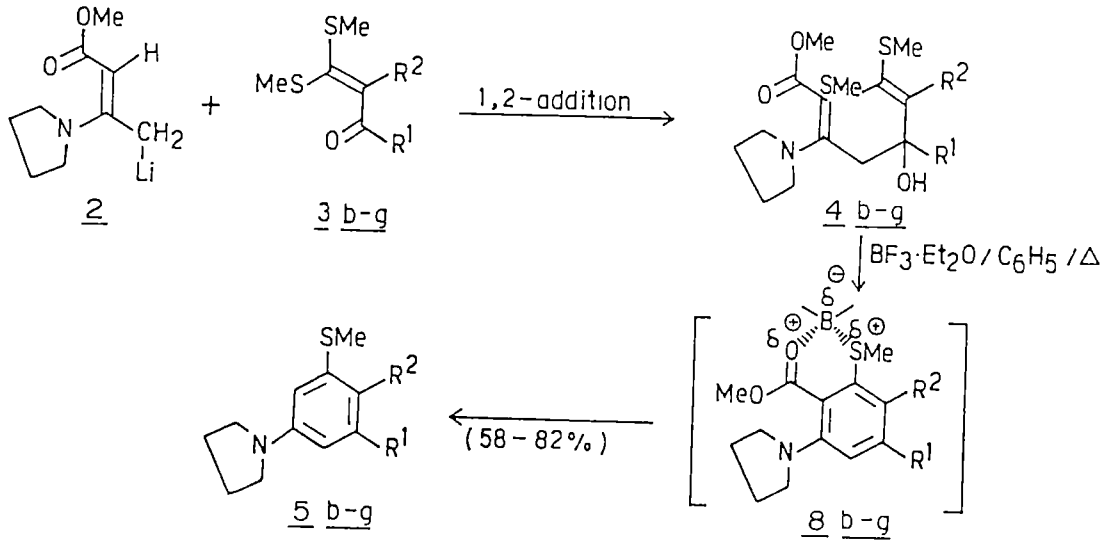
2. Satyanarayana, J.; Reddy, K.R.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 6173.



1 2 3a 4a 5a 6 7

3, 4, 5, a, $R^1 = C_6H_5$; $R^2 = H$

Scheme-2



2 + 3 b-g → 4 b-g → 8 b-g → 5 b-g

3, 4, 8, 5 b, R^1 = 4-ClC_6H_4 ; R^2 = H

c, R^1 = 4-MeO C_6H_4 ; R^2 = H

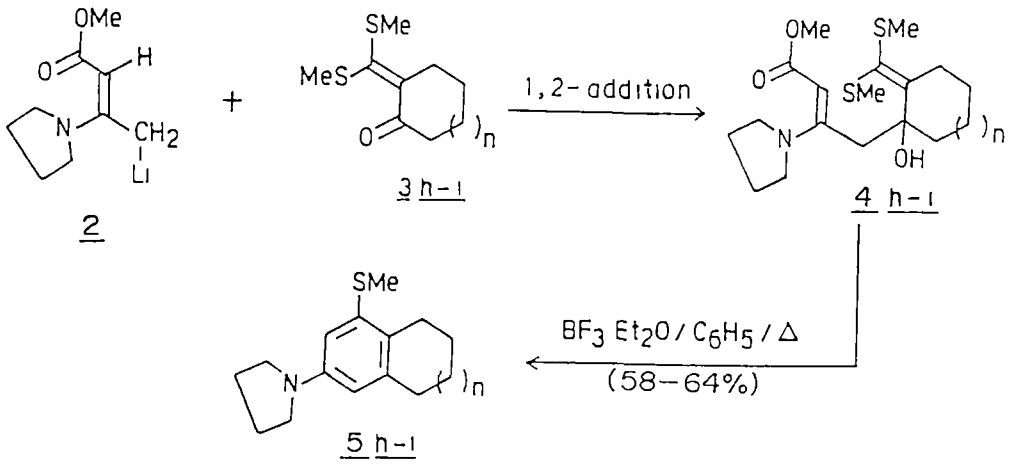
d, R^1 = 2-naphthyl ; R^2 = H

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

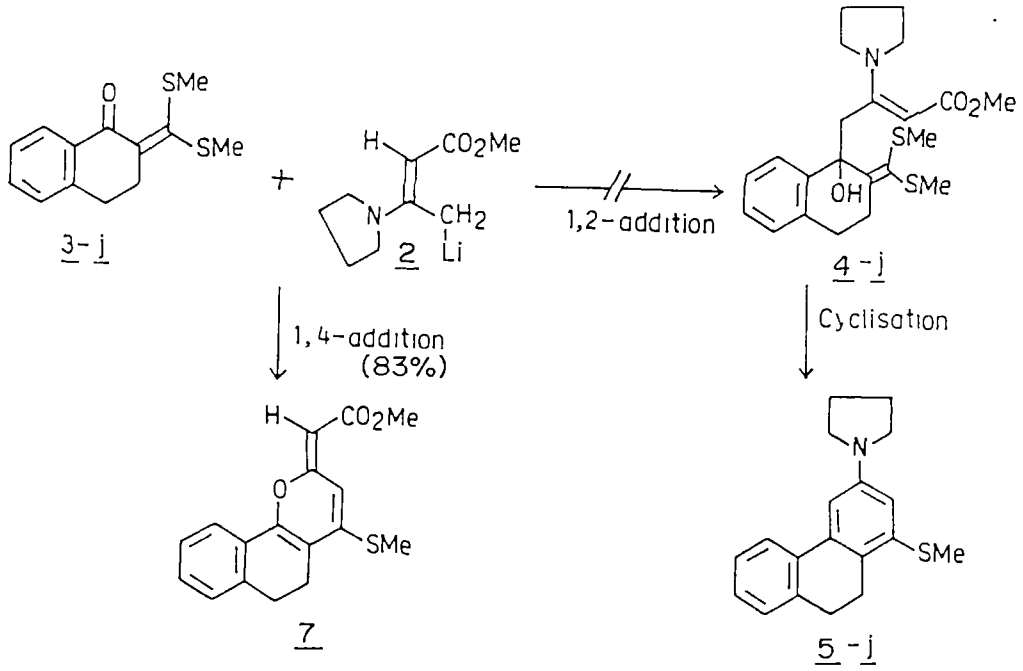
f, R^1 = 2-Thienyl ; R^2 = H

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

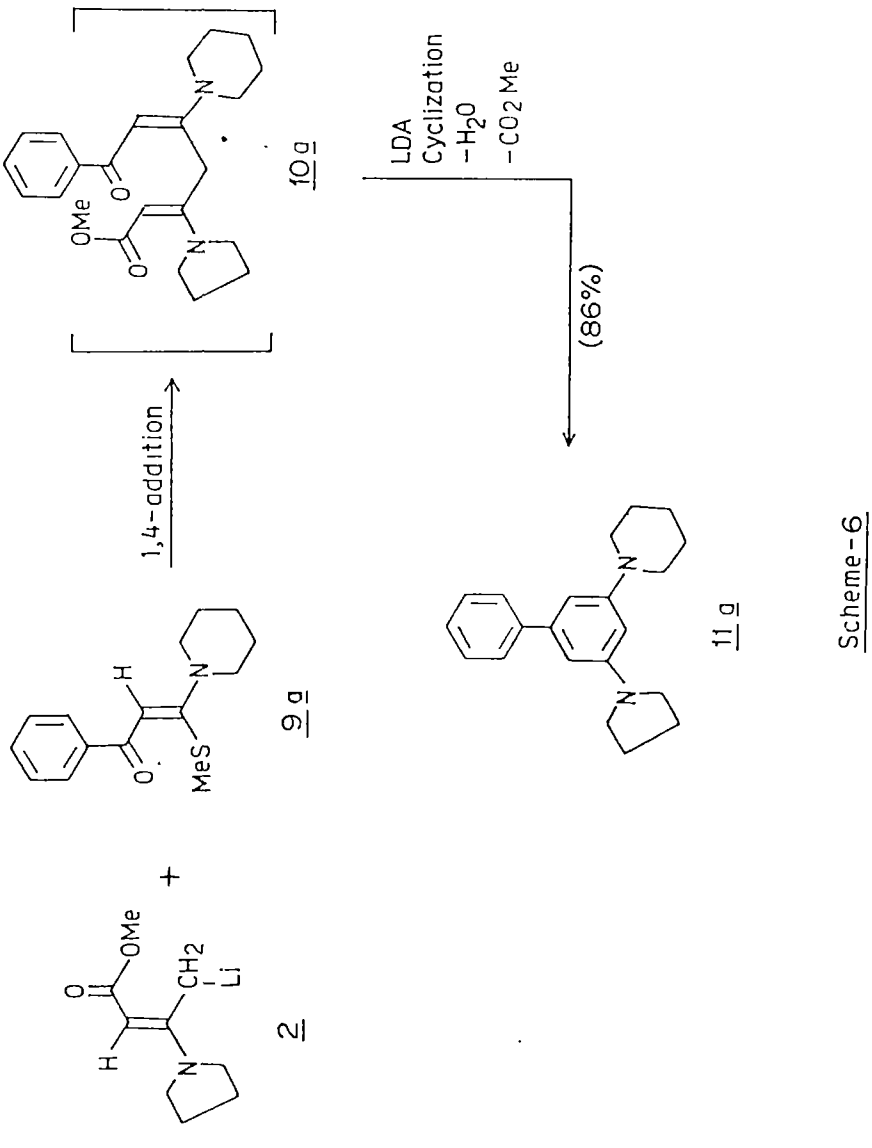
Scheme - 3


OMe
O
H
N
CH2
Li
2
+
SMe
MeS
O
)n
3 h-1
1,2-addition
OMe
SMe
O
SMe
N
OH
)n
4 h-1
SMe
N
)n
5 h-1
BF3 Et2O / C6H5 / Δ
(58–64%)
3, 4, 5, h, n=1
1, n=2

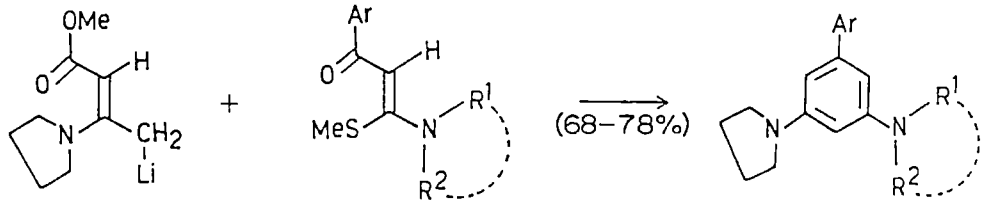
Scheme-4


O
SMe
SMe
3-j
+
H
CO2Me
N
CH2
Li
2
1,2-addition
N
CO2Me
SMe
OH
SMe
4-j
1,4-addition
(83%)
Cyclisation
H
CO2Me
O
SMe
7
N
SMe
5-j

Scheme - 5


OMe
CH2
Li
2
9 a
MeS
1,4-addition
10 a
OMe
LDA
Cyclization
-H2O
-CO2 Me
(86%)
11 a

Scheme-6

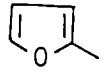


2 + 9 b-e ⟶ 11 b-e

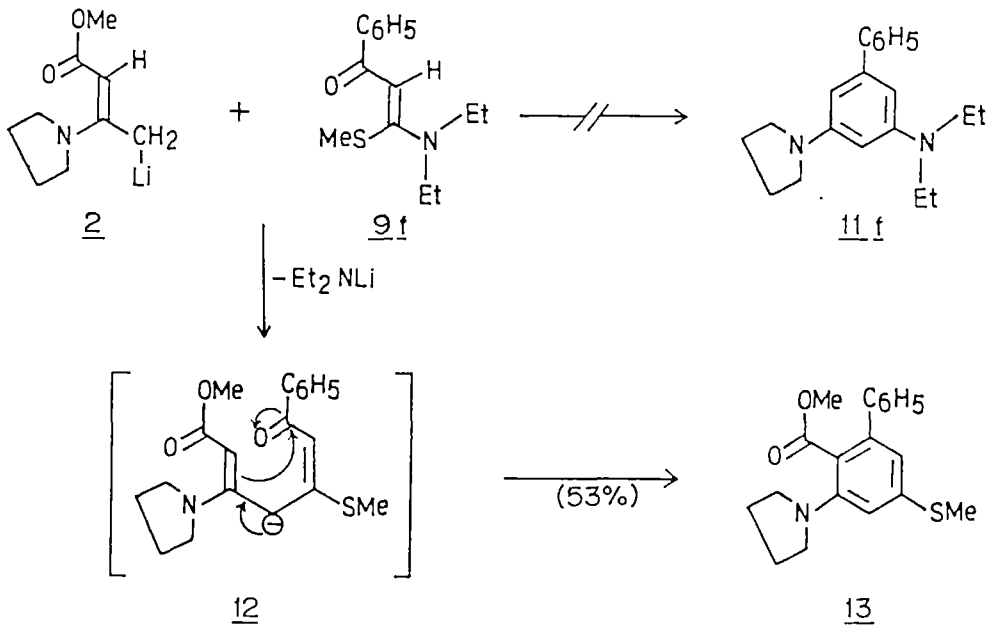
9, 11, b, Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_4-$

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-7


OMe
H
O
N
CH2
Li
2
+
C6H5
H
O
MeS
N
Et
Et
9f
C6H5
N
Et
N
Et
Et
11f
-Et2 NLi
OMe
C6H5
O
O
N
SMe
12
(53%)
OMe
C6H5
O
N
SMe
13

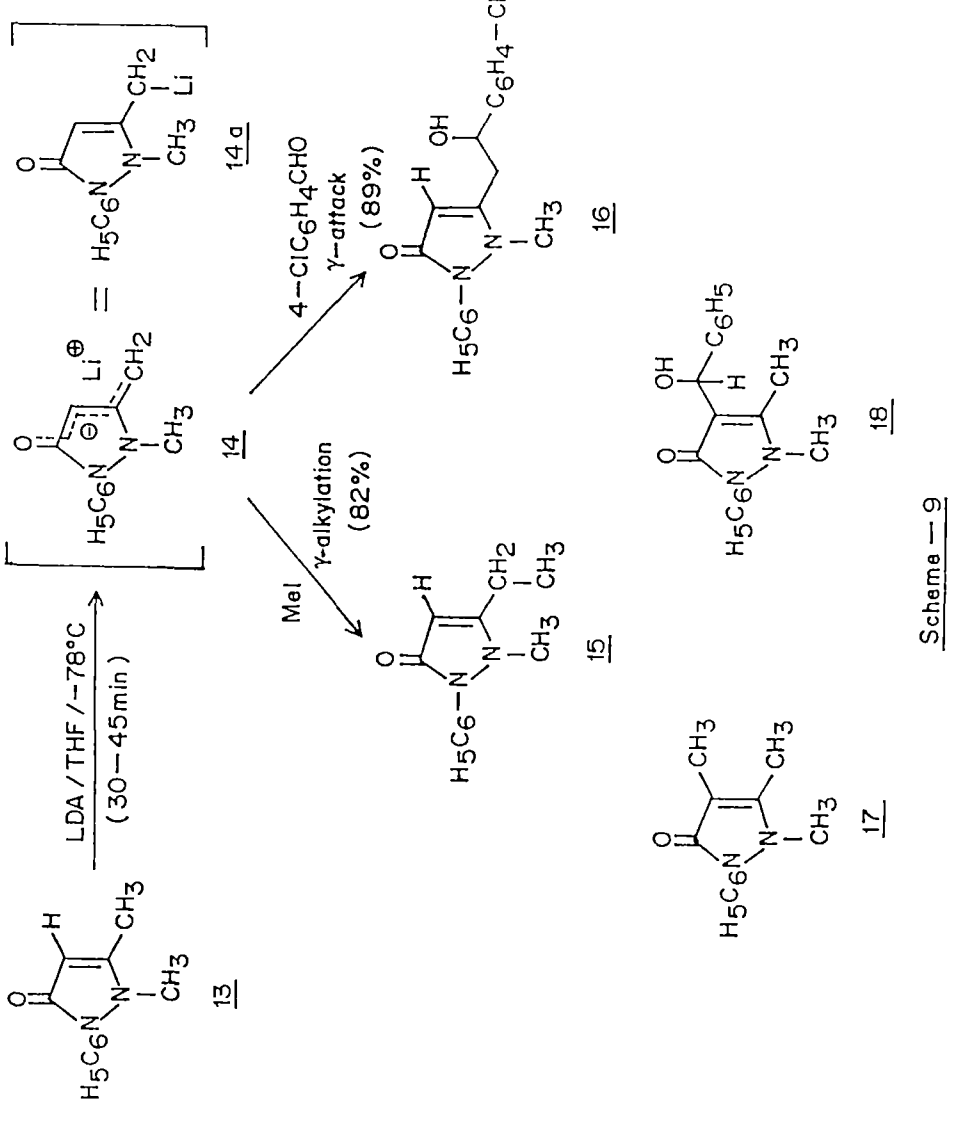
Scheme - 8

display diverse reaction mode to afford the corresponding aromatic rings. And the structural diversity is largely dependent on the amino crotonate anion, depending on the nature of secondary amine used as well as the nature of amine in S,N-acetals also.

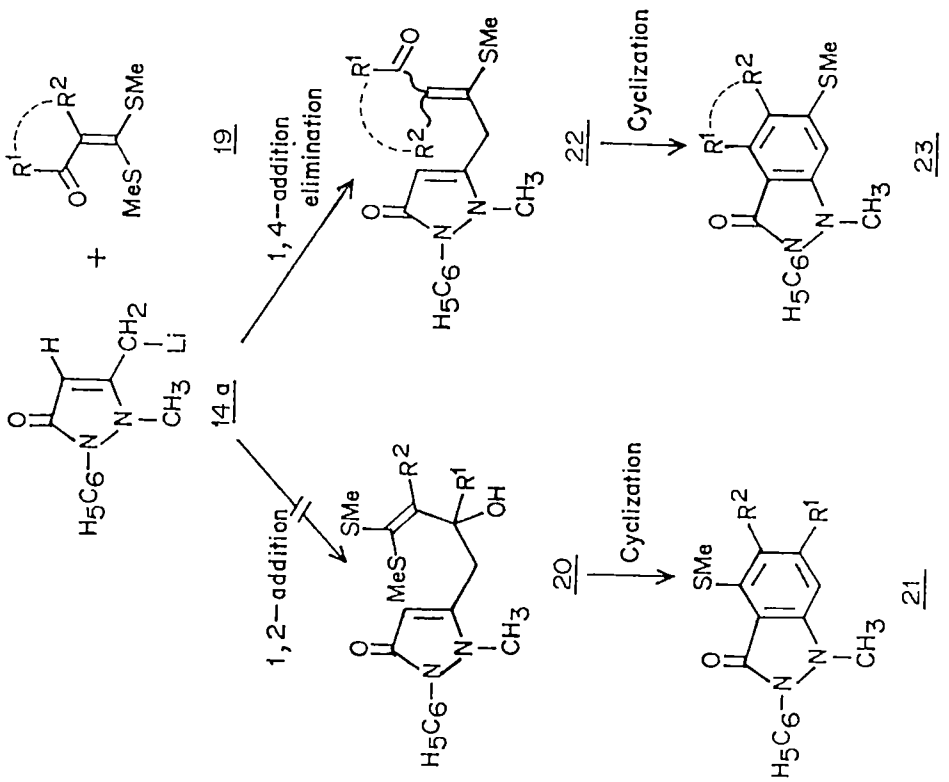
The heteroaromatic annelation methodology is well explained for the synthesis of hitherto unreported 1,2-disubstituted indazolones and their condensed analogs. Some preliminary reactions of **14** were examined with different electrophiles to assess the formation of **14a** and the regioselectivity towards various electrophiles. Thus **14a** on reaction with iodomethane, the corresponding 1,2-dihydro-1-phenyl-2-methyl-3-ethyl pyrazolin-5-one **15** was obtained in good yield. It was also reacted with p-chlorobenzaldehyde to afford the corresponding γ-secondary alcohol **16** in good yield (scheme 9).

It is interesting to note that the isomeric alkylated product **17** expected from α-alkylation and the corresponding carbinol **18** expected from α-1,2-addition were not detected in the reaction mixture. Thus the anion **14** displayed exclusively γ-regioselectivity in its reaction with electrophiles (scheme 9).

When **14a** was reacted with **19** under the identical conditions and the crude adducts **22** were as such subjected to cyclization with $BF_3.Et_2O$ without any purification to afford the corresponding 1,2,4-trisubstituted-6-methylthio-3H-indazol-3-one **23** in moderate to good yields (scheme 10). In none of these reaction, formation of regioisomeric products **21** (through γ-1,2-addition of **14** to **19**) was observed (scheme 10).


LDA / THF / −78°C
(30−45 min)
MeI
γ-alkylation
(82%)
4−ClC6H4CHO
γ-attack
(89%)
13
14
14a
15
16
17
18

Scheme — 9


1,4-addition
elimination
1,2-addition
Cyclization
Cyclization
19
14a
20
21
22
23

Scheme—10

The reaction of **14a** with various acyclic α-oxoketene dithioacetals **19a-f** yielded the correspodning 1,2-dihydro-1,2,4-trisubstituted-6-methylthio-3H-indazol-3-one **23a-f** in moderate to good yields (scheme 11). Cyclic α-oxoketene dithioacetals **19g-k** similarly yielded the one regio isomer (angularly fused indazolone) **23g-k** (scheme 11) although, two regioisomers (linearly and angularly fused indazolones) are plossible. Thus the anion **14** showed exclusive γ -1,4-regioselectivity in its reaction with various α-oxoketene dithioacetals. Versatility and scope of benzoannelation methodology was further demonstrated by reacting **14a** with various S,N-acetals to introduce tertiary amino group at 6-position in indazolone ring. Thus anion **14a** when reacted with various α-oxoketene S,N-acetals **25a-f** in the presence of excess LDA at -78°C the intermediate -1,4-adduct **26** were not observed instead the corresponding 6-amino-3H-indazol-3-one **27a-f** were formed in good yields (scheme 12).

When various activated olifines **30** reacted with anion **29** derived from bifunctional ketene S,S-acetal yielded the functionalized cyclopentenes **32** in highly stereo- and regioselective manner in good yield[3] (Table). In principle such anionic cyclo addition should follow one of the following pathways: In route a, where the Michael-induced ring closure (MIRC) involving Tandem Michael additions was not considered of stereoelectronically favourable route it involved *5-Endotrig* ring closure which is disfavoured. However, in route b, the anion behaves as having

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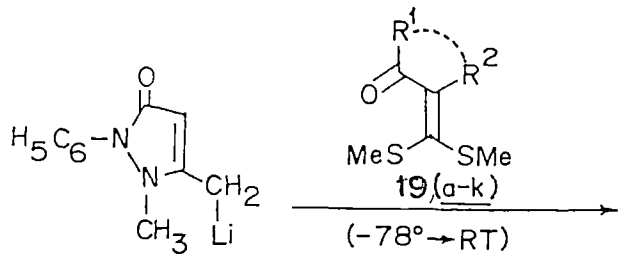
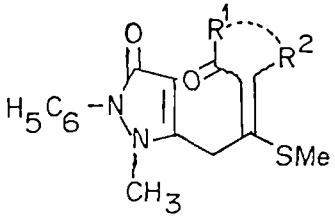
3. Reddy, K.R.; Singh, L.W.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin Trans.I*, **1994**, 2439.



14 a

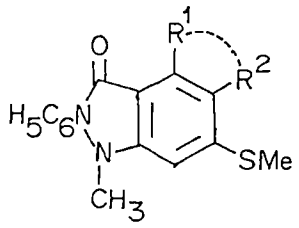
19,(a-k)

(-78°→RT)



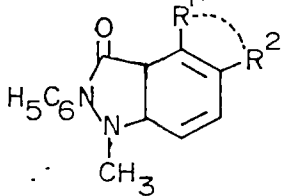
22,(a-k)

$BF_3 \cdot Et_2O/C_6H_6/\Delta$

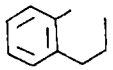
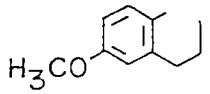
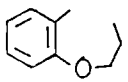


23,(a-k)

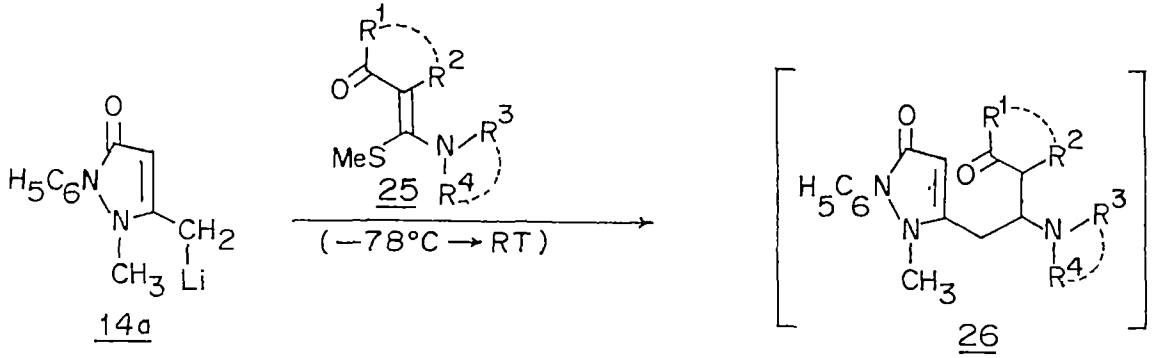
1. Raney-Ni/EtOH/ RT (97-99%)

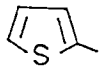
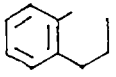


24, b,g,i,j

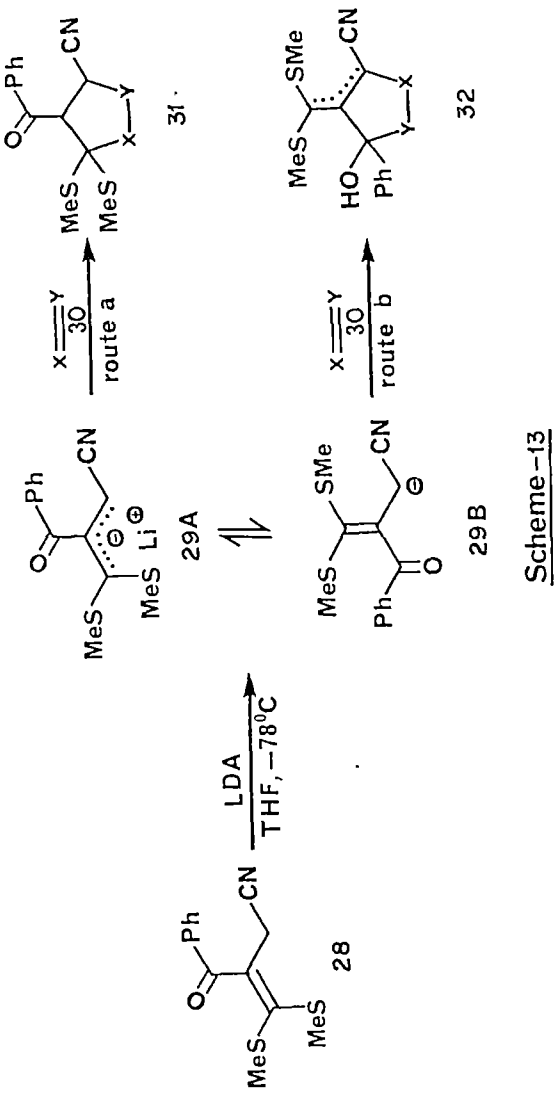
19,22,23	R^1	R^2	% Yield 76
a	C_5H_6	H	81
b	4-$MeOC_6H_4$	H	87
c	4-ClC_6H_4	H	88
d	2-Furyl	H	64
e	2-naphthyl	H	74·5
f	CH_3	H	68
g	$-(CH_2)_4-$		62
h	$-(CH_2)_6-$		69
i			88
j			92
k			91

Scheme-11



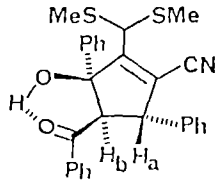
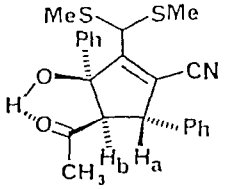
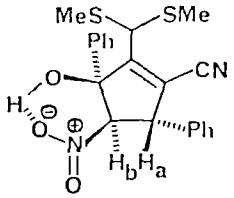
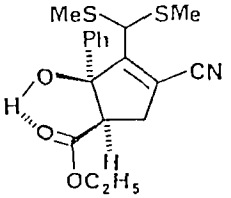
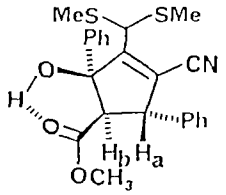
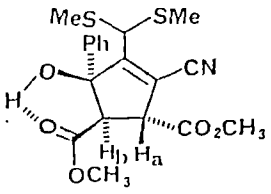
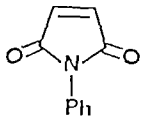
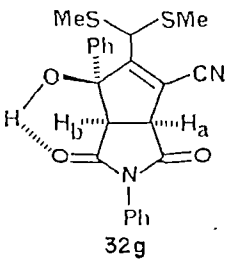
25,26,27	R^1	R^2	R^3 R^4	% Yield 80
a	C_6H_5	H	$-(CH_2)_4-$	98
b	C_6H_5	H	$-(CH_2)_2O(CH_2)_2-$	77
c		H	$-(CH_2)_4-$	72
d	4-ClC_6H_4	H	$-(CH_2)_2O(CH_2)_2-$	78
e	4-MeOC_6H_4	H	$-(CH_2)_4-$	94
f			$-(CH_2)_5-$	83·5

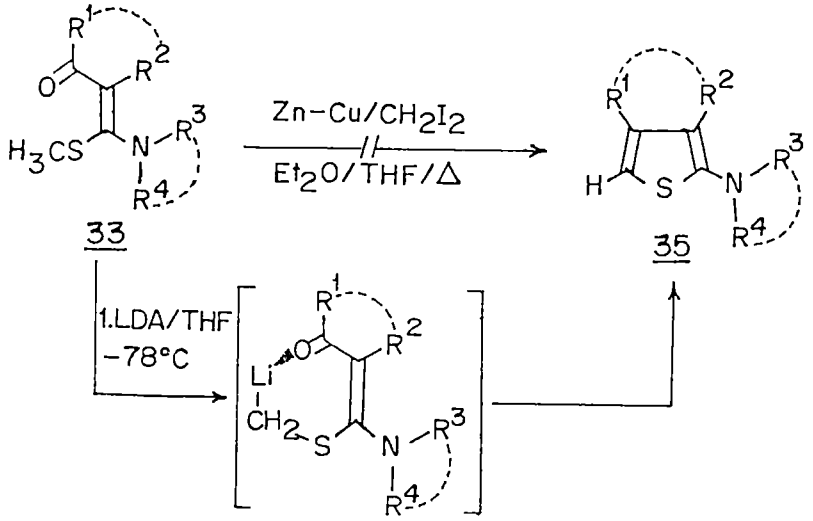
Scheme–12


Ph
O
CN
MeS
MeS
28
LDA
THF, −78°C
MeS Li⊕
29A
29B
route a
route b
30
31
32
SMe
HO

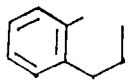
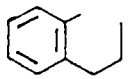
Scheme-13

Table Synthesis of Cyclopentene Derivatives

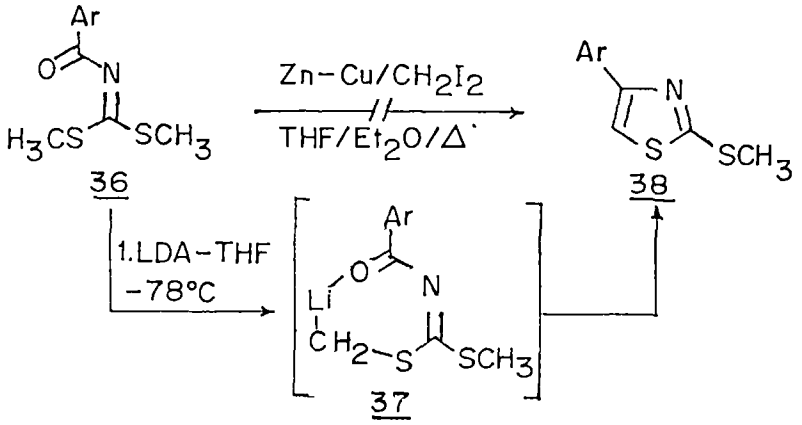
Entry	Dienophile	Product	%Yield	m.p(°C)
1.	$C_6H_5CH=CHCOC_6H_5$ 30a	 32a	88	162-163
2.	$C_6H_5CH=CHCOCH_3$ 30b	 32b	61	167-168
3.	$C_6H_5CH=CHNO_2$ 30c	 32c	66	148-150
4.	$CH_2=CHCO_2Et$ 30d	 32d	75	93-94
5.	$C_6H_5CH=CHCO_2Me$ 30e	 32e	71	164-165
6. 7.	$MeO_2CCH=CHCO_2Me$ 30f, *E* 30g, *Z*	 32f	72	146-148
8.		 32g	65	-



33 34 35

33,34,35	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-14



36,37,38	Ar	% Yield 90
a	C_6H_5	74
b	4-MeC_6H_4	68
c	2-ClC_6H_4	70·5

Scheme-15

bis(methylthio)mercapto functionality as trimethylene methane (TMM) equivalents which are excellently suited for Tandem Michael followed by aldol addition to afford the corresponding cyclopentenoids. These precursors were therefore considered equivalents of trimethylene methane (TMM) and should give cyclopentanoid annelation reaction with electron withdrawing olefines (scheme 13).

With a view to synthesis aminothiophenes and methylthiothiazoles various α-oxoketene S,N-acetals 33 and dimethyl N-aroylcarbimidodithioates 36 were subjected to Simmon-Smith condition. It was observed that the starting materials remained unchanged even after prolonged exposure to Simmon-Smith reagent. Interestingly under base condition (Lithium diisopropyl amide-LDA) at -78°C yielded the corresponding 2-aminothiophenes 35 and 2-methylthiothioazoles 38 in moderate to good yields (scheme 14 & 15). Involving the heteroatom assisted deprotonation of thiomethylproton which underwent intramolecular aldol type addition elimination sequence.

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

BY

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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 INDIA
1994

Dedicated

To

My Beloved Late Uncle

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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.

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Research Supervisor

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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

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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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Finally, I thank all my family members, near and dear ones for their consistent support, patience and moral boost during my research.

Shillong,
December 1994

(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.

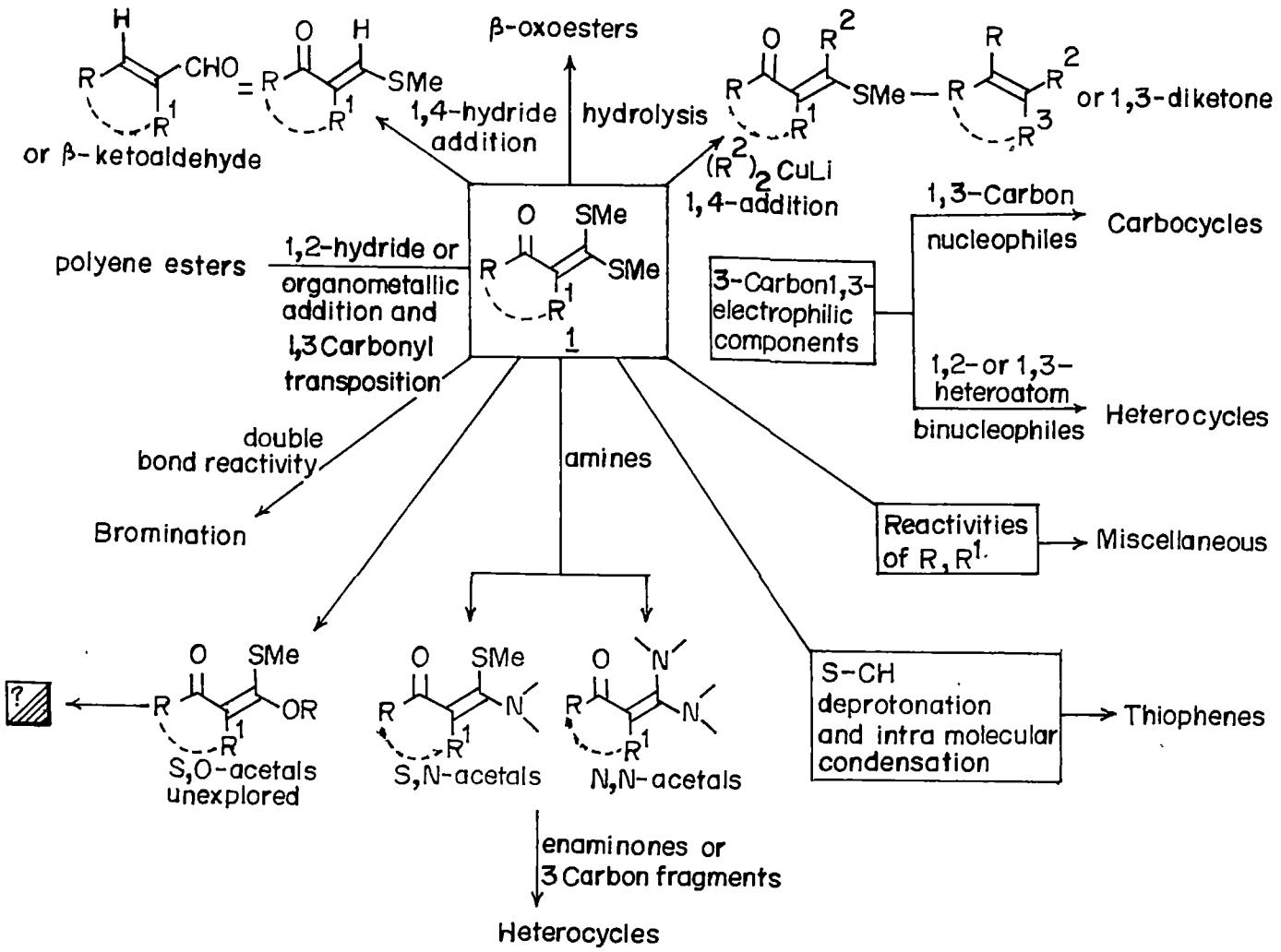
In 1910 Kelber and co-workers[10,11] reported the first synthesis of α-oxoketene dithioacetals. Much of the earlier works on oxoketene dithioacetals were confined to their preparation and properties, while little attention was paid for their synthetic utility. Hence, more than half a century the synthetic 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

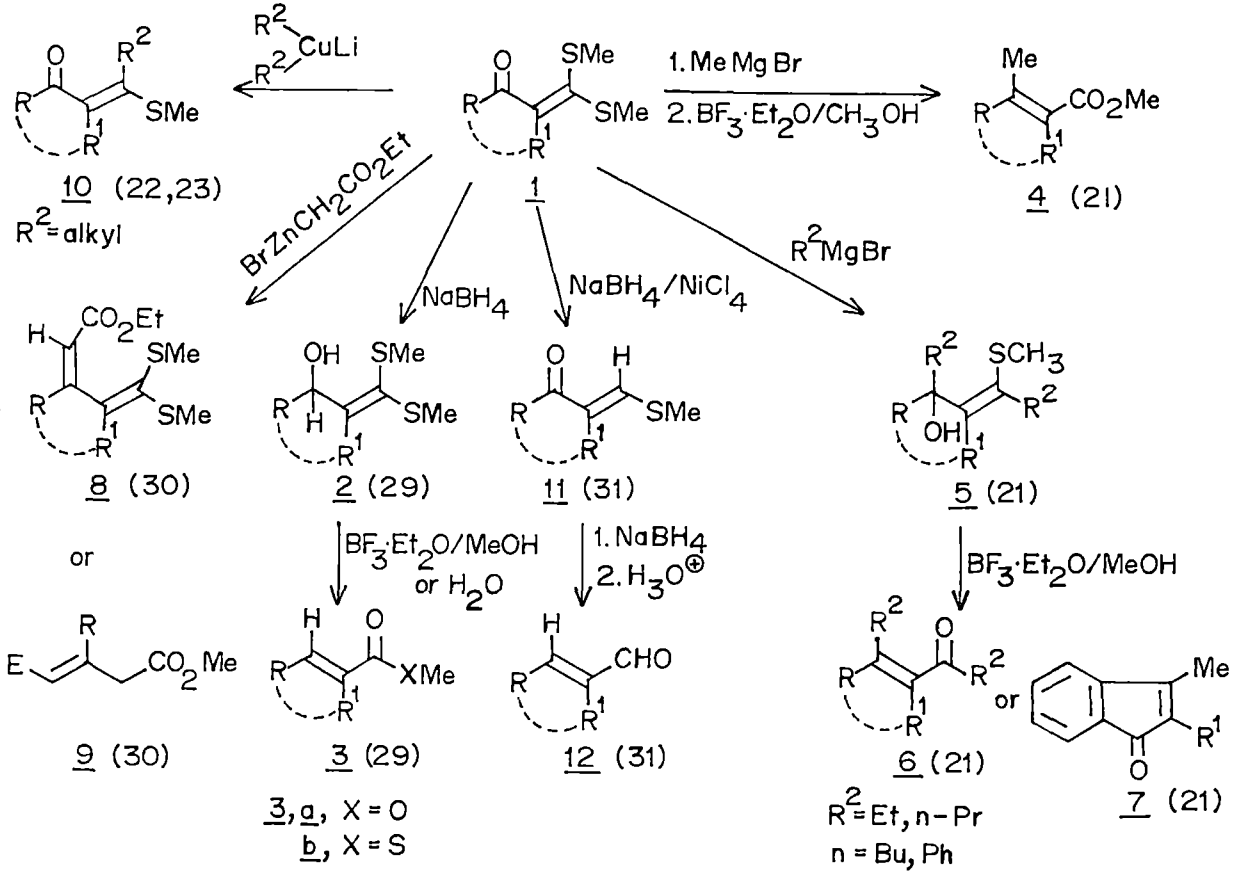

β-oxoesters
or β-ketoaldehyde
1,4-hydride addition
hydrolysis
or 1,3-diketone
(R2)2CuLi
1,4-addition
1,3-Carbon nucleophiles
Carbocycles
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
3-Carbon 1,3-electrophilic components
1,2-or 1,3-heteroatom binucleophiles
Heterocycles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

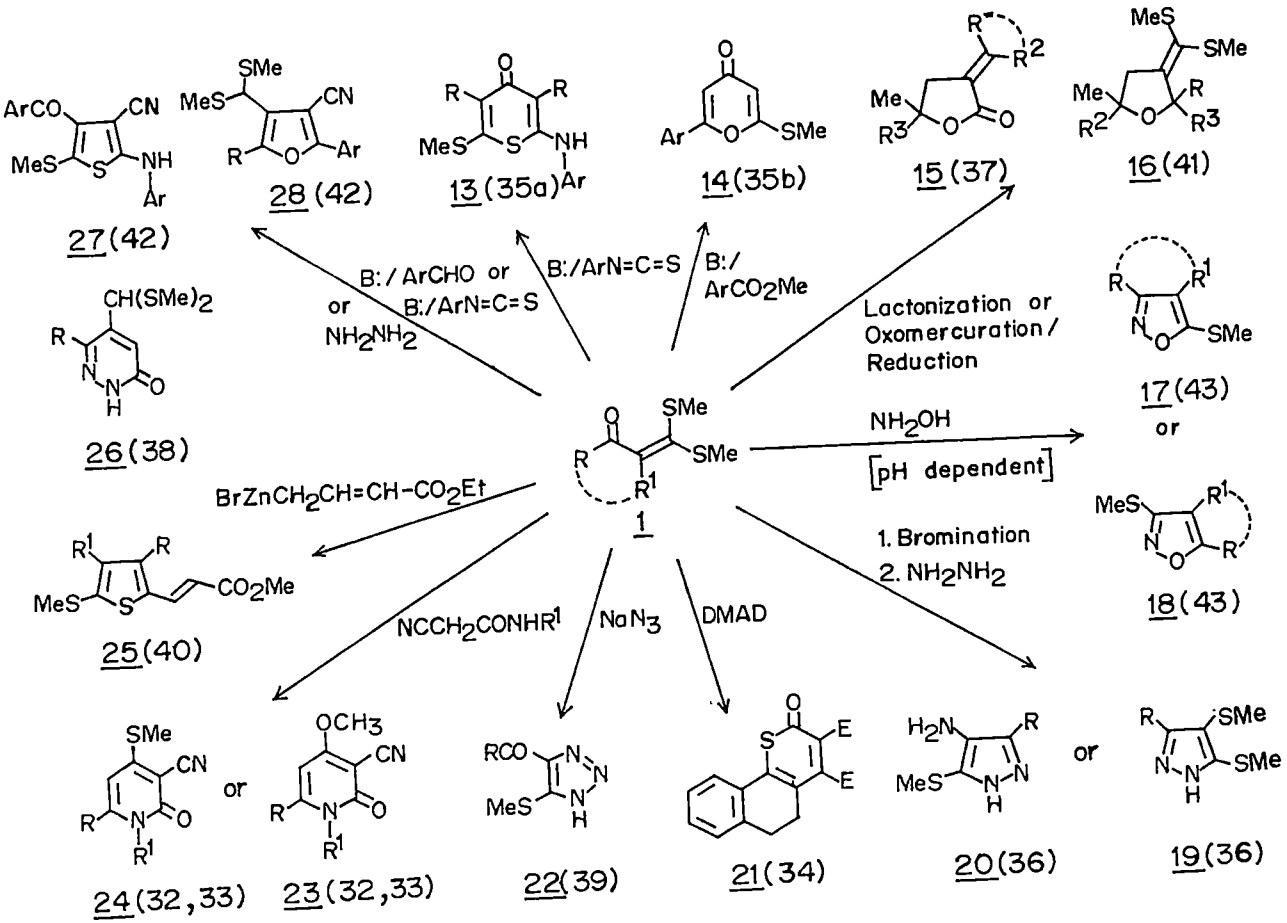

R2CuLi
1. MeMgBr
2. BF3·Et2O/CH3OH
BrZnCH2CO2Et
NaBH4
NaBH4/NiCl4
R2MgBr
10 (22,23)
R2=alkyl
1
4 (21)
8 (30)
2 (29)
11 (31)
5 (21)
or
BF3·Et2O/MeOH
or H2O
1. NaBH4
2. H3O⊕
BF3·Et2O/MeOH
9 (30)
3 (29)
12 (31)
3, a, X=O
b, X=S
6 (21)
R2=Et, n-Pr
n=Bu, Ph
or
7 (21)

Scheme-2

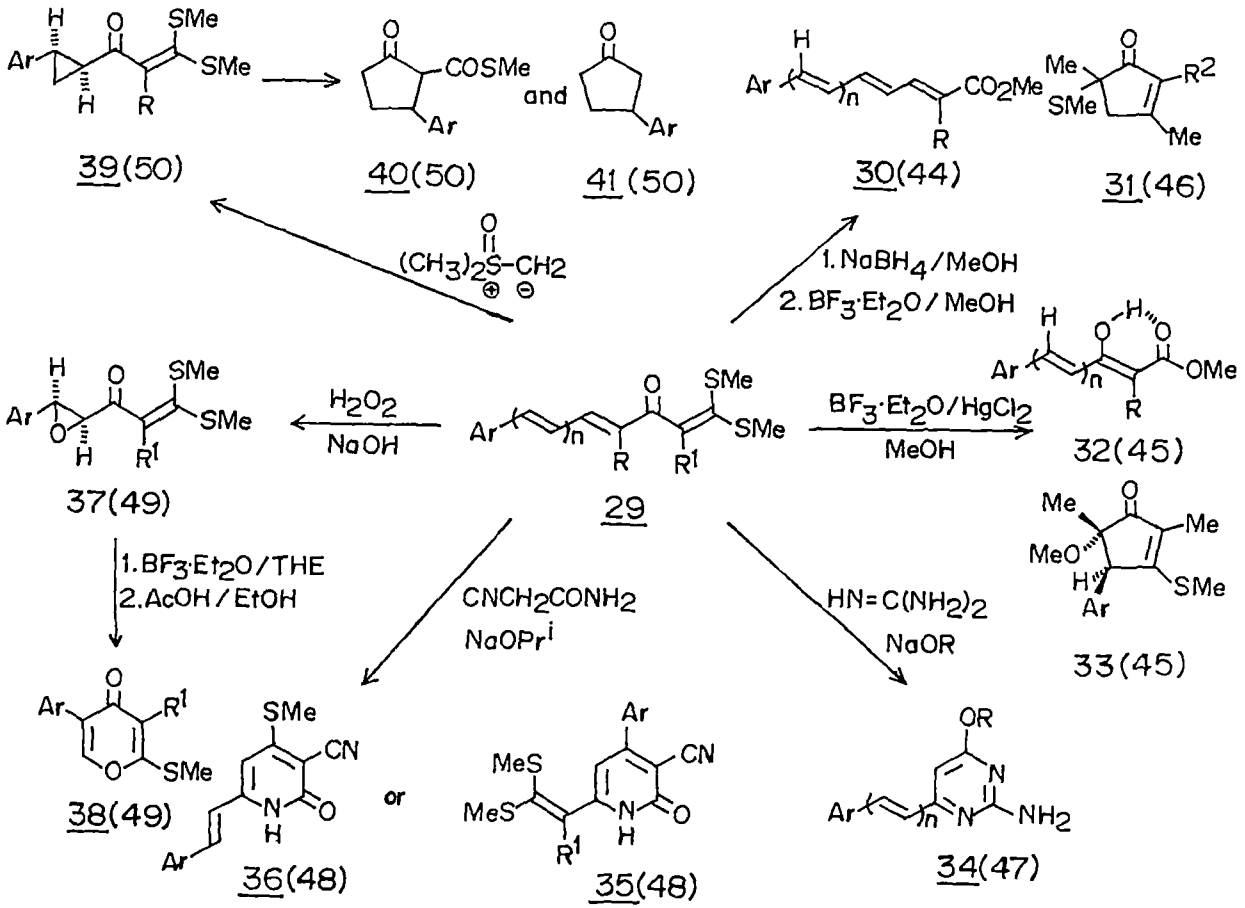
either β-substituted α,β-unsaturated esters **4** or the corresponding ketene **6**[21] (scheme 2) in good yields. However, when the R is alkyl or aryl group the open chain cinnamates were not formed, instead the corresponding 2,3-disubstituted indenones **7** were formed[21]. The Reformatsky reaction 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)
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]
1. Bromination
2. NH2NH2
BrZnCH2CH=CH-CO2Et
NCCH2CONHR1
NaN3
DMAD
or
or

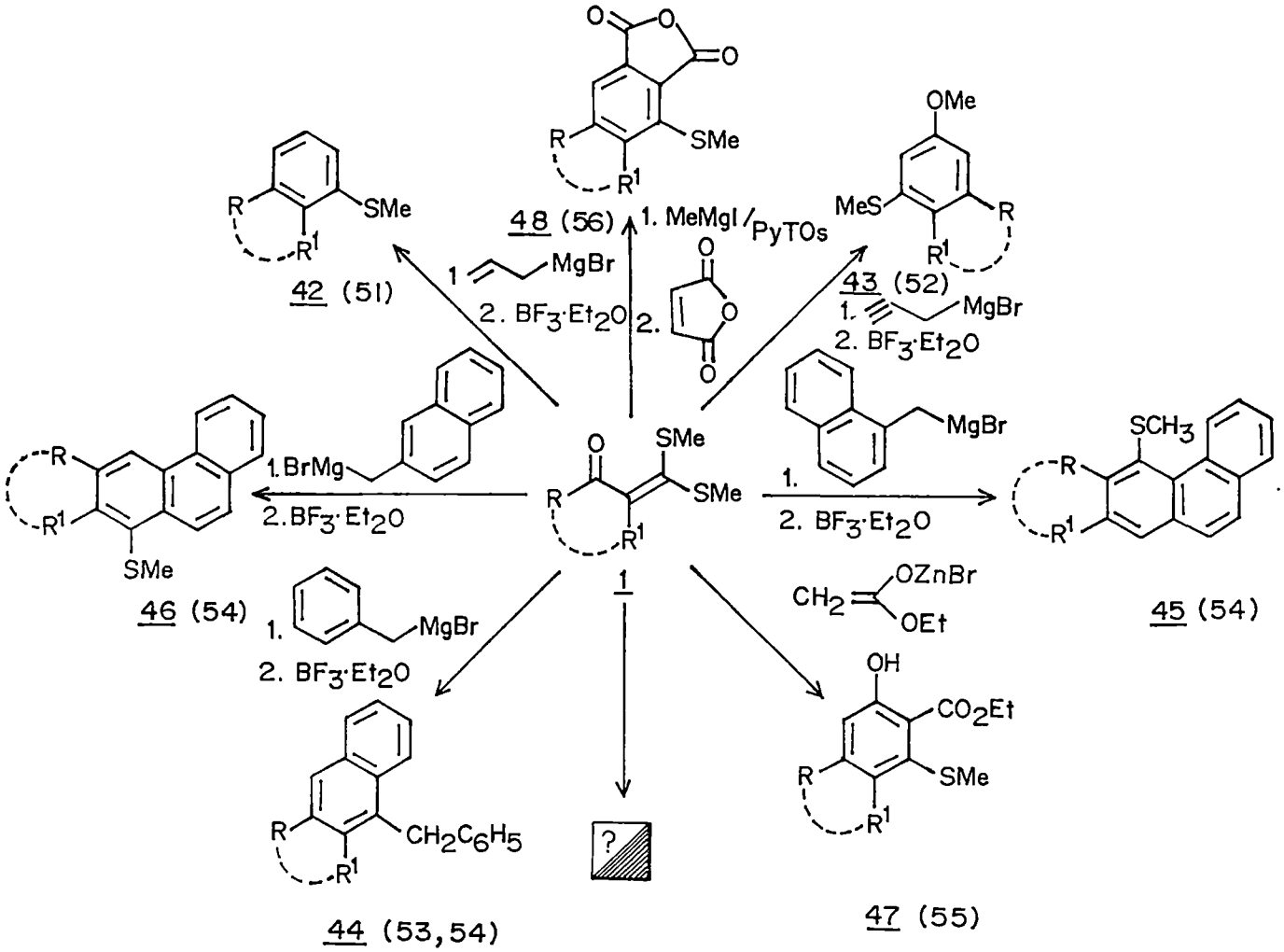
Scheme-3


39(50)
40(50)
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/THE
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].

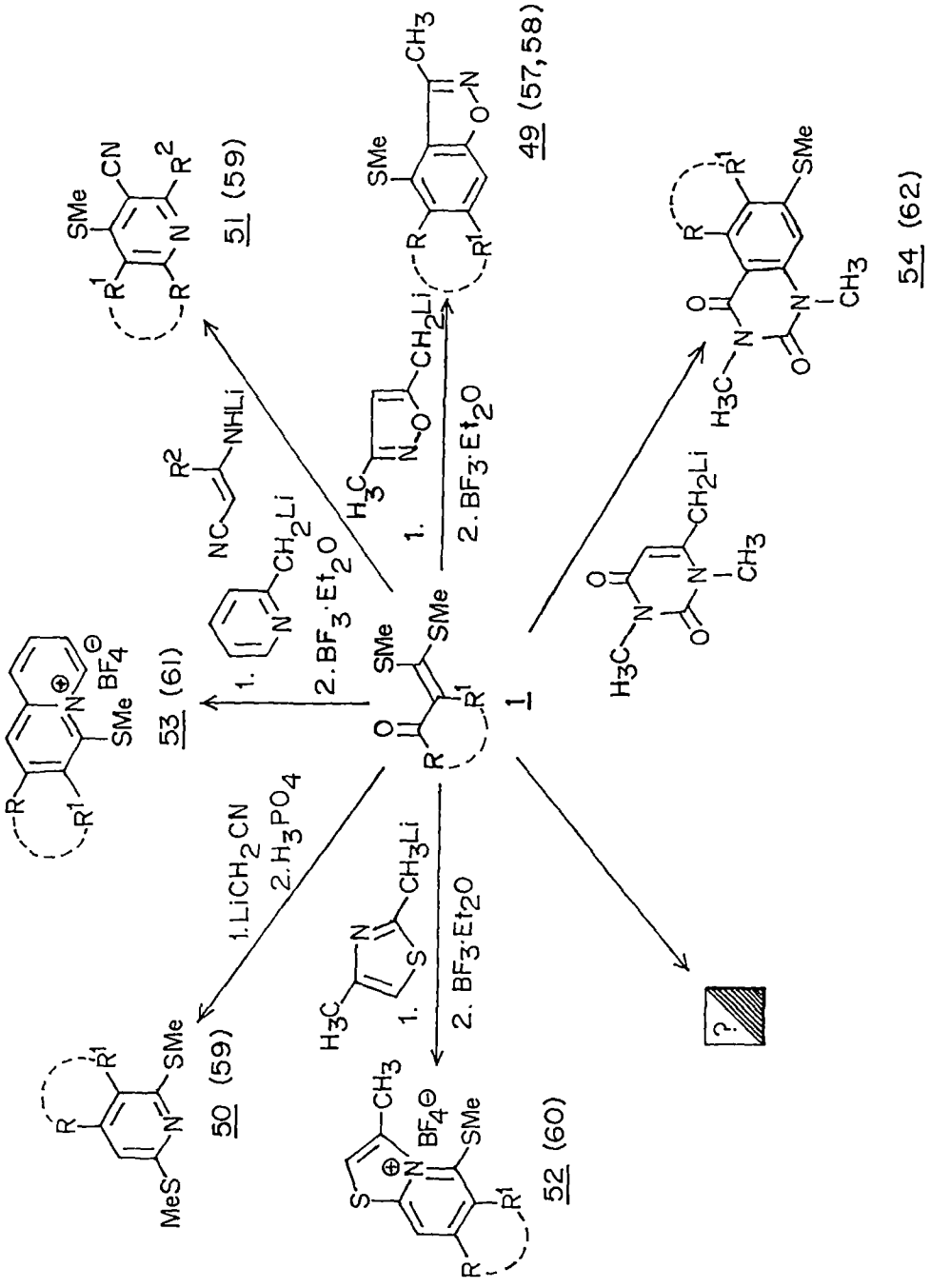
Aromatic annelation via α-oxoketene dithioacetals, developed from this laboratory has emerged as an area of great synthetic potential. Some of the important synthetic outcome of this aromatic annelation methodology is outlined in scheme 5. The reaction of allylmagnesium bromide with α-oxoketene dithioacetals 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
2.
42 (51)
1
MgBr
2. BF3·Et2O
43 (52)
1.
MgBr
2. BF3·Et2O
1.BrMg
2.BF3·Et2O
46 (54)
1.
MgBr
2. BF3·Et2O
1
1.
2. BF3·Et2O
45 (54)
OZnBr
CH2
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



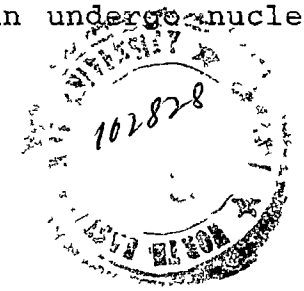
Scheme—6

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].

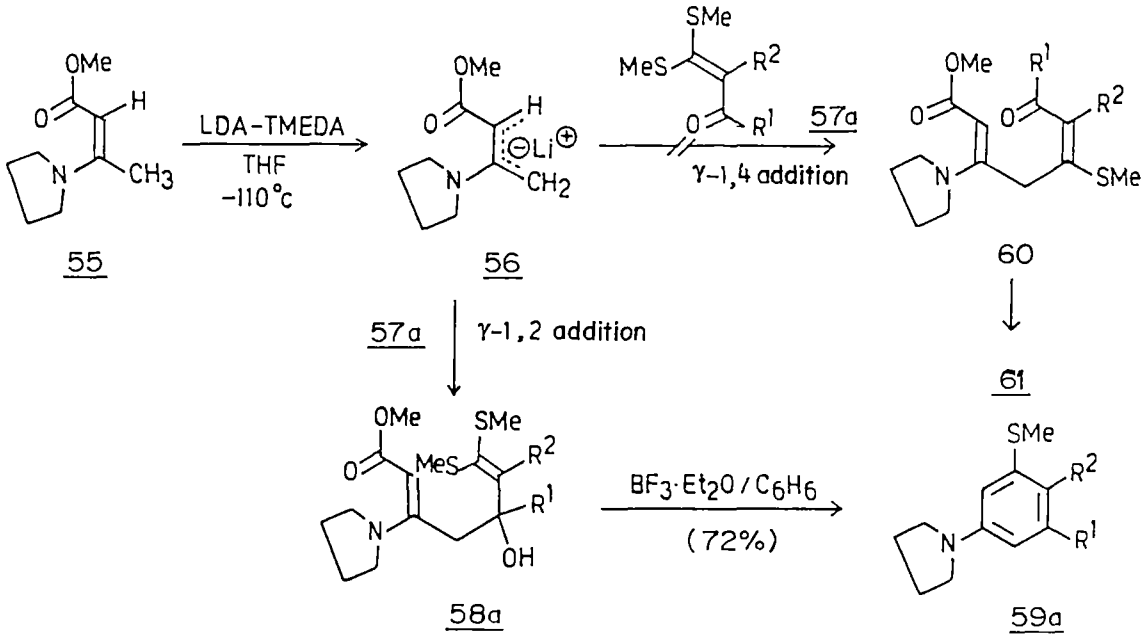
The α-oxoketene S,N- and N,N-acetals like oxoketene S,S-acetals, are well defined compounds which can be preserved without apparent decomposition. They can be considered as vinylogous amides if they are derived from ketones and as vinylogous amines if they are derived from other methylene compounds. 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

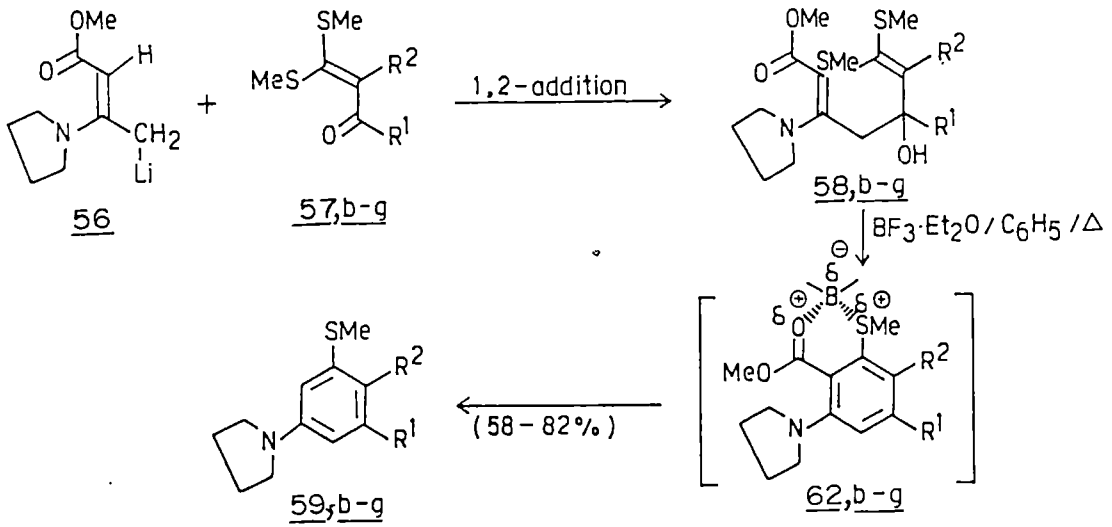
In continuation of these studies and as a part of the present research programme on α-oxoketene S,S- and S,N-acetals, it was proposed to undertake some of the transformations of these synthons. In the second chapter, aromatic annelation methodology was well explained for the synthesis of regiospecifically 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-MeO C_6H_4 ; R^2 = H

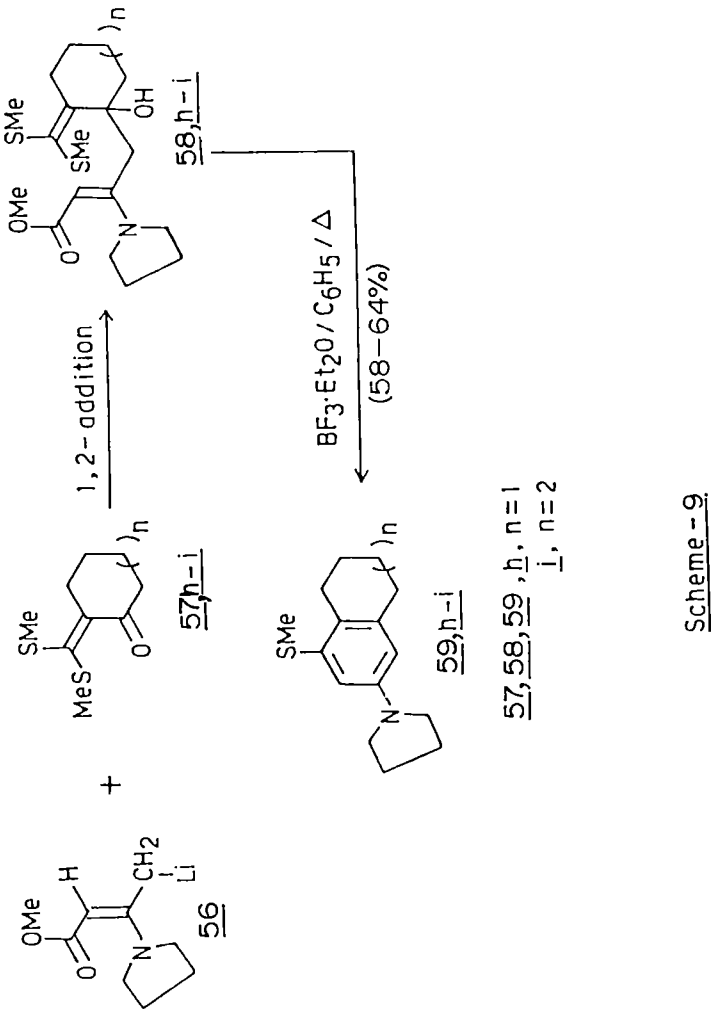
d, R^1 = 2-naphthyl ; R^2 = H

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



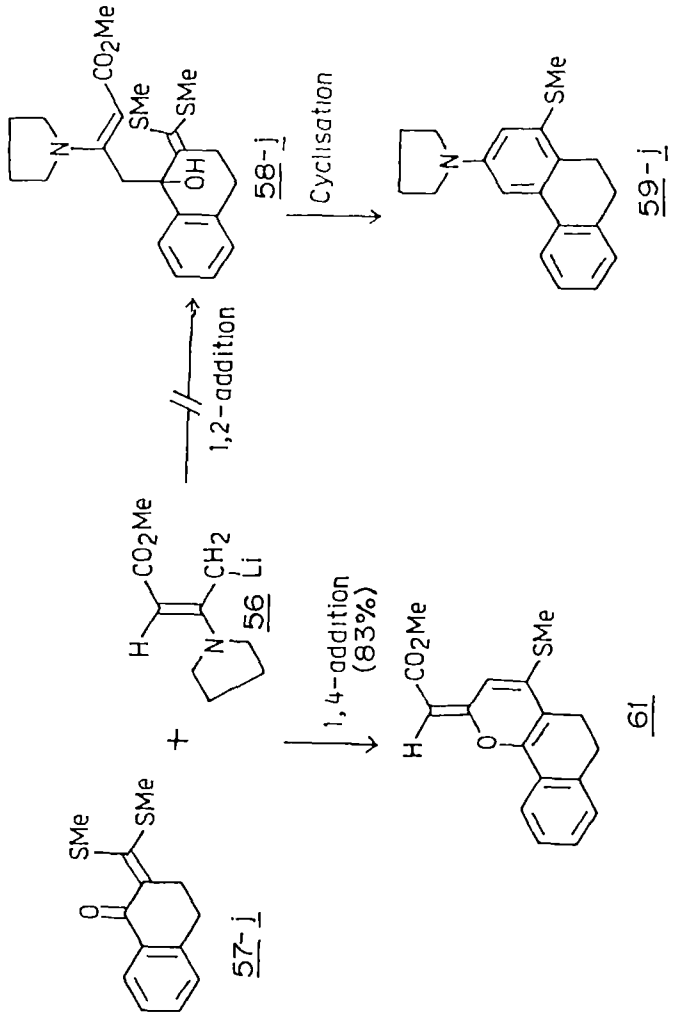
57, 58, 59, h, n=1
i, n=2

Scheme-9

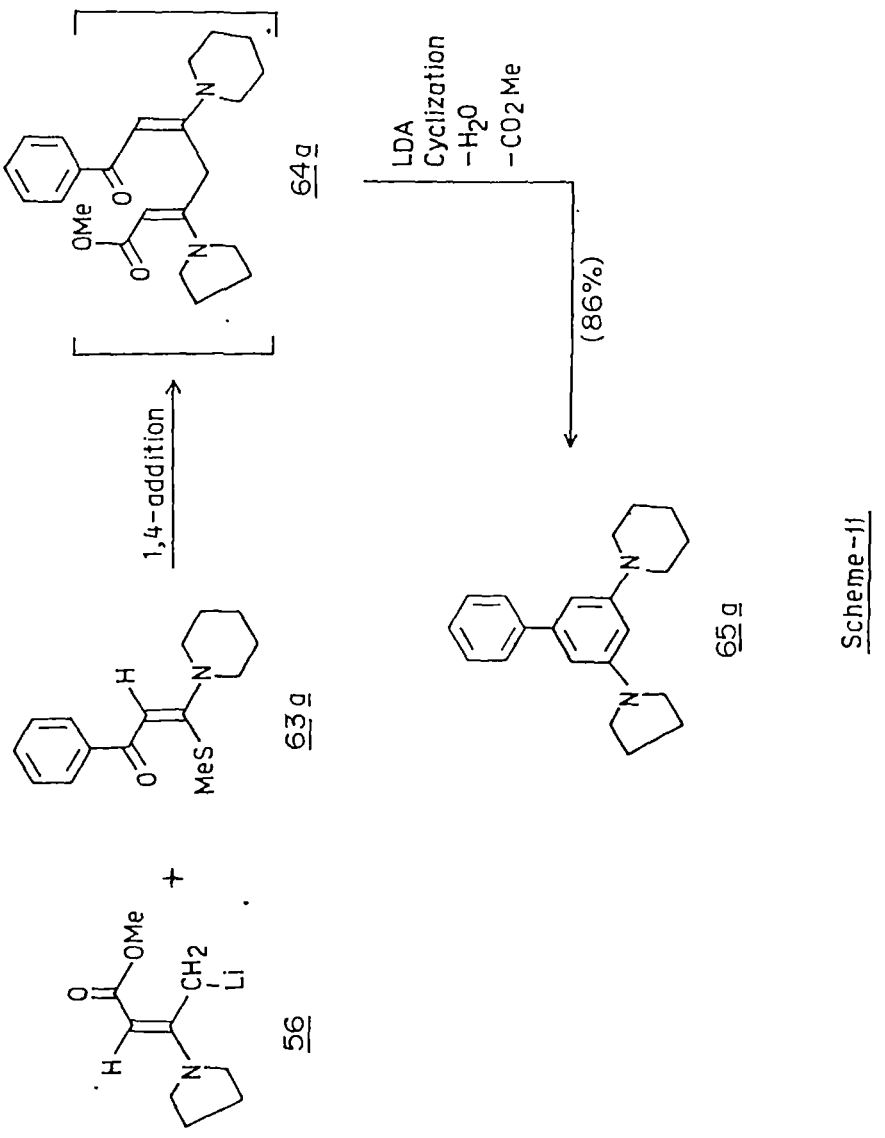
methylthio-2H-naphtho[1,2-b]pyran-2-ylidene) acetate **61** in 83% yield (scheme 10). To show further generality for the synthesis of electron rich aromatic compounds carrying two regiospecifically substituted dicycloalkylamino groups, this methodology was extended to α-oxoketene S,N-acetals. The diverse 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).

