SYNTHETIC STUDIES ON ∝-OXOKETENE DITHIOACETALS

(ABSTRACT)

BY

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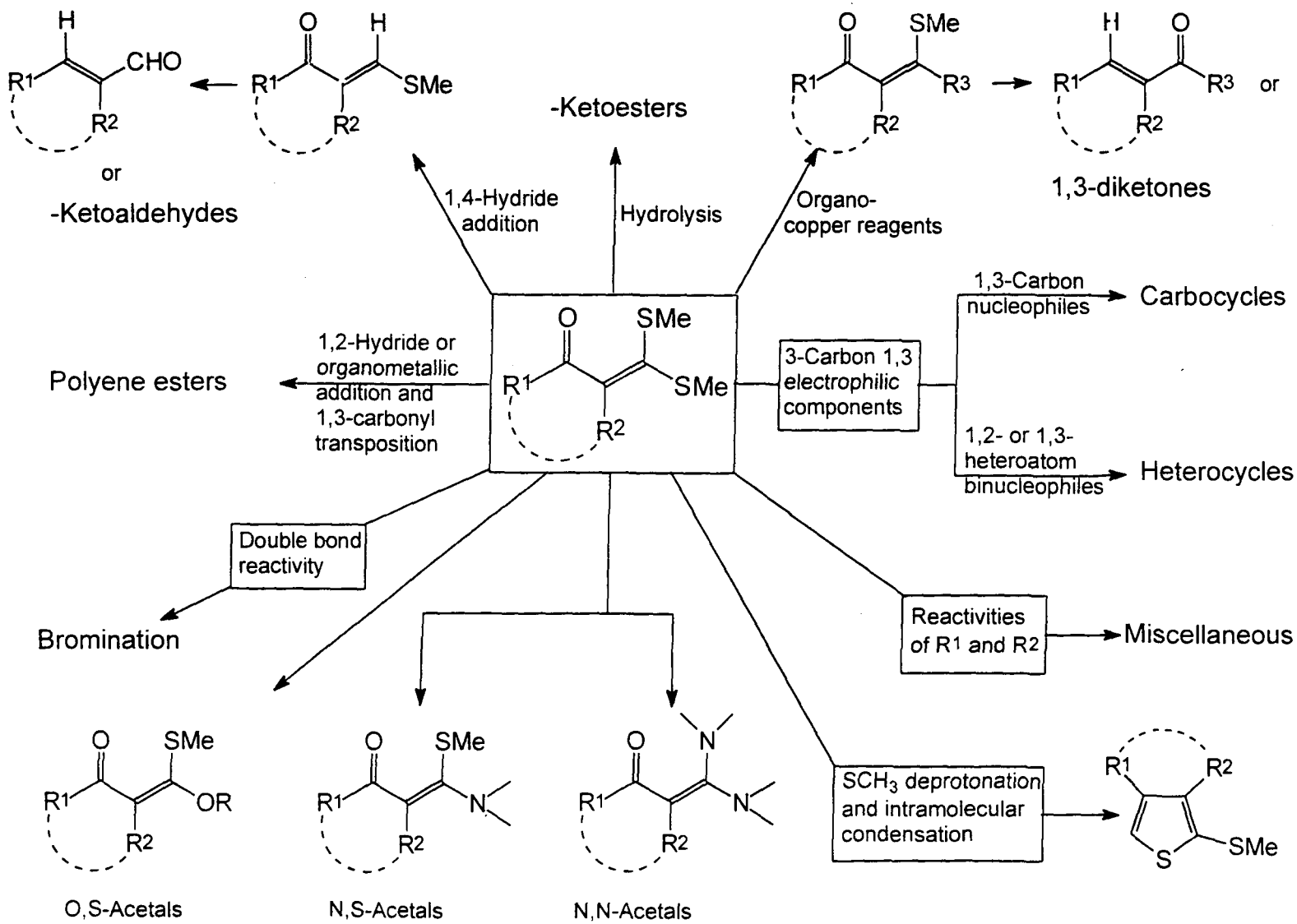
α-Oxoketene dithioacetals[1] are emerging as intermediates of choice for the synthesis of various carbocycles and hetrocycles. (Scheme-1). Their reactivity pattern and their importance is brought out in Chapter-I.

Preparation and Synthetic applications of 4,4-Bis(methylthio)-1,1, Dimethoxy-3-buten-3-one. Reaction with hydrogen hydrazinamine, Simmons-Smith reagent, guanidine, thiourea and cyano acetamide- A versatile new synthon for the synthesis of hetero cyclic aldehydes acetals and aldehydes.

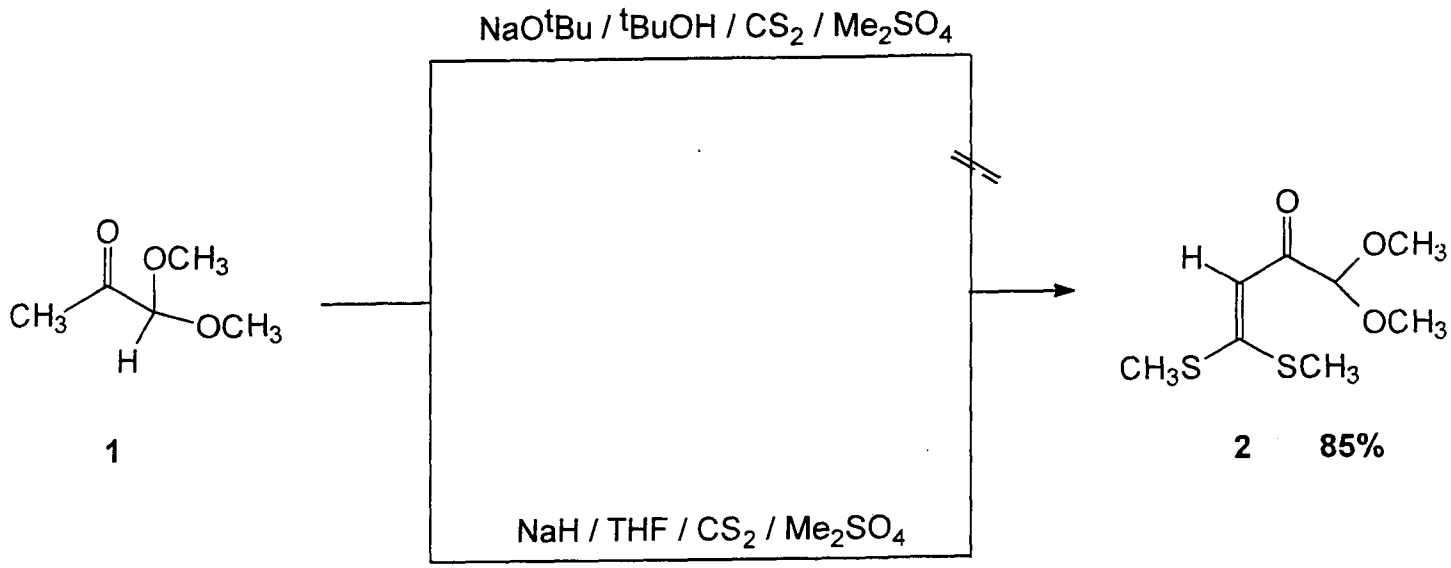
The α-oxoketene dithioacetals undergo regiospecific reactions with 2- atom binucleophiles and 3-atom binucleophiles depending on the nature of the nucleophilic terminals on both ends, without resulting in the product isomers. Therefore it was considered of interest to prepare a new α-oxoketen dithioacetal with a masked aldehyde as a substituent, so that its reaction with various nucleophiles would result in the synthesis of various heterocyclic aldehydes. This was indeed achieved with the preparation of α- oxoketene dithioacetal from pyruvaldehyde dimethyl acetal, namely 4,4- Bis(methyl thio)-1,1-Dimethoxy-3-buten-3-


-Ketoaldehydes
-Ketoesters
1,3-diketones
1,4-Hydride addition
Hydrolysis
Organo-copper reagents
1,2-Hydride or organometallic addition and 1,3-carbonyl transposition
Polyene esters
3-Carbon 1,3 electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
Double bond reactivity
Bromination
Reactivities of R1 and R2
Miscellaneous
SCH3 deprotonation and intramolecular condensation
O,S-Acetals
N,S-Acetals
N,N-Acetals

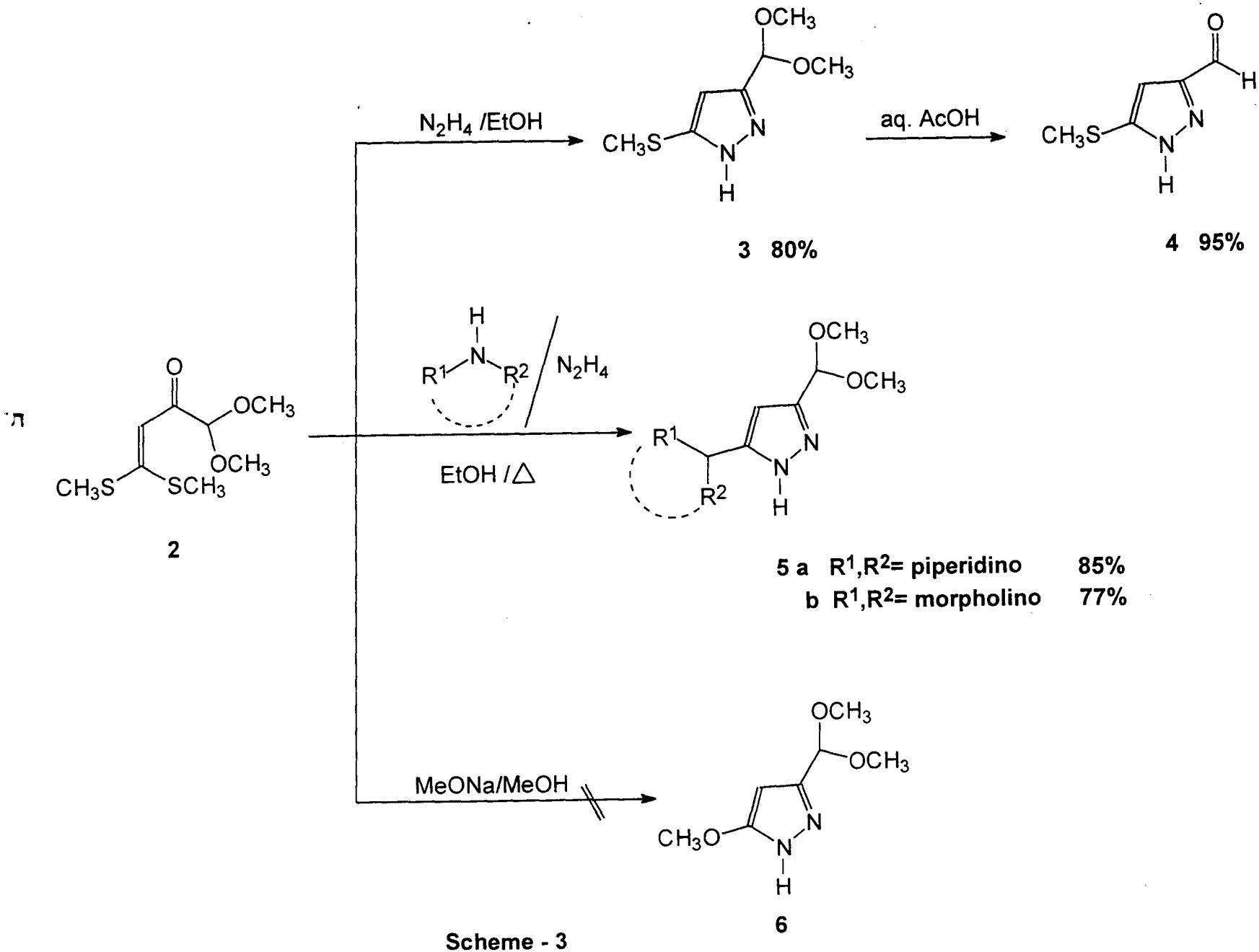
Scheme 1

one **2** in 85% yield (Scheme-2). Its reaction with hydrazine in ethanol at pH =7 led to the formation of 3(5)-dimethoxymethyl-5(3)-methylthio pyrazole **3** in 85% yield (Scheme-3). The aldehyde **4** was liberated in 95% yield from this acetal on treatment with aqueous acetic acid . Similarly the 2- amino -4-dimethoxymethyl pyrazoles **5a,b** were prepared in 77% and 85% yields respectively, by pretreating **2** with amines and then adding N_2H_4 in portions.

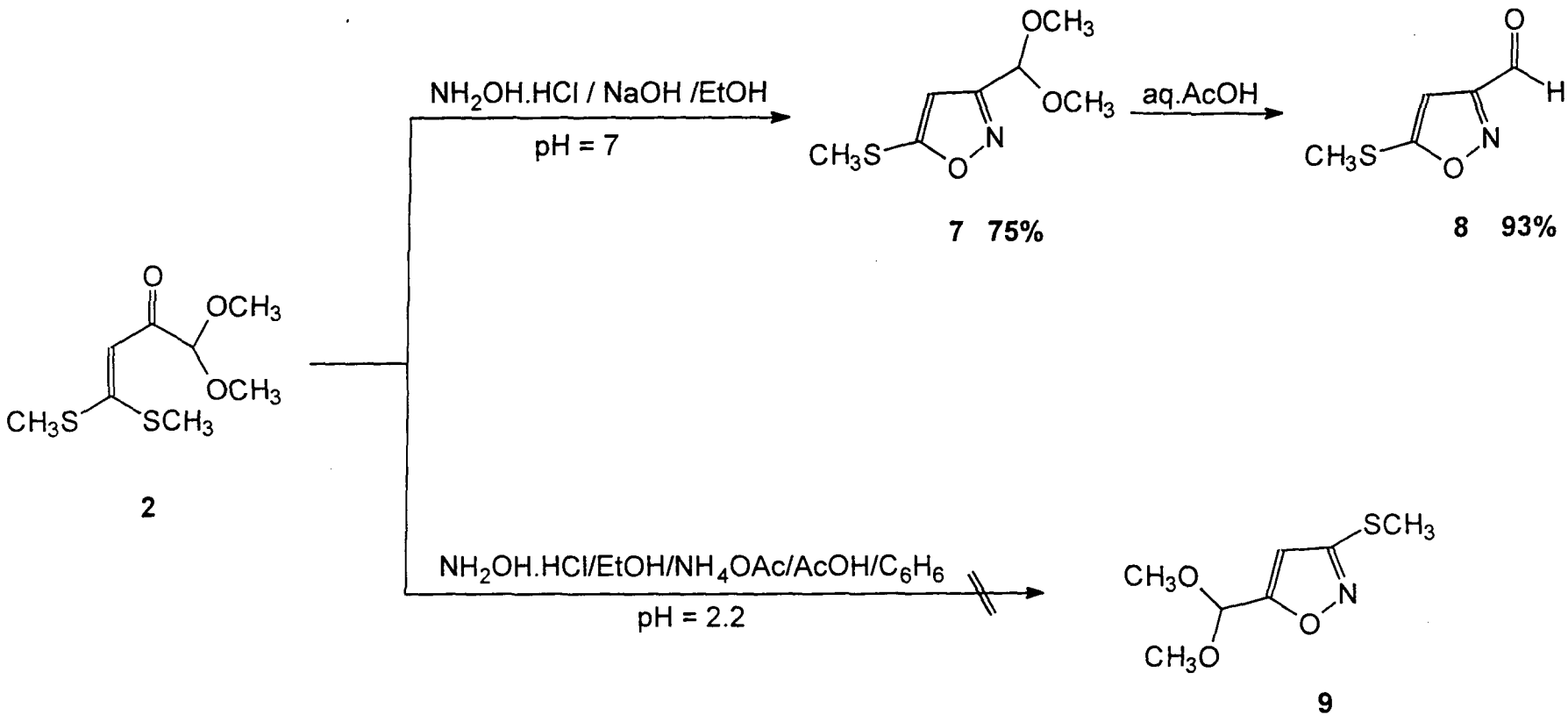
Similarly the reaction of **2** with NH_2OH in ethanol resulted in the 2-methylthio-4-dimethoxy methyl isoxazole **7** in 75% yield (Scheme-4). Its aldehyde **8** was liberated on acid hydrolysis in 93% yield. 2-Methylthio -thiophene -3-aldehyde **10** was prepared in 65% yield by reaction with Simmons-Smith reagent (Scheme-5). 2-amino/mercapto-6-dimethoxymethyl-6-Pyrimidines **12a -d** were prepared in 56-65% yields by the reaction of **2** with guanidine **11a** and thiourea **12b** (Scheme-6). 3-cyano-6-dimethoxymethyl-4-methylthio-2(1H) pyridone **14** was synthesised in 67% yield using **2** and the sodio derivative of cyano acetamide **13** (Scheme-7).


NaO^{t}Bu / ^{t}BuOH / CS_2 / Me_2SO_4
NaH / THF / CS_2 / Me_2SO_4
O
OCH_3
CH_3
OCH_3
H
1
O
H
OCH_3
OCH_3
CH_3S
SCH_3
2
85%

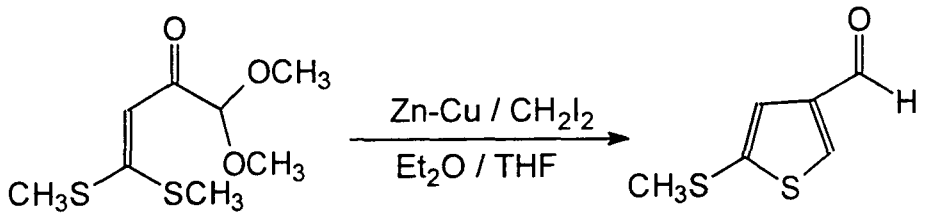
Scheme - 2


N2H4 /EtOH
aq. AcOH
3 80%
4 95%
2
EtOH /△
5 a R1,R2= piperidino 85%
b R1,R2= morpholino 77%
MeONa/MeOH
6

Scheme - 3


NH2OH.HCl / NaOH /EtOH
pH = 7
aq.AcOH
7 75%
8 93%
2
NH2OH.HCl/EtOH/NH4OAc/AcOH/C6H6
pH = 2.2
9

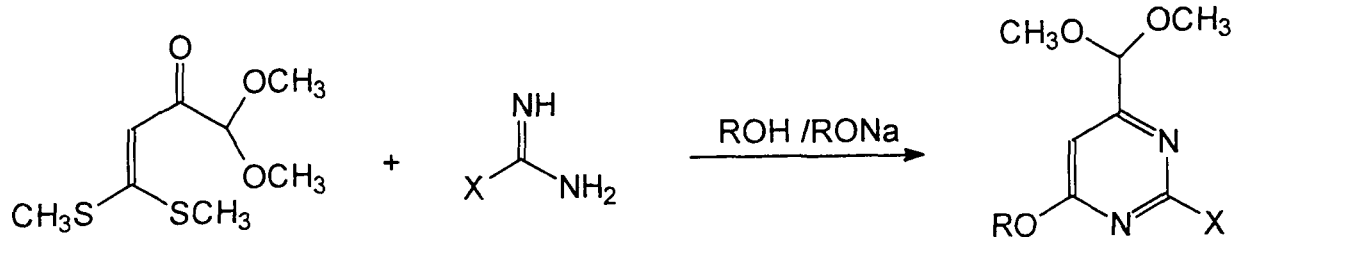
Scheme - 4



2

10 65%

Scheme - 5

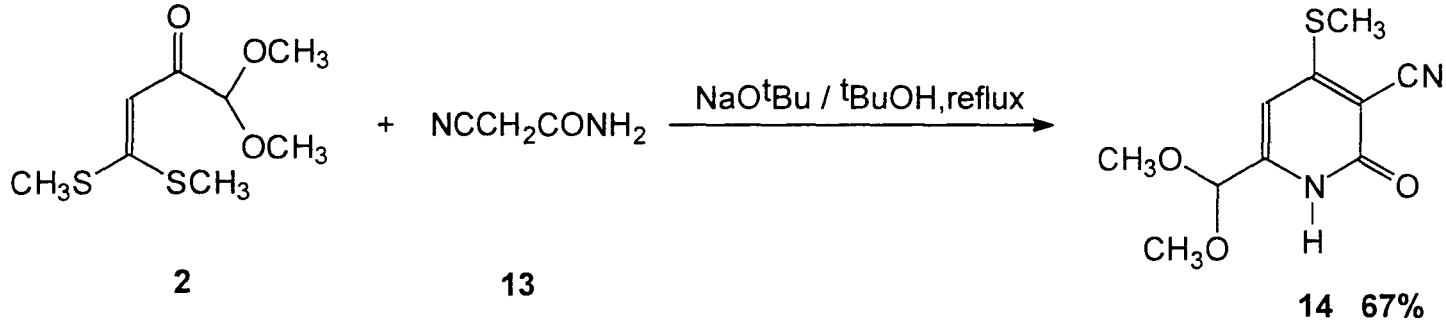


2

11a X=NH_2
b X=SH

12a X=NH_2,R=Me 65%
b X=NH_2,R=Et 60%
c X=SH, R=Me 61%
d X=SH, R=Et 56%

Scheme-6



2 **13** **14 67%**

Scheme -7

It must be mentioned here that the most of the above mentioned aldehydes[2-11] are not accessible by routine methods of formylation and therefore their preparation acquires considerable synthetic importance.

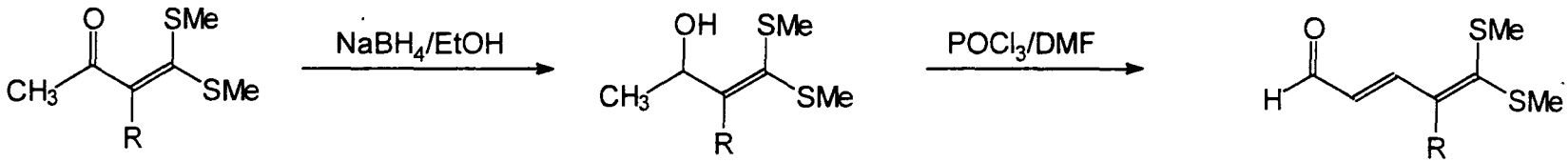
Synthesis of Novel push-Pull Donor- Acceptor Ethylenes and Polyenes: Potential Second Order Non Linear Chromophores.

The molecular non-linear optical respose generally quantified as the first order hyper polarisibility, represented by β, is found in certain type of push-pull ethylenes and polyenes possessing intrinsic dipole moment. These molecules behave like charge transfer complexes providing a source of charge at one end and electron deficiency at the other end and therefore experience a natural propensity for charge transfer through electron redistribution over the entire conjucation. The non-linear optical property displayed by these molecules[12-17] can find application in opto- electronics, telecommunication, optical data storage, optical information processing, laster scanning control functions and in general in all integrated optical tehcnology. Chemistry, at present is advanced enough to design and construct many polymers and polyenes with specific properties and consequently a large volume of synthetic work is being devoted for the construction of such molecules. In our

laboratory, we have utilized α-oxoketene dithioacetals for the synthesis of polyene aldehydes and polyenes[18]. It was therefore contemplated that these polyenes, if connected to strong donor-accetor terminals, their ability as NLO chromophores will be unravelled and would lead to more information on molecular design of these push-pull polyenes.

This goal was achieved by condensing the polyene aldehydes **17a,b** **20** and **23** with various active methylene compounds like diethyl malonate, ethyl cyanoacetate, malanonitrile, p-nitro phenylcyanide, nitromethane, and thiophene -2- acetonitrile and barbitiuric acid. (Schemes 10-13, Tables- 1-3). The conditions for these condensations and the yields (good to excellent) of the polyenes are presented in the above mentioned schemes and tables. The UV- Vis spectra of all these compounds were than taken to assess their charge transfer properties, while the electrical properties (ground dipole moment D and β) of some of them so measured are promising for NLO activity.