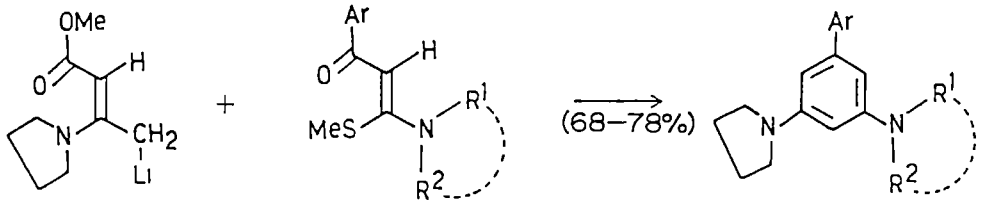
In chapter IV, the reactivity of various activated olefins with the anion derived from bifunctional ketene S,S-acetal, which functions as 1,3-dipole are described in detail. In principle such anionic cycloadditions should follow one of the following


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

Scheme-10


OMe
O
CH2
Li
H
N
56
+
H
O
MeS
63 g
1,4-addition
OMe
64 g
LDA
Cyclization
-H2O
-CO2 Me
(86%)
65 g

Scheme-11

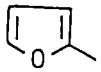


56 63 b-e 65 b-e

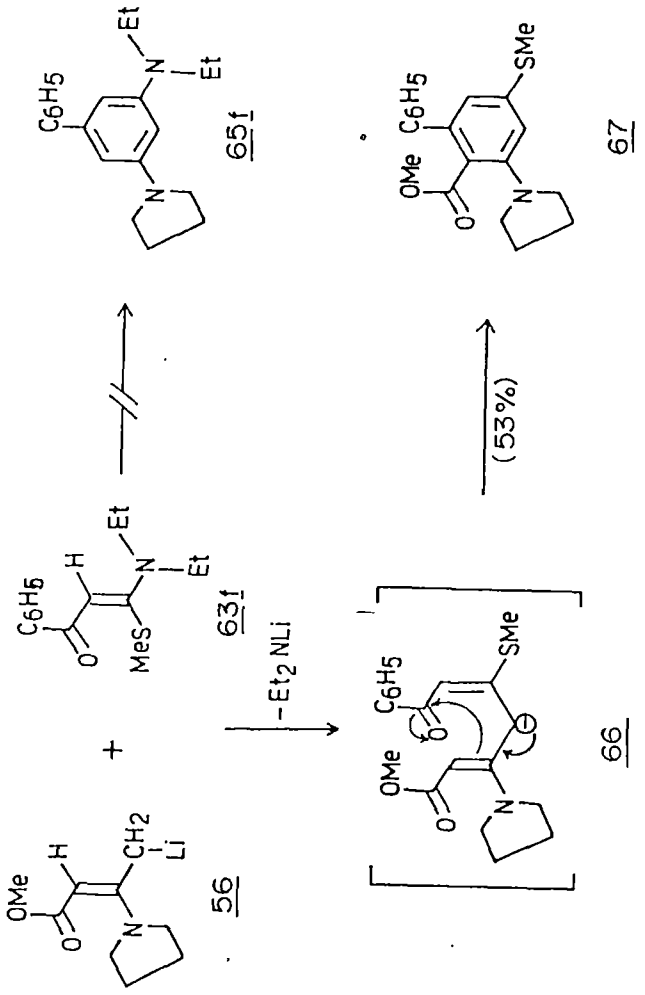
63, 65, b, Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_4-$

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

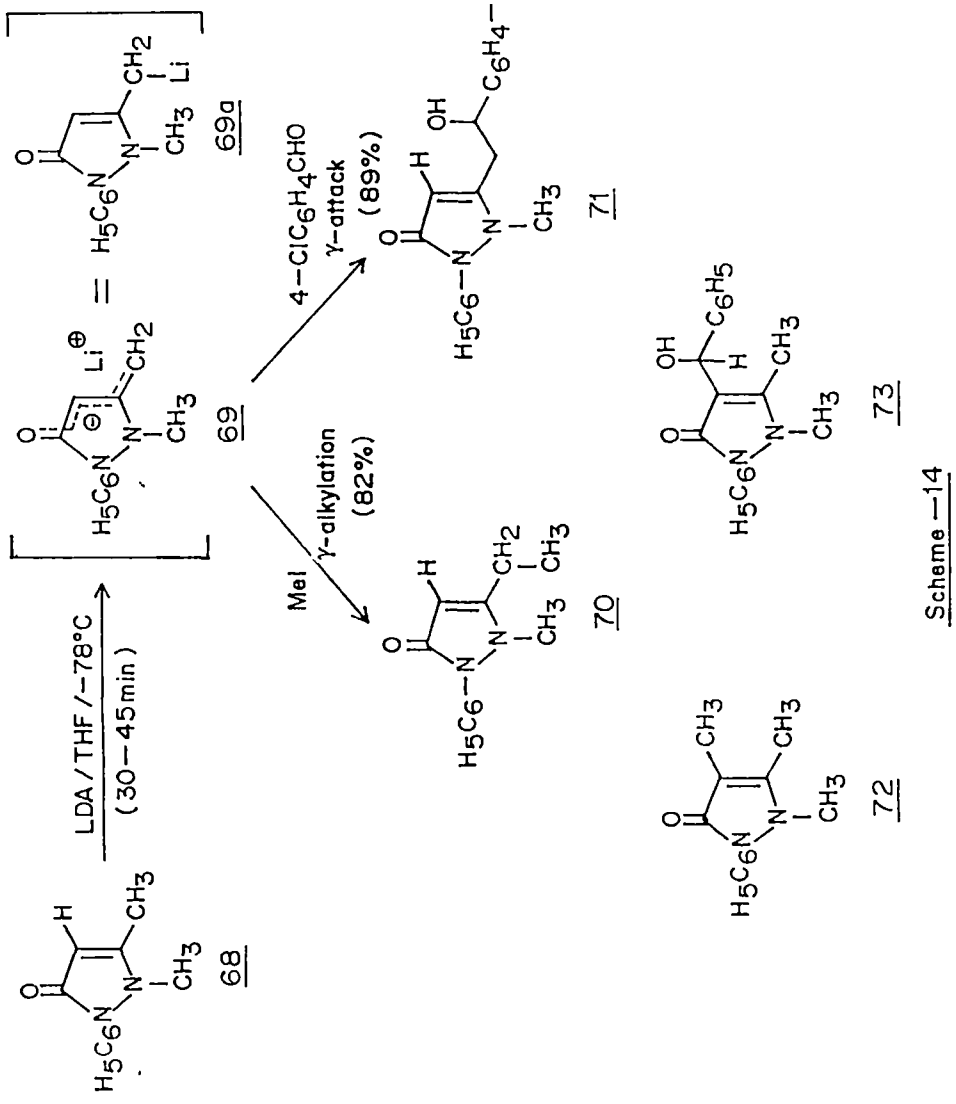
d, Ar = 4-MeO C_6H_4 ; $R^1 = R^2 = -(CH_2)_5-$

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

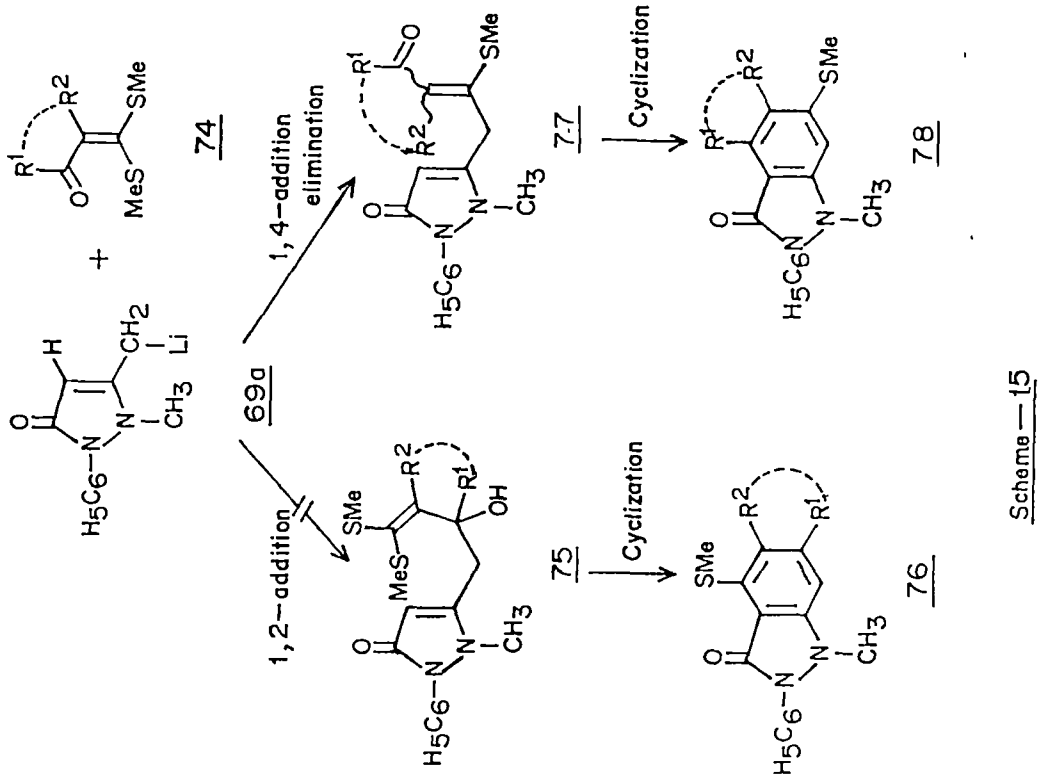
Scheme-12



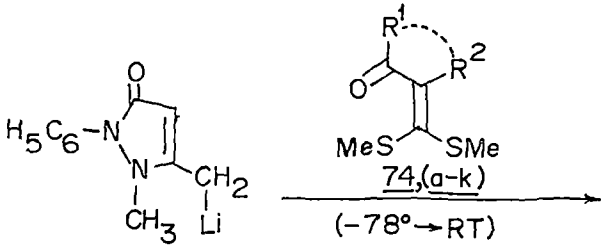
Scheme-13


LDA / THF / −78°C
(30−45 min)
Mel
γ-alkylation
(82%)
4-ClC6H4CHO
γ-attack
(89%)
68
69
69a
70
71
72
73

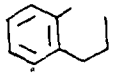
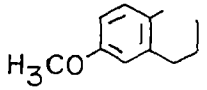
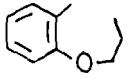
Scheme —14


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

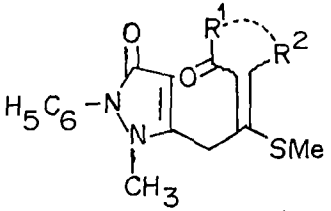
Scheme — 15



69a

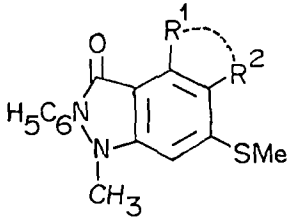
74,75,76	R^1	R^2	% Yield 76
a	C_5H_6	H	81
b	4-$MeOC_6H_4$	H	87
c	4-ClC_6H_4	H	88
d	2-Furyl	H	64
e	2-naphthyl	H	74·5
f	CH_3	H	68
g	$-(CH_2)_4-$		62
h	$-(CH_2)_6-$		69
i			88
j			92
k			91

Scheme-16



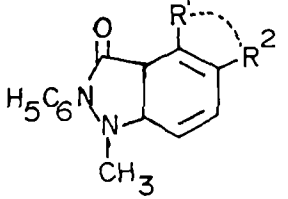
75,(a-k)

$BF_3 \cdot Et_2O/C_6H_6/\Delta$

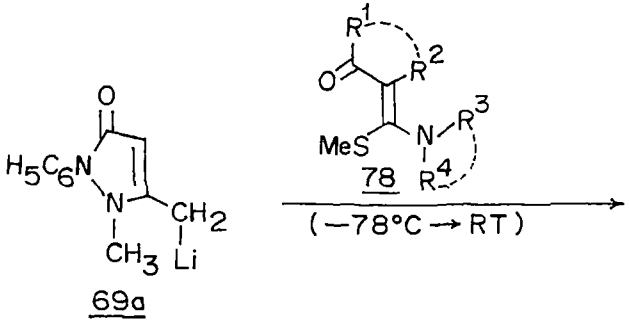


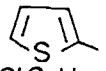
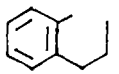
76,(a-k)

1 Raney-Ni/EtOH/ RT (97-99%)

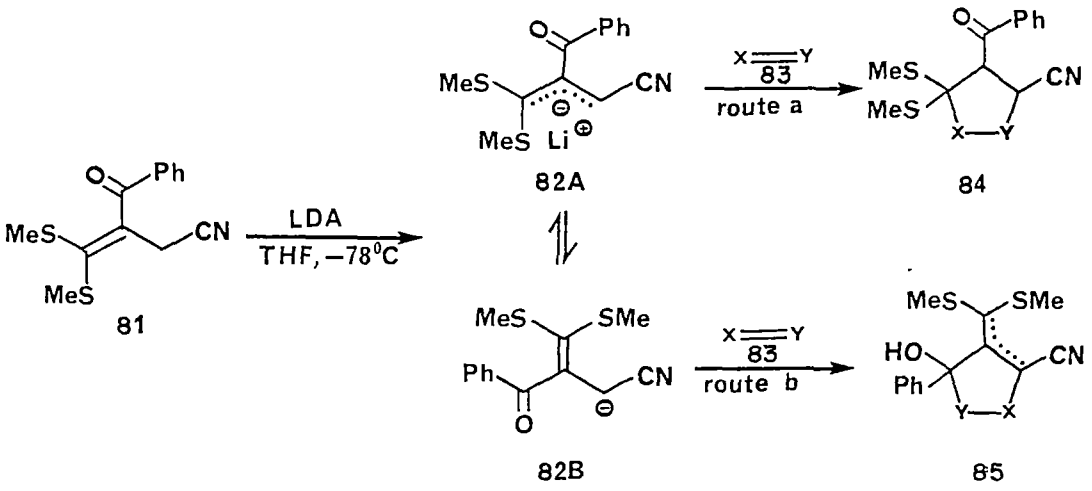


77, b,g,i,j



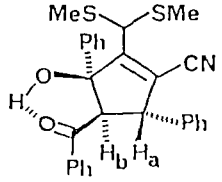
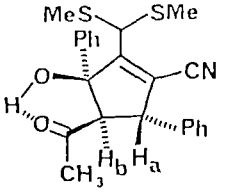
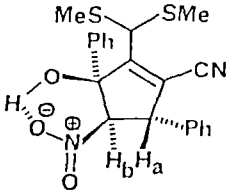
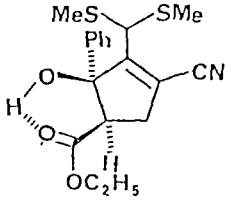
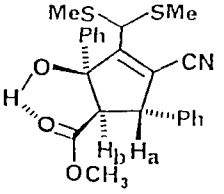
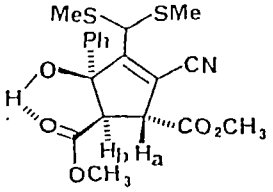
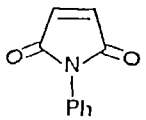
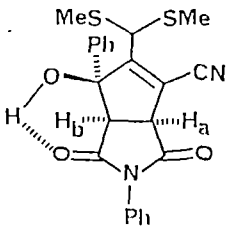
78,79,80	R^1	R^2	R^3 R^4	% Yield 80
a	C_6H_5	H	$-(CH_2)_4-$	98
b	C_6H_5	H	$-(CH_2)_2O(CH_2)_2-$	77
c		H	$-(CH_2)_4-$	72
d	4-ClC_6H_4	H	$-(CH_2)_2O(CH_2)_2-$	78
e	4-$MeOC_6H_4$	H	$-(CH_2)_4-$	94
f			$-(CH_2)_5-$	83·5

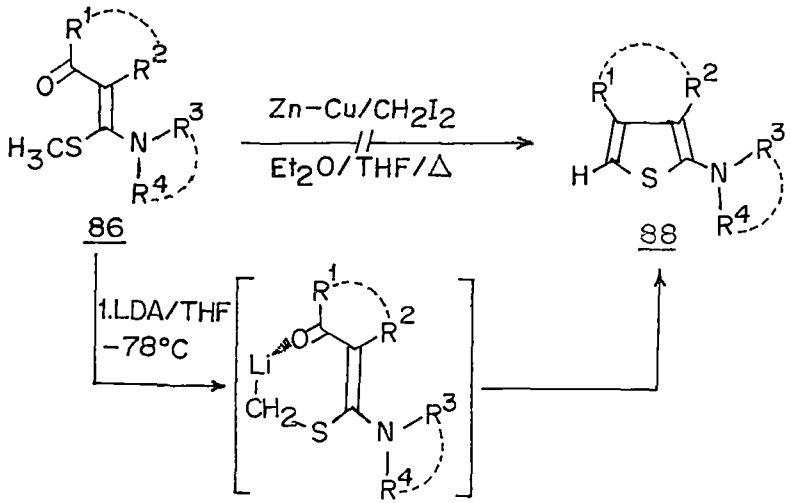
Scheme–17


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

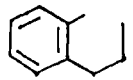
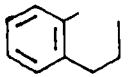
Scheme-18

Table Synthesis of Cyclopentene Derivatives

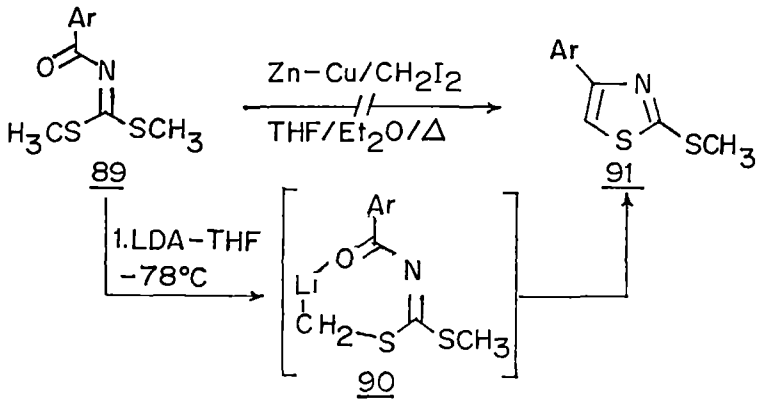
Entry	Dienophile	Product	%Yield	m.p(°C)
1.	$C_6H_5CH=CHCOC_6H_5$ **83a**	 **85a**	88	162-163
2.	$C_6H_5CH=CHCOCH_3$ **83b**	 **85b**	61	167-168
3.	$C_6H_5CH=CHNO_2$ **83c**	 **85c**	*66*	148-150
4.	$CH_2=CHCO_2Et$ *83d*	 **85d**	75	93-94
5.	$C_6H_5CH=CHCO_2Me$ **83e**	 **85e**	71	164-165
6.	$MeO_2CCH=CHCO_2Me$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



86 87 88

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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CHAPTER II

REACTIONS OF ENAMINONE DERIVED CARBANIONS WITH α-OXOKETENE ACETALS: CYCLOAROMATIZATION STUDIES ON OPEN CHAIN PRECURSORS*

II.1 *Introduction*

The construction of aromatic rings from open chain aliphatic precursors constitute an important synthetic operation in organic chemistry[1]. Both Robinson annelation[2] and modified Diel's Alder reaction[3a,3b] involve cyclocondensation of two molecules. Recently, several new approaches involving the combination of 3-carbon fragments, one with two electrophilic sites and the other with dinucleophilic sites have been investigated[4a,4b,5]. The 1,3-dielectrophilic species employed in these reactions include

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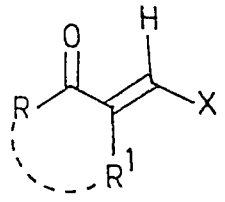
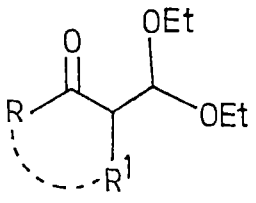
*Satyanarayana, J.; Reddy, K.R.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 6173.

β-N,N-dimethyl amino enones 1a[5], β-silyloxy enones 1b[6], and β-ketoacetals 2[7] which are generally prepared from active methylene





1a, X = $-N(Me)_2$

b, X = $-Si(Me)_3$

c, X = $-S-{}^nBu$

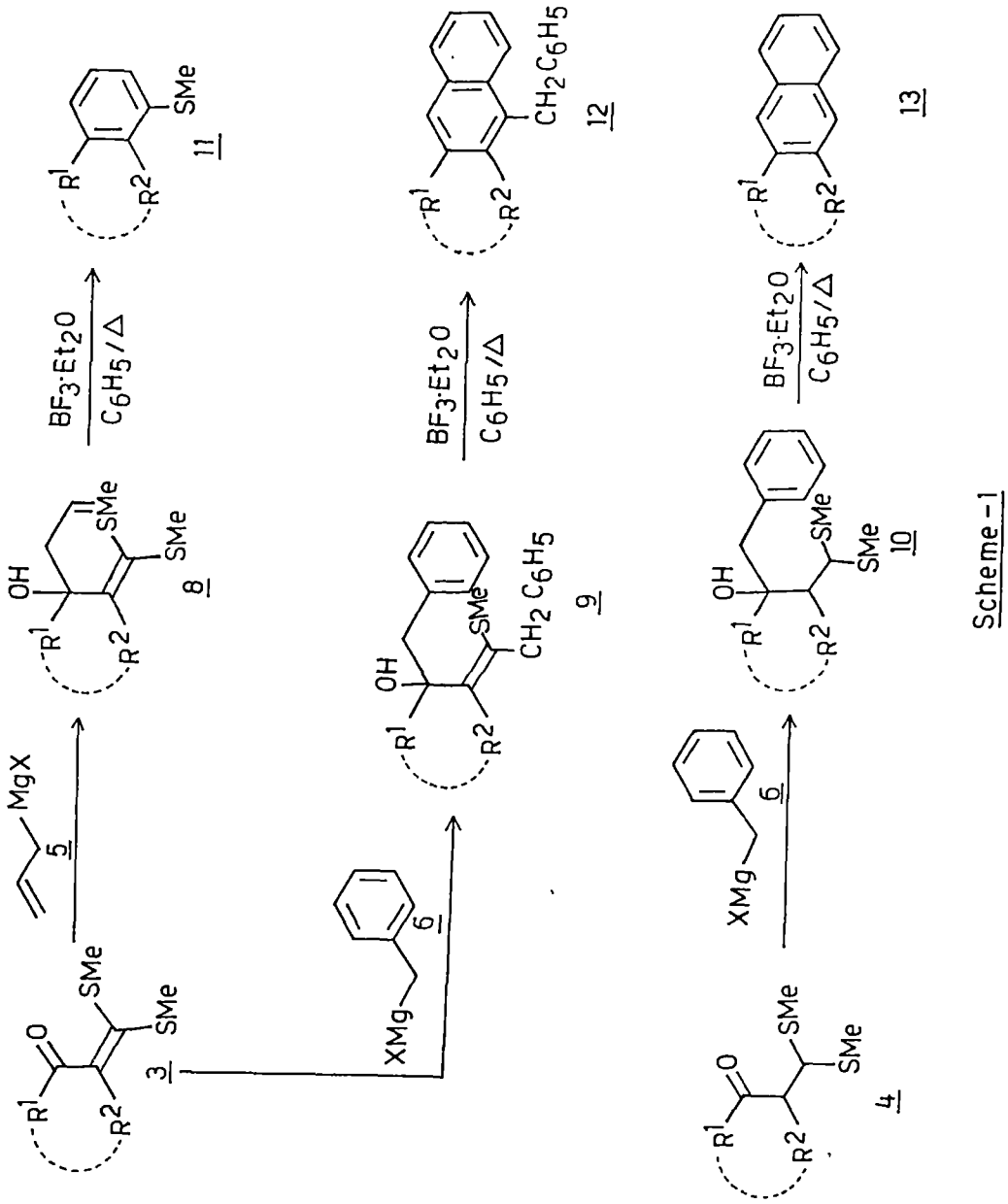
2

ketones. These condensations with 1,3-carbanionic species (or their synthetic equivalents) is reported to give substituted benzene derivatives. After the nucleophilic addition, the addition product was generally treated with lewis acid to yield the corresponding benzoannelated product. Interestingly, the corresponding thiomethyleneketone 1c did not give the expected benzoannelated product under identical reaction conditions[6c].

Our interest in the chemistry of α-oxoketene dithioacetals of general formula 3 as three carbon fragments with 1,3-dielectrophilic centers has resulted in development of new synthetic methods for a variety of new heterocyclic compounds[4b]. Their preparation involves much simpler reaction conditions than that required for the preparation of 1a, 1b and 2. Any active methylene ketone can be made to react either with carbon disulfide or trithiocarbonate in the presence of suitable base, followed by alkylation. The products generally are obtained in attractive preparative yields with well defined physical

properties which can be purified by conventional purification methods. They have displayed considerable chemical flexibility towards numerous reagents to yield a variety of sulfur containing as well as sulfur free organic molecules[4b]. They were reduced with sodium borohydride to give exclusively 1,2-adducts resulting in the corresponding allyl carbinols which underwent a facile solvolytic rearrangement in the presence of methanol to yield the corresponding eneesters[7]. Similarly, a number of carbon nucleophiles have been shown to react in a 1,2-manner which also underwent 1,3-carbonyl transposition in the presence of methanolic $BF_3.Et_2O$ to yield the corresponding eneesters[8].

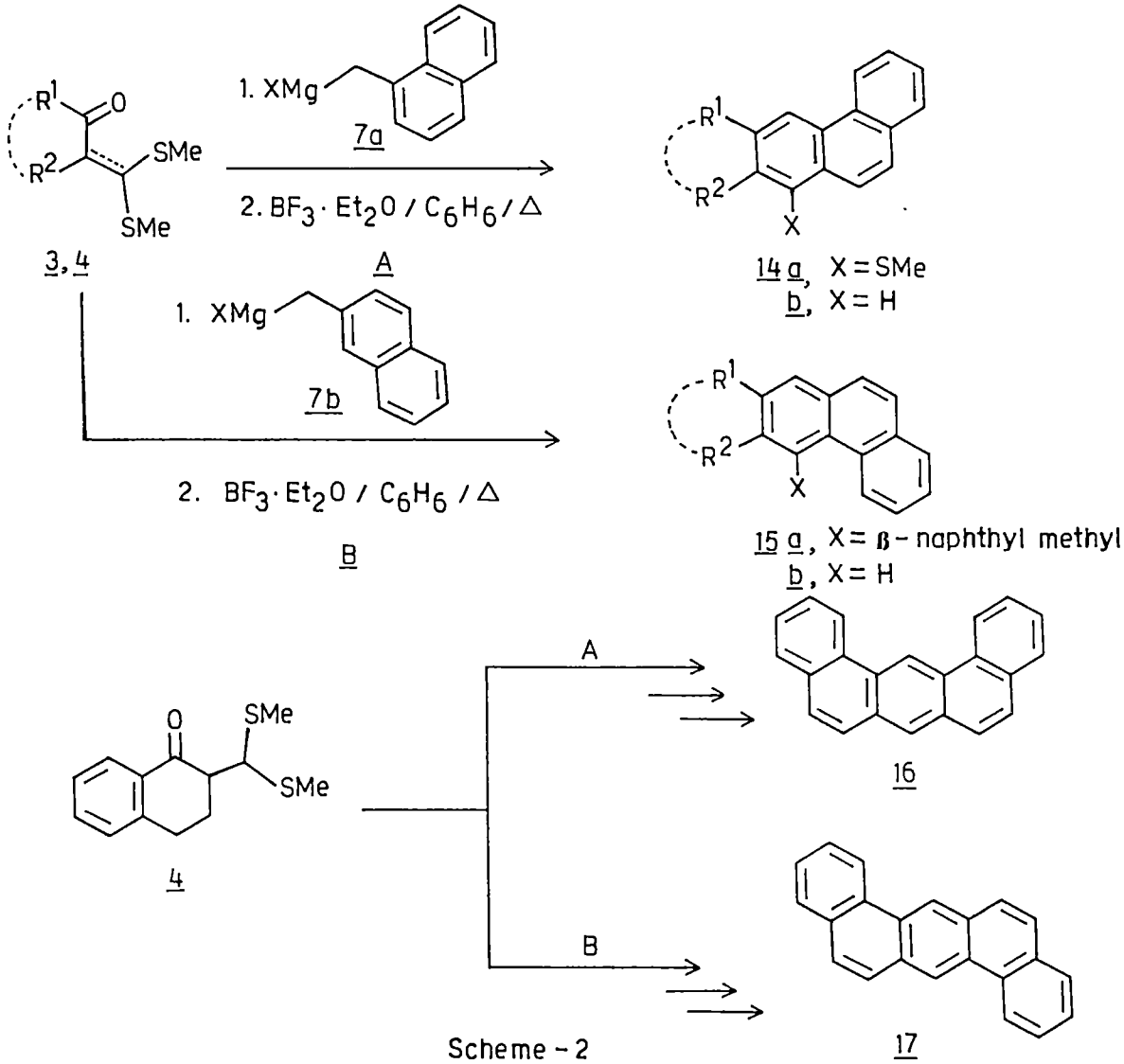
The allylmagnesium halide 5 on reaction with α-oxoketene dithioacetals 3 afforded the corresponding allyl carbinol acetals 8 which on treatment with boron trifluoride etherate in refluxing benzene afforded the corresponding benzenoids 11 in good yields[10] (scheme 1). This method was subsequently explored in this laboratory for the synthesis of a wide variety of aromatic and hetero aromatic annelations[4b]. Thus, benzyl magnesium halide 6 on reaction with 3 gave the corresponding carbinol acetal 9 involving sequential 1,4-followed by 1,2-addition of the anion. Thus it requires benzyl magnesium halide in excess quantity, since two moles of this reagent reacted with 3. These carbinol acetals 9 on lewis acid treatment yielded the corresponding naphthoannelated products 12 in high yields[11] (scheme 1). However, the naphthoannelated product carried the benzyl group in place of methylthio functionality which could have been easily removed under Raney Nickel desulphurization. Thus, the naphthoannelation process involving the reaction of 6 with 3



Scheme-1

suffers limitations if one wants to make the naphthalene derivatives without carrying the benzyl group. Subsequently, this limitation was circumvented by reacting **6** with β-oxodithio acetals **4** to afford the corresponding sulfur free naphthalene derivatives **13** in excellent yields[12] (scheme 1). β-oxodithio acetals **4** were conveniently prepared by reduction of mercapto double bond 3 either with sodium borohydride in acetic acid[13a] or zinc in acetic acid [13b] in high yields.

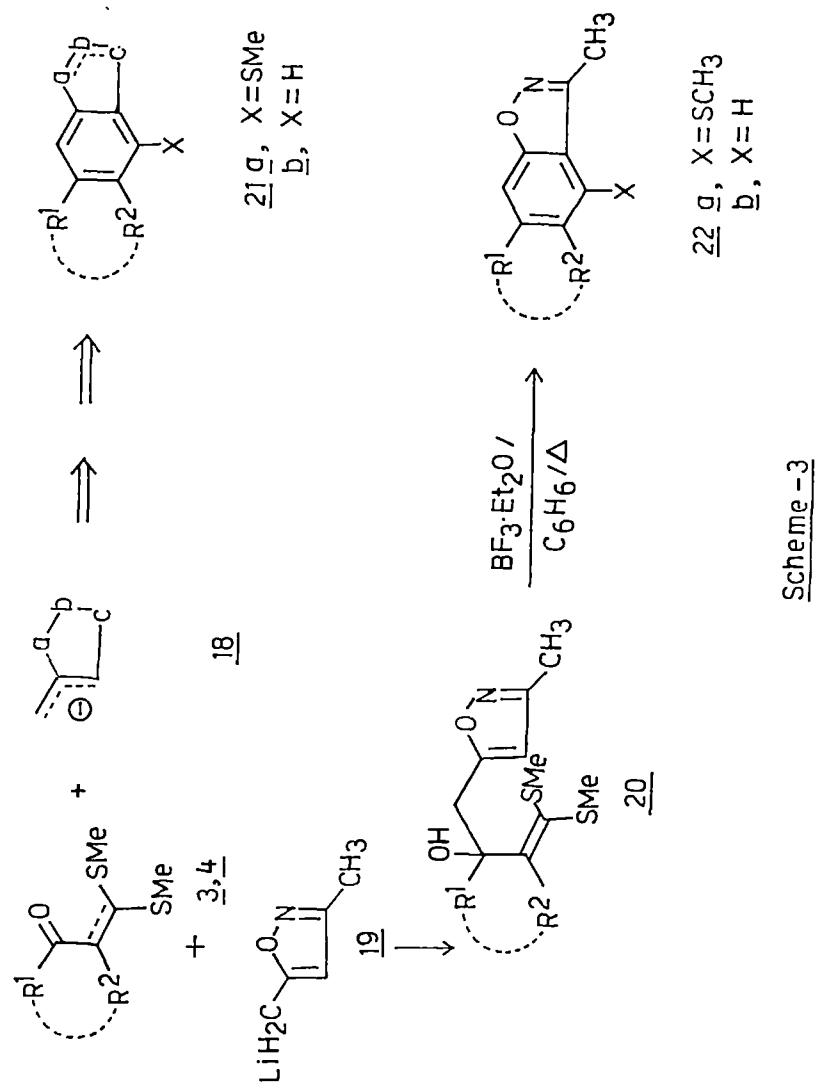
Subsequently, α-(naphthylmethyl)magnesium halide **7a** and β-(naphthylmethyl)magnesium halide **7b** were reacted with **3,4** with a view to developing convenient methodology for condensed aromatics such as phenanthrenes and benzanthracenes etc. The reaction of these two anions with **3,4** was of further interest in terms of regioselectivity. Since the benzyl magnesium halide had shown sequential 1,4-followed by 1,2-addition pattern, in the α-(naphthylmethyl) magnesium halide **7a**, the possible *peri* interaction might hinder the liberal delocalization of the negative charge over the ring and allow the preferred charge controlled 1,2-addition[12a-c]. On the other hand, β-(naphthyl-methyl) magnesium halide **7b** might simply follow sequential 1,4-followed by 1,2-addition pattern in the absence of steric inhibition for the charge delocalization[12a-c]. The reaction of **7a** with **3** indeed has been shown to follow exclusively 1,2-addition to afford the phenanthrene **14a** in high yields. On the other hand,the β-(naphthylmethyl) magnesium halide **7b** reacted with **3** as expected to yield the corresponding phenanthrene carrying β-(napthylmethyl) ring **15a** in high yields[12d] (scheme 2). When **7b**


1. XMg
7a
2. $BF_3 \cdot Et_2O$ / C_6H_6 / Δ
3, 4
A
1. XMg
7b
2. $BF_3 \cdot Et_2O$ / C_6H_6 / Δ
B
14 a, X = SMe
b, X = H
15 a, X = β-naphthyl methyl
b, X = H
4
A
B
16
17

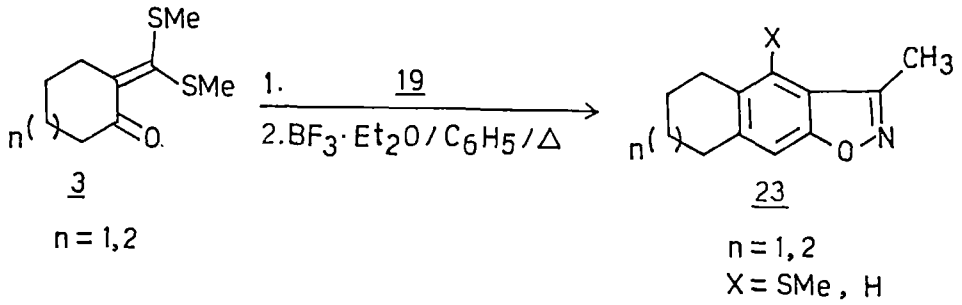
Scheme – 2

was used in excess, again this limitation was circumvented by reacting **7b** with **4** when the corresponding sulfur free **15a**, **15b** were obtained in excellent yields[12d] (scheme 2). The methodology was efficiently extended to the synthesis of isomeric benzanthracenes **16** and **17** (scheme 2) using **7a** or **7b** respectively with β-oxodithioacetal **4** and these reactions were extensively investigated and the details of these studies were discussed elsewhere[12d,14].

In continuation of these studies, an interesting reaction which had got wide synthetic application for the synthesis of hetero aromatic compounds was initiated as the basis of general plan proposed in scheme 3. Thus, in principle it should be possible to generate the heterocyclic lithioallyl anions of general formula **18** which on reaction with **3,4** should furnish the corresponding hetero aromatic products of general formula **21**. Thus the reaction of lithiomethylisoxazole **19** with **3,4** yielded the corresponding benzisoxazoles **22** in excellent yields[15]. This methodology was of considerable synthetic importance for the synthesis of benzisoxazoles and their condensed structural varients. The typical examples of the reaction of lithiomethylisoxazole with **3** and **24** represent the application of benzisoxazole synthesis to these condensed varients **23** and **25** (scheme 4). Therefore, in this new method of aromatic annelation we have shown that α-oxoketene dithioacetals or the corresponding β-oxodithio acetals can be used as the case may be, to realize aromatic annelation. The method has been extensively investigated in this laboratory and found to be a versatile methodology for aromatic annelation with few exceptions. Only a


SMe
SMe
O
R1
R2
+
3,4
18
21 a, X=SMe
b, X=H
LiH2C
19
OH
20
BF3·Et2O/
C6H6/Δ
CH3
22 a, X=SCH3
b, X=H

Scheme-3



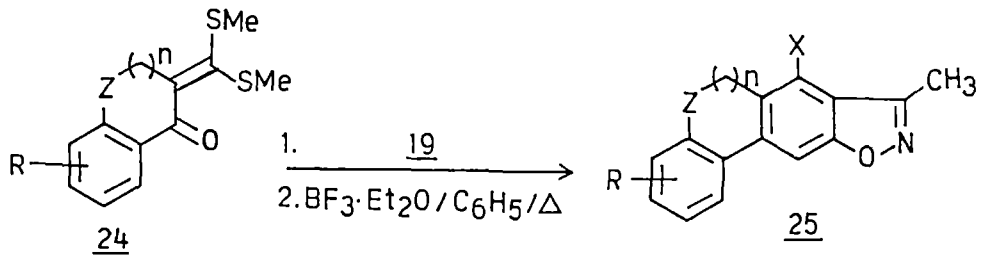
3

n = 1,2

23

n = 1,2

X = SMe , H



24

25

X = SMe , H

R = H , Me , MeO ; Z = CH_2 , S , O

n = 1,2.

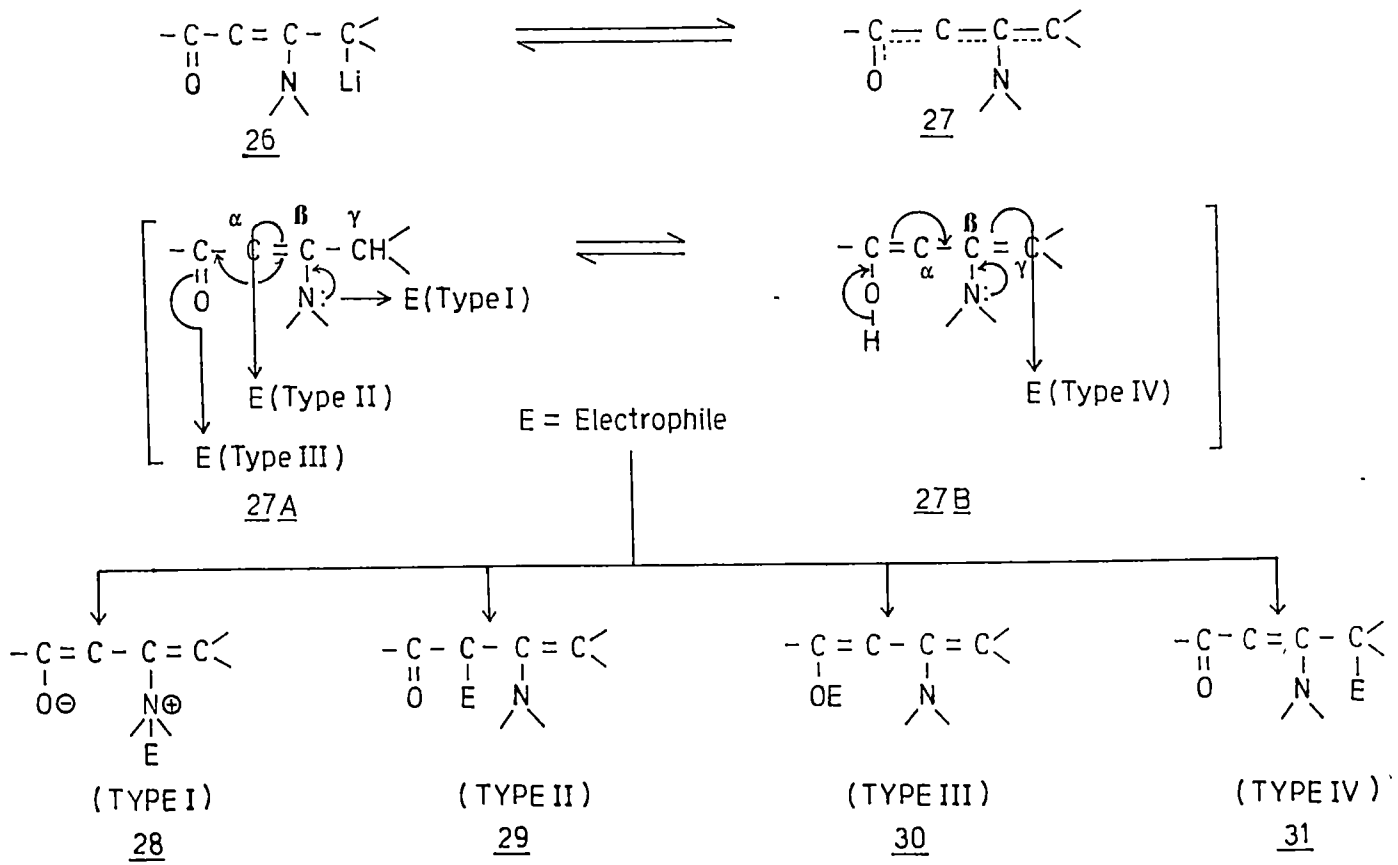
Scheme-4

few selected examples of this methodology are described in this chapter to facilitate and justify its further application to more important hetero aromatic annelation of immense synthetic potential.

It was further considered of interest to examine the reaction of lithioaminocrotonates with α-oxoketene dithioacetals to expand the scope of the present methodology for the synthesis of amino substituted aromatics. The aminocrotonate displays ambident behaviour towards electrophiles leading to different types of products. It therefore became necessary to make a brief literature survey[16] regarding the reactivity pattern of these ambident anions towards various electrophiles before we start studying the reaction of anion 61 with α-oxoketene dithioacetals 3.

II.2 *Enaminone Derived Allyl Carbanions and their Reactivity Profile*

Aminocrotonate anion of the general formula 27 display multicentered nucleophilic reactivity (N, C-α, -O-, C-γ) with various electrophiles as illustrated in scheme 5. In 28 type I, the nitrogen lone pair may directly attack the electrophile, in 29, type II the electrophile may attack the α-position, in type III, 30, the electrophile may attack oxygen and in type IV the electrophile attacks the γ-position to give 31. The first three 28, 29 and 30 have been well documented[17,18], and the type IV examples involving the attack through γ-carbon are not investigated extensively[19]. However, the γ-regioselectivity was


26
27
α
β
γ
E(Type I)
E(Type II)
E(Type III)
27A
E(Type IV)
27B
E = Electrophile
(TYPE I)
28
(TYPE II)
29
(TYPE III)
30
(TYPE IV)
31

Scheme-5

first reported by Yoshimoto, Ishida and Hiraoka[16b], through the reaction of the aminocrotonate anion **33** with aldehyde and alkylhalides. A clear addition reaction through γ-carbon with benzaldehyde to afford the corresponding alcohol **34** (scheme 6) was observed, this is the first example of γ-regioselectivity towards aromatic aldehydes. Similarly, alkylation studies revealed that γ-alkylation is preferred over the other reactive sites and the anion followed thus exclusive γ-regioselectivity towards its reaction with alkyl halides and aldehydes. Subsequently, Bryson and Gammill[20a] discovered novel example of -alkylation as outlined in scheme 7. For example vinylogous amide **36** with a 4-methyl (or) 4-(3-methyl-2-butenyl) substituents when treated with LDA* (-78°C, THF) and alkylating agent, anion **37** underwent exclusive γ-carbanion alkylation to give **38** in good yields. The same authors[20b] reported treatment of cyclic enaminone **39** with LDA (1.1 eq, -78°C) which underwent γ-alkylative intramolecular ring closure to afford the corresponding N-benzyl-2,3,3a,4-tetrahydro-6(5H)-oxoindole **40** in good yield. Similarly, the complex enaminoester **41** underwent -alkylation in the presence of LDA* to afford the corresponding alkylated product **43** indicating exclusive γ-regioselectivity.

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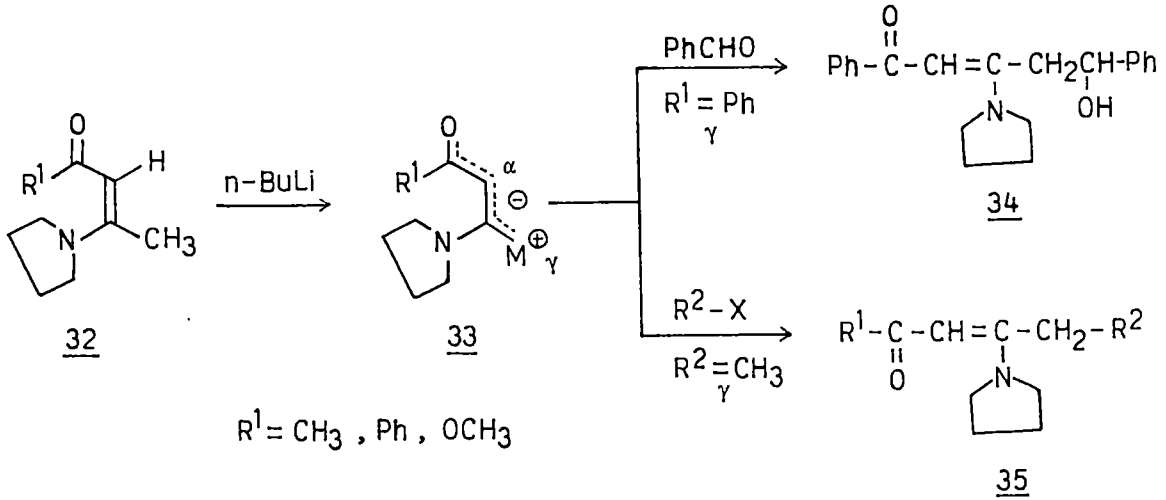
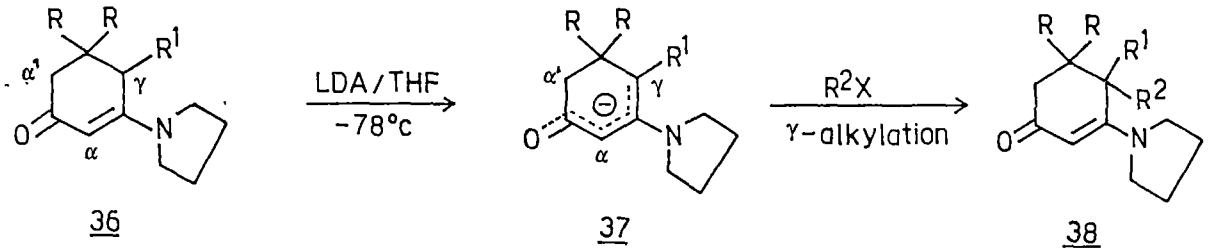
* γ-alkylation of enaminoketones, esters is best accomplished by using Lithium diisopropylamide (LDA) as carbanion generating species rather than n-butyllithium.[20a]

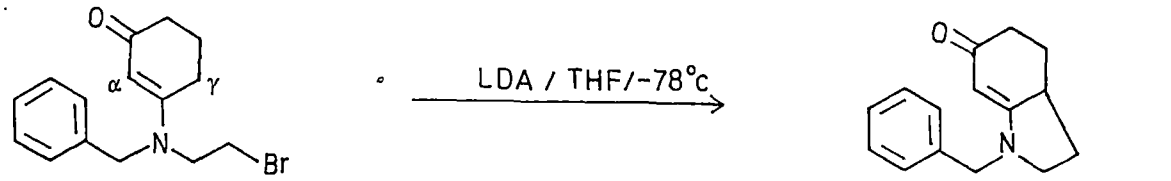


$R^1 = CH_3$, Ph , OCH_3

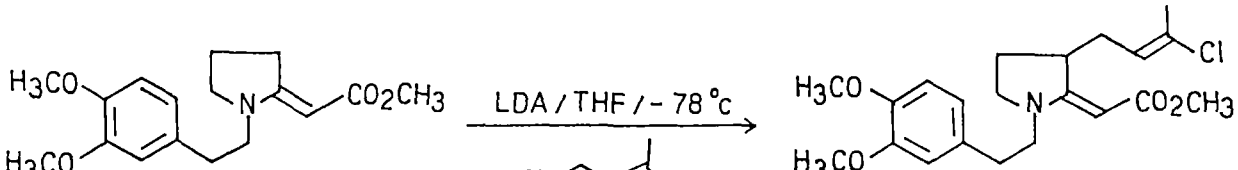
Scheme-6



36 37 38



39 40



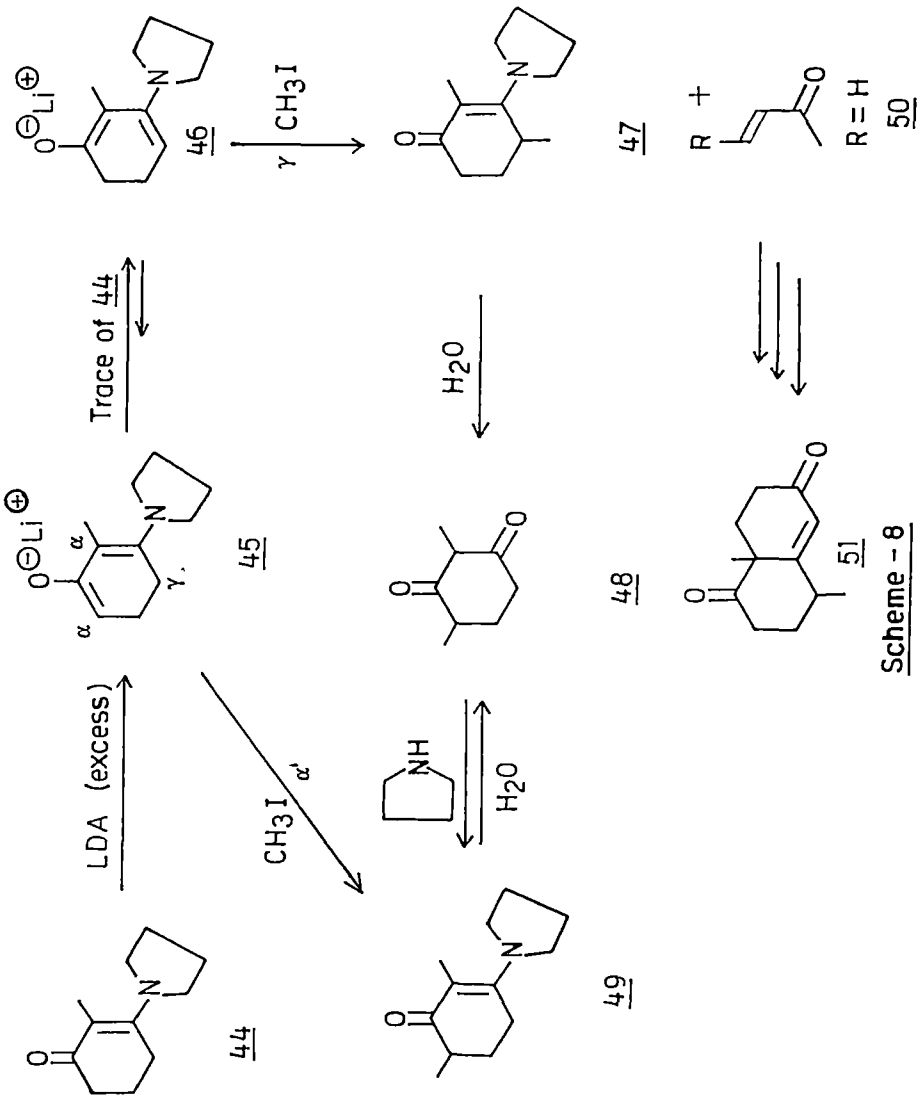
41 42 43

Scheme - 7

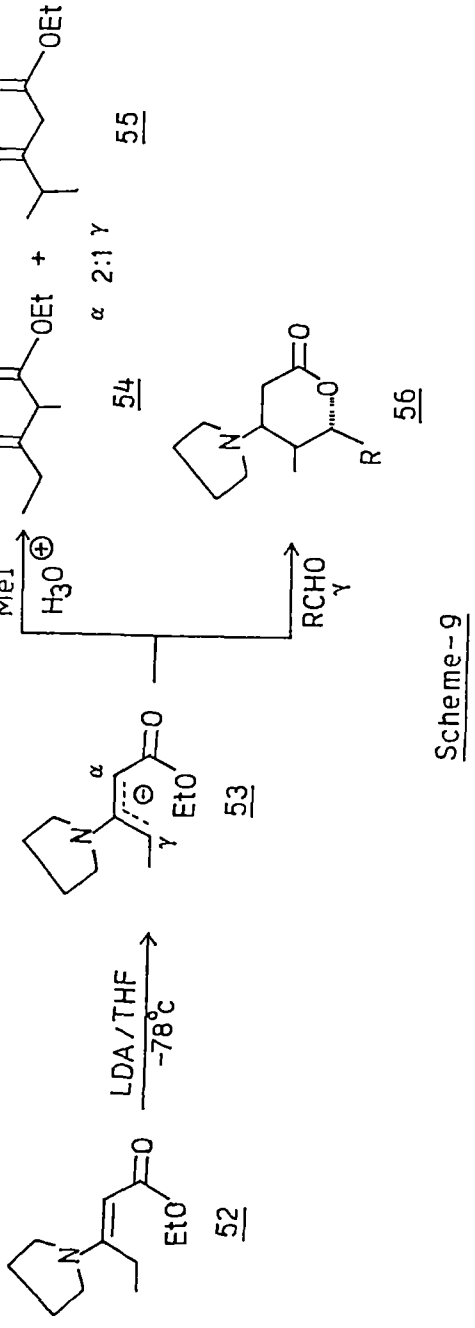
The γ-regioselectivity was further confirmed by the work of Reusch et al[21], as depicted in scheme 8, when the enaminoketone **44** on treatment with excess LDA gave the cross conjugated intermediate **45** exclusively, which on methylation gave dimethyl enamino ketone **49** through α' alkylation. Alternatively, in the presence of slight excess of **44**, an equilibrium between **45** and **46** was observed which on alkylation yielded the γ-alkylated product **47**, which on further hydrolysis yielded the corresponding 1,3-diketone **48**. The γ-alkylation was proved by these authors through the formation of the isomeric Wieland-Miescher ketone **51**.

In 1992, Gallagher et al[22a] have examined the behaviour of enamino ketones and esters **52** in the presence of LDA to generate the corresponding anions **53** and studied the regioselectivity with aldehydes and alkyl halides, the anion **53**[22b-c] reacted with aldehydes to give **56** at γ-site with a high degree of both regioselectivity and either anti- or syn-diastereoselectivity depending on the nature of the secondary amine used. Quenching enolate **53** with iodomethane gave a 2:1 mixture of **54** and **55** corresponding to α- and γ-alkylated products in quantitative yield (scheme 9). The nature of alkylhalide plays an important role in the regioselective distribution of isomers.

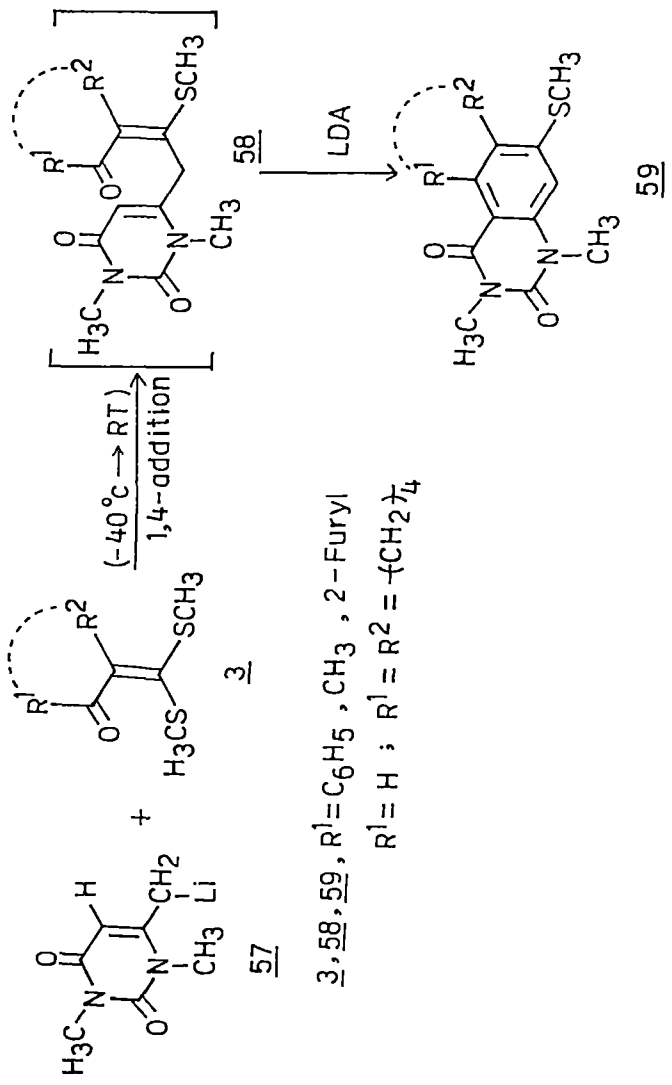
Greater γ-1,4-regioselectivity was observed in this laboratory[23], when the anion of 1,3,6-trimethyl uracil **57** (scheme 10) reacted with α-oxoketene dithioacetal **3** yielding the corresponding 6-methylthio-8-substituted/7,8-disubstituted quinazolines **59** which could be explained on the basis of γ-1,4-adduct.


LDA (excess)
CH3I α'
Trace of 44
H2O
γ CH3I
H2O
R +
R = H
44
45
46
47
48
49
50
51

Scheme - 8



Scheme-9


(-40°c → RT)
1,4-addition
LDA
57
3
58
59
3, 58, 59, R¹ = C6H5 , CH3 , 2-Furyl
R¹ = H ; R¹ = R² = -(CH2)4-

Scheme-10

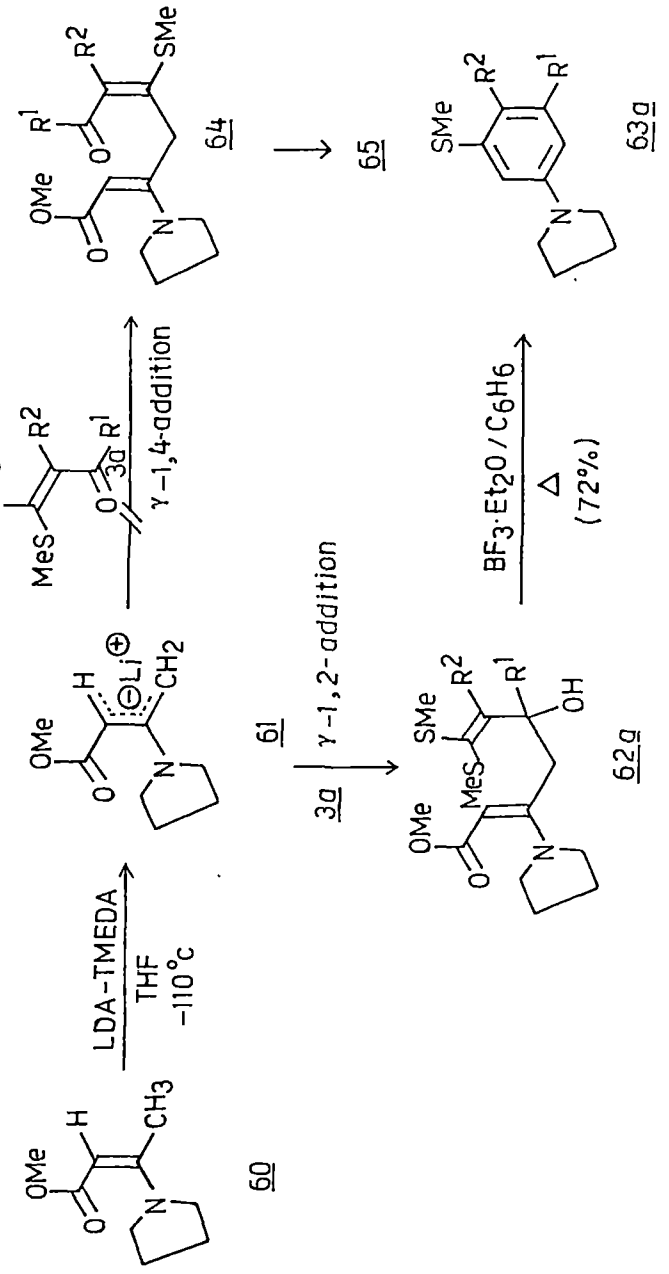
II.3 *Results and Discussion*

In the preceeding section an introduction on aromatic and hetero aromatic annelation has been discussed. Similarly, the γ - regioselectivity of the lithioallyl anion derived from enaminones towards their reaction with various electrophiles have been discussed. In the present chapter it was decided to examine the reactivity of lithioallyl anions derived from aminocrotonates with various α-oxoketene S,S- and S,N-acetals. The anions thus derived may react with α-oxoketene dithioacetals in four different categories.

a. α-1,2 addition mode
b. α-1,4 addition mode
c. γ-1,2 addition mode and
d. γ-1,4 addition mode

It is therefore interesting to note that the reaction of **61** with α-oxoketene S,S-and S,N-acetals generally have yielded one product indicating highly regioselective participation of both anionic and electrophilic components. The adducts have been *in situ* cyclised to the corresponding aromatic compounds and on the basis of the structural features of these compounds the regio selectivity of the substrate is evaluated, their results are projected in this chapter.

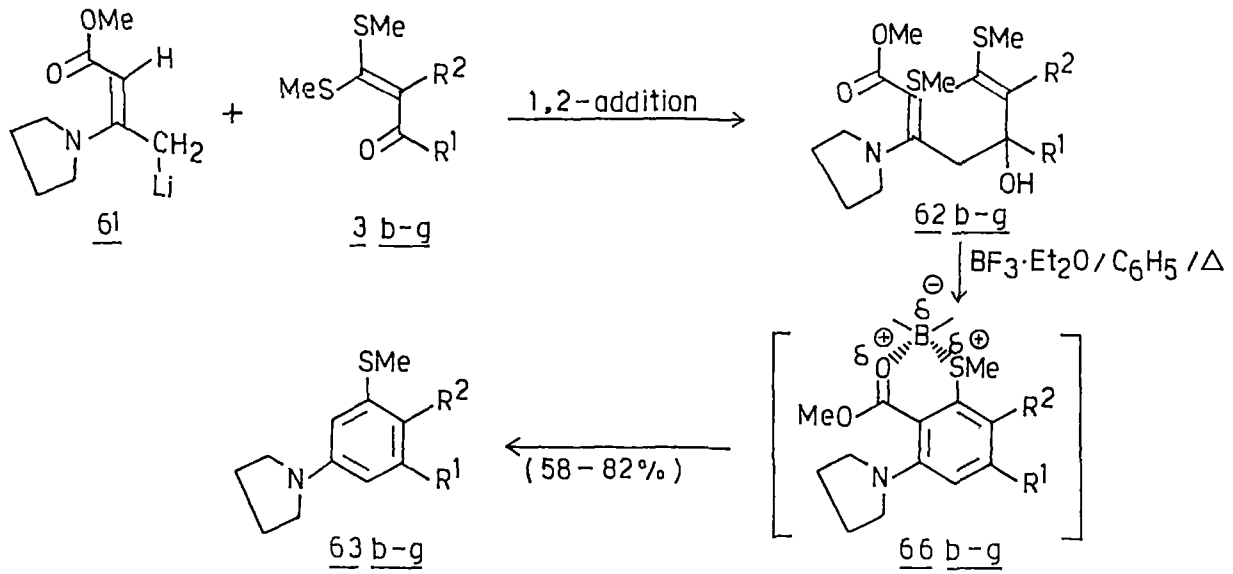
In scheme 11, as a typical example lithiomethyl 3-pyrrolidyl-2-butenoate **61** was generated from **60** as reported earlier[16c] and reacted with α-oxoketene dithioacetal **3a** and the adduct **62a** was examined as crude carbinol from its IR, ^{1}H NMR spectrum. IR band



3, 62, 63, a, $R^1 = C_6H_5$; $R^2 = H$

Scheme-11

at 3070 cm^{-1} was inferred for the presence of hydroxy group, ^1H NMR ($CDCl_3$) spectrum further indicated the formation of carbinol acetal **62a** arising from γ-1,2-addition. The product showed a broad singlet centered at δ 5.40 for OH group which was exchangeable with deuterium oxide. The presence of two methylthio signals at δ 2.22 and 2.42 also confirms the γ-1,2-addition mode. Carbinol acetal **62a** on treatment with $BF_3.Et_2O$ yielded a product which was assigned the structure 1-methylthio-3-phenyl 5-(1-pyrrolidyl) benzene **63a** as colourless crystals (chloroform-hexane) in 72% yield mp 95-96°C. The structure of this compound was established on the basis of its analytical and spectral data. The IR (KBr) spectrum displayed major bands at 1597, 1570, 1572, 1438 and 1109 cm^{-1}. The structure was further confirmed from ^1H NMR ($CDCl_3$) spectrum. The pyrrolidino methylene protons appeared as multiplet at δ 1.85-2.10. The methylthio proton appeared at δ 2.40. Other four methylene protons adjacent to nitrogen of pyrrolidine ring appeared as multiplet between δ 3.15-3.41. The broad singlets at δ 6.30 and 6.37 were assigned to two aromatic protons adjacent to aryl group while the other proton appeared as broad singlet at δ 6.67. The five protons of the phenyl group showed a broad multiplet between δ 7.13-7.58. The compound was analysed for molecular formula $C_{17}H_{19}NS$ with molecular weight 269.39, and confirmed by its mass spectrum which exhibited a peak at m/z 269 (M^+, 60%), 268 (29%). The other α-oxoketene dithioacetals **3b-g** were similarly reacted with **61** to afford the corresponding 1-methylthio-3-substituted-5-(1-pyrrolidyl) benzenes **63b-g** in 58-82% overall yields as depicted in scheme 12. And it is interesting to note that the carbomethoxy



3, 62, 66, 63 b, R^1 = 4-Cl C_6H_4 ; R^2 = H

c, R^1 = 4-MeO C_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

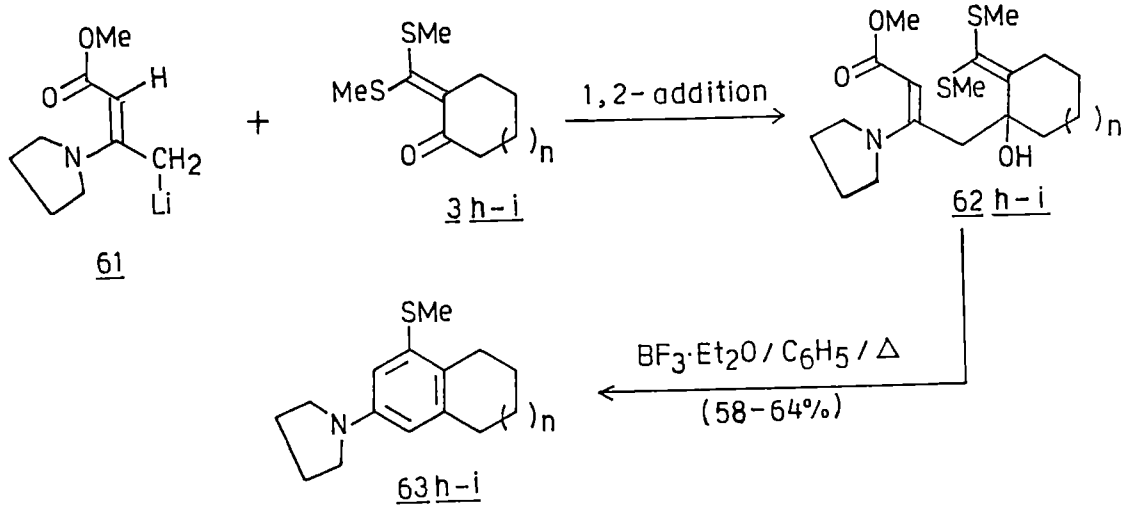
g, R^1 = Me ; R^2 = H

Scheme -12

group was knocked off in all the cases examined. Attempts to isolate methyl thiomethyl carbonate however was not successful. Therefore the mechanism governing the carbomethoxy group elimination remains unresolved.