Rearrangement studies of heteroaryl substituted cyclopropyl ketones from α- oxoketene dithioacetals: A Novel tandem

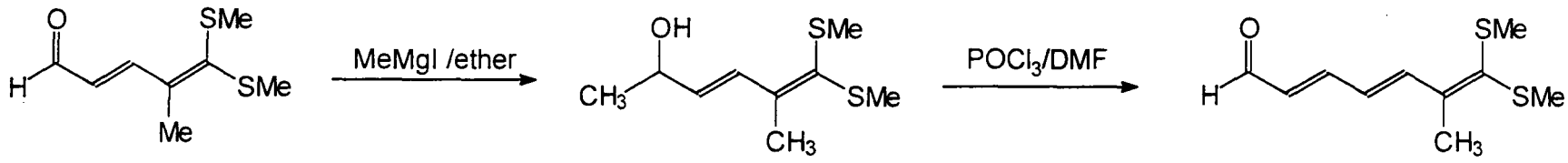


15 a R = H
b R = CH_3

16 a,b

17a R = H 59%
b R =Me 70%

Scheme -8

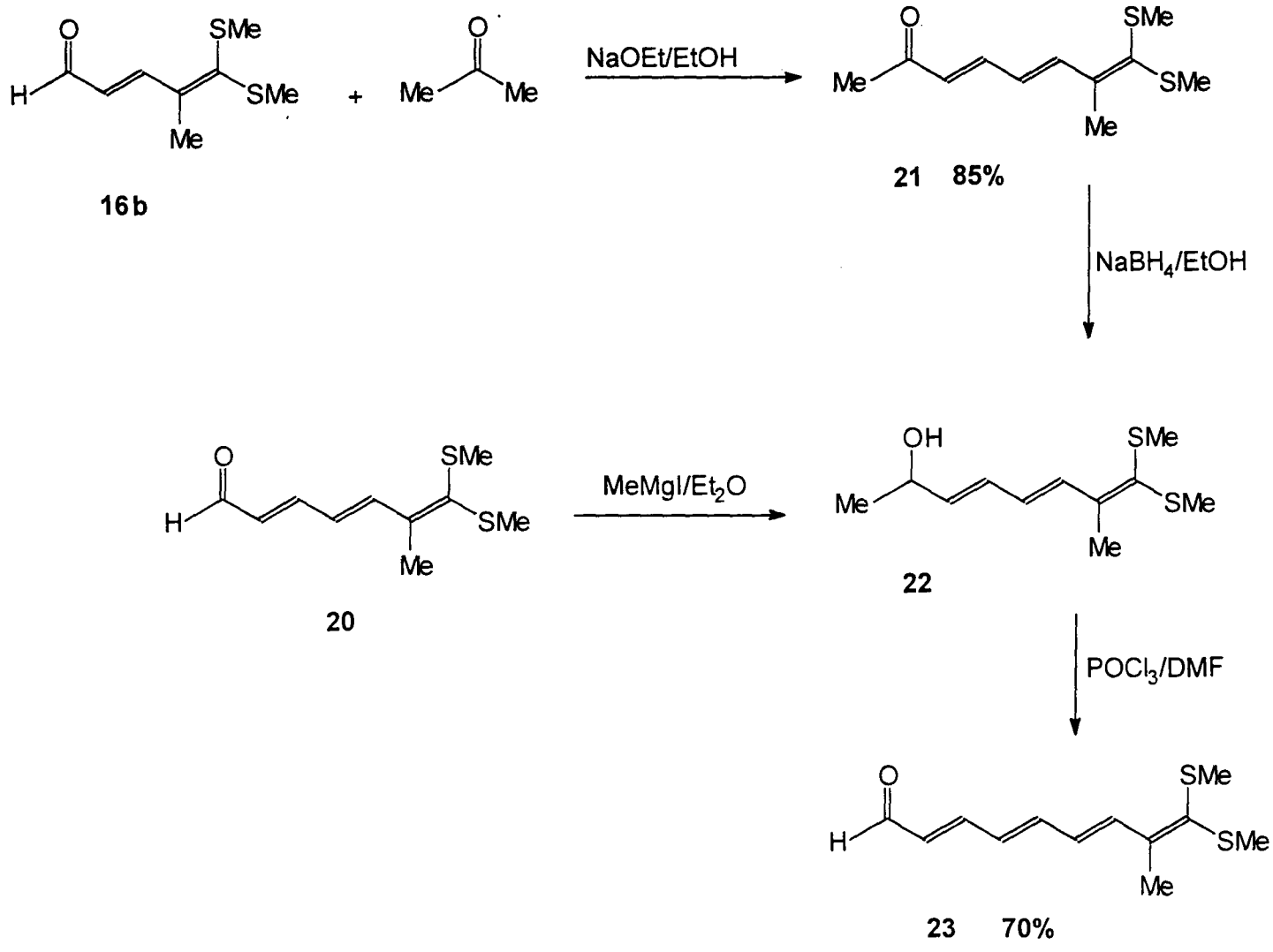


18

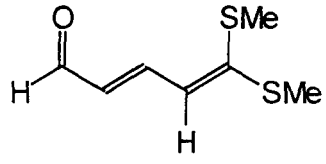
19

20 80%

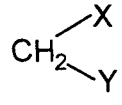
Scheme - 9

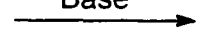

O
SMe
H
SMe
Me
16b
+
O
Me
Me
NaOEt/EtOH
O
SMe
Me
SMe
Me
21 85%
NaBH4/EtOH
O
SMe
H
SMe
Me
20
MeMgI/Et2O
OH
SMe
Me
SMe
Me
22
POCl3/DMF
O
SMe
H
SMe
Me
23 70%

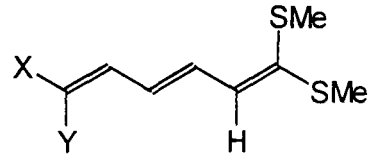
Scheme - 9



17 a







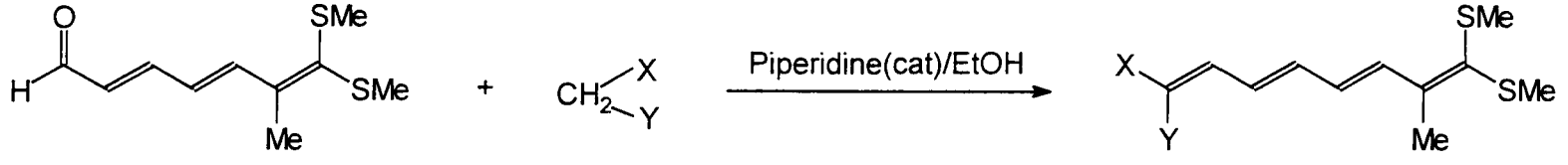
24 a X = Y = COOEt
b X= CN Y= COOEt
c X= Y = CN
d X= CN Y = p-$NO_2C_6H_4$
e X= CN Y = 2- thienyl

Scheme - 10

17 b

24 f X = Y = COOEt
g X = CN Y = COOEt
h X = Y = CN
i X = CN Y = p-$NO_2C_6H_4$
j X = CN Y = 2-thienyl
k X = H Y = NO_2
l X,Y = N,N, dimethyl -5-barbituryl

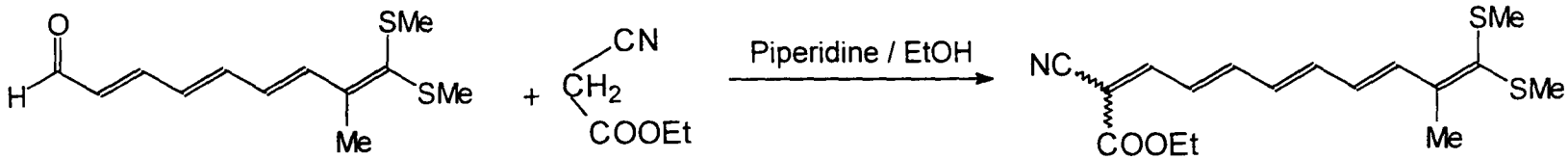
Scheme - 11



20

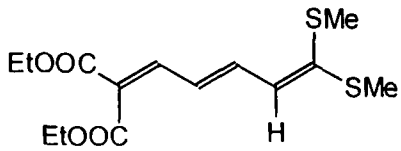
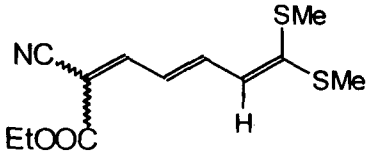
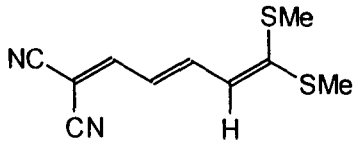
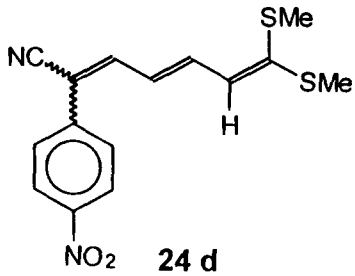
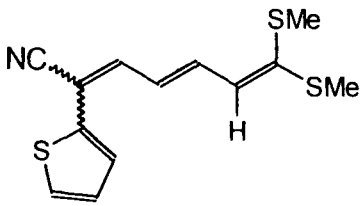
25 a X = CN Y = COOEt
b X = CN Y = p-$NO_2C_6H_4$

Scheme - 12



23 **26**

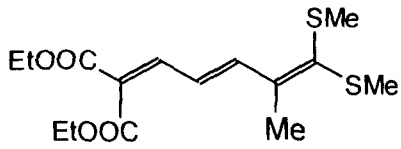
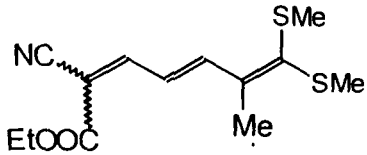
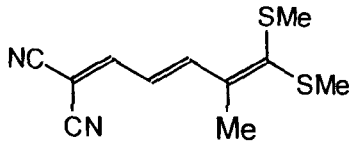
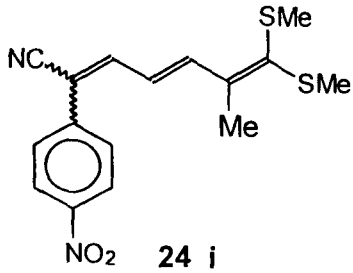
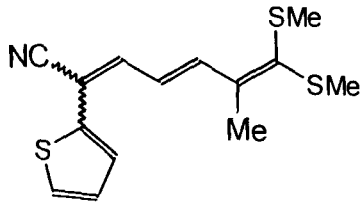
Scheme - 13

S.No	PRODUCT	BASE	YIELD (%)	
1	 24 a	i	90	1.32 (375)
2	 24 b	i	87	6.65 (409)
3	 24 c	i	80	6.57 (411)
4	 24 d	i	90	3.34 (430)
5	 24 e	ii	65	5.40 (411)

Base : i - Piperidine(cat) / EtOH

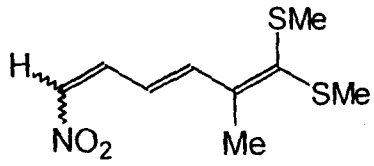
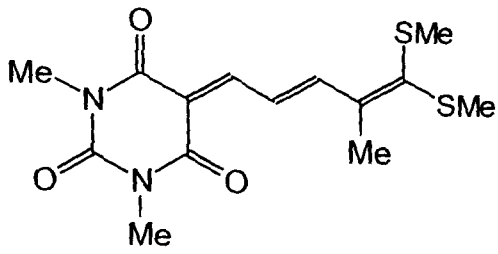
ii - K_2CO_3 / Acetone

Table - 1

S.No	PRODUCT	BASE	YIELD (%)	
1	 24 f	i	91	2.22 (374)
2	 24 g	i	88	2.12 (409)
3	 24 h	i	82	4.55 (417)
4	 24 i	i	87	3.02 (430)
5	 24 j	ii	70	4.57 (410)

Base : i - Piperidine(cat) / EtOH
ii - K_2CO_3 / Acetone

Table - 2

S.No	PRODUCT	BASE	YIELD(%)	
6	 24 k	iii	65	1.88 (364)
7	 24 l	iii	73	2.50 (390)

Base : iii NaOEt /EtOH

Table - 2 (contd)

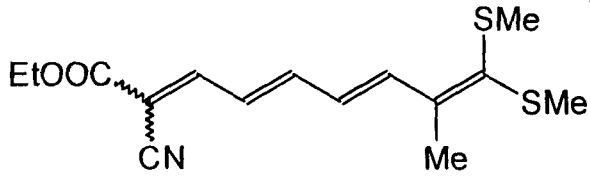
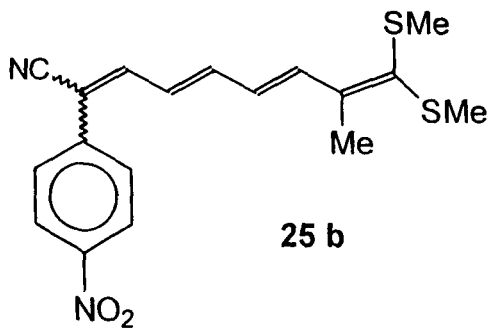
S.No	PRODUCT	YIELD (%)	
1	 25 a	73	3.83 (432)
2	 25 b	78	2.69 (445)

Table - 3

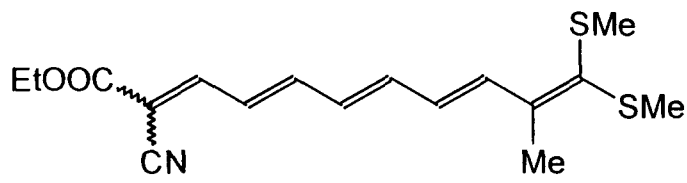
S.No	PRODUCT	YIELD (%)	
1	 26 a	58	4.22 (443)

Table - 4

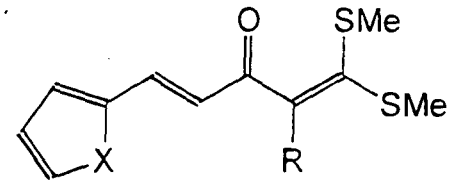
carbocationic approach for the synthesis of hetero aryl fused diquinane systems.

The chemistry of cyclo pentanoids[18-23] is receiving much attention in recent years since several terpenoids, isolated from natural sources, contain this carbocyclic frame work. Several synthetic approaches involving inter and intra-molecular rearrangements have been developepd for this purpose. The propensity of the cyclization process of γ-halo ketones and their corresponding β keto esters to lead to alkylidine tetrahydrofurans rather than cyclopentanoids, has made the above mentioned approaches even more important.

In our laboratory, the acid- catalysed rearrangement of α-oxoketene dithioacetals have been utilised for the construction of various cyclopentanoids[24-26,28-32]. This novel cyclopenta-annulation strategy was further enhanced to synthesize cyclopenta[a] indenes in good yields involving a novel tandem carbocationic cyclization approach. It was therefore considered of interest to extend this strategy to synthesise heteoaryl fused diquinane frame work. The successful accomplishment of this aim is the content of the fourth chapter.

The required furo, thieno and pyrrolo substituted enones **30-32 a,b** (Scheme-14) were chosen as starting materials. The enones **30,31** underwent smooth cyclopropantion in the presence of dimethyl oxosulphonium methylide generated under phase transfer conditions[27] (Scheme-15). Both the cyclopropyl ketones **33a**(X=O) and **34a**(X=S) (Scheme-16) yielded the heteroaryl substituted cyclopentanone ketene dithioacetals **35, 36** on treatment with $SnCl_4$ in nitromethane at O°C. Both the α- methyl substituted cyclopropyl ketones **33b**(X=O) and **34b(X=S)** yielded the corresponding hetero aryl fused bicyclo octanes **37** and **41** in good yields among other products under the above mentioned conditions. (Schemes-17,18). The pyrole substituted enones **32a,b** however underwent a novel lone pair assisted cyclopropyl ring opening to yield cyclopentanone derivatives **44** and **45** under the conditions of cyclopropanations itself. (Scheme-19,20). Similarly the enones **46 a,b** derived from N- Methyl Indole-3- aldehyde **46** underwent cyclopenta- annulation to yield cyclopentanones **49** and **50** (Scheme 22,23) under condtions of cyclopropanation.

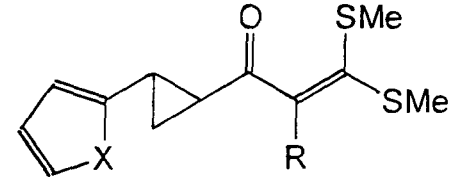
Thus these results constitute a successful extension of our cyclopenta-annulation protocol to the synthesis of hetero aryl fused



30,31 a,b

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ /NaOH soln(50%)

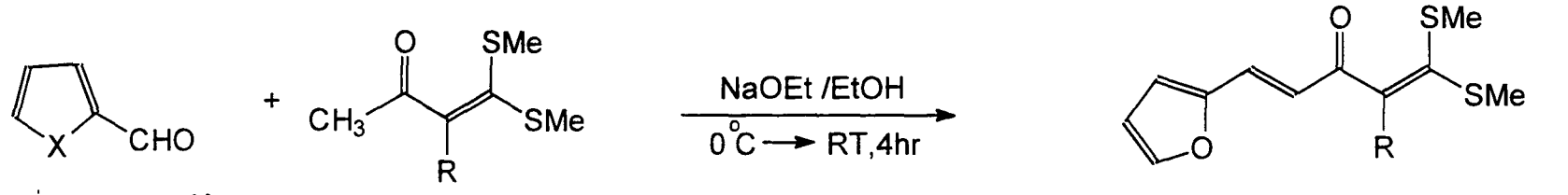
CH_2Cl_2 /$Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$ /40 °C



33 X = O a R = H 90%
b R = CH_3 95%

34 X = S a R = H 92%
b R = S 96%

Scheme - 14



27 X = O a R = H
b R = CH_3

28 X = S a R = H
b R = CH_3

29 X = N-Me a R = H
b R = CH_3

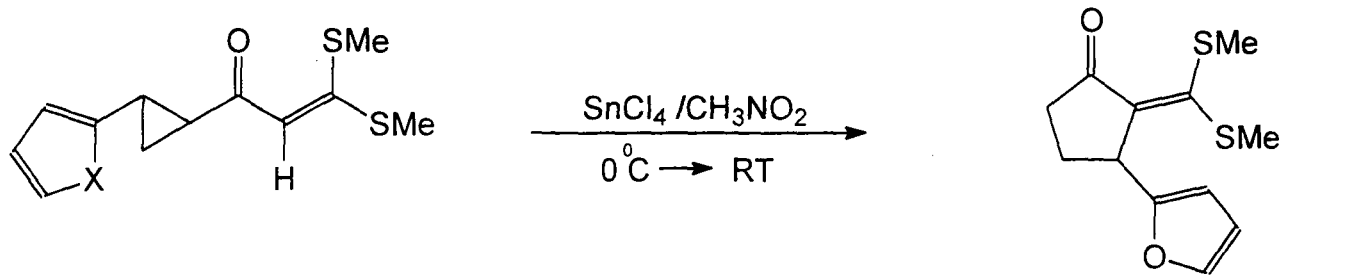
16 a R = H
b R = CH_3

30 X = O a R = H 65%
b R = CH_3 75%

31 X = S a R = H 67%
b R = CH_3 73%

32 X = N-Me a R = H 67%
b R = CH_3 81%

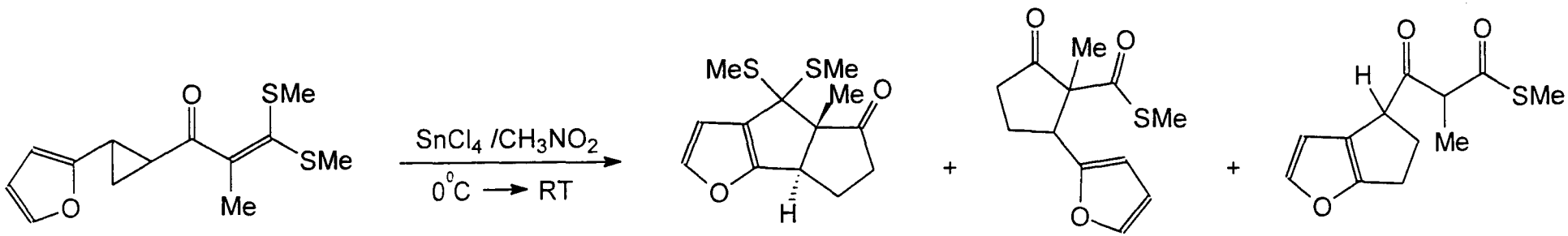
Scheme - 15



33a X = O
34b X = S

35 X = O 75%
36 X = S 68%

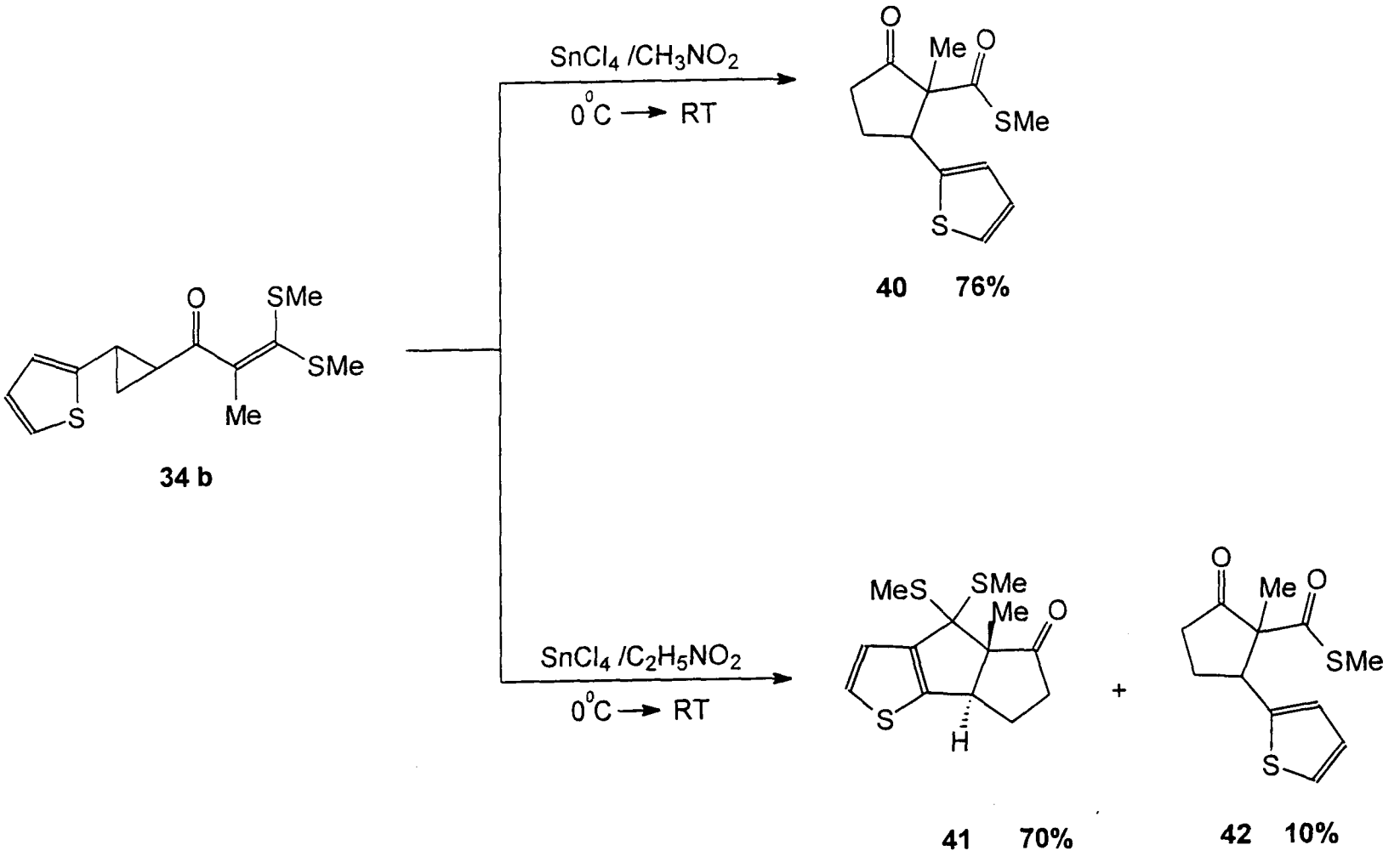
Scheme - 16



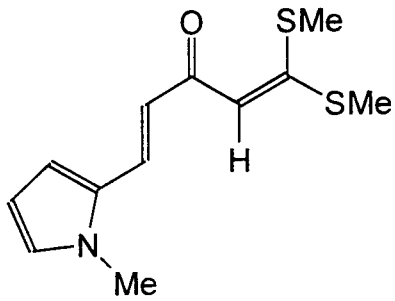
28

33 b **37 70%** **38 15%** **39 5%**

Scheme - 17


SnCl4 /CH3NO2
0°C → RT
Me
O
SMe
S
40 76%
O
SMe
SMe
Me
S
34 b
SnCl4 /C2H5NO2
0°C → RT
MeS
SMe
Me
O
S
H
41 70%
+
O
Me
O
SMe
S
42 10%

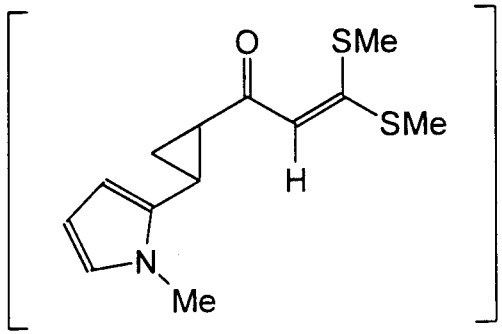
Scheme-18



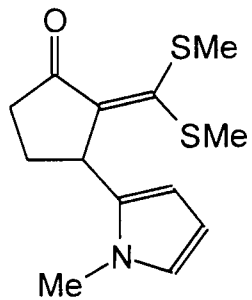
32 a

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ / NaOH soln (50%)

CH_2Cl_2 / $Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$ /40° C

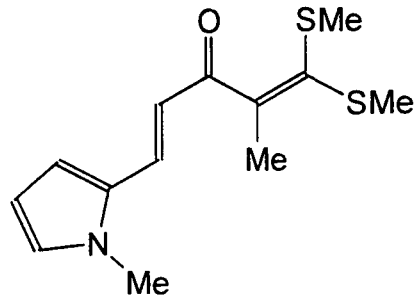


43 a



44 69%

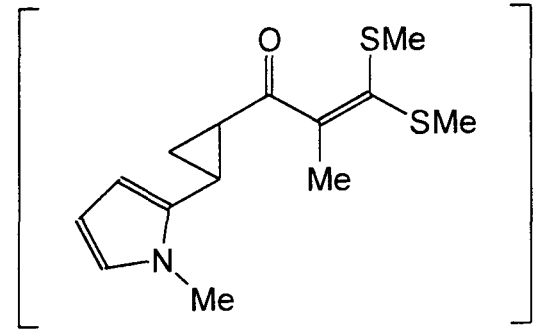
Scheme - 19



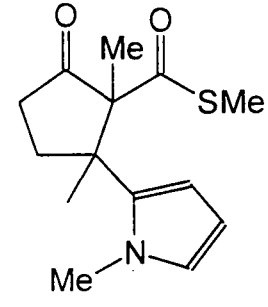
32 b

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ / NaOH soln (50%)

CH_2Cl_2/ $Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$ / 40 °C

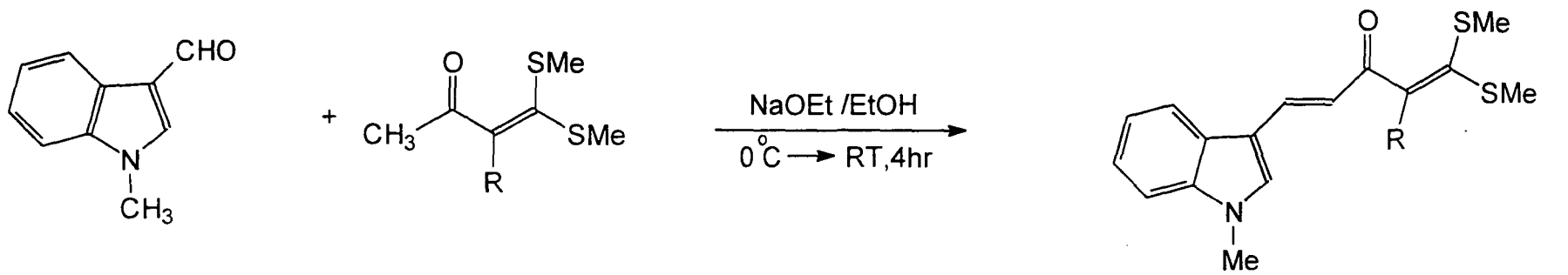


43 b



45 73%

Scheme - 20

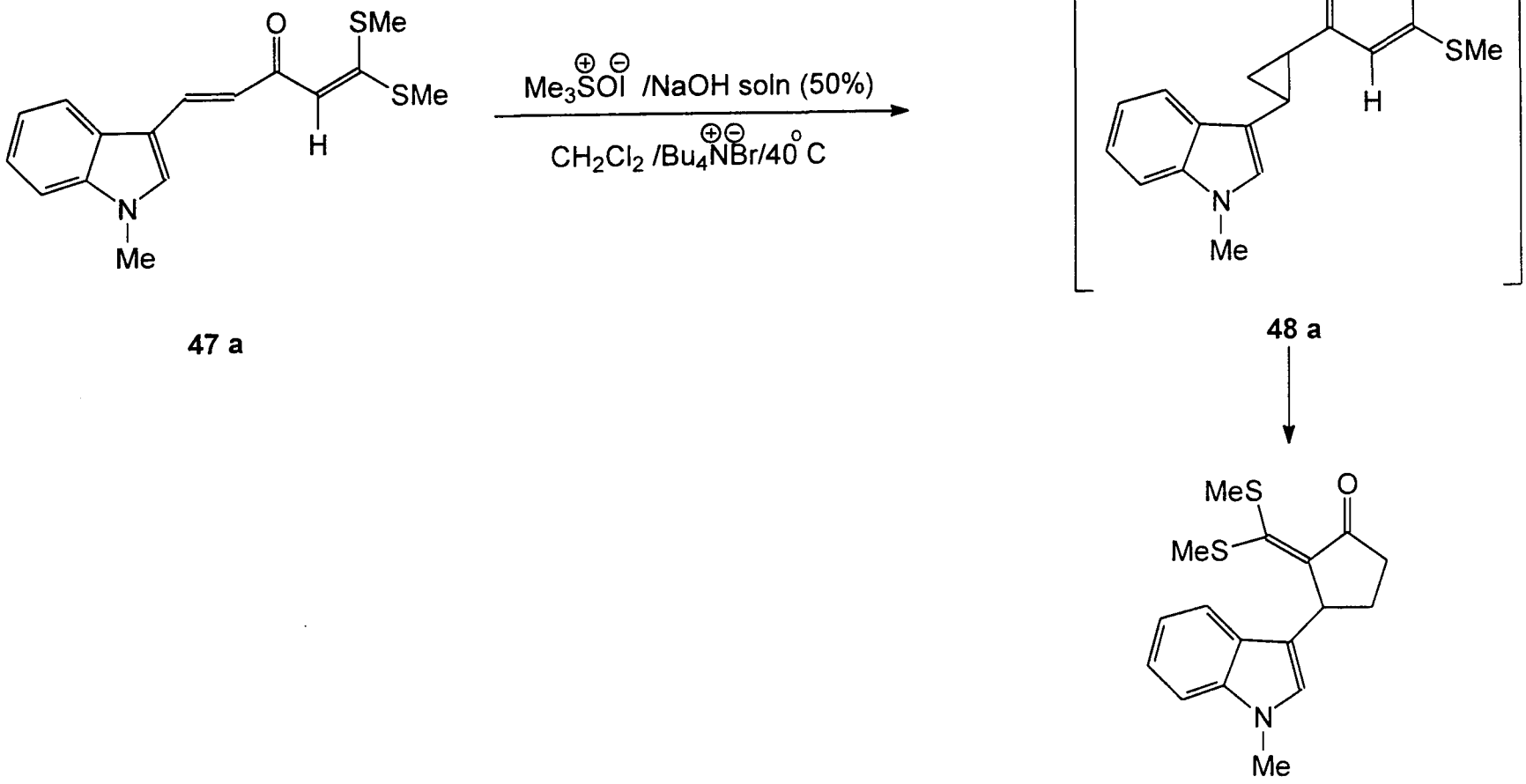


46

16 a R = H
b R = CH_3

47 a R = H 61%
b R = CH_3 81%

Scheme - 21

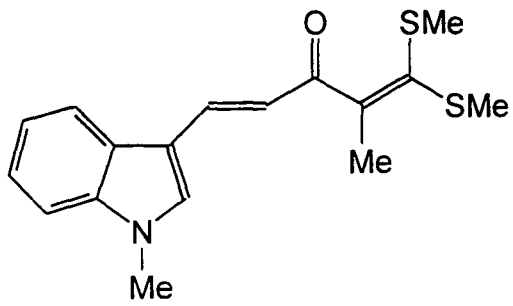


47 a

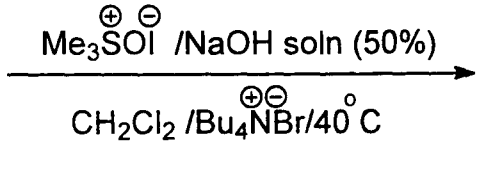
48 a

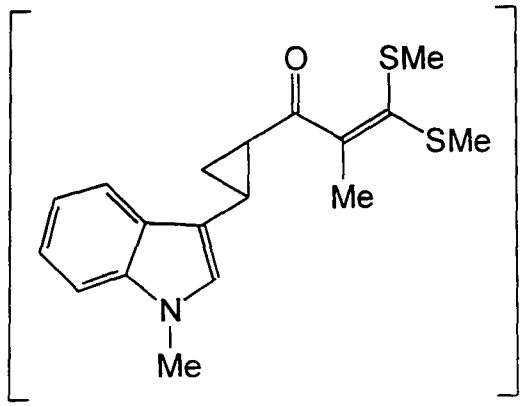
49 63%

Scheme - 22

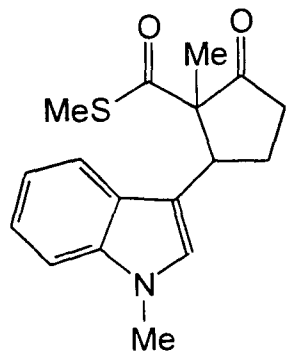


47 b





48 b



50 76%

Scheme - 23

bicyclo octanes. This also includes examples of a novel lone pair assisted cyclopenta-annulation.