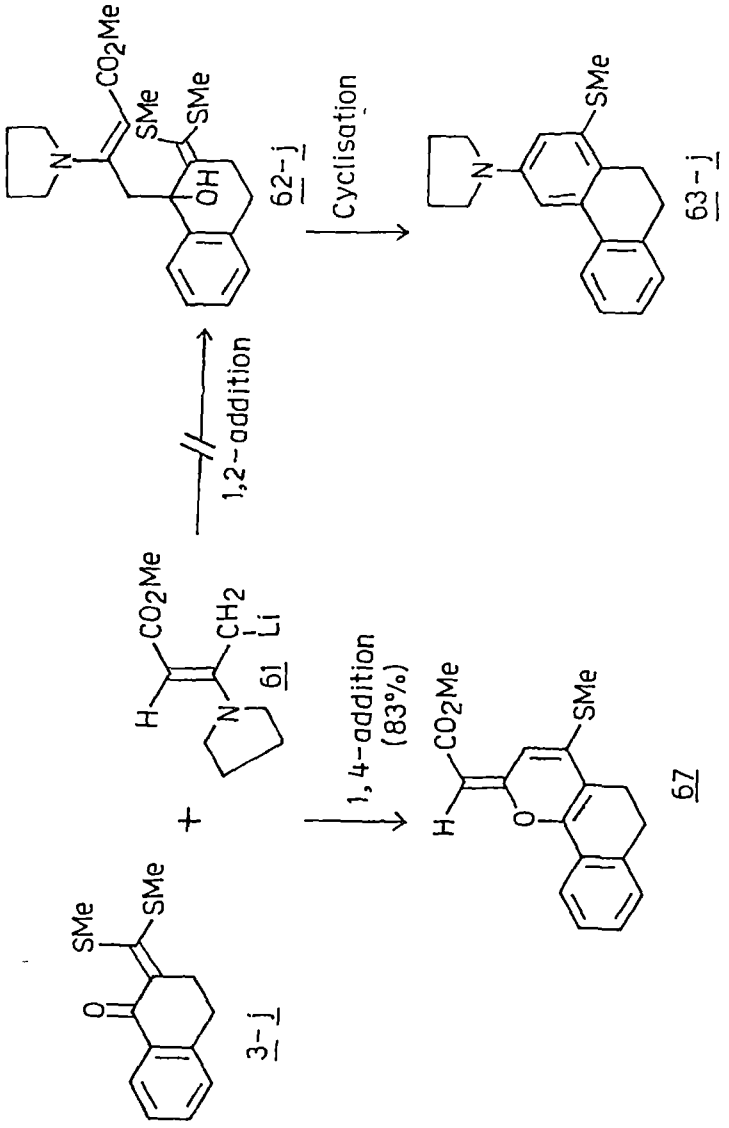
Oxoketene dithioacetals derived from cyclohexanone **3h** and cycloheptanone **3i** also reacted with **61** to afford the γ-1,2-adducts **62h** and **62i** respectively which on $BF_3.Et_2O$ treatment yielded the corresponding 1-methylthio-3-pyrrolidino 5,6,7,8-tetrahydronaphthalene **63h** (64%) and 1-methylthio-3-(1-pyrrolidyl)-6,7,8,9 tetrahydro-5H-benzo-1-cycloheptene **63i** (58%) (scheme 13). The structural assignment of **63h** and **63i** were established on the basis of their analytical (CHN) and spectral (IR, ^1H NMR, Mass) data which were in confirmity with the assigned structures described in the experimental section.

Interestingly, another cyclic variant of oxoketene dithioacetal derived from α-tetralone **3j** reacted with **61** not in the same manner to yield the corresponding methyl (5,6-dihydro-4-methylthio-2H-naphtho[1,2-b] pyran-2-ylidene) acetate **67** in 83% yield (scheme 14) as bright orange needles (chloroform-hexane) mp 138-140°C instead of **63j**. The compound was analysed for molecular formula $C_{17}H_{16}O_3S$. The IR (KBr) spectra showed $_{C=O}$ at 1700 cm^{-1} indicating the presence of carbomethoxy group. In its ^1H NMR ($CDCl_3$) spectrum (Fig. 1), the singlet for methylthio protons appeared at δ 2.50. The multiplet at δ 2.50-2.70 and the other multiplet at δ 2.76-2.96 (4H) were assigned to tetralone methylene protons. The singlet at δ 3.60 was assigned to carbomethoxy proton, the vinylic proton appeared at δ 5.40 as



3, 62, 63, h, n = 1
i, n = 2

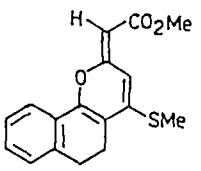
Scheme -13


CO2Me
SMe
SMe
OH
62-j
Cyclisation
63-j
1,2-addition
CO2Me
CH2
Li
61
1,4-addition
(83%)
67
3-j

Scheme-14

singlet, four aromatic protons appeared as a multiplet between δ 7.10-7.36 and H-5 proton showed a broad singlet at δ 7.63. The absence of pyrrolidine protons and the presence of ester methyl singlet, the exo-cyclic vinyl proton and the aromatic proton adjacent to the four protons of the ring confirms the structure for Methyl(5,6-dihydro-4-methylthio-2H-naphtho [1,2-b] pyran-2-ylidene) acetate **67**. Its molecular weight (300.364) was confirmed by its mass spectrum: m/z 300 (M^+,100%) which was in agreement with the assigned structure of **67**. The structure was further confirmed by its ^{13}C NMR ($CDCl_3$) spectrum. The signal observed for C-10b carbon showed marked up- field shift at δ 136.87, while C-2 carbon which is β- to carbomethoxy group showed marked down-field shift at δ 164.19. The characteristic ester carbonyl carbon showed signal at δ 168.998. The other important signals are described in Fig.2. The mechanism governing the formation of **67** is depicted in scheme 15. **61** in the presence of excess LDA yielded directly **67** in 83% yield without a trace of other isomeric product **63j**. The anion **61** appears to add in a γ-1,4-mode to yield the corresponding enaminoketone **64j** which appears to undergo intramolecular displacement of the pyrrolidine ring by oxygen to yield **67**. Because of strong donor pyrrolidine ring the β-carbon to the carbomethoxy group appears to facilitate intramolecular displacement to afford **67**. It is not necessary that all γ-1,4 adducts of anion **61** will lead to corresponding pyran ring system as such examples are illustrated in the following study. It therefore appears that the preferential pyran ring formation is due to the molecular orientation as shown in **69** where the nucleophilic β-carbon is thrown far away from

Fig.1 ^{1}H NMR (*400 MHz, $CDCl_3$*) spectrum of 67.

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EXPNO                    133
PROCNO                     1

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PW                         0
TE                         0
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Date                  911127
Time                    2.19
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DE                  77.5 usec
SWH               8064.52 Hz
NS                        64
OS                         2

F2 - Processing parameters
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SF          400 1343942 MHz
WDW                       no
SSB                        0
LB                  0.10 Hz
GB                      0.1
PC                     4.00

1D NMR plot parameters
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F1P                10.247 ppm
F1                 4100.00 Hz
F2P                -0.250 ppm
F2                 -100.00 Hz
PPMCM              0.34988 ppm/cm
HZCM              140.00000 Hz/cm
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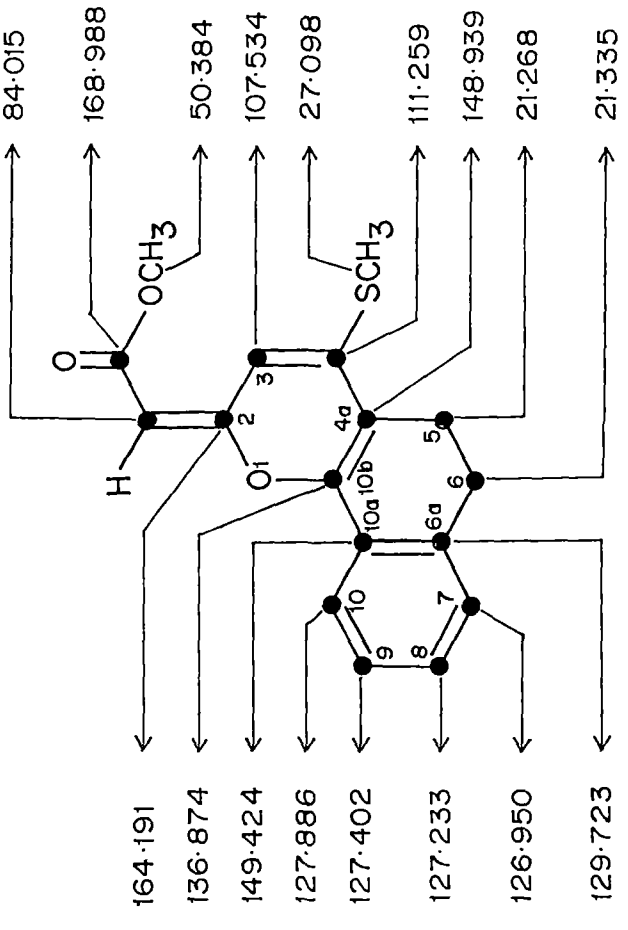
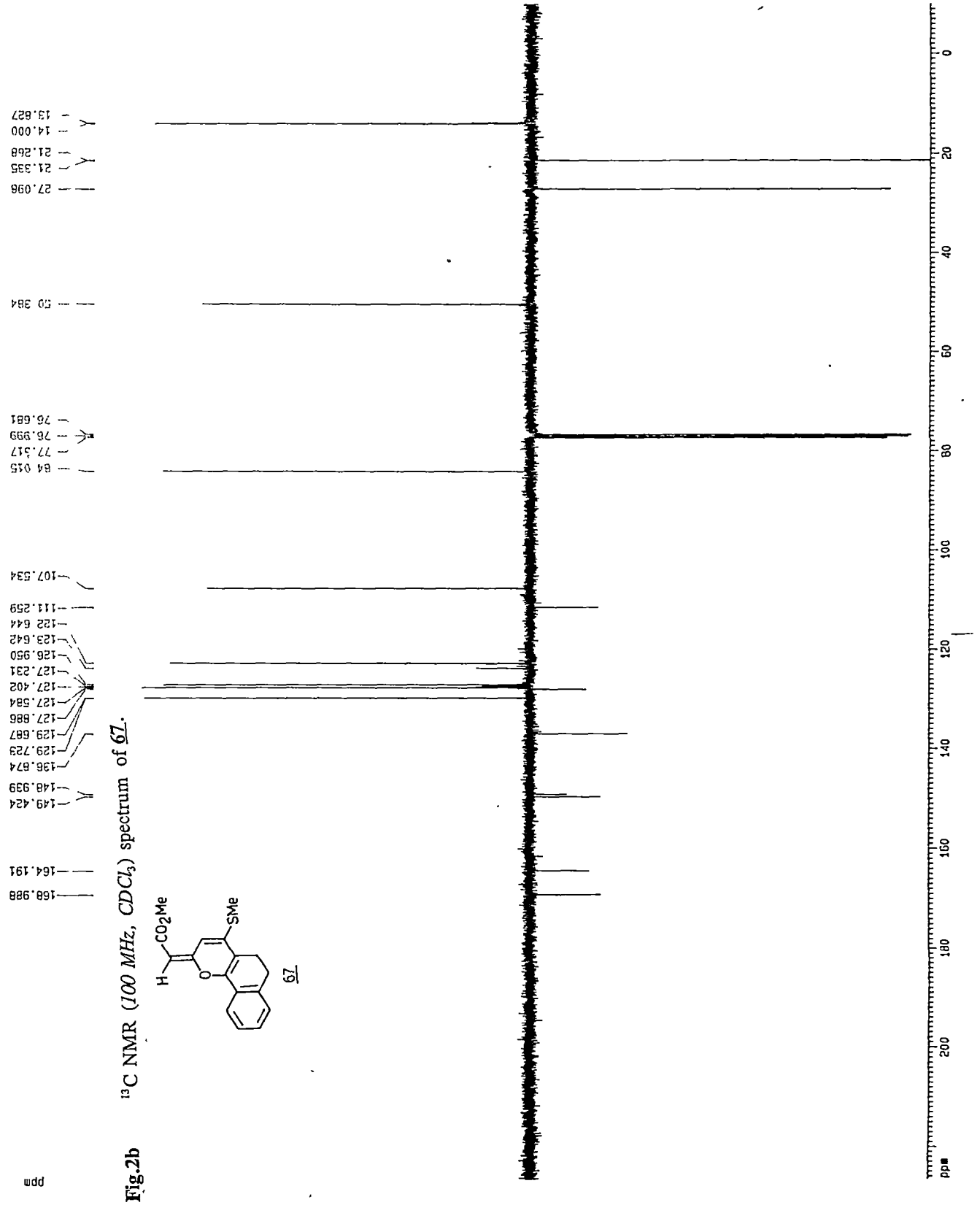
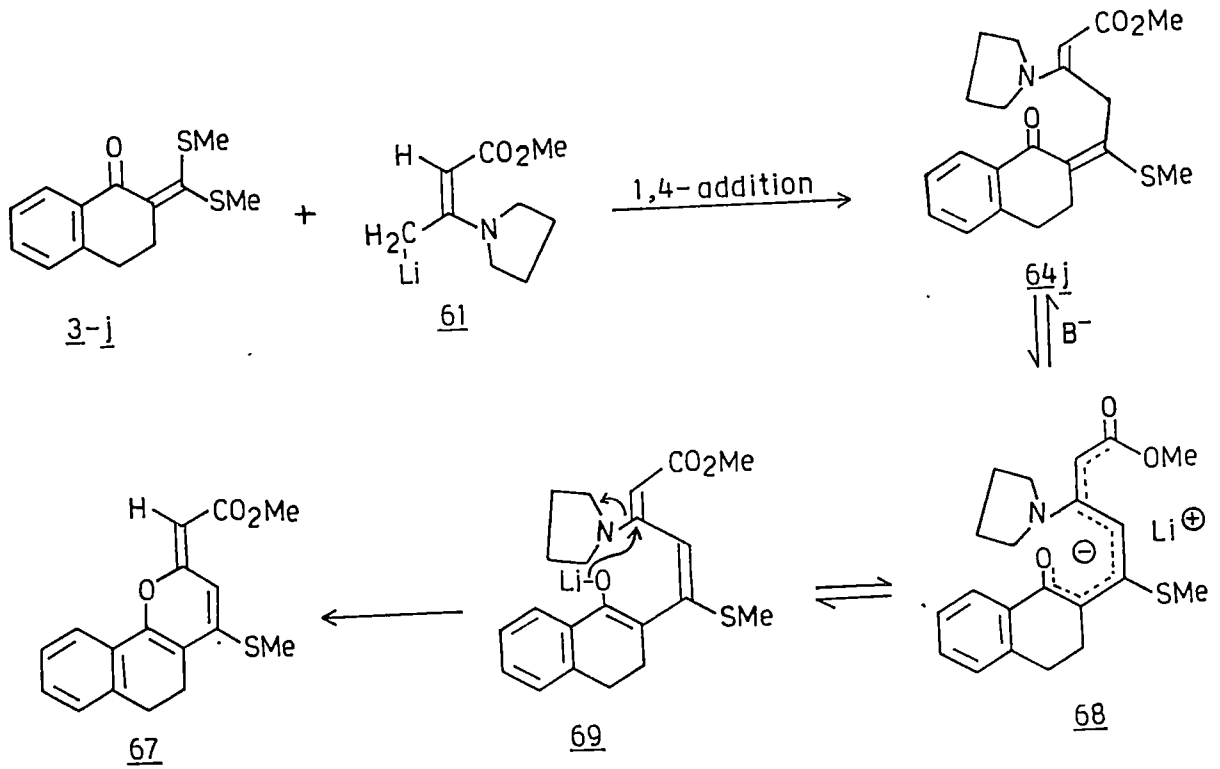
Fig.2a Structure & ^{13}C NMR data of *67*.





67

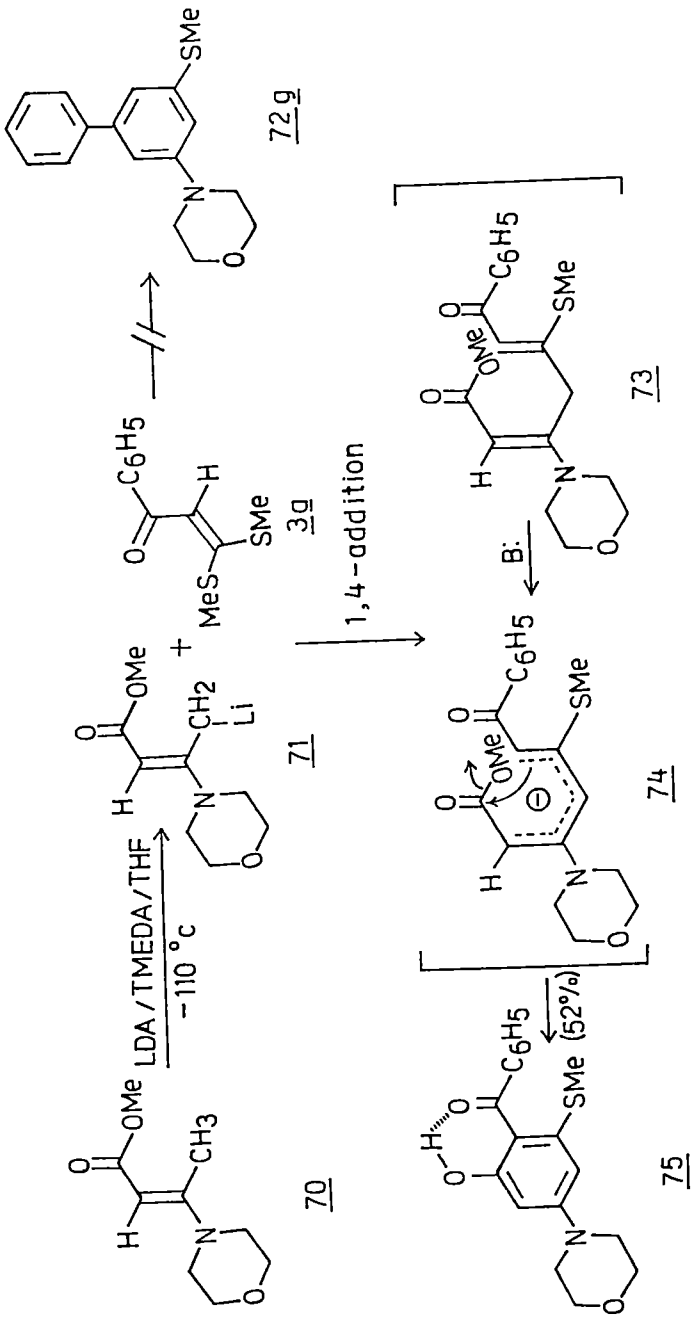
Fig.2b ^{13}C NMR (*100 MHz, $CDCl_3$*) spectrum of **67**.


O
SMe
SMe
3-j
+
H
CO2Me
H2C
Li
N
61
1,4-addition
CO2Me
N
O
SMe
64j
B⁻
O
OMe
N
Li⊕
O
SMe
68
CO2Me
N
Li-O
SMe
69
H
CO2Me
O
SMe
67

Scheme-15

carbonyl function due to steric reasons.

The lithiomethyl morpholino crotonate 71 generated in the presence of LDA-TMEDA complex at -110°C reacted with 3a to afford 2-benzoyl-3-methylthio-5-(1-morpholinyl)phenol 75 in 52% yield (scheme 16). Here again the expected product 72g was not observed though 3a was recovered unreacted in 38% yield. The structure of 75 was established on the basis of analytical and spectral data. The compound was analysed for the molecular formula $C_{18}H_{13}NO_3S$ with a molecular weight 329.401. In its IR (KBr) spectrum a strong band for ν_{OH} associated with intra molecular hydrogen bonding with carbonyl oxygen appeared at 3408 cm^{-1}. The characteristic low frequency carbonyl stretching at 1602 cm^{-1} (Benzophenone $\nu_{(C=O)}$ 1670-1660 cm^{-1} was attributed to electron donating morpholino group in the β-position coupled with a strong intramolecular hydrogen bonding. The structure was further confirmed from its ^1H NMR ($CDCl_3$) spectrum (Fig. 3). The singlet at δ 2.22 was assigned to thiomethyl protons and the multiplet at δ 2.23-2.30 was assigned to the morpholine (4H) protons neighbouring nitrogen and the other multiplet at δ 3.75-3.92 was assigned to other four protons of morpholine adjacent to oxygen atom. The double doublet at δ 6.30 with J = 3Hz was assigned to the phenolic aromatic proton next to hydroxy group. The other double doublet at δ 6.40 with J = 3Hz was assigned to the proton next to methylthio group. The aryl protons (5H) appeared as multiplet between δ 7.45-7.80. The hydroxy proton appeared at δ12.00 which disappeared on deuterium oxide shake. The mechanism governing the transformation in the presence of excess LDA appears to be the formation of anion 74 which undergoes



Scheme-16

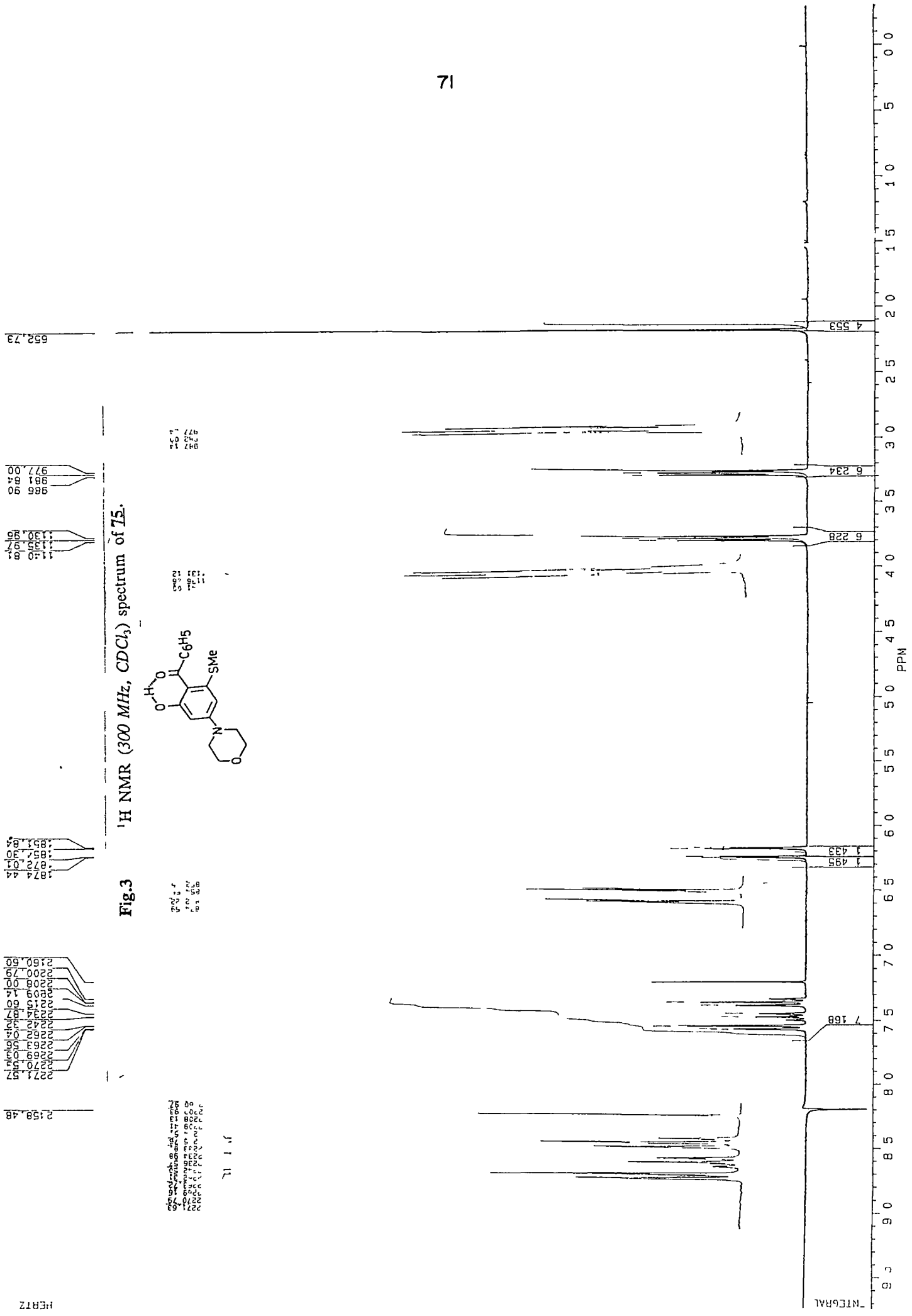


Fig.3 ^1H NMR (*300 MHz, $CDCl_3$*) spectrum of **75**.

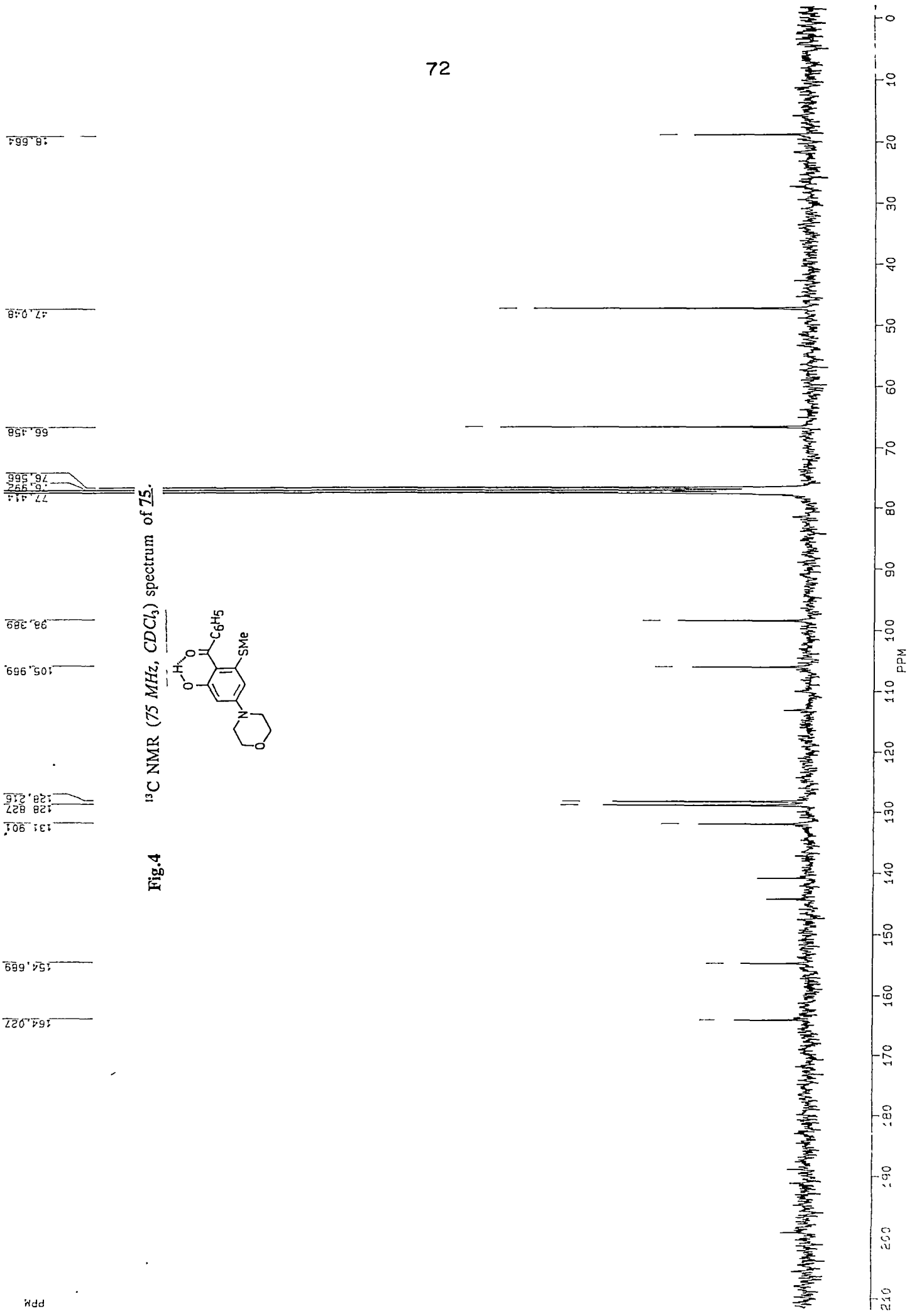
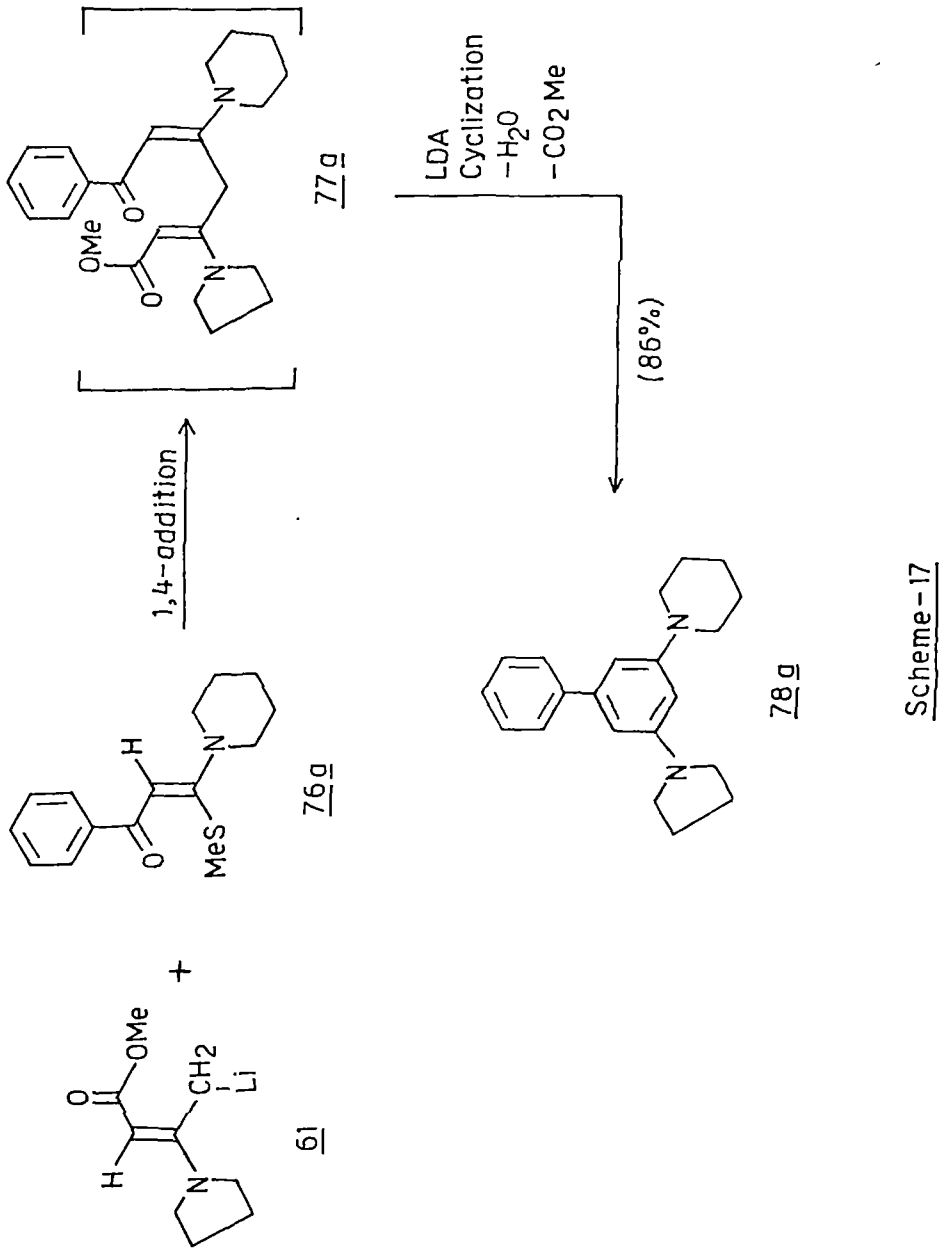


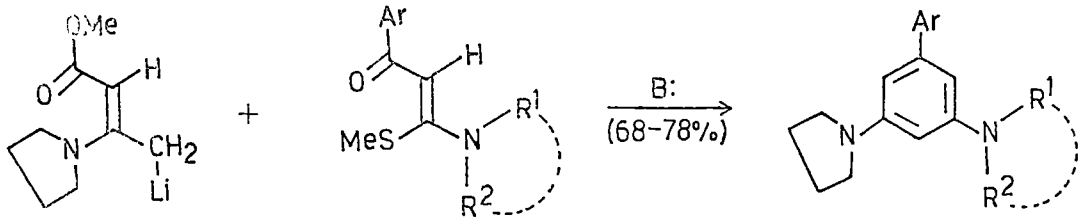
Fig.4 ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of *75*.

intramolecular condensation with ester carbonyl to yield amino phenol **75** (Fig. 4 for ^{13}C NMR). This reaction is under investigation for its general applciation and synthetic scope.

The reaction of Lithiomethyl pyrrolidino crotonate **61** with S,N-acetals **76a-c** (scheme 17 & 18) were next investigated with a view to synthesizing electron rich aromatic compounds carrying two cycloalkylamino groups. The anion **61** when reacted with **76a** underwent *in situ* cyclisation to afford the corresponding **78a** 1-(1-piperidyl)-3-phenyl-5-(1-pyrrolidinyl) benzene in 86% yield as colourless crystals (chloroform-hexane) mp 128-130°C. Its structure was established by its analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data which are described in the experimental section. The other diamino biphenyls **78b-e** were similarly obtained in 52-86% overall yields. Their analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data are in conformity with the assigned structures, described in the experimental section. The amino group in both the components appeared to play important role in isomeric distribution of the products. In the presence of stoichiometric amount of LDA-TMEDA complex, often the unreacted S,N-acetal were recovered, while in the presence of excess LDA-TMEDA complex the initial 1,4-adduct **77** appeared to rapidly undergo anionic cyclisation to yield the corresponding diamino biphenyls **78** leaving no chance for the isolation of adduct **77** for acid induced cyclization. In case of γ-1,4-adduct of α-tetralone mercaptal there was different behaviour as illustrated in page 11. However, there was one exception, where we observed the elimination of diethylamine when **61** was added to corresponding


1,4-addition
LDA
Cyclization
$-H_2O$
$-CO_2Me$
(86%)
OMe
MeS
CH_2
Li
77 a
76 a
61
78 a

Scheme-17

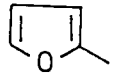


61 76 b-e 78 b-e

76,78,b, Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_4-$

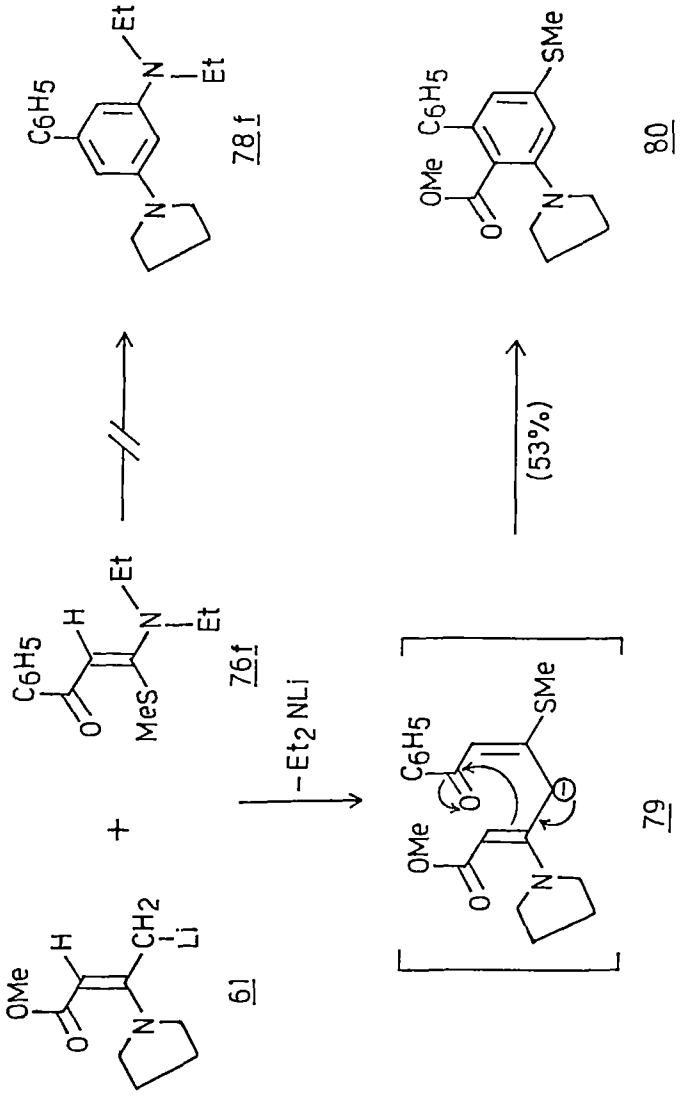
c, Ar = 4-Cl C_6H_4 ; $R^1 = R^2 = -(CH_2)_5-$

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-18

diethylamino S,N-acetals **76f** under the described reaction conditions to yield the corresponding carboxylate **80** (scheme 19) as colourless crystals (chloroform-hexane) mp 73-74°C involving the intermediacy of **79** instead of the expected diethylamino biphenyl **78f**. In all the reaction of the anionic addition to S,N-acetals generally the methylthio group is preferentially eliminated and few examples of this nature have been observed in the course of this investigation. The structure of biphenyl **80** was established on the basis of its analytical and spectral data. It was analysed for molecular formula $C_{19}H_{21}NO_2S$ and molecular weight 327.429 was confirmed by its mass spectrum (Fig. 5) at m/z 295 (M^+-32,100%). Its IR(KBr) spectrum shows ester carbonyl stretching at 1714 cm^{-1}. In its ^1H NMR ($CDCl_3$) spectrum the multiplet (4H) of methylene protons appeared at δ 1.83-2.13. The methylthio proton appeared as singlet at δ 2.33, the NCH_2 four protons appeared at δ 3.23-3.50, and a singlet at δ 3.93 was assigned to ester methoxy protons. The broad singlet centered at δ 6.84 was assigned to the two aromatic protons. The five aromatic protons appeared between δ 7.31-7.81 as multiplet (Fig. 6 for ^{13}C NMR). However, in one case a mixture of biphenyls **72,78** was observed. When **61** was reacted with morpholino S,N-acetal **76g** which afforded the corresponding **72g** in 15% and **78g** in 85% yields respectively. Similarly, **76h** yielded the corresponding mixtures of **72h** (40%) and **78h** (60%) (scheme 20). The pure biphenyls were isolated by column chromatography using silica gel (ethylacetate-Hexane) and the structures were established on the basis of their analytical (CHN) and spectral (IR, ^1H NMR, ^{13}C NMR, Mass) data (Fig. 7-10) which are described in the experimental section. When



Scheme-19

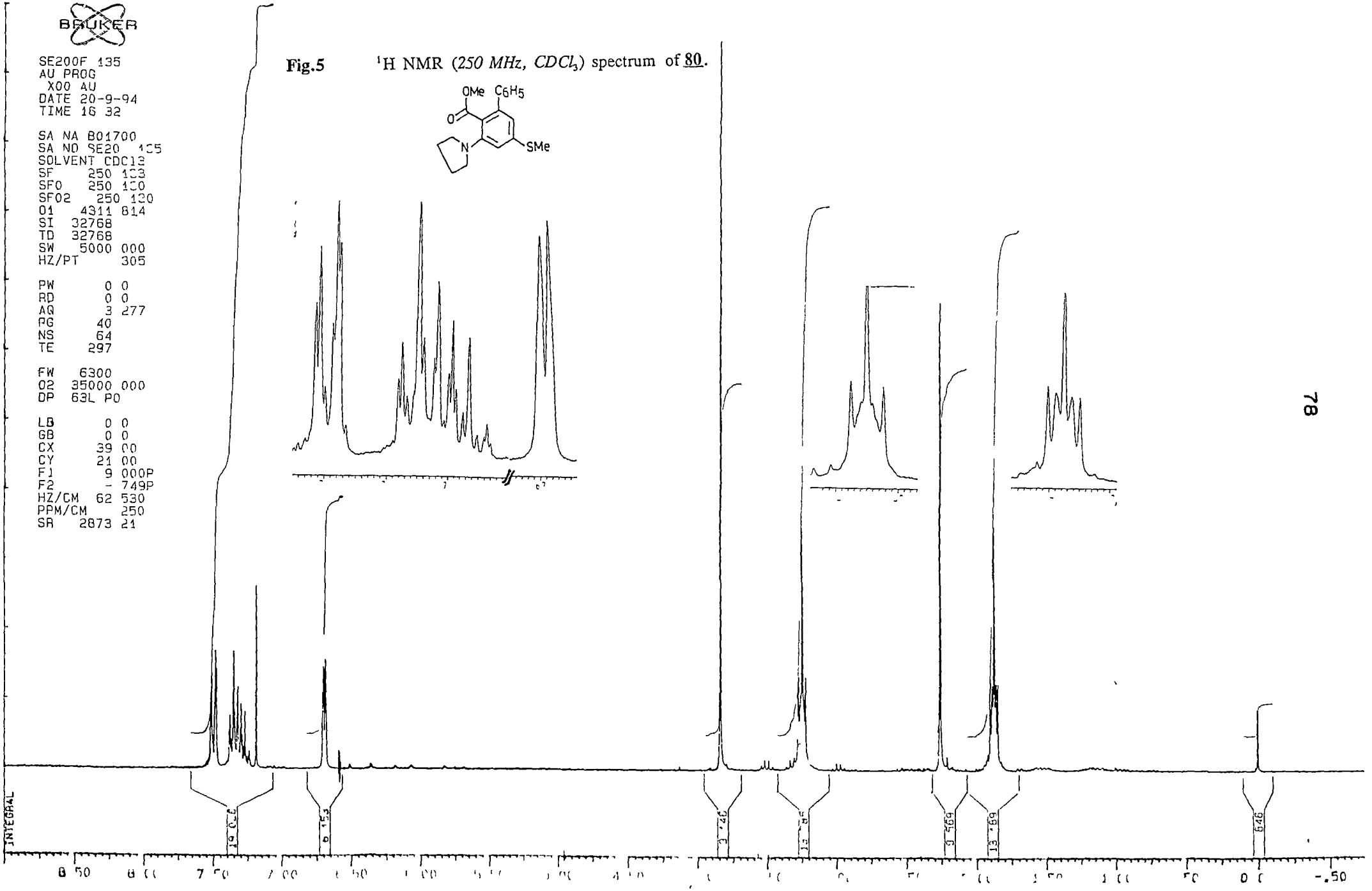


Fig.5 ^{1}H NMR (*250 MHz, $CDCl_3$*) spectrum of **80**.

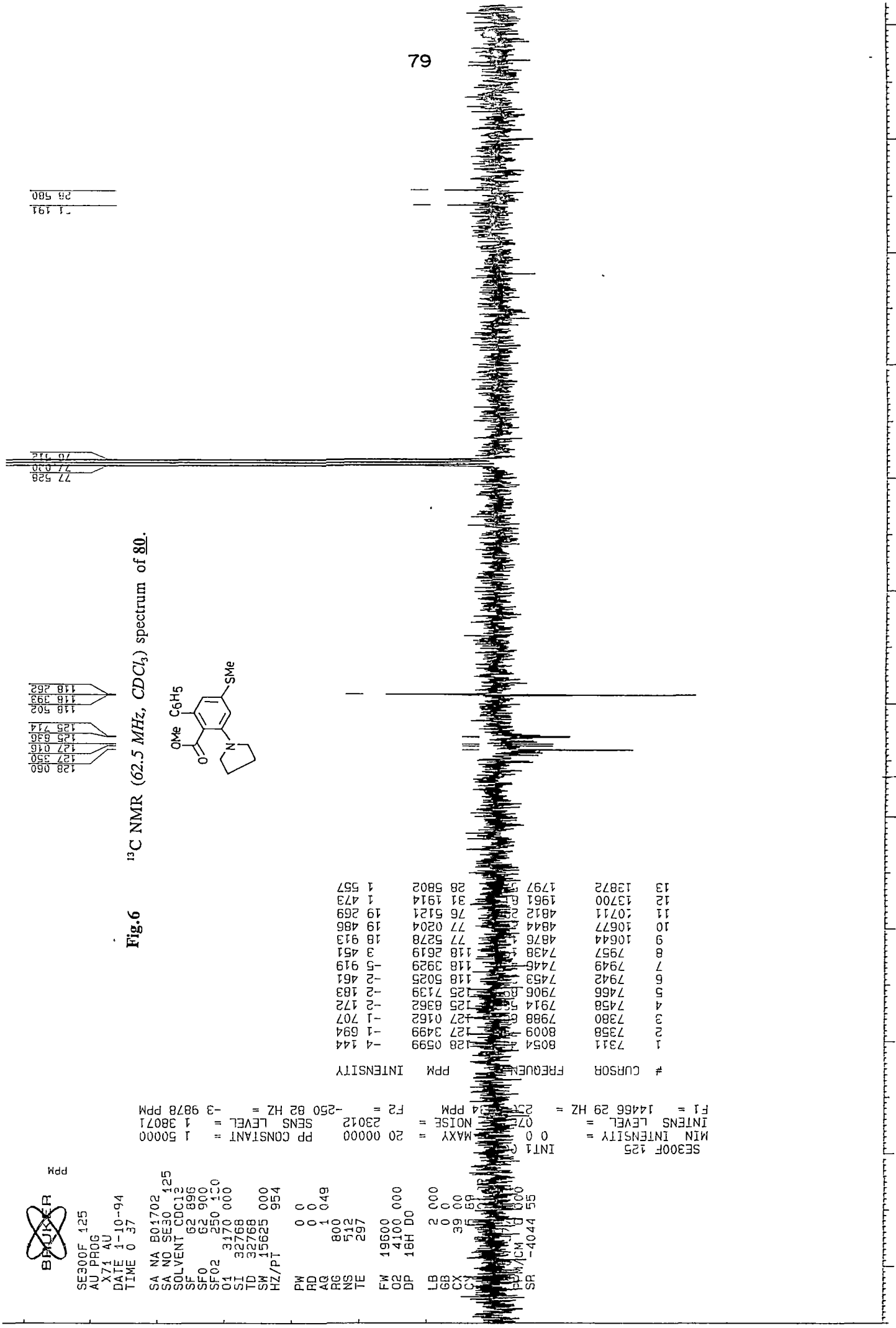
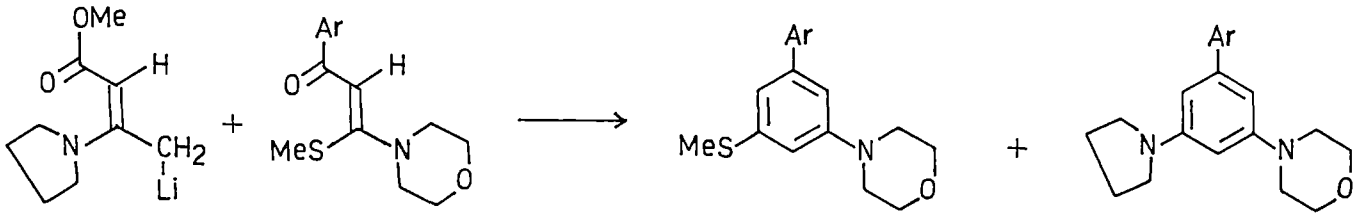


Fig.6 ^{13}C NMR (*62.5 MHz, $CDCl_3$*) spectrum of **80**.



61 + 76 g-h → 72 g-h + 78 g-h

76, 72, 78, g, Ar = C_6H_5

h, Ar = 4-Cl C_6H_4

	72 : 78
g	15 : 85
h	40 : 60

Scheme-20

Fig.7 ^{1}H NMR (*300 MHz, $CDCl_3$*) spectrum of 72h.

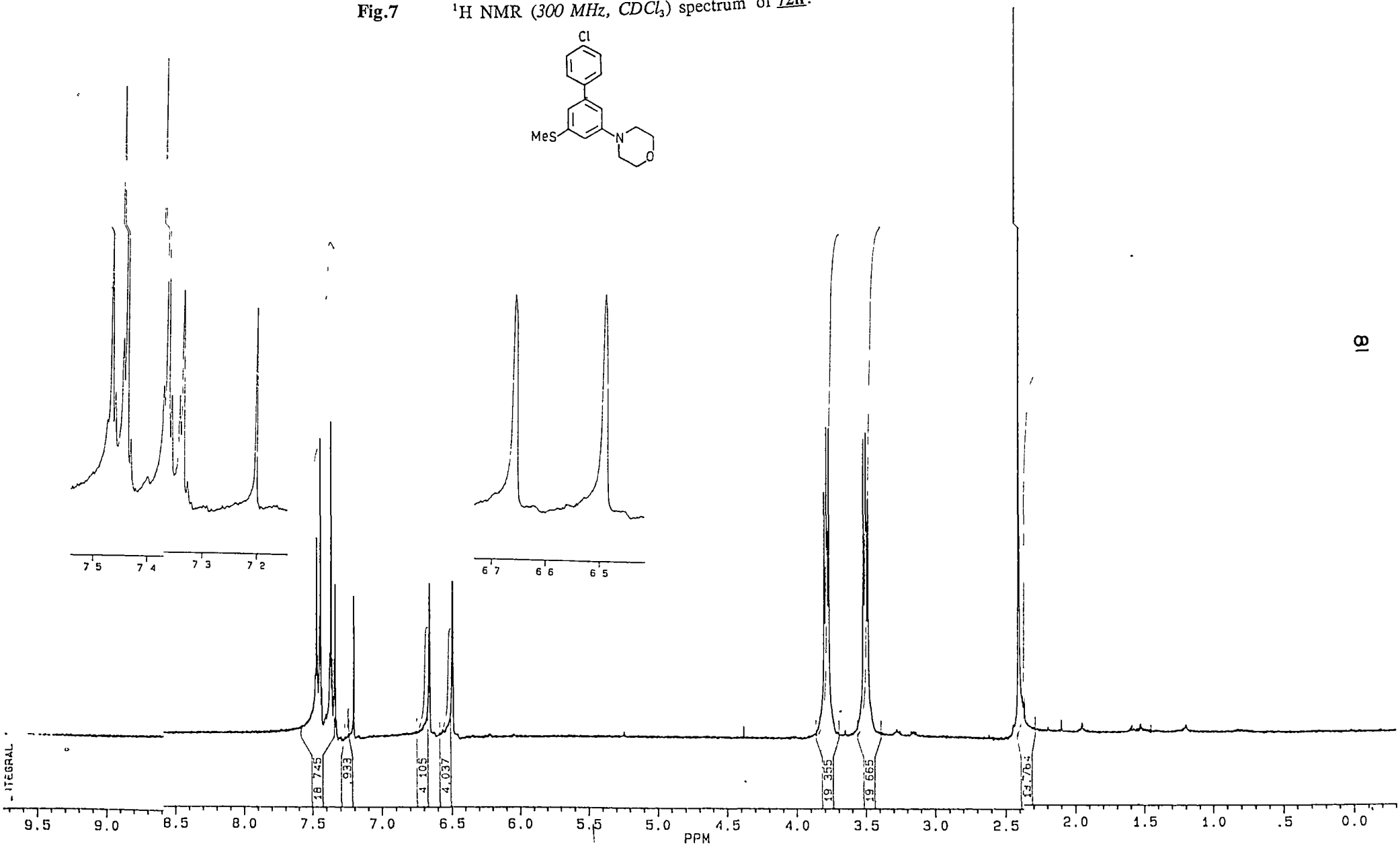
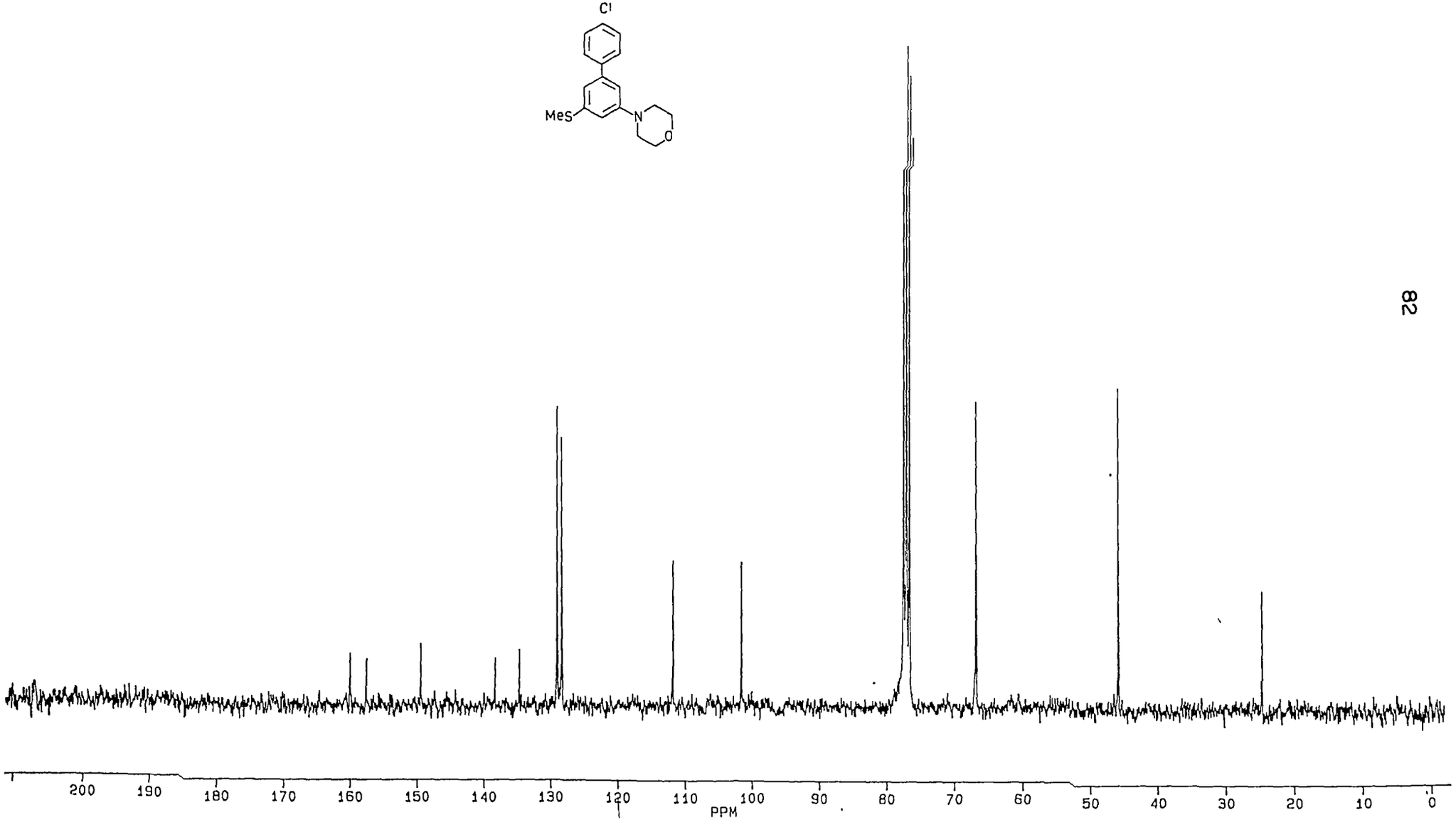


Fig.8 ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of 72h.



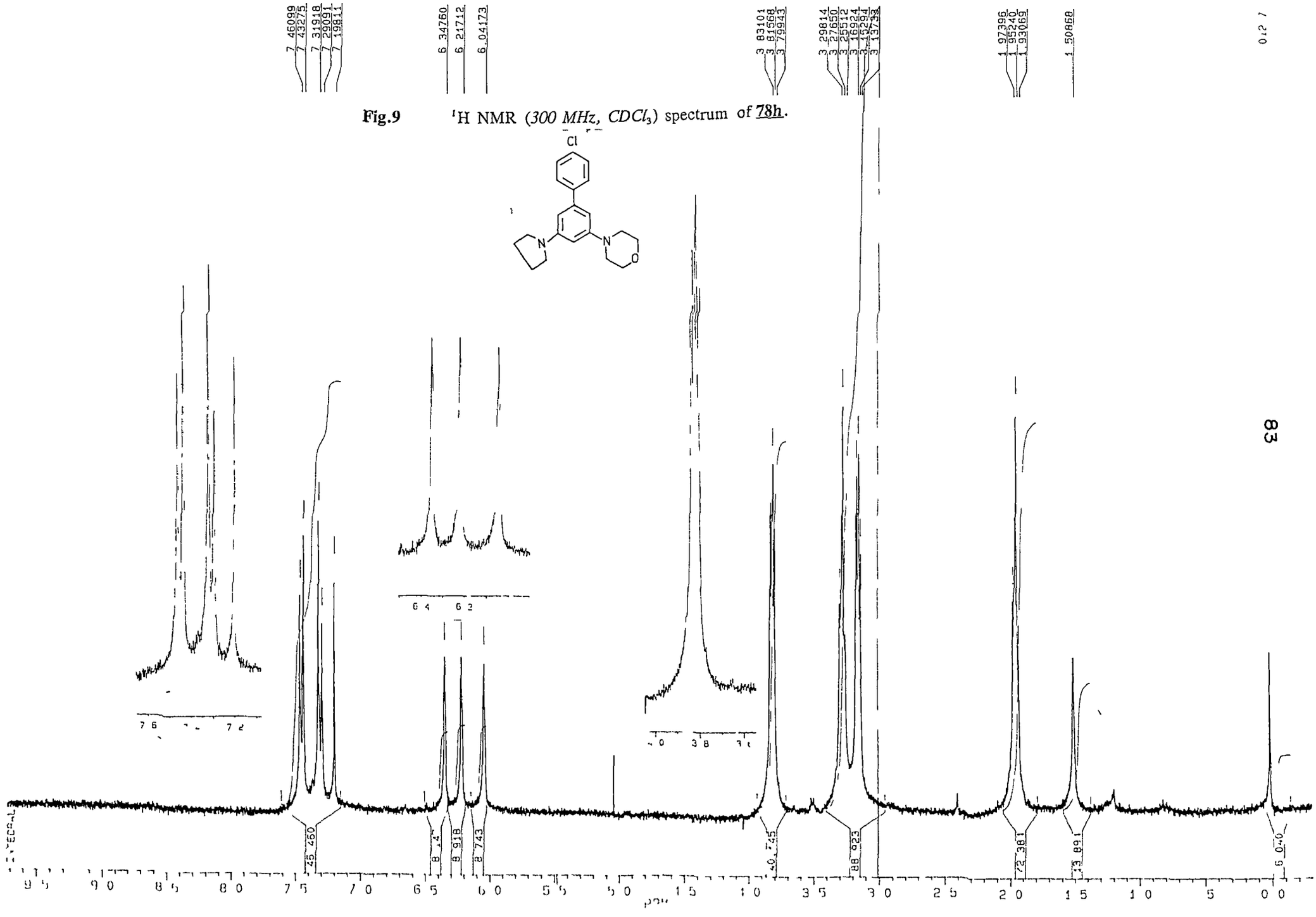


Fig.9 ^{1}H NMR (*300 MHz, $CDCl_3$*) spectrum of <u>78h</u>.

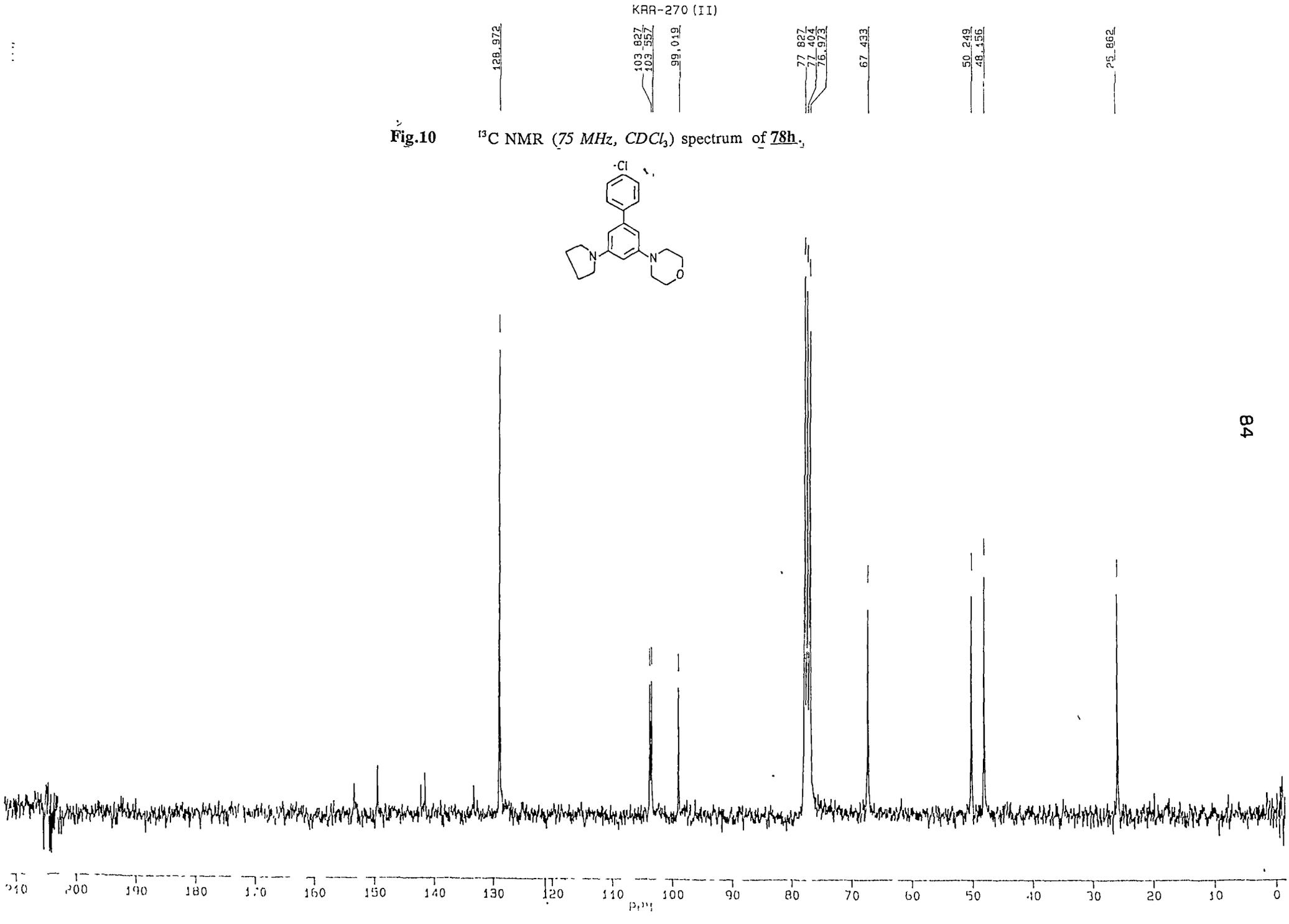
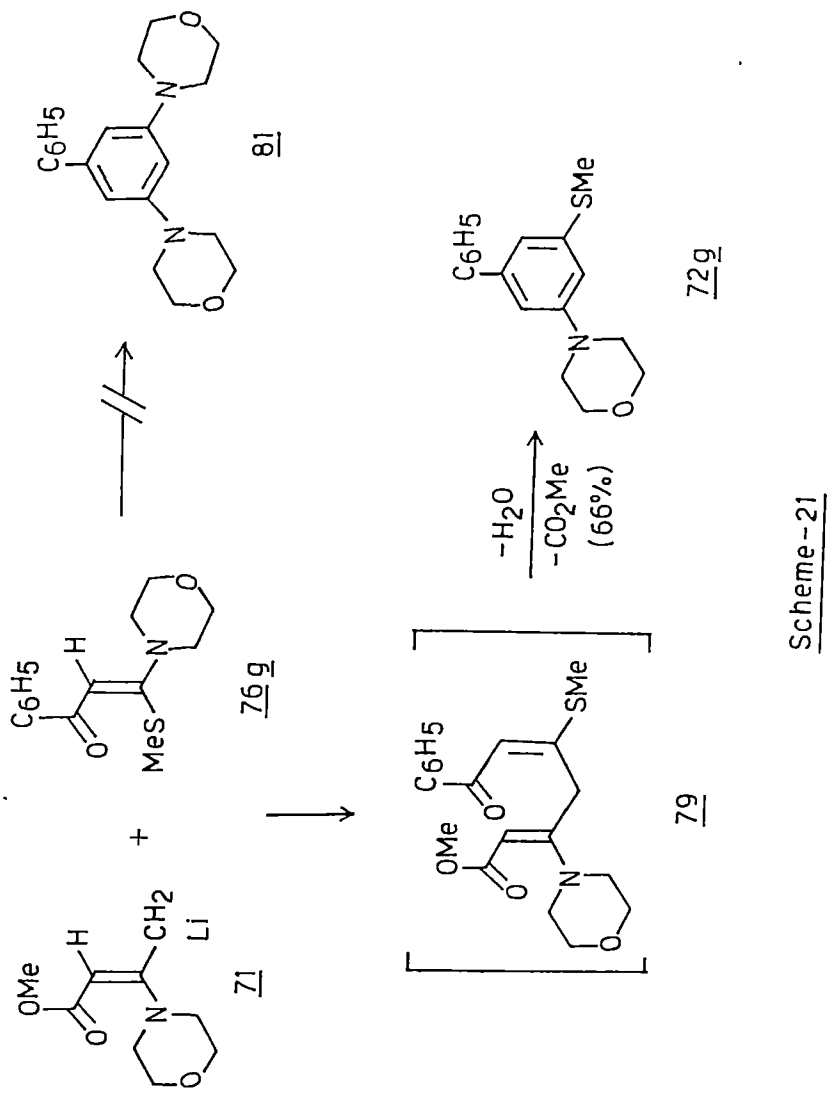


Fig.10 ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of 78h.



Scheme-21

morpholino lithiocrotonate **71** was reacted with S,N-acetal **76g** under similar reaction conditions 3,5-dimorpholino biphenyl **81** was not formed while the corresponding 1-methylthio-5-(1-morpholinyl)-3-phenyl benzene **72g** was obtained in 28% yield alongwith unreacted starting materials **76g** in 52% yield (scheme 21). The structure of **72g** was in conformity with its analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data which are described in experimental section.