REFERENCES :

1) For a review see.

(a) Dieter, R.K. Tetrahedron. **1986**, *42*, 3029.

(b) Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron*. **1990**, *46*, 5423.

(c) Kolb, M. *Synthesis*. **1990**, 171.

2) Bredereck, H.; Sell, R.; Effenberger, F.; *Chem. Ber*. **1964**, 3467.

3) Huttel, R.; *Chem. Ber*., **1941**, *74 B*, 1680.

4) Abdallah, H; Gree, R.; *Tetraahedron Lett*. **1980**, *21*, 2239.

5) Finar, I.L.; Manning, M. *J. Chem. Soc*. **1961**, 2733.

6) Finar, I.L.; Lord, G.H. *J. Chem. Soc*., **1959**, 1819.

7) Yamanaka, H.; Sakamoto, T. *Heterocycles*, **1977**, *7*, 5.

8) Kallury, R.K.M.R.; Devi, P.S.U., *Tetrahedron Lett*. **1977**, *41*, 3655.

9) Caramella, P.; Cereda, E. *Synthesis*, **1971**, 433.

10) Gronowitz. *Arkiv.kemi*, **1955**, *8*, 441.

11) Campaigne, E.; Burgeos, R.C.; McCarthy, W.C. *Org. Synth. Coll. Vol IV*, p 918.

12) Materials for Nonlinear Optics: Chemical Perspective, Ed. S.R. Marder, J.E. Sohn and G.D. Stucky, *ACS Symposium series No. 455, ACS, Washington, DC,* **1991**.

13) Polymers for second-order Nonlinear Optics; G.A. Lindsay, K.D. Singer, Eds., *ACS Symposium Series 601; American Chemical Society; Washington, DC,* **1995**.

14) A.F.Garito ,; A.K.-Y, Jen ,; C.Y.-C. Lee,; L.R. Dalton; Eds., Electrical, Opitcal and Magnetic Properties of Organic Solid State Materials, *Mater. Res. Soc. Symp. Proc.* **1994**,328.

15) P.N. Prasad, D.J. Williams, Introduction to Nonlinear Optical effects in Molecules and Polymers, Wiley, New York. **1991**

16) Organic Materials for Nonlinear Optics, Eds. R.A. Hann, D. Bloor, Royal Society of Chemistry, London, **1989.**

17) Nonlinear Optical properties of Organic Molecules and Crystals, Vol. 1 and 2, Eds. D.S. Chemla, J. Zyss; Academic Press, New York, **1987**.

18a) Synthesis of stilbenes, Polyenes, Polyenes Esters and Aldehydes: B. Myrboh; C.V. Asokan,; H. Ila and H. Junjappa, *Synthesis* **1984**,50.

(b) M.Chandrashekharam; C.V. Asokan; H. Ila, and H. Junjappa, *Tetrahedron Lett.* **1990,** *31*,1766,.

19) Mitra, A. 'The Synthesis of Prostaglandins', John Wiley & Sons, New York, 1977.

20) Comer, F.W.; McCapra, F.; Qureshi, I.H.; Scott, A.I. *Tetrahedron*, **1967**, *23*, 4761.

21) Comer F.W.; Trotter, J.*J. Chem. Soc. B.* **1969,** 11.

22) Brown, N.M.D.; Cowley, D.*J. Alicyclic chemistry*, **1978**, *6*, 144.

23) Ono, M. *Syn. Org. Chem. Japan.* **1981**, 872.

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

25) Deb, B; Ila, H.; Junjappa, H. *J. Chem. Res(S)* **1990**, 356; *J. Chem. Res.(M)* **1990,** 2728.

26) Patro, B.; Deb. B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1992,** *57*, 2257.

27) Merz, A.; Mark, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845.

28) Patro, B.; Deb, B.; Ila, H.; Junjappa, H. *Tetrahedron* **1994**, *50*, 255.

29) Patra, P.K.; Patro B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993,** *34*,3951.

30) Pranab K. Patra.; V. Sriram; Ila, H.; Junjappa, H. *Tetrahedron* **1998**, *54*,531.

31) Patro,B. Ph.D Thesis.North Eastern Hill University

32) Satyanarayana, J.; Rao, M.V.B.; Ila, H.; Junjappa, H.; *Tetrahedron Lett.* **1996**, *37*, 3565.

SYNTHETIC STUDIES ON ∝-OXOKETENE DITHIOACETALS

BY

SRIRAM. V
DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

SUBMITTED
IN FULFILMENT OF THE DEGREE OF
DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

OF

NORTH-EASTERN HILL UNIVERSITY
SHILLONG - 793 003
INDIA

DEDICATED

TO

MY

DEAREST PARENTS

AND

BROTHER

The North-Eastern Hill University
Shillong
August 1999

I, **Sriram. V**, hereby declare that the subject matter of thesis is the record of work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else and that the thesis has not been submitted by me for any research degree in any other University / Institute.

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

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Head
(Prof. M.K. Mahanti)

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Supervisor
(Prof. H. Ila)

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I am indeed fortunate to have good friends who express limitless friendship. During my entire course of study of chemistry, Nana has been a constant source of happiness and a pillar of strength to me. It is with great pleasure I place on record my heartfelt thanks to him. Thanks are also due to Shankar and Balasubramanium (Balaji) for their good wishes and timely encouragement.

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them and mitigated my frustation. His friendship has been the only help available during moments of utter helplessness.

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My sincere thanks for Thomasji and Abijit Roy (Roy da) for typing this thesis with great personal care and attention.

I take this oppurtunity to thank Dr.V.S.V. Prasad, M.B.B.S, Senior Medical Officer, N.E.H.U. Health Centre, for his sound medical advice which helped me to keep good health during my stay in Shillong.

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(SRIRAM.V)
SHILLONG

CONTENTS

PREFACE

A wide variety of carbocycles and heterocycles have been prepared in our laboratory using α- oxoketene dithioacetals during the past two decades. The large pool of active methylene compounds, from which α-oxoketene dithioacetals are made, and their ease of preparation, coupled with their high regioselectivity during reactions with various reagents mark them as highly versatile synthons. The work described in this thesis has been carried out as a part of our ongoing investigations on α-oxoketene dithioacetals and cyclopropyl substituted α-oxoketene dithioacetals.

The thesis is divided into four chapters. The first chapter is in three parts and gives a general introduction to :

a) reactivity pattern of α-oxoketene dithioacetals

b) the field of non-linear optical activity and the role of organic compounds in it.

c) the role of ketene dithioacetals in intra-molecular electrophilic cyclizations

The second chapter elaborates a synthesis of a new acetal substituted α-oxoketene dithioacetals and its successfull application to the preparation of various hetero cyclic aldehyde acetal and aldehydes.

The third chapter involves the synthesis of novel push-pull polyenes as potential candidates for non-linear optically active chromophores. The optical properties of all and electrical properties of some of them are also presented in the chapter.

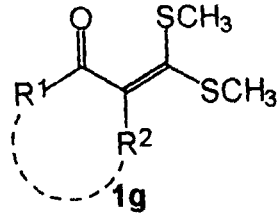
The fourth chapter concernes the logical extension and successful accomplishment of our novel cyclopentaannulation strategy to the synthesis of heteroarylfused diquinane framework from cyclopropyl substituted α-oxoketene dithioacetals.

CHAPTER ONE

INTRODUCTION

1.1 α-OXOKETENE DITHIOACETAL: A VERSATILE SYNTHETIC INTERMEDIATE - A GENERAL INTRODUCTION

α-Oxoketene dithioacetals[1] **1**



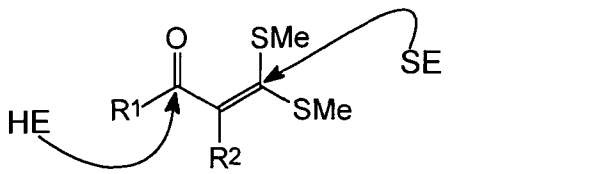
R^1 = alkyl,aryl,heteroaryl
R^2 = alkyl

Figure - 1

belong to the family of polarised ketene dithioacetal and can be easily prepared from the corresponding active methylene compound and carbon disulphide or trithiocarbonate using a suitable base followed by alkylation. They are either crystalline solids or distillable liquids and exhibit a prolonged shelf-life. They are stable at ambient temperature and are reasonably stable to mild acid and bases.

The first synthesis of an α-oxoketene dithioacetal was reported by Kelber et al in 1910[2]. Later Thuillier and co-workers[3] improved their yields and explored their chemistry as organic sulphur intermediates.

By suitable choice of base and conditions, ketenedithioacetals could be made from any active methylene compound[4-8]. Subsequent workers realized their synthetic versatility and explored their reactivity. The results of these efforts have been adequately reviewed[1].



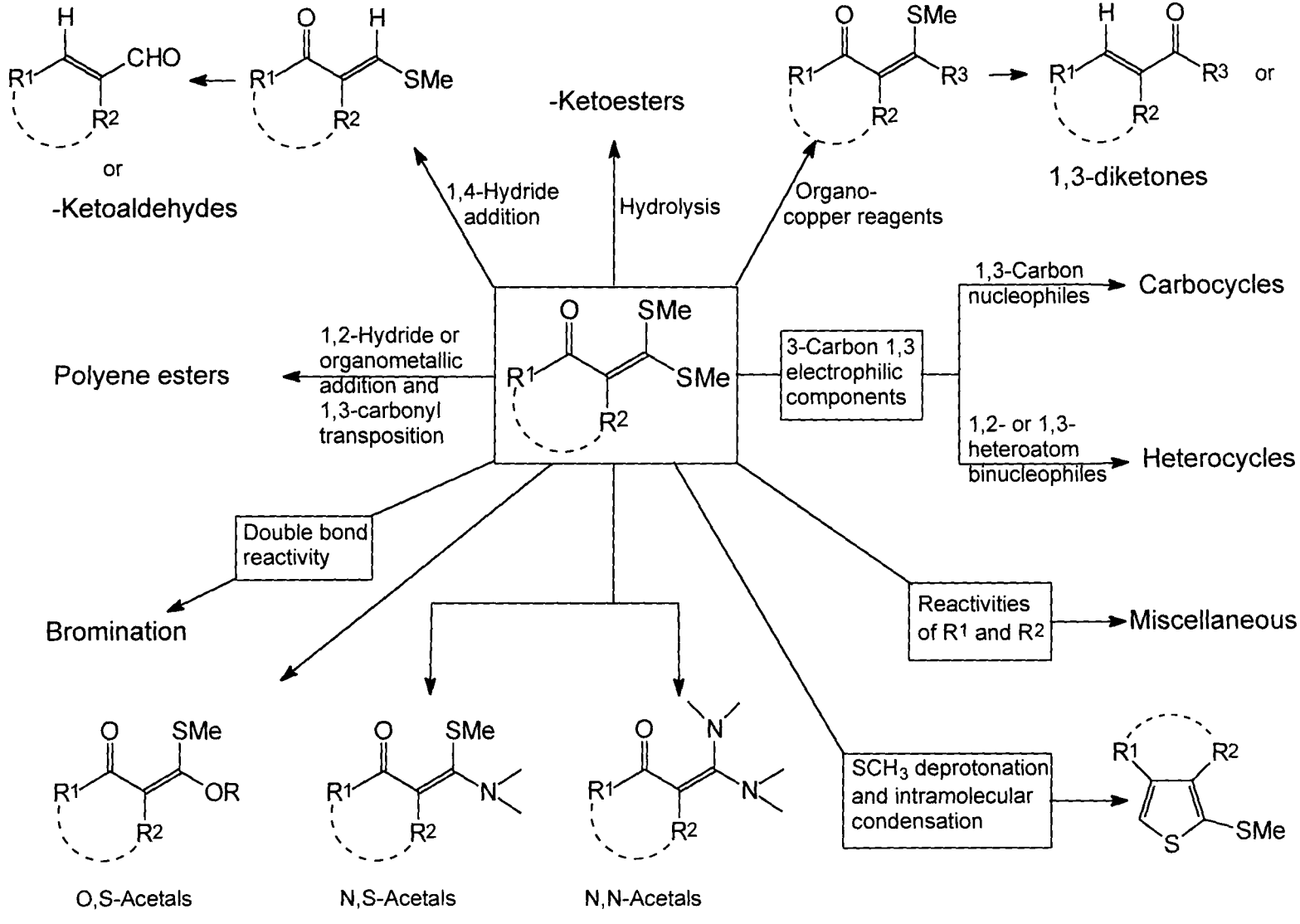
HE- Hard electrophile
SE- Soft electrophile

1

Figure - 2

The α-oxoketenedithioacetals **1** can be considered as a masked β-keto ester, as the ketene dithioacetal moiety can be readily converted to an ester. They may also be viewed as a 3-carbon 1,3 bielectrophilic fragment exhibiting differential electrophilicity. This differential electrophiticity leads to excellent regio and stereo selectivity in various transformations(figure- 2).The reactivity profile of these intermediates is sketched in scheme 1.

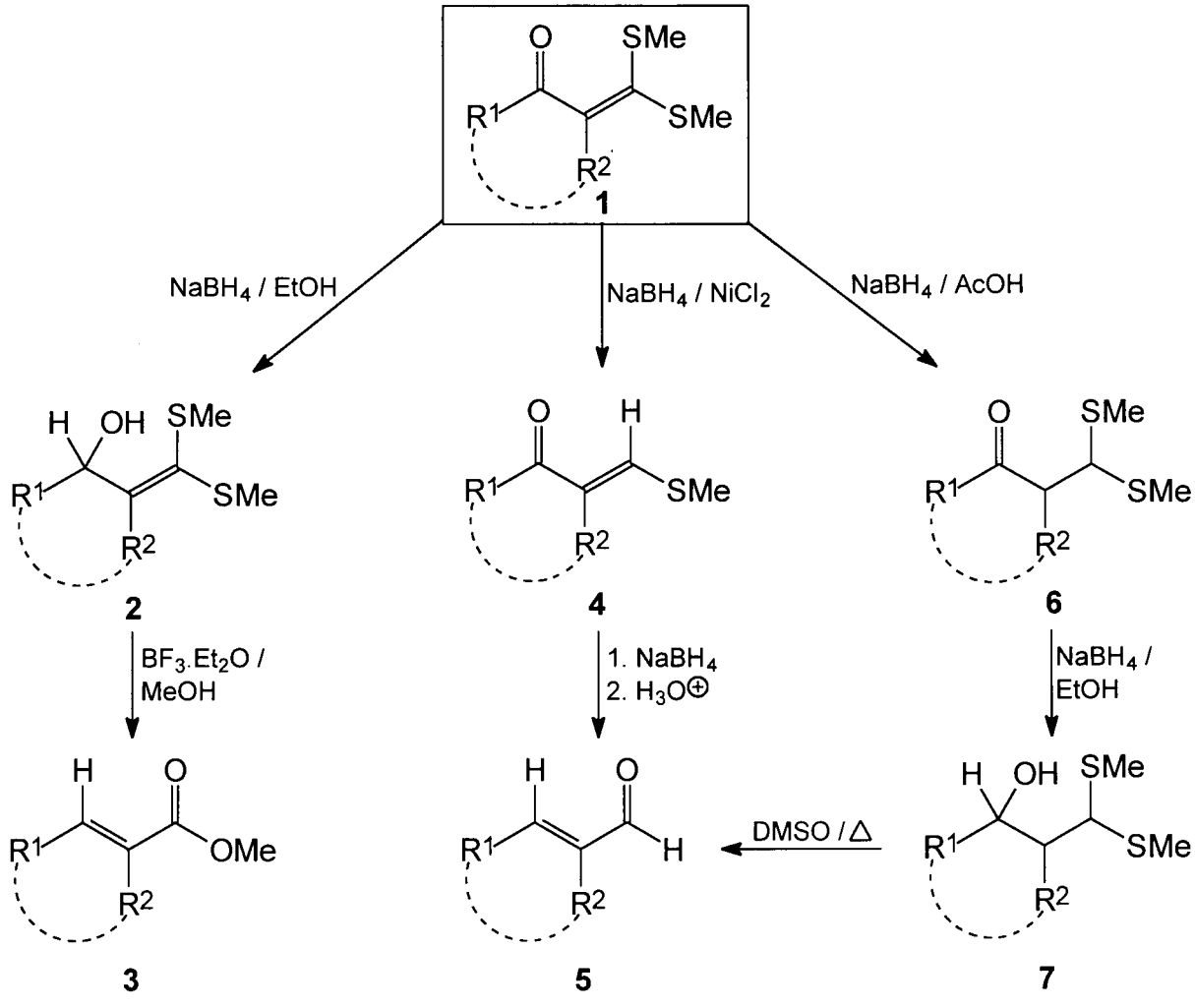
The α-oxoketene dithioacetals **1** have been reported to undergo chemoselective 1,2- reduction[9] with sodium borohydride to give the corresponding carbinol acetals **2**, which were shown to undergo smooth


-Ketoaldehydes
or
-Ketoesters
1,3-diketones
or
1,4-Hydride addition
Hydrolysis
Organo-copper reagents
1,3-Carbon nucleophiles
Carbocycles
1,2-Hydride or organometallic addition and 1,3-carbonyl transposition
Polyene esters
3-Carbon 1,3 electrophilic components
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
Double bond reactivity
Bromination
Reactivities of R1 and R2
Miscellaneous
SCH3 deprotonation and intramolecular condensation
O,S-Acetals
N,S-Acetals
N,N-Acetals

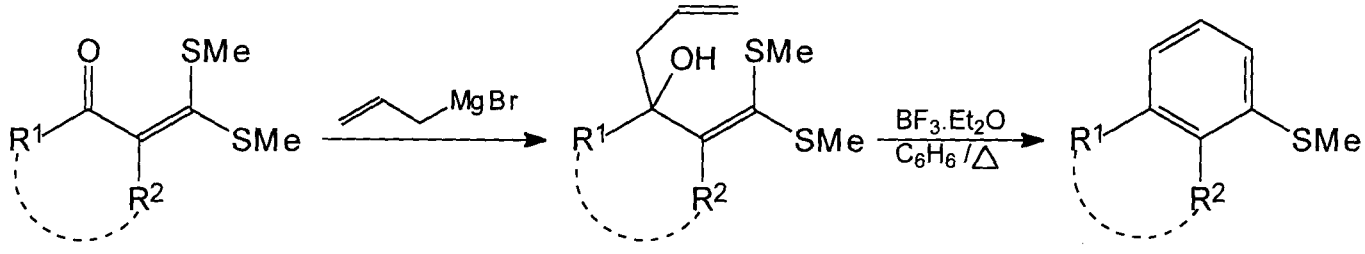
Scheme 1

methanolysis in the presence of boron triflouride etherate to afford α,β-unsaturated methyl esters **3**(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 oxoketene dithioacetals were shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction[10] to the corresponding β-methylthio alkenyl ketones **4** . These intermediates are further transformed to the corresponding α, β-unsaturated aldehydes **5** (Scheme-2). The exclusive regiospecific, 1,4-addition[11] of hydride ion to **1** was accomplished by using excess $NaBH_4$ in the presence of acetic acid to afford the β- oxodithioacetal **6**, which on further borohydride treatment in ethanol afforded the carbinol acetal **7**. The acetal on heating in DMSO to afford the corresponding α,β-unsaturated aldehydes **5** in high yields[12].

The reaction of allyl grignard reagent with **1** resulted in exclusive 1,2 addition to yield the carbinol acetal **8**.This on BF_3-etherate catalysed cycloaromatisation lead to the formation of substituted benzenes[13] **9** (Scheme-3). This approach of building an aromatic ring from acyclic precursors by a [3+3] approach with complete control of regioselectivity was first reported from our laboratory(Scheme-4). The versatility of this

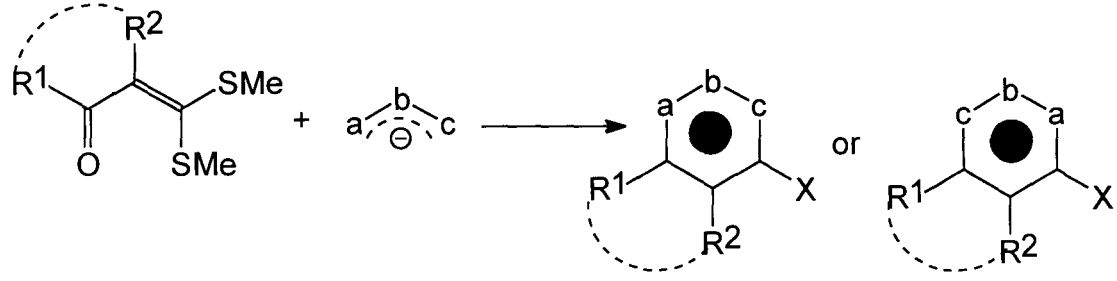

O
SMe
R1
SMe
R2
1
NaBH4 / EtOH
NaBH4 / NiCl2
NaBH4 / AcOH
H
OH
SMe
R1
SMe
R2
2
O
H
R1
SMe
R2
4
O
SMe
R1
SMe
R2
6
BF3.Et2O /
MeOH
1. NaBH4
2. H3O⊕
NaBH4 /
EtOH
H
O
R1
OMe
R2
3
H
O
R1
H
R2
5
DMSO / Δ
H
OH
SMe
R1
SMe
R2
7

Scheme 2



1 **8** **9**

Scheme - 3



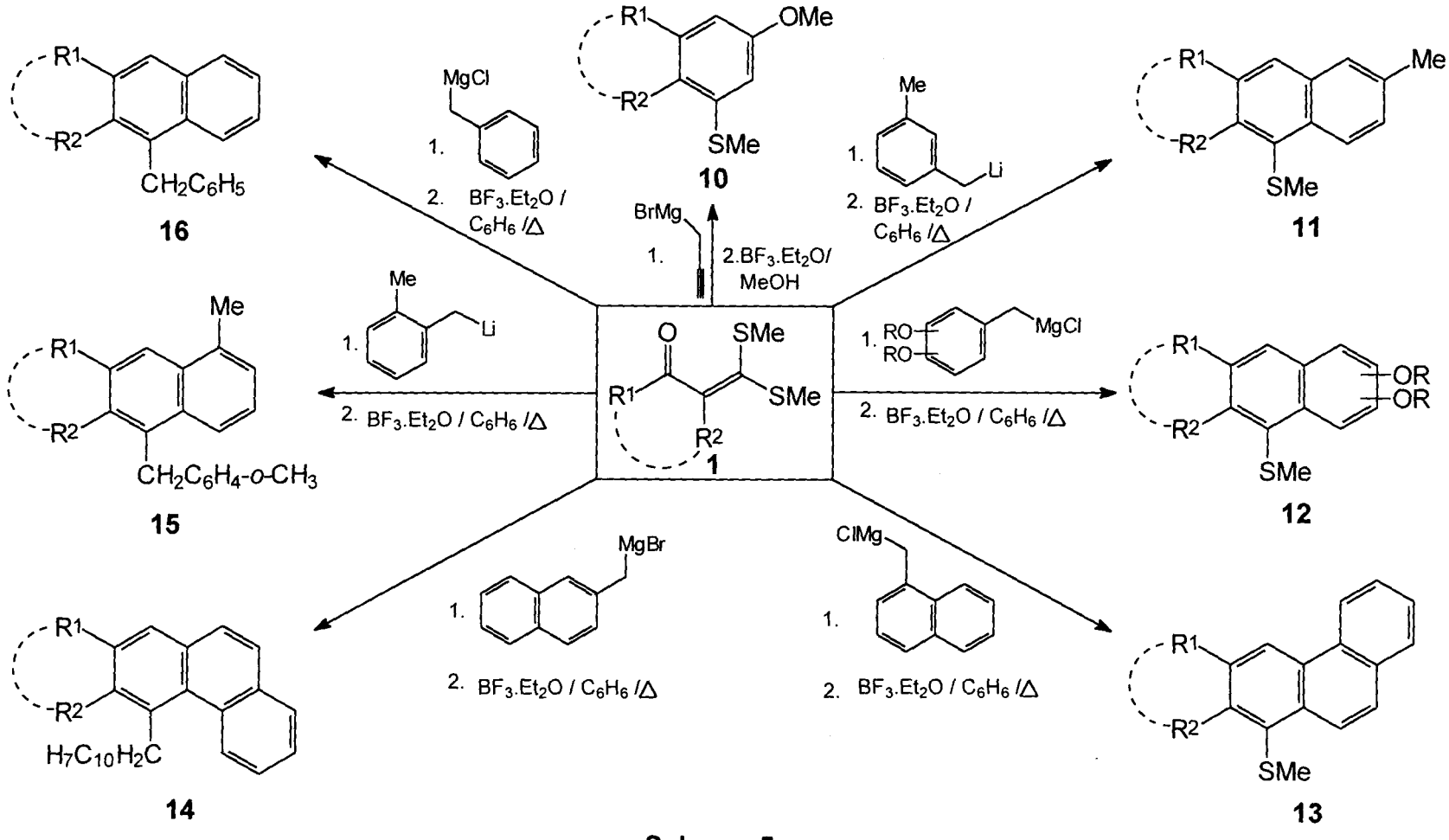
X=SMe; H

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

Scheme - 4

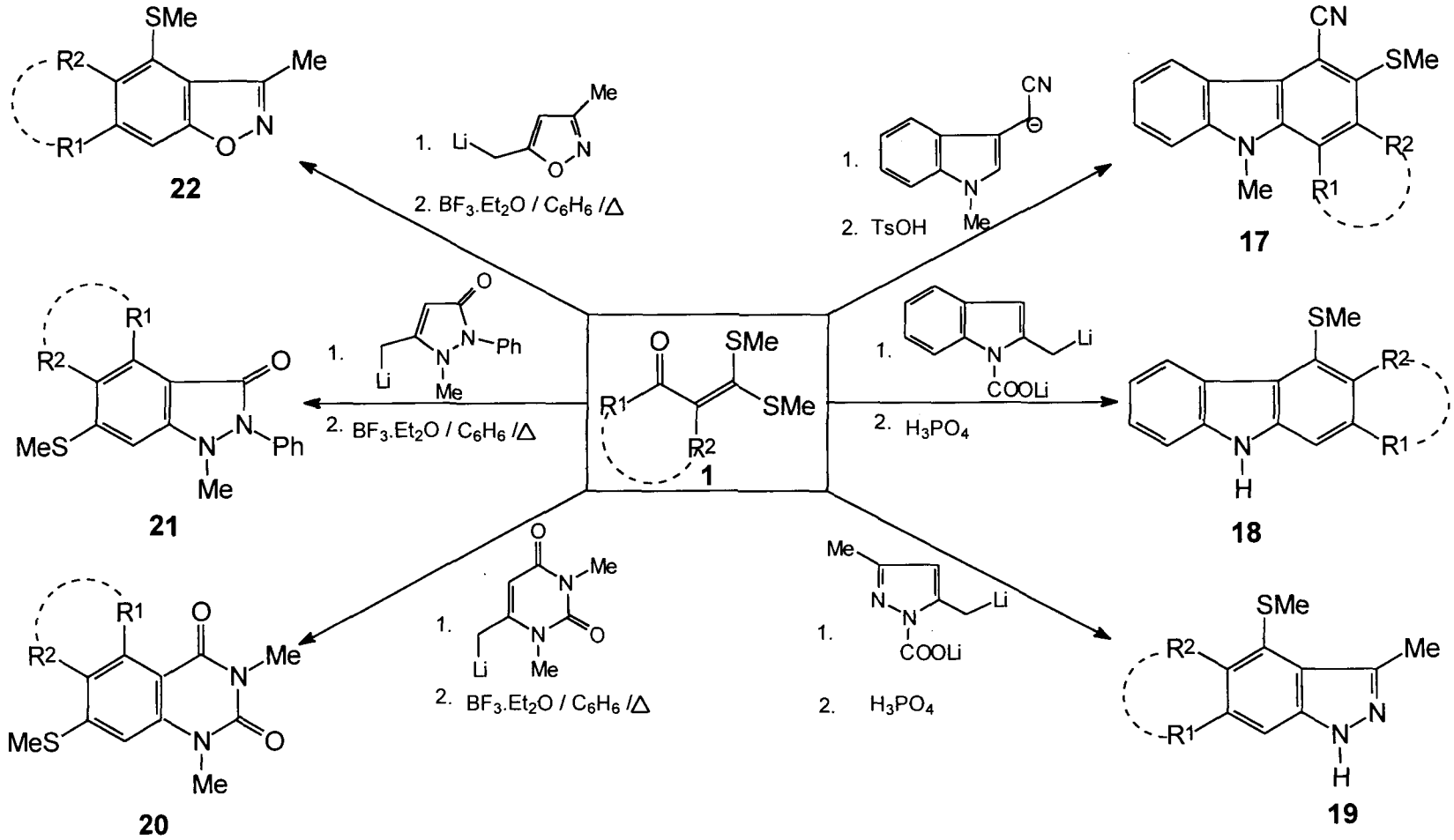
novel aromatic annelation protocol was subsequent established by the facile synthesis of various benz-annelated carbocycles[14]. The scope and success of this protocol is presented in scheme-5. The reaction of propargyl magnesium bromide with **1** followed by cyclisation by BF_3 - etherate in methanol lead to the formation of substituted anisoles[15] **10**. This method could be successfully extended to naptho-annelation. Benzyl magnesium chloride reacted with **1** in a 1,4 addition followed by 1,2 addition sequence, and subsequently on cycloaromatisation yielded napthalenes **16** with benzyl side chains[16]. Methyl substitued napthalenes 11 and 15 were synthesised by the reaction of lithioxylene[17] with **1** followed by aromatization.

Alkoxy substituted napthalenes **12** were prepared in good yields by the reaction of alkoxy substituted benzyl grignard reagents[18] with **1** . The grignard reagent prepared from 1- chloromethyl napthalene reacted with **1** to lead to thiomethyl substituted phenanthrenes **13** while that from 2- bromomethyl napthalene instead lead to napthyl substituted phenanthrenes[19] **14**.


R1
R2
CH2C6H5
16
MgCl
1.
2. BF3.Et2O / C6H6 /Δ
OMe
SMe
10
BrMg
1.
2.BF3.Et2O/ MeOH
Me
1.
Li
2. BF3.Et2O / C6H6 /Δ
Me
11
Me
1.
Li
2. BF3.Et2O / C6H6 /Δ
CH2C6H4-o-CH3
15
O
SMe
R1
SMe
R2
1
1. RO RO MgCl
2. BF3.Et2O / C6H6 /Δ
OR
OR
12
MgBr
1.
2. BF3.Et2O / C6H6 /Δ
H7C10H2C
14
ClMg
1.
2. BF3.Et2O / C6H6 /Δ
13

Scheme 5

The above mentioned annulation strategy could be successful extended to to the synthesis of various heterocycles and is shown in scheme-6. Thus the reaction of 2- lithiomethyl -4-methyl isoxazole with **1** followed by cycloarmatisation[20] led to the formation of benz-isoxazoles **22**. Cyanocarbazoles **17** were efficiently synthesised[21] using the reaction of sodio-3-cyano methyl indole with **1**. The synthesis of thiomethyl substituted carbazoles **18** were successfully achieved by first generating the dianion from 2- methyl indole and then reacting it with **1**, the cyclisation being done using TsOH as the acid catalyst[22]. The deprotonation was done by Katritzky's method[23] which involved first deprotonationof the N-H proton, followed by N- protection using CO_2, and its subsequent activation for CH_3 deprotonation. The dianion from 3- methyl pyrazole was generated for the first time from our laboratory[24] and successfully utilised for the construction of imidazolo-pyridines**19**. The dianion reacted smoothly with **1** and subsequently underwent cycloaromatization through the pyrazole nitrogen under phosphoric acid conditions to lead to the title compounds. 6-Lithio methyl uracil added smoothly with **1** to yield quinazolines **20** after cycloaromatization using BF_3.etherate in refluxing benzene[25]. By the same strategy 3- lithio


SMe
R2
R1
Me
N
O
22
1. Li
2. BF3.Et2O / C6H6 /Δ
CN
SMe
N
Me
R2
R1
17
1.
2. TsOH
R1
R2
O
N
Ph
MeS
Me
21
1. Li
2. BF3.Et2O / C6H6 /Δ
O
SMe
R1
SMe
R2
1
1. Li
N
COOLi
2. H3PO4
SMe
R2
R1
N
H
18
R1
R2
O
N
Me
MeS
N
O
Me
20
1. Li
2. BF3.Et2O / C6H6 /Δ
Me
N
N
Li
1.
COOLi
2. H3PO4
SMe
R2
Me
R1
N
N
H
19

Scheme 6

methyl -2-methyl-1-phenyl pyrazoline - 5 - one was utilised for the synthesis of 1,2 disubstituted indazalones**21** and condensed analogs[26].

α- oxoketene dithioacetals have also been successfully utilised for the synthesis of various other heterocycles and these aspects are covered in the introductory part of Chapter two. In this thesis, the α-oxoketene dithioacetal is utilised for the synthesis of heterocyclic aldehyde acetals and aldehydes and is discussed in Chapter two.

1.2: Organic Compounds as Second Order Non Linear Optical Chromophores

Photons can carry information faster, more effeciently and over longer distances(with less signal degradation) than electrons.Photonics will replace electronics very soon in information and communication technologies. During this transition, the hybrid technology called opto-electronics is expected to gain importance. The success of lithum niobate in manipulating light with electricity brought out the possibility of merging electronics and photonic technologies.

Organic polymers are being considered better candidates in this regard as they are proving to be more efficient ; their ease of preparation

and less expensive price being added advantages. Moreover they are more easily introduced ino a device, leading to a greater rate of success in fabrication. The key property of these polymers is their second order optical non-linearity[27-31]. Another useful property is their ability to function electro optically. In this regard they are more useful then even lasers. It is precisely for these reasons that the field of non linear optical polymers have been recognised as a thrust area of research in organic chemistry. Research done so far in this field have clearly identified two key factors for a compound to be successfully work as a NLOP. The first factor is the presence of NLO-active chromophore i.e. a conjucated molecule that contains an electron donating group at one end (push) and an electron accepting group (pull) at the other end. The second factor is thermal stability which is acheived by the presence of a thiophene moiety in a polyene bridge . This is relevant because the molecule needs to withstand the high temperature(300°C) needed for the fabrication of the opto-electric device.

It is by now well established that molecules containing electron donor and electron acceptor groups separated by large conjugated frame

work possess large value of the seond order nonlinear molecular hyperpolarizability(β). Therefore organic chemists major research efforts have been focussed on design, development and synthesis of NLO chromorphores possessing ever larger molecular non linearity, good thermal stability, as well as improved solubility and processability. During the past decade several electron donor and acceptor substituted conjugated compounds such as functionalized benzenes, biphenyls, stilbenes, acetylene, Schiff's bases, azobenzene have been developed for second order application. In all these classes benzene rings with or without a bridge have been employed as the conjugating moieties to connect donor and acceptor functional groups. In general, conclusion is that the molecular non linear susceptibility (β) increases with increasing donor and acceptor strength and with increasing conjugation length. A variety of acceptor such as carbonyl, nitro, sulfonyl, disulphonylvinyl, dicyanovinyl, cyanonitrovinyl, tricyanovinyl, thiobarbituric acid and rhodanine have been examined for their role in influencing the molecular NLO properties, while a few electron donors such as alkoxy and dialkylamino groups have received the most attention.

Polyenes are often used as conjugating units as they provide most effective pathway for the efficient charge transer betwen donor and acceptor groups. Although there have been several computational studies of the first hyperpolarizability (β) of these simple donor-acceptor polyenes only a few molecules in this class have been studied experimentally.

Despite the synthesis and study of large bumber of organic donor-acceptor molecules as NLO chromophores and the tidy understanding of various structural factors that enhance molecular NLO hyperpolarizability, only limited success has been achieved in the development of efficient (large β) donor-acceptor compounds due to synthetic and solubility constraints. Considering these limitations , there exists a need to explore and develop new organic chromophores with efficient nonlinearities, desired solubilities and high thermal and photochemical stability. Our research group has been engaged for several years in design and development of new synthetic methodology for carbocycles, heterocycles and polyenes[32] based on polarized ketene dithioacetals and aminals- a class of versatile push pull synthons easily

accessible from a variety of active methlene compounds. Based on our earlier synthetic experiences on these moelcules, we have now undertaken design and synthesis of novel donor-acceptor polyolefins as potential second order NLO chromophores and the present research work in this thesis is the outcome of our intial findings in this directions.

1.3 Ketene dithioacetals as intermediates for cationic cyclisations

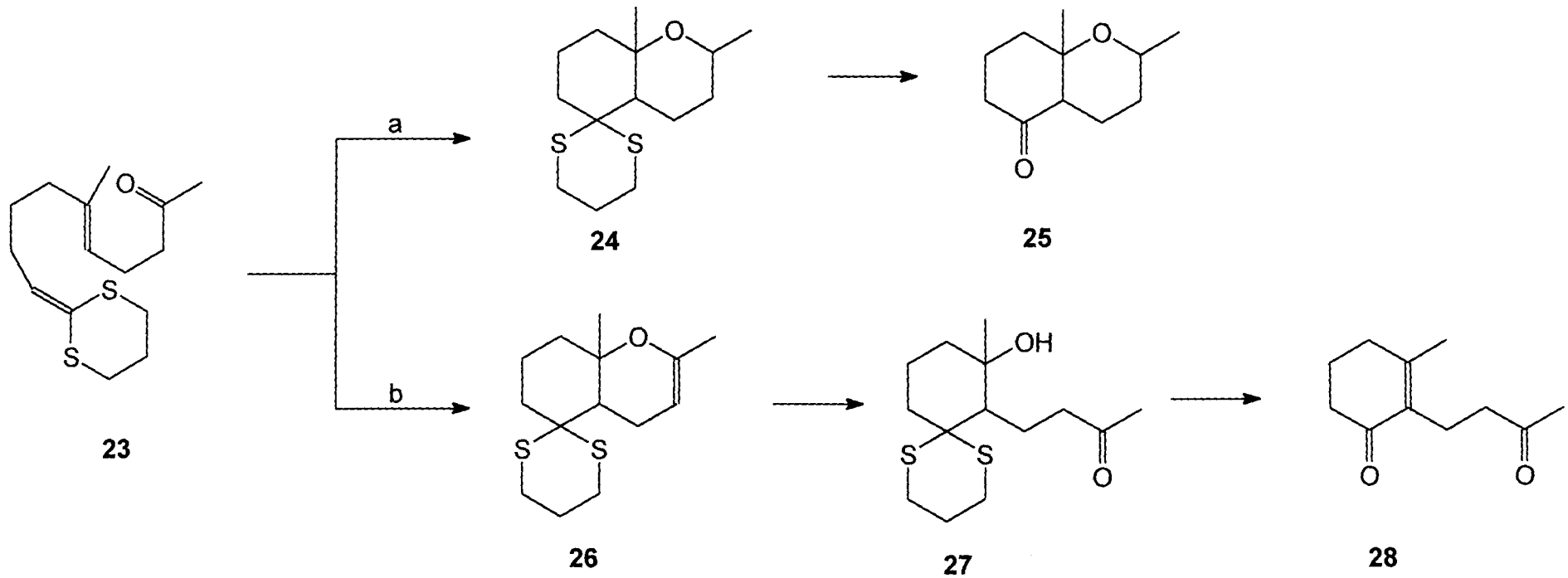
The versatile reactivity of α- oxoketene dithioacetal results from the stabilizing effect of the two sulphur atoms on both neighbouring positive as well as negative charges[33,34]. Consequently the mercapto double bond becomes sensitive to both electrophilic and nucleophilic reagents[35,36]. The useful property has been extensively used in the design and synthesis of various natural and related products.

The triflouro acetic acid assisted cyclizations[37] are very facile with the electrophilic double bond suitably positioned on the dithioacetal carbon. The trapping agent could sometimes be an oxygen atom instead of a double bond. The reaction of 2-(4-methyl)-8-oxo-(4-noncyclidine) 1,3 dithiane **23** on treatment with triflouro acetic acid in presence of

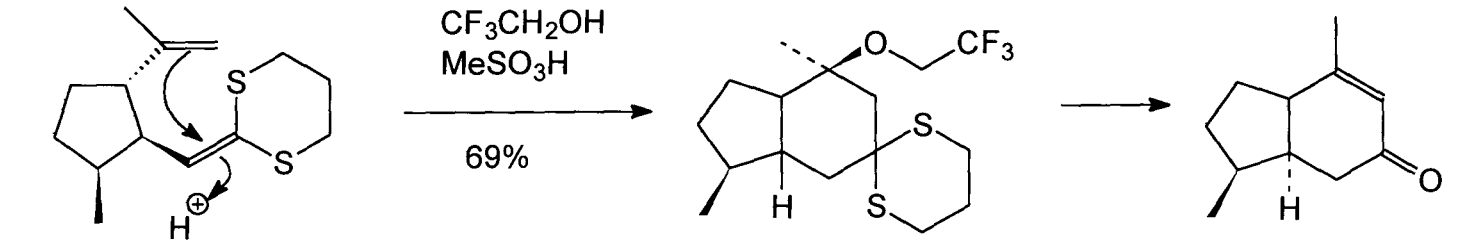
triethyl silyl hydride underwent smooth cyclization which on subsequent hydrolysis afforded the corresponding annulated pyrenoyl ketone **25** (scheme- 7).When **28** is formed through **27**, the double bond is retained by triflouro acetic acid.

Ketene dithioacetals has been used as cationic initiators in intramolecular electrophilic cyclisations[38]. The protonated mercapto double bond in **29** is attacked by the olefinic double bond to afford the cyclic thioketal **30** in 69% yield in the presence of trifluoro- ethanol and methane sulphonic acid. (Scheme-8). The decaline dione **34** results due to the traping of the sulfur assisted cation by the double bond in a tandem ring closure[39].

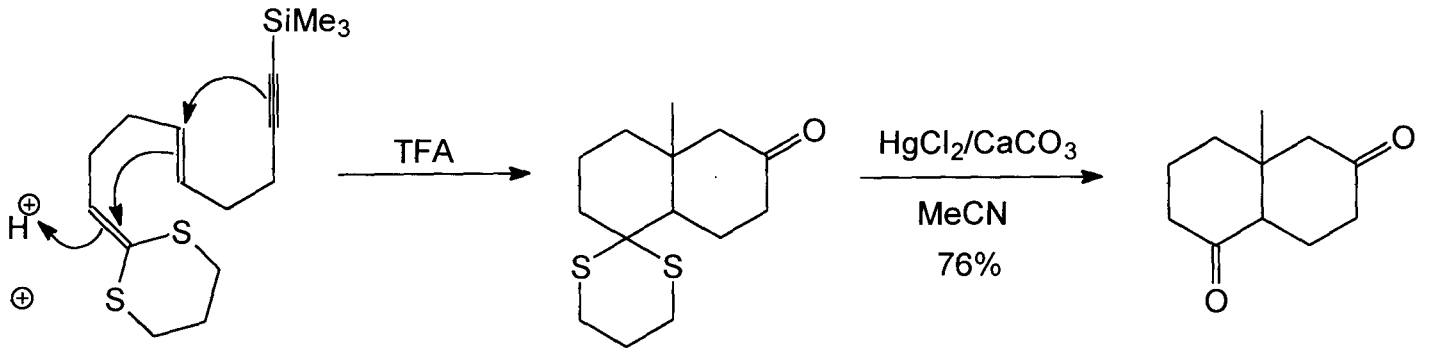
Sulfur stabilized cations have been used with participation of the aryl ring through a double bond to synthesise the tricyclicketone **37**[38] (Scheme-9). The synthesis of the tetralone **40** and tetralene **41** were accomplished by similar approaches. The utilization of an mercapto intermmediate had resulted in a facile ring closure, requiring only a catalytic amount of p-toluene sulphonic acid. Alternative approaches involving a Friedel- Crafts reaction using a strong Lewis acid led to undesirable tar.



Scheme - 7

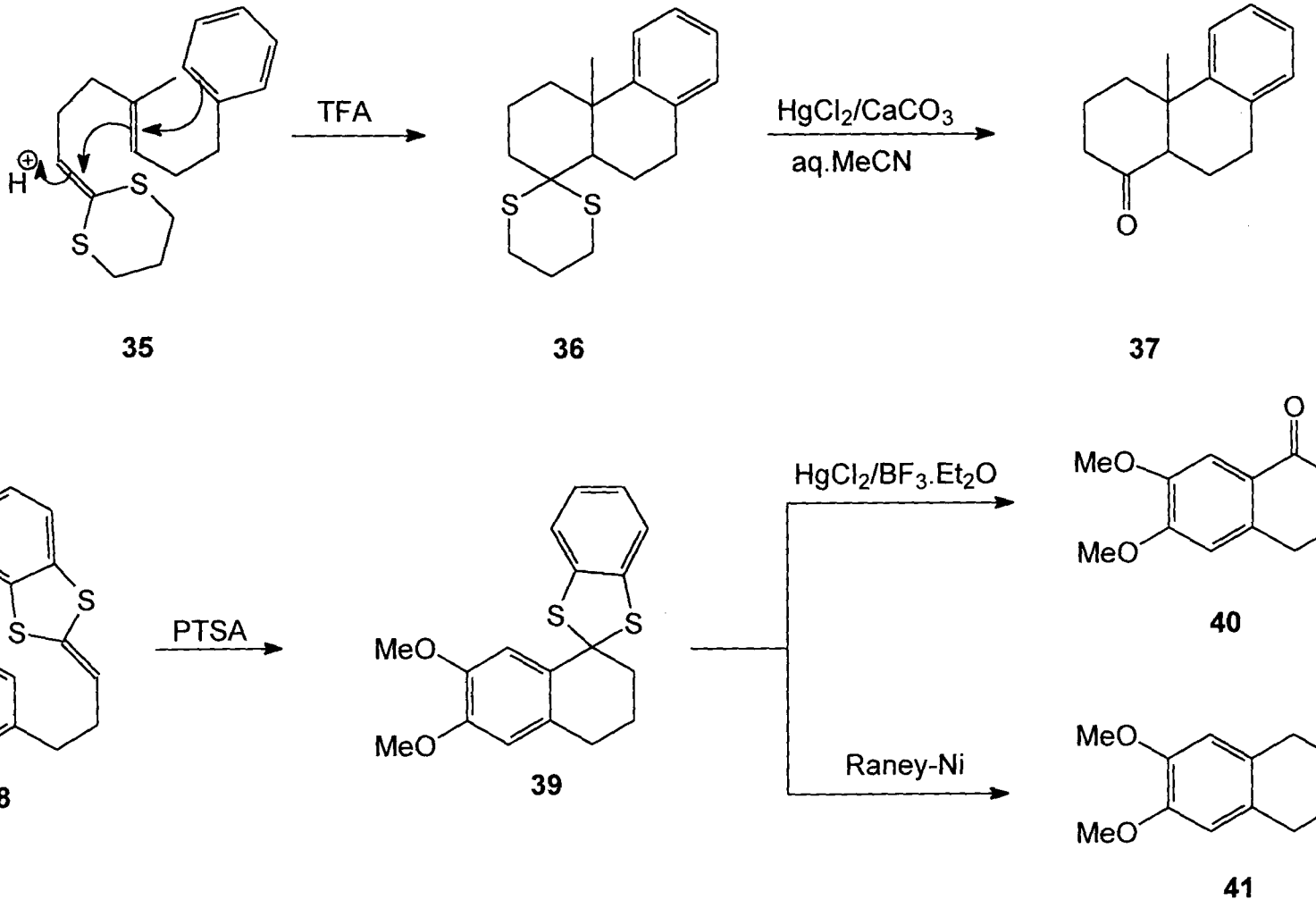


29 **30** **31**



32 **33** **34**

Scheme - 8



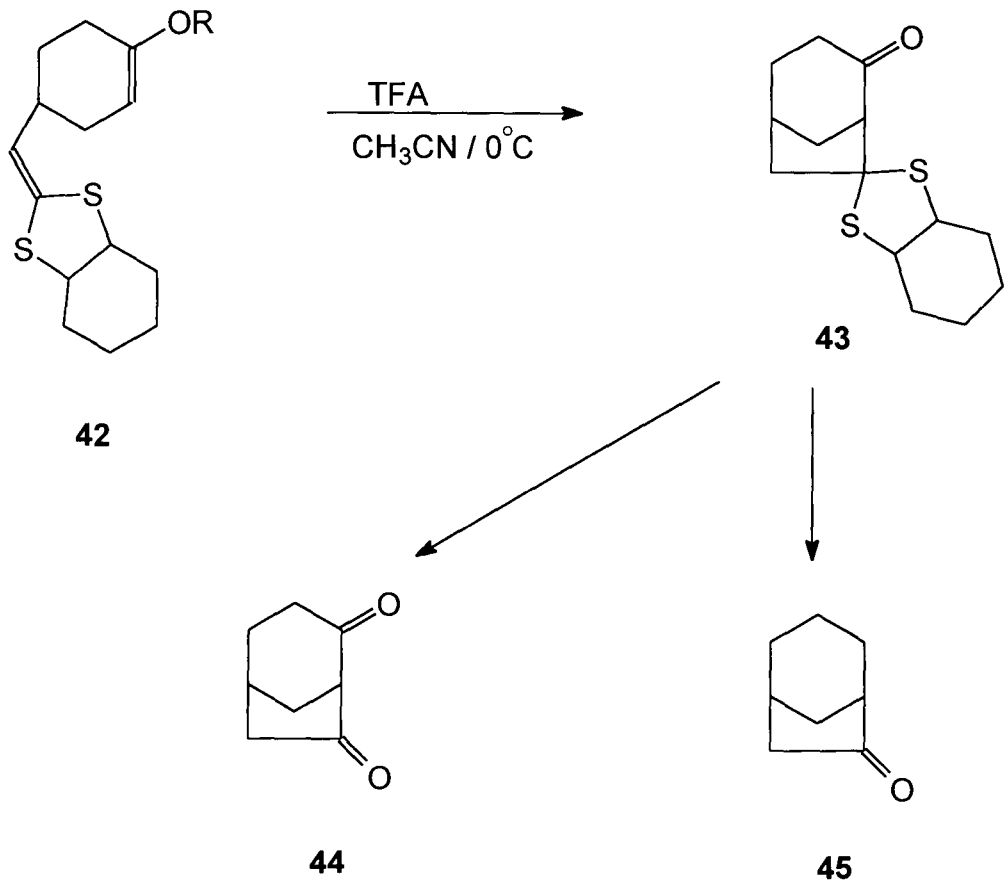
35 **36** **37**

38 **39** **40** **41**

Scheme - 9

The synthesis of bicyclo [3,2,1] octane ring systems was achieved by using an activated double bond to trap a sulphur stabilized carbocation in a three - step process (Scheme-10). The silyl enol ether **42**, present as a protected ketone, facilitates excellent double bond participation with the cation, and subsequently cleaves to form the bicyclic ketal **43** from which the ketones **44** and **45** could be liberated[40]. It is thus a versatile approach for the synthesis of a very important class of [3,2,1] bicyclo octane framework.

A novel cyclopenta-annelation strategy was evolved in our laboratory based on the efficient cationic terminating ability of sulphur present in **1**. This strategy was later improved to effect a tandem ring closure sequence to from diquinane frameworks. The work in this thesis involves the successful application of this strategy to the synthesis of hetero aryl fused diquinane framework.



42 43 44 45

Scheme - 10

References :

1) For a review see.

(a) Dieter, R.K. Tetrahedron. **1986**, *42*, 3029.

(b) Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron.* **1990**, *46*, 5423.

(c) Kolb, M. *Synthesis*. **1990**, 171.

2a) Kelber, C. *Chem. Ber.* **1910**, *43*, 1252.

b) Kelber, C.; Schwarz, A. *Chem. Ber.* **1911**, *44*, 1693.

c) Kelber, C.; Schwarz,A. *Ibid*, **1912**,*45*,137.

3a) Thuiller, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1959**, 1398.

b) Thullier,A.; Vialle, *Ibid.* **1962**, 2187.

c) Thullier, A.; Vialle, *Ibid*, **1962**, 2194.

4) Gompper, R.; Schmidt, R.R.; Kutter, E.*Leibigs Ann. Chem.* **1965**, *37*, 687.

5) Corey, E.J.; Chen, R.H.K., *Tetrahedron Lett.* **1973**, 3817.

6) Shahak,L., Sassow, Y. *Tetrahedron.* **1976**, *32*, 1779.

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

8) Dieter, R.K. *J. Org. Chem.* **1981**, *46*, 5031.

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

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

11) Rao, Ch. S. ; Chakrasali, R.T.; Ila, H.; Junjappa, H. *Tetrahedron.* **1990**, *46*,2195.

12) Rao, Ch. S.; Chandrasekharam, M.; Patro, B. Ila, H.; Junjappa, H.; *Tetrahedron.* **1994**, *50*, 5783.

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

14) Junjappa, H.; Ila, H.; *Phosphorus, Sulfur and Silicon.* **1994**, *95*, 35.