II.4 *Conclusion*

The reaction of aminocrotonates with both α-oxoketene S,S-acetals and S,N-acetals display diverse reaction mode to afford the corresponding aromatic rings. And the structural diversity is largely dependent on the aminocrotonate anion, depending on the nature of secondary amine used as well as the nature of amine in S,N-acetals also. An efficient method is developed for the synthesis of amino aromatics by reacting aminocrotonate anion with α-oxoketene S,S- and S,N-acetals. The methodology was of further scope for its synthetic applications with a variety of amino group at 3,5 position of one of the benzene rings. This methodology gives access to the synthesis of hitherto unknown bis(cycloalkylamino)biphenyls which constitutes important class of compounds as potential electron donors and bases. These compounds are of further interest as liquid crystal display devises which will be tested for their liquid crystal properties elsewhere. All the diamino compounds displayed voilet intense colour when they were dissolved in halogenated solvents such as CCl_4, $CHCl_3$, CH_2Cl_2. The violet colour turned to dark black on

keeping the solutions, the nature of solvent interaction with these compounds are being investigated.

II.5 *Experimental Section*

General

Melting points were determined on a "Thomas-Hoover" capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 and Perkin-Elmer 983 spectrometers. ^{1}H NMR (90MHz) were recorded on Varian EM-390. High resolution ^{1}H NMR (250 MHz, 300 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker ACF 300 spectrometer. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethyl silane (for ^{1}H NMR), the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR). The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, dd= double doublet, t = triplet, q = quartet, m = multiplet. Mass measurements were carried out with Jeol JMS D-300 spectrometer. Masses (MS) are reported in unit of mass over charge (m/z), the molecular and base peaks are indicated by (M) and (%) respectively. Elemental analyses were performed on a Heraeus CHN-O-Rapid Analyzer.

All reactions involving organolithium were performed in oven-dried glassware under a dry nitrogen/argon atmosphere using standard syringe-septum technique. Low temperature reactions were carried in a bath made of methanol, pentane (50:50 v/v) mixture and liquid nitrogen. Analytical thin layer

chromatography (tlc) were performed on glass plates (18x6 and 18x4 cm) coated with ACME's silicagel containing 13% calcium sulphate as binder and various combinations of ethyl acetate-hexane, ethylacetate-benzene, benzene were used as eluents. Visualization of spots was accomplished by exposure to Iodine vapour or potassium permanganate (acidic) solution. ACME's silicagel (60-120 mesh) is used for column chromatography. Solvents for chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals and Reagents

Commercial available pyrrolidine, piperidine, morpholine, diethyl amine (secondary amines) were purified by simple distillation. N,N,N',N'-tetramethylethylenediamine (TMEDA) and diisopropyl amine were distilled from potassium hydroxide prior to use. Tetrahydrofuran (THF) was obtained anhydrous by distillation after the characteristic blue colour of *in situ* generated sodium diphenyl ketyl[24] was found to persist. Dry benzene[25a] was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Dry ether[25b] was obtained by keeping over calcium chloride (fused) and stored over sodium wire. Borontrifluoride-ethyl ether complex (Merck) was used as such. Lithium Ingot (Aldrich) were cut into smaller pieces and washed with dry ether twice before use. n-Butyl lithium was prepared according to the reported procedure[26]. Lithium diisopropyl amide (LDA) was prepared according to the literature procedures[27].

Starting materials

Commercial available ketones of acetophenone, 4-chloroacetophenone, 4-methoxyacetophenone, acetone, cyclohexanone and cycloheptanone were purified either by simple distillation/ distillation under reduced pressure or crystallisation before use. 2-Acetyl furan was purchased from Aldrich and used as such. 1-Tetralone bp 140-150°C (10 mm)[28], 2-acetyl thiophene bp 214°C[29], methyl 2-napthyl ketone (2-acetyl naphthalene) mp 49°C (lit.[30], 53°C), dimethyltrithiocarbonate bp 225°C (760 mm)[31], methyl 2-pyrrolidine-2-butenoate mp 70-71°C (lit.,[32]72°C) methyl 2-morpholino-2-butenoate were prepared according to the earlier reported procedures[32]. α-oxoketene S,S-acetals **3a-j**[33], S,N-acetals **76a-h**[34] required for the present investigation were prepared according to the earlier reported literature procedures which are given below.

<u>General procedure for the preparation of oxoketene dithioacetals 3(a-j) using sodium tert. butoxide</u>

A mixture of ketone (0.2 mol) and carbon disulphide (0.2 mol) was added dropwise to an ice-cold and well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (200 ml) and the reaction mixture was allowed to stir at ambient temperature for 5-6 hrs. Acid free dimethyl sulphate (0.2 mol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stir at room temperature for 6-10 hrs. The reaction mixture was poured over aqueous saturated ammonium chloride solution (250 ml) and the layers were separated. The

aqueous layer was extracted with benzene (100 ml) and combined benzene extracts were washed with water (4x250 ml), dried (Na_2SO_4) and evaporated. Trituration of the oil residue with hexane gave the dithioacetals as yellow crystalline solid in good yields. Liquid dithioacetals were purified by passing through silica gel column using hexane-ethylacetate (9:1 to 8:2) as eluent.

All the known dithioacetals were characterized by comparison of their melting points, NMR, IR spectra with those of reported data and of authentic sample.

Preparation of oxoketene S,N-acetals (76a-h); General procedure:

(i) Preparation of methyl β-oxodithio carboxylate; General procedure

To a well stirred suspension of NaH (5g, 0.01 mol, 50% suspension) in dry benzene (100 ml), dimethyl trithiocarbonate (7.60g, 0.054 mol) is added and the mixture is refluxed with stirring for 10 min. A solution of the appropriate ketone (0.05 mol) in dry benzene (50 ml) is slowly added dropwise over a period of 3.5-4h, the mixture is further refluxed for 2h, then allowed to cool and poured into ice cold water (250 ml). The aqueous layer is separated, washed with benzene (200 ml) acidified with 3N HCl or 20% CH_3COOH, and extracted with chloroform (2x150 ml). The combined organic extract is dried over sodium sulfate and evaporated to give the product (single spot on tlc) which is pure enough (>95% purity according to NMR analysis) for further reactions.

(ii) Preparation of β-oxodithioaceticacidamide; General procedure:

A solution of methyl β-oxodithiocarboxylate (0.01 mol) and the appropriate secondary amine (0.01 mol) in ethanol (25 ml) was refluxed for 5-7 hr (monitored by tlc), ethanol removed on a water bath, residue triturated with hexane, and the crude thiamides thus obtained were crystallised from ether-hexane as yellow crystalline solids.

(iii) Preparation of oxoketene S,N-acetals; General procedure:

A suspension of thiamide (0.004 mol) and potassium carbonate (0.56g, 0.004 mol) in acetone (30 ml) was refluxed for 3 hr with stirring, it was cooled and to this was added methyl iodide (0.71g, 0.005 mol) with stirring and the mixture further stirred for 3 hr at room temperature. It was then poured over crushed ice, acidified with 20% acetic acid and extracted with chloroform, dried (Na_2SO_4) and solvent evaporated to give ketene S,N-acetals (73a-i) which were purified by passing through silica gel column using hexane-ethylacetate (2:1) as an eluent.

All the known S,N-acetals were characterised by comparison of their melting points, NMR, IR spectra with those of reported data and of authentic sample.

General procedure for the generation and reaction of lithium methyl 3-pyrrolidyl-2-butenoate (61) with α-oxoketene dithioacetals (3a-i); 1-methylthio 3(1-pyrrolidyl)-5-substituted/ 5,6-annelated benzenes (63a-i)

To a chilled (0°C) solution of 0.87 ml (70 mmol) of diisopropyl

amine in 10 ml of dry tetrahydrofuran (THF) under dry nitrogen was added 60 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropylamide (60 mmol) under dry nitrogen at -110°C was added 0.68g (0.90 ml, 60 mmol) TMEDA, and reaction mixture was stirred at the same temperature for 10-15 min. followed by addition of 0.85g (50 mmol) of methyl 3-pyrrolidyl-2-butenoate in 20 ml of dry THF. The resulting solution was stirred at -110°C for 30-40 min. Then the coolant was removed and stirring was continued for 1 hr. To the resulting homogenous solution was added 50 mmol of α-oxoketene dithioacetals in 20 ml dry THF dropwise at -110°C stirred for 30-45 min and overnight at ambient temperature. The reaction mixture was quenched with saturated ammonium chloride solution (100 ml) and extracted with chloroform (2x50 ml), the combined organic phase was washed with water (2x50 ml), dried over sodium sulfate and evaporated to give crude carbinol **59a-i** in moderate to good yields.

To a solution of crude carbinol (Ca. 50 mmol) in dry benzene (25 ml), borontrifluride-etherate (75 mmol) was added and the reaction mixture was stirred under reflux for 30-45 min. After the reaction was complete (monitored by tlc), it was brought to room temperature and poured into saturated sodiumbicarbonate solution (100 ml), extracted with ether (3x25 ml) and the combined organic extracts were washed with water (2x50 ml), dried over sodium sulfate and concentrated to give the crude product which were chromatographed on silica gel using hexane as eluent.

1-Methylthio-3-phenyl-5-(1-pyrrolidyl) benzene 63a:

Colourless crystals; yield 0.97g (72%); mp 95-96°C (chloroform-

hexane); R_f 0.79 (benzene).
IR(KBr) :γ_{max} = 1597, 1570, 1472, 1435, 1009 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$); δ = 1.85-2.10 (m, 4H, CH_2); 2.40 (s, 3H, SCH_3); 3.15-3.41 (m, 4H, NCH_2); 6.30 (brs, 1H, ArH); 6.37 (brs, 1H, ArH); 6.67 (brs, 1H, ArH); 7.15-7.58 (m, 5H, ArH).
MS : m/z (%) = 269 (M^+,60), 268 (29).
Anal : Calc. for $C_{17}H_{19}NS$ (269.391): C 75.79; H 7.12; N 5.20. Found C 75.80; H 7.09; N 5.20%.

3-(4-Chlorophenyl)-1-methylthio-5-(1-pyrrolidyl) benzene 63b:
Colourless crystals; yield; 1.18g (78%); mp 98-99°C (chloroform-hexane); R_f 0.89 (benzene)
IR (KBr): γ **max** = 2946, 1640, 1610, 1515, 1440, 1180, 1040 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 1.90-2.12 (m, 4H, CH_2); 2.54 (s, 3H, SCH_3); 3.20-3.46 (m, 4H, NCH_2); 6.50 (brs, 2H, ArH); 6.75 (brs, 1H, ArH); 7.23-7.60 (m, 4H, ArH).
MS: m/z(%) = 303 (M^+,15.61).
Anal : Calc. for $C_{17}H_{18}ClNS$ (303.834): C 67.20; H 5.97; N 4.67. Found C 67.20; H 7.09; N 5.20%.

1-Methylthio-3-(4-methoxyphenyl)-5-(1-pyrrolidyl) benzene 63c:
Colourless crystals; yield 1.15g (77%); mp 88.5°C (chloroform-hexane); R_f 0.87 (benzene).
IR(KBr): γ_{max} = 2918, 1589, 1452, 1247 cm^{-1}.
^1H NMR (90MHz, CCl_4): δ=1.85-2.10 (m, 4H, CH_2); 2.41 (s, 3H, SCH_3); 3.18-3.38 (m, 4H, NCH_2); 3.75 (s, 3H, OCH_3); 6.32 (d, 2H, J=4.15Hz, ArH); 6.72-6.82 (m, 2H, ArH); 7.31-7.52 (m, 2H, ArH).
MS: m/z (%) = 299 (M^+,52.71).
Anal : Calc. for $C_{18}H_{21}NOS$ (299.421): C 72.20; H 7.07; N 4.68.

Found C 72.20; H 7.09; N 4.80%.

1-Methylthio-3-(2-naphthyl)-5-(1pyrrolidyl)benzene 63d:

Brown crystals; yield 1.60g (82%); mp 123°C (chloroform-hexane); R_f 0.83 (benzene).

IR(KBr) :γ_{max} = 2829, 1588, 1453, 809 cm^{-1}.

^1H NMR (90MHz, CCl_4): δ=1.90-2.22 (m, 4H, CH_2); 2.48 (s, 3H, SCH_3); 3.22-4.42 (m, 4H, NCH_2); 6.41 (brs, 1H, ArH); 6.55 (brs, 1H, ArH); 6.81 (brs, 1H, ArH); 7.2-7.48 (m, 2H, ArH); 7.60-7.98 (m, 5H, ArH).

MS: m/z (%) = 319 (M^+,47.09).

Anal: Calc. for $C_{21}H_{21}NS$ (319.451): C 64.43; H 5.41; N 3.58. Found C 64.51; H 5.49; N 3.62%.

3-(2'-Furyl)-1-methylthio-5-(1-pyrrolidyl)benzene 63e:

Viscous liquid ; yield 0.80g (62%); R_f 0.75 EtoAc/hexane (1:9).

IR (neat): γ_{max} = 2850, 1580, 1460, 1360, 1260 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ = 1.73-2.00 (m, 4H, CH_2); 2.37 (s, 3H, SCH_3); 3.06-3.35 (m, 4H, NCH_2); 6.16 (brs, 1H, ArH); 6.30 (d, 1H, J=1.5Hz, ArH); 6.45 (s, 1H, 3'-furyl); 6.48 (brs, 1H, 4'-furyl); 6.78 (brs, 1H, ArH); 7.36 (brs, 1H, 5'-furyl).

MS: m/z (%) = 259 (M^+,100).

Anal: Calc. for $C_{15}H_{17}NOS$ (259.361): C 69.46; H 6.61; N 5.40. Found C 69.67; H 6.62; N 5.59%.

1-Methylthio-5-(1-pyrrolidyl)-3-(2'-thienyl) benzene 63f:

Viscous liquid; yield 0.93g (68%); R_f 0.84 EtOAc/hexane (1:9).

IR(neat): γ_{max} = 2945, 1620, 1498, 1435, 1265 cm^{-1}.

^1H NMR (90MHz, CCl_4): δ = 1.89-2.30 (m, 4H, CH_2); 2.40 (s, 3H, SCH_3) 3.09-3.37 (m, 4H, NCH_2); 6.28 (brs, 1H, ArH); 6.41 (brs,

1H, ArH); 6.71 (brs, 1H, ArH).
Anal: Calc. for $C_{19}H_{17}NS_2$ (275.417): C 65.41; H 6.22; N 5.08. Found C 65.50; H 6.41; N 5.90%.

3-Methyl-1-methylthio-5-(1-pyrrolidyl)benzene 63g:
Viscous liquid; yield 0.83g (80%): R_f 0.68 (benzene).
IR(neat) : γ_{max} = 3010, 1655, 1589, 1562, 1430, 1225 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=1.65-1.95 (m, 4H, CH_2); 2.12 (s, 3H, CH_3); 2.39 (s, 3H, SCH_3); 2.95-3.26 (m, 4H, NCH_2); 6.05 (brs, 1H, ArH); 6.18 (brs, 1H, ArH); 6.3 (brs, 1H, ArH).
MS: m/z (%) = 207 (M^+, 53.34).
Anal: Calc. for $C_{12}H_{17}NS$ (207.331): C 69.51; H 8.27; N 6.75. Found C 69.70; H 8.40; N 6.90%.

1-Methylthio-3-pyrrolidino 5,6,7,8-tetrahydronaphthalene 63h:
Pale yellow crystals; yield 0.79g (64%); mp 93-94°C (chloroform-hexane): R_f 0.86 (benzene).
IR(KBr): γ_{max} = 3015, 2945, 1644, 1522, 1418, 1195 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 1.51-2.04 (m, 8H, $-CH_2-$); 2.35 (s, 3H, SCH_3); 2.52-2.78 (m, 4H, CH_2); 3.03-3.35 (m, 4H, NCH_2); 6.08 (brs, 1H, ArH); 6.19 (brs, 1H, ArH).
MS: m/z(%) = 247 (M^+,60), 239(20).
Anal: Calc. for $C_{15}H_{21}NS$ (247.291): C 72.85; H 8.52; N 5.66. Found C 72.87; H 8.67; N 5.68%.

1-Methylthio-3-(1-pyrrolidinyl)-6,7,8,9-tetrahydro-5H-benzo-1-cycloheptene 63i:
Viscous liquid; yield 0.61g (58%); R_f 0.85 EtOAc/hexane (1.5:8.5).
IR(KBr): γ_{max} = 2914, 1675, 1445, 1183 cm^{-1}.

^{1}H NMR (90MHz, $CDCl_3$): δ = 1.40-1.83 (m, 6H, $-CH_2-$); 1.89-2.16 (m, 4H, CH_2); 2.31 (s, 3H, SCH_3); 2.63-2.84 (m, 2H, CH_2); 2.84-3.03 (m, 2H, CH_2); 3.16-3.40 (m, 4H, NCH_2); 6.33 (d, 1H, J=3Hz, ArH); 6.50 (d, 1H, J=3Hz, ArH).

Anal: Calc. for $C_{16}H_{23}NS$ (213.371): C 67.54; H 10.86; N 6.56. Found C 67.57; H 10.90; N 6.72%.

Procedure for the preparation of methyl (5,6-dihydro-4-methylthio-2H-naphtho[1,2-b] pyran-2-ylidene) acetate (67)

To an ice-cold solution of 2.61 ml (210 mmol) of diisopropyl amine in 10 ml of dry tetrahydro furan (THF) under dry nitrogen was added 180 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropylamide (180 mmol) under dry nitrogen at -110°C was added 2.04g (2.70 ml, 180 mmol)TMEDA, and the reaction mixture was stirred at the same temperature for 10-15 min, followed by addition of 0.85g (50 mmol) of methyl-3-pyrrolidyl-2-butenoate in 20 ml of dry THF. The resulting solution was stirred at -110°C for 45 min, then cooling bath was removed and stirring was continued for 1 hr. To the resulting homogenous solution was added 1.25g (50 mmol) 2-[bis(methylthio)methylene]-1-tetralone 3j in 20 ml of dry THF dropwise at -110°C and stirred for 45 min. and allowed to stir overnight at ambient temperature. The reaction mixture was quenched with saturated ammonium chloride solution (100 ml) and extracted with chloroform (2x50 ml), the combined organic phase was washed with water (2x50 ml), dried over sodium sulfate and distilled off to give crude product which was chromatographed by passing through silica gel column using ethylacetate-hexane (2:98) as eluent.

Methyl(5,6-dihydro-4-methylthio-2H-naphtho[1,2-b] pyran-2-ylidene) acetate 67:

Bright orange needles; yield 1.25g (83%); mp 138-140°C (chloroform-hexane); R_f 0.62 EtOAc/benzene (1:9).

IR(KBr):ν_{max} = 1700, 1570, 1260, 1145, 1055 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ = 2.50 (s, 3H, SCH_3); 2.50-2.70 (m, 2H, CH_2); 2.76-2.96 (m, 2H, CH_2); 3.60 (s, 3H, OCH_3); 5.04 (s, 1H, vinylic); 7.10-7.36 (m, 4H, ArH); 7.63 (s, 1H, H-5).

MS: m/z(%) = 300 (M^+,100), 270(59.8).

Anal: Calc. for $C_{17}H_{16}O_3S$ (300.364): C 67.97; H 5.37.

Found C 68.02; H 5.51%.

Procedure for the preparation of 2-benzoyl-3-methylthio-5-(1-morpholinyl)phenol (75):

To a chilled (0°C) solution of 0.87 ml (70 mmol) of diisopropylamine in 10 ml of dry tetrahydrofuran (THF) under dry nitrogen was added 60 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropyl amide (60 mmol) under dry nitrogen at -110°C was added 0.68g (0.90 ml, 60 mmol) TMEDA, and reaction mixture was stirred at the same temperature for 15 min followed by addition of 0.90g (50 mmol) of methyl 3-morpholino-2-butenoate in 20 ml of dry THF. The resulting solution was stirred at -110°C for 30-45 min, then cooling bath was removed and stirring was continued for 1hr. To the resulting homogenous solution was added 1.29g (50 mmol) of 3,3-bis(methylthio)-1-phenyl-2-propen-1-one 3a in 20 ml dry THF dropwise at -110°C, stirred for 45 min. and overnight at ambient temperture. The

reaction mixture was quenched with saturated ammonium chloride solution (100 ml) and extracted with chloroform (2x50 ml), the combined organic phase was washed with water (2x50ml), dried over sodium sulfate and distilled and chromatographed over silica gel column using ethylacetate-hexane (1:99) as eluent.

2-Benzoyl-3-methylthio-5-(1-morpholinyl)phenol 75:
Colourless crytals; yield 0.86g (52%); mp 138-140 (chloroform-hexane); R_f 0.77 EtOAc/benzene (2:8).
IR(KBr): ν_{max} = 3408, 1602, 1538, 1332, 1109 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ 2.22 (s, 3H, SCH_3); 3.22-3.40 (t, 4H, NCH_2); 3.75-3.92 (t, 4H, OCH_2); 6.30 (dd, 1H, J=3Hz, ArH); 6.4 (dd,1H, J = 3Hz, ArH); 7.45-7.8 (m, 5H, ArH); 12.00 (brs, 1H,OH).
Anal: Calc. for $C_{18}H_{19}NO_3S$ (329.401): C 65.63; H 5.81; N 4.25. Found C 65.82; H 5.82; N 4.37%.

<u>General procedure for the preparation of 1,3,5-trisubstituted benzenes (78a-e) and 1,3,4,5-tetrasubstituted benzene (80):</u>

To an ice cold (0°C) solution of 2.61 ml (210 mmol) of diisopropylamine in 10 ml of dry tetrahydrofuran (THF) under dry nitrogen was added 180 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropyl amide (180 mmol) under dry nitrogen at -110°C was added 2.04g (2.70 ml, 180 mmol) TMEDA, and reaction mixture was stirred at the same temperature for 10-15 min. followed by addition of 0.85g (50 mmol) of methyl-3-pyrrolidyl-2-butenoate in 20 ml of dry THF. The resulting solution was stirred at -110°C for 30-45 min., then cooling bath was removed and stirring was continued for 1h. To the resulting homogeneous solution was added 50 mmol of oxoketene S,N-acetals

76a-f in 20 ml of dry THF dropwise at -110°C, stirred for 30-45 min and left overnight at ambient temperature (monitored by tlc). The reaction mixture was quenched with saturated ammonium chloride solution (100 ml), and extracted with chloroform (2x50 ml), combined organic phase was washed with water (2x50 ml), dried over sodium sulfate and distilled off to give crude product which was chromatographed by passing through silica gel column using ethylacetate-hexane (3:97) as eluent.

1-(1-Piperidyl)-3-phenyl-5-(1-pyrrolidyl)benzene 78a:

Colourless crystals; yield 1.32g (86%); mp 128-130°C (chloroform-hexane); R_f 0.48 EtoAc/benzene (1:9).

IR(KBr):γ_{max} = 2950, 1610, 1230, 760 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ 1.53-2.13 (m, 10H, CH_2); 3.03-3.50 (m, 8H, NCH_2); 6.40 (brs, 2H, ArH); 6.63 (brs, 1H, ArH); 7.36-7.73 (m, 5H, ArH).

MS: m/z(%) = 306(M^+,65.9).

Anal. Calc. for $C_{21}H_{26}N_2$ (306.44): C 82.30; H 8.55; N 9.14. Found C 82.05; H 8.62; N 9.35%.

3-Phenyl-1,5-(dipyrrolidyl) benzene 78b:

Colourless crystals;yield 1.07g (73%);mp 173-174°C (chloroform-hexane); R_f 0.79 EtoAc/hexane (6:4).

IR(KBr):γ_{max} = 2827, 1592, 1570, 1354, 1177 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ = 1.80-2.20 (m, 8H, CH_2); 3.26-3.56 (m, 8H, NCH_2); 5.90 (brs, 1H, ArH); 6.30 (brs, 2H, ArH); 7.42-7.63 (m, 3H, ArH); 7.72-7.80 (m, 2H, ArH).

MS: m/z(%) = 292 (M^+,100).

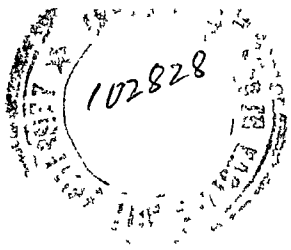
Anal: Calc. for $C_{20}H_{24}N_2$ (292.41): C 82.14; H 8.27; N 9.58.

Found C 82.21; H 8.35; N 9.63%.

3-(4-Chlorophenyl)-1-(1-piperidyl)-5-(1-pyrrolidyl) benzene 78c:
Colourless crystals; yield 1.15g (68%);mp 152-153°C (chloroform-hexane); R_f 0.73 EtoAc/hexane (2.5:7.5).
IR(KBr):γ_{max} = 3420, 2940, 1600, 1450, 1220, 1100 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 1.50-1.80 (m, 6H, CH_2); 1.86-2.1 (m, 4H, CH_2); 3.03-3.43 (m, 8H, NCH_2); 5.97 (brs, 1H, ArH); 6.10 (brs, 1H, ArH); 6.32 (brs, 1H, ArH); 7.26-7.56 (m, 4H, ArH).
MS: m/z (%) = 340 (M^+, 100).
Anal: Calc. for $C_{21}H_{25}ClN_2$ (339.883): C 73.91; H 7.41; N 8.24.
Found C 74.03; H 7.57; N 8.41%.

3-(4-Methoxyphenyl)-1-(1-piperidyl)-5-(1-pyrrolidyl) benzene 78d:
Colourless cyrstals;yield 1.31g (78%);mp 122-124°C (chloroform-hexane); R_f 0.86 EtoAc/hexane (4:6).
IR(KBr) :γ_{max} = 2800, 2750, 1600, 1460, 1250, 1040 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 1.30-1.96 (m, 10H, CH_2); 2.96-3.36 (m, 8H, NCH_2); 3.72 (s, 3H, OCH_3); 6.06 (brs, 1H, ArH); 6.21 (brs, 1H, ArH); 6.42 (brs, 1H, ArH); 6.87 (d, 2H, J = 9Hz, ArH); 7.47 (d, 2H, J = 9Hz, ArH).
MS: m/z (%) = 336 (M^+, 100).
Anal: Calc. for $C_{22}H_{28}N_2O$ (336.46): C 78.53; H 8.39; N 8.83.
Found C 78.72; H 8.47; N 8.51%.

3-(2'-Furyl)-1-(1-morpholinyl)-3-(1-pyrrolidyl) benzene 78e:
Colourless crystals; yield 1.01g (68%); mp 68-70°C (chloroform-hexane); R_f 0.70 EtoAc/hexane (4:6).
IR(KBr):γ_{max} = 1610, 1580, 1460, 1230, 1122, 1020 cm^{-1}.



^{1}H NMR (90MHz, $CDCl_3$): δ = 1.89-2.19 (m, 4H, CH_2); 3.18-3.59 (m,8H,NCH_2); 3.84-4.14 (m, 4H, OCH_2); 6.27 (brs, 1H, ArH); 6.63-6.83 (m, 2H, 3'-furyl, ArH); 6.83-6.99 (m, 2H, 4'-furyl, ArH); 7.77 (brs, 1H, 5'-furyl).

MS: m/z (%) = 298 (M^+,100).

Anal: Calc. for $C_{18}H_{22}N_2O_2$ (293.37): C 72.45; H 7.43; N 9.39. Found C 72.62; H 7.57; N 9.61%.

4-Methylthio-6-phenyl-2-(1-pyrrolidyl)-1-methylbenzoate 80:

Colourless crystals; yield 0.87g (53%); mp 73-74°C (chloroform-benzene); R_f 0.78 EtoAc/hexane (4:6).

IR(KBr): γ_{max} = 3450, 1714, 1410, 1248m 1075 cm^{-1}.

^{1}H NMR (250MHz, $CDCl_3$): δ = 1.86 (t,4H, J=9.3Hz,CH_2); 2.26 (s, 3H, SCH_3); 3.25 (t, 4H, J=9.3Hz, NCH_2); 3.84 (s, 3H, OCH_3); 6.68 (d, 2H, J=3.1Hz, ArH); 7.25-7.37 (m, 3H, ArH); 7.50 (d, 2H, J = 9.3Hz, ArH).

MS: m/z (%) = 295 (M^+ -32,100)

Anal: Calc. for $C_{19}H_{21}NO_2S$ (327.429): C 69.69; H 6.46; N 4.28. Found C 69.75; H 6.71; N 4.43%.

Procedure for the preparation of 1-methylthio-5-morpholinyl-3-aryl benzene (72g-h) and 1-pyrrolidyl-5-morpholinyl-3-aryl benzene (78g-h):

To an ice cold (0°C) solution of 2.61 ml (210 mmol) of diisopropylamine in 10 ml of dry tetrahydrofuran (THF) under dry nitrogen was added 180 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropylamide (180 mmol) under dry nitrogen at -110°C was added 2.04g (2.70 ml, 180 mmol) TMEDA, and reaction mixture was stirred at the same temperature for 15 min,

followed by addition of 0.90g (50 mmol) of methyl-3-morpholino-2-butenoate in 20 ml of dry THF, the resulting solution was stirred at -110°C for 45 min, then cooling bath was removed and stirring was continued for 1 hr. To the resulting homogeneous solution was added 50 mmol of α-oxoketene S,N-acetals **76g-h** in 20 ml of dry THF dropwise at -110°C, stirred for 30-45 min. and allowed to *stir overnight at ambient temperature. The reaction mixture was* quenched with saturated ammonium chloride solution (100 ml), and extracted with chloroform (2x50 ml), combined organic phase was washed with water (2x50 ml), dried over sodium sulfate and evaporated to give crude residue. The residue obtained was purified by column chromatography over silica gel. Elution with ethylacetate-hexane (1:4) gave **72g-h** followed by **78g-h**.

1-Methylthio-5-(1-morpholinyl)-3-phenyl benzene 72g:
Colourless crystals; yield 0.21g (15%); mp 98-100°C (chloroform-hexane); R_f 0.65 EtoAc/hexane (1:9).
IR(KBr): γ_{max} = 3474, 2918, 1588, 1239, 1114 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 2.30 (s, 3H, SCH_3); 3.33-3.54 (m, 4H, NCH_2); 3.54-3.80 (m, 4H, OCH_2); 6.46 (brs, 1H, ArH); 6.63 (brs, 1H, ArH); 7.20-7.56 (m, 5H, ArH).
Anal: Calc. for $C_{17}H_{19}NOS$ (285.393): C 71.54; H 6.71; N 4.91. Found C 71.62; H 6.91; N 5.03%.

3-(4-Chlorophenyl)-1-methylthio-5-(1-morpholinyl)benzene 72h:
Colourless crystals; yield 0.64g (40%); mp 112-114°C (chloroform-hexane); R_f 0.80 EtoAc/benzene (2:8).
IR(KBr): γ_{max} = 2834, 1588, 1438, 1238, 1119 cm^{-1}.
^1H NMR (90MHz, CCl_4): δ = 2.40 (s, 3H, SCH_3); 3.40-3.60 (m, 4H,

NCH_2); 3.68-3.86 (m, 4H, OCH_2); 6.46 (brs, 1H, ArH); 6.63 (brs, 1H, ArH); 7.30-7.60 (m, 4H, ArH and 1H, ArH).

Anal: Calc. for $C_{17}H_{18}NOClS$ (319.838): C 63.83; H 5.67; N 4.38. Found C 63.92; H 5.67; N 4.37%.

1-(1-Morpholinyl)-3-phenyl-5-(1-pyrrolidyl) benzene 78g:

Colurless crystals; yield 1.31g (85%); mp 148-149°C (chloroform-hexane); R_f 0.60 EtoAc/benzene (1:9).

IR(KBr): γ_{max} = 3457, 2960, 1593, 1430 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): 1.83-2.10 (m, 4H, CH_2); 3.10-3.46 (m, 4H, NCH_2); 3.73-3.93 (m, 4H, OCH_2); 6.14 (brs, 1H, ArH); 6.40 (brs, 1H, ArH); 6.53 (brs, 1H, ArH); 7.33-7.76 (m, 5H, ArH).

MS: m/z (%) = 308 (M^+, 100).

Anal: Calc. for $C_{20}H_{24}N_2O$ (308.41): C 77.88; H 7.84; N 9.08. Found C 77.90; H 7.92; N 9.31%.

3-(4-Chlorophenyl)-1-(1-morpholinyl)-5-(1-pyrrolidyl)benzene 78h:

Yellow crystals; yield 0.8g (60%); mp 158-160°C (chloroform-hexane); R_f 0.75 EtoAc/benzene (2:8).

IR(KBr): γ_{max} = 3329, 2822, 1581, 1214, 1117 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ = 1.90-2.20 (m, 4H, CH_2); 3.13-3.56 (m, 8H, NCH_2); 3.80-4.03 (m, 4H, OCH_2); 6.18 (brs, 1H, ArH); 6.36 (brs, 1H, ArH); 6.50 (brs, 1H, ArH); 7.36-7.73 (m, 4H, ArH).

Anal: Calc. for $C_{20}H_{23}ClN_2O$ (358.915): C 66.92; H 6.46; N 7.80. Found C 67.03; H 6.54; N 7.97%.

II.6 *References and Notes*

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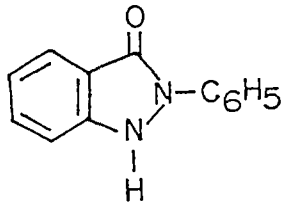
CHAPTER III

REGIOSPECIFIC GENERATION AND REACTION OF 3-LITHIOMETHYL-2-METHYL-1-PHENYL PYRAZOLIN-5-ONE(ANTIPYRINE LITHIO-METHYL ANION) AND ITS APPLICATION IN HETERO AROMATIC ANNELATION: A NEW GENERAL METHOD FOR THE SYNTHESIS OF 1,2-DISUBSTITUTED INDAZOLONES AND THEIR CONDENSED ANALOGS

III.1 *Introduction*

1,2-Disubstituted-3H-indazol-3-ones have not been reported in the literature involving direct synthesis from the open chain precursors. Several methods are known for the synthesis of 2-aryl Indazolones 1 which are subsequently subjected to alkylation



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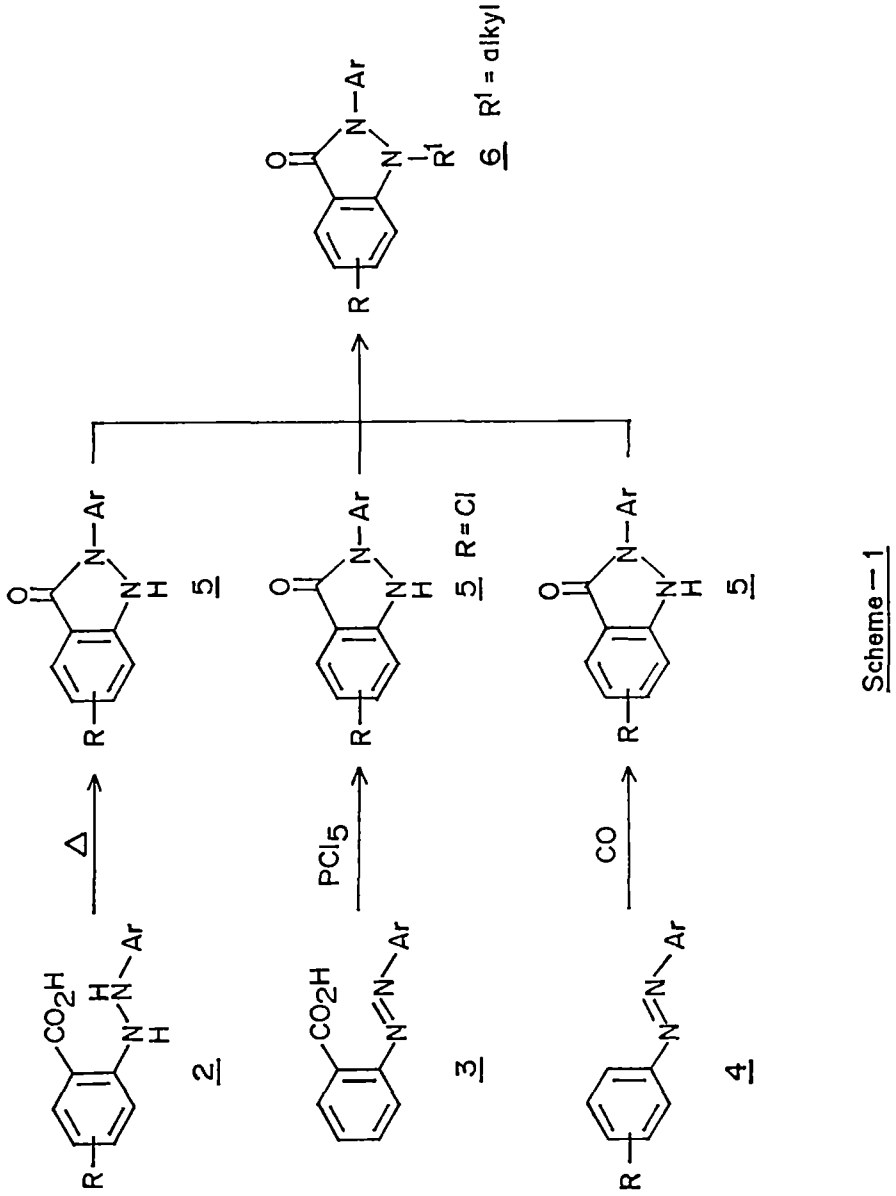
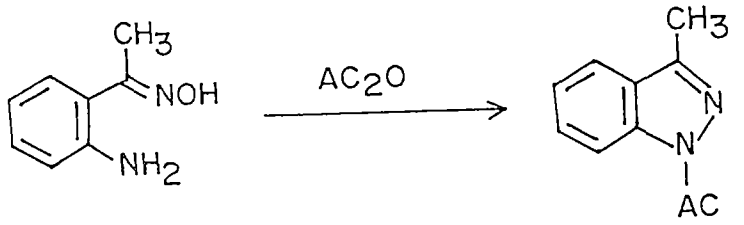
to yield the corresponding 1,2-disubstituted indazolones. The earliest approach employed for these compounds involves treatment of 2-carboxy hydrazobenzene thermally to afford the corresponding 2-aryl indazolones 1 in good yields. Freundler[1] reported the 2-phenyl indazolones substituted with chlorine in the benzene ring, during the action of phosphorous pentachloride on various phenylazobenzoic acids 3 (scheme 1). However, this reaction besides taking place with a rather unexpected stoichiometry, results in a product with a melting point that does not coincide with that described by other authors[2]. Efficient synthesis of 2-aryl indazolones was reported by Murahashi et al[2b] in 1956 and extended to a series of these derivatives[3], involving the reaction of azobenzenes 4 (scheme 1) with carbon monoxide. These 2-aryl indazoles were subsequently used to prepare the corresponding 1,2-disubstituted indazoles 6 using alkylative methods, which are described in the literature[4]. Except one or two unusual cases the 1,2-disubstituted indazoles are obtained by alkylation of monosubstituted indazoles[5]. It therefore appears that the direct synthesis of 1,2-disubstituted-3H-indazole-3-ones were not at all reported in the literature[4]. The indazole chemistry as a whole is developed through the functionalized benzene derivatives by creation of the N-N bond[6a] as the final step of the ring synthesis. For example, the dehydration of oxime 7 with acetic anhydride yields corresponding 1-acetyl indazole 8[6b]. The corresponding condensed indazoles such as naphtho indazoles and their varients are totally unknown in the literature. Thus, the chemistry of these compounds is developed in a modest rate involving construction of simple indazoles using


CO2H
H
N
N
Ar
R
2
Δ
5
O
N
N
Ar
H
R
PCl5
3
CO2H
N
N
Ar
5 R=Cl
CO
4
N
N
Ar
5
6 R¹ = alkyl
R¹

Scheme – 1



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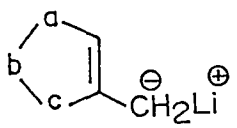
functionalized benzene derivatives. The literature describing the chemistry of these compounds has been reviewed[4].

The discovery of our aromatic and hetero aromatic annelation involving the reaction of allyl anions with α-oxoketene dithioacetals[7] has been shown to be of general application to yield the corresponding benzenoids, naphthalenes, polycyclic aromatic and hetero aromatic compounds in good yields[8]. The overall aim was to create the aromatic ring system from easily available aliphatic precursors. Based on these investigations a broad based plan was explored for annelating aromatic ring over preconstructed 5-membered heterocycles 9 and or 6-membered heterocycles 10 by condensing with α-oxoketene dithioacetals.



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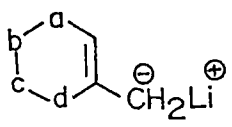

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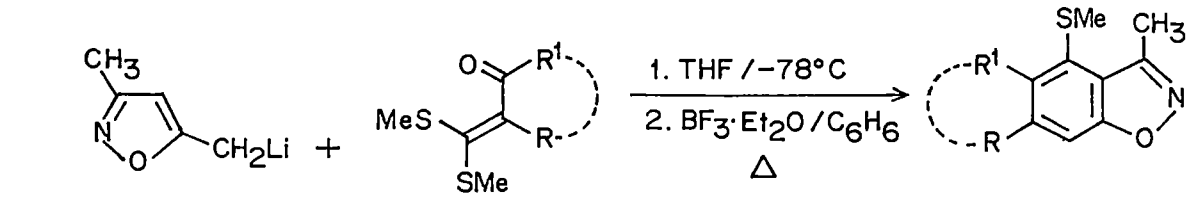
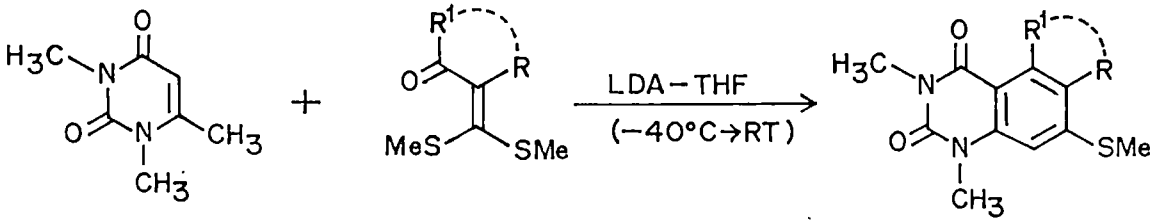
3-Methyl-5-lithiomethyl isoxazole 11 was successfully condensed with α-oxoketene dithioacetal 12 to yield the corresponding

substituted annelated 1,2-benzisoxazoles 13 (scheme 2) in excellent yields[9]. Similarly, an example of constructing aromatic ring over the pre-constructed uracils was successfully accomplished. Thus 1,3,6-trimethyl uracil **14** was reacted with α-oxoketene dithioacetals 12 in the presence of lithium diisopropylamide (LDA) (2.2 eq., THF, -40°C) to yield the corresponding substituted quinazolines **15** (scheme 3) in good yields[10]. This new approach has a potential for broad synthetic applications for the synthesis of hetero aromatics through suitably functionalized heterocycles having allyl anion moiety, followed by their reaction with α-oxoketene dithioacetals to build the corresponding benzo and condensed benzo hetero aromatics. It should be noted however, a large volume of hetero aromatic chemistry involves the construction of heterocyclic rings over the pre-constructed aromatic rings resulting in posing severe limitations on the synthesis of a large number of hetero aromatic compounds. The present approach of constructing benzenoids and condensed benzenoid systems over the pre-constructed suitably substituted parent heterocyclic ring should open new avenues of high synthetic potential in hetero aromatic chemistry. As a part of this broad based synthetic strategy, it was contemplated to investigate the reaction of 3-lithiomethyl 2-methyl 1-phenylpyrazolone as 3-carbon 1,3-dinucleophilic species with α-oxoketene dithioacetals as ambident 1,3-dielectrophiles with a view to developing a new efficient method for the synthesis of the corresponding 1,2-disubstituted-3H-indazolone.



11 12 13

Scheme — 2

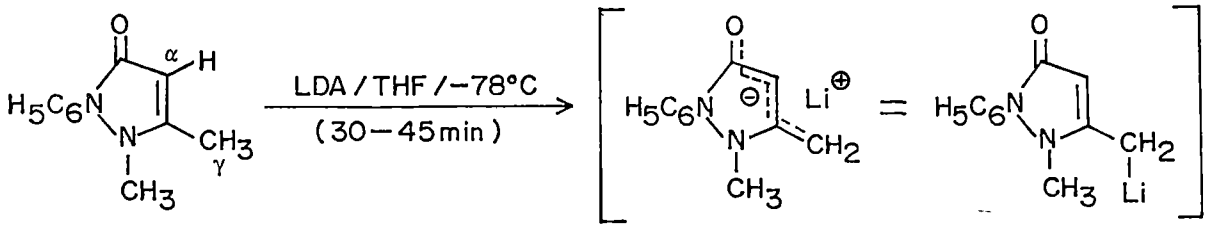


14 12 15

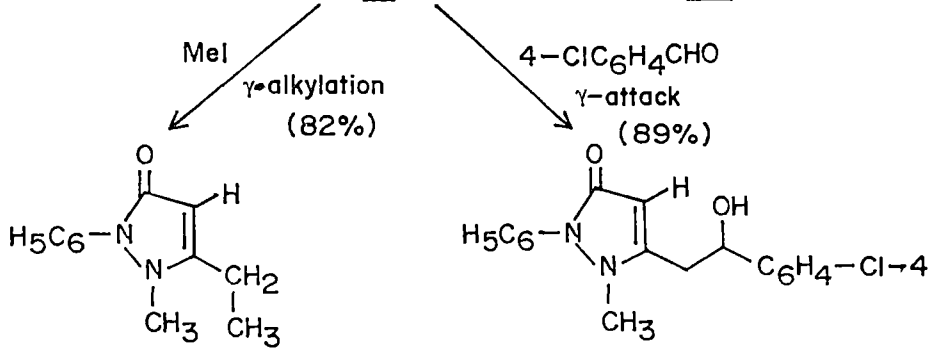
Scheme — 3

III.2 *Results and Discussion*

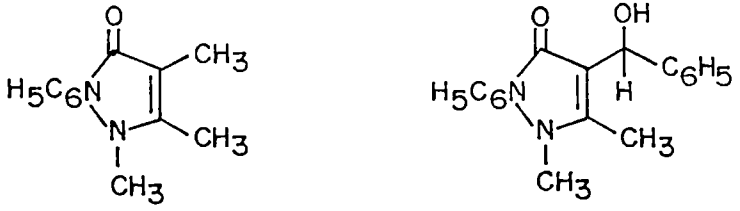
The present chapter deals with hitherto unreported 1-phenyl-2-methyl-3-lithiomethyl pyrazolin-5-one **17a**[11] derived from antipyrine **16** (scheme 4). The anion **17a** was prepared in near quantitative yield from antipyrine **16** by treating it with lithium diisopropylamide (LDA) at -78°C. Some preliminary reaction of **17** were examined with different electrophiles to asses the formation of **17a** and its regioselectivity towards various electrophiles. Thus **17a** on reaction with methyl iodide, the corresponding 1-phenyl-2-methyl-3-ethyl pyrazolin-5-one **18** was obtained in 82% yield. The product thus formed was found to be identical with that reported in the literature[12b] (superimposable IR, ^{1}H NMR). It was also reacted with p-chlorobenzaldehyde to afford the corresponding -secondary alcohol **19** in 86% yield. The structure of this compound was established on the basis of its analytical and spectral data. It was analysed for molecular formula $C_{18}H_{17}ClN_2O_2$ (328.793). Its structure was established from its IR and ^{1}H NMR spectral data. ν_{max} at 3095 cm^{-1} in its IR (KBr) spectrum was assigned to the hydroxy streching vibration. The carbonyl band appeared at 1692 cm^{-1}. In its ^{1}H NMR ($CDCl_3$) spectrum the signal at δ 2.75 was assigned to the exocyclic methylene protons as doublet with J = 9Hz. The signal at δ 2.9 for three protons was assigned to N-methyl group. The broad singlet at δ3.35 was assigned to the hydroxy group exchangeable with deuterium oxide. The tertiary hydrogen appeared at δ4.48 as triplet with J=9Hz. The vinylic protons appeared as singlet at δ4.88 and the multiplet at δ7.24-7.58 accounted for nine aryl protons.



16 17 17a



18 19

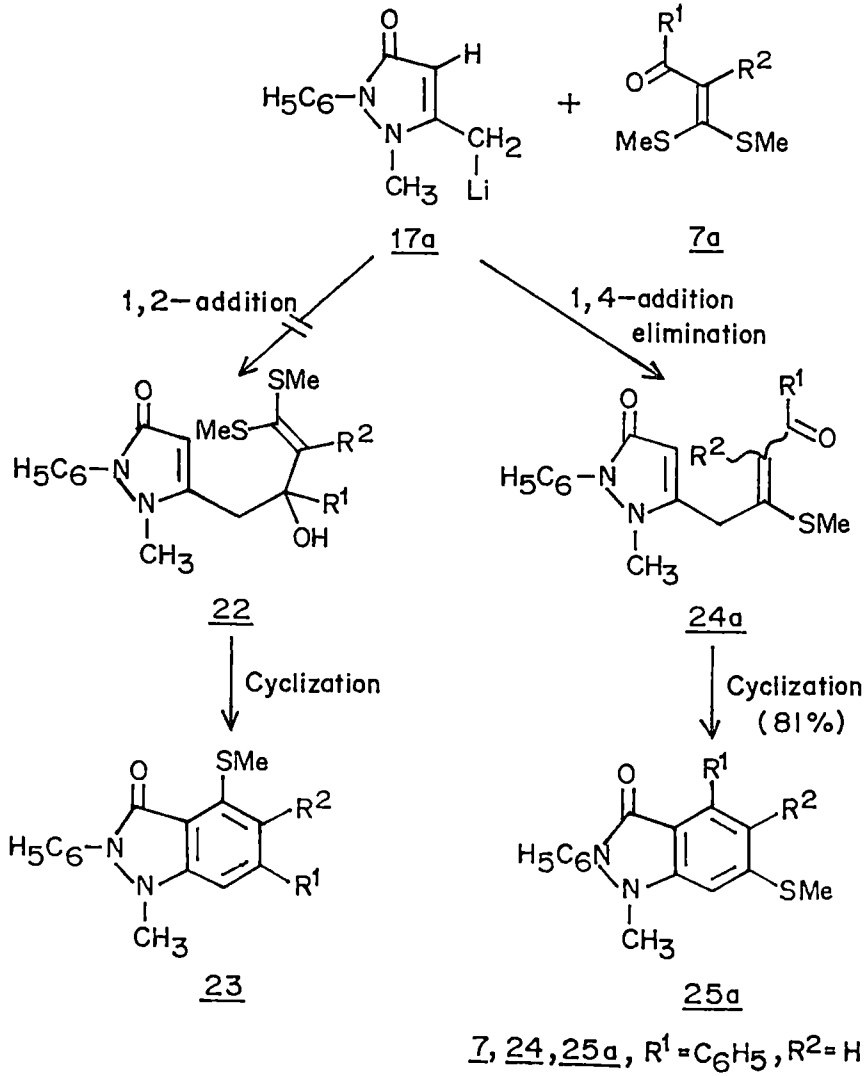


20 21

Scheme —4

It is interesting to note that the isomeric alkylated product **20** expected from α-alkylation and the corresponding carbinol **21** expected from α-1,2 addition were not detected in the reaction mixture. Thus the anion **17a** displayed exclusively - regioselectivity in its reaction with electrophiles.

The reaction of **17a** with various α-oxoketene dithioacetals were next investigated. When **17a** was treated with α-oxoketene dithioacetal **7a**, the γ-1,4 adduct **24a** was isolated in crude form after work-up. The γ-1,4-regioselectivity was confirmed from the crude ^{1}H NMR ($CDCl_3$) spectrum of **24a**. The singlet for two methylthio group protons appeared at δ 2.31 and 2.44. N-methyl protons of pyrazolone ring at δ 3.15 and two vinylic protons at δ 5.46 and 5.76 confirmed the structure of **24a** as -1,4 mode of reaction. The crude **24a** after treatment with borontrifluride-ethereate in refluxing benzene yielded the corresponding 2,4-diphenyl-1-methyl-6-methylthio 3H-indazolone **25a** as colourless crystals (chloroform-hexane) mp 175-176°C in 81% yield (scheme 5). The structure of indazolone **25a** was established on the basis of its analytical and spectral data. It was analysed for $C_{21}H_{18}N_2OS$ and its molecular weight (346.432) was confirmed from its mass spectrum with a peak at m/z 346 (M^+,77.2%), 331 (M^+-15,38.3%). In its IR (KBr) spectrum γ_{max} at 1678 cm^{-1} was assigned to the ring carbonyl group. The structure was further confirmed from its ^{1}H NMR ($CDCl_3$) spectrum. The three methylthio protons appeared as singlet at δ2.43. The singlet at δ3.03 of three protons was assigned to N-methyl group. The two indazolone ring protons appeared as a broad singlet at δ6.96. The ten aryl

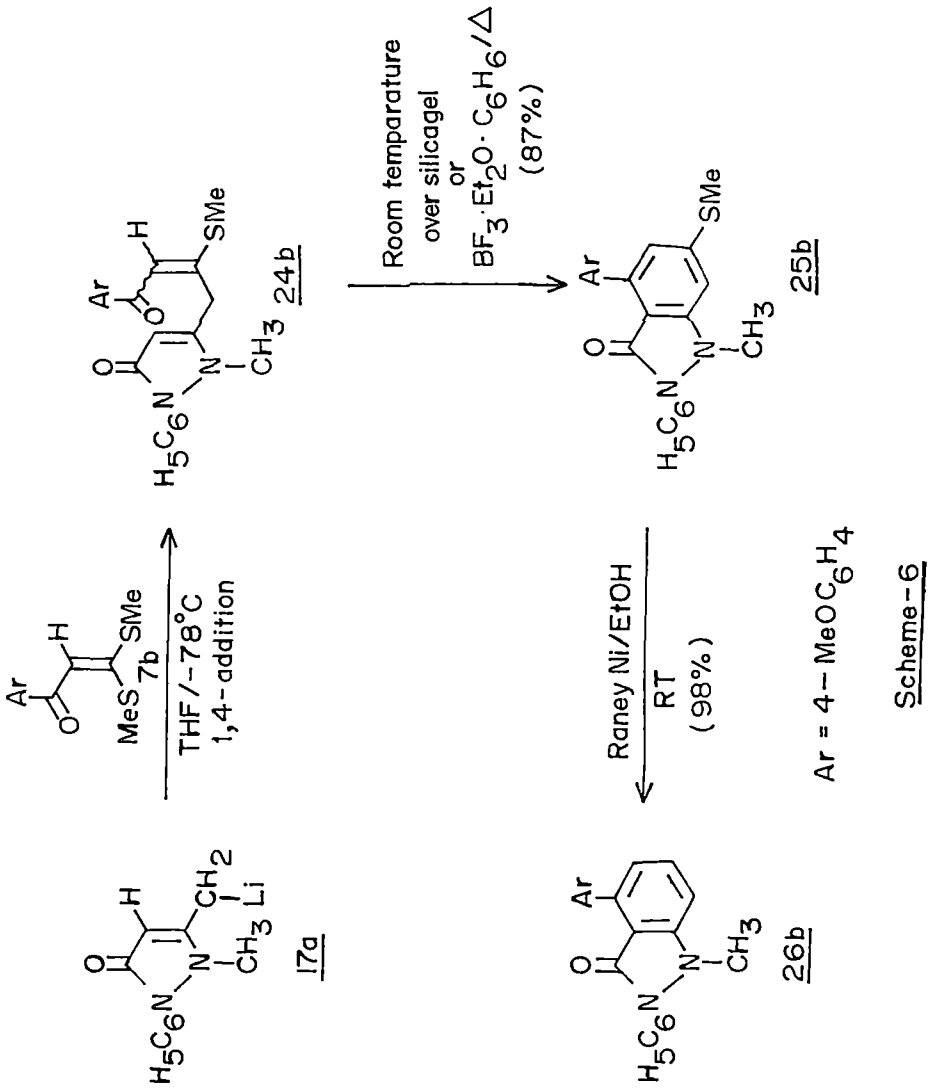

17a
7a
1,2-addition
1,4-addition
elimination
22
24a
Cyclization
Cyclization
(81%)
23
25a
7, 24, 25a, R1 = C6H5, R2 = H

Scheme — 5

protons appeared as broad multiplet between δ 7.17-7.69. On the basis of the open-chain structure **24a** the isomeric 1,2-adduct **22** and the corresponding indazolone **23** were ruled out.

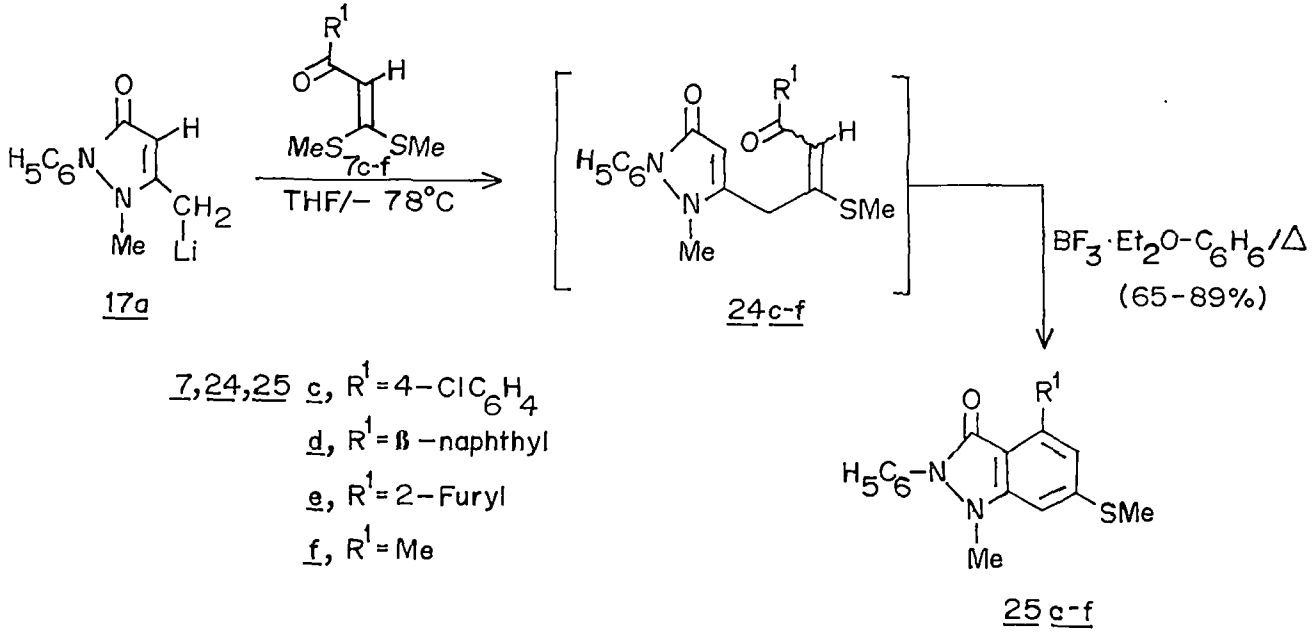
When **17a** was reacted with α-oxoketene dithioacetal **7b** derived from 4-methoxy acetophenone, quantitative conversion to a new product was observed within 6 h. The ^{1}H NMR ($CDCl_3$) spectrum of the crude product characterised it as 1,4-adduct **24b**. However, attempted purification of the adduct by column chromatography over silicagel (60-120 mesh) was not possible since it was slowly transformed into the cycloaromatized product **25b**. This was further confirmed by $BF_3.Et_2O$ induced cyclization of **24b** in refluxing benzene to give **25b** in 87% yield (scheme 6) as colourless needles (chloroform-hexane) mp 145-146°C. The structure and regio chemistry of **25b** was confirmed with the help of spectral (IR, ^{1}H NMR, Mass) and analytical (CHN) data which are in accordance with assigned structure described in experimental section. The characteristic 5,7-aryl ring protons appears as singlet at δ6.90 -7.00. The reported value for the 7-aryl ring proton of indazolone[4] is also at δ7.05. On Raney Ni(W4) hydrogenation **25b** was converted into its sulfur free 4-(4-methoxyphenyl)-1-methyl-2-phenyl-3H-indazolone **26b** as colourless needles (chloroform-hexane) mp 152-153°C in 98% yield (scheme 6). The structure of **26b** was further confirmed from its analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data (experimental section).

The other oxoketene dithioacetals **7c-f** were similarly reacted with **17a** under identical reaction conditions to yield the

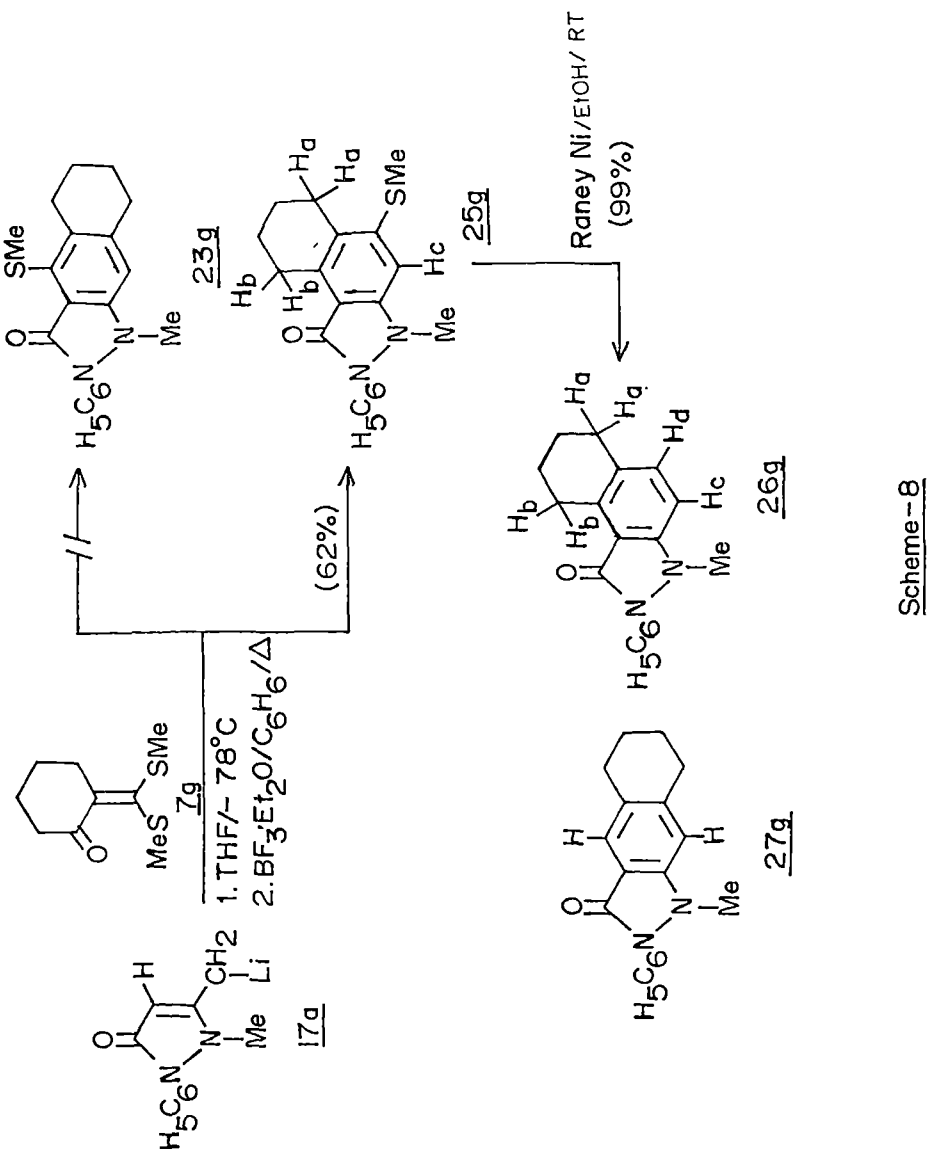

Ar
MeS
SMe
7b
THF/-78°C
1,4-addition
17a
24b
Room temparature
over silicagel
or
$BF_3 \cdot Et_2O \cdot C_6H_6/\Delta$
(87%)
25b
Raney Ni/EtOH
RT
(98%)
26b
Ar = 4-$MeOC_6H_4$

Scheme-6

corresponding 1-methyl-2-phenyl-4-substituted 6-methylthio indazolones **25c-f** respectively in 65-89% overall yields (scheme 7). The analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data of these compounds were in accordance with the assigned structure which are described in experimental section. The reaction of **17a** with oxoketene cyclic S,S-acetal **7g** derived from cyclohexanone also yielded the corresponding indazolone **25g** through γ-1,4-addition pathway in 62% yield (scheme 8) mp 158-160°C as colourless needles (chloroform-hexane). The structure of **25g** was established from its analytical and spectral data. It was analysed for molecular formula $C_{19}H_{20}N_2OS$ (324.434) and exhibited in its mass spectrum a peak at m/z 324 (M^+,100%). In its IR (KBr) spectrum , ν_{max} at 1665 cm^{-1} was assigned to the carbonyl group. In its ^{1}H NMR ($CDCl_3$) spectrum (Fig. 1), a multiplet at δ1.75-2.03 for four hydrogens was assigned to C_5,C_6 protons of cyclohexanone ring. Methylthio group appeared as singlet overlapping with cyclohexane protons at δ 2.53. The up-field multiplet at δ2.40-2.59 was assigned to C_7 protons (Ha) of cyclohexane ring. The singlet at δ3.10 for N-methyl protons were overlapping with C_4 protons of cyclohexane. Two protons (Hb) appeared as multiplet at δ3.10-3.40 due to deshiedling effect of carbonyl group. The lone aromatic C_9 ring proton (Hc) of indazolone ring appeared at δ6.85 as singlet. While the multiplet between δ7.32-7.81 was assigned to five N-aryl protons. The angular postion of cyclohexane ring was further confirmed by subjecting **25g** to Raney Ni desulfurisation when the corresponding sulfur free indazolone **26g** was obtained in 99% yield (scheme 8). In its ^{1}H NMR ($CDCl_3$) spectrum (Fig. 4), the signal due to one


R1
O
H
MeS
SMe
7c-f
THF/– 78°C
H5C6N
N
Me
CH2
Li
17a
24c-f
BF3·Et2O-C6H6/Δ
(65-89%)
25c-f
7,24,25 c, R1 = 4-ClC6H4
d, R1 = ß-naphthyl
e, R1 = 2-Furyl
f, R1 = Me

Scheme-7


SMe
MeS
SMe
7g
1. THF/- 78°C
2. BF3·Et2O/C6H6/Δ
(62%)
17a
23g
25g
Raney Ni/EtOH/ RT
(99%)
26g
27g
Scheme-8

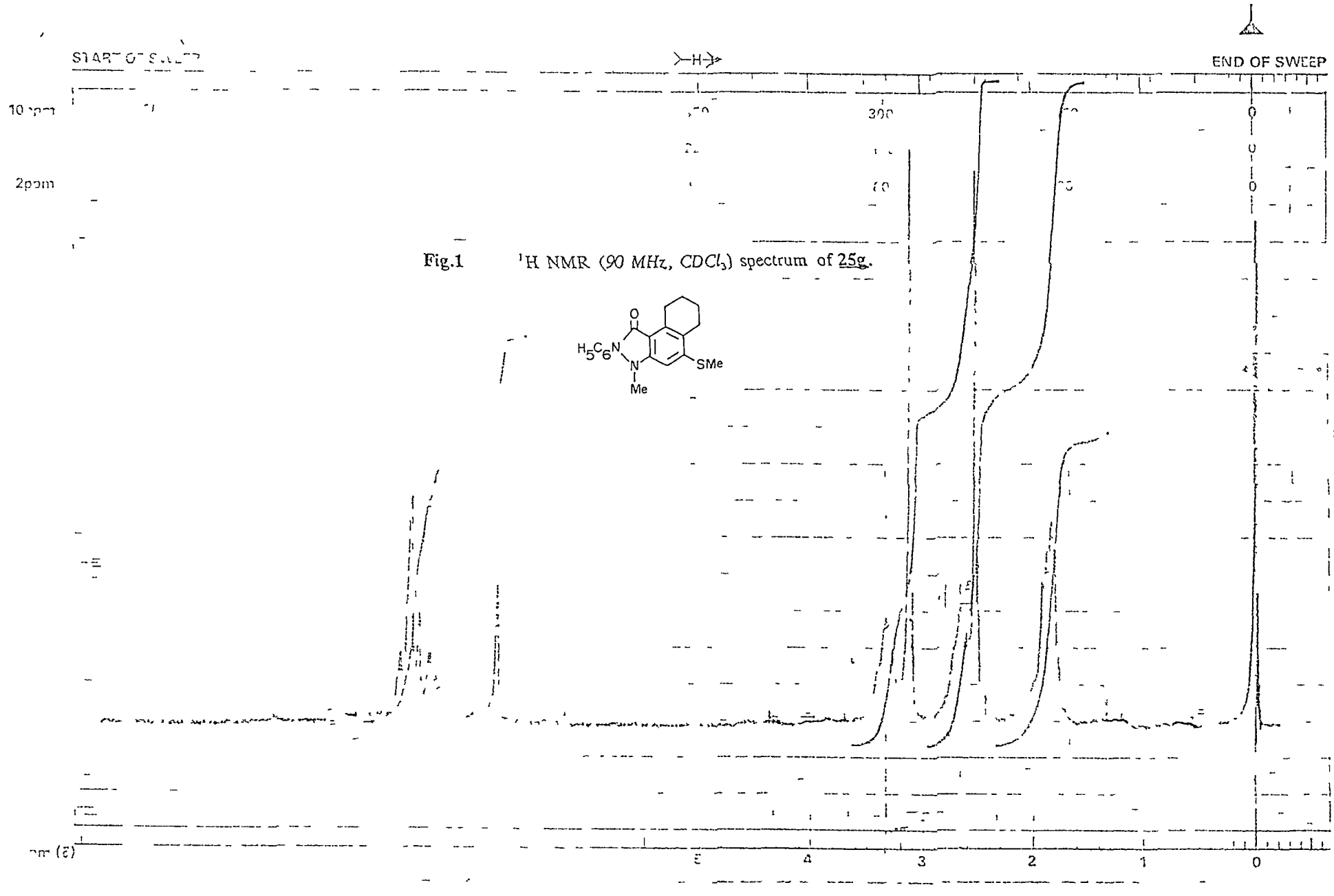


Fig.1 ^1H NMR (*90 MHz*, $CDCl_3$) spectrum of 25g.