15) Gupta, A.K.; Ila, H.;Junjappa, H. *Tetrahedron Lett.* **1987**, 1459.

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

17) Yadav,K.M.;Mohanta,P.K.; Ila, H.; Junjappa, H., *Tetrahedron* **1996, *52*,** 14049.

18) Mehta,B.K.; Ila,H.; Junjappa,H., *Tetrahedron Lett.* **1995**, *36*, 1925.

19) Rao, Ch.S.; Balu, M.P.; Ila, H.; Junjappa, H. *Tetrahedron.* **1991**, *47*, 3499.

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

21) Patra,P.K.;Suresh, J.R.;Ila, H.; Junjappa, H., *Tetrahedron Lett.* **1997, *38*,** 3119.

22) Syam kumar,U.K.; Patra,P.K.; Ila,H.; Junjappa,H., *TetrahedronLett.* 1998, *39*, 2029

23) Katritzky, A. R.; Akutagawa, K., *J. Amer. Chem. Soc.*, **1986**, *108*, 6808.

24) Kaushal Kishore, K.R.Reddy, J.R.Suresh, H,Ila and H. Junjappa; *Tetrahedron*,**1999**,*55*,7645.

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

26) Reddy K.R.; Roy, A.; Ila, H; Junjappa, H., *Tetrahedron* **1995**, *51*, 10941.

27) For a review see:

a) D.M. Burland, R.D. Muller and C.A. Walsh, *Chem. Rev.*, **1994**, *94*, 31.

b) R. Dagani, *Chem. And Eng. News*, **1966,** 22.

c) D.J. Williams, *Angwandte Chem. Int. Ed. Engl.*, **1984**; *23*, 690.

d) Materials for Nonlinear Optics: Chemical Perspective, Ed. S.R. Marder, J.E. Sohn and G.D. Stucky, *ACS Symposium series No. 455, ACS, Washington, DC,* **1991**.

(e) Polymers for second-order Nonlinear Optics; G.A. Lindsay, K.D. Singer, Eds., *ACS Symposium Series 601; American Chemical Society; Washington, DC,* **1995**.

28a) A.F.Garito ,; A.K.-Y, Jen ,; C.Y.-C. Lee,; L.R. Dalton; Eds., Electrical, Opitcal and Magnetic Properties of Organic Solid State Materials, *Mater. Res. Soc. Symp. Proc.* **1994**,328.

b) P.N. Prasad, D.J. Williams, Introduction to Nonlinear Optical effects in Molecules and Polymers, Wiley, New York. **1991**

29a) Organic Materials for Nonlinear Optics, Eds. R.A. Hann, D. Bloor, Royal Society of Chemistry, London, **1989.**

(b) Nonlinear Optical properties of Organic Molecules and Crystals, Vol. 1 and 2, Eds. D.S. Chemla, J. Zyss; Academic Press, New York, **1987**.

30) A.F. Garito, R.F. Shi, M.H. Wu, *Phys. Today*, **1994**, *47*, 51.

31a) J.L. Bredas, R.J. Silbey, Eds. Conjugated Polymers: The Novel Science and Technology of Highly Conducting and Nonlinear Optically Active materials; Kluwer: Dordrecht, The Netherlands, **1991**.

b) K. Clays, A.Persoons, *Phys. Rev. Lett.*, **1991**, *66*, 2980: Adv. Chem. Phys., **1994,** *85*, 455.

32a) Synthesis of stilbenes, Polyenes, Polyenes Esters and Aldehydes: B. Myrboh; C.V. Asokan,; H. Ila and H. Junjappa, *Synthesis* **1984,**50.

(b) M.Chandrashekharam; C.V. Asokan; H. Ila, and H. Junjappa, *Tetrahedron Lett.* **1990,** *31*,1766,.

33) Barvett, G.C. in " Baston and Ollis Comprehensive Ofrganic Chemistry", Jones, D.N. ed. Pergamon Press Ltd., **1979**, *Vol.3*, Part 11. 1; 11.3 and references cited therein.

34) Kolb, M. In "The Chemistry of Ketenes, Allenes and related compounds" Patai, S. Ed., Wiley, Chichester, **1980**, *Part 2*, 669.

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

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

37) Mizyuk,V.L.; Semenovsky,A.V.*Tetrahedron Lett.* **1978**, 3603

38) Anderson, N.H.; Yamamoto, Y.; Denniston, A.D. *Tetrahedron Lett.* **1975**, 4547.

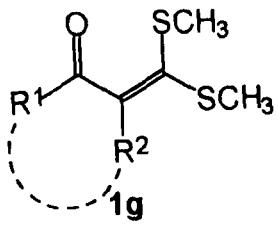
39) Brinkmeyer, R.S. *Tetrahedron Lett.* **1979**, 207.

40) Rigby, J.H.; Kotnis, A.S. *Tetrahedron Lett.* **1987**, *28*, 4943.

CHAPTER TWO

PREPARATION AND SYNTHETIC APPLICATIONS OF 4,4-BIS(METHYLTHIO)-1,1-DIMETHOXY-3-BUTEN-2-ONE. REACTION WITH HYDRAZINE, HYDROXYLAMINE, SIMMONS-SMITH REAGENT, GUANIDINE, THIOUREA, AND CYANOACETAMIDE : A VERSATILE NEW SYNTHON FOR THE SYNTHESIS OF HETEROCYCLIC ALDEHYDE ACETALS AND ALDEHYDES

The α-oxoketene S,S acetals[1a,b,2] of the general formula **1**



1g

R^1 = alkyl,aryl,heteroaryl
R^2 = alkyl

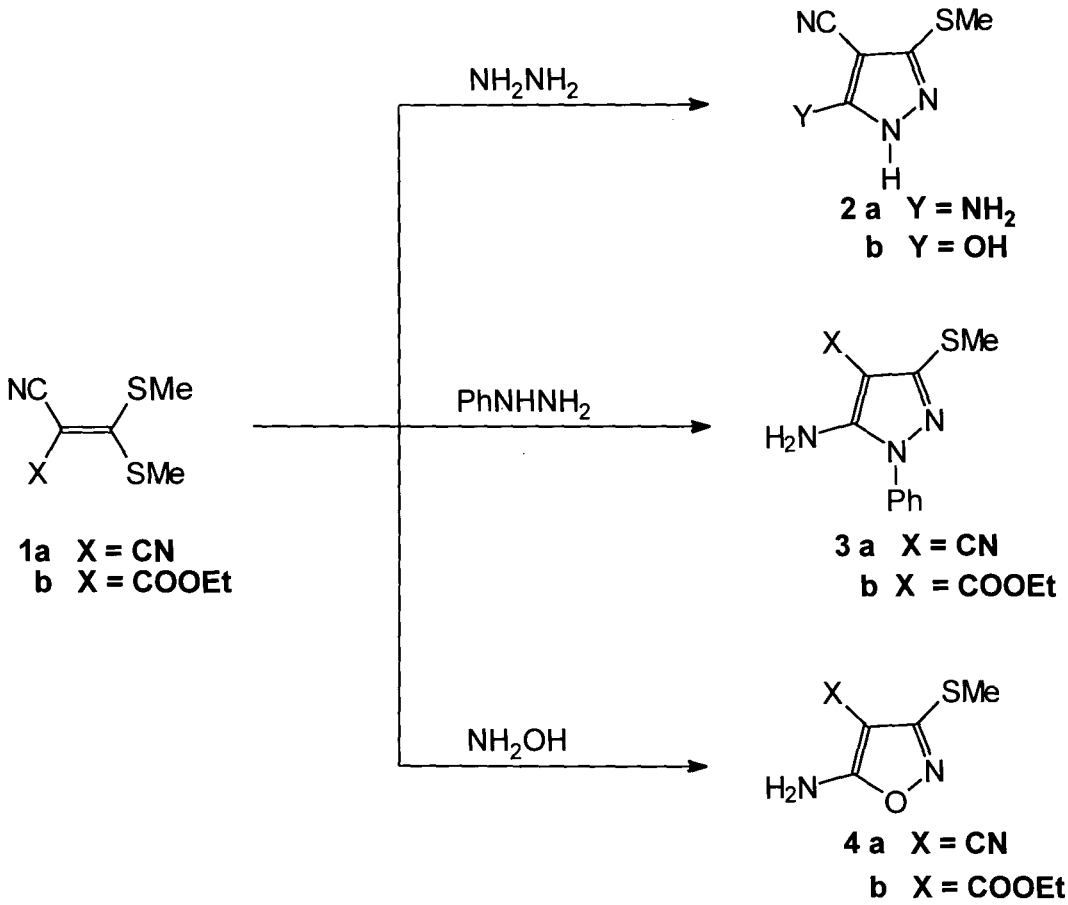
are among the widely investigated synthetic intermediates which generally are prepared from a wide range of active methylene

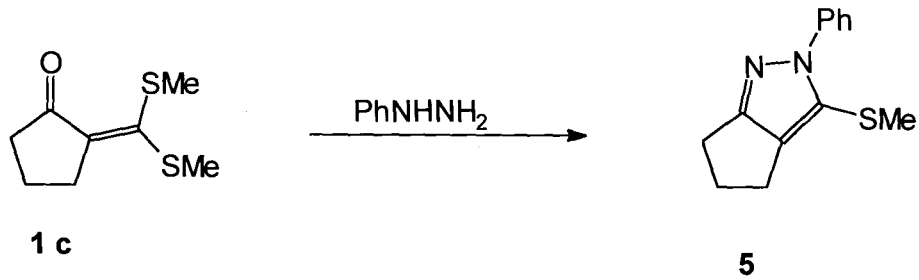
aldehydes,ketones, esters, amides, nitriles, and other activating groups. They are generally prepared in a one pot reaction by treating the active methylene compound with a suitable base in the presence of carbondisulphide to afford the corresponding dithioate salt which is generally alkylated *in situ* to yield **1** in good to excellent yields. The characteristic feature of α-oxoketenedithioacetals is their ability to undergo initial displacement reaction with various nucleophiles with a loss of one methylmercaptan group depending on the reaction conditions and nature of nucleophiles. It has been possible to replace one MeSH group at a time or both in sequence. This type of reaction is generally termed as 1,4 addition-elimination sequence and besides these reactions the oxoketene dithioacetals **1** also undergo 1,2 addition over carbonyl function by those generally classified as hard nucleophiles. Thus it is possible to choose nucleophiles which follow charge controlled 1,2 addition mode or orbital controlled 1,4 addition mode. Therefore, the α-oxoketene dithioacetals can undergo regiospecific reactions with 2-atom binucleophiles or 3-atom binucleophiles depending on the nature of the nucleophiles on both ends. This regioselectivity observed in the reaction of binucleophiles with **1** has given an unambiguous methodology for the synthesis of various

heterocycles without resulting in the product isomers. On the other hand, the corresponding dicarbonyl compounds, particularly those with unsymmetrical substituents, react with unsymmetrical binucleophiles to yield generally a mixture of isomers, since the nucleophilic terminals cannot distinguish the two carbonyl functions.

Extensive studies have been carried out on the reactions of α-oxoketene dithioacetals **1** with various 1,2- and 1,3-binucleophiles to afford a large variety of 5- and 6-membered heterocyclic compounds[1,2]. We briefly survey some of these reactions to illustrate their applications for the synthesis of a variety of heterocycles in the following section.

Gompper and co-workers,[3] in 1962, prepared the ketene dithioacetal from malononitrile **1a** (Scheme-1) and reacted it with hydrazine hydrate to afford the corresponding 5(3)-amino-3(5)-methythio-4-cyanopyrazoles in excellent yield. However when the ketene dithioacetal derived from ethylcyano acetate namely **1b** was reacted with N_2H_4, the ester group participated to afford the corresponding 4-cyano -3(5)-methylthio-5(3)-hydroxy pyrazole **2b** in excellent yield. Similarly when phenylhydrazine was reacted with **1a** and **1b** both the

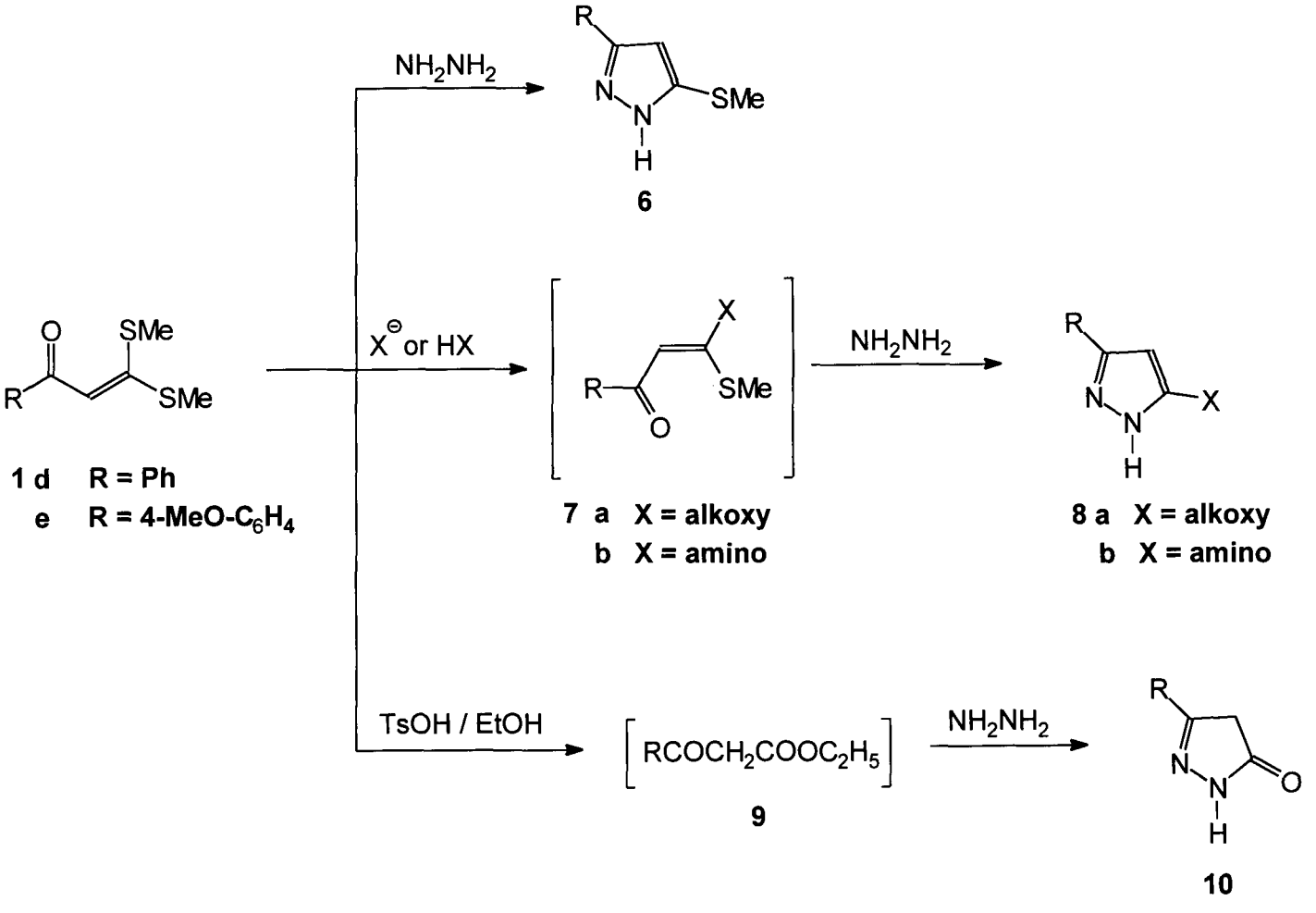

NC
SMe
X
SMe
1a X = CN
b X = COOEt
NH2NH2
PhNHNH2
NH2OH
NC
SMe
Y
N
N
H
2 a Y = NH2
b Y = OH
X
SMe
H2N
N
N
Ph
3 a X = CN
b X = COOEt
X
SMe
H2N
O
N
4 a X = CN
b X = COOEt


O
SMe
SMe
1 c
PhNHNH2
Ph
N
N
SMe
5

Scheme - 1

product pyrazoles **3a** and **3b** carried 5-amino group resulting in the participation of only one cyano group in both the cases. Similarly the same authors reacted hydroxylamine with **1a** and **1b** to afford the corresponding 5-amino-3-methylthio- 4 cyano / carbethoxy isoxazoles **4a** and **4b** in excellent yields. It is apparent that out of the possible isomers only one regioisomer in each case is formed which is characteristic of the reactive pattern of **1**.

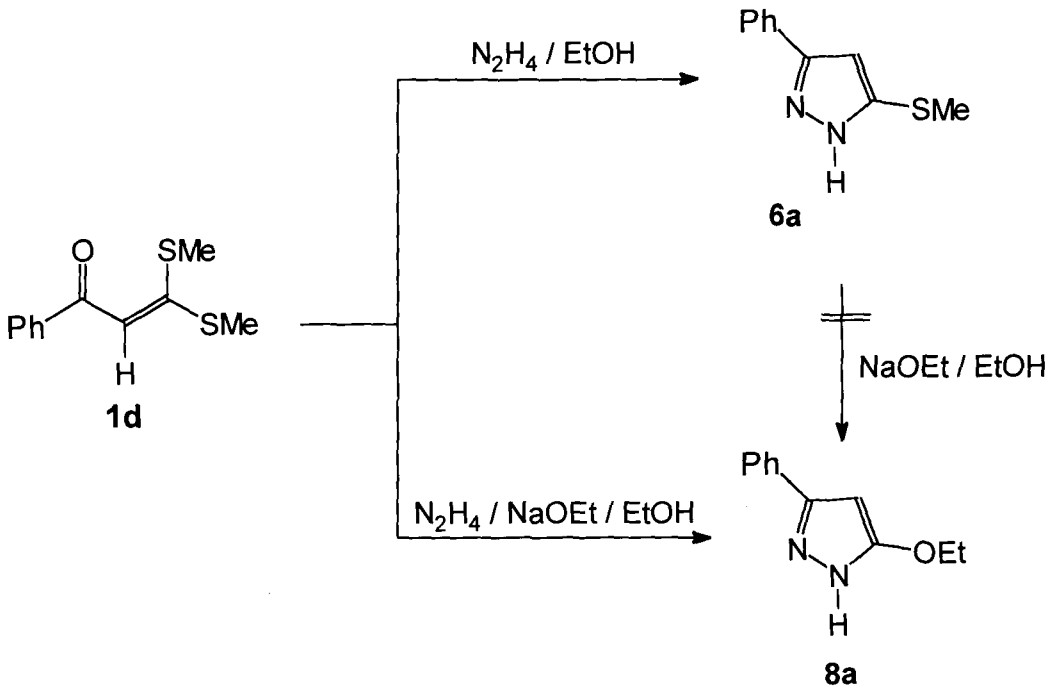
Similarly the oxoketene dithioacetal **1c** derived from cyclopentanone was reacted with phenylhydrazine by Thuillier and co-workers[4] to afford the corresponding pyrazole in high yield. In 1975, an interesting synthetic application of α-oxoketene dithioacetals was investigated in our laboratory[5,6] as formulated in Scheme-2. The reaction of **1d** and **1e** with hydrazinehydrate in refluxing ethanol yielded the expected 3(5)-methylthio-5(3)-arylpyrazoles **6** in excellent yields. However when **1d,** and **1e** were pre-reacted with alkoxides in refluxing corresponding alcohols, followed by slow and dropwise addition of hydrazine hydrate, the corresponding 3(5) alkoxy pyrazoles **8a** were formed in high yields. Similarly when **1d** and **1e** was pre-treated with amines in refluxing


NH2NH2
R
N
N
H
SMe
6
O
SMe
R
SMe
X⊖ or HX
X
R
SMe
O
NH2NH2
R
N
N
H
X
1 d R = Ph
e R = 4-MeO-C6H4
7 a X = alkoxy
b X = amino
8 a X = alkoxy
b X = amino
TsOH / EtOH
RCOCH2COOC2H5
9
NH2NH2
R
N
N
H
O
10

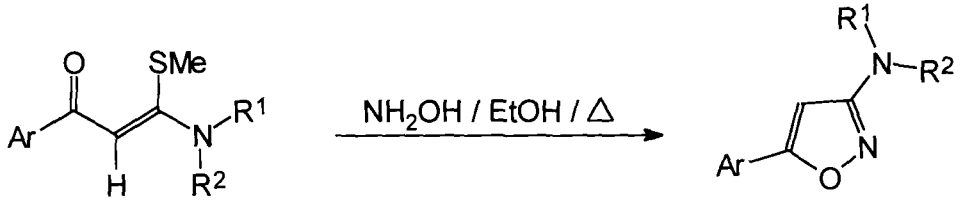
Scheme - 2

ethanol followed by slow and dropwise addition of hydrazine hydrate the corresponding 5-amino pyrazoles were formed in excellent yields. In a further experiment, **1** was reacted with p-toluene suphonic acid followed by slow addition of hydrazine hydrate to afford pyrazol-5-ones **10**. These reactions described in Scheme-2 demonstrate the versatile applications of **1** for the synthesis of 5 methylthio **6**, 5-alkoxy **8a**, 5-amino **8b** and 5-oxo **10** pyrazoles, on altering only the experimental conditions. These reactions were essentially designed to demonstrate that the methylthio group in **6a** is not displaceable by sodium alkoxides, and that the formation of **8a**, and for that matter, **8b** arise from initial displacement of methylthio group in **1** followed by addition of hydrazine hydrate to afford these pyrazoles.

Subsequently in our laboratory we showed that α-oxoketene S,N-acetals[7] of general formula **11** react with hydroxylamine hydrochloride to afford the highly regiospecifically substituted isoxazoles **12** in excellent yields.(Scheme-4) The amino terminal of hydroxyl amine attacks **11** exclusively in the 1,4 addition-elimination mode to afford single regio isomer in all the reactions examined. However, we have



Scheme - 3

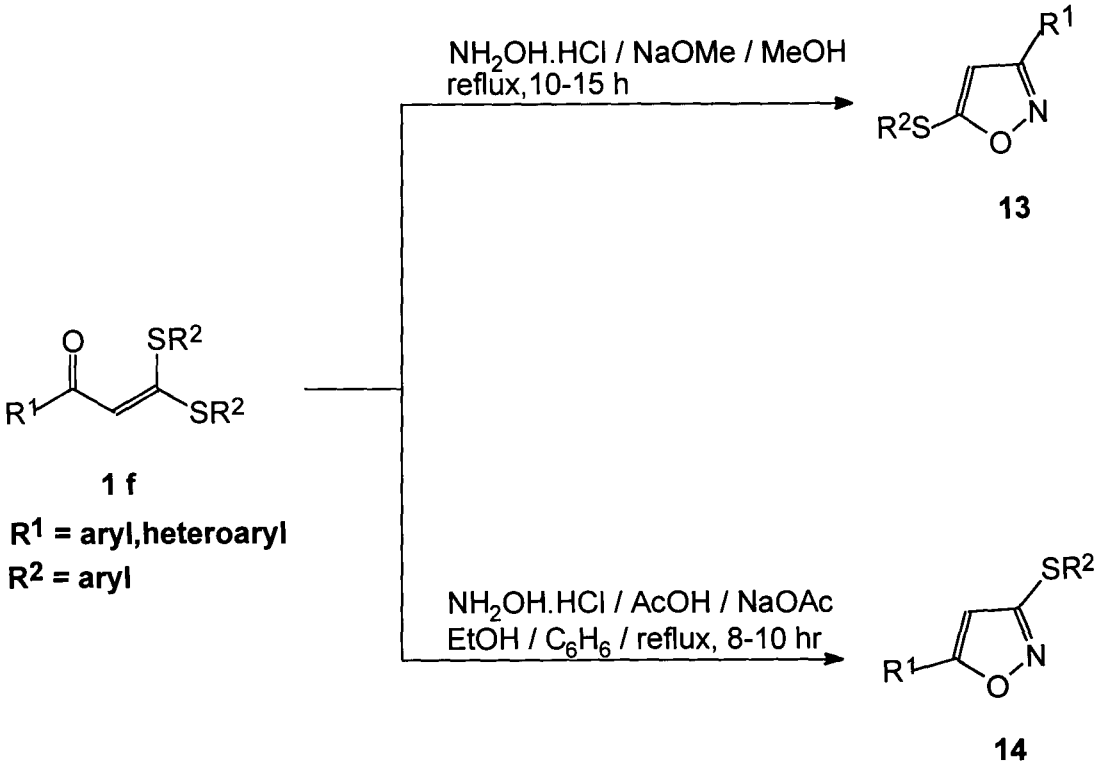


11
R^1=aryl
R^2=alkyl,aryl

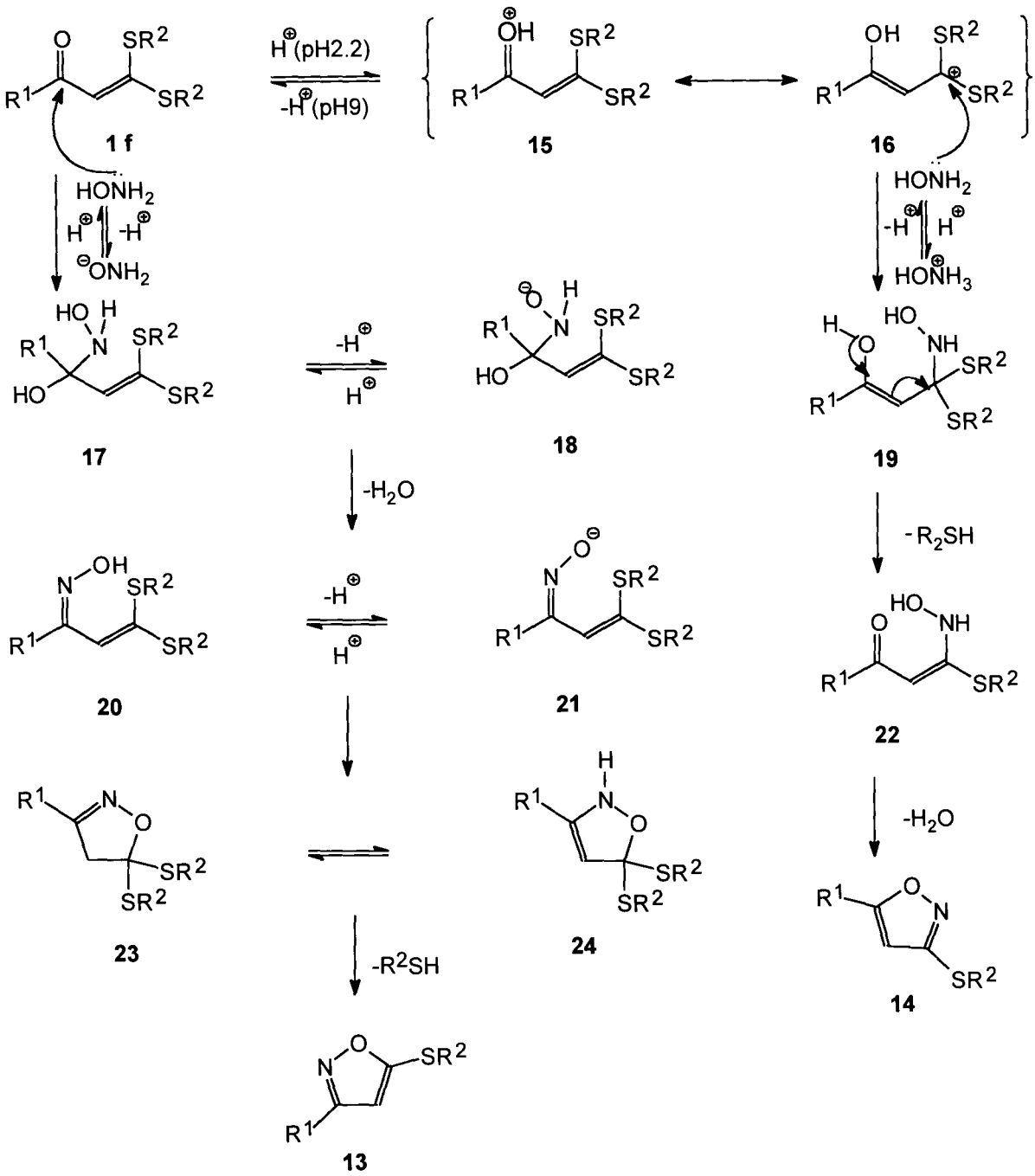
12

Scheme - 4

subsequently demonstrated[8] that the necessary reaction conditions could be evaluated to direct the course of reaction to follow one of the two regio pathway as the case may be depending on the regioisomer we need. Thus when oxoketenedithioacetal **1** (Scheme-5) was reacted with hydroxylamine hydrochloride in the presence of sodium methoxide in refluxing methanol, it yielded one single regioisomer namely 5-alkylthio-3-arylisoxazole **13** in 78% yield. The other isomer **14** was not detected even in traces under this reaction condition. However when hydroxylamine hydrochloride was reacted with **1** in a acetic acid-sodium acetate buffer medium,the pH of the reaction mixture being maintained at 2.2..The product isoxazole **14** thus obtained carried the alkyllthio group at 3 position and the aryl group at 5 position, exactly in the reverse fashion of the previous isomer **13** and no trace of isomer **13** was detected under the reaction conditions. The mechanism governing these highly regioselective pathways are due to reactivity change occurring under different pH conditions . Thus at pH 7, the free amino terminal of the hydroxylamine follows charge controlled 1,2 addition to afford the oxime in an aldol-type of addition-elimination sequence, followed by ring closure through the OH terminal and elimination of MeSH to yield 5-methylthioisoxazole **13** (Scheme -6). On the other hand at pH 2.2, the


NH2OH.HCl / NaOMe / MeOH
reflux,10-15 h
R1
R2S
N
O
13
O
SR2
R1
SR2
1 f
R1 = aryl,heteroaryl
R2 = aryl
NH2OH.HCl / AcOH / NaOAc
EtOH / C6H6 / reflux, 8-10 hr
SR2
R1
N
O
14

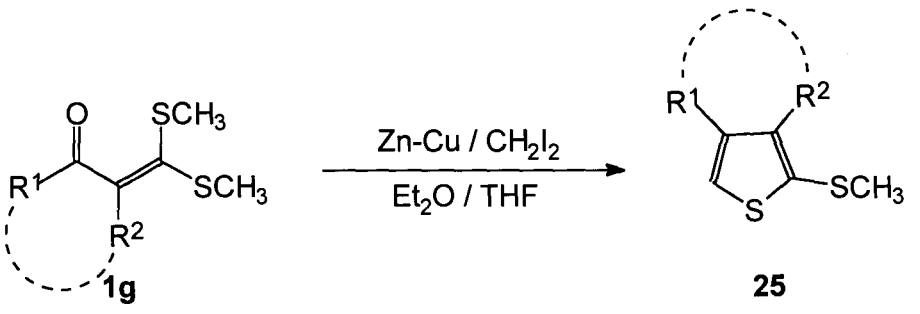
Scheme - 5



Scheme - 6

carbonyl oxygen of the oxoketene dithioacetal is protonated thereby facilitating affinity inversion. The hydroxylamine, which is in microscopic concentration under the reaction conditions, attacks through its amino terminal on the carbon atom bearing the positive charge to afford the isomeric isoxazole 3-methylthio-5-arylisoxazole **14** in excellent yields. Thus it has been demonstrated that reactivity of **1** could be altered under appropriate pH conditions so that unsymmetrical nucleophiles such as hydroxylamine species can attack both 1,2 as well as 1,4 addition to afford the respective regioisomers.

The utilization of **1** for the synthesis of 2-methylthio-3,4-disubstituted and annelated thiophenes[9] is shown in Scheme-7. Thus the α-oxo ketene dithioacetal **1g** when reacted under the Simmons-Smith reaction conditions the corresponding 2-methylthio-3,4- disubstituted thiophenes **25** were obtained in 58-65% overall yields. Its an interesting discovery and the first report on the formation of thiophene from **1** under Simmons-Smith reaction conditions. This mechanism is very interesting that the thiomethyl group which is cis to the carbonyl function attacks the carbenoid-methylene reagent to afford *insitu* the

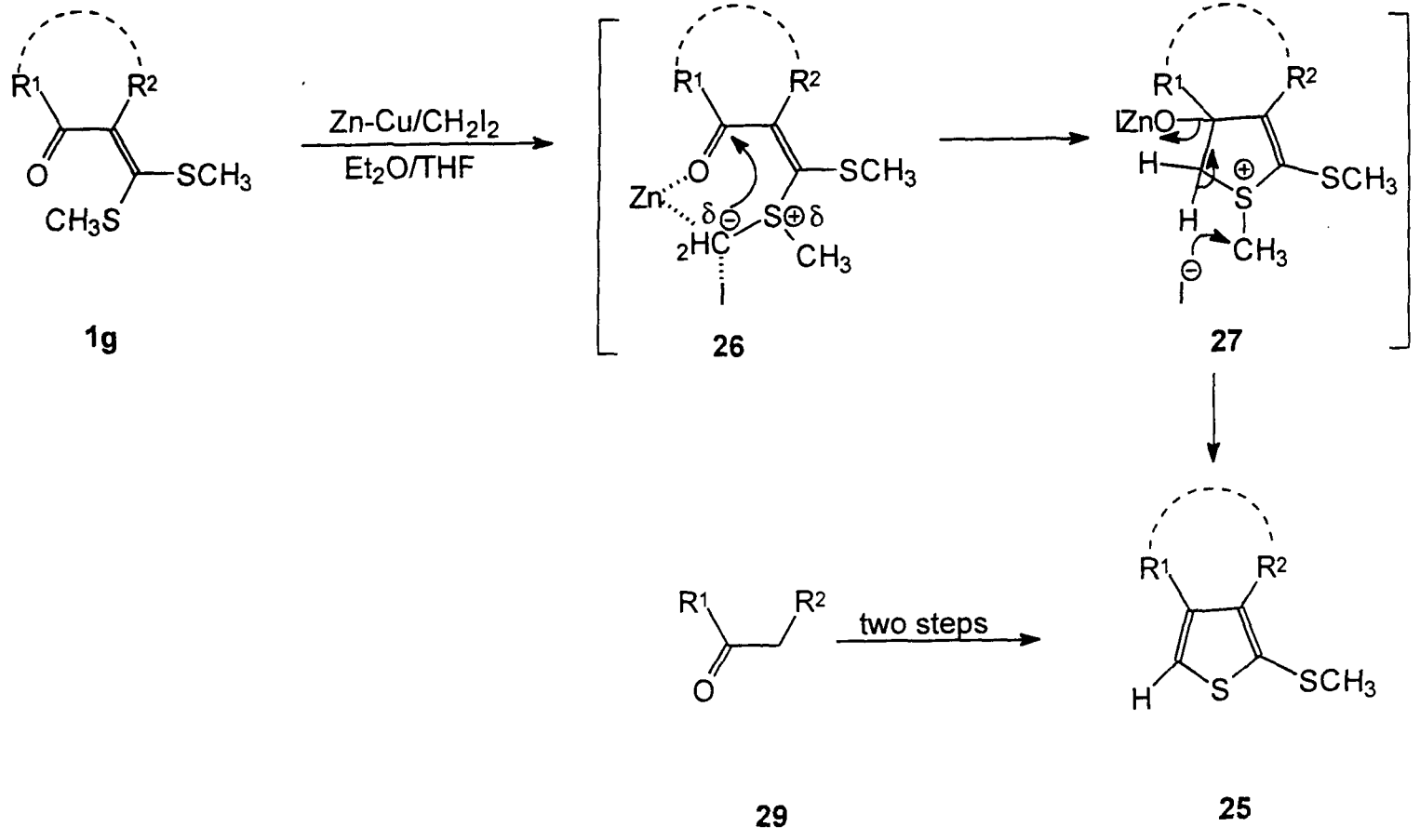


R^1 = alkyl,aryl,heteroaryl
R^2 = alkyl

Scheme -7

corresponding ylid **26** which follows intramolecular aldol addition - elimination sequence with simultaneous dethiomethylation of the quaternary thiomethyl group.(Scheme-8) This is a new method of thiophene synthesis developed in our laboratory which has wide applications for the synthesis of a large number of thiophenes. It is also possible to use this method as a diagnostic tool to determine the position of thiomethyl group as to whether it is cis or trans to the carbonyl group, since only the cis thiomethyl group yields the corresponding thiophenes **25** (Scheme 8). Thus α-oxoketene O,S acetals **29** in which the thiomethyl group is in the 'Z' configuration (i.e SMe cis to carbonyl) react under Simmons-Smith condition to afford the corresponding 2-alkoxy thiophenes **27** [7].(Scheme-9)

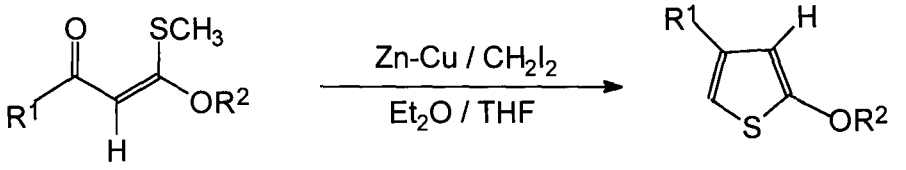
Middleton and co-workers [11] were the first to demonstrate the synthesis of pyrimidines from both cyanoketene S,S and O,O, acetals.(Scheme-10). Thus cyano ketene S,S acetal **1a** was reacted with guanidine in the presence of base to afford 5-cyano-2,4-diamino-6-methylthiopyrimidine **32a** in excellent yield. When they used the cyanoketene O,O-acetal **33** in the reaction with guanidine the corresponding 6-ethoxypyrimidine **32b** was obtained in high yield.



1g **26** **27**

29 **25**

Scheme - 8



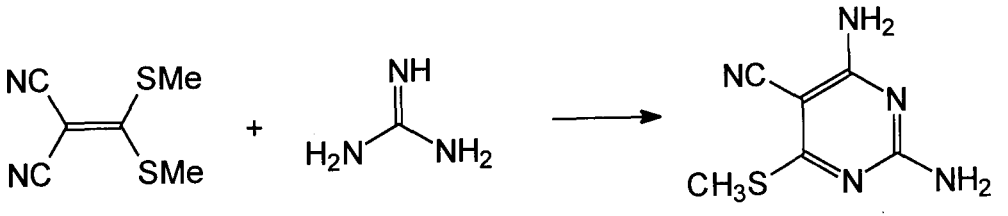
29

R^1 = aryl

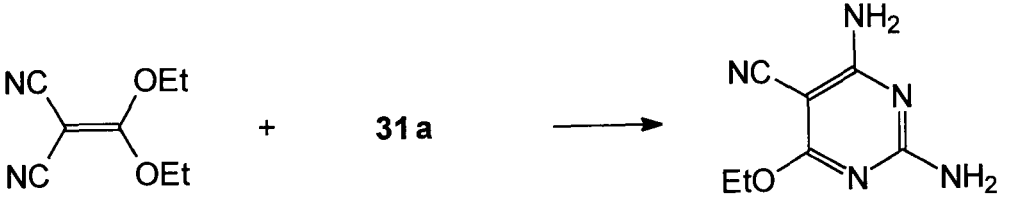
R^2 = alkyl,aryl

30

Scheme - 9

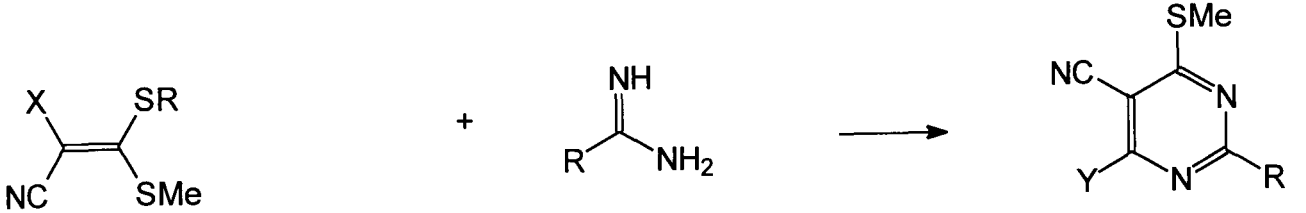


1a **31a** **32a**



33 **34b**

Scheme - 10



1h X=CN, R=Me
i X=COOEt, R=Me
j X=COOEt, R=3-thioindolyl

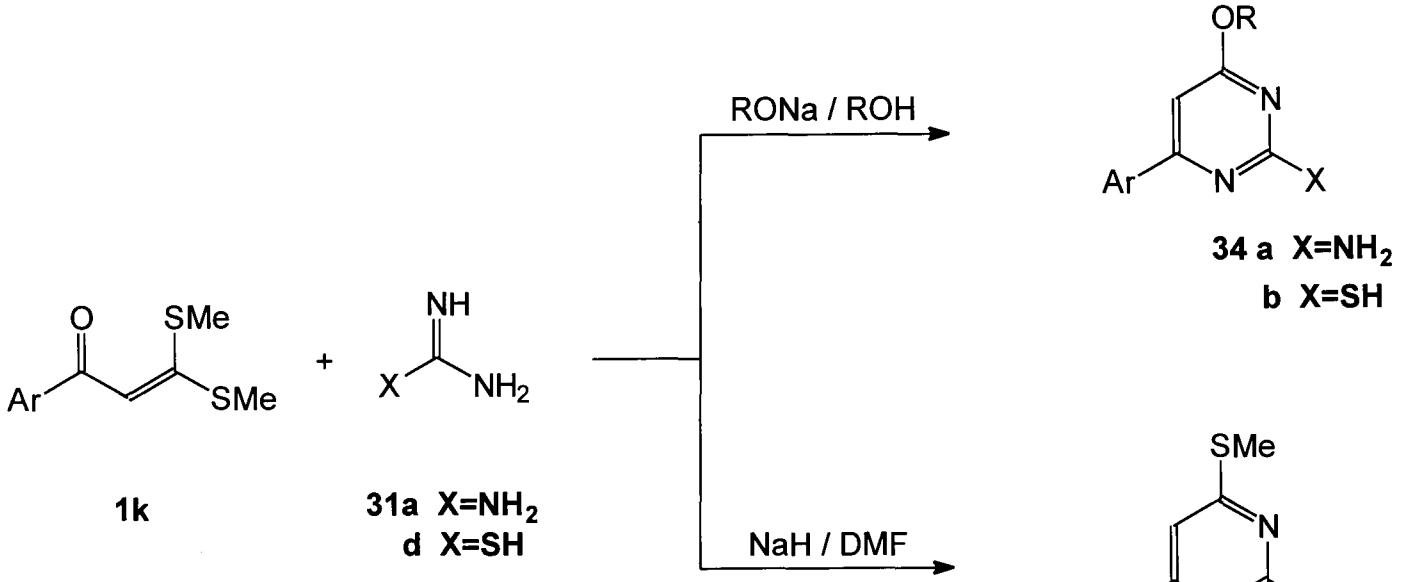
31a R=NH_2
b R=H
c R=Me

32c Y=NH_2
d Y=OH

Scheme - 11

Subsequently these reactions were further explored by later workers[12,13] by reacting the corresponding cyanoketene S,S-acetals with amidines/guanidine to afford the corresponding 4-methylthiopyrimidines 3**2c,d** (Scheme-11) in good yields.

In our laboratory, subsequently in 1974[14], it was demonstrated that the ∝-oxoketene dithioacetal **1k** were shown to be common intermediate for the synthesis of both 4-alkoxy **34c** and 4methylthio pyrimidine 3**5c** and that the retention of MeSH or its displacement by alkoxy group depends on the reaction of **1k** and guanidine and the medium of the reaction mixture.(Scheme-12) Thus when **1** was reacted with guanidine nitrate, in sodium ethoxide in boiling ethanol the corresponding 2-amino-4-ethoxy-5-arylpyrimidine **34a** was formed in excellent yields. On the other hand when the same reaction was carried out in the presence of NaH in an aprotic solvent such as DMF the product pyrimidine contained the thiomethyl group of the original oxoketene dithioacetal. In the reaction of **1** with guanidine to afford the alkoxy pyrimidines it is necessary to change the alcohol to have the respective alkoxy substituent in the product pyrimidine. The exchange



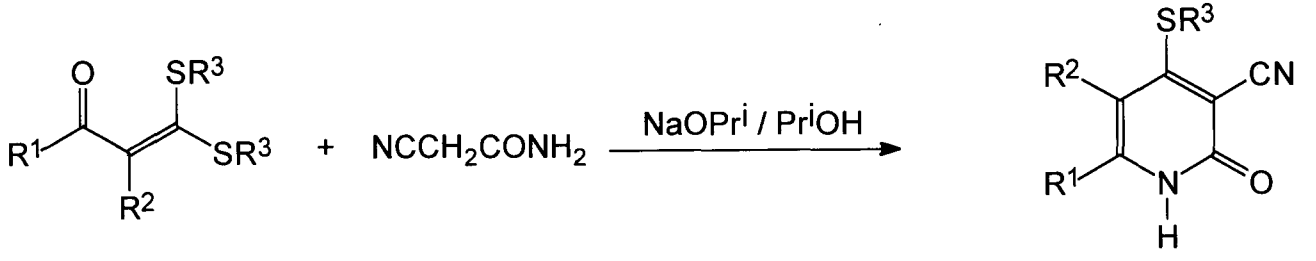
1k

31a X=NH_2
d X=SH

34 a X=NH_2
b X=SH

35 a X=NH_2
b X=SH

Scheme - 12



1l

36

37

Scheme - 13

of thiomethyl group by alkoxy group was unequivocally proved to have occurred in the pre-cyclisation α -oxoketene dithioacetal itself and not after the cyclisation to the 4-methylthiopyrimidines. The reactions to prove the pathway were conducted on the formation of pyrazoles (Scheme-3). This is a very useful method and unique for the reason that the same α-oxoketenedithioacetal can act as a common starting material to the alkoxy ,methylthio and amino pyrimidines .It must be mentioned here that in order to prepare the 4-alkoxy substituted pyrimidines, Middleton et al had to use the dicyanoketeneO,O acetals (Scheme-10) which besides being sensitive to moisture and reaction conditions, are more difficult to prepare.

The oxoketene dithioacetal of general formula **1** were also shown to react with the sodioderivative of cyanoacetamide and yield the corresponding 2(1H) pyridones[15,16] in excellent yields.(scheme-13). This method was extensively explored in our laboratory for the synthesis of not only 2(1H) pyridones but also for the corresponding napthyridines.[17]

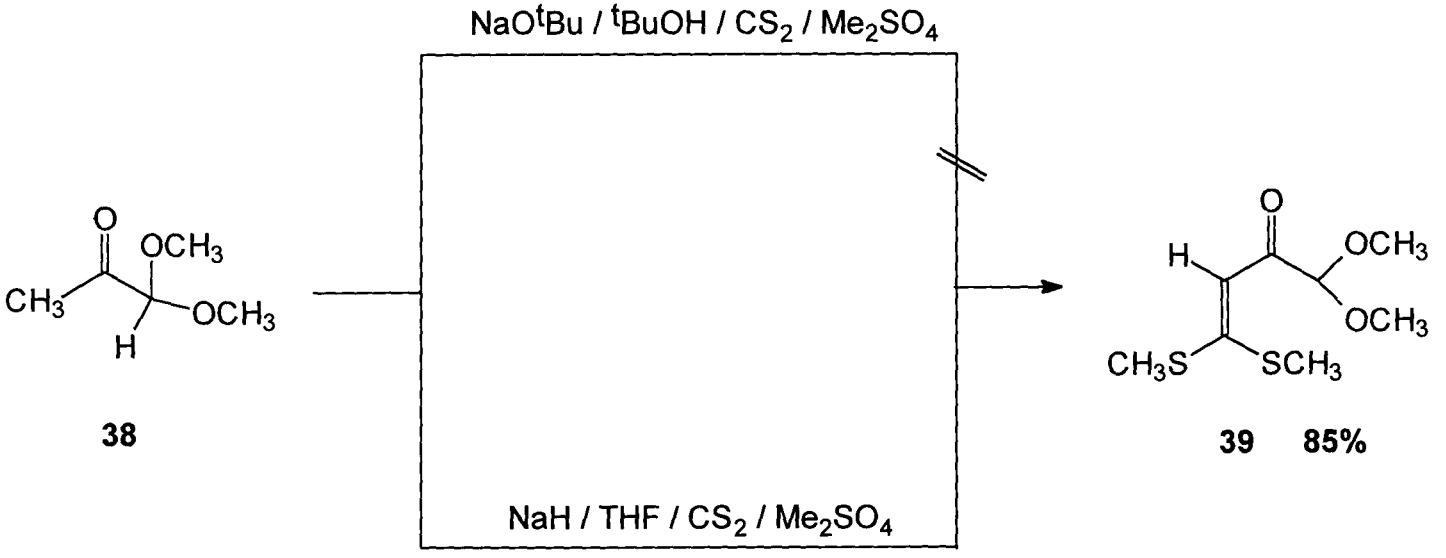
In the above section we have described some of the related reactions of α -oxoketenedithioacetals with various 1,2 and 1,3 binucleophiles to afford the corresponding 5-membered and 6-membered hetrocycles in high yields. However, none of these α-oxoketene dithioacetals carry any functional group on the carbon atom attached to the α-atom, which will become part of the product heterocycle. To achieve this goal it was contemplated to explore in the present investigation the possibilities of the preparation of a new oxoketene dithioacetal from pyruvaldehyde dimethyl acetal. The ketene dithioacetal derived from this active methylene ketone would possess an aldehyde function masked as its acetal so that its reaction with various bincucleophiles described in the present section would provide the heterocycles with an aldehyde acetal function. We have examined the synthetic characterisation of 4,4-bis(methylthio)-1,1-dimethoxy-3-buten-2-one and its synthetic application which are described as follows:

Synthesis and Properties of

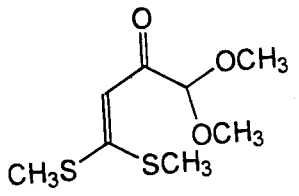
4,4-bis(methylthio)-1,1-dimethoxy-3-buten-2-one.

The commercially available pyruvaldehyde dimethylacetal **38** was used for the preparation of the α-oxo ketenedithioacetal **39**(Scheme-14). The use of base was critical since the reaction of **39** with CS_2 in the presence of sodium tertiary butoxide in tertiary butanol failed without yielding any well defined product. The method was abandoned as even the starting material could not be recovered . When **38** was treated with CS_2 in THF as solvent in the presence of NaH, the reaction was clean and yielded, after alkylation with Me_2SO_4,the desired product 4,4 bis(methylthio)-1,1-dimethoxy-3-buten-2-one **39** in 85% yield as deep red cubes (m.p.36°C, recrystallised from hexane: ethylacetate (98:2). The structure of **39** was established on the basis of its analytical and spectral data.

Ordinarily, the low melting solid of **39** was stable as a thick liquid without apparent decomposition even at r.t. on keeping even for months. Interestingly, the product was obtained in high yield and good purity only in THF and attempts to improve the yield by a change of solvent

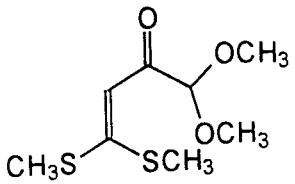

NaO^{t}Bu / ^{t}BuOH / CS_2 / Me_2SO_4
O
OCH3
CH3
OCH3
H
38
NaH / THF / CS_2 / Me_2SO_4
O
H
OCH3
OCH3
CH3S
SCH3
39 85%

Scheme - 14



39

^{1}H NMR SPECTRUM : 300MHz



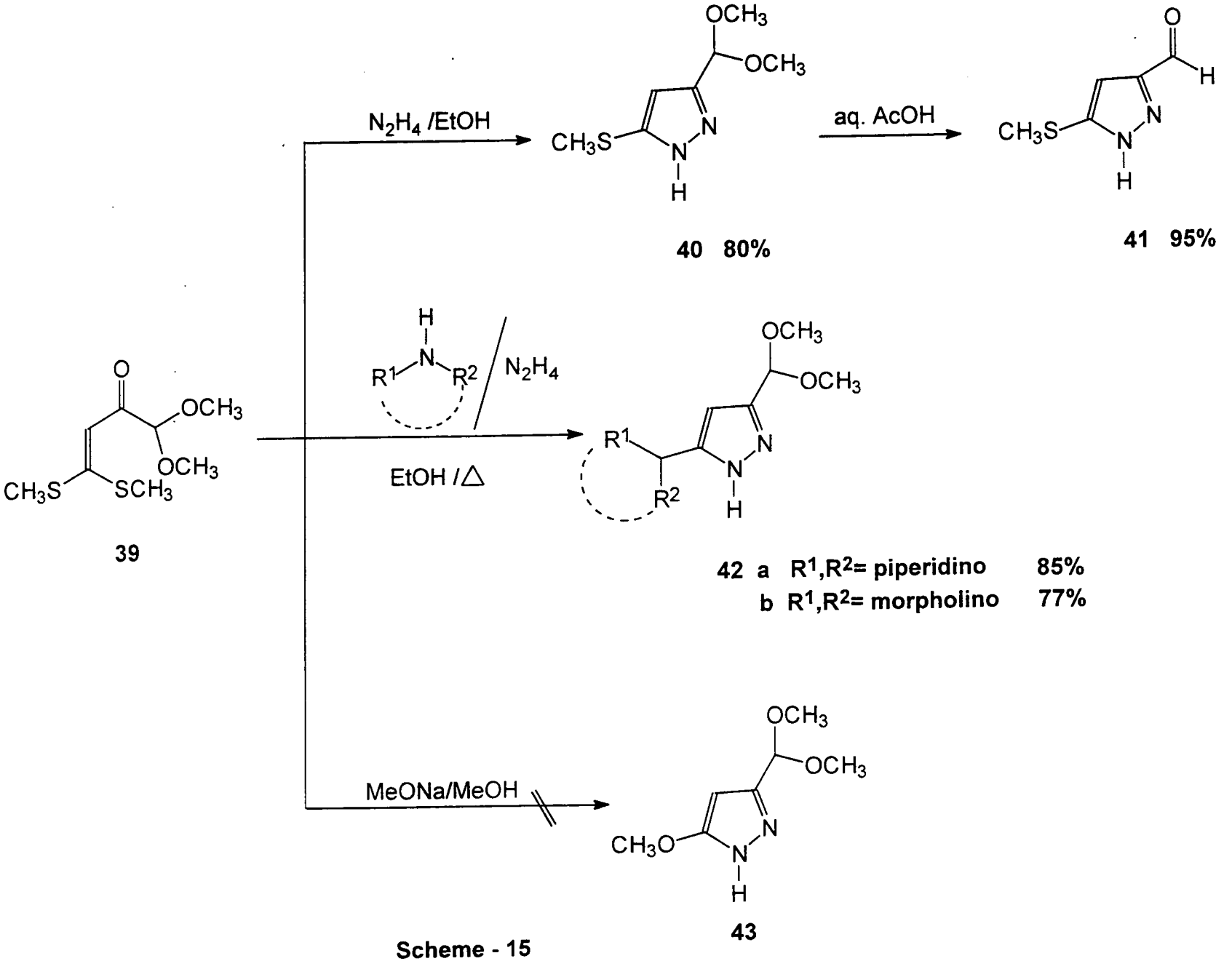
39

^{13}C NMR SPECTRUM : 75MHz

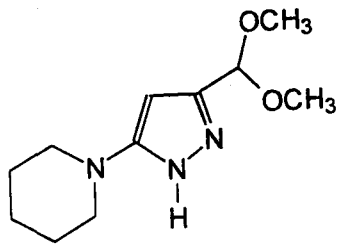
led to total loss of desired product. Some of the heterocycles prepared from this intermediate are described as follows:

In a typical experiment, when **39** was reacted with $N_2H_4.H_2O$ in refluxing ethanol for 2hr, the reaction mixture after removal of excess ethanol and work up yielded 3(5)-dimethoxymethyl-5(3)-methylthiopyrazole **40**(Scheme-15) in 80% yield. The pyrazole aldehyde acetal was obtained as brown flakes on long standing. The structure of **40** was established on the basis of its analytical and spectral data. The compound was subsequently subjected to acid hydrolysis in aqueous acetic acid (50% V/V) to afford the corresponding 5(3)-methylthiopyrazole-3(5) -aldehyde **41** in 95% yield. The structure of the aldehyde was established on the basis of its analytical and spectral data.