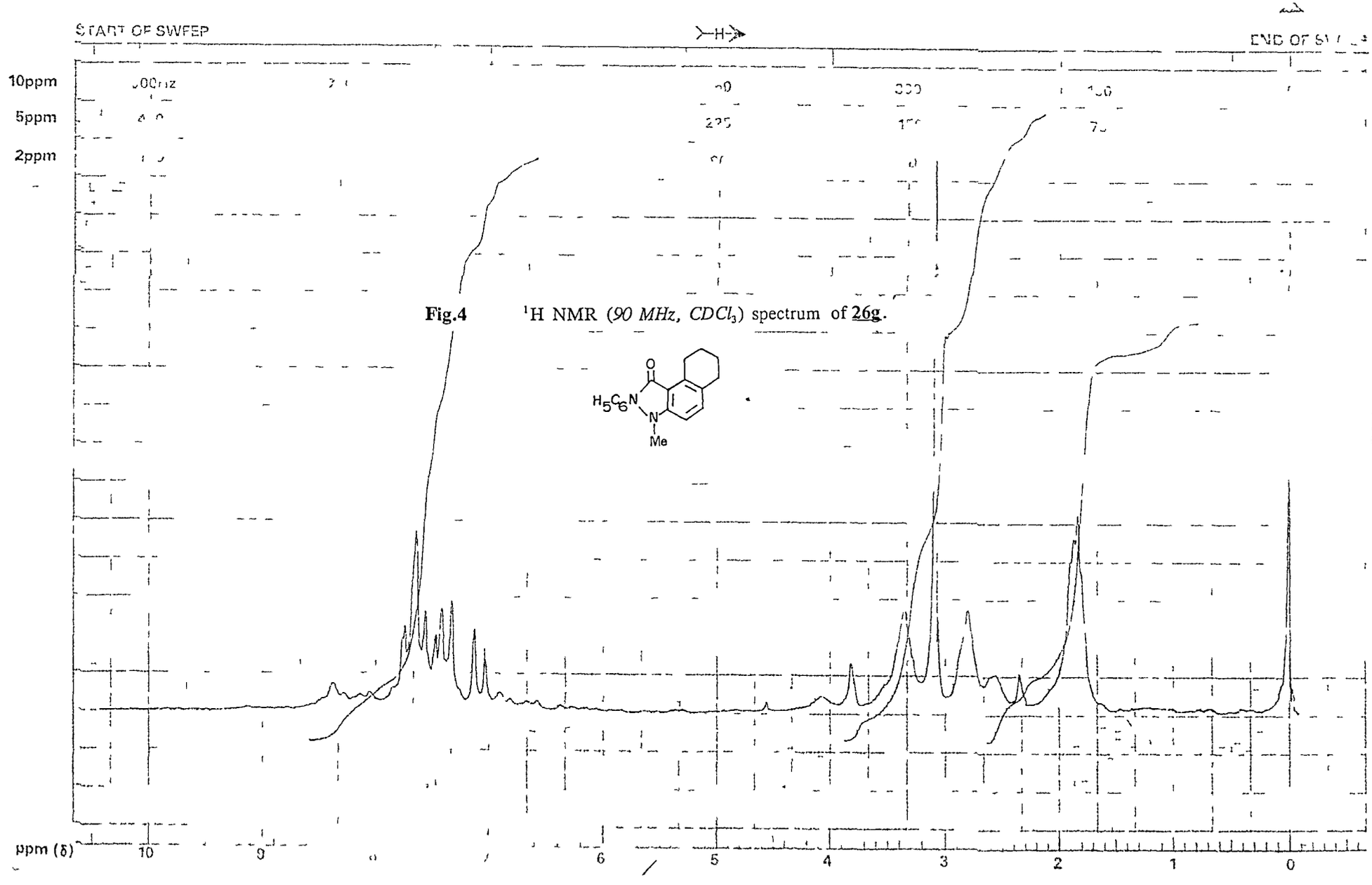
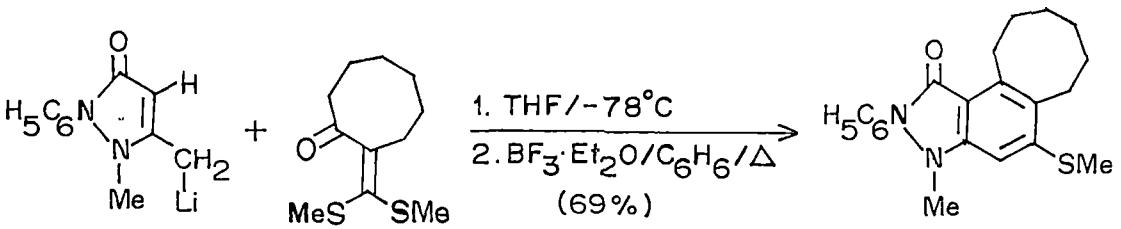


Fig.4 ^{1}H NMR (*90 MHz, $CDCl_3$*) spectrum of **26g**.

set of benzylic methylene protons (Hb) appeared at lower field (δ3.33) than Ha (δ2.76) due to deshielding effect of carbonyl group. It also displayed two consecutive proton signals at δ7.07 and 7.37 as doublet with ortho-coupling constant (J=9Hz). If it were a linear compound such as **27g** the two aromatic protons of indazolone ring would have appeared as singlets. This confirmed the structure of angularly annelated indazolone **25g**.

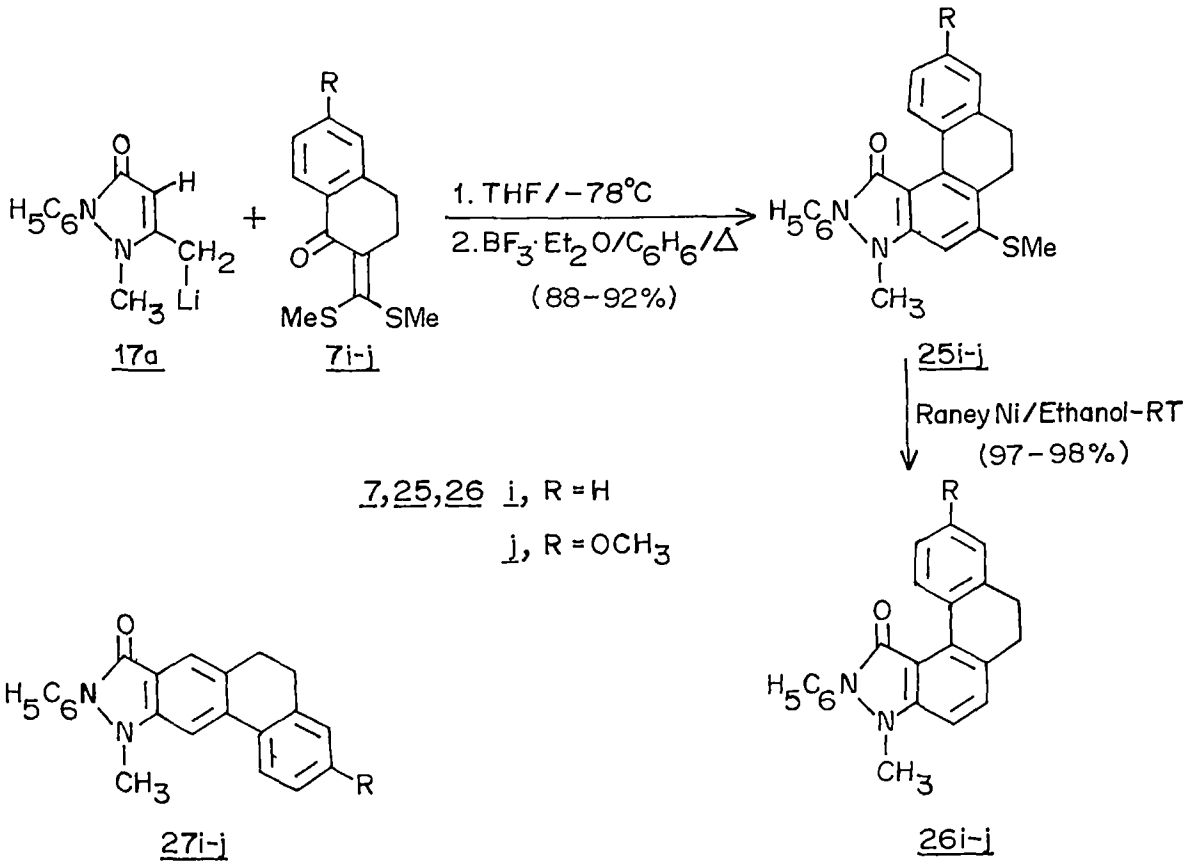
Similarly, **17a** was condensed with **7h** derived from cyclooctanone to yield the corresponding 2,3,6,7,8,9,10,11-octahydro-3-methyl-5-methylthio-2-phenyl-1H-cycloocta[e]indazol-1-one **25h** in 69% yield (scheme 9) under the described reaction conditions. Structure of **25h** was found to be in accordance with that of analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data which are described in experimental section.

Cyclization of **17a** with dithioacetals derived from tetralone **7i-j** was of interest since the analogous open-chain 1,4-adduct from **7i** and 6-lithiomethyl uracil failed to cycloaromatize under different conditions to give angularly benzo annelated product probably due to steric repulsion (*peri* interaction) in the transition state of cyclization[10]. However **17a** with **7i-j** and the crude 1,4-adducts underwent facile cyclization in the presence $BF_3.Et_2O$ to afford angularly substituted tetracyclic condensed indazolones **25i-j** in 88 and 92% yields (scheme 10) respectively. Apparently,the *peri* interaction is significantly absent in these systems. Both **25i** and **25j** were transformed into sulfur free indazolones **26i** and **26j** in 97 and 98% yields. The high resolution ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **26j** displayed *ortho*-coupled



17a + 7h → 25h

Scheme – 9


1. THF/−78°C
2. BF3·Et2O/C6H6/Δ
(88–92%)
Raney Ni/Ethanol-RT
(97–98%)
17a
7i-j
25i-j
26i-j
27i-j
7,25,26 i, R = H
j, R = OCH3

Scheme-10

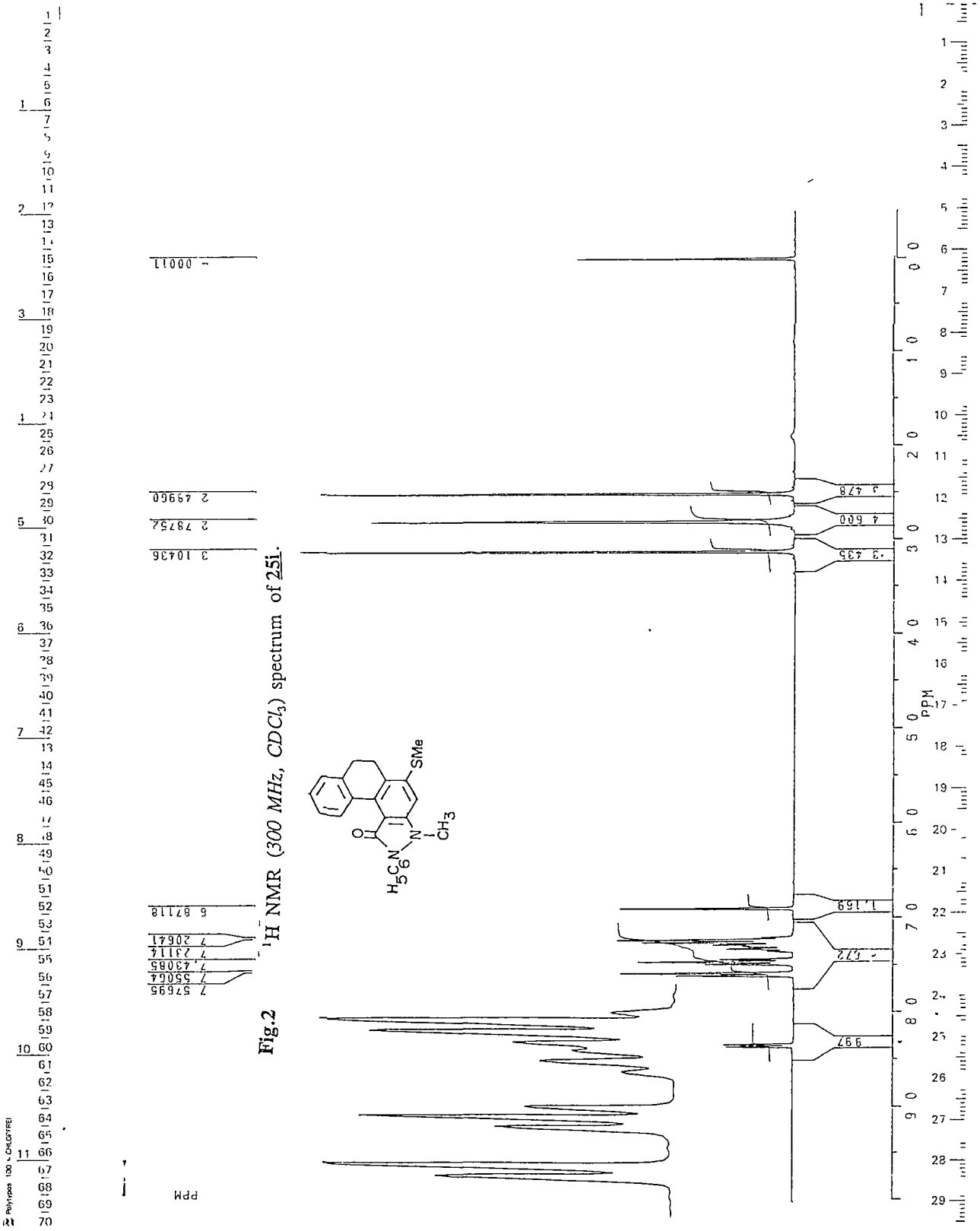


Fig.2 ^1H NMR (*300 MHz, $CDCl_3$*) spectrum of 25i.

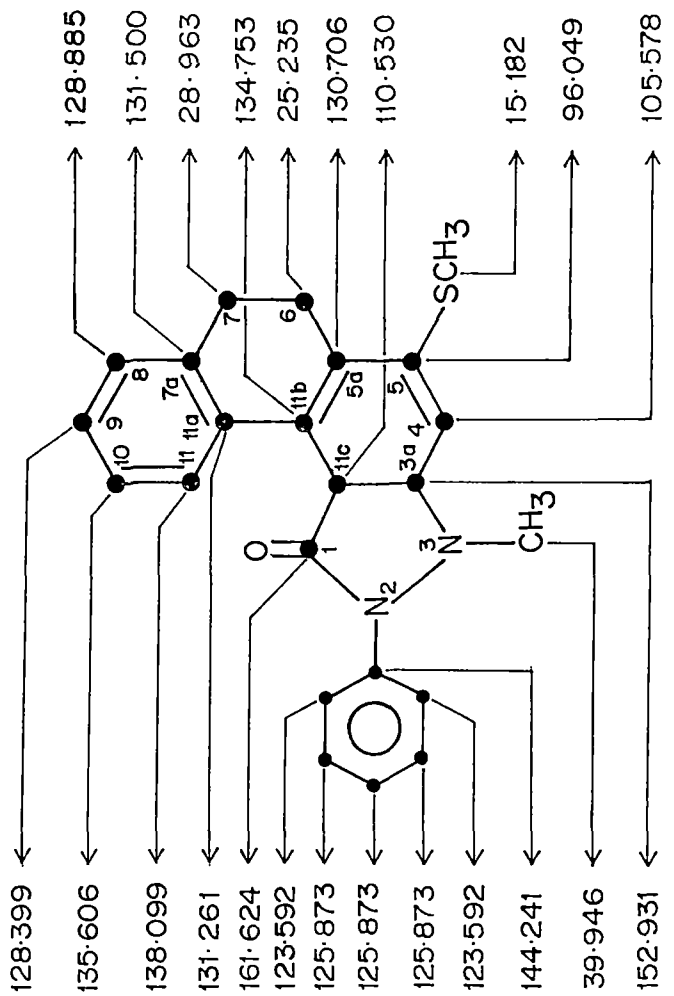


Fig.3a Structure & ^{13}C NMR data of 25i.

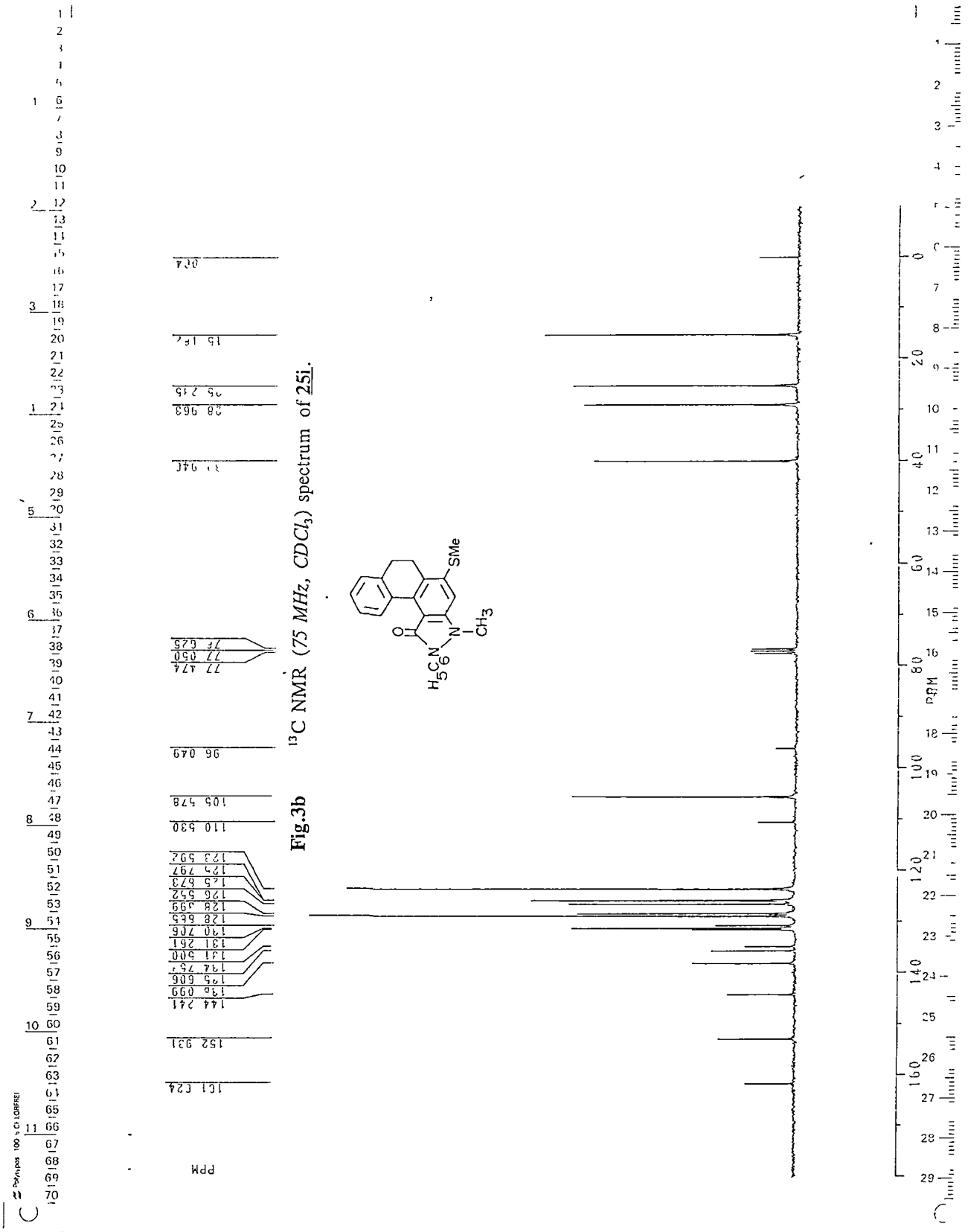


Fig.3b ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of **25i**.

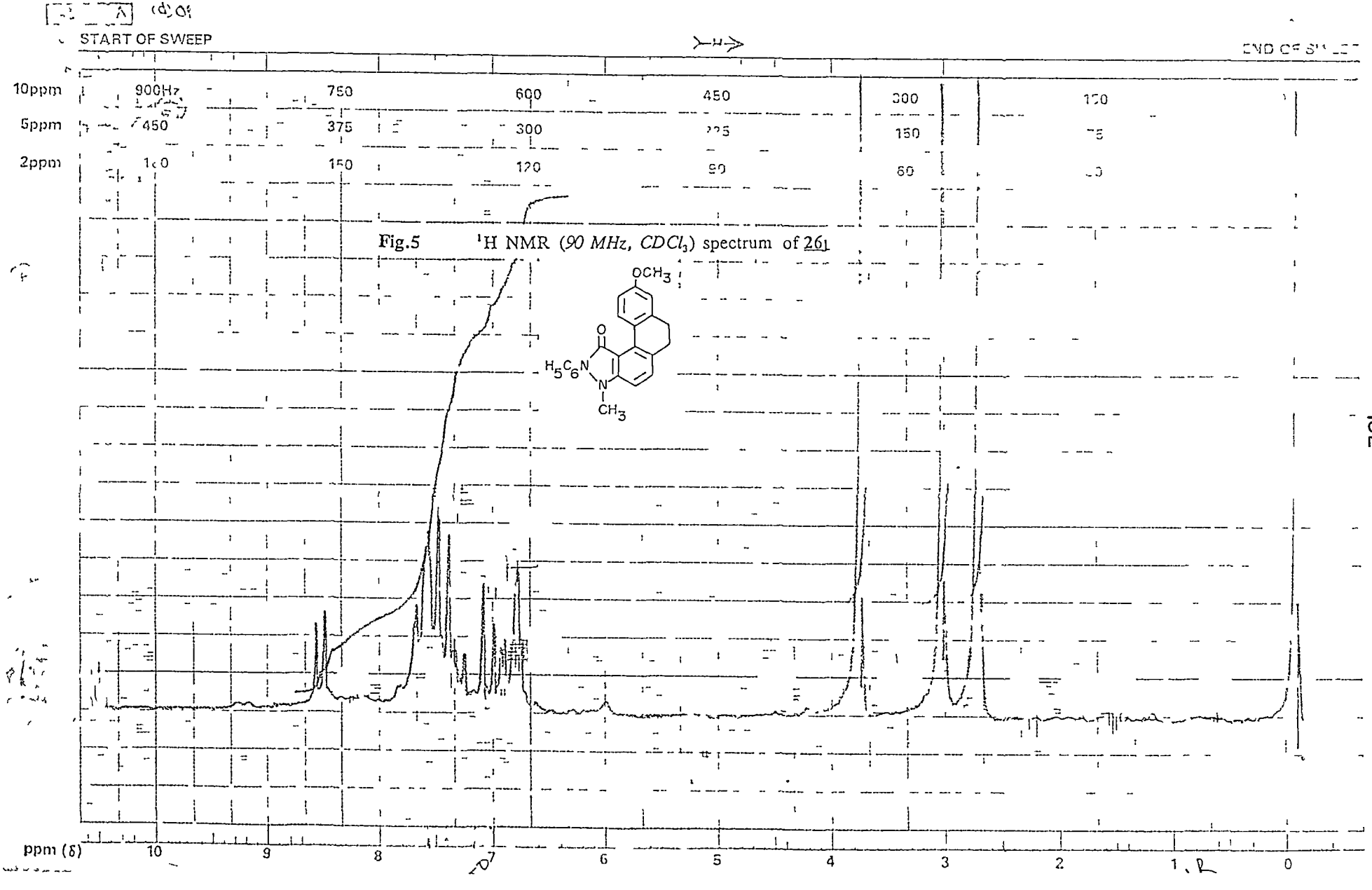
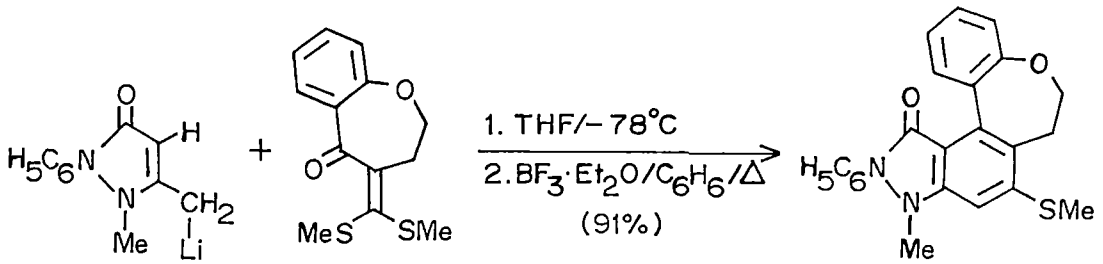


Fig.5 ^{1}H NMR (*90 MHz, $CDCl_3$*) spectrum of 26

protons (Ha, Hb, J = 9Hz) at δ 7.19 and δ 7.58 respectively. Thus supporting the angular arrangement of six membered ring in **25i-j** and **26i-j** rather than linear structures **27i-j**. The low field position of *peri* proton in **26i-j** (δ 8.87 and δ 8.40) also supported the angular structure. The analytical (CHN) and spectral (IR, ^{1}H NMR, ^{13}C NMR, Mass) data (Fig. 2,3 & 5) are in accordance with the assigned structure (experimental section).

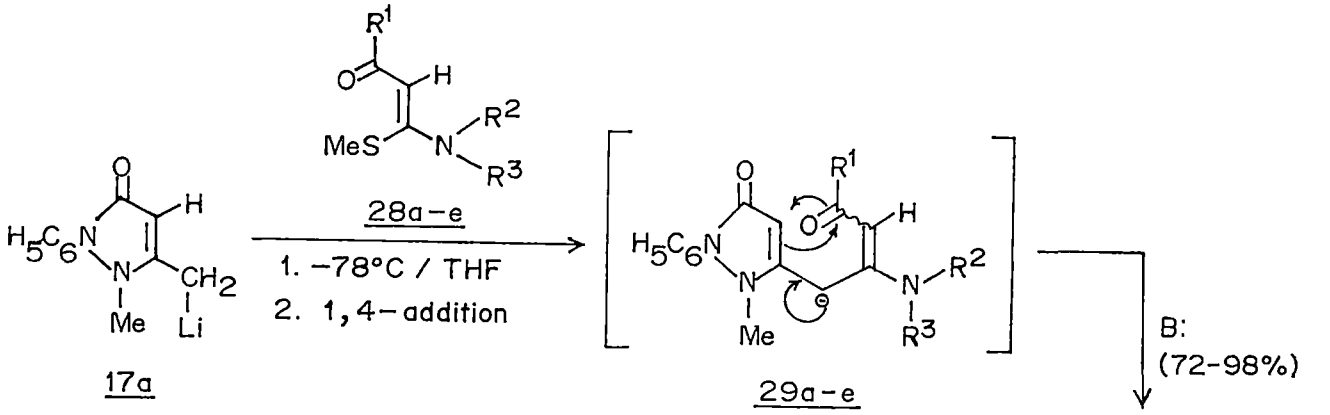
As a representative example of elaboration of benzoheterocyclic ring over indazolone, **17a** was reacted with dithioacetal **7k** derived from 3,4-dihydro-1-(2H)-benzoxepin-5-one to yield the corresponding benzoxepinoindazolone **25k** in 91% yield (scheme 11). The analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data which are in accordance with the assigned structure and are described in experimental section.

In order to demonstrate further versatility and scope of benzoannelation methodology it was considered of interest to examine the reaction of **17a** with the S,N-acetals **28a-f** to introduce tertiary amino group at 6-position in indazolone ring. Thus when **17a** was reacted with α-oxoketene S,N-acetal **28** in the presence of excess of lithium diisopropylamide (LDA) at -78°C the intermediate γ-1,4-adduct **29** were not observed, instead the corresponding 6-amino indazoles **30** were directly formed in excellent yields. Thus, **28a** directly yielded corresponding 1-methyl 2,4-diphenyl-6-pyrrolidino indazolone **30a** in 98% yield (scheme 12) and was crystallized from chloroform and hexane as colourless needles mp 158-159°C without requiring chromatographic purification. The structure was in conformity with its



17a 7k 25k

Scheme-11



28, 29, 30 a, $R^1 = C_6H_5$, $-NR^2R^3$ = N

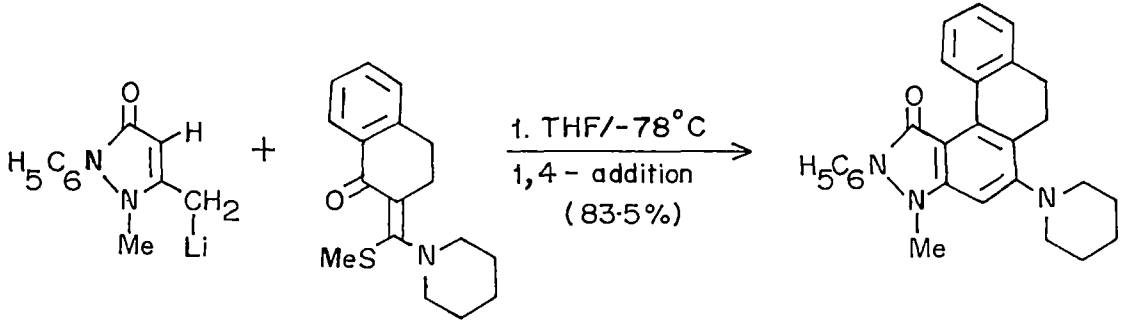
b, $R^1 = C_6H_5$, $-NR^2R^3$ = N O

c, R^1 = S, $-NR^2R^3$ = N

d, $R^1 = 4\text{-}Cl\text{-}C_6H_4$, $-NR^2R^3$ = N O

e, $R^1 = 4\text{-}OCH_3\text{-}C_6H_4$, $-NR^2R^3$ = N

Scheme−12



17a 28f 30f

Scheme–13

Fig.6 [1]H NMR (*250 MHz, CDCl$_3$*) spectrum of **30f**.

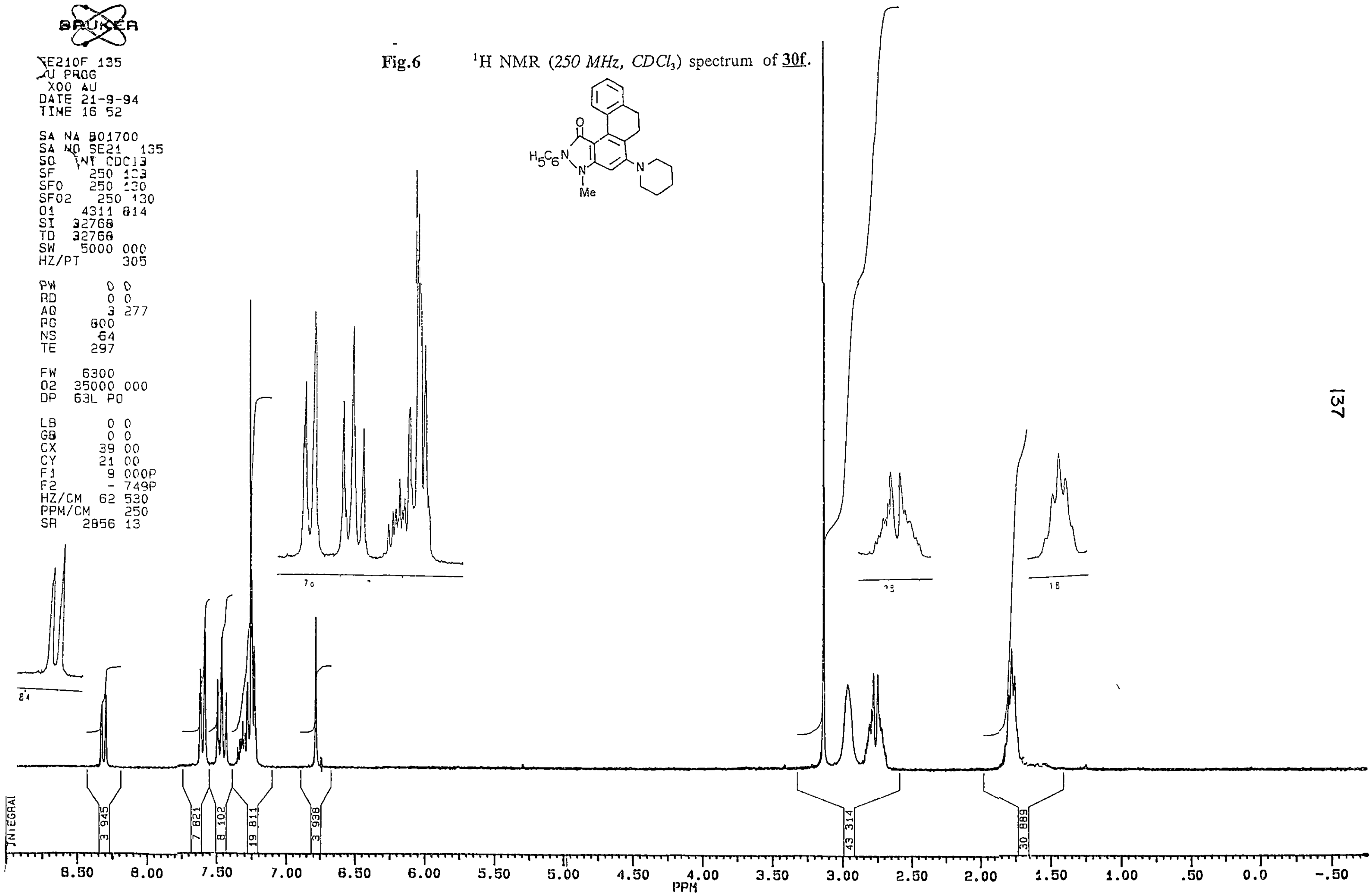
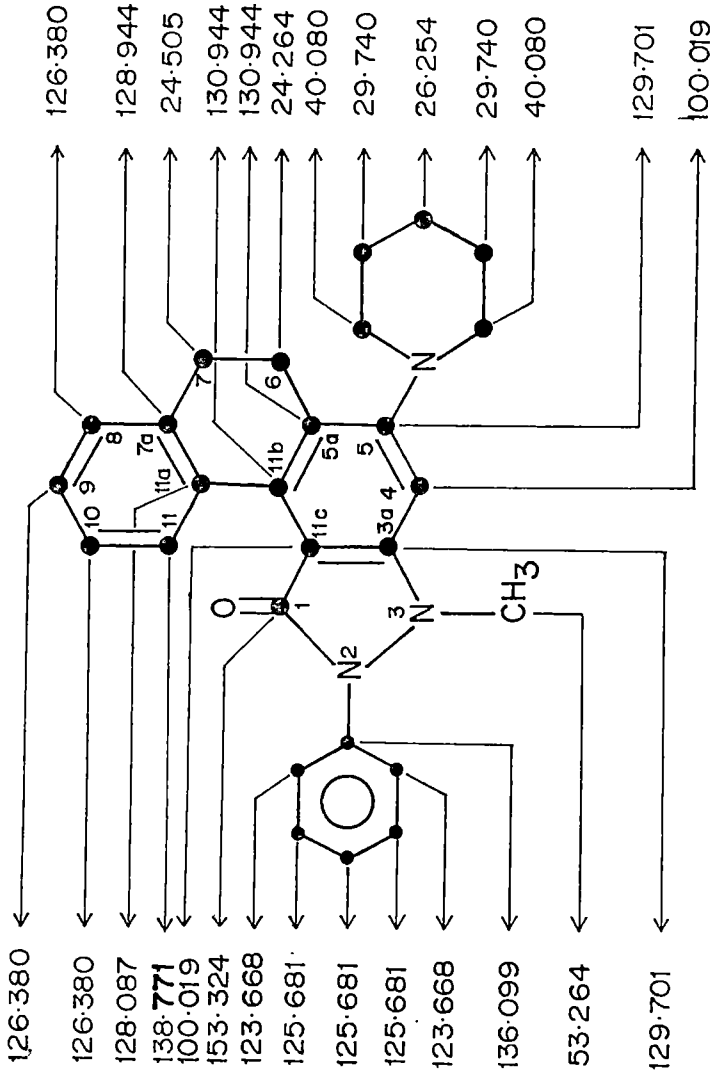


Fig.7a Structure & ^{13}C NMR data of 30f.



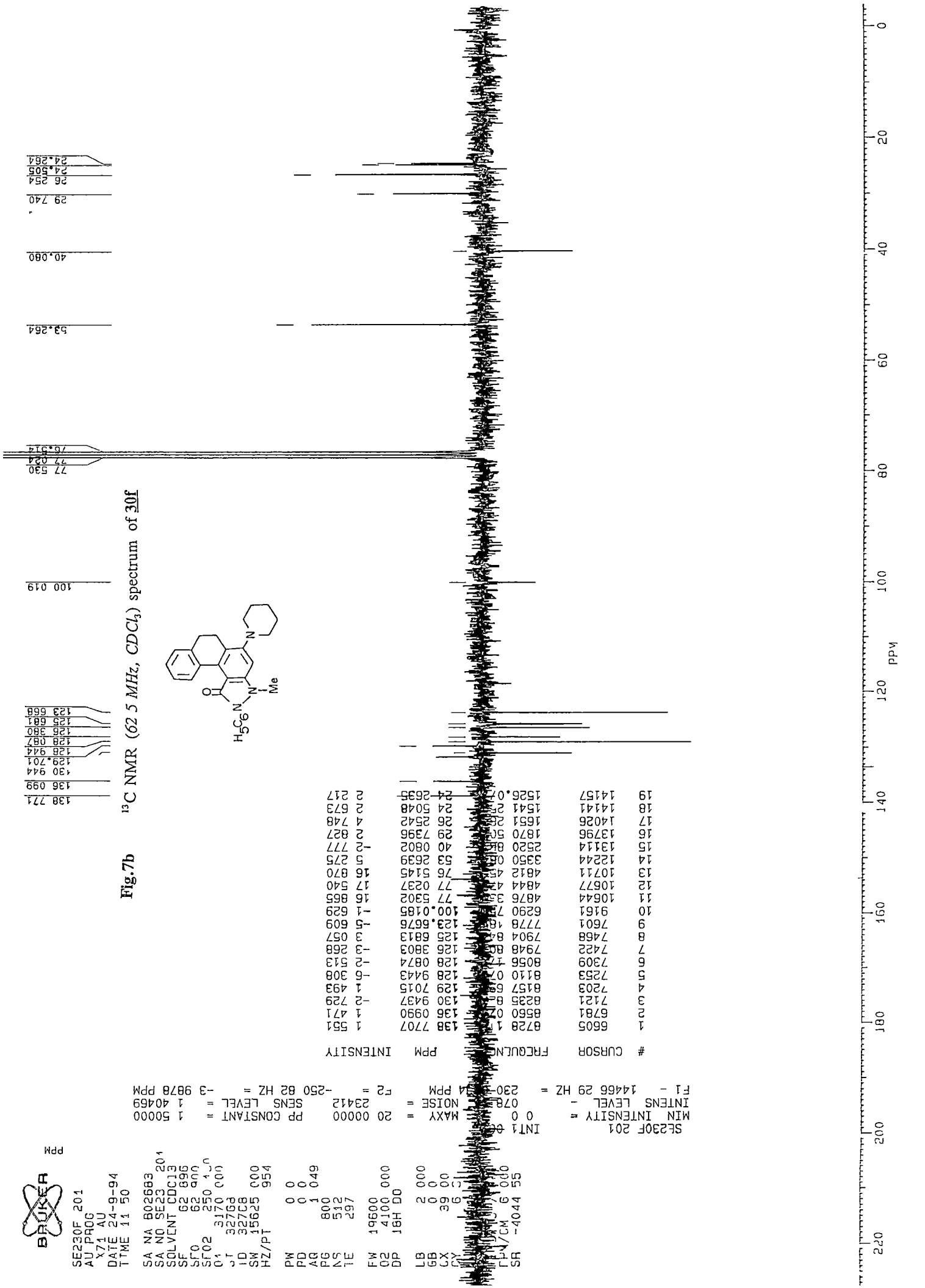


Fig.7b ^{13}C NMR (*62 5 MHz, $CDCl_3$*) spectrum of **30f**

analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data (experimental). The S,N-acetals **28b-e** were similarly treated with **17a** where substituted indazolones **30b-e** were obtained in one pot reaction in 72-94% overall yields (scheme 12). Some of them required chromatographic purification as described in experimental section. The structures were in conformity with their analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data which are described in experimental section. Similarly, the tetracyclic indazolone **30f** with regiospecifically substituted piperidino group could be synthesized in 83.5% yield (scheme 13) by reaction of **28f** with **17a** under the identical condition. The structure was in conformity with its analytical (CHN) and spectral (IR, ^{1}H NMR, ^{13}C NMR, Mass) data (see fig. 6 & 7).

III.3 *Conclusion*

A new efficient method of substituted indazolones and annelated (condensed) indazolones has been developed which has enormous potential of further application to many structural variants of both allyl anionic component and α-oxoketene S,S- and S,N-acetals. To our knowledge condensed indazolones are not known in the literature and have been synthesized for the first time by this methodology. The present method provides one of the most versatile routes for the synthesis of indazolone frame work by annelation of benzene ring over preconstructed pyrazolone ring.

III.4 *Experimental Section*

General

M.ps were obtained on a "Thomas Hoover" melting point (capillary

method) apparatus and are uncorrected. The Infrared spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H NMR (90MHz) were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR (250,300 MHz), ^{13}C NMR (62.90, 75.43 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either tetramethyl silane as internal lock (for ^{1}H NMR) the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR). The followed abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (MS) were measured on a Jeol JMS-D 300 Mass spectrometer. Masses are reported in units of mass over charge (m/z), the molecular and base peaks are indicated by (M^{+}) and (%) respectively. Elemental analysis were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions involving organolithium were performed in an oven dried (120°C) glassware under a positive dry argon/nitrogen atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven dired (120°C) syringe using standard syringe-septum technique. Low temperature reactions were carried in a bath made of ethyl acetate and liquid nitrogen. Analytical thin layer chromatography (tlc) were performed on glass plates (18x6 and 18x4 cm) coated with ACME's silicagel containing 13% calcium sulfate as binder and various combinations of ethylacetate-hexane, ethylacetate-benzene, benzene were used as eluents.

Visualization of spots was accomplished by exposure to iodine

vapour or potassium permanganate (acidic) solution. ACME's silica gel (60-120 mesh) is used for column chromatography, solvents for column chromatography were used after simple distillation of commercial materials. All solvents evaporations were done using a steam bath.

Chemicals and Reagents

Commercial available pyrrolidine, piperidine, morphiline (secondary amines) were purified by simple distillation. Diisopropyl amine was distilled from potassium hydroxide prior to use. Tetrahydrofuran (THF) was obtained anhydrous by distillation after the characteristic blue colour of *in situ* generated sodium diphenyl ketyl[12b] was found to persist. Dry benzene[13a] was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Dry ether[13b] was obtained by keeping over calcium chloride (fused) and stored over sodium wire. Boron trifluoride-ethyl ether complex (Merck) was used as such. Lithium Ingot (Aldrich)were cut into smaller pieces and washed with dry ether twice before use. n-Butyl Lithium was prepared according to the reported procedure[14]. Lithium diisopropyl amide (LDA) was prepared according to the litrature procedure[15].

Starting Materials

Commercial available ketones of acetophenone, 4-methoxy acetophenone, acetone, 4-chloroacetophenone, cyclohexanone and cyclooctanone were purified either by simple distillation/ distillation under reduced pressure or crystallisation before

use. 2-Acetyl furan, 6-methoxy tetralone was purchased from Aldrich and used as such, 1-tetralone bp 140-150°C (10 mm)[16], 2-acetyal thiophene bp 214°C[17], methyl-2-naphthyl ketone (2-acetylnaphthylene) mp 50°C (lit.,[18] 53°C), 3,4-dihydro-1-benzoxepin-5-(2H)-one (5-homochromanone) bp 170-174°C (6 mm Hg) [lit.,[19] bp 100-130°C 4 mm Hg) dimethyltrithio carbonate bp 225°C (760 mm)[20], Raney Ni (W4)[21] were prepared according to earlier reported procedure.

General experimental details for the preparation of α-oxoketene dithioacetals[22] and α-oxoketene S,N-acetals[23-25] are described in the experimental section of Chapter II. All ketene dithioacetals 7a-k, S,N-acetals 28a-f used for the present investigation were prepared using this procedure and were characterized by physical (mp) and spectral (IR, ^{1}H NMR) data.

General procedure for the generation and reaction of 3-lithiomethyl 2-methyl-1-phenyl pyrazolone 17a with electrophiles (iodomethane and 4-chloro benzaldehyde) : Synthesis of 1-phenyl-2-methyl-3-ethyl pyrazolone 18[6] and 1,2-dihydro-5-[2-(4-chloro-phenyl)-hydroxyethyl]-1-methyl-2-phenyl-3H-pyrazol-3-one 19.

To a solution of diisopropylamine 1.97ml (14 mmol) in sodium dried tetrahydrofuran (THF) 10 ml under dry and inert atmosphere was added a 10 mmol of n-BuLi in ether, over 20 min. with stirring and temperature control at 0°C with an ice bath. The resulting solution of lithium diisopropylamide (LDA) at -78°C was added a solution of 0.9g (5 mmol) of antipyrine in 25 ml dry THF, the reaction mixture was stirred at the same temperature for 30-40 min. To the resulting enolate solution at -78°C was added 4

mmol of electrophile in 15 ml dry THF dropwise and stirred for 30-45 min. (-78°C) and then allowed to warm to room temperature (monitored by tlc). Quenched with aqueous saturated ammonium chloride solution (100 ml) extracted with chloroform (3x25 ml). The combined extracts were washed with water (3x25 ml), dried (sodium sulphate) and then evaporated to give the crude product, which was purified by column chromatography over silica gel using ethylacetate-hexane (3:7) as eluent.

1,2-Dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one 16:
Colourless crystals; mp 108-110°C (lit.,[25] 111-114°C) (chloroform-hexane); R_f 0.37 EtoAc/benzene (6:4).
IR(KBr): ν_{max} = 3084,1651(CO), 1476,1299,764 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 2.22 (s, 3H, CH_3); 3.04 (s, 3H, NCH_3); 5.41 (s, 1H, vinylic); 7.26-7.64 (m, 5H, ArH).

1,2-Dihydro-5-ethyl-1-methyl-2-phenyl-3H-pyrazol-3-one 18:
Light brown viscous liquid ; yield 0.83g (82%); R_f 0.5 EtoAc/benzene (9:4).
IR(KBr): ν_{max} = 3417,2963,1642 (CO), 1298, 757 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 1.25 (t, 3H, J=7.5Hz, CH_3); 2.49 (q, 2H, J=6Hz, CH_2); 2.99 (s, 3H,CH_3); 5.33 (s,1H, vinylic); 7.25-7.60 (m,5H,ArH).
Anal: Calc. for $C_{12}H_{14}N_2O$ (202.246): C 71.26; H 6.98; N 13.85. Found C 71.50; H 6.95; N 13.90%.

1,2-Dihydro-5-[2-(4-chlorophenyl)-hydroxyethyl]-1-methyl-2-phenyl-3H-pyrazol-3-one 19 :
Colourless crystals;yield 1.46g (86%); mp 160-163°C (chloroform-

hexane);R_f 0.29 EtOAc/benzene (6:4).
IR(KBr):γ_{max} = 3095, 1622(CO), 1478, 1064, 762 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): 2=2.75 (d,2H,J=9Hz,CH_2); 2.90 (s,3H,NCH_3); 3.35 (brs,1H,OH exchangeable with D_2O); 4.88 (t, 1H, J=9Hz, benzylic); 4.88 (s, 1H, vinylic); 7.24-7.58.
Anal: Calc. for $C_{18}H_{17}ClO_2N_2$ (328.993): C 65.75; H 5.21; N 8.52. Found C 66.70; H 5.22; N 8.54%.

General procedure for the generation and reaction of 3-lithiomethyl-2-methyl-1-phenyl pyrazolone 17a with α-oxoketene dithioacetals 3a-k; Synthesis of 1,2-dihydro-1,2,4-trisubstituted-6-methylthio-3H-indazol-3-one 25a-k

Under dry and inert atmosphere, a chilled (0°C) solution of 1.97ml (14 mmol) of diisopropyl amine in 10 ml of dry tetrahydrofuran (THF) was added 10 mmol of n-butyl lithium in ether. The resulting solution of lithium diisopropylamide (10 mmol) at -78°C was added a solution of 0.9g (5 mmol) of antipyrine in 25 ml dry THF. The reaction mixture was stirred at the same temperature for 30-45 min. To the resulting enolate solution at -78°C was added 4 mmol of α-oxoketene dithioacetal in 25 ml dry THF dropwise and kept there for 30-45 min, allowed to warm to room temperature, stirred for 6-8 hr. (monitored by tlc), and quenched with aqueous saturated ammonium chloride solution (100 ml), extracted with chloroform (3x25 ml), the organic layer was washed with water, dried over anhydrous sodium sulfate, removal of organic layer gave a crude -1,4-adduct 24a-k in quantitative yields.
To a solution of crude γ-1,4-adduct (Ca. 5 mmol) in dry benzene

(30 ml), boron trifluride-etherate (7.5 mmol) was added and the reaction mixture was stirred under reflux for 30-45min. after the reaction was complete (monitored by tlc), it was brought to room temperature and poured into aqueous saturated sodium bicarbonate solution (100 ml), extracted with chloform (3x25 ml), the combined organic extracts were washed with water (2x50 ml) dried over anhydrous sodium sulfate and concentrated to give the crude cycloaromatized product which was chromatographed by passing through silica gel column using ethylacetate-hexane (2:88-10:90) as eluent.

1,2-Dihydro-1-methyl-6-methylthio-2,4-diphenyl-3H-indazol-3-one 25a: Colourless crystals; yield 1.40g (81%); mp 175-176°C ((chloroform-hexane); R_f 0.40 (benzene).
IR(KBr): γ_{max}= 1678(CO), 1308, 1131, 759 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.43 (s, 3H, SCH_3); 3.03 (s, 3H, NCH_3); 6.96 (brs, 2H, ArH); 7.17-7.69 (m, 10H, ArH).
MS: m/z(%) = 346 (M^+, 77.2), 331 (M^+-15,38.3).
Anal: Calc. for $C_{21}H_{18}N_2OS$ (346.432): C 72.80; H 5.24; N 8.09. Found C 72.81; H 5.25; N 8.08%.

1,2-Dihydro-4-(4-methoxyphenyl)-1-methyl-6-methylthio-2-phenyl-3H-indazol-3-one 25b:
Brown coloured crystals; yield 1.64g (87%); mp 145-146°C (chloroform-hexane); R_f 0.44 EtoAc/benzene (1:9).
IR(KBr): γ_{max}=1672 (CO), 1588, 1242, 1023 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.50 (s, 3H, SCH_3); 3.10 (s, 3H, NCH_3); 3.79 (s, 3H, OCH_3); 6.88-7.08 (m, 4H, ArH); 7.40-7.67 (m, 7H, ArH).

MS: m/z (%) = 376 (M^+, 100), 361(M^+-15,53.9).
Anal: Calc. for $C_{22}H_{20}N_2O_2S$ (376.304): C 70.21; H 5.36; N 7.45.
Found C 70.22; H 5.38; N 7.50%.

1,2-Dihydro-4-(4-chlorophenyl)-1-methyl-6-methylthio-2-phenyl-3H-indazol-3-one 25c:

Colourless crystals; yield 1.67g (88%); mp 165-168°C (chloroform-hexane): R_f 0.88 EtoAc/benzene (5:5).
IR(KBr): γ_{max}=1673(CO), 1584, 1314, 1087 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.51 (s, 3H, SCH_3); 3.10 (s, 3H, NCH_3); 6.94 (d, 2H, J=3Hz, ArH); 7.26-7.63 (m, 9H, ArH).
MS: m/z(%) = 380 (M^+,100),365 (M^+-15,52.3).
Anal: Calc. for $C_{21}H_{17}ClN_2O$ (380.887): C 66.22; H 4.50; N 7.36.
Found C 66.38; H 4.75; N 7.52%.

1,2-Dihydro-1-methyl-6-methylthio-4-[2-naphthyl]-2-plhenyl-3H-indazol-3-one 25d:

Colourless crystals; yield 1.48g (74.5%); mp 178-179°C (chloroform-hexane); R_f 0.74 EtoAc/benzene (2:8).
IR(KBr): γ_{max}=1673(CO), 1587, 1088, 817 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.56 (s, 3H, SCH_3); 3.11 (s, 3H, NCH_3); 7.01 (brs, 1H, ArH); 7.11 (brs, 1H, ArH); 7.37-7.65 (m, 5H, ArH); 7.74-7.98 (m, 4H, ArH);8.02 (m, 2H, ArH); 8.46 (brs, 1H, ArH).
MS: m/z(%) = 396 (M^+,29), 381 (M^+-15,20.1).
Anal: Calc. for $C_{25}H_{20}N_2OS$ (396.488): C 75.73; H 5.08; N 7.07.
Found C 75.75; H 5.06; N 7.09%.

1,2-Dihydro-4-(2'-Furyl)-1-methyl-6-methylthio-2-phenyl-3H-indazol-3-one 25e:

Viscous liquid; yield 1.08g (64%); R_f 0.87 EtoAc/benzene (2:8).

IR(KBr): ν_{max}=2992, 1666(CO), 1574, 1311, 1094 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.57 (s, 3H, SCH_3); 3.13 (s, 3H, NCH_3); 6.63-6.67 (m, 2H, ArH); 6.93 (brs, 1H,5'-Furyl); 7.35 (brs, 1H, 4'-Furyl); 7.55-7.71 (m, 5H,ArH); 8.39 (brs, 1H, 3'-Furyl).
Anal: Calc. for $C_{19}H_{16}N_2O_2S$ (336.396): C 67.83; H 4.79; N 8.33. Found C 67.84; H 4.80; N 8.35%.

1,2-Dihydro-1,4-dimethyl-6-methylthio-2-phenyl-3H-indazol-3-one 25f: Colourless crystals; yield 0.97g (68%); mp 90-92°C (chloroform-hexane); R_f 0.71 EtoAc/benzene (2:8).
IR(KBr): ν_{max}=1654(CO), 1584, 1305 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.50 (s, 3H, CH_3); 2.66 (s, 3H, SCH_3); 3.09 (s, 3H, NCH_3); 6.81 (brs, 2H, ArH); 7.20-7.68 (m, 5H, ArH).
MS: m/z(%) = 284 (M^+,100), 269 (M^+-16,57.1).
Anal: Calc. for $C_{16}H_{16}N_2OS$ (284.366): C 67.57; H 5.67; N 9.58. Found C 67.59; H 5.66; N 9.86%.

2,3.6,7,8,9-Hexahydro-3-methyl-5-methylthio-2-phenyl-1H-benz[e]indazol-1-one 25g:
Colourless crystals; yield 1g (62%); mp 158-160°C (chloroform-hexane): R_f 0.65 EtoAc/benzene (1:9).
IR(KBr): ν_{max}=2904, 1665(CO), 1303, 1127 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ 1.75-2.03 (m, 4H, CH_2); 2.53 (s, 3H, SCH_3); 2.76 (brs, 2H, CH_2); 3.08 (s, 3H, NCH_3); 3.33 (brs, 2H, CH_2); 6.85 (s, 1H, ArH); 7.32-7.81 (m, 5H, ArH).
MS: m/z(%) = 324 (M^+,100), 309 (M^+-15,44.9).
Anal: Calc. for $C_{19}H_{20}N_2OS$ (324.434): C 70.38; H 6.21; N 8.64. Found C 70.34; H 6.23; N 8.66%.

2,3,6,7,8,9,10,11-Octahydro-3-methyl-5-methylthio-2-phenyl-1H-cycloocta[e]indazol-1-one 25h:

Colourless crystals; yield 1.22g (69%); mp 132-135°C (chloroform-hexane): R_f 0.2 EtoAc/benzene (1:9).

IR(KBr): ν_{max}=2896, 1663(CO), 1586, 1441, 1301, 1121 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ=1.27-1.54 (m, 4H, CH_2); 1.57-2.04 (m, 4H, CH_2); 2.51 (s, 3H, SCH_3); 3.02(t,2H,CH_2); 3.12 (s, 3H, NCH_3); 3.45 (t,2H,CH_2); 6.92 (s, 1H, ArH); 7.34-7.83 (m, 5H, ArH).

MS: m/z(%) = 352 (M^+,100), 337 (M^+-15, 73).

Anal: Calc. for $C_{21}H_{24}N_2OS$ (352.48): C 71.55; H 6.86; N 7.95. Found C 71.57; H 6.85; N 7.98%.

2,3,6,7-Tetrahydro-3-methyl-5-methylthio-2-phenyl-1H-naphth[1,2,-e]indazol-1-one 25i:

Colourless crystals; yield 1.64g (88%); mp 180-182°C (chloroform-hexane); R_f 0.23 (benzene).

IR(KBr): ν_{max}=3154, 1651 (CO), 1296 cm^{-1}.

^1H NMR (300MHz, $CDCl_3$): δ = 2.48 (s, 3H, SCH_3); 2.78 (s, 4H, CH_2); 3.10 (s, 3H, NCH_3); 6.87 (s, 1H, ArH); 7.20-7.43 (m, 4H, ArH); 7.55-7.57 (m, 2H, ArH); 7.53-7.62 (m,2H,ArH); 8.87 (d, 1H, J=9Hz, ArH).

MS: m/z(%) = 372 (M^+,100) 357 (M^+-15,42.5).

Anal: Calc. for $C_{23}H_{20}N_2OS$ (372.474): C 74.16; H 5.41; N 7.52. Found C 74.17; H 5.43; N 7.55%.

2,3,6,7-Tetrahydro-9-methoxy-3-methyl-5-methylthio-2-phenyl-1H-naphth[1,2-e]-indazol-1-one 25j:

Colourless crystals; yield 1.85g (92%); mp 155-156°C (chloroform-hexane): R_f 0.63 EtoAc/benzene (1:9).

IR(KBr): γ_{max}=1648(CO), 1587, 1249, 1158 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ 2.60 (s, 3H, SCH_3); 2.85 (s, 4H, CH_2);3.20 (s, 3H, NCH_3); 3.89 (s, 3H, OCH_3); 6.89 (brs, 1H, ArH); 6.99 (brs, 1H, ArH); 7.35 (s, 1H, ArH); 7.44-7.80 (m, 5H, ArH); 8.48 (d, 1H, J = 9Hz, ArH).
MS: m/z(%) = 402 (M^+,100), 387(M^+-15,40.2).
Anal: Calc. for $C_{24}H_{22}N_2O_2S$ (402.504): C 71.61; H 5.51; N 6.96. Found C 71.63; H 5.53; N 6.94%.

2,3,6,7-Tetrahydro-3-methyl-5-methylthio-2-phenyl-1H-[1] benzoxepino[5,4-e]indazol-1-one 25k:
Light yellow crystals; yield 1.77g (91%); mp 175-176°C (chloroform-hexane): R_f 0.79 EtoAc/benzene (4:6).
IR(KBr): γ_{max} = 1672(CO), 1585, 1025 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.58 (s, 3H, SCH_3); 3.14 (s, 3H, NCH_3); 3.08-3.17 (m, 2H, CH_2); 4.41-4.66 (m, 2H, OCH_2); 7.10 (s, 1H, ArH); 7.22-7.91 (m, 9H, ArH).
MS: m/z(%) = 388 (M^+,100), 373(M^+-15,34).
Anal: Calc. for $C_{23}H_{20}N_2O_2S$ (388.474): C 71.11; H 5.19; N 7.21. Found C 71.13; H 5.20; N 7.19%.

<u>General procedure for dethiomethylation of 25b,g,i,j:</u>
To a stirred solution of 1,2,4-trisubstituted-6-methylthio-indazol-3-one 25b,g,i,j (2.5 mmol) in ethanol (25 ml) was added Raney Nickel (W4, 3 times by weight) and the mixture was stirred at ambient temperature for 6-8 h (monitored by tlc). The reaction mixture was filtered through G-3 cintered funnel and the residue was washed with ethanol (3x10 ml). The bulk of the ethanol was distilled off and chloroform (20 ml) was added. The solution was

washed with water (2x25 ml), dried over sodium sulfate and evaporated. Analytically pure compounds **26b,g,i,j** were obtained by passing through a short length silicagel column using hexane as eluent.

1,2-Dihydro-4-(4-methoxyphenyl)-1-methyl-2-phenyl-3H-indazol-3-one 26b:

Colourless crystals; yield 0.80g (98%) mp 152-153°C (chloroform-hexane); R_f 0.5 EtoAc/benzene (1:9).

IR(KBr): γ_{max}=1591(CO), 1302, 1245, 825 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ=3.21 (s,3H,NCH_3); 3.92 (s,3H,OCH_3); 7.04 (brs,1H, ArH); 7.14 (brs, 1H, ArH); 7.26-7.81 (m, 9H, ArH); 8.05 (brs, 1H, ArH).

MS: m/z(%) = 330 (M^+,100), 315(M^+-15,66.7).

Anal: Cacl. for $C_{21}H_{18}N_2O_2$ (330.37): C 76.34; H 5.50; N 8.48. Found C 76.31; H 5.51; N 8.49%.

2,3,6,7,8,9-Hexahydro-3-methyl-2-phenyl-1H-benz[e]indazol-1-one 26g: Colourless crystals; yield 0.69g (99%); mp 185-186°C (chloroform-hexane): R_f 0.68 EtoAc/benzene (1:9).

IR(KBr): γ_{max}=2915, 1654(CO), 1306 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ=1.70-2.00 (m, 4H, CH_2); 2.81 (brs, 2H, CH_2); 3.09 (s, 3H, NCH_3); 3.36 (brs, 2H, CH_2); 7.07 (d, 1H, J = 9Hz, ArH); 7.38 (d, 1H, J = 9Hz, ArH); 7.50-7.80 (m, 5H, ArH).

MS: m/z(%) = 278 (M^+,100), 263 (M^+-15, 15).

Anal: Calc. for $C_{18}H_{18}N_2O$ (278.34): C 77.67; H 6.52; N 10.07. Found C 77.68; H 6.55; N 10.06%.

2,3,6,7-Tetrahydro-3-methyl-2-phenyl-1H-naphth[1,2-e]indazol-1-one 26i:

Colourless crystals; yield 0.79g (97%); mp 196-197°C

(chloroform-hexane): R_f 0.28 (benzene).
IR(KBr): γ_{max}=1655(CO), 1476, 1327, 1134 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.84 (s, 4H, CH_2); 3.15 (s, 3H, NCH_3); 7.24-7.84 (m,10H, ArH); 8.64 (d,1H,J=7.5Hz, ArH).
MS: m/z(%) = 326 (M^+,100), 311 (M^+-15,67.5).
Anal: Calc. for $C_{22}H_{18}N_2O$ (326.38): C 80.95; H 5.56; N 8.59.
Found C 80.96; H 5.58; N 8.60%.

2,3,6,7-Tetrhydro-9-methoxy-3-methyl-phenyl-1H-naphth[1,2-e]indazole-1-one 26j:
Colourless crystals; yield 0.87g (98%); mp 161-163°C
(chloroform-hexane): R_f 0.68 EtoAc/benzene (1:9).
IR(KBr): γ_{max}=2925, 1656(CO), 1592, 1479 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=2.81 (s, 4H, CH_2); 3.13 (s, 3H, NCH_3); 3.85 (s, 3H, OCH_3); 6.89 (brs, 1H, ArH); 7.04 (d, 3H, J=3Hz,ArH); 7.19 d, 1H, J=9Hz, ArH); 7.58 (d, 1H, J=9Hz, ArH); 7.67-7.85 (m, 5H, ArH); 8.64 (d, 1H, J = 9Hz, ArH).
MS: m/z(%) = 356 (M^+,100), 341(M^+-15,54.1).
Anal: Calc. for $C_{23}H_{20}N_2O_2$ (356.49): C 77.49; H 5.66; N 7.86.
Found C 77.50; H 5.68; N 7.88%.

General procedure for the generation and reaction of 3-lithiomethyl-2-methyl-1-phenyl pyrazoline 17a with α-oxoketene S,N-acetals (28a-f): Synthesis of 1,2-dihydro-1,2,4-trisubstituted-6-dicycloalkylamino-3H-indazol-3-one (30a-e) and 2,3,6,7-tetrahydro-3-methyl-5-piperidyl-2-phenyl-1H-naphth[1,2-e]indazol-1-one 30f.

To an ice cold (0°C) solution of 2.95ml (21 mmol) of diisopropyl-

amine in 10 ml of dry tetrahydrofuran (THF) under dry argon was added 15 mmol of n-BuLi in ether. To the resulting solution of lithium diisopropyl amide (15 mmol) under dry argon at -78C was added 0.9g (5 mmol) of antipyrine in 25 ml of dry THF, and the solution was stirred for 30-45 min. To the resulting enolate solution at -78°C was added 4 mmol of α-oxoketene S,N-acetal in 25 ml dry THF dropwise and kept for 30-45 min, allowed to warm at room temperature, stirred for 6-8 hr (monitored by tlc) and quenched with aqueous saturated ammonium chloride solution (100 ml), extracted with chloroform, the combined organic phase was washed with water (3x25 ml), dried over anhydrous sodium sulfate. Removal of organic phase gave crude product which was purified by column chromatography over silica gel. Elution with ethylacetate-hexane (3:7) yielded the product which were further recrystallised from chloroform-hexane.

1,2-Dihydro-1-methyl-2,4-diphenyl-6-(1-pyrrolidyl)-3H-indazol-3-one 30a:

Light brown crystals; yield 1.81g (98%); mp 158-159°C (chloroform-hexane): R_f 0.45 EtoAc/benzene (2:8).

IR(KBr): ν_{max}= 1599(CO), 1273, 1127 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ=1.89-2.19 (m, 4H, CH_2); 3.08 (s, 3H, NCH_3); 3.29-3.54 (m, 4H, NCH_2); 6.18 (brs, 1H, ArH); 6.44 (brs, 1H, arH); 7.33-7.80 (m, 10H, ArH).

MS: m/z(%) = 369(M^+, 71.2), 354(M^+-15,100).

Anal: Calc. for $C_{24}H_{23}N_3O$ (369.44): C 78.02; H 6.27; N 11.37. Found C 78.04; H 6.29; N 11.38%.

1,2-Dihydro-1-methyl-2,4-diphenyl-6-(1-morpholinyl)-3H-indazol-3-one 30b:

Viscous liquid; yield 1.48 g (77%); R_f 0.48 EtoAc/benzene (2:8).
IR(KBr): γ_{max}= 1605(CO), 1490, 1270 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 3.17 (s, 3H, NCH_3); 3.27-3.50 (m, 4H, NCH_2); 3.78-4.00 (m, 4H, OCH_2); 6.68 (s, 1H, ArH); 6.90 (s, 1H, ArH); 7.34-7.73 (m, 10H, ArH).
MS: m/z(%) = 385 (M^+,18.2), 370 (M^+-15,1.3).
Anal: Calc. for $C_{24}H_{23}N_3O_2$ (385.44): C 74.78; H 6.01; N 10.90. Found C 74.76; H 6.03; N 10.50%.

1,2-Dihydro-1-methyl-2-phenyl-6-(1-pyrrolidyl)-4-(2'-thienyl)-3H-indazol-3-one 30c:

Colourless crystals; yield 1.35g (72%); mp 138-140°C (chloroform-hexane): R_f 0.75 EtoAc/benzene (2:8).
IR(KBr): γ_{max}= 1563 (CO), 1489, 1270 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=1.94-2.17 (m, 4H, CH_2); 3.13 (s, 3H, NCH_3); 3.32-3.54 (m, 4H, NCH_2); 6.14 (d, 1H, J = 3Hz, ArH); 6.62 (d, 1H, J = 3Hz, ArH); 7.19 (dd, 1H, J = 4.5Hz, 5'-furyl); 7.38 (dd, 1H, J=4.5Hz, 4'-furyl); 7.48-7.74 (m, 5H, ArH); 8.07 (d, 1H, J=4Hz, 3'-furyl).
MS: m/z(%) = 375 (M^+,100), 360 (M^+-15,82.9).
Anal: Calc. for $C_{22}H_{21}N_3OS$ (375.474): C 70.37; H 5.64; N 11.19. Found C 70.37; H 5.63; N 11.18%.