It may be noted that 3-aldehydes of pyrazole were generally prepared either by treating hydrazine hydrate with propargylaldehyde[18], or with diethoxyacetyl acetone and followed by hydrolysis[19].Gree et al[20] have reported a synthesis of pyrazoles aldehyde acetals and aldehydes from the reaction of of diazoacetaldehydedimethylacetal with


OCH3
OCH3
N2H4 /EtOH
CH3S
N
N
H
aq. AcOH
O
H
CH3S
N
N
H
40 80%
41 95%
O
OCH3
OCH3
CH3S
SCH3
39
H
N
R1
R2
N2H4
EtOH /△
OCH3
OCH3
R1
R2
N
N
H
42 a R1,R2= piperidino 85%
b R1,R2= morpholino 77%
MeONa/MeOH
OCH3
OCH3
CH3O
N
N
H
43

Scheme - 15



42a

^{1}H NMR SPECTRUM : 300MHz

acetylenes. There are also methods involving direct formylation,[21,22] in which the formyl group generally enters the ring at 4 position and not at 3 position. Therefore all the other methods described in the literature for the synthesis of pyrazole -3-aldehydes are generally designed from the open chain precursors.

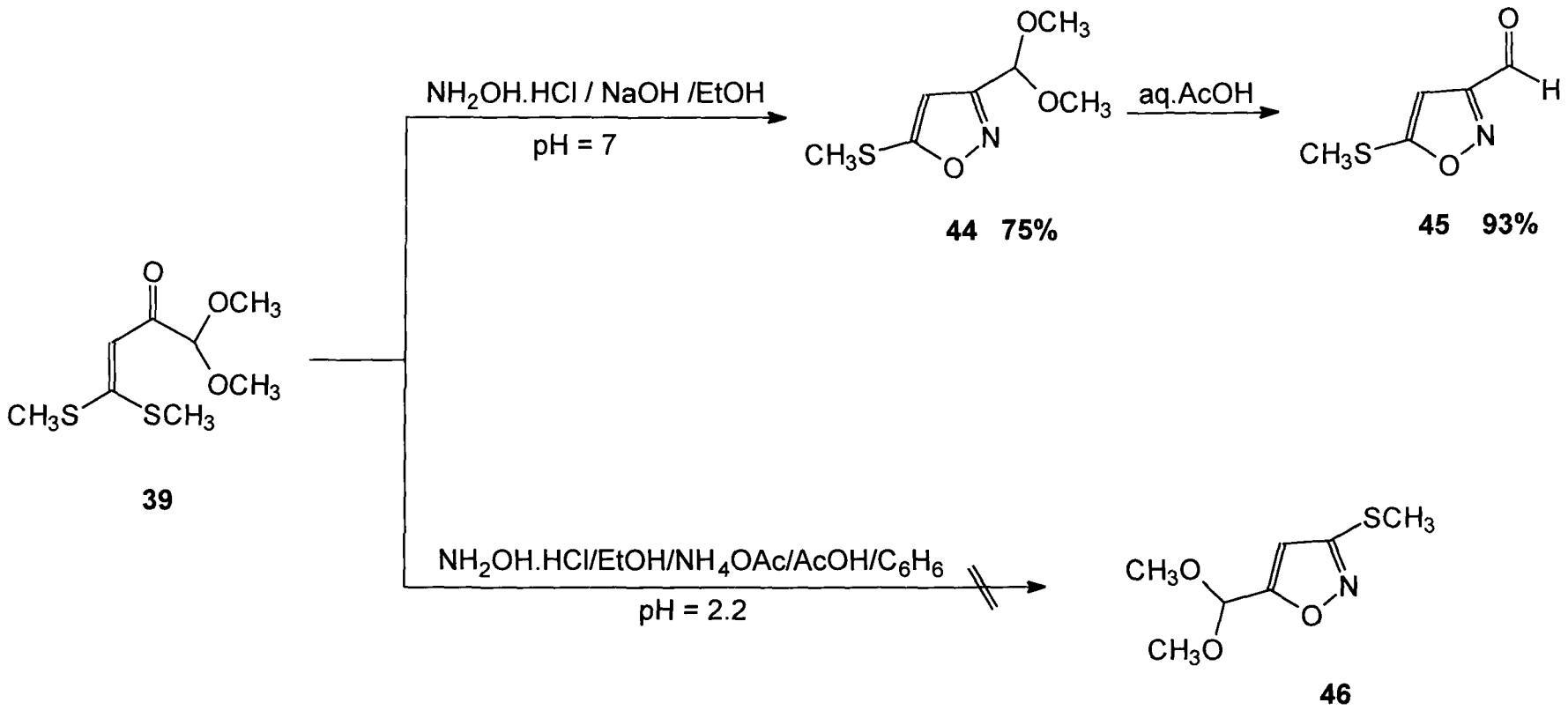
Interestingly when **39** was pre-treated *in situ* with piperidine in refluxing ethanol, followed by slow and dropwise addition of N_2H_4 it afforded the corresponding 3-dimethoxymethyl-5-piperidinyl pyrazole **42a** in 85% yield. The structure of the aldehyde acetal was fully established on the basis of analytical and spectral data. Similarly **39** was preheated with morpholine in boiling ethanol and $N_2H_4.H_2O$ was added slowly and dropwise to afford the corresponding pyrozole **42b** in 77% yield as pale brown flakes (hexane/ethylacetate). The structure was established based on its analytical and spectral data (see experimental).

In an another experiment when **39** was treated with sodium methoxide in methanol followed by addition of N_2H_4 as described above the expected 5-methoxy-3-dimethoxymethyl pyrazole **43** was not formed (Scheme-15). Thus other alkoxides were not tried.

The mercaptal **39** was then treated with $NH_2OH.HCl$ at pH=7 in EtOH.(Scheme-16) The reaction mixture after work up yielded the corresponding 3-dimethoxymethyl-5-methylthio isoxazole **44** as the only product in 75% yield. The structure of isoxazole was fully established by its analytical and spectral data.

The acetal **44** after hydrolysis with acetic acid as described earlier yielded the corresponding 5-methylthioisoxazole-3-carbaxaldehyde **45** in 95% yield. The carbonyl function displayed strong absorption in its IR spectrum at 1643 cm^{-1}. The aldehyde function exhibited a characteristic low field deshielded signal at 9.83 p.p.m. in the ^1H NMR spectrum, while its other analytical and spectral data support this structure.(See experimental section.).

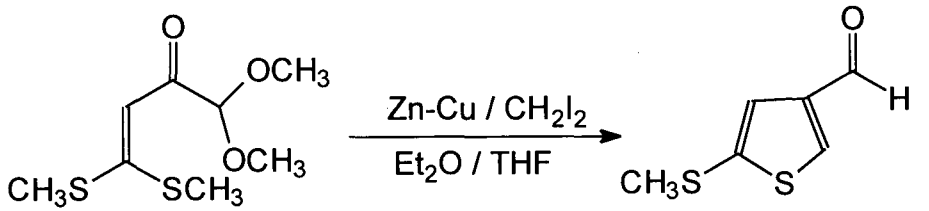
Interestingly attempts to extend this approach for the synthesis of the other regioisomer 5-dimethoxymethyl- 3 -methylthio isoxazole **46**


NH2OH.HCl / NaOH /EtOH
pH = 7
aq.AcOH
NH2OH.HCl/EtOH/NH4OAc/AcOH/C6H6
pH = 2.2
39
44 75%
45 93%
46

Scheme - 16

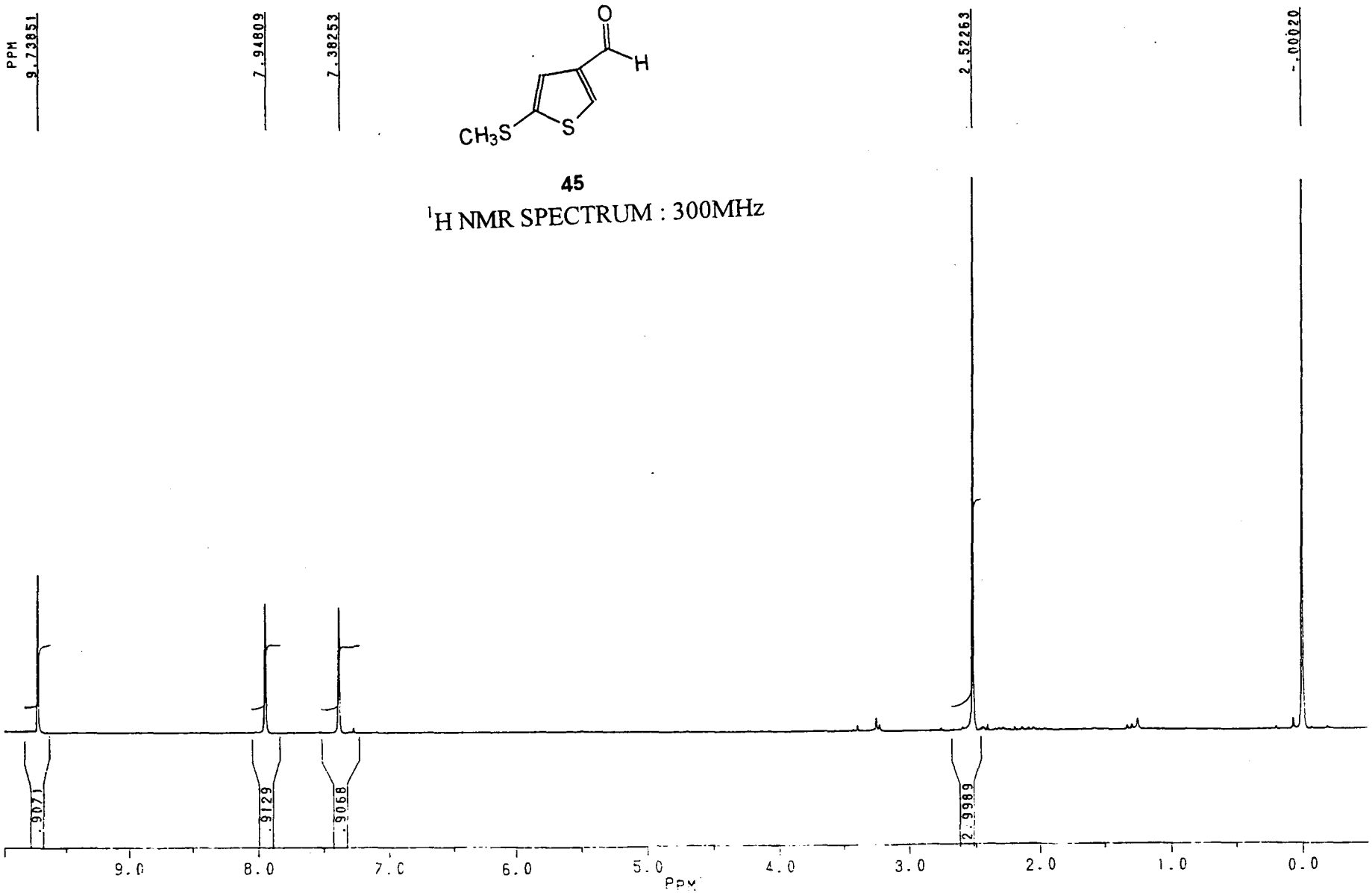
(Scheme-16) at pH 2.2 were not successful. Under the described reaction condition, the reaction did not yield any well defined product. It may be noted that isoxazole 3-aldehydes are reported in very poor yields[23,24] in the literature. Apparently, formylation after the ring formation is not possible at 3-position[24,25]. Thus only few reasonable synthetic methods are reported in the literature which involve carrying the aldehyde function from the open chain precursors and such effects have generally yielded poor yield of isoxozole aldehydes. Therefore, the present method is a very useful preparative method for a not so easily accessible aldehyde.

In the next experiment,when the mercaptal **39** was treated with the Simmons-Smith reagent, namely CH_2I_2 and Zn-Cu couple in a mixture of THF and ether, the reaction mixture on work up directly yielded the corresponding 5-methylthiothiophene-3-carbaxaldehyde **47** in 65% yield.(Scheme-17). The corresponding acetal was not detected in the reaction mixture, even in traces. The structure was fully consistent with the aldehyde which appears to have arisen from the cleavage of the



39 **45** **65%**

Scheme - 17



45

^{1}H NMR SPECTRUM : 300MHz

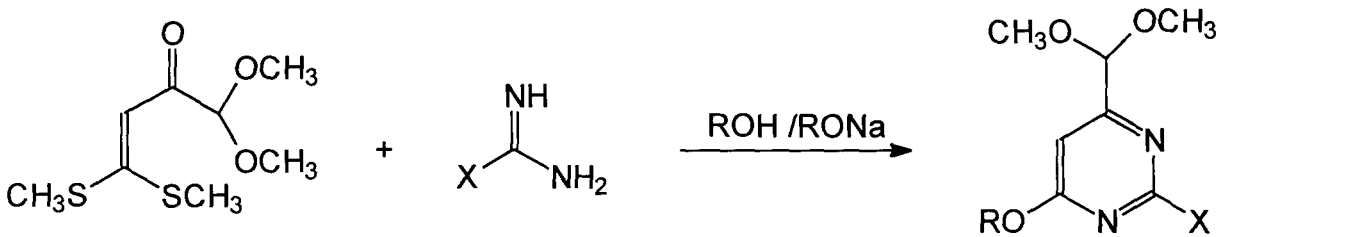
acetal during the reaction. Both the IR band at 1682 cm^{-1} and ^1H NMR signal at 9.73 p.p.m. proved the formation of the aldehyde.

Thiophene-3-aldehydes are also not accessible from ring-formylation through the Vilsmeier-Hack reaction, as it leads only to thiophene-2-aldehydes. One method involves the metallation of 3-bromothiophene with n-buLi followed by quenching with DMF to yield the 3-aldehyde[26]. The best method of preparation of thiophene-3-aldehyde is reported by Campaigne and co-workers[27], who reacted 3-bromomethylthiophene with hexamethelenetetramine followed by hydrolytic cleavage.

Other methods of obtaining thiophene-3-aldehyde based on modification of the pre-constructed thiophene ring, are not in attractive yields. The present method, starting from an easily accessible mercaptal, provides a direct synthesis of thiophene-3-aldehyde in good yield. The presence of thiomethyl group remains a handicap of this method as there is no convenient method at present for its removal

without affecting ring-sulphur. However, since the thiomethyl group can be replaced by alkyl, aryl and amino groups, this synthesis of substituted thiophene carboxaldehydes will acquire considerable synthetic value.

The mercaptal **39** was then utilised for the synthesis of pyrimidine aldehyde acetals. When **39** was reacted with guanidine nitrate in the presence of sodium methoxide in refluxing methanol the reaction mixture after work up yielded the corresponding 2-amino-6-dimethoxymethyl-4-methoxy pyrimidine **48a** in 65% yield(Scheme-18). The reaction as we had already observed underwent pre-cyclisation exchange of thiomethyl group by methoxy group to afford the direct synthesis of methoxy pyrimidines. The structure of **48a** was fully established based on its analytical and spectral data.. It is very difficult to introduce formyl group through electrophilic substitution at 4-position in the preconstructed pyrimidine ring. Thus only methods available are those which carry the aldehyde function from open chain precursors. Thus diethoxyacetylacetone[19] is known to react with guanidine to give the 4-aldehyde acetal which on subsequent hydrolysis yielded the desired aldehyde.



39

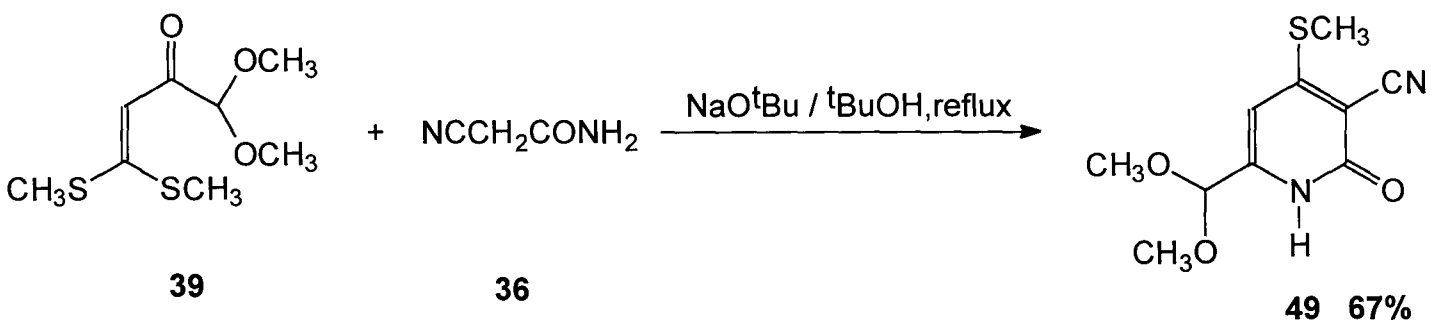
31a X=NH_2
d X=SH

48a X=NH_2,R=Me 65%
b X=NH_2,R=Et 60%
c X=SH, R=Me 61%
d X=SH, R=Et 56%

Scheme-18

The mercaptal **39** was also reacted with guanidine in the presence of ethanol and sodium ethoxide to yield the corresponding-6-ethoxy pyrimidine aldehyde acetal **48b** in 60% yield. Its structure was in conformity with its analytical and spectral data (see experimental). The mercaptal **39** was also reacted with thiourea in the presence of methanol/sodium methoxide as well as ethanol/sodium ethoxide to afford the corresponding 4-alkoxy-2-mercapto-6-dimethoxymethyl pyrimidines **48c, 48d** in 61% and 56% yield respectively. Both the compounds were assigned their structures based on their analytical and spectral data.

The mercaptal **39** was also reacted with the sodio derivative of cyanoacetamide **36** in sodium tertiary butoxide in refluxing tertiary butanol to afford 3-cyano-6-dimethoxymethyl-4-methylthio-2(1H) pyridone **49** in 67% yield. The assigned structure is in conformity with its analytical and spectral data.



39 **36** **49 67%**

Scheme -19

In conclusion we have demonstrated the preparation and characterisation of an α-oxoketene dithioacetal derived from pyruvaldehyde dimethyl acetal and its use in the synthesis of various heterocyclic aldehydes. The mercaptal may have other applications which we continue to explore.

References:

1a) Junjappa,H.; Ila,H.; Asokan,C.V. *Tetrahedron*,**1990**,*46*,5423.

b) Dieter,R.K.; *Tetrahedron*,**1986**,*42*,3029.

2) Yokoyama, M..; Togo, M.;. Kondo,S.*Sulfur Rep.***1990**,*10*,23

3) Gompper,R.; Topfl.W.; *Chem. Ber.* **1962** *95*, 2881.

4) Saquet, M.; Thuillier,A. *C.R. Acad. Sci.; Paris, Ser.C. 266*, 290.

(**1968**); Chem. Abstr. *69*, 36019 (**1968**).

5) Chauhan, S.M.S.; Junjappa,, H. *Synthesis,* **1975**, 798.

6) Singh,G.; Deb,B.; Ila,H.;Junjappa,H.; *Synthesis.***1987**,280.

7) Rahman, A.; Vishwakarma, J.N.; Yadav, R.D.; Ila, H.; Junjappa,H. *Synthesis*, **1984**, 247.

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

9) Thomas, A.; Singh, G.; Ila, H.; Junjappa, H.; *Tetrahedron Lett.* **1989**, 3093.

10) Bhat, L.; Ila, H.; Junjappa, H.; *Synthesis,* **1993**, 959.

11) Middleton, W.J.; Engelhardt, V.A. *J. Am.Chem. Soc.* **1958**, 2829.

12) Dornow, A.; Dehmar, K. *Chem. Ber.* **1967**, *100*, 2577.

13) Kisaki, S.; Tominaga, Y.; Matsuda, Y.; Kobayashi, G. *Chem.Pharm. Bull.* **1974**, *22*, 2246.

14) Chauhan, S.M.S.; Junjappa, H. *Synthesis*, **1974**, 880

15) Rastogi, R.R.; Ila, H.; Junjappa, H. *J.C.S. Chem. Commun.* **1975**, 645.

16) Rastogi, R.R.; Kumar, A.; Ila, H.; Junjappa, H. *J.C.S. Perkin I* **1978**, 549.

17) Rastogi,R.R.; Kumar.; Ila,H.; Junjappa,H. *J.C.S.Perkin.I*, **1978**, 554.

18) Bredereck, H.; Sell, R.; Effenberger, F.; *Chem. Ber.* **1964**, 3467.

19) Huttel, R.; *Chem. Ber.*, **1941**, *74 B*, 1680.

20) Abdallah, H; Gree, R.; *Tetraahedron Lett.* **1980**, *21*, 2239.

21) Finar, I.L.; Manning, M. *J. Chem. Soc.* **1961**, 2733.

22) Finar, I.L.; Lord, G.H. *J. Chem. Soc.*, **1959**, 1819.

23) Yamanaka, H.; Sakamoto, T. *Heterocycles*, **1977**, *7*, 5.

24) Kallury, R.K.M.R.; Devi, P.S.U., *Tetrahedron Lett.* **1977**, *41*, 3655.

25) Caramella, P.; Cereda, E. *Synthesis*, **1971**, 433.

26) Gronowitz. *Arkiv.kemi*, **1955**, *8*, 441.

27) Campaigne, E.; Burgeos, R.C.; McCarthy, W.C. *Org. Synth. Coll. Vol IV*, p 918.

Experimental Section

General: Melting points were obtained on a "Thomas Hoover" (capillary method) apparatus and are uncorrected. The Infrared spectra were recorded on a Perkin-Elmer 983 Spectrometer. ^{1}H NMR (90 MHz) were recorded on a Varian EM-390 spectrometer. High resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75.43 MHz) were recorded on a Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either tetramethyl silane (TMS) as internal lock (for ^{1}H NMR), or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C NMR). Mass spectra were recorded on a Jeol JMS-D 300 Mass spectrometer. Masses are reported in units of mass over charge (m/z), the molecular ion peak and other peaks are indicated by "M^{+}" and "%" respectively. Elemental analysis were carried out in a Hereaus CHN-O-Rapid Analyser.

Analytical thin layer chromatography (TLC) were performed on glass plates coated with silicagel obtained from ACME. Spots were visualized using Iodine vapour or acidic pottassium permanganate solution. ACME's silica gel (60-120 mesh) was used for column

chromatography, for which eluents were used after simple distillation of commercial materials. All solvent evaporations were done using a water bath.

Chemicals and Reagents:

Commercially available NaH, 50% suspension (SPECTRO-CHEM) was used. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl. Hydrazine hydrate, hydroxylamine hydrochloride were purchased from SD fine chemicals and used as such. Zinc-copper couple, diiodomethane and pyruvaldehyde dimethyl acetal were purchased from Aldrich and used as such. Common solvents were used after a simple distillation from commercially available materials.

Preparation of 4,4-Bis(methylthio)-1,1-dimethoxy-3-buten-2-one(39)

To a suspension of NaH (9.6g, 0.2 mol) in dry THF (30 ml) was added dropwise a solution of pyruvaldehyde dimethyl acetal (12.1 ml, 0.1 mol) and carbon disulfide (6.2 ml, 0.1 mol) in dry THF (75ml) at 0°C and allowed to stir for 8 hours at 5-10°C. Neutral dimethyl sulphate (40 ml, 0.4 mol) in 50 ml THF was added dropwise at 0°C and allowed

to stir for 8 hours. It was then poured into saturated ammonium chloride solution (250 ml). It was extracted with chloroform (2x100 ml), washed with brine, dried over anhydrous sodium sulphate and concentrated. Column chromatography over silica gel using hexane/ethyl acetate: (99:1) yielded the product as deep red flakes in 85% yield (18.9 g).

4,4 - Bis(methylthio)-1,1-dimethoxy-3-buten-2-one (39)

Dark red flakes; m.p 36°C;(hexane:ether) yield 18.9g (85%); IR (CCl_4) 1642,1102,1069,1013 cm^{-1};^1H NMR(300MHz, CCl_4): 2.47 (s,3H,SCH_3), 2.50(s,3H,SCH_3),3.38(s,6H,OCH_3),4.43(s,1H,H-C(OCH_3)$_2$), 6.29 (s,1H, =CH); ^{13}C NMR ($CDCl_3$, 75mhz) 14.52, 16.94, 53.97, 104.02, 107.84, 166.00, 187.49; MS m/z: 222 (M^+, 222, (13.6%), 148,(100%). (Anal calcd. for $C_8H_{14}O_3S_2$: 222.32, C, 43.22%; H,6.35%. Found, C, 43.33%; H, 6.25%).

Preparation of 3(5)-dimethoxymethyl-5(3)-methylthiopyrazole (37)

A mixture of **39** (1.1g, 5 mmol) and hydrazine hydrate (0.2 ml, 5 mmol) in ethanol (25 ml) was refluxed for 2 hours (monitored

by TLC) and the solvent was removed by distillation at reduced pressure. The residue was diluted with water and extracted with chloroform (2x50 ml), washed with water, dried over anhydrous sodium sulphate and concentrated to yield analytically pure product. It crystallized as brown flakes on long standing.

3(5) dimethoxy methyl-5(3)-methylthio pyrazole (40)

brown flakes; m.p. 135-136°C; yield 0.75 g (80%); IR (KBr) 3240, 1437,1365,1120,1091cm^{-1}; ^{1}H NMR(300MHz, $CDCl_3/CCl_4$)2.49(s, 3H, SCH_3), 3.34(s,6H OCH_3), 5.54 (s,1H,H-$C(OCH_3)_2$), 6.25 (s,1H, H-3); ^{13}C NMR. (75MHz,$CDCl_3$) 16.43, 51.79, 97.25, 104.5, 143.09, 144.25; MS m/z 188 (M^+ 188, (43.3%), 157 (100%) 156, 96.3%) (Anal Calcd. For $C_7H_{12}N_2O_2S$ 188.25 ; C, 44.66%, H, 6.43%, N, 14.88%; Found C, 44.80 %, H,6.31 %. N ,14.69%.)

General procedure for preparation of 3(5)dimethyoxymethyl-5(3) amino pyrazoles.

A mixture of **39** (1.1 g 5 mmol) and the amine (10 mmol) in ethanol (25 ml) is refluxed for 2 hours then hydrazine hydrate (0.2 ml, 5 mmol) in ethanol (5 ml) is added portionwise over 2 hours and reflux

continued for 3 hours (monitored by TLC). The solvent is then distilled off and the residue is diluted with water. It is then extracted with chloroform (2x50 ml), washed with brine(2x25ml), dried over anhydrous sodium sulphate and concentrated to yield a brown solid. Recrystallisation from chloroform:hexane yielded analytically pure pyrazoles.

3(5)-Dimethoxymethyl-5(3)(1-piperidino) pyrazole (42a)

Brown crystals m.p 93-94°C ($CHCl_3$:hexane); yield 0.96 g (85%); IR(KBr): 3191, 2928, 1568,1362,1108 cm^{-1}; ^1H NMR(300MHz, $CDCl_3$) 1.51-1.59(m,2H,CH_2), 1.64-1.71(m,4H,CH_2), 3.16(t,4H,J=Hz,N-CH_2), 5.49 (s, 1H, H-C(OCH_3)$_2$) 5.72 (s, 1H, H-3) (Anal. Calcd. for $C_{11}H_{19}N_3O_2$ 225.29 C, 58.65%, H, 8.50%, N, 18.65%; Found C, 58.53% H, 8.59 % N, 18.76 %).