1,2-Dihydro-4-(4-chlorophenyl)-1-methyl-6-(1-morpholinyl)-2-phenyl-3H-indazol-3-one 30d:

Viscous liquid; yield 1.58g (78%); R_f 0.55 EtoAc/benzene (1:9).
IR(KBr): γ_{max}=1590 (CO), 1495, 1207 cm^{-1}.
^1H NMR (90MHz, CCl_4): δ=3.01-3.22 (m, 4H, OCH_2); 3.66-3.92 (m,

4H, OCH_2); 6.31 (d, 1H, J = 3Hz, ArH); 6.67 (d, 1H, J = 3Hz, ArH); 7.25-7.58 (m, 7H, ArH); 7.66-8.03 (m, 2H, ArH).

Anal: Calc. for $C_{24}H_{22}N_3OCl$ (403.89): C 71.37; H 5.49; N 10.40. Found C 71.38; H 5.50; N 10.42%.

1,2-Dihydro-4-(4-methoxyphenyl)-1-methyl-2-phenyl-6-(1-pyrrolidyl)-3H-indazol-3-one 30e:

Light brown crystals; yield 1.88g (94%); mp 216-218°C (chloroform-hexane): R_f 0.8 EtoAc/benzene (4:6).

IR(KBr): ν_{max} = 1595 (CO),1270, 1122 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ 1.92-2.14 (m, 4H, CH_2); 3.11 (s, 3H, NCH_3); 3.28-3.54 (m, 4H, NCH_2); 3.84 (s, 3H, OCH_3); 6.20 (d, 1H, J = 3Hz, ArH); 6.45 (d, 1H, J = 3Hz, ArH); 7.00 (d, 2H, J=9Hz, ArH); 7.43-7.78 (m, 7H, ArH).

MS: m/z(%) = 399 (M^+,100), 384(M^+-15,71.4).

Anal: Calc. for $C_{25}H_{25}N_3O_2$ (399.47): C 75.16; H 6.31; N 10.52. Found C 75.18; H 6.31; N 10.54%.

2,3,6,7-Tetrahydro-3-methyl-5-piperidyl-2-plhenyl-1H-naphth[1,2-e]indazol-1-one 30f:

Colourless crystals; yield 1.71g (83.5%); mp 169-171°C (chloroform-hexane): R_f 0.8 EtoAc/benzene (1:9).

IR(KBr): ν_{max}= 1591 (CO), 1204, 1109 cm^{-1}.

^1H NMR (250MHz, $CDCl_3$): δ = 1.75-1.82 (m, 6H, CH_2); 2.68-2.85 (m, 4H, NCH_2); 2.95 (brs, 4H, CH_2); 3.15 (s, 3H, NCH_3); 6.78 (s, 1H, ArH); 7.20-7.33 (m, 4H, ArH); 7.43-7.51 (m, 2H, ArH); 7.60 (d, 2H, J = 9Hz, ArH); 8.30 (d, 1H, J = 9Hz, ArH).

MS: m/z(%) = 409 (M^+,100), 394 (M^+-15,27.5).

Anal: Calc. for $C_{27}H_{27}N_3O$ (409.51): C 79.18; H 6.65; N 10.26. Found C 79.20; H 6.66; N 10.25%.

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CHAPTER IV

HIGHLY DIASTEREOSELECTIVE ANIONIC [3+2] ANNULATION STRATEGY FOR FUNCTIONALIZED CYCLOPENTENES VIA α-OXOKETENE DITHIOACETALS*

IV.1 *Introduction*

Renewed interest in the construction of cyclopentanoid ring system continues to attract attention of many synthetic organic chemists as a direct consequence of the isolation and characterization of many new cyclopentanoid natural products[1,2]. New strategies have been developed to facilitate the preparation of cyclopentanoids, through novel strategies involving inter-

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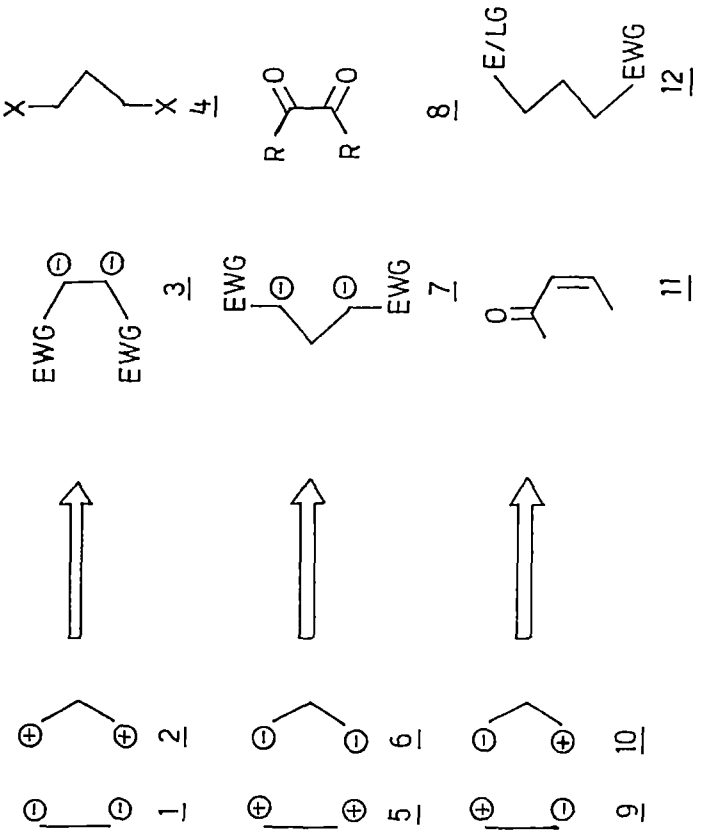
*Reddy, K.R.; Singh, L.W.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin Trans.I*, 1994, 2439.

and intramolecular processes. Many efforts have been made to meet these objectives through the methods that run parallel to the versatile Diel's-Alder reaction to contain the effectiveness of this approach. However, to date, no efficient parallel method involving Diels-Alder strategy has been evolved. The closest approach to this Diels-Alder strategy should be [4n+1] or [3+2] cycloaddition which have been attempted with increasing success in recent years. Of these, [4n+1] approach has more limitations than the corresponding [3+2] cycloaddition processes. The disconnection approach for the synthesis of cyclopentanes that are theoretically close to [3+2] cycloaddition as depicted in scheme 1, of which the reaction of dianions derived from 3-carbon fragment and their reactions with electron deficient olefins involving alkylative approaches appears to be the most commonly employed methodology. Many of these reactions follow greater degree of stereocontrolled cycloaddition even though they may or may not follow concerted reaction pathway. The process of these dianion reactions may also follow Michael-aldol sequential approach of ring formation depending on the structural parameters and functional group combinations of both the participating substrate fragments. For the present investigation few select examples have been reviewed involving these two approaches since the present work falls in the category of Michael-aldol-Tandem process of cyclopentanoid synthesis. The following examples from literature illustrates as a prelude to the present work. Many comprehensive reviews[2-7] have been published describing several approaches for the construction of cyclopentanoids which are not covered in this section.

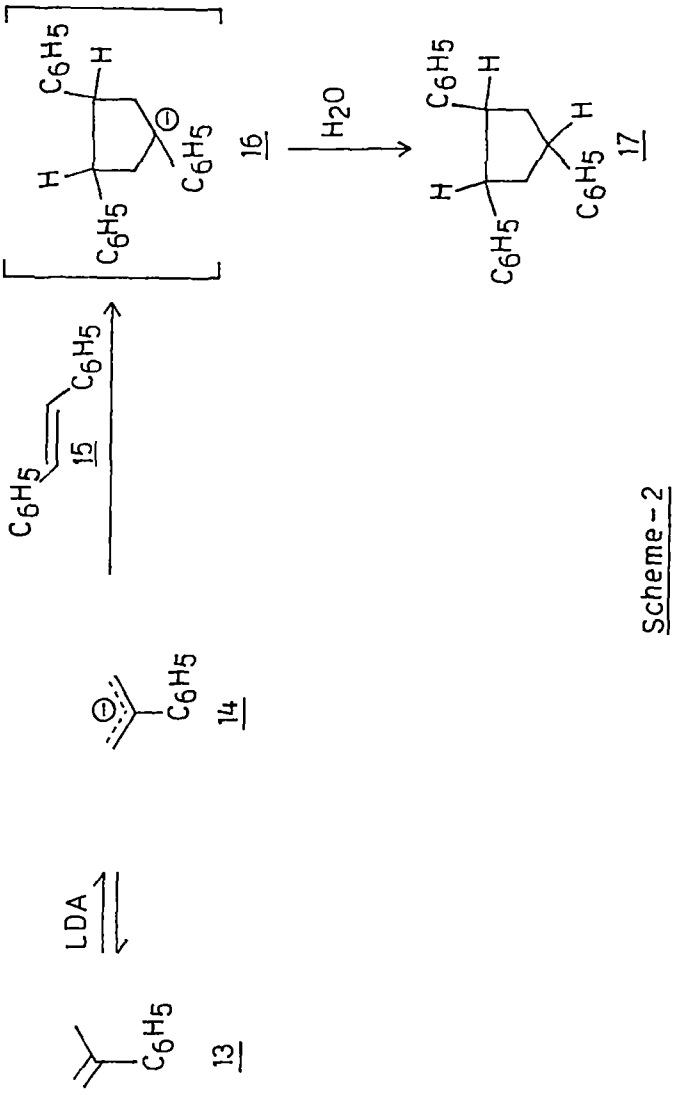
[3+2] DISCONNECTIONS IN CYCLOPENTANE SYNTHESIS



Scheme - 1

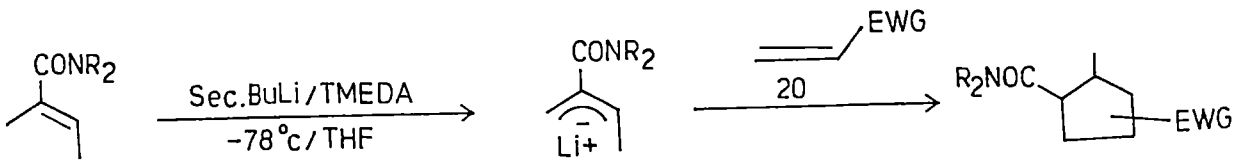
Kauffmann et al[8,9,10,11], have made the pioneering investigations in the synthesis of five membered carbocycles involving 1,3-anionic cycloadditions. They derived their experiences from these studies on two azaallyl anions and their cycloaddition to multiple bonded olefines. They reasoned that the negative charge from the two peripheral carbon atoms of the two azaallyl anion systems is transfered to the more electronegative central nitrogen atom so that the cycloaddition process is facilitated. They argued that the cycloaddition of allyl anion with multiple C-C bond should be favoured by any substituent that makes it easy for electrons to be taken up by central carbon atom. On this basis they studied allyl anion **14** where the presence of C-2 phenyl group should facilitate the negative charge from the terminal carbon atoms to central carbon atoms due to the presence of phenyl group. The cycloadduct **17** thus formed in 41% yield was a novel example of [3+2] anionic cycloaddition strategy resulting in cyclopentane ring formation as outlined in scheme 2.

Beak and co-workers[12] examined the (2-carbamoylallyl)lithium reagents with electron-deficient olefins in formal [3+2] cycloaddition reactions. They generated reagents from α,β-unsaturated amides **18** and treated them as π^4 component in a formal [3+2] cycloaddition with π^2 component resulting in cyclopentane enolate and eventually the corresponding cyclopentanes. α,β-unsaturated amides **18** were subjected to β'-lithiation using stoichiometric amount of sec-butyl lithium in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) and reacted with electron-deficient olefins **20** to yield the


C6H5
H
H
C6H5
C6H5
16
H2O
C6H5
H
H
C6H5
C6H5
17
C6H5
15
C6H5
LDA
C6H5
14
C6H5
13

Scheme-2

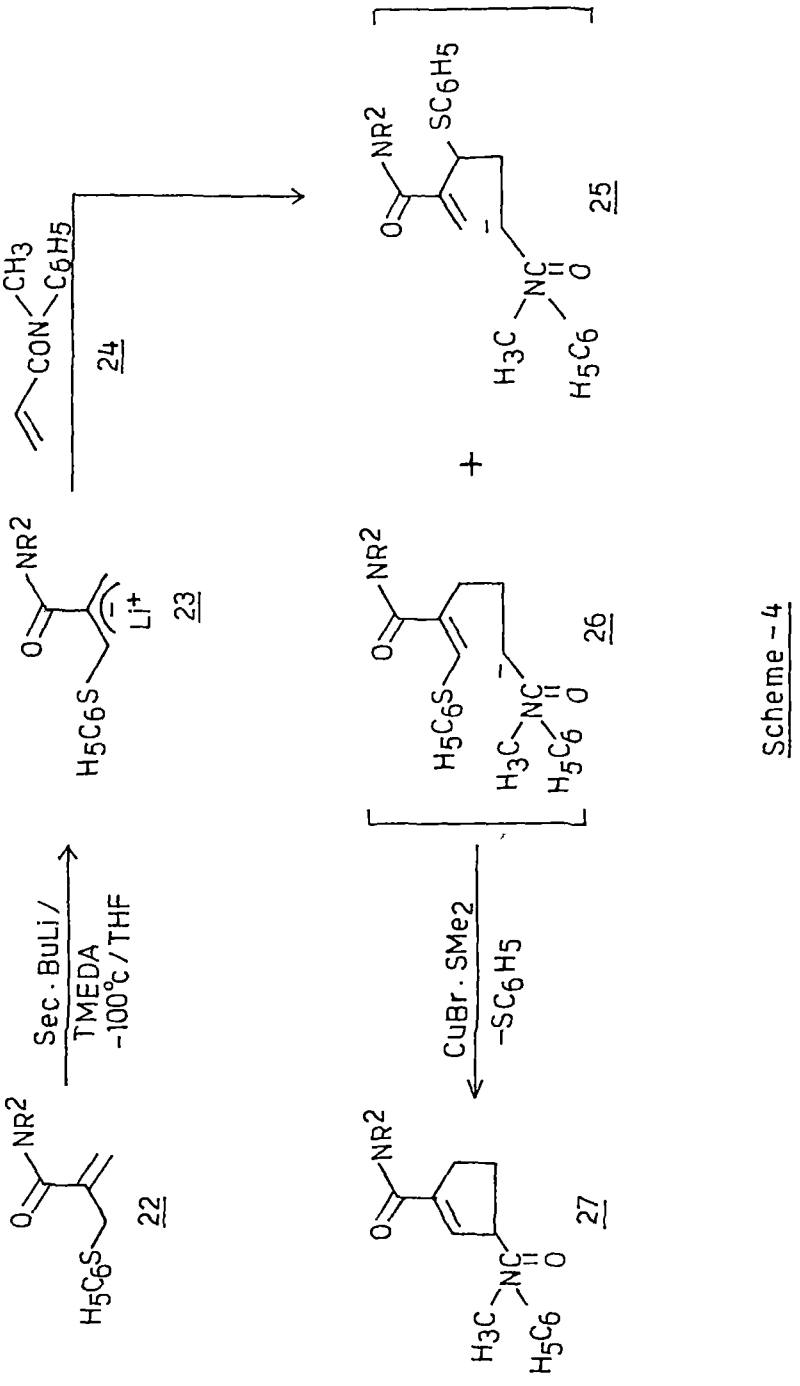
corresponding cyclopentanoids 21 in good yields as shown in scheme 3. These reactions are considered to follow stepwise pathway instead of concerted cycloaddition sequence. However, these reactions demonstrated the possibility of developing a methodology for the synthesis of cyclopentanoids. In their continued studies they used β'-(phenylthio) group to increase the reactivity of the reactant in addition to the expected regio control in the cycloaddition reaction, in addition to that the phenylthio group is expected to act as a leaving group at the end of the reaction thus driving the reaction in the forward direction. The anion 23 reacted with acrylamide 24 to yield the cyclopentenes 27 (scheme 4). Subsequently, Beak and co-workers[13], extended the anionic [3+2] cycloaddition studies to [1-(phenylsulfonyl)-2-(diisopropylcarbamoyl)allyl] lithium 29 which, when allowed to react with olefins bearing an electron withdrawing group 30 yielded the corresponding 4-substituted cyclopent-1-enecarboxamides 31 in 22-89% overall yields as depicted in scheme 5. Methyl-substituted analogues of 29 reacted in a similar manner to produce the corresponding cyclopentenes with methyl groups at 2 or 5-positions. A number of structural varients in the allyl anion component and olefins with electron withdrawing group were examined to study the efficacy of the methodology. The formation of the cyclopentenes was shown to follow stepwise regioselective addition to the electron-deficient olefins followed by *5-Endo-Trig* cyclization to cyclopentenes after elimination of benzenesulfinate. The presence of phenylsulfonyl group had helped in the increasing acidity of the β'-protons as well as in the control of the



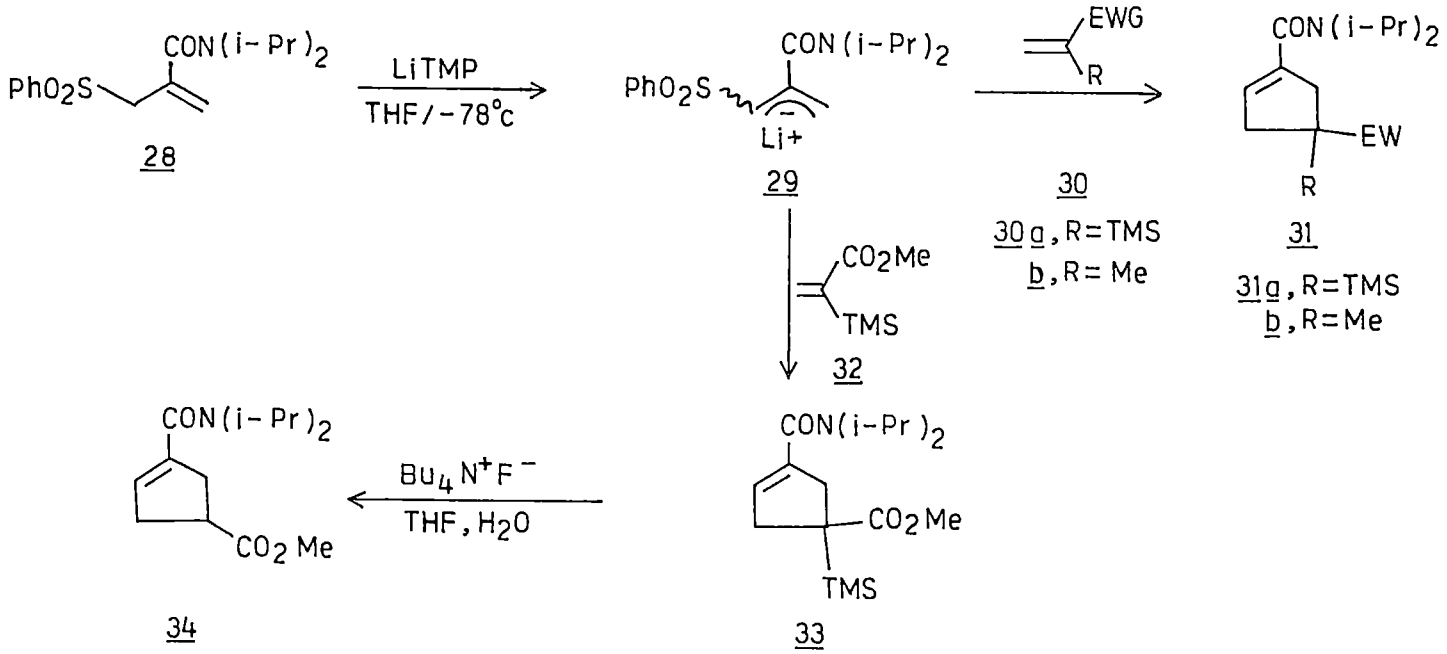
18 19 21

18, 19, 21, R = $CH(CH_3)_2$

Scheme-3



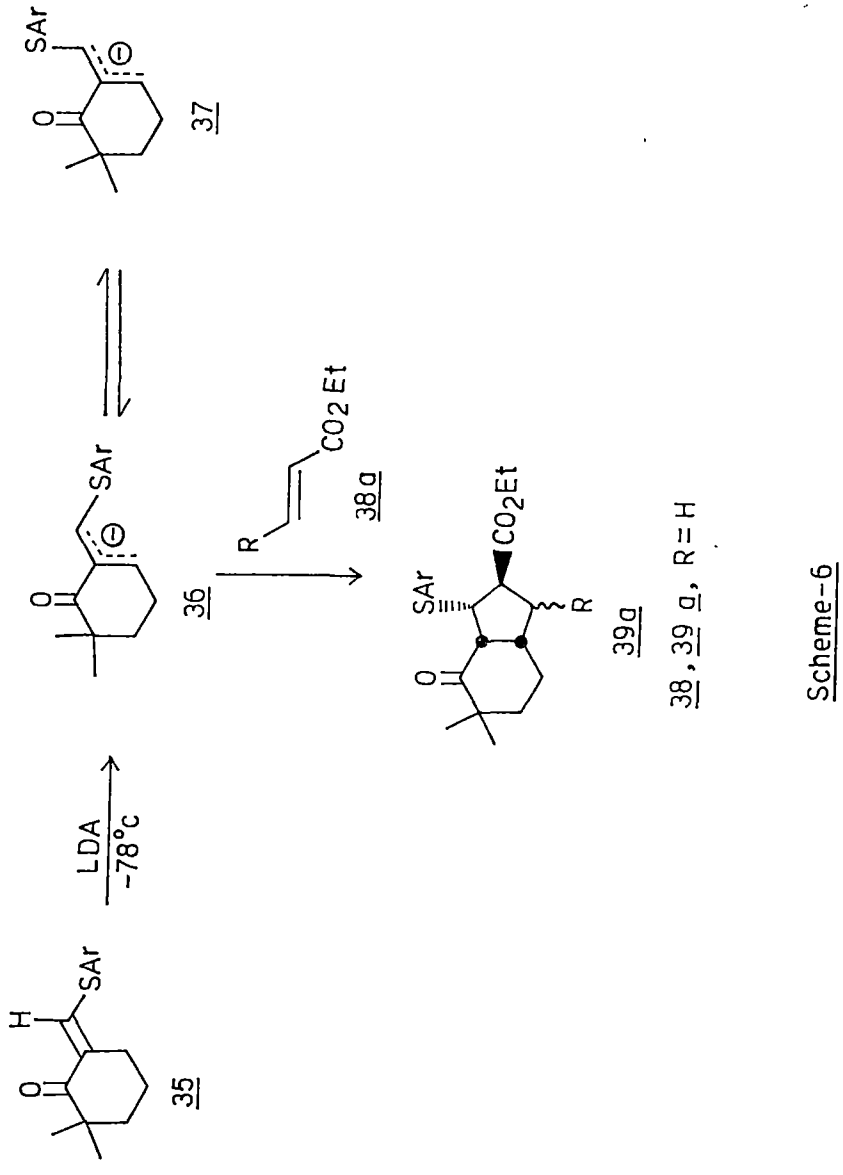
Scheme - 4


CON(i-Pr)2
PhO2S
LiTMP
THF/-78°C
28
CON(i-Pr)2
PhO2S
Li+
29
EWG
R
30
30a, R=TMS
b, R=Me
CON(i-Pr)2
EW
R
31
31a, R=TMS
b, R=Me
CO2Me
TMS
32
CON(i-Pr)2
CO2Me
TMS
33
Bu4N+F−
THF, H2O
CON(i-Pr)2
CO2 Me
34

Scheme - 5

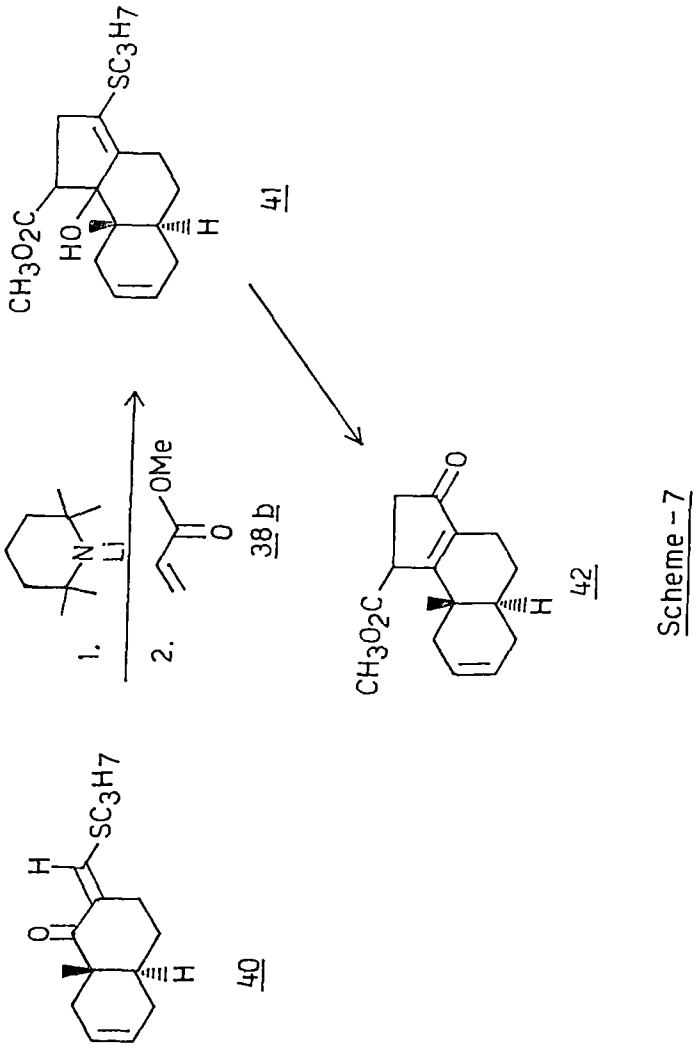
regioselectivity observed in those reactions. Subsequently, Marino and co-workers[14] reported an efficient pentannelation involving cycloaddition of 2,2-dimethyl-6-(p-chlorothiophenyl-methylene) cyclohexanone **35** with ethyl acrylate **38a** to yield the corresponding cycloadduct **39a** in good yields (scheme 6). The rigid *trans* stereo chemistry of -SAr group with reference to carbethoxy group was established through their nmr studies. Umpolung approach to cyclopentanone synthesis was efficiently developed by Marnio and co-workers[15]. They used the 2,2,6,6-tetramethyl piperidide for deprotonation of the vinylic hydrogen in β-oxo-stabilized species **40** to get the corresponding lithio derivatives and treated with Michael acceptor such as methyl acrylate **38b** which yielded the corresponding cyclopentenols **41** which were efficiently hydrolysed to the corresponding cyclopentenone **42** (scheme 7), thus, constituting a novel example of Umpolung approach.

Boche and co-workers[16] and Ford and co-workers[17] studied the stereochemistry of addition of 1,3-diphenylallyl-2-carbonitrile lithio anion to trans-stilbene. The allyl anions **E, E-45** and **E, Z-46** which were elegantly derived from the 2-cyano-1,3-diphenylallyllithium **43** through *con* rotatory ring opening to yield the allyl anions. These anions underwent cycloaddition with trans-stilbene **15** to yield the corresponding only two of the ten possible diastereomeric 2,3,4,5-tetraphenylcyclopentane-1-carbonitriles **48** and **49**. The configuration of **48** and **49** were established by X-ray studies. However, they observed that anions failed to react with cis-stilbene while trans-stilbene adds so readily. They reasoned that in cis-stilbene the phenyl groups are



38, 39 a, R = H

Scheme-6



Scheme - 7

twisted out of the plane of the central double bond so that their ortho hydrogens lie above and below the central carbon atoms which blocked the attack of the nucleophiles at the double bond. Also interestingly, only (E,E) conformer was formed while the (E,Z) conformer was not detected when **45** and **46** were reacted with trans-stilbene* as depicted in scheme 8.

Padwa and co-workers[18] treated (phenylsulfonyl) allene **50** with activated olefins in the presence of nucleophilic reagent which helps formation of carbanion **51**, which is then reacted with olefins **11** to give the intermediate anion **52** followed by its cyclization-elimination sequence to provide the corresponding cyclopentenone **53** (scheme 9).

Hassner and co-workers[19] developed a novel new diastereoselective [3+2] cyclopentane annulation as described in scheme 9. They prepared 1-bromo-2-methylene-3-phenylsulfonyl- propane **54** and reacted with α,β-unsaturated esters **55** under the Michael reaction conditions to yield the corresponding cyclopentane derivatives **56** with complete diastereoselectivity. The compound **54** in the presence of LDA yielded the corresponding stabilized anion next to sulfonyl group which on reaction with olefins with electron - withdrawing group underwent initial Michael addition followed by ring closure to yield **56**.

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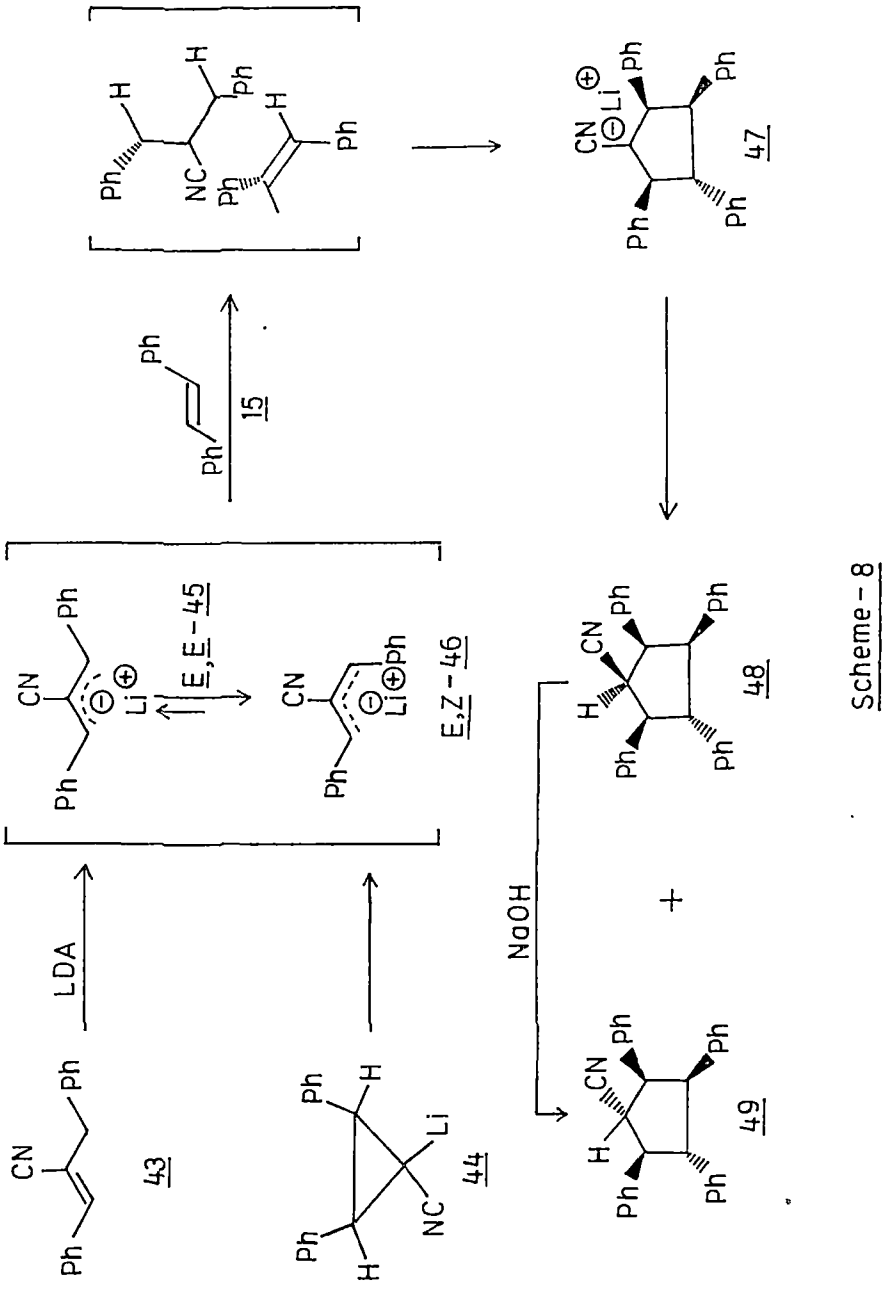
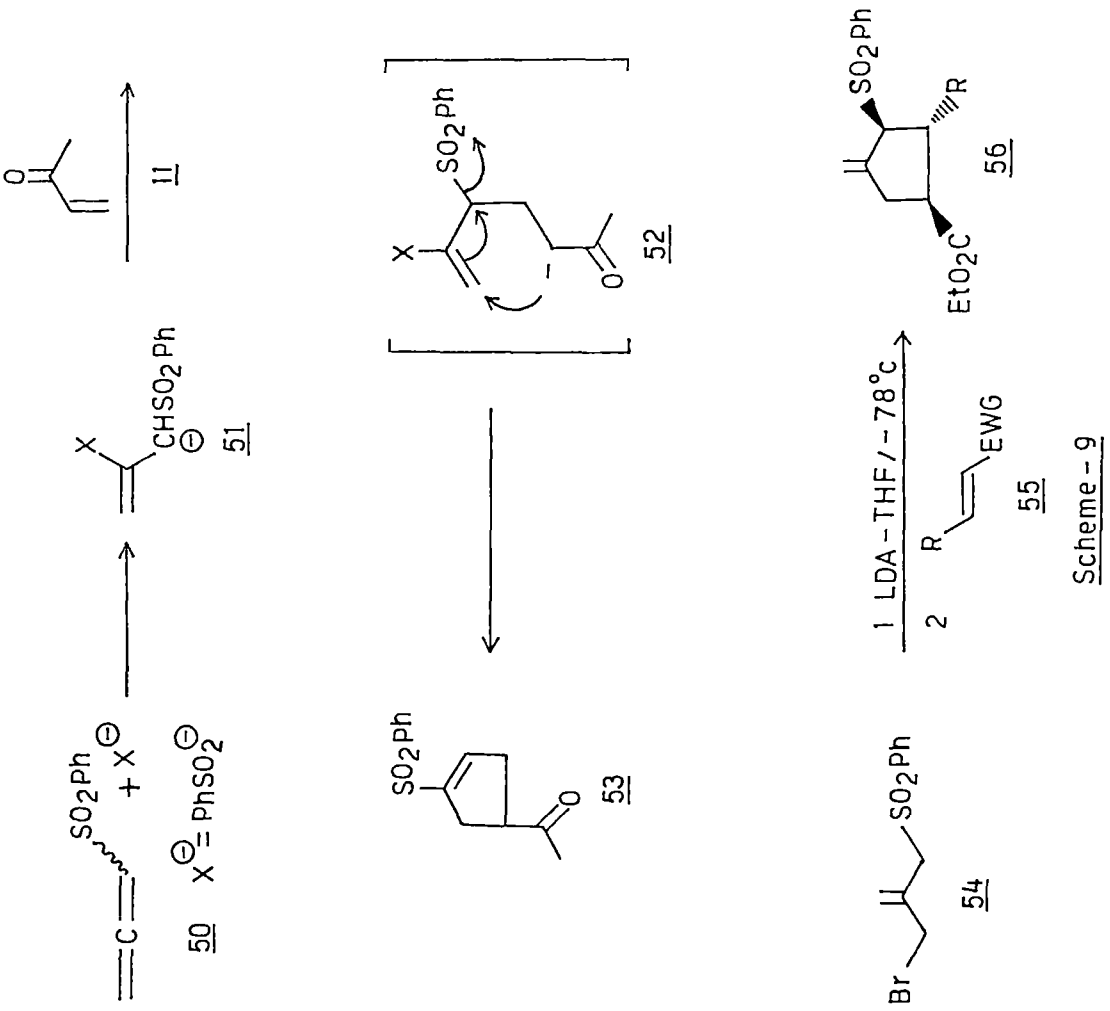
*Steric hindrance to contact ion pairing between the α-cyano carbon atom and the THF- solvated lithium ion raises the energy of the transition state for cycloaddition of the (E,Z) conformer.



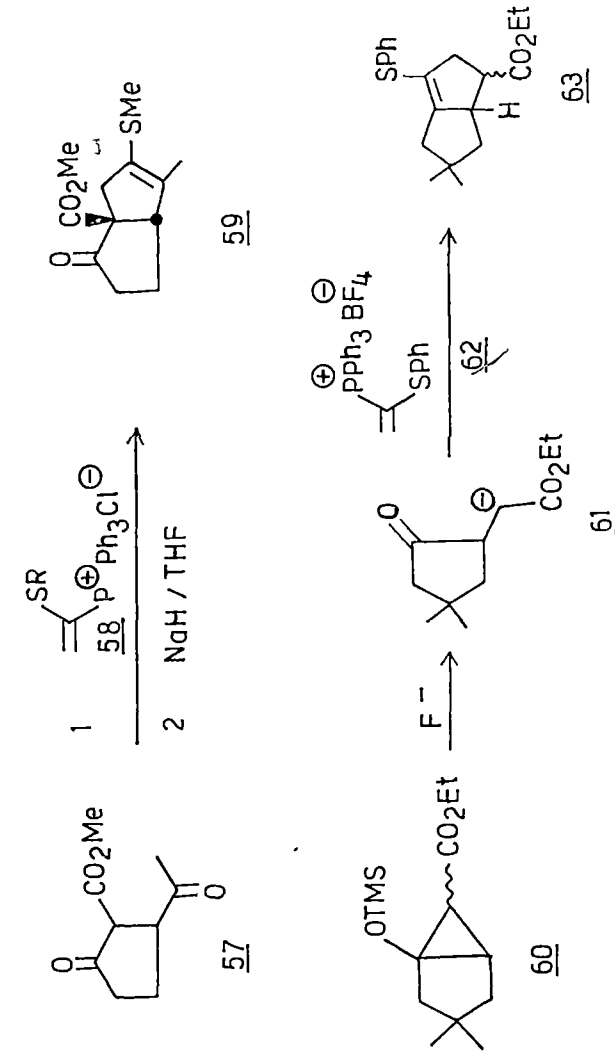
Scheme - 8


SO2Ph
+ X⊖
C
X⊖ = PhSO2⊖
50
X
CHSO2Ph⊖
51
11
O
X
SO2Ph
O
52
SO2Ph
O
53
1 LDA-THF/-78°C
2
R
EWG
55
SO2Ph
R
EtO2C
56
Br
SO2Ph
54

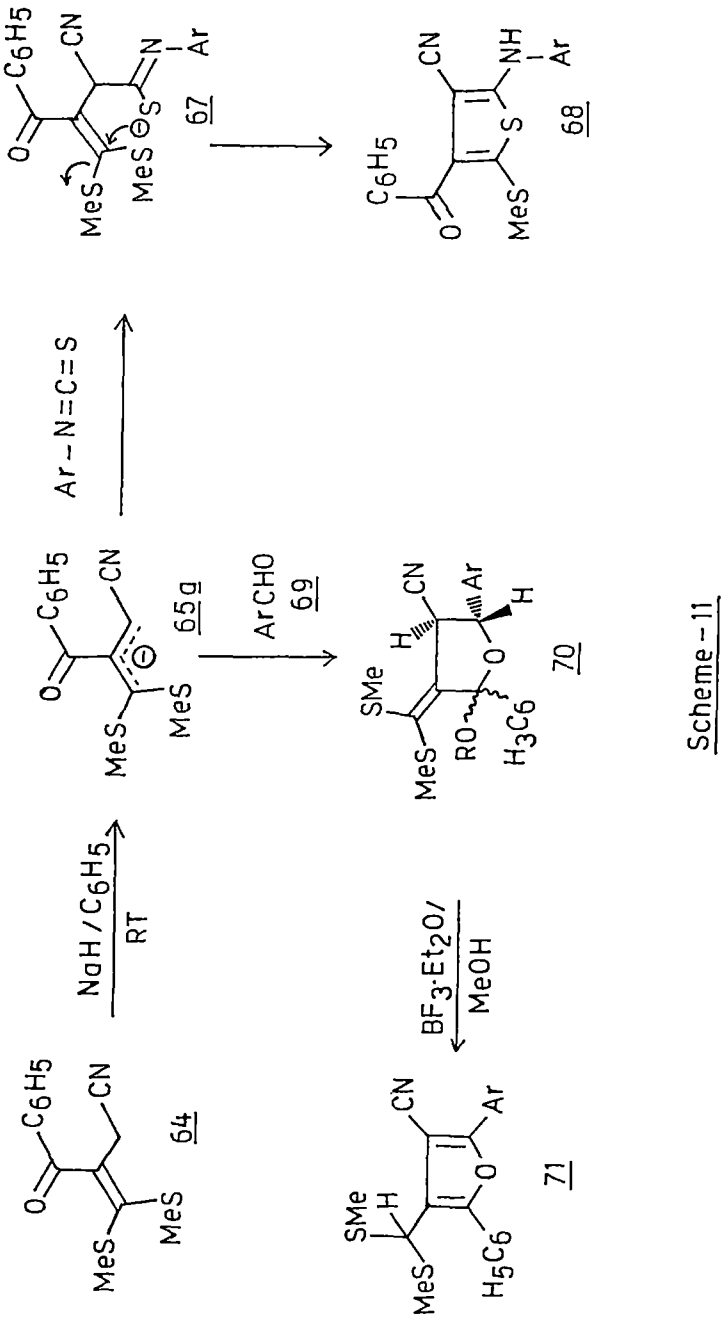
Scheme-9

Hewson and co-workers[20] prepared highly functionalised bicyclo [3.3.0] octane and achieved the total synthesis of loganin through the Michael aldol type annulation process. When the carbethoxy oxycyclopentanone (diketoester) **57** treated with vinyl phosphonium salt **58** in the presence of sodium hydride, corresponding bicyclo [3.3.0] octane **59** was obtained in 97% yield (scheme 10). The method was generally applicable and the initial Michael addition followed by intramolecular Wittig C-C bond formation the bicyclo octane was obtained. Novel strategy for the construction of cyclopentanoids was developed by Marino and co-workers[21] using [3+2] cycloaddition strategy involving combination of 3-carbon synthons in the formation of γ-oxo α-ester enolate **61**. This was used as Michael donor with various Michael acceptors to prepare many annulated cyclopentanoids. Thus, the cyclopropane **60** was cleaved in the presence of fluoride ion to give the γ-oxo α-ester enolate **61** which on addition to the triphenylphosphonium salt **62** in the Michael fashion followed by intramolecular Wittig C-C bond formation yielded the corresponding bicyclo [3.3.0] octane systems **63** in good yields (scheme 10).

In the light of these discussions, it was considered of interest to develop an efficient anionic 3-carbon fragments of general formula **65A** (scheme 11) derived from easily accessible oxoketene dithioacetal **64**[22]. The reaction of **65** towards olefins with electron- withdrawing group was intended to construct cyclopentanoid annelation in the present work. Prior to the investigations, the reactivity of these anions **65A** with various


CO2Me
O
O
57
1
2 NaH / THF
SR
58
⊕P Ph3Cl⊖
CO2Me
SMe
O
59
OTMS
CO2Et
60
F⁻
O
⊖
CO2Et
61
⊕PPh3 BF4⊖
SPh
62
SPh
H
CO2Et
63

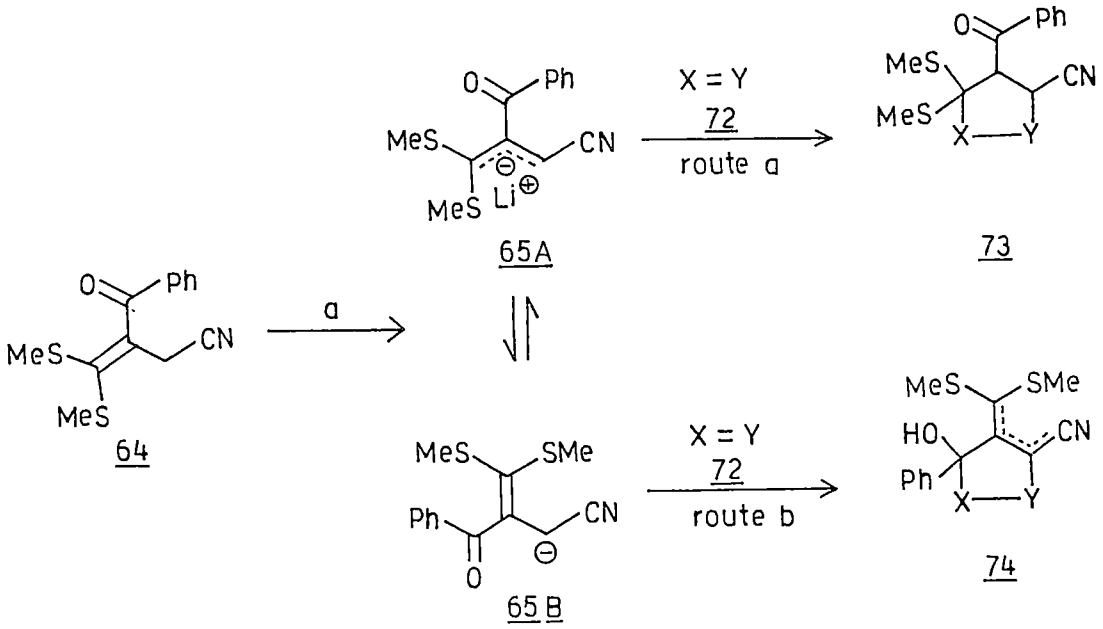
Scheme -10



Scheme-11

electrophiles were examined in this laboratory[23,24]. Thus, **65A** on reaction with arylisothiocyanate **66** yielded the corresponding thiophene **68** in excellent yields[25] (scheme 11). Similarly, anion **65A** reacted with aldehyde **69** to give the corresponding tetrahydrofuran **70** which was subsequently aromatized to the corresponding furan **71**[26] (scheme 11).

It was contemplated, that the anion derived from bifunctional ketene S,S-acetal should function as 1,3-dipole to react with various activated olefins. Such anionic cycloadditions may follow one of the following path ways: 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[27]. However, in route b, the anion behaves as having bis(methylthio) mercapto functionality as trimethylenemethane (TMM) equivalents which are excellently suited for Tandem Michael followed by aldol addition to afford the corresponding cyclopentanoids of general formula **74**. These precursors **64** were therefore considered equivalents of trimethylenemethane (TMM) as observed by Hassner and co-workers[19] and should give cyclopentanoid annelation reaction with electron- withdrawing olefins. We have examined the reactivity of the anion **65A** with various activated olefins **72** under [3+2] cycloaddition conditions and found that the reaction follows route b, in highly stereo-regio selective manner to yield the cyclopentenes **74** in good yields (scheme 12). The results of these studies are described in this chapter.



a, LDA, THF, - 78°C, 0·5-1h

Scheme -12

IV.2 *Results and Discussion*

The anion **65A** was generated by reacting α-oxoketene dithioacetal **64** with LDA-THF at -78°C under the blanket of dry argon. To a stirred solution of **65A** which had intense voilet colouration, equivalent amount of benzylideneacetophenone **75** was added in THF and the reaction mixture after work-up, separated in 88% as colourless crystals mp 162-163°C (chloroform-hexane), which was characterized as 5-benzoyl-2-[bis(methylsulfonyl)methyl]-3-cyano-1,4-diphenylcyclopent-2-enol **74a**. The structure was established on the basis of analytical and spectral data. The compound was analysed for $C_{28}H_{25}NO_2S_2$, for a molecular weight 471.601 confirmed by its mass spectrum m/z 471 (M^+,3%) and 405 (M^+-48). In its IR (KBr) spectrum ν_{max} showed absorption band at 3425 cm-1 for OH streching due to free and intramolecularly hydrogen bonded OH group. The other bands at 2210 cm^{-1} was assigned to nitrile group while 1660 cm^{-1} was assigned to carbonyl group. There was no significant shift in the position of 3425 cm^{-1} band when the spectra were recorded at different dilutions, thus pointing to intramolecular hydrogen bonded OH group in **74a**.* The presence of intramolecular hydrogen bonding between 1-hydroxy and 5-benzoyl group demonstrates that these two groups are *cis* to each other in **74a**. Our attempts to acylate **74a** with either

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*The high Δ value ($\backsim$ 150 cm^{-1}) between free and hydrogen bonded OH frequency also points to an intramolecular H-bonded OH-group. Intramolecular H-bonding in α- and β-hydroxyketones has been extensively studied[28-31].

acetyl chloride or with D-(+)-(O-methyl) mandalyl chloride* under various conditions were not successful. In one condition (pyridine/toluene) the curde O-acylated products **77a** and **77b** were isolated which could be characterized by ^{1}H NMR ($CDCl_3$) spectrum (>95% purity). However, attempted crystallization of these products from ethanol or methanol yielded only starting material **74a** back. These experiments demonstrate that hydroxy group in **74a** is not stable in acylated form probably due to steric crowding in the molecule, due to the presence of *cis* benzoyl group and is stablized in free OH form **74a** by intramolecular hydrogen bonding. Our attempts to dehydrate **74a** in the presence of various lewis acids were also not successful. The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum further confirmed the structural assignment. Thus the singlet at δ 2.11 was assigned to three methylthio protons and the singlet at δ 2.25 for the other three methylthio protons. Singlet at δ 4.14 was assigned to bis methylthiomethine carbon proton. The singlet at δ 4.18 which was exchangeable with deuterium oxide was assigned to OH proton. The doublet at δ 4.26 was assigned to Hb ring proton with J=7.6Hz. While the other doublet at δ 5.21 with J=7.6Hz was assigned to Ha proton. The low-field position of Ha proton is in accordance with allylic position and the high-field Hb proton is due to shielding of

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*We are thankful to Dr. S. Apparao, University of Konstanz, Konstanz to carry out these experiments. In fact the corresponding D-(+)-(O-methyl)mandalyl derivative was planned to synthesis for the purpose of X-ray crystallographic data.

phenyl group. The multiplet between δ 7.02-7.36 was assigned to fifteen protons of phenyl rings. The stereochemical relationship between Ha and Hb* of **74a** was further established by comparison of their coupling constants with the values estimated from Karplus equation[31,32*] which shows a dihedral angle of >125° between Ha-C(4)-C(5)-Hb (Newman formula **78**) thus pointing to a Ha-Hb *trans* stereochemical relationship.** Inspection of dreiding model also revealed favoured conformation **78** for **74a** since a molecule with *cis* substituents on C-4 and C-5 atoms will be energetically very unfavourable due to steric crowding.*** The compound was further confirmed from its ^{13}C NMR spectrum (experimental). Apparently, only one pure diastereomeric isomer **74a** was formed and the reaction is highly diastereospecific since no other isomeric mixture was detected by any of the spectral data examined. And the other possible isomeric cyclopentane **73a** that could have arisen out of [3+2] cycloaddition with **75** was not detected at all in the reaction mixture. Thus, the reaction path-b involving Tandem Michael

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*_cis_ Coupling constants are usually found to be larger than _trans_ coupling constants in substituted cyclo pentane derivatives[31-33].

A _trans_ stereo chemical assignment for Ha and Hb in **74a was further supported by its NOE difference spectra showing very weak (<1%) NOE enhancement.

***In the [3+2] cyclization of (2-carbamoylallyl)lithium reagents with substituted acryl amides, the predominant cyclopentane stereoisomer also has C-4 carbamoyl group _trans_ to C-5 substituent[12b].

aldol sequential process is the sole pathway followed to afford **74a**. In addition to other data employed to assign the structural assignment an X-ray crystallographic study was done for compound **74a** which furthe confirms the strong intramolecular hydrogen bonding and the stereo chemical assignments.*

Similarly, **74b** was formed in 61% yield (scheme 13), mp 167-168°C (chloroform-hexane) when the anion **65A** was reacted with **76** under the described reaction conditions. The structural assignment to **74b** was made on the basis of analytical and spectral data which revealed that the observed diastereoselectivity and the Michael aldol type pathway were exactly the same as observed in **74a**. The analytical (CHN) and spectral (IR, ^{1}H NMR, Mass) data confirming this assignment is described in experimental section.

The anion **65A** was similarly reacted with phenyl nitro styrene **79** and ethyl acrylate **38a** and the corresponding cyclopentenes **74c** and **74d** were obtained in 66% and 75% yields respectively (scheme 15). The assignment of **74c** was based on high resolution ^{1}H NMR

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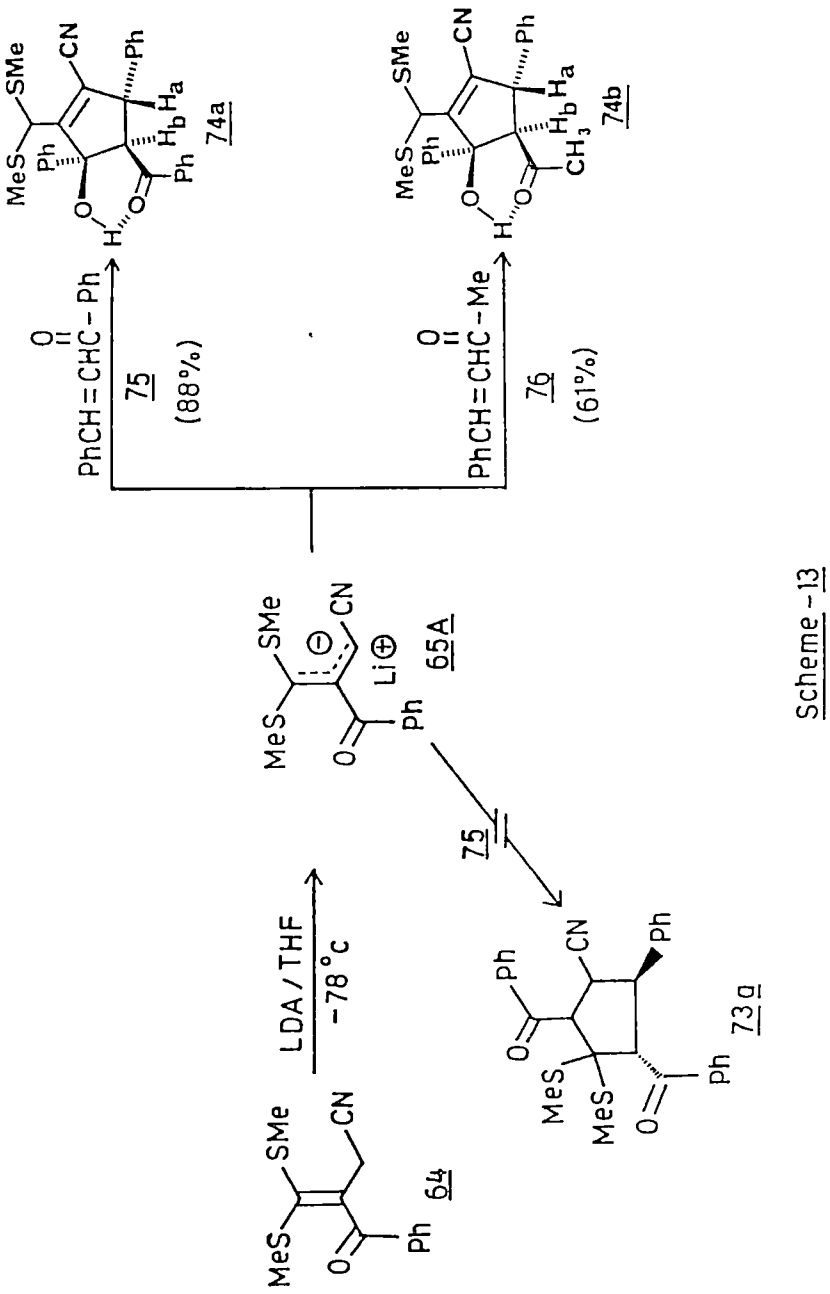
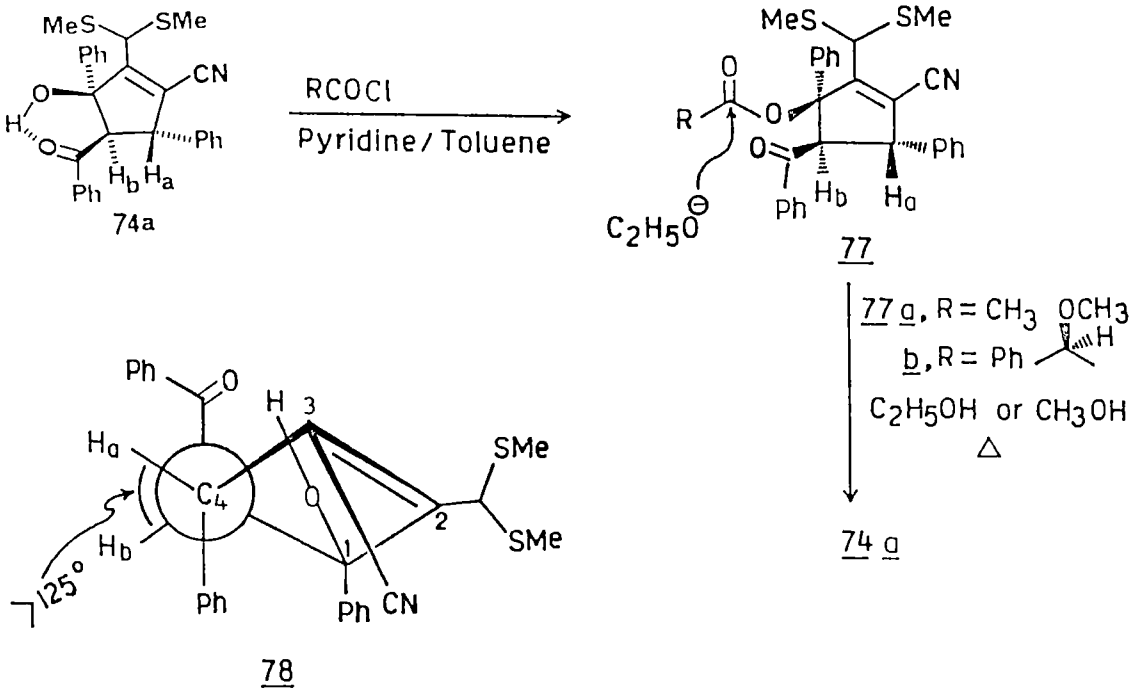
*The X-ray data were collected using a CAD4 diffractometer and Ni-filtered cu-Kα radiation (λ =1.54178 A). The structure was solved via use of direct methods and refined by full-matrix least squares. In view of the small number of observed data (a result of small size of crystals), phenyl rings were refined as idealized rigid bodies. Otherwise all non-hydrogen atoms were refined anisotropically and non-phenyl hydrogens isotropically (Table).



Scheme-13


MeS
SMe
Ph
CN
O
H
O
Ph
Ph
Ph
Hb
Ha
74a
RCOCl
Pyridine / Toluene
MeS
SMe
Ph
CN
R
O
O
O
Ph
Ph
Hb
Ha
C2H5O⊖
77
77 a, R = CH3 OCH3
b, R = Ph
C2H5OH or CH3OH
△
74 a
Ph
O
H 3
Ha
C4
O
SMe
SMe
2
1
Hb
125°
Ph
Ph CN
78

Scheme - 14

Table 1

Crystal Data, Intensity Data, Collection Parameters and Details of Refinement for C28H25NO2S2.

Crystal Data:

Stoichiometry	C28 H25 N O2 S2
M.W	471.44
a, Å	12.155(1)
b, Å	20.491(2)
c, Å	10.933(2)
Alpha, o	90.0
Beta, o	114.95(1)
Gamma, o	90.0
V, Å^3	2468.93
System	Monoclinic
Space Group	P21/C
Dc, g/cm.	1.26
Z	4
F(000)	992
Radiation	Cu-k alpha (1.5418)
Mu,cm-1	20.35

Data Collection:

Theta min./max.	3.0, 60.0
Ttemperatur	R.T
Total number of feflection measured	4130
Total number of unique reflection	3654
Total number of reflection used in Refinement	1488
Significant test	Fo> Fo

Refinement:

Number of Parameters	288
Weighting scheme	$w = 1/[\text{sigma}^2(Fo) + g(Fo)^2]$
Parameter g	0.00052
Final R = $\Sigma \Delta F / (\Sigma F_o)$	0.067
Final Rw = $\Sigma(\omega\Delta F)^2 / \Sigma(wF_o)^2$	0.061

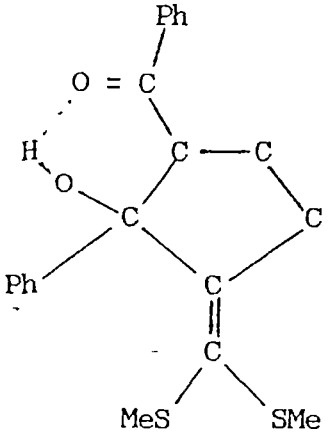
Table 2. Crystal data and details of structural determination.

Crystal data	
Mol. Formula	$C_{28}H_{25}NO_2S_2$
M	471.44
System and space group	monoclinic, P21/c
a,b,c (A°)	12.155(1), 20.491(2), c=10.933(2)
α, β, γ (°)	90.0, 114.95 (1), 90.00
V($A^{\circ 3}$)	2468.93
Z	4
Dc ($g\ cm^{-3}$)	1.26
F (000) (e^-)	992
λ(Cu-Kα) (A°)	1.5418
crystal size (mm)	0.20 x 0.14 x 0.02
shape and colour	colourless small platelets
Data collection	
Temperature (K)	RT
Radiation (A°)	1.5418
Theta min/max (°)	3.0, 60.0
Scan type	$\omega/2\Theta$
Total number of reflection measured	4130
Total number of unique reflection	3654
Total number of reflection used in refinement	1488
Significant test	Fo>Fo
Refinement	
Number of parameters	288
Weighting scheme	$W=1/[sigma^2(Fo)+g(Fo)^2]$
Parameter g	0.00052
Final R = (ϵ , ΔF/(Fo)	0.067
Final $R_W = \epsilon(\omega \Delta F)^2/\epsilon(\omega Fo)^2$	0.061

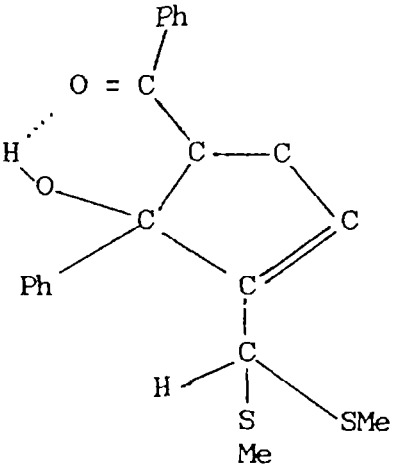
Structure Determination on Compound 74a (May & Baker, July 1987)

The crystals were obtained as very small platelets. The specimen used measured .2 x .14 x .02 mm3. Data were collected using a CAD4 diffractometer and Ni-filtered Cu-Ka radiation (λ= 1.54178Å). The structure was solved via use of direct methods and refined by full-matrix least squares. In view of the small number of observed data (a result of the small size of the crystal), phenyl rings were refined as idealised rigid bodies. Otherwise all non-hydrogen atoms were refined anisotropically and non-phenyl hydrogens isotropically. Full experimental data are given in Table 1.

The structure found is shown in the Figure; bond lengths and angles are given in Tables 2 and 3. The structure is similar to that proposed except that the double bond proposed as exo to the five-membered ring is in fact endo:



proposed



found

The structure analysis does confirm hydrogen bonding between the hydroxy hydrogen and the carbonyl oxygen.

TABLE 2a

Bond lengths (Å) for C28H25NO2S2

C(26)-S(1)	1.812(11)	C(27)-S(1)	1.800(10)
C(26)-S(2)	1.817(10)	C(28)-S(2)	1.769(11)
C(2)-C(1)	1.518(12)	C(5)-C(1)	1.314(11)
C(6)-C(1)	1.444(13)	C(3)-C(2)	1.527(12)
C(12)-C(2)	1.503(11)	C(4)-C(3)	1.579(12)
C(13)-C(3)	1.513(13)	C(5)-C(4)	1.538(12)
O(2)-C(4)	1.424(9)	C(25)-C(4)	1.501(12)
C(26)-C(5)	1.511(12)	N(1)-C(6)	1.156(11)
C(8)-C(7)	1.395	C(12)-C(7)	1.395
C(9)-C(8)	1.395	C(10)-C(9)	1.395
C(11)-C(10)	1.395	C(12)-C(11)	1.395
O(1)-C(13)	1.227(9)	C(19)-C(13)	1.483(12)
C(15)-C(14)	1.395	C(19)-C(14)	1.395
C(16)-C(15)	1.395	C(17)-C(16)	1.395
C(18)-C(17)	1.395	C(19)-C(18)	1.395
C(21)-C(20)	1.395	C(25)-C(20)	1.395
C(22)-C(21)	1.395	C(23)-C(22)	1.395
C(24)-C(23)	1.395	C(25)-C(24)	1.395

TABLE 2b

Hydrogen bond lengths (Å) for C28H25NO2S2

H(21)-C(2)	0.987(55)	H(31)-C(3)	1.116(69)
H(71)-C(7)	0.960	H(81)-C(8)	0.960
H(91)-C(9)	0.960	H(101)-C(10)	0.960
H(111)-C(11)	0.960	H(141)-C(14)	0.960
H(151)-C(15)	0.960	H(161)-C(16)	0.960
H(171)-C(17)	0.960	H(181)-C(18)	0.960
Ho(21)-O(2)	1.004(84)	H(201)-C(20)	0.960
H(211)-C(21)	0.960	H(221)-C(22)	0.960
H(231)-C(23)	0.960	H(241)-C(24)	0.960
H(261)-C(26)	0.961(57)	H(271)-C(27)	0.960
H(272)-C(27)	0.960	H(273)-C(27)	0.960
H(281)-C(28)	0.960	H(282)-C(28)	0.960
H(283)-C(28)	0.960		

TABLE 3a

Bond angles (deg.) for C28H25NO2S2

C(27)-S(1)-C(26)	101.9(5)	C(28)-S(2)-C(26)	103.0(5)
C(5)-C(1)-C(2)	114.7(9)	C(6)-C(1)-C(2)	117.0(8)
C(6)-C(1)-C(5)	128.1(9)	C(3)-C(2)-C(1)	100.4(8)
C(12)-C(2)-C(1)	114.9(7)	C(12)-C(2)-C(3)	112.5(8)
C(4)-C(3)-C(2)	106.5(7)	C(13)-C(3)-C(2)	114.7(8)
C(13)-C(3)-C(4)	111.3(7)	C(5)-C(4)-C(3)	100.1(7)
O(2)-C(4)-C(3)	111.3(7)	O(2)-C(4)-C(5)	108.6(7)
C(25)-C(4)-C(3)	113.3(7)	C(25)-C(4)-C(5)	114.6(7)
C(25)-C(4)-O(2)	108.7(7)	C(4)-C(5)-C(1)	110.5(8)
C(26)-C(5)-C(1)	129.9(9)	C(26)-C(5)-C(4)	119.5(8)
N(1)-C(6)-C(1)	174.6(10)	C(12)-C(7)-C(8)	120.0
C(9)-C(8)-C(7)	120.0	C(10)-C(9)-C(8)	120.0
C(11)-C(10)-C(9)	120.0	C(12)-C(11)-C(10)	120.0
C(7)-C(12)-C(2)	120.5(5)	C(11)-C(12)-C(2)	119.5(5)
C(11)-C(12)-C(7)	120.0	O(1)-C(13)-C(3)	121.0(9)
C(19)-C(13)-C(3)	119.7(8)	C(19)-C(13)-O(1)	119.3(9)
C(19)-C(14)-C(15)	120.0	C(16)-C(15)-C(14)	120.0
C(17)-C(16)-C(15)	120.0	C(18)-C(17)-C(16)	120.0
C(19)-C(18)-C(17)	120.0	C(14)-C(19)-C(13)	118.1(5)
C(18)-C(19)-C(13)	121.4(5)	C(18)-C(19)-C(14)	120.0
C(25)-C(20)-C(21)	120.0	C(22)-C(21)-C(20)	120.0
C(23)-C(22)-C(21)	120.0	C(24)-C(23)-C(22)	120.0
C(25)-C(24)-C(23)	120.0	C(20)-C(25)-C(4)	119.6(5)
C(24)-C(25)-C(4)	120.4(5)	C(24)-C(25)-C(20)	120.0
S(2)-C(26)-S(1)	115.9(6)	C(5)-C(26)-S(1)	109.8(7)
C(5)-C(26)-S(2)	113.3(7)		

TABLE 3b

Hydrogen bond angles (deg.) for C28H25NO2S2

H(21)-C(2)-C(1)	108.5(34)	C(3)-C(2)-H(21)	108.4(35)
C(12)-C(2)-H(21)	111.4(34)	H(31)-C(3)-C(2)	106.2(37)
C(4)-C(3)-H(31)	105.4(35)	C(13)-C(3)-H(31)	112.2(36)
H(71)-C(7)-C(8)	120.0	H(71)-C(7)-C(12)	120.0
H(81)-C(8)-C(7)	120.0	H(81)-C(8)-C(9)	120.0
H(91)-C(9)-C(8)	120.0	H(91)-C(9)-C(10)	120.0
H(101)-C(10)-C(9)	120.0	H(101)-C(10)-C(11)	120.0
H(111)-C(11)-C(10)	120.0	H(111)-C(11)-C(12)	120.0
H(141)-C(14)-C(15)	120.0	H(141)-C(14)-C(19)	120.0
H(151)-C(15)-C(14)	120.0	H(151)-C(15)-C(16)	120.0
H(161)-C(16)-C(15)	120.0	H(161)-C(16)-C(17)	120.0
H(171)-C(17)-C(16)	120.0	H(171)-C(17)-C(18)	120.0
H(181)-C(18)-C(17)	120.0	H(181)-C(18)-C(19)	120.0
Ho(21)-O(2)-C(4)	103.1(48)	H(201)-C(20)-C(21)	120.0
H(201)-C(20)-C(25)	120.0	H(211)-C(21)-C(20)	120.0
H(211)-C(21)-C(22)	120.0	H(221)-C(22)-C(21)	120.0
H(221)-C(22)-C(23)	120.0	H(231)-C(23)-C(22)	120.0
H(231)-C(23)-C(24)	120.0	H(241)-C(24)-C(23)	120.0
H(241)-C(24)-C(25)	120.0	H(261)-C(26)-S(1)	111.4(38)
H(261)-C(26)-S(2)	100.0(36)	H(261)-C(26)-C(5)	105.5(37)
H(271)-C(27)-S(1)	111.7(5)	H(272)-C(27)-S(1)	112.5(5)
H(272)-C(27)-H(271)	109.5	H(273)-C(27)-S(1)	104.1(5)
H(273)-C(27)-H(271)	109.5	H(273)-C(27)-H(272)	109.5
H(281)-C(28)-S(2)	112.8(4)	H(282)-C(28)-S(2)	107.4(4)
H(282)-C(28)-H(281)	109.5	H(283)-C(28)-S(2)	108.1(4)
H(283)-C(28)-H(281)	109.5	H(283)-C(28)-H(282)	109.5

TABLE 4a

Fractional atomic co-ordinates ($x10^4$) for C28H25NO2S2

	x	y	z
S(1)	4705(2)	919(1)	-2861(2)
S(2)	6111(2)	634(1)	169(2)
C(1)	7478(7)	661(4)	-2222(8)
C(2)	8548(8)	349(4)	-2371(8)
C(3)	8243(7)	-373(4)	-2347(8)
C(4)	7432(7)	-422(4)	-1540(8)
C(5)	6853(7)	262(4)	-1816(7)
C(6)	7327(8)	1356(5)	-2438(9)
N(1)	7291(7)	1913(4)	-2623(8)
C(7)	9826(4)	663(3)	-3586(5)
C(8)	9940(4)	833(3)	-4763(5)
C(9)	8910(4)	876(3)	-5984(5)
C(10)	7767(4)	749(3)	-6027(5)
C(11)	7653(4)	579(3)	-4851(5)
C(12)	8683(4)	536(3)	-3630(5)
C(13)	9334(8)	-819(4)	-1755(8)
O(1)	10300(5)	-625(3)	-879(6)
C(14)	10044(5)	-1961(4)	-1338(6)
C(15)	10079(5)	-2595(4)	-1784(6)
C(16)	9295(5)	-2778(4)	-3094(6)
C(17)	8477(5)	-2326(4)	-3957(6)
C(18)	8443(5)	-1691(4)	-3512(6)
C(19)	9226(5)	-1509(4)	-2202(6)
O(2)	8159(5)	-486(3)	-129(5)
C(20)	6506(5)	-1423(3)	-1052(5)
C(21)	5684(5)	-1940(3)	-1468(5)
C(22)	4898(5)	-2010(3)	-2828(5)
C(23)	4933(5)	-1563(3)	-3772(5)
C(24)	5755(5)	-1045(3)	-3356(5)
C(25)	6541(5)	-975(3)	-1996(5)
C(26)	5746(8)	391(4)	-1557(8)
C(27)	3458(8)	978(6)	-2388(11)
C(28)	6724(9)	1426(5)	267(9)

TABLE 4c

Hydrogen fractional atomic co-ordinates ($\times 10^4$) and isotropic temperature factors ($Å^2 \times 10^3$) for C28H25NO2S2

	x	y	z	U
H(21)	9292(50)	446(26)	-1554(57)	11(18)
H(31)	7630(60)	-506(33)	-3408(71)	54(23)
H(71)	10535(4)	633(3)	-2746(5)	122(16)
H(81)	10727(4)	920(3)	-4733(5)	122(16)
H(91)	8989(4)	993(3)	-6794(5)	122(16)
H(101)	7058(4)	778(3)	-6867(5)	122(16)
H(111)	6866(4)	491(3)	-4881(5)	122(16)
H(141)	10583(5)	-1836(4)	-437(6)	164(21)
H(151)	10642(5)	-2906(4)	-1190(6)	164(21)
H(161)	9319(5)	-3214(4)	-3400(6)	164(21)
H(171)	7938(5)	-2451(4)	-4859(6)	164(21)
H(181)	7880(5)	-1380(4)	-4106(6)	164(21)
Ho(21)	8624(71)	-65(42)	110(81)	75(32)
H(201)	7047(5)	-1375(3)	-116(5)	155(21)
H(211)	5660(5)	-2248(3)	-818(5)	155(21)
H(221)	4332(5)	-2366(3)	-3114(5)	155(21)
H(231)	4392(5)	-1611(3)	-4708(5)	155(21)
H(241)	5779(5)	-737(3)	-4006(5)	155(21)
H(261)	5393(51)	-30(29)	-1571(57)	13(19)
H(271)	2896(8)	1313(6)	-2885(11)	114(16)
H(272)	3722(8)	1051(6)	-1439(11)	114(16)
H(273)	3068(8)	560(6)	-2625(11)	114(16)
H(281)	6816(9)	1656(5)	1069(9)	114(16)
H(282)	6184(9)	1664(5)	-512(9)	114(16)
H(283)	7502(9)	1384(5)	242(9)	114(16)

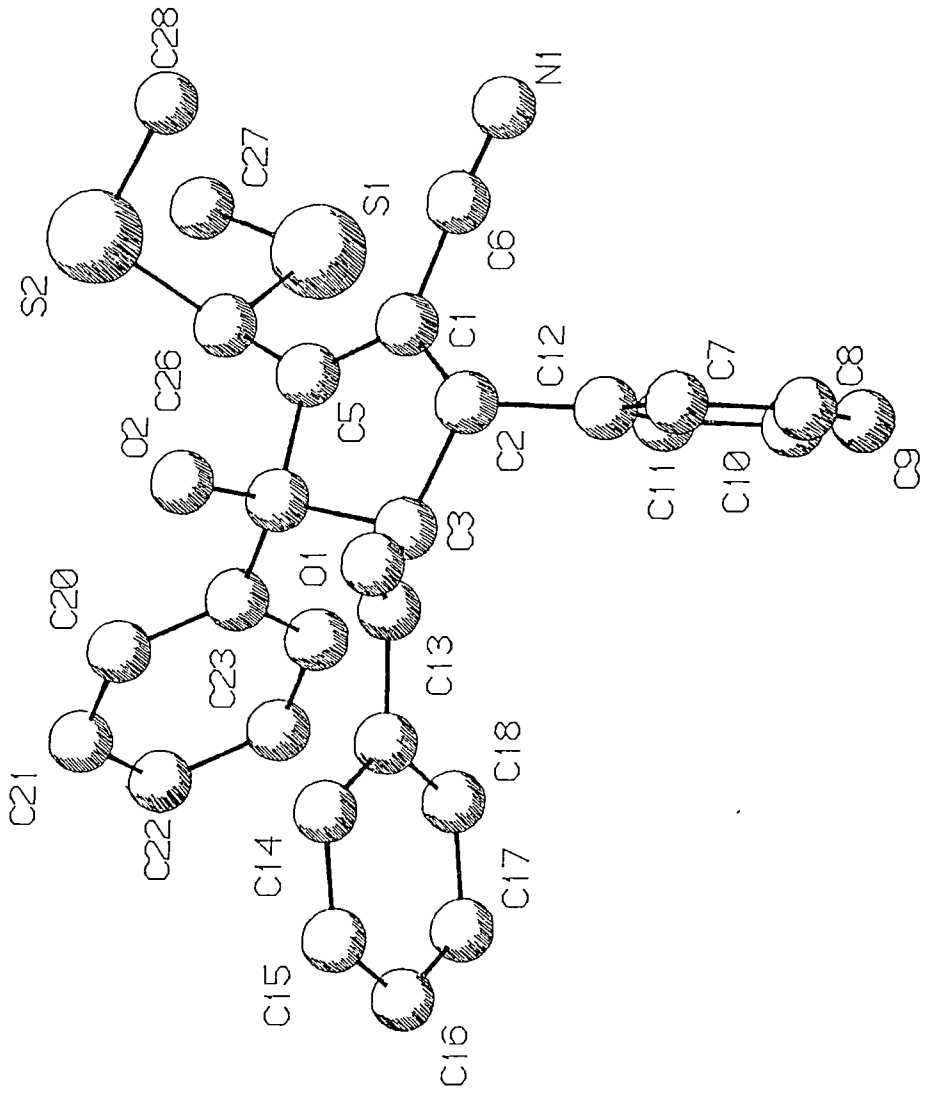
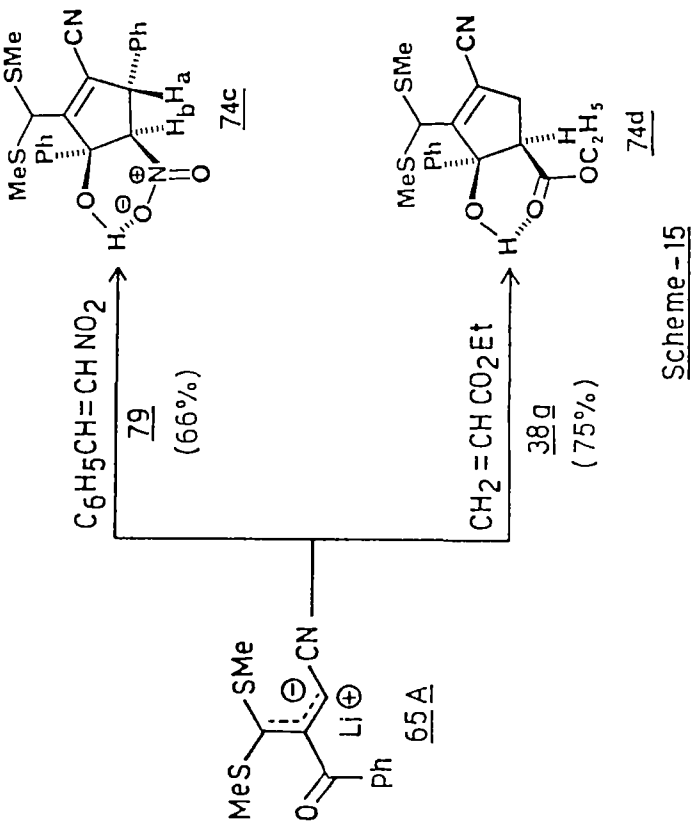
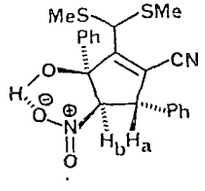


Fig.1 *X-Ray* molecular structure of 74a.


MeS
SMe
Ph
CN
Li⊕
O
65 A
C6H5CH=CH NO2
79
(66%)
74c
CH2=CH CO2Et
38 g
(75%)
74d

Scheme-15

Fig.2 ^{1}H NMR (*300 MHz, $CDCl_3$*) spectrum of 74c.



195

OBSERVE: Nucleus 1.000 | Freq 300 MHz | Spec Width 4500.5 Hz | Offset 0 Hz | Acq Time 3.555 sec | Delay 2.000 sec | Pulse Width 11.6 μsec | Transients 64

DECOUPLE: Nucleus 1.000 | Offset -450.0 Hz | Mode NNN | Power 1023.0 db | Modulation Mode C | Freq 10000 Hz | Pulse Width μsec | Power Mode 34.0

PLOT/PROCESSING: FN 32 K | RE sec | CD sec | LB Hz | AF sec | CCD | Width 2097.9 Hz/ppm | Start 304.4 Hz/ppm | Reference

EXPERIMENT: Pulse Sequence S2PUL | Tube O D mm | Temp °C | Solvent CDCL3

SAMPLE
KRR-120 NITROSTYRENE ADDUCT (D,O added)
GEMINI-300 BB
STANDARD 1H PARAMETERS

Number | File KRR0C | Date 09-26-9 17:54 | XL GEMA 3(

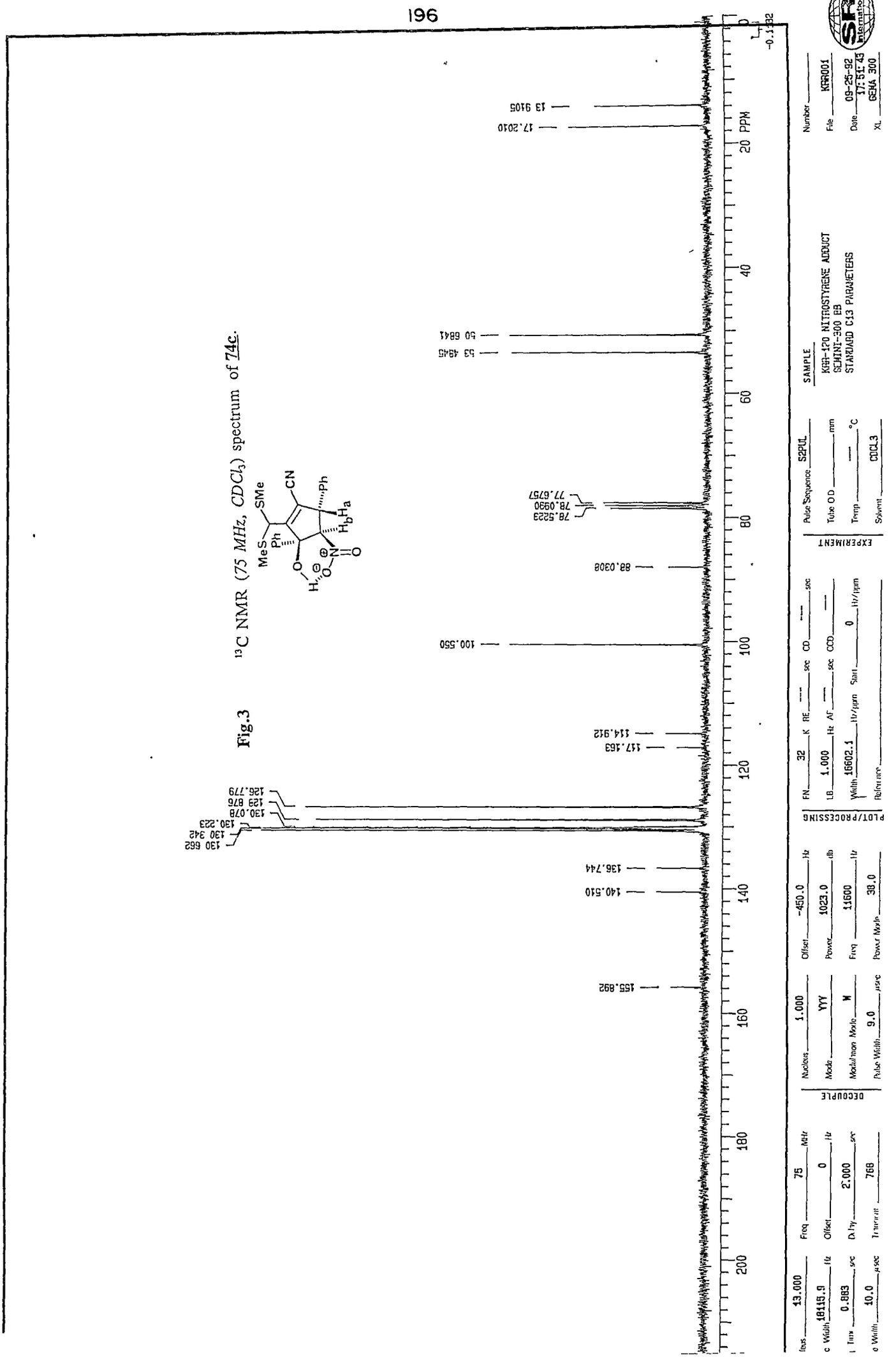
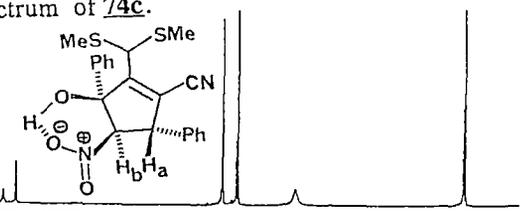


Fig.3 ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of *74c*.

Fig.4 2D NMR (*300 MHz, $CDCl_3$*) spectrum of 74c.



KRA-120 NITROSTYRENE ADDUCT
AUTOMATED 2D EXPERIMENT
EXP9 PULSE SEQUENCE: COSY
DATE 09-25-92
SOLVENT CDCL3
FILE KRAN02

COSY PULSE SEQUENCE
OBSERVE PROTON
FREQUENCY 300.075 MHZ
1D SPECTRAL WIDTH (F2) 2578.0 HZ
2D SPECTRAL WIDTH (F1) 2578.0 HZ
ACQ. TIME 0.199 SEC
RELAXATION DELAY 1.0 SEC
PULSE WIDTH 90 DEGREES
FIRST PULSE 90 DEGREES
AMBIENT TEMPERATURE
NO. REPETITI - 8
NO. INCREMENTS 256
SPIN RATE 20 HZ
DATA PROCESSING
PSEUDO-ECHO SHAPED
FT SIZE 1K X 1K
TOTAL TIME 53.3 MINUTES

eus ____ Freq ____ MHz
Width ____ Hz Offset ____ Hz
Time ____ sec Delay ____ sec
Width ____ μsec Tran ____

DECOUPLE
Nucleus ____ Offset ____ Hz
Mode ____ Power ____ db
Modulation Mode ____ Freq ____ Hz
Pulse Width ____ μsec Power Mode ____

PLOT/PROCESSING
FN ____ K RE ____ sec CD ____ sec
LB ____ Hz AF ____ sec CCD ____
Width ____ Hz/ppm Start ____ Hz/ppm
Reverse ____

EXPERIMENT
Pulse Sequence ____
Tube O.D ____ mm
Temp ____ °C
Solvent ____

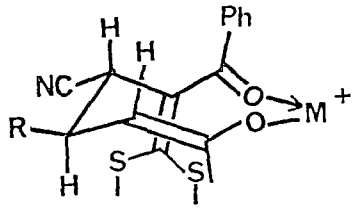
SAMPLE

Number ____
File ____
Date ____
XL ____

SRI International

(300 MHz, $CDCl_3$) spectrum, ^{13}C NMR (75 MHz, $CDCl_3$) spectrum and its 2D NMR (300 MHz, $CDCl_3$) spectral data, (Fig. 2-4) which confirms the assignment of the cyclopentene ring protons as assigned earlier. Similarly, **74d** was confirmed from its analytical (CHN) and spectral (IR, ^1H NMR, ^{13}C NMR) data which were in accordance with the conformed diastereoselectivity which are described in the experimental section.

Similarly, anion **65A** was reacted with methyl cinnamate **80** the corresponding cyclopentene **74e** was formed in 71% yield (scheme 16) with the same diastereoselective conformation as observed by spectral (IR, ^1H NMR, ^{13}C NMR, 2D NMR) and analytical (CHN) data described in the experimental section (Fig. 5-7). Interestingly, both dimethyl fumarate **81a** and maleate **81b** reacted with **65A** under the described reaction conditions to yield the single diastereoisomer **74f** in 72% yield (scheme 16). The asisgnment of **74f** was based on high resolution ^1H NMR (300 MHz, $CDCl_3$) spectrum, ^{13}C NMR (75 MHz, $CDCl_3$) spectrum and its 2D NMR (300 MHz, $CDCl_3$) spectral data (Fig. 8-10). This is in conformity with the observation made by Hassner and co-workers. The formation of single diastereoisomer in this case is due to reorganisation of the molecule before the aldolization involving an intramolecular chelation as shown in structure A in such a way

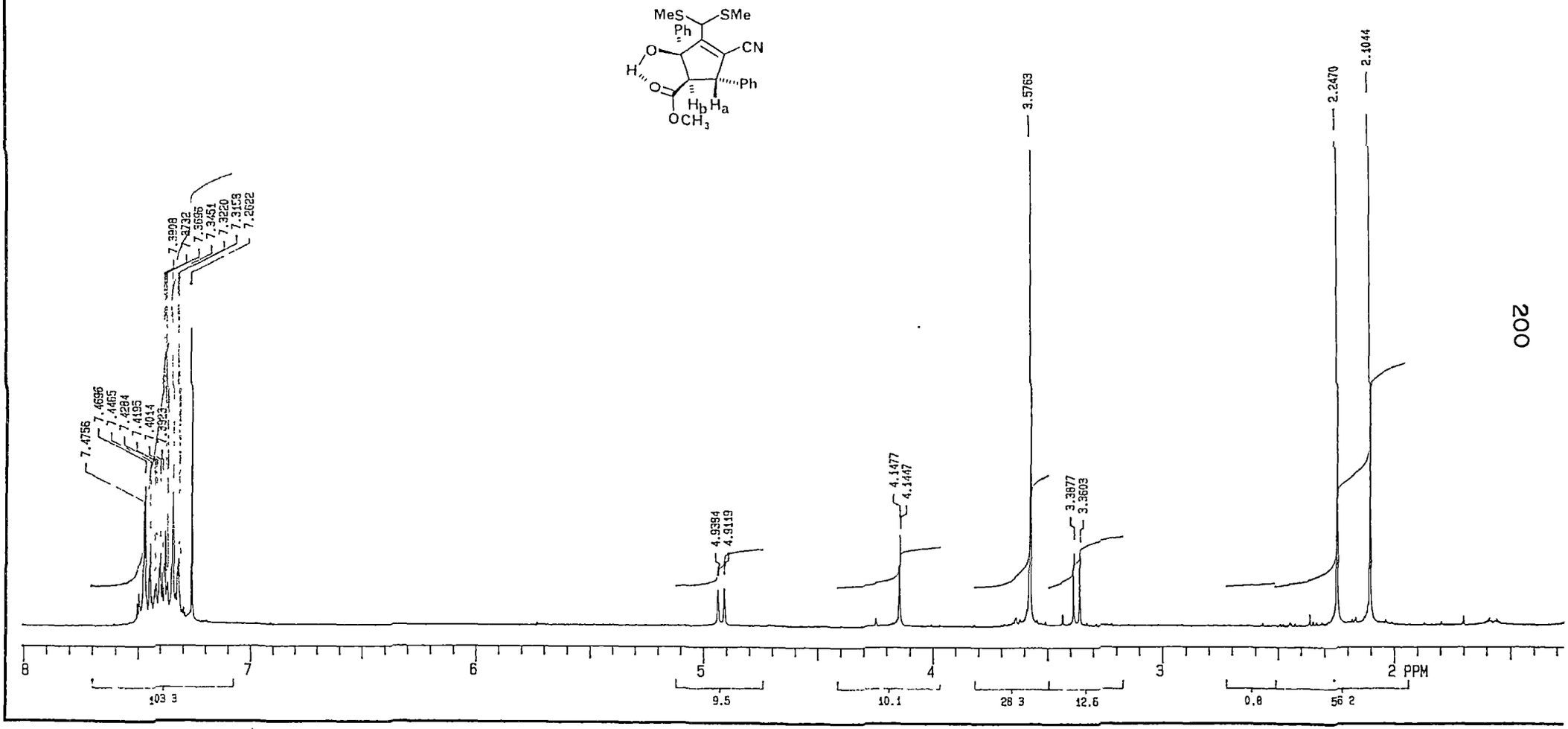


A

MeS
SMe
Ph
CN
Li⊕
O
65 A
PhCH=CHCO2 Me
80
(74%)
74e
H H
MeO2CC=CCO2 Me
81 a, E
b, Z
(72%)
74f

Scheme - 16

Fig.5 ^{1}H NMR (*300 MHz, $CDCl_3$*) spectrum of 74e.



200

OBSERVE: Nucleus 1.000 | Freq 300 MHz | Spec. Width 4500.5 Hz | Offset 0 Hz | Acq Time 3.555 sec | Delay 2.000 sec | Pulse Width 11.6 μsec | Transients 64

DECOUPLE: Nucleus 1.000 | Offset -450.0 Hz | Mode NNN | Power 1023.0 db | Modulation Mode C | Freq 10000 Hz | Pulse Width μsec | Power Mode 34.0

PLOT/PROCESSING: FN 32 K | RE sec | CD sec | LB Hz | AF sec | CCD | Width 2097.9 Hz/ppm | Start 304.4 Hz/ppm | Reference

EXPERIMENT: Pulse Sequence S2PUL | Tube OD mm | Temp °C | Solvent CDCL3

SAMPLE
KAA-147 PHCHCHCO2ME ADDUCT (D2O added)
GEMINI-300 BB
STANDARD 1H PARAMETERS

Number | File KAAG | Date 09-26-9 17:54 | XL GEMA 3

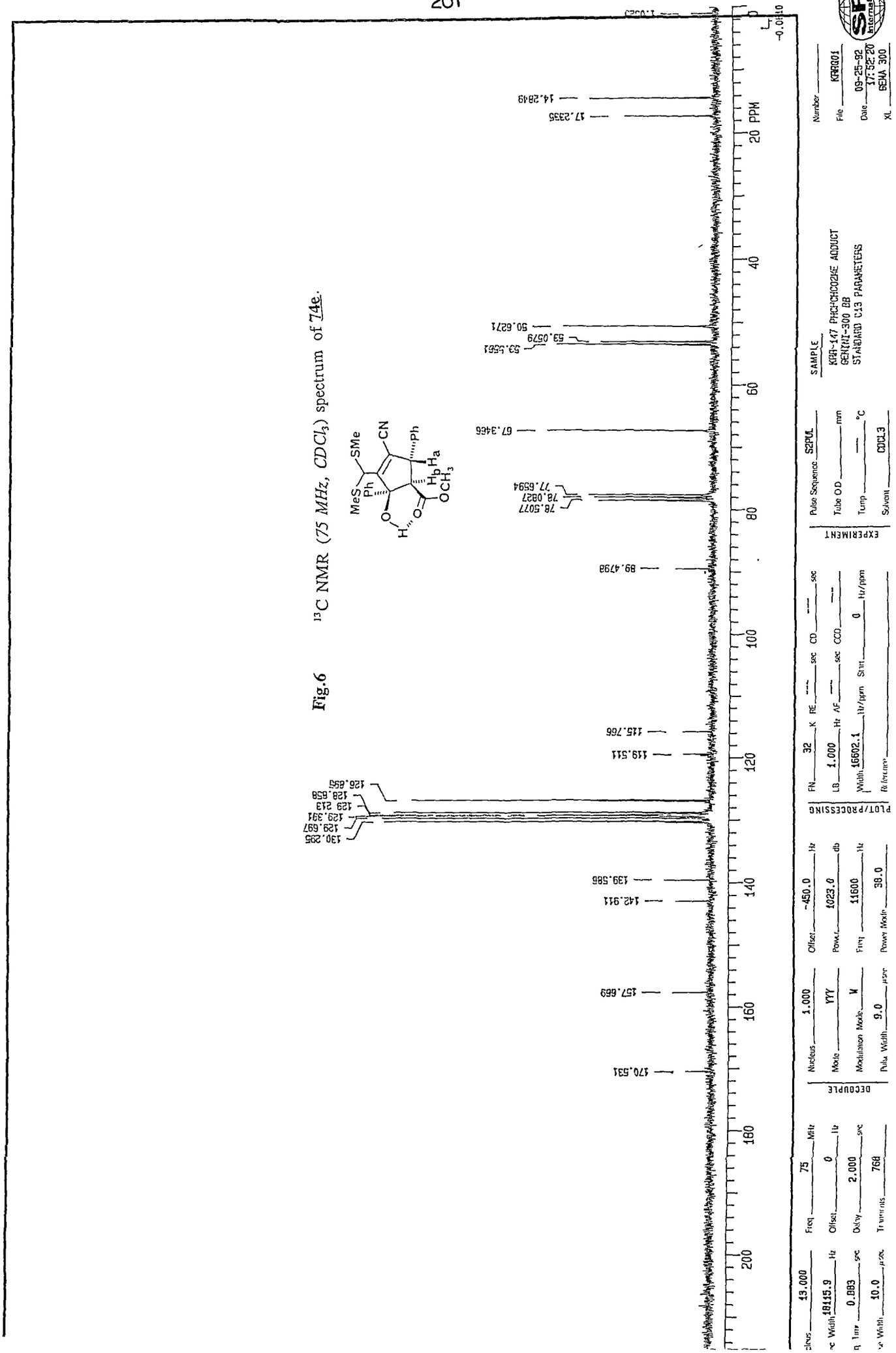
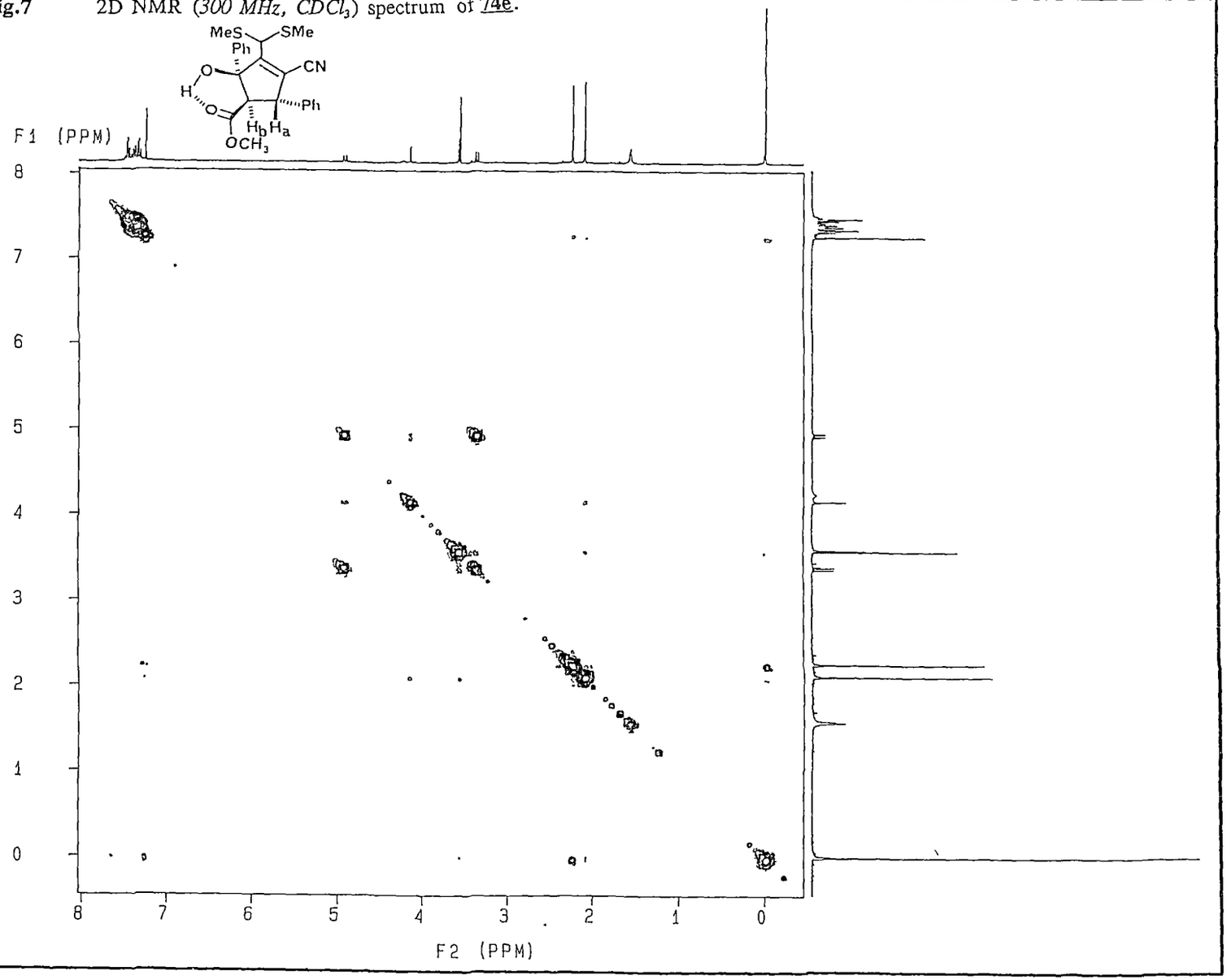


Fig.6 ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of 74e.

Fig.7 2D NMR (*300 MHz, $CDCl_3$*) spectrum of 74e.



KAR-147 PHCHCHCO2ME ADDUCT
AUTOMATED 2D EXPERIMENT
EXP9 PULSE SEQUENCE: COSY
DATE 09-25-92
SOLVENT CDCL3
FILE KAR02

COSY PULSE SEQUENCE
OBSERVE PROTON
FREQUENCY 300.075 MHZ
1D SPECTRAL WIDTH (F2) 2547.1 HZ
2D SPECTRAL WIDTH (F1) 2547.1 HZ
ACQ. TIME 0.201 SEC
RELAXATION DELAY 1.0 SEC
PULSE WIDTH 90 DEGREES
FIRST PULSE 90 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 8
NO. INCREMENTS 256
SPIN RATE 20 HZ
DATA PROCESSING
PSEUDO-ECHO SHAPED
FT SIZE 1K X 1K
TOTAL TIME 53.4 MINUTES

cus ____ Freq ____ MHz
Width ____ Hz Offset ____ Hz
Time ____ sec Delay ____ sec
Width ____ μsec Tension ____

DECOUPLE
Nucleus ____ Offset ____ Hz
Mode ____ Power ____ db
Modulation Mode ____ Freq ____ Hz
Pulse Width ____ μsec Power Mod ____

PLOT/PROCESSING
FN ____ K RE ____ sec CD ____ sec
LB ____ Hz AF ____ sec CCD ____
Width ____ Hz/ppm Start ____ Hz/ppm
Reference ____

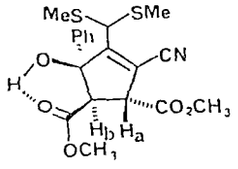
EXPERIMENT
Pulse Sequence ____
Tube OD ____ mm
Temp ____ °C
Solvent ____

SAMPLE

Number ____
File ____
Date ____
XL ____

SRI International

Fig.8 ^{1}H NMR (*300 MHz, $CDCl_3$*) spectrum of **74f**.



cleus 1.000	Freq 300 MHz	DECOUPLE Nucleus 1.000	Offset -450.0 Hz	PLOT/PROCESSING FN 32 K	RE sec	CD sec	EXPERIMENT Pulse Sequence S2PUL	SAMPLE	Number
ec Width 4500.5 Hz	Offset 0 Hz	Mode NNN	Power 1023.0 db	LB Hz	AF sec	CCD	Tube OD mm	KRR-149 MEO2CCHCHCO2ME ADDUCT	File KRRU01
q Time 3.555 sec	Delay 2.000 sec	Modulation Mode C	Freq 10000 Hz	Width 2086.1 Hz/ppm	Start 319.2 Hz/ppm		Temp °C	GEMINI-300 BB	Date 09-26-92
se Width 11.6 μsec	Transients 64	Pulse Width μsec	Power Mode 34.0	Reference			Solvent CDCL3	STANDARD 1H PARAMETERS	XL GEMA 300

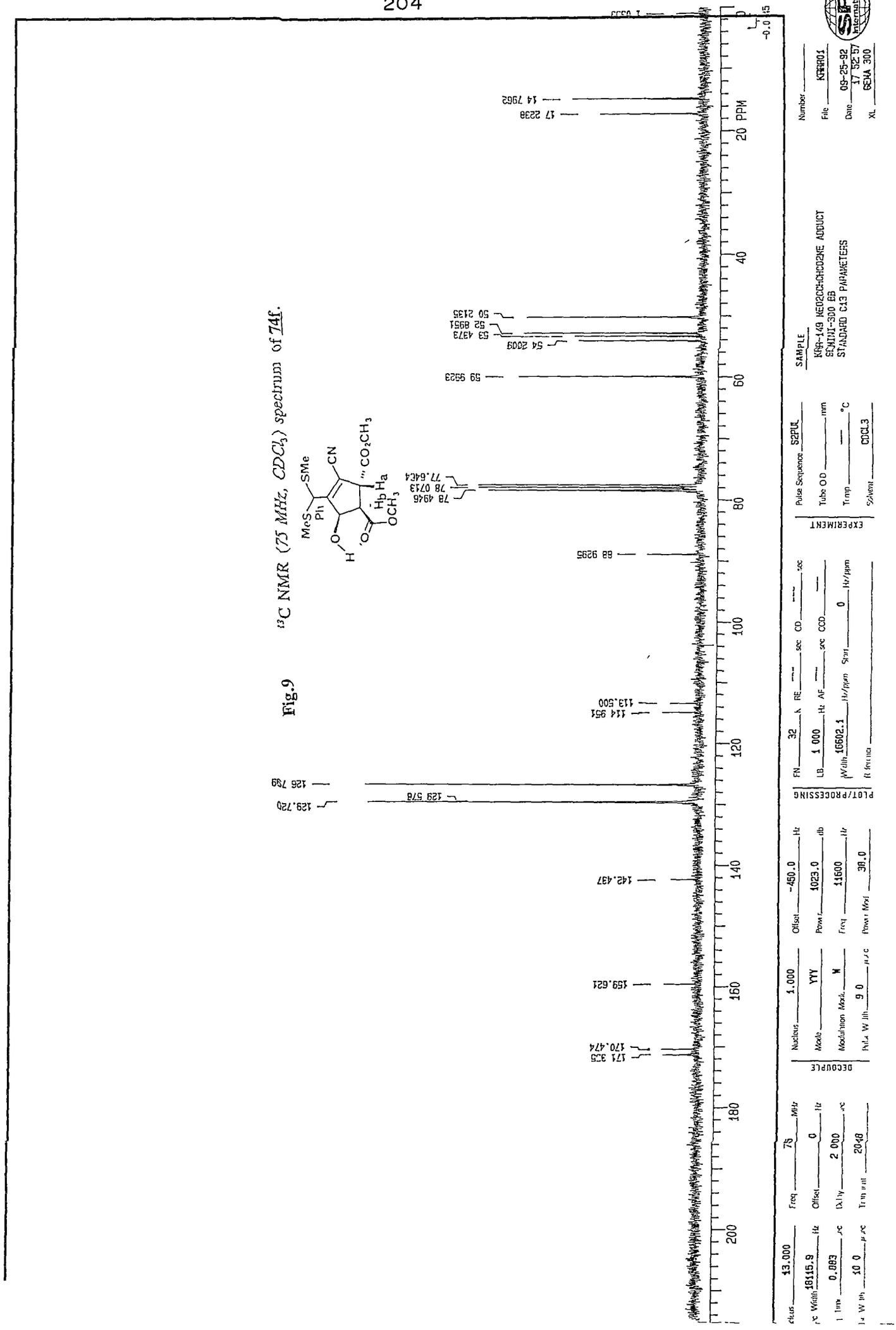
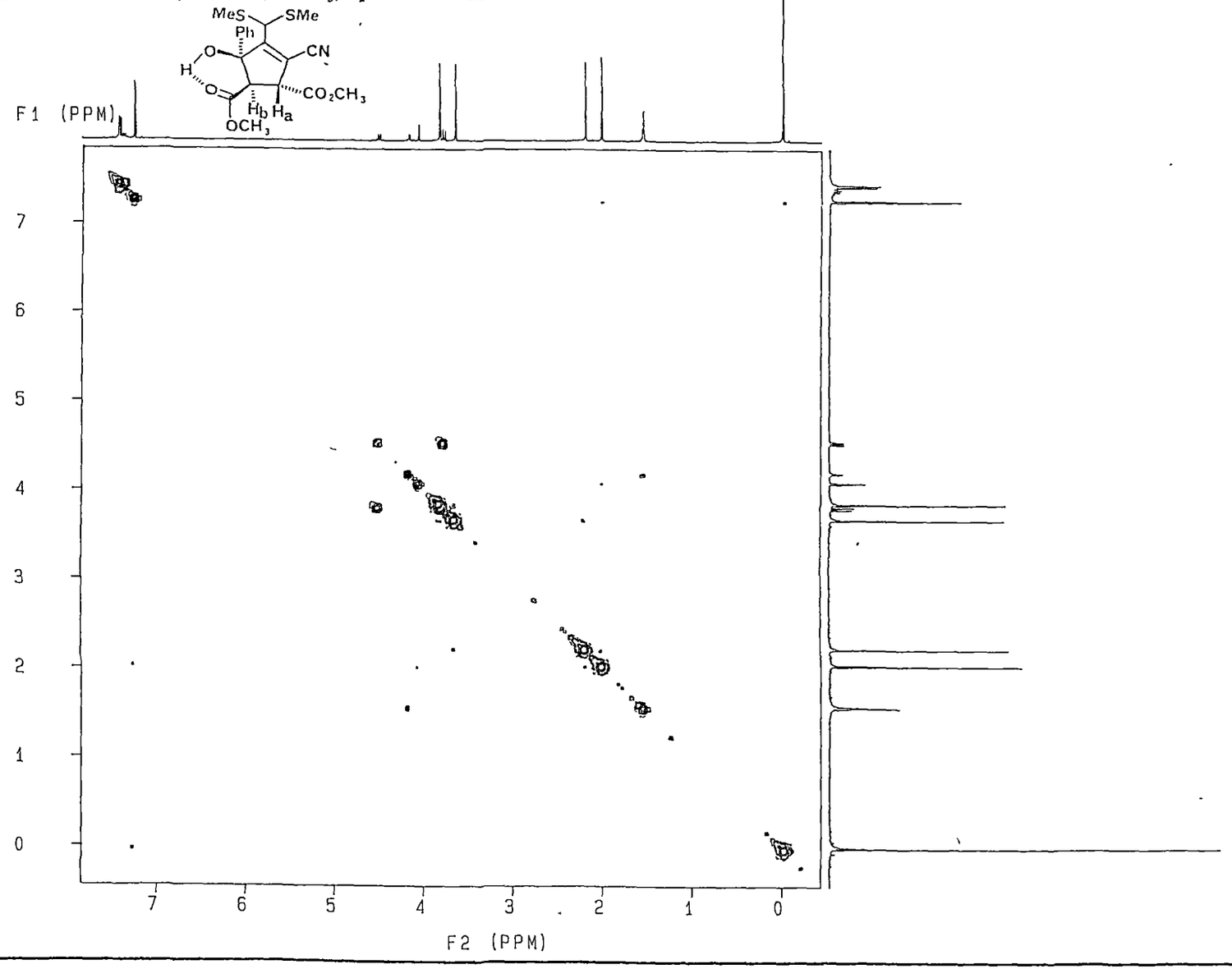


Fig.9 ^{13}C NMR (*75 MHz, $CDCl_3$*) spectrum of **74f**.

Fig.10 2D NMR (*300 MHz, $CDCl_3$*) spectrum of **74f**.



KRA-149 MEO2CCHCHCO2ME ADDUCT
AUTOMATED 2D EXPERIMENT
EXP9 PULSE SEQUENCE: COSY
DATE 09-25-92
SOLVENT CDCL3
FILE KRAW02

COSY PULSE SEQUENCE
OBSERVE PROTON
FREQUENCY 300.075 MHZ
1D SPECTRAL WIDTH (F2) 2485.7 HZ
2D SPECTRAL WIDTH (F1) 2485.7 HZ
ACQ. TIME 0.206 SEC
RELAXATION DELAY 1.0 SEC
PULSE WIDTH 90 DEGREES
FIRST PULSE 90 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 8
NO. INCREMENTS 256
SPIN RATE 20 HZ
DATA PROCESSING
PSEUDO-ECHO SHAPED
FT SIZE 1K X 1K
TOTAL TIME 53.7 MINUTES

Freq ____ MHz
Width ____ Hz Offset ____ Hz
Time ____ sec Delay ____ sec
Width ____ μsec Transmits ____

DECOUPLE
Nucleus ____ Offset ____ Hz
Mode ____ Power ____ db
Modulation Mode ____ Freq ____ Hz
Pulse Width ____ μsec Power Mod ____

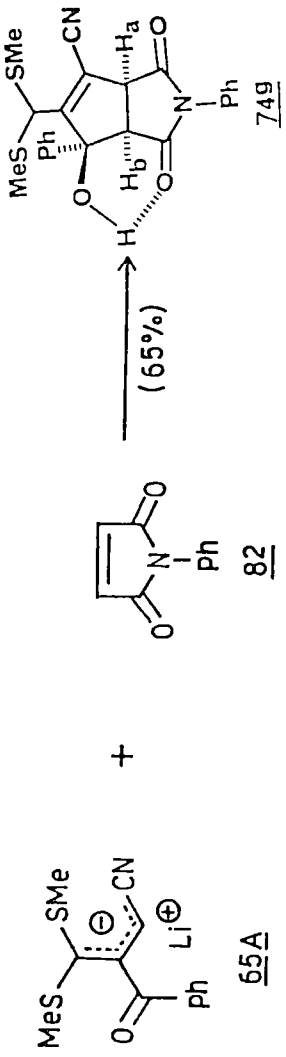
PLOT/PROCESSING
FN ____ K RE ____ sec CD ____ sec
LB ____ Hz AF ____ sec CCD ____
Width ____ Hz/ppm Start ____ Hz/ppm
Reference ____

EXPERIMENT
Pulse Sequence ____
Tube OD ____ mm
Temp ____ °C
Solvent ____

SAMPLE

Number ____
File ____
Date ____
XL ____

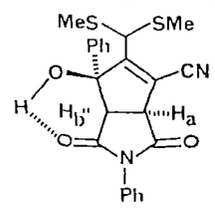
SRI International



65A 82 749

Scheme - 17

Fig.11 ^{1}H NMR (*300 MHz, $CDCl_3$*) spectrum of 74g.



207

OBSERVE: Nucleus 1.000 | Freq 300 MHz | Spec Width 4500.5 Hz | Offset 0 Hz | Acq Time 3.555 sec | Delay 2.000 sec | Pulse Width 5.8 µsec | Transients 64

DECOUPLE: Nucleus 1.000 | Offset -450.6 Hz | Mode NN | Power 1023.0 db | Modulation Mode C | Freq 10000 Hz | Pulse Width µsec | Power Mode 34.0

PLOT/PROCESSING: FN 32 K | RE sec | CD sec | LB Hz | AF sec | CCD | Width 2074.6 Hz/ppm | Start 316.2 Hz/ppm | Reference

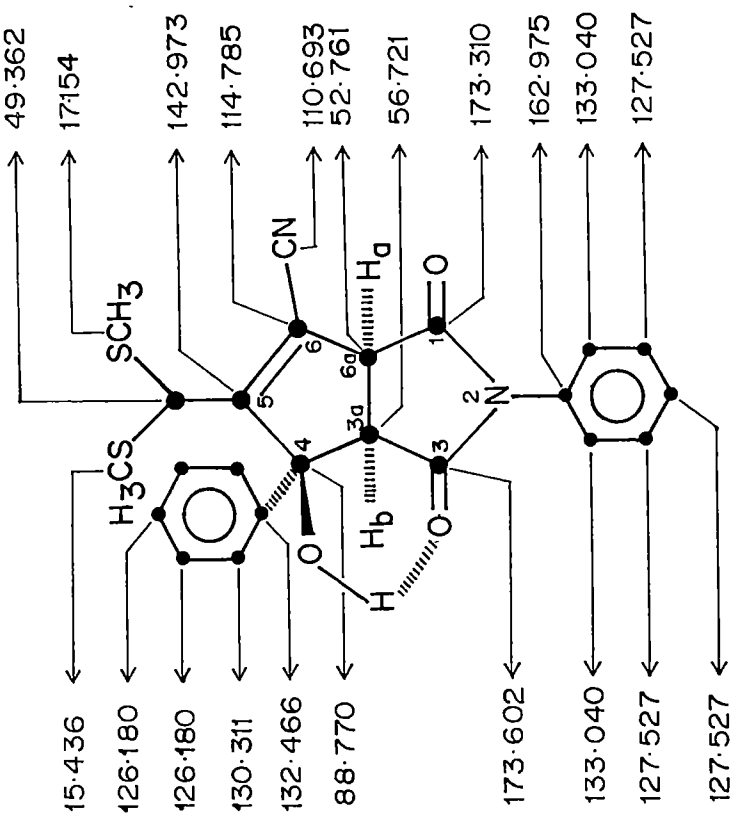
EXPERIMENT: Pulse Sequence S2PUL | Tube OD mm | Temp °C | Solvent CDCL3

SAMPLE

KBR-152 MALEIMIDE ADDUCT
GEMINI-300 BB
STANDARD 1H PARAMETERS

Number | File KBR | Date 12-05 | XL- GEMA

Fig.12a Structure & ^{13}C NMR data of 74g.



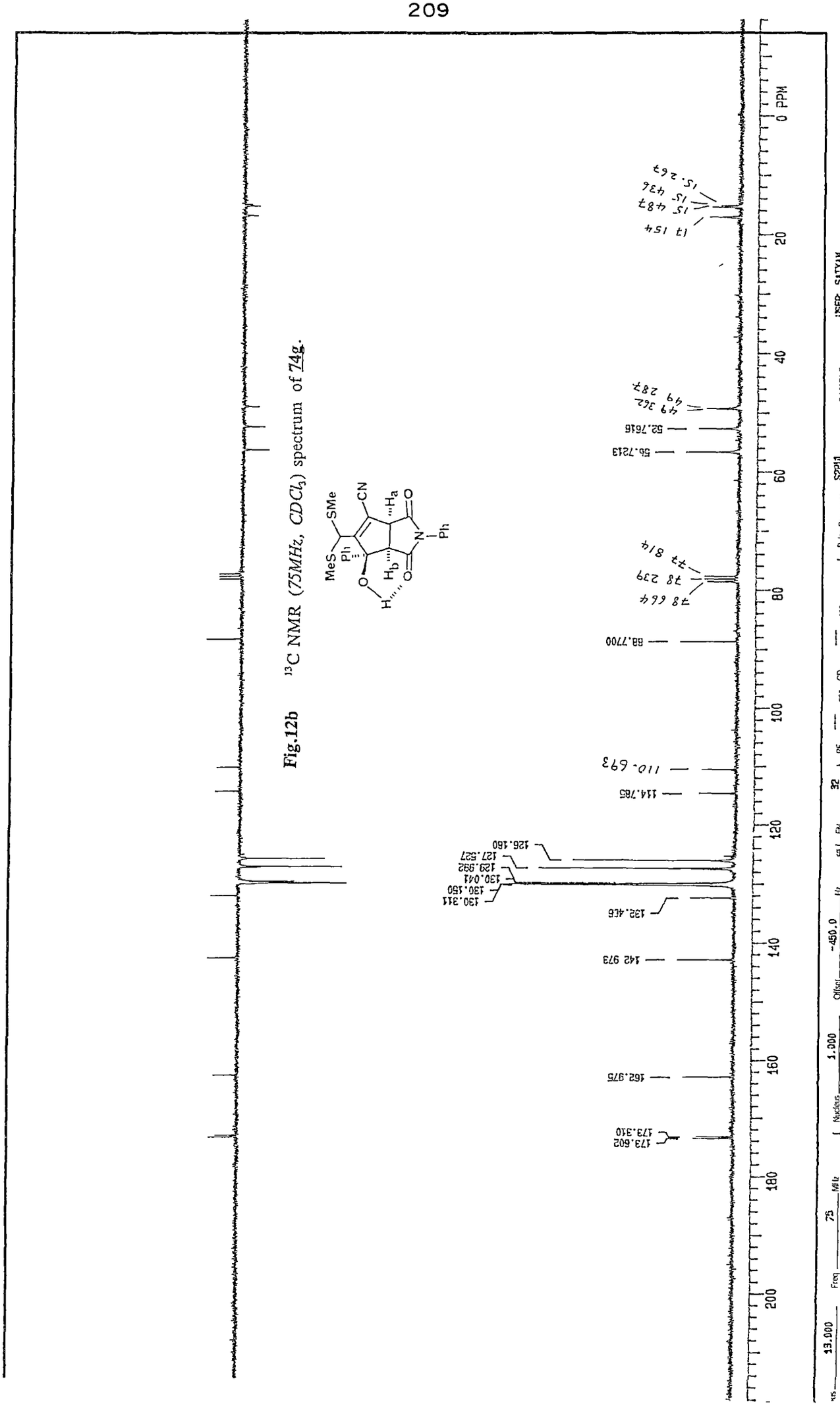
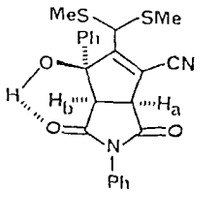


Fig.12b ^{13}C NMR (*75MHz, $CDCl_3$*) spectrum of **74g**.

Fig.13 2D NMR (*300 MHz, $CDCl_3$*) spectrum of 74g.



KRH-152 MALEIMIDE ADDUCT
AUTOMATED 2D EXPERIMENT
EXP9 PULSE SEQUENCE: COSY
DATE 12-06-92
SOLVENT CDCL3
FILE KRHX03

COSY PULSE SEQUENCE
OBSERVE PROTON
FREQUENCY 300.075 MHZ
1D SPECTRAL WIDTH (F2) 2679.5 HZ
2D SPECTRAL WIDTH (F1) 2679.5 HZ
ACQ. TIME 0.191 SEC
RELAXATION DELAY 1.0 SEC
PULSE WIDTH 90 DEGREES
FIRST PULSE 90 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 8
NO. INCREMENTS 256
SPIN RATE 20 HZ
DATA PROCESSING
PSEUDO-ECHO SHAPED
FT SIZE 1K X 1K
TOTAL TIME 52.9 MINUTES

Nucleus ____ Freq ____ MHz
Sweep Width ____ Hz Offset ____ Hz
Acq. Time ____ sec Delay ____ sec
Pulse Width ____ μsec Transmitter ____

DECOUPLE
Nucleus ____ Offset ____ Hz
Mode ____ Power ____ db
Modulation Mode ____ Freq ____ Hz
Pulse Width ____ μsec Power Mode ____

PLOT/PROCESSING
FN ____ K RE ____ sec CD ____ sec
LB ____ Hz AF ____ sec CCD ____
Width ____ Hz ppm Start ____ Hz/ppm
Reference ____

EXPERIMENT
Pulse Sequence ____
Tube OD ____ mm
Temp ____ °C
Solvent ____

SAMPLE

Number ____
File ____
Date ____
XI ____

SRI International

that the chelated intermediate directs the aldolization to single diastereoisomer. In the absence of such a rotational process when dimethyl maleate was used the possible *retro*-Michael process would have resulted in recovery of starting material. Indeed, acrylonitrile and trans-stilbene failed to give the corresponding cyclopentenes due to the lack of the ability to reorganize to intramolecular chelated complex and the starting material was recovered unreacted due to *retro*-Michael cleavage in these two cases.

The N-phenyl maleimide **82** also reacted with **65A** to afford the corresponding 5-[Bis(methylthio)methyl]-6-cyano-2,4-diphenyl-4-hydroxy-1,2,3,3a,4,6a hexahydro cyclopenta[c]pyrrole-1,3-dione **74g** in 65% yield (scheme 17), mp 85-86°C (dichloromethane-hexane). It should be noted however, when the reaction mixture was allowed to rise to room temperature after work-up, no well defined product could be isolated and the reaction mixture resulted in intractable tar. However, when the reaction was quenched at -78°C **74g** was obtained. The compound displayed the same diastereoselectivity in the same pattern as observed in preceeding examples (Fig. 11-13).

IV.3 *Conclusion*

It has been demonstrated that bifunctional α-oxoketene dithioacetals are potential substrates for anionic [3+2] cyclopentannelation with a number of acyclic and cyclic Michael acceptors in highly diastereoselective manner. The diastereoselectivity prevails with both the geometrical isomers

as observed in dimethyl fumarate and dimethyl maleate indicating intramolecular rearrangement after the first step of the Michael addition forming intramolecular chelated complex followed by its aldolization. This has been further proved that those molecules such as acrylonitrile and stilbene could not participate in intramolecular chelation of type A and consequentely, *retro*-Michael process resulted in the recovery of unreacted starting dithioacetal. The method is of considerable synthetic application to prepare large a number of diastereoselective functionalized cyclopentenes by choosing appropriate combination of functionalised oxoketene dithioacetals as well as Michael acceptors.

IV.4 *Experimental Section*

General

M.ps were measured on a "Thomas-Hoover" melting point (capillary method) apparatus and are uncorrected. IR spectra were registered on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR (90MHz) spectra were recorded on a Varian EM-390 spectrometer. Highfield ^{1}H NMR (300MHz), 2D-NMR (300MHz) and ^{13}C NMR (75MHz) spectra were recorded on a Gemini 300BB spectrometer. In ^{1}H NMR chemical shifts are reported in δ units down field from tetramethylsilane, ^{13}C NMR chemical shifts are reported relative to the central line of a triplet at δ=77.0 for $CDCl_3$. The followed abbreviations are used to describe peak patterns when appropriate : br=broad, S=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra (MS) were obtained on a Jeol JMS D-300 and G:L2903 spectrometers respectively. Masses

are reported in units of mass over charge (m/z) the molecular and base peaks are indicated by (M) and (%) respectively. Elemental analyses were preformed on a Heraeus CHN-O-Rapid analyzer.

All reaction involving, organolithium were conducted in a oven-dried (120°C) glassware under a positive argon atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried (120°C) syringe using standard syringe-septum technique. Low temperature reactions were carried in a bath made of ethyl acetate and liquid nitrogen. Analytical thin layer chromatography (tlc) were performed on glass plates (18x6 and 18x4 cm) coated with ACME's silicagel containing 13% calcium sulfate as binder and various combinations of ethylacetate-hexane, ethyl acetate-benzene were used as eluents. Iodine vapour, acidic potassium permanganate solution were used to visualize chromatograms. Column chromatography was performed on (60-120 mesh) silicagel purchased from ACME's. Solvents for chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steambath.

Chemicals and Reagents

Commercial available dimethyl amine, paraformaldehyde, potassium cyanide, aniline, acetic anhydride, maleic anhydride, nitromethane, maleic acid, fumaric acid, cinnamic acid, acetophenone were purified either by simple distillation/ distillation under reduced pressure or crystallized before use.

Diisopropyl amine was distilled from potassium hydroxide prior to use. Tetrahydrofuran (THF) was obtained anhydrous by distillation after the characteristic blue clour of *in situ* generated sodium diphenyl ketyl[34] was found to persist. Dry benzene[35a] was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire, dry methanol[35b] was obtained by distillation over magnesium cake and sotred over molecular sieves (4A), dry ether[35c] was obtained by keeping over calciumchloride (fused) and stored over sodium wire, dry DMF[35d] was obtained by azeotropic distillation and stored over molecular sieves (4A). Lithium Ingot (Aldrich) were cut into smaller pieces and washed with dry ether twice before use. n-Butyllithium was prepared according to the reported procedure[36]. Lithium diisopropyl amide (LDA) was prepared according to the literature procedures[37].

Starting Materials

Commercial available benzaldehyde was freed from acid by treating with saturated sodium bicarbonate solution followed by distillation prior to use. Benzylidene acetophenone (chalcone) **75** mp 52-53°C (lit.,[38a] 56-57°C), benzylidene acetone (4-phenylbut-3-ene-2-one) **76** mp 38°C (lit.,[38b] 42°C), ethylacrylate **38a** bp 99°C (760 mm) were purified either by distillation under reduced pressure or crystallisation before use. Nitrostyrene **79** mp 54-56°C (lit.,[38c,39] 57-58°C), methyl cinnmate **80** mp 29-30°C (lit.,[40a] 33-34°C), dimethyl fumarate **81a** mp 98-99°C (lit.,[40b] 103-104°C), dimethyl maleate **81b**[40b] bp 205°C (760 mm), N-phenyl maleimide **82** mp 86-87°C (lit.,[41] 89-89.8°C) (Michael acceptors)

were prepared according to the earlier reported procedures. 4-Phenyl-4-oxo butane nitrile mp 72°C (lit.,[42] 76°C), 4-phenyl-3-[bis(methylthio)methylene]-4-oxo-butane nitrile **64** mp 72-73°C (lit.,[22] 76°C) required for the present investigation were prepared by previously reported literature procedures which are given below.

Procedure for the preparation of 4-phenyl-3-[bis(methylthio) methylene]-4-oxobutanenitrile (64) using sodium tert.butoxide

A mixture of 4-phenyl-4-oxobutanenitrile 15.9g (0.1 mol) and carbondisulfide 7.6g (6.2 ml, 0.1 mol) was added to a well stirred and cooled suspension of sodium tert.butoxide 19.2g (0.2 mol) in dry benzene (150 ml) and dry DMF (10 ml). After stirring the reaction mixture at 5-10°C for 5h, methyl iodide 33.35g (14.5 ml, 0.22 mol) was gradually added with external cooling, the reaction mixture was stirred at room temperature for 5h, left overnight, and again stirred at 30-35°C for 3h. The reaction mixture was poured on crushed ice (150g) and the benzene layer was separated, the aqueous portion was extracted with benzene (2x50 ml) and the combined extract was washed with water (2x50 ml), dried (sodium sulfate) and concentrated to give the crude **64**, chromatographed on silicagel (elution with 1:3 v/v benzene-hexane) to leave colourless crystals, which were recrystallised (chloroform-hexane) to give the compound **64** as colourless crystals: mp 72-73°C (lit.,[22] 76°C): R_f 0.82 benzene/hexane (1:1) spectral data (IR, ^1H NMR) were identical with those of reported data and of authentic sample.

General procedure for the generation and reaction of 1,1-[Bis(methylthio)]-2-phenyl-3-cyano allyl lithium (65A) with dienophiles (75, 76, 79, 38a, 80, 81a, 81b and 82); synthesis of substituted cyclopentenes (74a-f) and substituted cyclopenta[c] pyrrole-1,3-dione (74g)

To a solution of diisopropylamine 1.87 ml, (13 mmol) in sodium dried tetrahydrofuran (THF) 10 ml under a positive dry argon atomosphere was added a 10 mmol of n-BuLi in ether, with stirring for 20 min. and temperature control at 0°C with an ice bath. The solution is then cooled to -78°C and the 4-phenyl-3-[bis(methylthio)methylene]-4-oxobutanenitrile 64g (10 mmol) in 25 ml THF was added over a 5 min period. The mixture, which becomes intense voilet colour, is kept at -78°C for 30-45 min. followed by addition of appropriate dienophile (10 mmol) in 15 ml THF at -78°C, and kept there for 30-45 min., and allowed to warm to room temperature (monitored by tlc), and quenched with aqueous saturated ammonium chloride solution (100 ml), extracted with dichloromethane (3x25 ml). The combined organic phases were washed with water (3x25 ml), dried (sodium sulfate), and concentrated. The residue was purified by column chromatography over silica gel using ethylacetate-hexane (2:1 - 4:1) as eluent.

5-Benzoyl-2-[bis(methylsulfonyl methyl]-3-cyano-1,4-diphenyl cyclopent-2-enol 74a :

Colourless crystals; yield 2.06g (88%); mp 162-163°C (chloroform-hexane); R_f: 0.35 EtOAC/benzene (1:9).

IR (KBr): γ_{max} = 3425 (OH), 2210 (CN), 1660(CO) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s,3H,SCH_3); 2.22 (s, 3H,

SCH_3); 4.14 [s, 1H, $CH(SCH_3)_2$]; 4.18 (s, 1H, OH exchangeable with D_2O); 4.26 (d, 1H, J=7.6Hz, Hb), 5.21 (d, 1H, J = 7.6Hz, Ha), 7.02-7.36 (m, 15H, ArH).

^{13}C NMR (75MHz, $CDCl_3$) : δ = 13.79, 16.20 (SCH_3); 49.51, 52.51, 68.11 [$CH(SCH_3)_2$, 4-CH, 5-CH]; 88.85 (C-1); 114.70 (C≡N); 118.58 (C-3); 126.02, 127.60, 127.88, 127.94, 128.41, 128.63, 128.65, 129.23, 132.98 (CHAr); 136.89, 139.0, 141.91 (C-1',Ar); 156.74 (C-2); 196.5 (CO).

MS : m/z (%) = 471 (M^+,3), 405 (M^+-48).

Anal : Calc. for $C_{28}H_{25}NO_2S_2$ (471.607) : C 71.30; H 5.43; N 2.97. Found C 71.50; H 5.70; N 3.10%.

5-Acetyl-2-[bis(methylthio)methyl]-3-cyano-1,4-diphenylcyclopent-2-enol 74b:

Colourless crystals; yield 1.24g (61%); mp 167-168°C (chloroform-hexane); R_f 0.26 EtOAC/benzene (1:9).

IR (KBr): γ_{max} = 3445 (OH), 2240 (CN), 1718(CO) cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$):δ 1.78 (s, 3H, CH_3); 2.08 (s, 3H, SCH_3); 2.21 (s, 3H, SCH_3); 3.52 (d, 1H, J=75Hz, Hb); 4.11 [s, 1H, $CH(SCH_3)_2$]; 4.27 (s, 1H, OH, exchangeable with D_2O); 5.06 (d, 1H, J=7.5Hz, Ha); 6.81-7.72 (m, 10H, ArH).

Anal: Calc. for $C_{23}H_{23}NO_2S_2$ (409.537); C 67.45; H 5.66; N 3.42. Found C 67.70; H 5.90; N 3.65%.

2-[Bis(methylthio)methyl]-3-cyano-5-nitro-3,5-phenyl cyclopent-2-ene 74c:

Light yellow crystals; yield 1.35g (66%); mp 148-150°C (chloroform-hexane); R_f 0.28 EtOAC/hexane (2:8).

IR(KBr): γ_{max} = 3352(OH), 2250(CN), 1568 (NO_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3H, SCH_3); 2.27 (s, 3H, SCH_3); 4.22 [s, 1H, $CH(SCH_3)_2$]; 4.33 (s, 1H, OH, exchangeable with D_2O); 5.08 (d, 1H, J=7.1Hz, Hb); 5.28 (d, 1H, J=7.1Hz, Ha); 7.25-7.47 (m, 10H, ArH).

^{13}C NMR (75MHz, $CDCl_3$): δ=13.91, 17.20 (SCH_3); 50.68, 53.48 [4-CH, $CH(SCH_3)_2$]; 88.03 (1-C); 100.55 (5-CH); 114.91, 117.16, (C≡N and 3-C); 126.77, 128.87, 130.07, 130.22, 130.34, 130.66 (CH, Ar); 136.74, 140.51 (C-1', Ar); 155.89 (2-C).

MS: m/z (%) = 365 (M^+-47,50), 318 [M^+-2(SCH_3),100].

Anal: Calc. for $C_{21}H_{20}N_2O_3S_2$ (412.51): C 61.14; H 4.89; N 6.79. Found C 61.40; H 4.90; N 7.00%.

Ethyl 3-[bis(methylthio)methyl]-4-cyano-2-hydroxy-2-phenyl cyclopent-3-ene carboxylate 74d:

Colurless cyrstals; yield 1.35g (75%); mp 93-94°C (chloroform-hexane); R_f 0.55 EtOAC/benzene (2:8).

IR(KBr): γ_{max} = 3450 (OH), 2242 (CN), 1728 (CO) cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ =1.20 (t, 3H, J=7Hz, CH_3); 2.03 (s, 3H, SCH_3); 2.21 (s, 3H, SCH_3); 2.70-3.55 (m, 3H, CH_2 and 1-CH); 4.01-4.40 [3H, distorted q, CH_2 and $CH(SCH_3)_2$]; 7.43 (brs, 5H, ArH).

^{13}C NMR (75MHz, $CDCl_3$): δ=13.3, 13.9 (SCH_3); 16.01 (CH_3); 35.6 (CH_2); 49.0 (1-CH); 55.2 [$CH(SCH_3)_2$]; 61.1 (OCH_2); 88.3 (C-2); 112.50 (C-4); 117.3 (C≡N); 125.30, 128.20, 128.50 (CH, Ar); 134.3 (C-1', Ar); 156.9 (C-3); 170.9 (CO).

MS: m/z (%) = 363 (M^+,12), 316 (M^+-47,50).

Anal: Calc. for $C_{18}H_{21}NO_3S_2$ (363.477): C 59.50; H 5.82; N 3.85. Found C 59.70; H 6.00; N 4.00%.

Methyl 3-[bis(methylthio)methyl]-4-cyano-3,5-diphenyl-2-hydroxy cyclopent-3-ene carboxylate 74e:

Light yellow crystals; yield 1.50g (71%); mp 164-165°C (chloroform-hexane); R_f 0.67 EtOAC/benzene (2:8).

IR (KBr): γ_{max} = 3430 (OH), 2230 (CN), 1721 (CO) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H, SCH_3); 2.24 (s, 3H, SCH_3); 3.36 (d, 1H, J = 8Hz, Hb); 3.57 (s, 3H, OCH_3); 4.15 [s, 1H, $CH(SCH_3)_2$]; 4.22 (brs, 1H, OH exchangeable with D_2O); 4.91 (d, 1H, J=8Hz, Ha); 7.26-7.50 (m, 10H, ArH).

^{13}C NMR (75MHz, $CDCl_3$): δ = 14.28, 17.23 (SCH_3); 50.62, 53.07, 53.55 [1-CH, 5-CH, $CH(SCH_3)_2$]; 57.34 (OCH_3); 89.47 (C-2); 115.76, 119.51 (C≡N, C-4); 126.89, 128.85, 129.21, 129.39, 129.69, 130.29 (CH, Ar); 139.58, 142.91 (C-1', Ar); 157.66 (C-3); 170.53 (CO).

MS: m/z (%) = 378 (M^+-47,55), 360 (M^+-47-HOH,100).

Anal: Calc. for $C_{23}H_{23}NO_3S_2$ (425.537): C 64.91; H 5.44; N 3.29. Found C 65.20; H 5.70; N 3.50%.

Dimethyl 4-[bis(methylthio)methyl]-3-cyano-5-hydroxy-5-phenyl cyclopent-3-ene-1,2-dicarboxylate 74f:

Colourless crystals; yield 1.46g (72%); mp 146-148°C (chloroform-hexane); R_f 0.27 EtOAc/benzene (1:9).

IR (KBr): γ_{max} = 3371 (OH), 2216 (CN), 1732, 1706 (CO) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H, SCH_3); 2.22 (s, 3H, SCH_3); 3.67 (s, 3H, OCH_3); 3.79 (d, 1H, J=7.1Hz, Hb); 3.84 (s, 3H, OCH_3); 4.08 [brs, 2H, $CH(SCH_3)_2$ and OH exchangeable with D_2O]; 4.52 (d, 1H, J=7.1Hz, Ha); 7.39-7.43 (m, 5H, ArH).

^{13}C NMR (75MHz, $CDCl_3$): δ = 14.79, 17.22 (SCH_3); 50.21, 52.89, 53.43 [1-CH, 2-CH, $CH(SCH_3)_2$], 54.20, 59.99 (OCH_3); 88.92 (C-5);

113.50, 114.95 (C≡N, C-3); 126.79, 129.57, 129.72 (CH, Ar); 142.43 (C-1', Ar); 159.62 (C-4); 170.47, 171.35 (CO).

MS: m/z (%) = 360 (M^+-47,40), 342 (M^+-47-HOH,92).

Anal: Calc. for $C_{19}H_{21}NO_5S_2$ (407.467): C 55.99; H 5.19; N 3.44. Found C 56.20; H 5.40; N 3.70%.

5-[Bis(methylthio)methyl]-6-cyano-2,4-diphenyl-4-hydroxy-1,2,3,3a,4,6a-hexahydro cyclopenta[c]pyrrole-1,3-dione 74g:

Yellow solid; yield 1.42g (65%); mp 85-86°C (dichloromethane-hexane); R_f 0.39 EtoAc/benzene (1:9).

IR (KBr); γ_{max} = 3450 (OH), 2250 (CN), 1723 (CO) cm^{-1}.

^1H NMR (300MHz, $CDCl_3$): δ=1.89 (s, 3H, SCH_3); 2.16 (s, 3H, SCH_3); 3.74 (d, 1H, J=8Hz, Hb); 4.13 [s, 1H, $CH(SCH_3)_2$]; 4.24 (d, 1H, J=8Hz, Ha); 4.49 (s, 1H, OH, exchangeable with D_2O); 7.24-7.48 (m, 10H, ArH).

^{13}C NMR (75MHz, $CDCl_3$): δ=15.43, 17.15 (SCH_3); 49.36, 52.76, 56.72 [$CH(SCH_3)_2$, 3-CH, 4-CH]; 88.70 (C-5); 110.69, 114.78 (C≡N, C-2); 126.18, 127.52, 129.99, 133.04, 130.15, 130.31 (CH, Ar); 132.46 (C-1', Ar); 142.97 (C-1); 162.97 (C-1'>Nph); 173.31, 173.60 (CO).

MS: m/z (%) = 389 (M^+-47,12).

Anal: Calc. for $C_{23}H_{20}N_2O_3S_2$ (436.53): C 63.28; H 4.62; N 6.42. Found C 63.60; H 4.90; N 6.70%.

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CHAPTER – V

DEPROTONATION STUDIES OF α-OXOKETENE S,N-ACETALS AND DIMETHYL N-AROYL CARBIMIDO-DITHIOATES : A NOVEL APPROACH TO 2-AMINO-THIOPHENES AND 2-METHYLTHIOTHIAZOLES

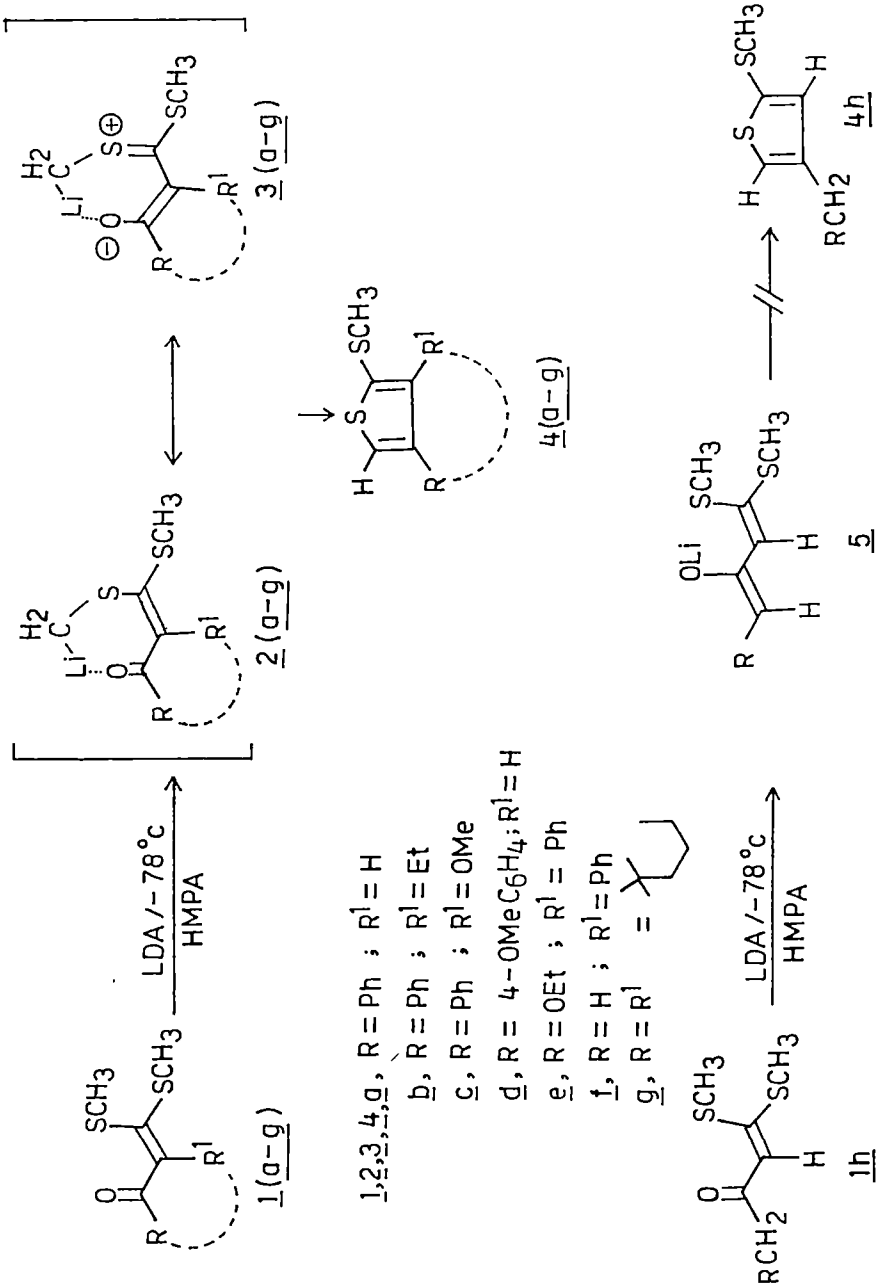
V.1 *Introduction*

The α-oxoketene dithioacetals have been extensively employed as 3-carbon 1,3-dielectrophilic fragments for the construction of a number of heterocycles[1]. Among others the construction of thiophene ring has been variously attempted with a large variation in the degree of success[2-9]. While some of the methods are of academic interest, some of them are important as methods for immense preparative value.

The reported methods on the synthesis of thiophenes have been briefly described in this chapter, as an introduction to the present investigation.

Marino and co-workers[10] studied deprotonation of various α-oxoketene dithioacetals under LDA/HMPA conditions, and observed kinetic deprotonations at three different sites depending on structural variations and base combinations. It is important for the present reference that the reaction involved deprotonation of the thiomethyl group cis to carbonyl group to give the dipole-stabilized carbanions[11] **3a-g** by treating **1a-g** with LDA/HMPA at -78°C which *in situ* underwent intramolecular aldol addition-elimination sequence to yield the corresponding thiophene **4a-g** in 22-55% overall yields (scheme 1). However, this method failed to give thiophene when acyl ketene dithioacetals **1h** were used as substrates. The reason for the failure with acyl ketenedithioacetals was due to their competative deprotonation of the acyl group to form the corresponding enolate anion **5** (scheme 1) in preference to methylthio group deprotonation. Though yields were moderate the synthesis of thiophene from the oxoketene dithioacetals constitute a novel approach involving aldol type addition-elimination sequence.

Marino and co-workers[12] also examined deprotonation of **1a** to afford a mixture of **2a** and **3a** anions. **2a** on treatment with deuterium oxide and methyl iodide yielded the corresponding deuterated dithioacetal **6** and α-methyl oxoketene dithioacetal **1i** respectively. It adaquentaly proves that, the kinetic deprotonation at these two positions were established through the


LDA/-78°c
HMPA
1 (a-g)
2 (a-g)
3 (a-g)
4 (a-g)
1,2,3,4 a, R = Ph ; R¹ = H
b, R = Ph ; R¹ = Et
c, R = Ph ; R¹ = OMe
d, R = 4-OMeC6H4 ; R¹ = H
e, R = OEt ; R¹ = Ph
f, R = H ; R¹ = Ph
g, R = R¹ =
1h
5
4h

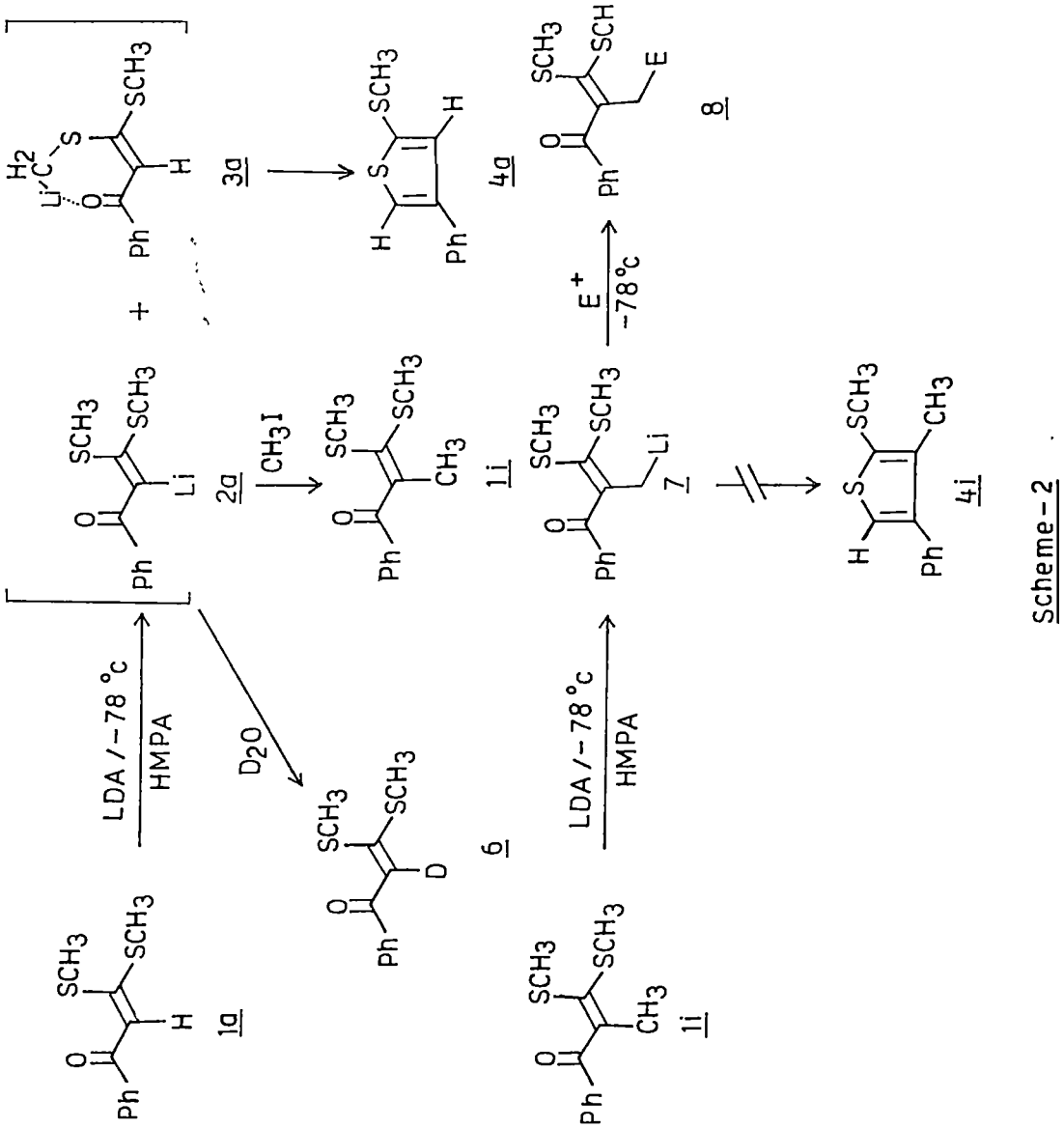
Scheme-1

formation of **6,1i** and thiophene **4a** which are obtained by anion **3a**. Similarly, they examined α-methyl ketene dithioacetal under the described basic conditions and the side chain deprotonation was observed to afford **7** which was confirmed by alkylation to afford the corresponding **8** in moderate yields (scheme 2).

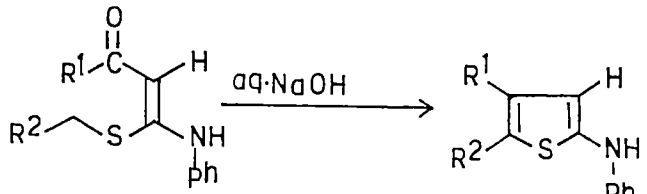
Augustin and co-workers[13] studied an activated S-alkyl side chain as in **9** (scheme 3), so that the anion could be generated under ordinary conditions (aq. NaOH) and undergo intramolecular aldol addition-elimination sequence to afford the corresponding aminothiophene **10**. Similarly, Yokoyama and co-workers[14] examined the deprotonation of S,N-acetal **11** derived from malanonitrile which underwent intramolecular addition to afford the corresponding iminothiophene **13**, which on acetylation yielded 2,4-diaminothiophene **14** in high yields (scheme 3).

Yokoyama and co-workers[15] have also reported the synthesis of 5-amino-3,6-dicyano-2,7-bis(dialkylamino)-1-thieno[3,2-b]pyridine **19** involving sequential intramolecular addition sequence in a tandem process. Thus, the deprotonated S,N-acetal **16** appears to displace methylthio group from unreacted S,N-acetal **15**. Thus the anion **17** underwent intramolecular addition to yield the corresponding **19** over **18** as depicted in scheme 4.

In our laboratory, a new thiophene methodology using α-oxoketene dithioacetals as precursors under Simmons-Smith reaction conditions in a one-pot reaction operation[16] was developed. Originally it was intended to introduce cyclopropane ring over the mercapto double bond which were required in connection with our synthetic work. However, under these reaction conditions



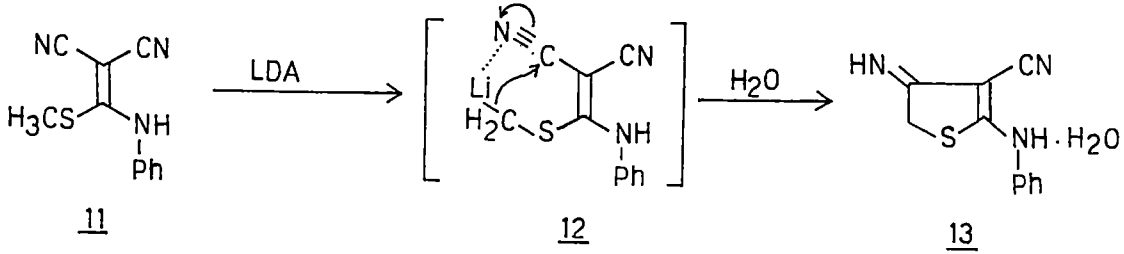
Scheme-2



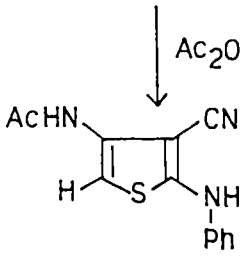
9 10

9, 10, $R^1 = C_6H_5$

$R^2 = CO_2Et$, $CONH_2$

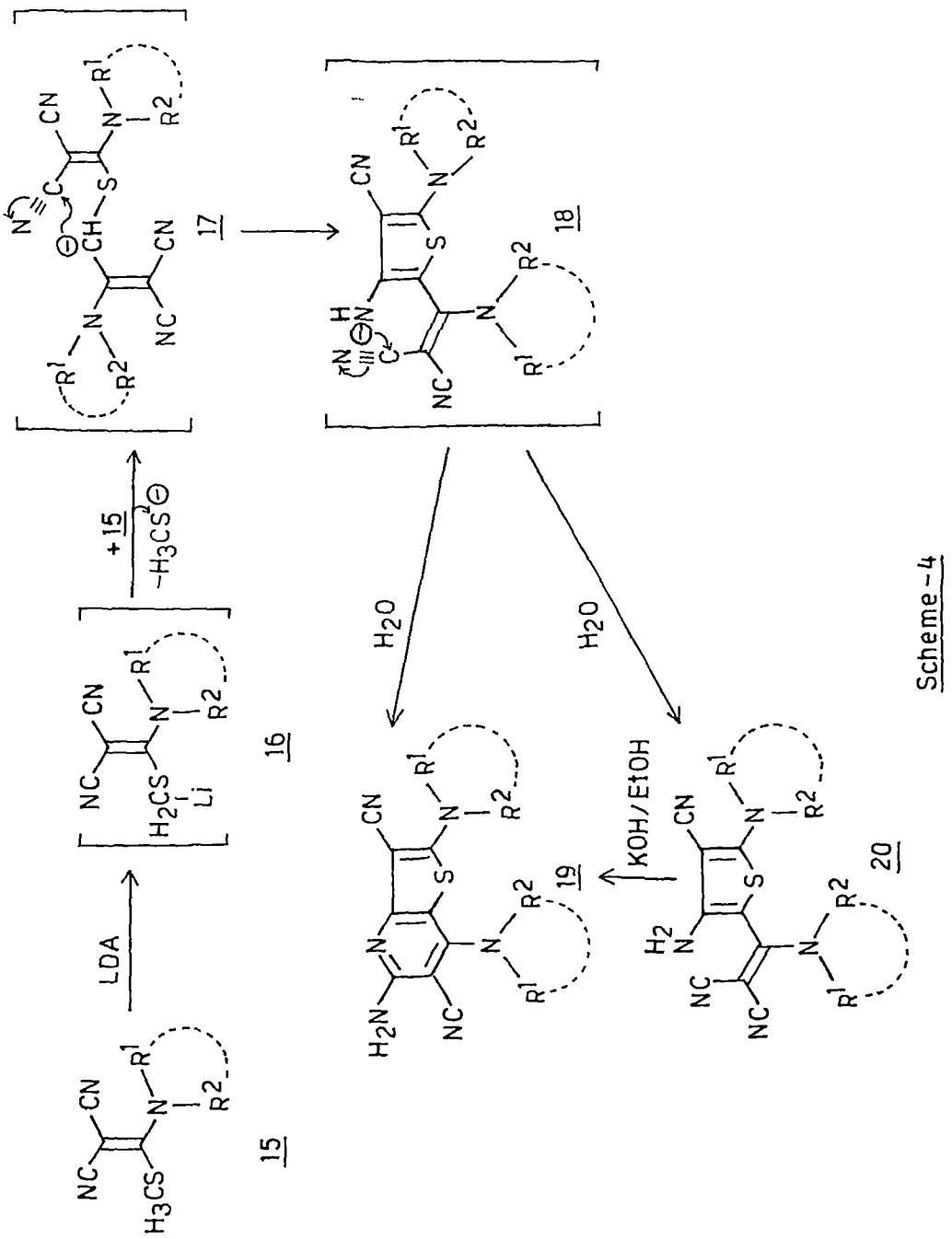


11 12 13



14

Scheme-3

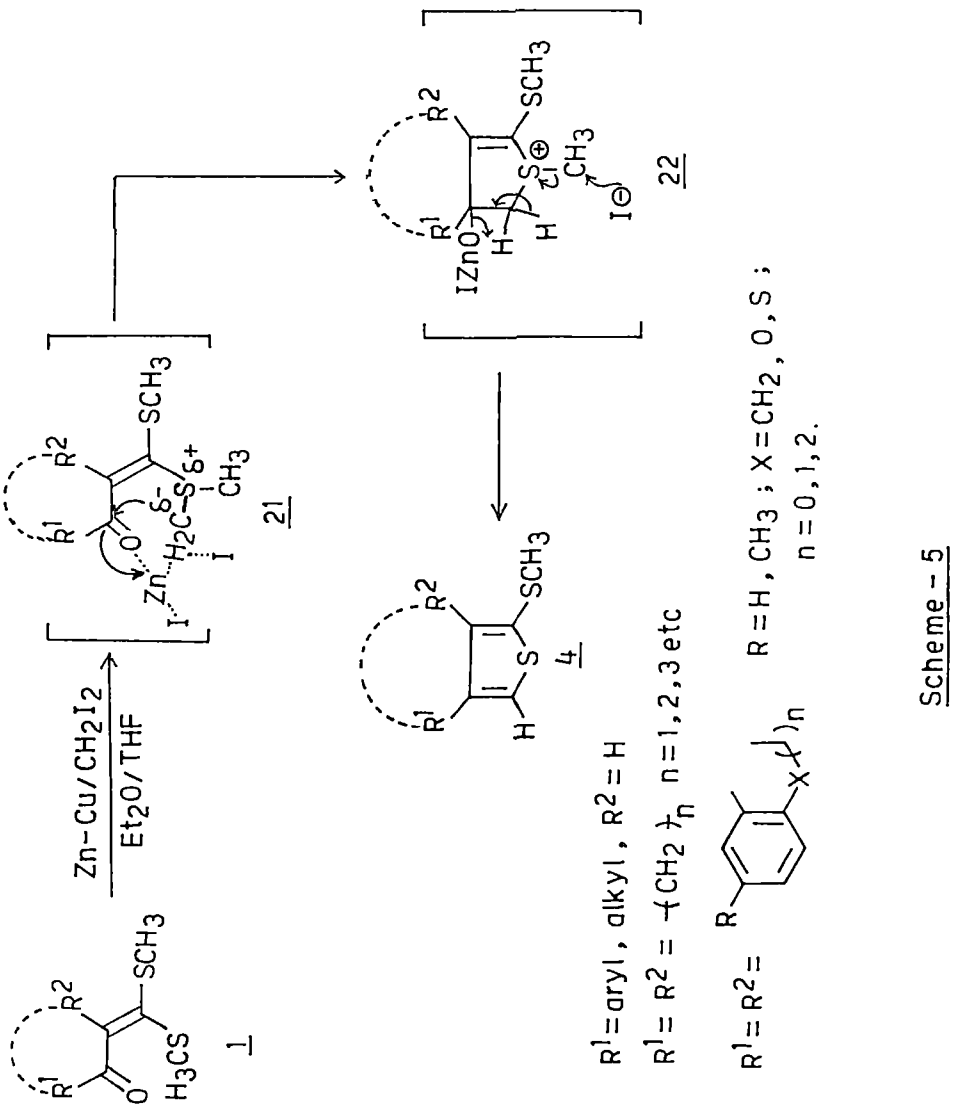


Scheme-4

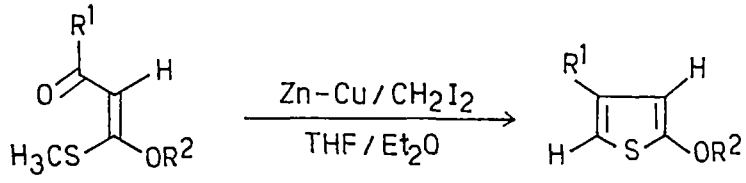
excellent yields of thiophene **4** (scheme 5) were obtained from 1. The mechanism governing this facile transformation is described in scheme 5. The divalent sulfur appears to attack the electrophilic carbenoid methylene to afford the corresponding ylid **21**, which undergoes an intramolecular addition-elimination sequence to afford the corresponding 5-methylthio-3,4-substituted/annelated thiophenes **4** in high yields. In continuation of this work an efficient method for the synthesis of 2-alkoxy/aryloxythiophenes from acylketene O,S-acetals was developed. It is of interest to note that, the O,S-acetals possess only one geometrical (*Z*) isomer where the methylthio group is on the side of the carbonyl function. Thus the reaction of O,S-acetals **23** and **24** under Simmons-Smith reaction conditions yielded the corresponding 2-alkoxy/aryloxy-4-aryl/3,4-annelated thiophenes **24** and **26** in moderate to good yields[17] (scheme 6). This constitutes an excellent method for the synthesis of the 2-alkoxy/aryloxy thiophenes. Other methods of alkoxy/aryloxy thiophene synthesis involves classical displacement or coupling reaction resulting in overall poor yields[18-25].

V.2 *Results and Discussion*

It was intended to extend Simmons-Smith reaction conditions for the synthesis of amino thiophene of general formula **28** (scheme 7) by reacting α-oxoketene S,N-acetals **27** under Simmons-Smith reaction conditions, it was observed that the starting S,N-acetals **27** remains un-changed even after prolonged exposure to Simmons-Smith reagents. After work-up the starting material was recovered unchanged.


Zn-Cu/CH2I2
Et2O/THF
SCH3
H3CS
1
21
22
4
R1=aryl, alkyl, R2=H
R1=R2=-(CH2)n n=1,2,3 etc
R1=R2=
R=H, CH3 ; X=CH2, O, S ;
n=0,1,2.

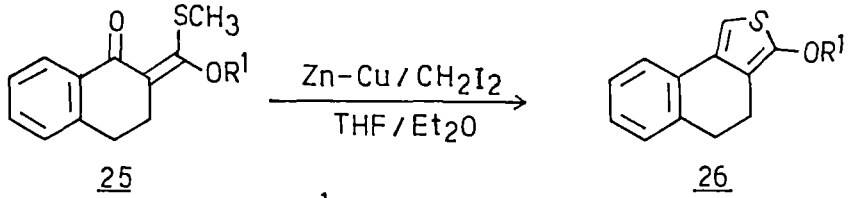
Scheme - 5



23 24

R^1= Substituted aryl

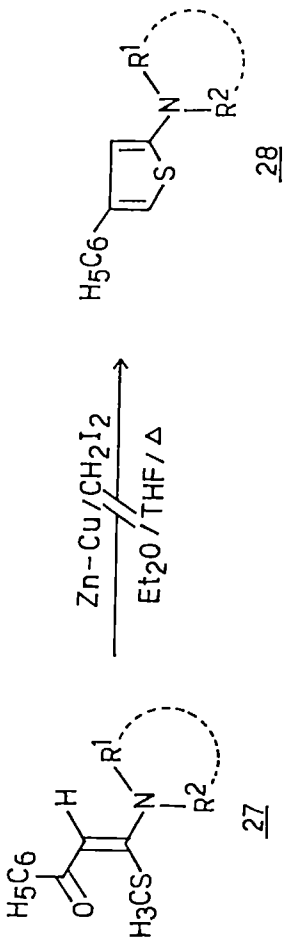
R^2= Me , Et , n-Pr , n-C_8H_{18} , C_6H_5



25 26

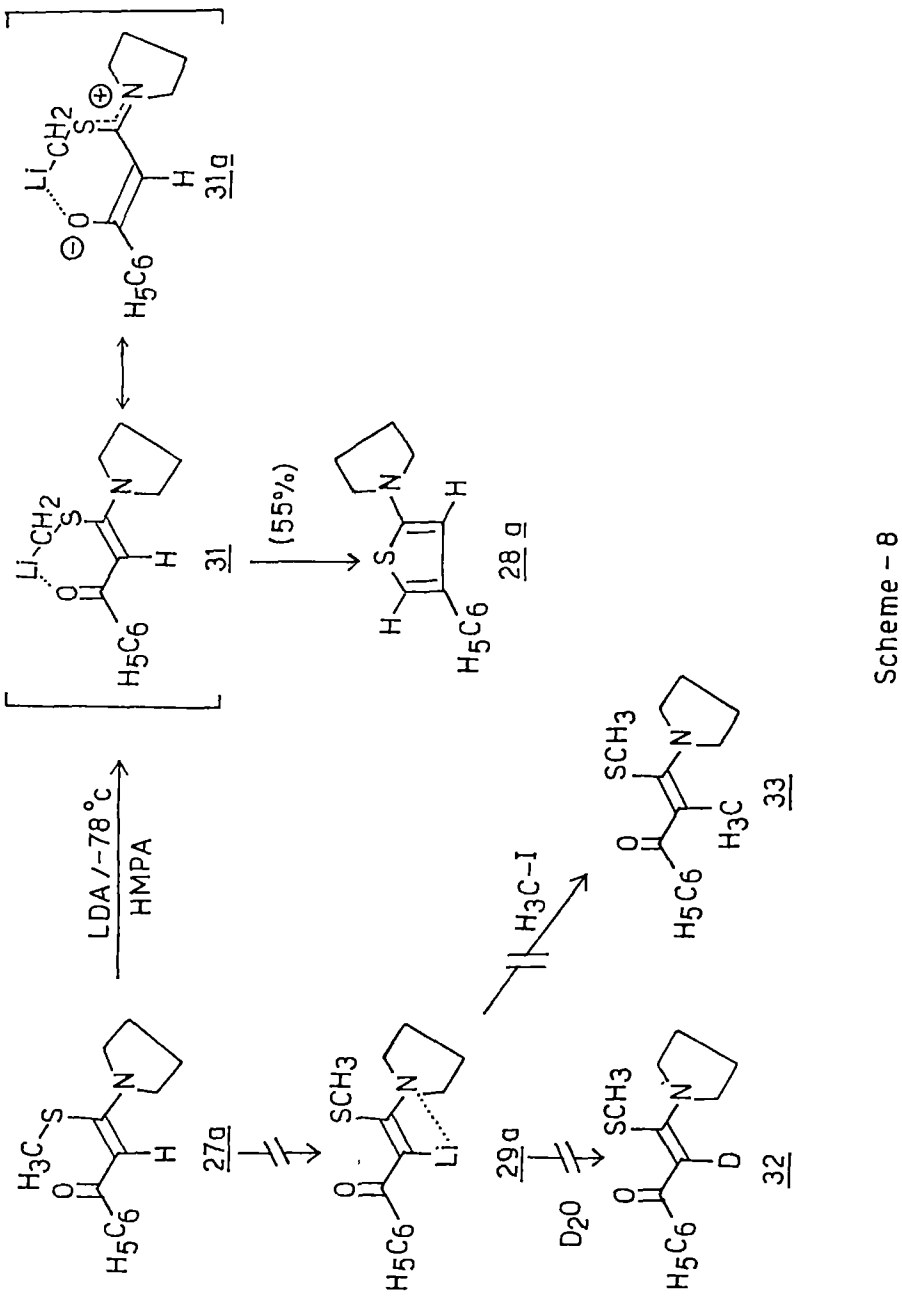
R^1 = Me , C_6H_5

Scheme - 6

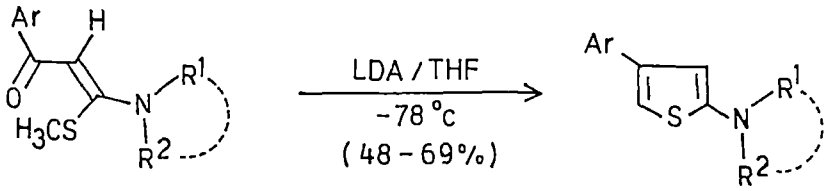


Scheme-7

The S,N-acetal **27a** was investigated under strong basic conditions to examine the mode of competative deprotonation. Thus, **27a** on treatment with lithium diisopropylamide (LDA) could afford either **29a** on α-deprotonation or **30a** on deprotonation of the thiomethyl proton. On treatment of the anion **29a** with deuterium oxide (D_2O) and methyliodide (MeI) in two separate experiments the starting material **27a** was recovered un-reacted. In other reaction mixture after work-up 2-pyrrolidino 4-phenyl thiophene **28a** was obtained in 55% yield (scheme 8). The structure of thiophene **28a** was in accordance with the analytical and spectral data. It was analyzed for $C_{14}H_{15}NS$ for molecular weight 229.331. In its IR(KBr) spectrum strong bands appeared at 3386, 2960, 1539 cm^{-1}. In its ^1H NMR ($CDCl_3$) spectrum the multiplet for pyrrolidino (4H) protons appeared at δ1.85-2.18 and the other (4H) methylene protons adjacent to nitrogen appears as multiplet at δ 3.11-3.45. The broad singlet at δ 5.99 was accounted for thiophene ring-4 carbon proton and the other broad singlet at δ 6.49 was assigned to thiophene ring-5 carbon proton. The aromatic five protons appear as multiplet between δ 7.11-7.67. Similarly, the other α-oxoketene S,N-acetals **27b-e** were also transformed to the corresponding 2-amino thiophenes **28b-e** in 48-69% overall yields (scheme 9) [See Fig.1 for **28e** ^1H NMR (90 MHz, CCl_4) spectrum]. All these compounds were isolated exclusively without having any other side products. Where ever there was low yields, the appropriate amount of unreacted starting S,N-acetal **27** was recovered. The combined yield of thiophene and S,N-acetal usually exceeded 90%. Increasing the number of equivalents of LDA did not have any significant effect on the yield of thiophenes.



Scheme - 8



27 (b-e) 28 (b-e)

27, 28, b, Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_5$

c, Ar = C_6H_5 ; $R^1 = R^2 = -(CH_2)_2O(CH_2)_2$

d, Ar = C_6H_5 ; $R^1 = R^2$ = Et

e, Ar = 4-MeO C_6H_4 ; $R^1 = R^2 = -(CH_2)_4$

Scheme - 9

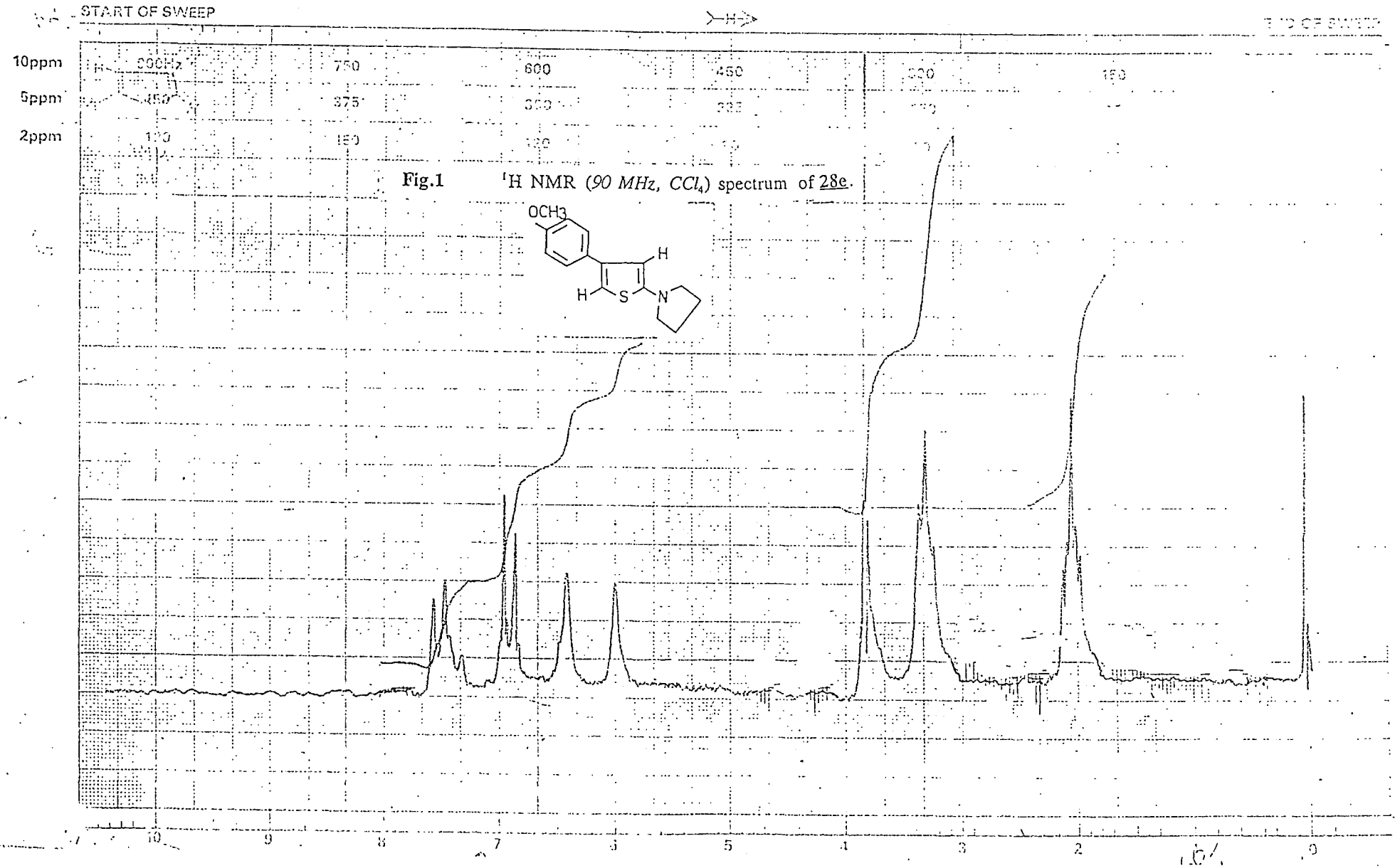
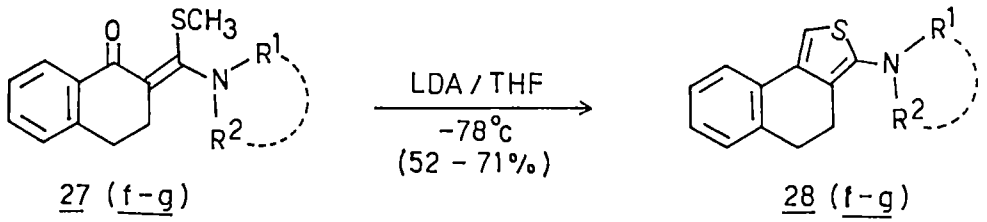


Fig.1 ^{1}H NMR (*90 MHz, CCl_4*) spectrum of 28e.

The structural assignments for all these thiophenes were in accordance with the data described in the experimental section.

Cyclic α-oxoketene S,N-acetals were next investigated with a view to extending the present methodology for the syntheasis of 3,4-annelated amino thiophenes. The literature methods available for the synthesis of 3,4-fused thiophenes are scanty and suffers from lack of generality[10,26]. The cyclic α-oxoketene S,N-acetals **27f-g** derived from α-tetralone under the described basic conditions yielded the corresponding 2-pyrrolidyl-3,4-dihydronaptho[2,1-c]thiophene **28f** (52%) and 2-piperidyl-3,4-dihydronaptho[2,1,c] thiophene **28g** (71%) respectively (scheme 10)[27]. Their analytical and spectral data are in aggreement with assigned structures (experimental). It is interesting to note that the S,N-acetal yielded the corresponding amino thiophenes in much improved yields than the corresponding S,S-acetals as observed by Marino and co-workers. Also, the kinetic deprotonation observed in the case of S,S-acetals at three different sites did not manifest in the case of S,N-acetals. It therefore appears that the nitrogen ligands with lithium more strongly (hard-hard) than sulfur (soft-hard), so that an exclusive deprotonation of thiomethyl proton is taking place involving hetero atom assisted deprotonation.

It was considered of interest to examine dimethyl N-aroyl carbimidodithioates under both Simmons-Smith and lithium diisopropylamide (LDA) conditions. When **34** was subjected to Simmons-Smith reaction conditions the corresponding thiazole **35** was not formed and the unreacted starting material was recovered in quantitative yield (scheme 11). When **34a** was then treated

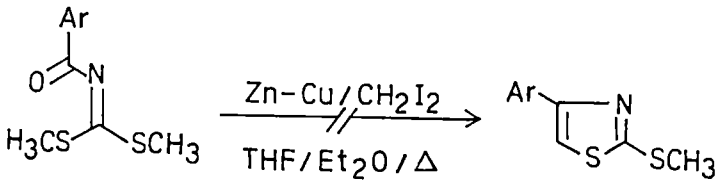


27 (f-g) 28 (f-g)

27, 28, f, $R^1 = R^2 = -(CH_2)_4$

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

Scheme-10



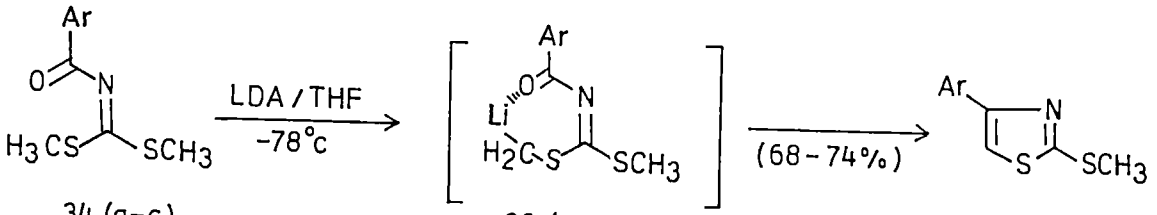
34 35

Scheme-11

with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C the corresponding 2-methylthio-4-phenylthiazole **35a** was obtained in 74% yield (scheme 12). **35a** was found to be identical with that reported in the literature[28] (superimposable IR and ^{1}H NMR) [See Fig. 2 for ^{1}H NMR (90 MHz, $CDCl_3$) spectrum]. Similarly, **34b** and **34c** underwent deprotonation and thiazole ring formation to yield the corresponding 2-methylthio 4-(4-methylphenyl) thiozole **35b** and 2-methylthio 4-(2-chlorophenyl) thiazole **35c** in 68 and 70.5% yields respectively (scheme 12). The analytical (CHN) and spectral (IR, ^{1}H NMR) data of these compounds are in agreement with the assigned structure (experimental section).

There are a few related examples described in the literature which are illustrated in the following sections. Thus, the carbonimido dithioate **37** was shown to undergo preferential benzylic proton deprotonation in the presence of lithium diisopropylamide (LDA) to yield anion **38** which was trapped by various carbonyl compounds **39** followed by cyclization to yield **41** (scheme 13).

Yokoyama and co-workers studied the deprotonation of dimethyl cyanodithioimidocarbonate **42** and showed that the 2,4-diaminothiazoles **46** are formed in good yields[14] (scheme 14). In an another experiment they have reported the synthesis of isomeric 2-amino-5-cyano-4-substituted aminothioazoles **53** via **52** by reacting aminomethylthiomethylenecyanamide **47** with lithium diisopropylamide (LDA). The proposed mechanism involves the formation of an intermediate episulfide **49b** followed by its



34 (a-c) 36 (a-c) 35 (a-c)

34, 36, 35, a, Ar = C_6H_5

b Ar = 4-Me C_6H_4

c Ar = 2-Cl C_6H_4

Scheme-12

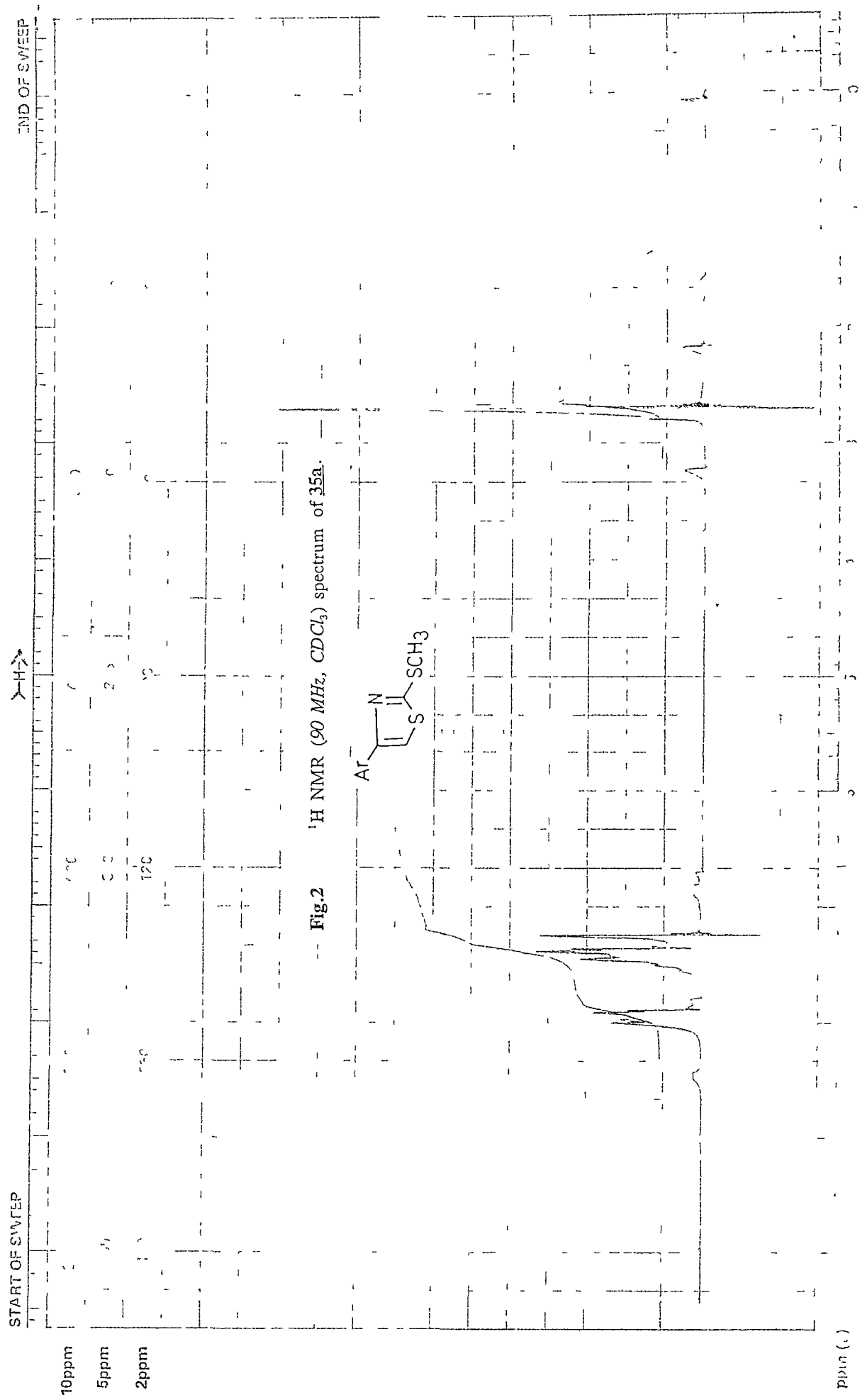
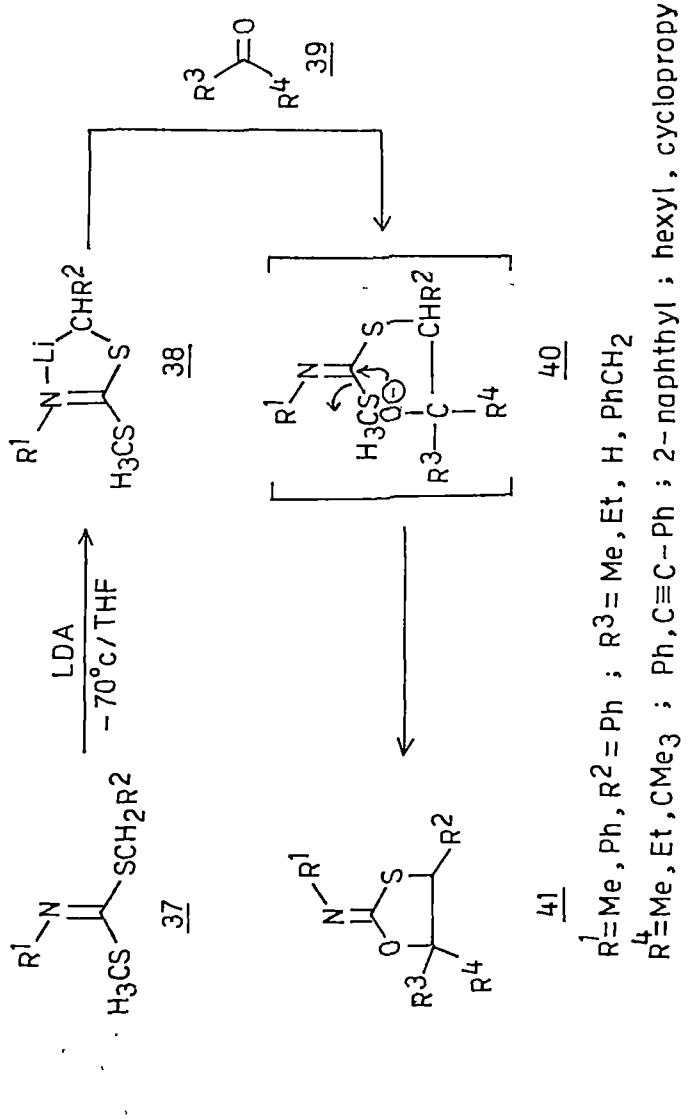
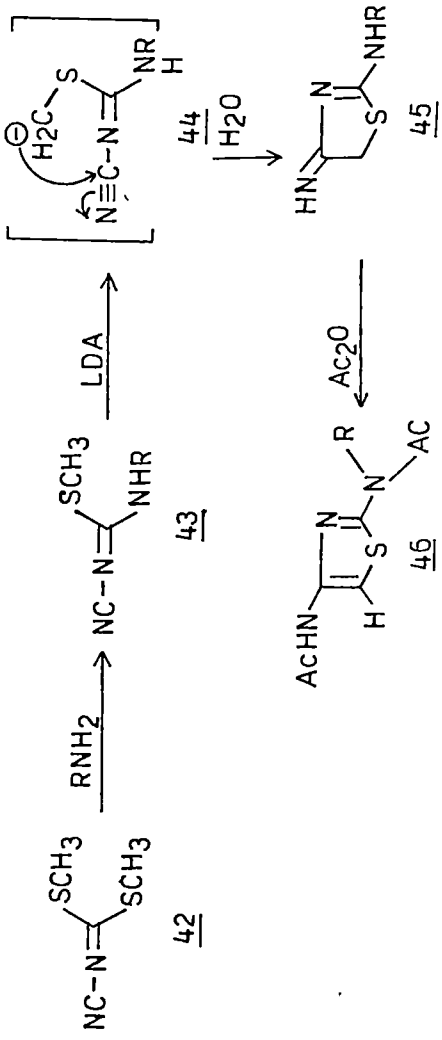


Fig.2 ^1H NMR (*90 MHz, $CDCl_3$*) spectrum of 35a.



R^1=Me, Ph, R^2=Ph ; R^3= Me, Et, H, $PhCH_2$
R^4=Me, Et, CMe_3 ; Ph, C≡C-Ph ; 2-naphthyl ; hexyl, cyclopropyl

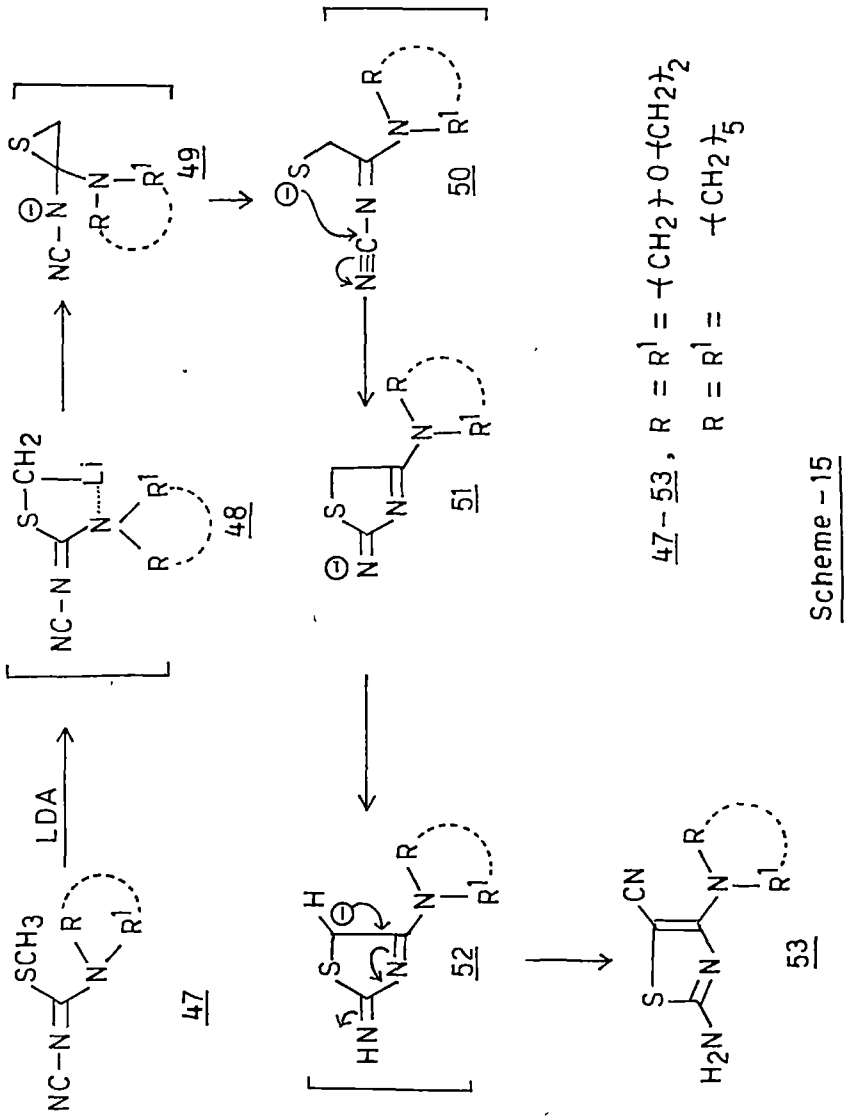
Scheme-13



42 43 44 45 46

43-46, R= ph , Cyclohexyl.

Scheme-14



Scheme - 15

clevage and ring closure to yield 53 in good yields[15] (scheme 15).

V.3 *Conclusion*

Attempts to convert α-oxoketene S,N-acetals to the corresponding aminothiophenes under Simmons-Smith reaction conditions failed.

The S,N-acetals underwent methylthio group deprotonation in the presence of lithium diisopropyl amide (LDA) and yielded the corresponding aminothiophenes in improved yields.

The method is generally applicable and suitable for the synthesis of 2-aminothiophenes.

V.4 *Experimental Section*

General

Melting points were determined on a "Thomas Hoover" capillary melting point apparatus and are uncorrected. The Infrared spectra were recorded on a Perkin-Elmer 297, Perkin-Elmer 983 spectrometers. ^{1}H NMR (90MHz) spectra were recoreded on varian EM-390. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to tetramethyl silane. The followed abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (MS) were obtained on a Jeol JMS D-300 spectrometer. Masses are reported in units of mass over charge (m/z), the molecular and base peaks are indicated by (M) and (%)

respectively. Elemental analyses were performed on a Carlo Erba 1108 Heraeus analyzer.

All reactions involving organolithium were performed in oven dried (120°C) glassware under a dry nitrogen/argon atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven dried (120°C) syringe using standard syringe septum technique. Low temperature reactions were carried in a bath made of ethyl acetate and liquid nitrogen. Analytical thin layer chromatography (tlc) were performed on glass plates (18x6 and 18x4 cm) coated with ACME's silica gel containing 13% calcium sulfate as binder and various combinations of ethylacetate-hexane, ethylacetate-benzene, benzene were used as eluents. Iodine vapour, acidic potassium permanganate solution were used to visualize chromatograms. Column chromatography was performed on (60-120 mesh) silica gel purchased from ACME's. Solvents for chromatography were used after simple distillation of commercial materials. All solvent evaporations were done using a steam bath.

Chemicals and Reagents

Commercial available pyrrolidine, piperidine, morpholine, diethyl amine (secondary amines), thionyl chloride were purified by simple distillation. Diisopropylamine is distilled from potassium hydroxide prior to use. Tetrahydrofuran (THF) was obtained anhydrous by distillation after the characteristic blue colour of *in situ* generated sodium diphenyl ketyl[29] was found to persist. Dry benzene[30a] was obtained by washing with

concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Dry diethyl ether[30b] was obtained by keeping over calcium chloride (fused) and stored over sodium wire. Lithium Ingot (Aldrich) were cut into smaller pieces and washed with dry ether twice before use. n-Butyl lithium was prepared according to the reported procedure[31]. Lithium diisopropylamide (LDA) was prepared according to the literature procedures[32].

Starting Materials

Commercial available ketones of acetophenone, 4-methoxy acetophenone, amides of benzamide were purified either by simple distillation or distillation under reduced pressure or crystallisation before use. α-tetralone bp 140-150°C (10 mm)[33], dimethyl trithiocarbonate bp 225°C (760mm)[34], 4-methoxy benzamide mp 160-161°C (lit.,[35] 166.5-167.5°C), 2-chloro benzamide mp 136-137°C (lit.,[35] 142-143°C) were prepared according to the earlier reported procedures.

General experimental details for the preparation of α-oxoketene S,N-acetals **27a-g**[36-39] are described in the experimental section of chapter 2. All S,N-acetals used for the present investigation were prepared using this procedure and were characterised by physical (mp) and spectral (IR, ^{1}H NMR) data. Dimethyl N-phenyl carbimidodithioate **34a** mp 40-41°C (lit.,[40] 46-47°C), dimethyl N-(4-methoxyphenyl) carbimidodithioate **34b** mp 59-60°C (lit.,[40] 65-66°C) and dimethyl N-(2-chlorophenyl) carbimidodithioate **34c** mp 82-83°C (lit.,[40] 88-89°C) used for the present study were prepared according to the earlier reported literature procedure

which are given below.

General procedure for the preparation of 2,4-disubstituted thiophenes (28a-c) and 2-substituted 3,4-annelated thiophenes (28f-g):

To a solution of diisopropylamine 1.21g (1.68 ml, 12 mmol) in sodium dried tetrahydrofuran (THF) 10 ml under a dry argon atmosphere was added 10 mmol of n-BuLi in ether, over 20 min with stirring and temperature control at 0°C with an ice bath. The solution is then cooled to -78°C and the appropriate α-oxoketene S,N-acetal 7.5 mmol in 25 ml THF was added. The resulting light green-coloured reaction mixture was stirred for 30-45 min (-78°c) and then allowed to warm to room temperature (monitored by tlc). Quenching with aqueous saturated ammonium chloride solution (100 ml), and extracted with chloroform (3x25 ml). The combined extracts were washed with water (3x25 ml), dried over sodium sulphate and then distilled off to give the crude product, which was purified by column chromatography over silica gel using hexane as eluent.

2-(1-Pyrrolidyl)-4-phenylthiophene (28a):

Low melting solid, yield 0.94g (55%); R_f 0.68 benzene/hexane (5:5).

IR(CCl_4): γ_{max} = 3386, 2960, 1539 cm^{-1}.

^1H NMR (90MHz, CCl_4): δ 1.85-2.18 (m, 4H, CH_2); 3.11-3.45 (m, 4H, NCH_2); 5.99 (brs, 1H, 3'-thienyl); 6.49 (brs, 1H, 5'-thienyl); 7.11-7.67 (m, 5H, ArH).

Anal: Calc. for $C_{14}H_{15}NS$ (229.331): C 73.32; H 6.59; N 6.11.
Found C 73.54; H 6.72; N 6.29%.

2-(1-Piperidyl)-4-phenylthiophene (28b):

Viscous liquid; yield 0.95g (52%); R_f 0.68 benzene/hexane (5:5).

IR(neat): γ_{max}=3208, 2925, 1668, 1442 cm^{-1}.

^1H NMR (90MHz, CCl_4): δ = 1.43-1.91 (m, 6H, CH_2); 3.00-3.29 (m, 4H, NCH_2); 6.36 (brs, 1H, 3'-thienyl); 6.68 (brs, 1H, 5'-thienyl); 7.24-7.58 (m, 5H, ArH).

MS: m/z(%) = 243 (M^+, 62.4)

Anal: Calc. for $C_{15}H_{17}NS$ (243.361): C 74.02; H 7.04; N 5.75.
Found C 74.28; H 7.20; N 5.91%.

2-(1-Morpholinyl)-4-phenylthiophene (28c):

Light yellow viscous liquid; yield 0.96g (52%); R_f 0.19 benzene/hexane (5:5).

IR(neat): γ_{max}=2946, 1684, 1443, 1027 cm^{-1}.

^1H NMR (90MHz, $CDCl_3$): δ = 3.0-3.22 (m, 4H, NCH_2); 3.68-3.98 (m, 4H, OCH_2); 6.44 (d, 1H, J = 3Hz, 3'-thienyl); 6.78 (d, 1H, J = 3Hz, 5'-thienyl); 7.23-7.61 (m, 5H, ArH).

MS: m/z(%) = 245 (M^+, 100).

Anal: Calc. for $C_{14}H_{15}NOS$(245.331): C 68.53; H 6.16; N 5.71.
Found C 68.72; H 6.30; N 5.91%.

2-(N,N-Diethylamino)-4-phenyl thiophene (28d):

Green viscous liquid; yield 0.83g (48%); R_f 0.87 benzene/hexane (5:5).

IR(neat): γ_{max} 2959, 1443, 1257 cm^{-1}.

^1H NMR (90MHz, CCl_4): δ 1.00-1.27 (t, 6H, J = 6Hz, CH_3); 3.11-3.39 (q, 4H, J = 6Hz, CH_2); 6.49 (brs, 1H, 2'-thienyl); 6.75(brs,

1H, 5'-thienyl); 7.20-7.60 (m, 5H, ArH).
Anal: Calc. for $C_{14}H_{17}NS$ (231.351): C 72.68; H 7.41; N 6.05.
Found C 72.73; H 7.68; N 6.25%.

2-(1-Pyrrolidyl)-4-(4-methoxyphenyl) thiophene (28e):
Green colour crystals; yield 1.34g (69%); mp 105-107°C (chloroform-hexane); R_f 0.77 EtoAc/benzene (1:9).
IR(KBr): γ_{max}=3370, 3080, 2940, 1505, 1238 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ=1.90-2.18 (m, 4H, CH_2); 3.09-3.44 (m, 4H, NCH_2); 3.82 (s, 3H, OCH_3); 6.00 (brs, 1H, 3'-thienyl) 6.41 (brs, 1H, 5'-thienyl); 6.88 (d, 2H, J = 9Hz, ArH); 7.52 (d, 2H, J = 9Hz, ArH).
MS : m/z (%) : 259 (M^+, 100).
Anal: Calc. for $C_{15}H_{17}NOS$ (259.361): C 69.46; H 6.61; N 5.40.
Found C 69.52; H 6.78; N 5.57%.

2-(1-Pyrrolidyl-3,4-dihydronaphtho[2,1-c] thiophene (28f):
Low melting solid; yield 0.99g (52%); R_f 5.5 benzene/hexane (5:5).
IR(neat) : γ_{max} = 2938, 1616, 1558, 1216 cm^{-1}.
^1H NMR (90MHz, $CDCl_3$): δ = 1.87-2.20 (m, 4H, CH_2); 2.88 (s, 4H, CH_2); 3.13-3.42 (m, 4H, NCH_2); 6.93 (s, 1H, 5'-thienyl); 7.17-8.21 (m, 4H, ArH).
Anal: Calc. for $C_{16}H_{17}NS$ (255.371): C 75.25; H 6.71; N 5.48.
Found C 75.44; H 6.87; N 5.67%.

2-(1-Piperidyl-3,4-dihydronaphtho[2,1-c] thiophene (28g):
Low melting solid; yield 1.43g (0.71%); R_f 0.67 benzene/hexane (5:5).
IR(neat): γ_{max} = 3345, 2926, 1501, 1213 cm^{-1}.

^{1}H NMR (90MHz, CCl_4): δ = 1.42-1.85 (m, 6H, CH_2); 2.30 (brs, 2H, CH_2); 2.93 (brs, 2H, CH_2); 2.63-2.98 (m, 4H, NCH_2); 6.94 (s, 1H, 5'-thienyl); 7.04-7.36 (m, 3H, ArH); 7.43-7.63 (m, 1H, ArH).
MS: m/z(%) = 269 (M^+,100).
Anal: Calc. for $C_{17}H_{19}SN$ (269.391): C 75.79; H 7.11; N 5.20.
Found C 75.89; H 7.32; N 5.42%.

General procedure for the preparation of dimethyl N-aroyl carbimido dithioates (34a-c):

A mixture of amide (0.01 mol), sodium hydride (1g, 50% dispersion in oil; 0.02 mol), and tetrahedrofuran (THF) 40 ml was stirred at -10 to 10°C for 0.5 to 1 h, and then carbon disulphide (2.5g, 0.033 mmol) was added. After an additional 0.5 to 1 hr stirring, a solution of methyl iodide (4.5g, 0.032 mmol) in 10 ml THF was added and the mixture was stirred at -10 to 0°C for 3h. Ice and water (100g) are added and aqueous solution was extracted with benzene (2x30 ml). The benzene extract was dried with sodium sulfate after removal of solvent. The yellow solid product was collected and recrystallized. The yellow oil was purified by column chromatrography on silicagel. (Ethylacetate/benzene 2:8 as eluent).

General procedure for the preparation of 2-methylthio-4-aryl thiozole (35a-c)

To a chilled (0°C) solution of 1.21g (1.68 ml, 12 mmol) of diisopropyl amine in 10 ml of dry tetrahydrofuran (THF) under dry argon was added 10 mmol of n-BuLi in ether. To the resulting solution of Lithium diisopropylamide (10 mmol) under

dry argon at -78°C was added 75 mmol of dimethyl N-aroyl carbimidodithioate. The resulting reaction mixture was stirred for 30-45 min (-78°C) (monitored by tlc). Quenching with aqueous saturated ammonium chloride solution (100 ml), and extracted with chloroform (3x25 ml). The combined extracts were washed with water (3x25 ml) dried (sodium sulphate) and then evaporated to give the crude product, which was purified by column chromatography over silicagel using hexane as eluent.

2-Methylthio-4-phenyl thiazole (35a):

Colourless viscous liquid; yield 1.15g (74%); R_f 0.86 (benzene).
IR(neat): γ_{max} = 1419, 1035 cm^{-1}.
^1H NMR (90MHz, CCl_4): δ= 2.65 (s, 3H, SCH_3); 7.19 (s, 1H 5'-thiazolo); 7.20-7.38 (m, 3H, ArH); 7.81-7.94 (m, 2H, ArH).
Anal: Calc. for $C_{10}H_9NS_2$ (207.299): 57.93; H 4.38; N 6.76.
Found C 59.82; H 4.23; N 6.57%.

2-Methylthio-4-(4-methylphenyl)thiazole (35b):

Light yellow oily liquid; yield 1.29g (68%); R_f 0.76 (benzene).
IR(neat): γ_{max} = 3003, 2914, 1475, 1033 cm^{-1}.
^1H NMR (90MHz, CCl_4): δ = 2.38 (s, 3H, CH_3); 2.74 (s, 3H, SCH_3); 7.19 (d, 2H, J = 9Hz, ArH); 7.24 (s, 1H, 5'-thiazolo); 7.80 (d, 2H, J = 9Hz, ArH).
Anal: Calc. for $C_{11}H_{11}S_2NS_2$ (221.327): C 59.69; H 5.01; N 6.33.
Found C 59.79; H 5.28; N 6.49%.

2-Methylthio-4-(2-chlorophenyl)thiazole (35c):

Light brown liquid; yield 1.28g (70.5%); R_f 0.69 (benzene).
IR(neat): γ_{max}= 3433, 2988, 1423 cm^{-1}.

^{1}H NMR (90MHz, $CDCl_3$): δ = 2.72 (s, 3H, SCH_3); 7.27-7.63 (m, 3H, ArH); 7.78 (s, 1H, 5'-thiazolo); 8.02-8.20 (m, 1H, ArH).

Anal: Calc. for $C_{10}H_8NS_2ClNS_2$ (241.744): C 49.68; H 3.33; N 5.79.

Found C 49.79; H 3.52; N 5.91%.

V.5 *References and Notes*

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