3(5)-Dimethoxymethyl-5(3)-(4-morpholino)pyrazole (42b)

Pale brown crystals.;m.p. 79.80°C ($CHCl_3$-hexane) yield 0.87 g (77%); IR(KBr): 3190, 2827, 1560, 1490, 1121 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$),3.18-3.21 (m,4H,N-CH_2), 3.34 (s,6H, OCH_3), 3.81-3.85 (t, 4H,

O-CH_2 J = 4.8 Hz), 5.51 (s,1H, H-C (OCH_3)$_2$), 5.73 (s,1H, H-3) (Anal. Calcd. for $C_{10}H_{17}N_3O_3$, 227.25 C, 52.85%, H, 7.54%, N, 18.49%; Found C, 52.78%; H, 7.59%, N, 18.58%)

Preparation of 3-(dimethoxymethyl)-5-(methylthio)isoxazole (44): A mixture of **39** (1.1g, 5 mmol) and hydroxylamine (5 mmol) (generated from hydroxylamine hydrochloride (0.34g, 5 mmol) and NaOH (0.2g, 5 mmol) is refluxed in ethanol (25 ml) for three hours (monitored by TLC). The solvent is then distilled off at reduced pressure and the residue is diluted with water. It is then extracted with chloroform, washed with water, and concentrated. Brown crystals were obtained on long standing.

3-dimethoxymethyl-5-methylthio isoxazole (44)

brown crystals; m.p.75-76°C; yield 0.82g(75%); IR (KBr) 2994, 2934,1544, 1443,1194, 1115 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) 2.58 (s, 3H, SCH_3), 3.35 (s, 6H, OCH_3), 5.30 (s, 1H, H-C (OCH_3)2), 6.07 (s, 1H, H-5). (Anal. Calcd. for $C_7H_{11}NO_3$ 189.23 ; C, 44.43 %, H, 5.86 %, N, 7.40 % ; Found C, 44.56%, H, 5.92%, N, 7.51 %).

Preparation of 2-methylthio thiophene-4-carboxaldehyde(45)

The Simmons - Smith reagent is first prepared. To a well stirred suspension of zinc-copper couple (3g) in dry ether (25 ml) under nitrogen atmosphere, a small crystal of iodine and CH_2I_2 (1.34 ml, 6.7 mmol) (2.5 eq) are added and the reaction mixture is refluxed for 45 min. A solution of **39** (1.5g, 6.7 mmol) in dry THF (25 ml) is added and the reaction mixture is further refluxed with stirring for 6 hr. (monitored by TLC). The solvent is removed under reduced pressure and the residue is diluted with water (200 ml) followed by addition of chloroform (150 ml). The reaction mixture is filtered, the residue washed with chloroform and the combined organic layer is washed with satd. NH_4Cl solution and water, dried over anhydrous sodium sulphate and evaporated to give crude aldehyde, which is purified by column chromatography over silica gel using hexane as eluent.

2-(methylthio) thiophene-4-carboxaldehyde (47)

brown liquid; yield (65%) IR (CCl_4); 1682 ,1506,1387 cm^{-1}, ^1H NMR (300MHz, CCl_4). 2.52 (s,3H, SCH_3), 7.38 (s, 1H, H-3), 7.95 (s,1H,H-5), 9.74 (s, 1H, CHO); ^{13}C NMR (75MHz, $CDCl_3$) 20.93, 127.41, 136.56, 140.31, 143.22, 182.00; MS m/z 158, M^+ (48.1), 83 (100%) (Anal. Calcd. for $C_6H_6OS_2$, 158.24 ; C, 45.54%, H 3.82 %, Found C,45.39 %, H,3.96 %).

Preparation of 2-amino-4-dimethoxymethyl-6-alkoxy pyrimidine :

To a solution of sodium alkoxides (prepared by dissolving sodium [0.23g, 10 mmol] in 50 ml of respective alcohol) guanidine nitrate (0.61g, 5mmol) was added and the reaction mixture was stirred for 10-15 minutes. Then **39** (1.1g, 5 mmol) was added and refluxed for 6 hours (monitored by TLC). The solvent was distilled under reduced pressure and the residue was quenched in ice. It was extracted with chloroform, washed with brine, dried over anhydrous sodium sulphate and concentrated. The crude products were then crystalized froma $CHCl_3$/ether to yield pure pyrimidines.

2-amino-4-dimethoxymethyl-6-methoxy pyrimidine (48a)

Colourless crystals, m.p. 112-113°C ($CHCl_3$/ether); yield 0.65g (65%)

IR(KBr):3438,3267,1624,1581,1105,1061 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) 3.36 (s, 6H, $(OCH_3)_2$), 3.88 (s,3H,OCH_3), 5.10(s, 1H, H-$C(OCH_3)_2$), 5.51 (brs, 2H, NH_2), 6.29 (s, 1H, H-5); ^{13}C NMR (75MHz, $CDCl_3$). 53.17, 53.53, 95.51, 101.99, 163.20, 166.24, 171.47; MS m/z 199 (M^+, (3.2%), 153 (100) (Anal. calcd. for $C_8H_{13}O_3N_3$ 199.20; C, 48.24 %, H, 6.58 %, N, 21.09 %. Found C, 48.35% , H, 6.69 %, N, 21.20 %)

2-amino-4-dimethoxy methyl-6-ethoxy pyrimidine (48b)

Colourless crystals, m.p. 115-116°C ($CHCl_3$/ether); yield 0.63g (60%) IR (KBr) 3301, 1632, 1575, 1169, 1057 cm-1. ^1H NMR (300MHz, $CDCl_3$) 1.36 (t, 3H, CH_3 J= 6Hz), 3.36 (s,6H, OCH_3), 4.31 (q, 2H, CH_2, J=6Hz), 5.08 (s, 1H, H-$C(OCH_3)_2$), 5.35(brs, 2H, NH_2), 6.27(s, 1H, H-5) ^{13}C NMR (75MHz, $CDCl_3$) (14.39, 53.22, 62.06, 95.70, 102.08, 163.14, 166.26, 171.12); MS m/z 213 (M^+ 24.9%) 181 (100%). (Anal. calcd. for $C_9H_{15}N_3O_3$ 213.23; C, 50.70%, H,7.09 %, N, 19.71 %. Found C, 50.82%, H, 7.21 %, N, 19.90 %).

Preparation of 4-dimethoxymethyl-6alkoxy-2-mercapto pyrimidine :(48c)

To a mixture of thiourea (0.38g, 5 mmol) and sodium alkoxides (prepared by dissolving 0.2g of sodium in 25 ml of respective alcohol), **39** (1.1g,5mmol) was added and the reaction mixture was refluxed for 6 hours (monitored by TLC). The solvent was removed by distillation at reduced pressure and the residue was treated with glacial acetic acid (10 ml). The reaction mixture was then poured on crushed ice and extracted with chloroform (2x75 ml). The extracts are then washed with water, dried over anhydrous sodium sulphate and concentrated. Recrystalisation from chloroform/ether yielded pure pyrimidines.

4-dimethoxymethyl-2-mercapto-6-methoxy pyrimidine (48c)

Colourless crystals, m.p. 107-108°C($CHCl_3$/ether); Yield = 0.59g (55%) IR (KBr) 3421, 1621 1567, 1472,1186, 1049 cm^{-1}, ^1H NMR (90MHz, $CDCl_3$) 3.5 (s,6H, $(OCH_3)_2$), 4.1 (s,3H, OCH_3), 5.4 (s,1H, H-$C(OCH_3)_2$), 6.3 (s,1H, H-5); MS m/z 216 (M^+, 8%), 74 (100%), (Anal. Calcd. for $C_8H_{12}N_2O_3S$ 216.35; C, 44.43%, H, 5.59 %, N, 12.95 % Found C, 44.61 %, H, 5.69 %, N, 13.09 %).

4-dimethoxymethyl-6-ethoxy-2-mercapto pyrimidine (48d)

colourless crystals, m.p 118-119°C, ($CHCl_3$/ether); yield 0.6g (53%) IR(KBr): 1581, 1536 cm^{-1}, ^1H NMR (300MHz, $CDCl_3$) 1.3 (t, 3H, CH_3, J=5Hz), 3.4 (s,6H, OCH_3), 4.29 (q, 2H,CH_2, J = 5Hz), 5.2 (s, 1H, H-$C(OCH_3)_2$), 6.2 (s, 1H, arom); (Anal. Calcd for $C_9H_{14}N_2O_3S$ 230.28 ; C, 46.94 %, H, 6.13 %, N, 12.17 %. Found C, 46.71%, H, 5.98 %, N, 12.31 %).

Preparation of 3-cyano-6-dimethoxymethyl-4- methylthio-2(1H) pyridone:(49)

To a solution of sodium tertrary butoxide in tertiary butanol (prepared by dissolving molecular sodium [0.12g, 5 mmol] in 50 ml tertiary butanol), cyanoacetamide (0.42g 5 mmol) was added and the mixture was shaken for 10 minutes. Then **39** [1.1g, 5 mmol] was added and the mixture refluxed for 5 hours (monitored by TLC). Evaporation of the solvent yielded the sodium salt of the pyridone as a yellow solid, which was dissolved in water (15 ml) and carefully acdified with 8% HCl to

yield the pyridone acetal as an amorphous solid. It was filtered, washed, first with water and then with ether. Recrystalisation from $CHCl_3$ yielded the analytically pure pyridone.

3-cyano-6-dimethoxymethyl-4-methylthio-2(1H) pyridone(49)

yellow solid, m.p. 149-150°C ($CHCl_3$); yield 0.89g(67%) IR (KBr): 2213, 1656,1602,1468;1353,1205 cm^{-1}. ^1H NMR (300MHz, DMSO-d_6) 2.62 (s,3H,SCH_3), 3.34 (s,6H, OCH_3), 5.22 (s,1H, H-C(OCH_3)$_2$), 6.37 (s,1H, =CH); ^{13}C NMR (75MHz, DMSO-d_6) 13.91, 53.8, 98.75, 99.16, 114.82, 148.23, 153.68, 159.53, 164.17. (Anal. Calcd. $C_{10}H_{12}N_2O_3S$ 240.28 ; C, 49.99%, H, 5.03%, N, 11.66 %. Found C ,49.79 %, H, 5.17 %, N, 11.79 %).

Procedure for Hydrolysis of acetals to aldehydes

To 5 mmol of the aldehyde acetal (**40** or **44**) 15 ml of aqueous acetic acid (50%) is added and allowed to stir for 6 hours at 60°C (monitored by TLC). It is then neutralized with K_2CO_3 and the precipitated aldehyde is filtered. It is then washed first with water and then with ether and dried. It is then recrystalized from hot chloroform.

3(5)-Methylthiopyrazole-5(3)-aldehyde (41)

pale brown flakes, m.p.160-161°C;($CHCl_3$), yield = 0.67g (95%); IR (KBr) 3154, 1696, 1535 cm^{-1} ; ^1H NMR (DMSO-d_6, 90 MHz), 2.4 (s,3H, SCH_3), 6.9 (s,1H, =CH) 10.1 (s,1H,CHO); (Anal calcd for $C_5H_6N_2OS$: 142.18; C, 42.24%, H, 4.25%, N, 19.70%. Found C, 42.35, H, 4.23%, N, 19.51%.)

5-methylthio isoxazole-3-aldehyde:(45)

Pale brown flakes m.p. 122- 123°C ($CHCl_3$); Yield 0.66g (95%). IR(KBr) 1643,1535 cm^{-1}, ^1H NMR(300MHz, DMSO-d_6), 2.39 (s,3H, SCH_3), 6.83 (brs, s,1H, =CH), 9.83 (s, 1H, CHO), Anal. Calcd for $C_5H_5NO_2S$, 143.17, C, 41.95%, H, 3.52%, N, 9.78%. Found C, 42.19%, H, 3.63%, N, 9.89%.

CHAPTER THREE

SYNTHESIS OF NOVEL PUSH-PULL DONOR-ACCEPTOR ETHYLENES AND POLYENES : POTENTIAL SECOND ORDER NON-LINEAR OPTICAL CHROMOPHORES

INTRODUCTION:

The molecular non-linear optical response generally quantified as the first order hyper polarisability, represented by β, is found in certain types of push-pull ethylenes and polyenes possessing intrinsic dipole moment. These molecules through their π conjucation provide a pathway for redistribution of electronic charge under the influence of an electric field. For a situation like this, the donor and the acceptor substituents separated by π conjucation generally display varying β values depending upon their donor-acceptor capabilities. The length of conjucation separating these two terminals also affects the β-value of the system. Generally these molecules behave like charge transfer complexes providing a source of charge at one end and electron

deficiency at the other end, and experience a natural propensity for charge transfer through electron redistribution over the entire conjugation. Incorporation of benzene rings in the polyenes limit the molecular non-linearity but enhance thermal stability.[1] The energy barrier due to aromatic delocalisation is considered to be responsible for lowered β-values of these systems. Thus there has been synthetic activity to incorporate easily delocalisable 5-membered heterocycles instead of benzenoids to create push-pull ethylenes with improved β-values[2,3,4]. Substituting thiophene for benzene as an conjugating segment in donor-acceptor compounds has been found to enhance β values.[2a]

The non-linear optical property displayed by these molecular systems can find application in optoelectronics, telecommunication, optical data storage, optical information processing, laser scanning control functions and in general in all integrated optical technology. Chemistry, at present is advanced enough to design and construct many polymers and polyenes with specific properties and consequently a

large volume of synthetic work is being devoted for the construction of such molecules .

Due to their electron withdrawing nature, groups such as carbonyl, nitro, nitrovinyl, nitroso, sulphones, disulphonyl vinyl, cyano, tricyanovinyl and barbituric acid etc. have been generally examined as potential acceptor terminals. On the other hand, only a few electron donor functional groups such as alkoxy, and dialkylamino have been studied for their potential donor properities. Lehn and co-workers[5] have examined a number of push-pull carotenoids in which a benzodithia group was inducted as an electron donor functionality and concluded that these molecules displayed very large βvalues. Similarly, Rao and co-workers[6] have reported that the ketene dithioacetyl group is a very effective electron donor group and incorporated it in the design and synthesis of efficient and thermally stable NLO chromophores.

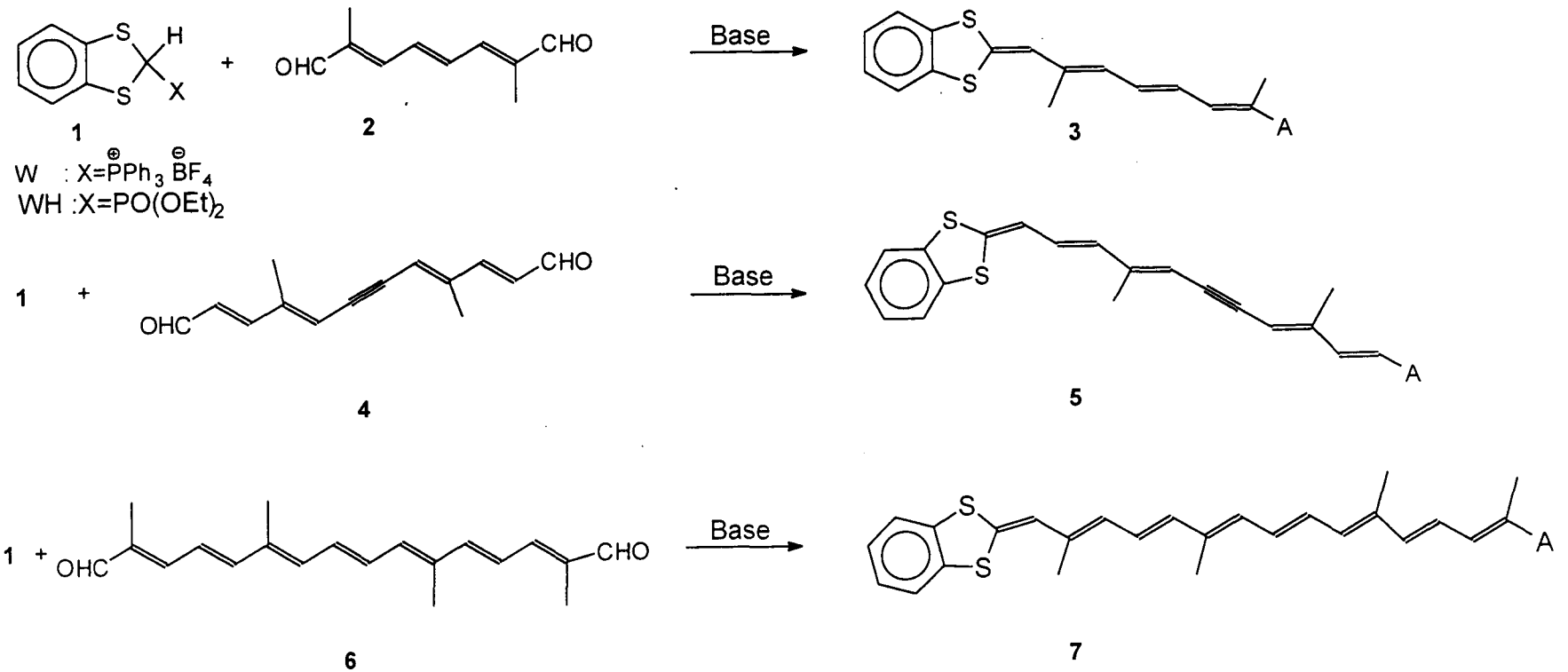
Despite enormous amount of work of synthesis and characterization of many donor-acceptor molecules as potential NLO chromophores, only limited success has been achieved in developing

practically applicable donor-acceptor molecules. Much attention is being devoted to synthesise organic chromophores with pronounced NLO effects such as improved thermal stability, photochemical stability etc. In our laboratory over the years we have gained extensive experience in using α-oxoketenedithioacetals [7a,b,c,] as intermediates in design and synthesis of polyenes.[8] It was therefore contemplated that these polyenes if they are connected to strong donor-acceptor terminals their ability as NLO chromophores will be unravelled and would lead to more information on molecular design of these push-pull polyenes.

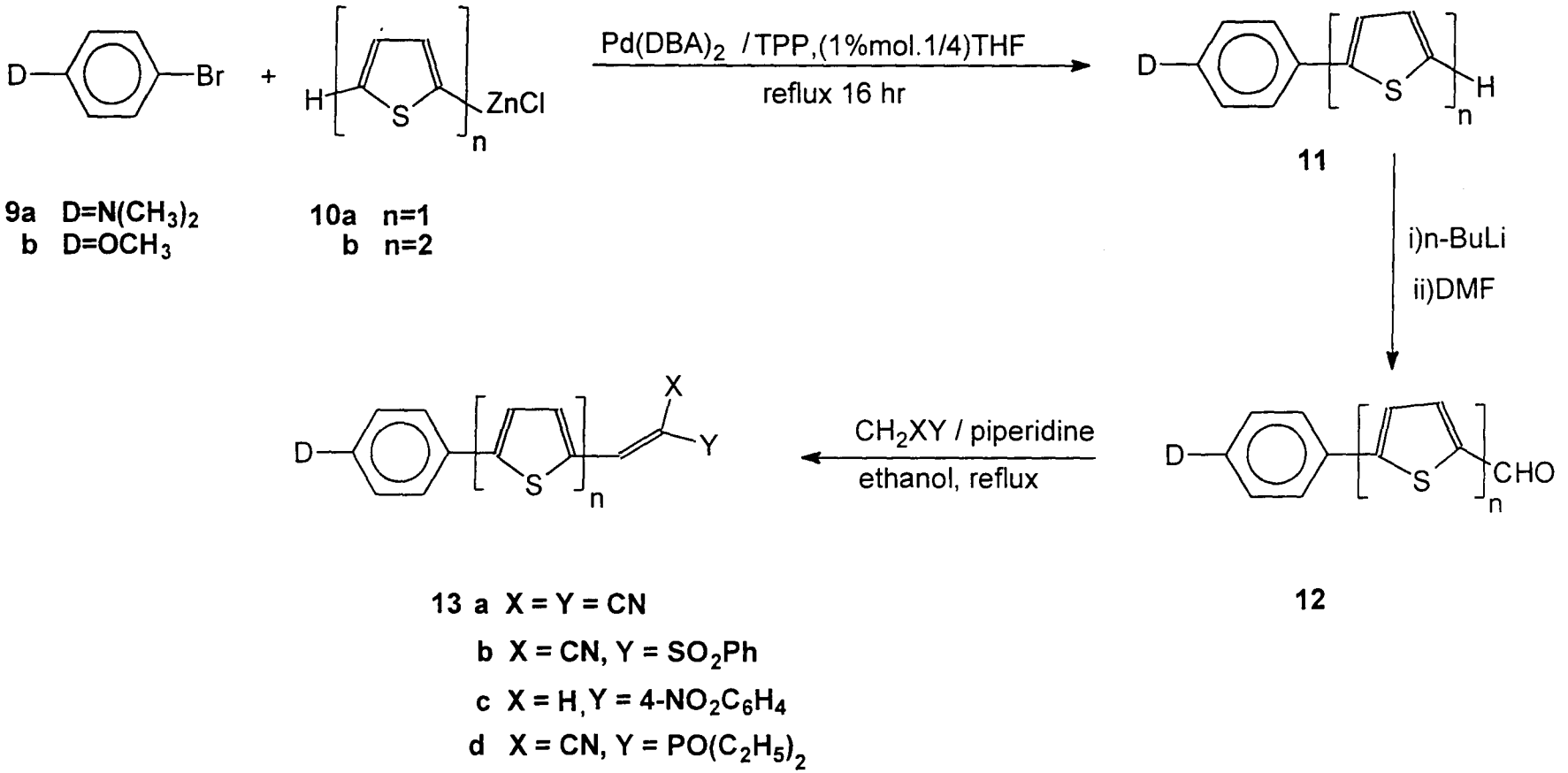
A brief survey of a few selected push-pull polyenes reported in the literature has been presented in the following paragraphs. The pronounced donor ability of the thio functionality was borne out by a series of push-pull carotenoids prepared by Lehn and co-workers.[5] These NLO chromophores had a benzodithia functionality as a donor group while functionalities like aldehyde, dicyanomethylene, pyridine, N-methyl pyridinium, e.t.c. were the acceptor groups. Thus the triphenyl sulphonium salt **1** was condensed with the dialdehyde **2** under Wittig reaction conditions in the presence of a suitable base, either n-BuLi in THF, or NaH or NaOH under P.T.C.conditions to afford the polyene

aldehyde **3a** in moderate to good yield.(Scheme-1) The aldehyde thus obtained, was then condensed with malanonitrile to yield the corresponding dicyanomethylene derivative **3b** in high yield. The Wittig reagent **1** was also condensed with dialdehydes **4** and **6** to yield the corresponding polyene aldehydes **5a** and **7a** under the described reaction conditions. The aldehydes **5a** and **7a** thus obtained were condensed with various active methylene compounds to create the electron deficient terminal of the polyene chain. These molecules **5b-f** and **7b-f** displayed broad and intense absorption in the visible region characteristic of internal charge transfer. Each series displayed a bathochromic effect with successively increasing conjucation.

The French group led by Mignani[9] reported the synthesis of novel thiophene analogues (Scheme-2). The benzene derivatives **9** with electron donating substituents were coupled with the thiophenes **10** in the presence of a Pd catalyst to afford the corresponding thienyl benzenoids **11** in good yields. These were then deprotonated in the presence of n-BuLi, followed by quenching with DMF to afford the corresponding terminal aldehydes **12.** These aldehydes were then condensed with various active methylene groups to yield the push-pull


1
2
Base
3
W : X=PPh3 BF4
WH :X=PO(OEt)2
1 +
4
Base
5
1 +
6
Base
7
A = Acceptor groups
A =
8 a
b
c
d
e
f

Scheme -1



9a D=$N(CH_3)_2$
b D=OCH_3

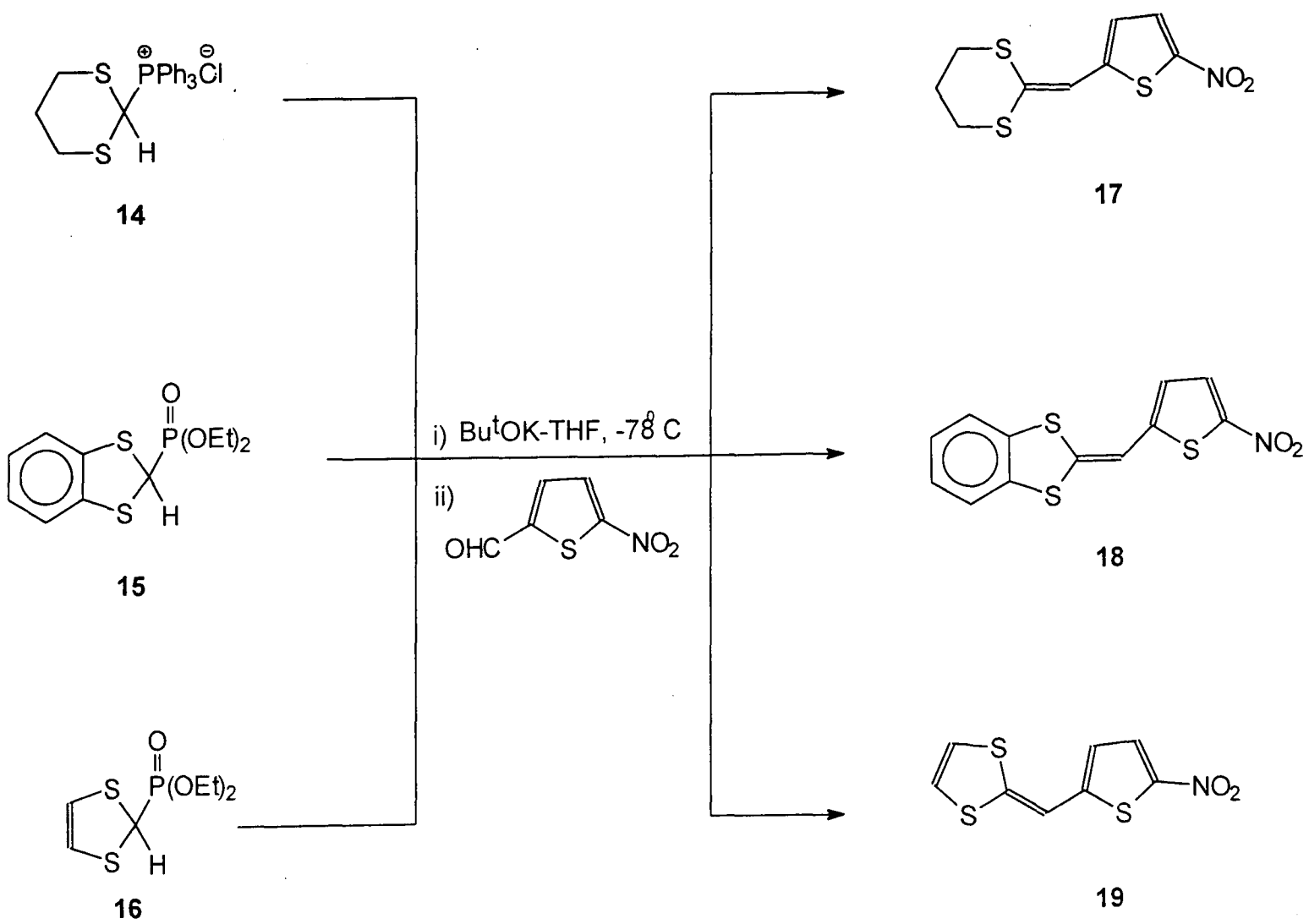
10a n=1
b n=2

13 a X = Y = CN
b X = CN, Y = SO_2Ph
c X = H, Y = 4-$NO_2C_6H_4$
d X = CN, Y = $PO(C_2H_5)_2$

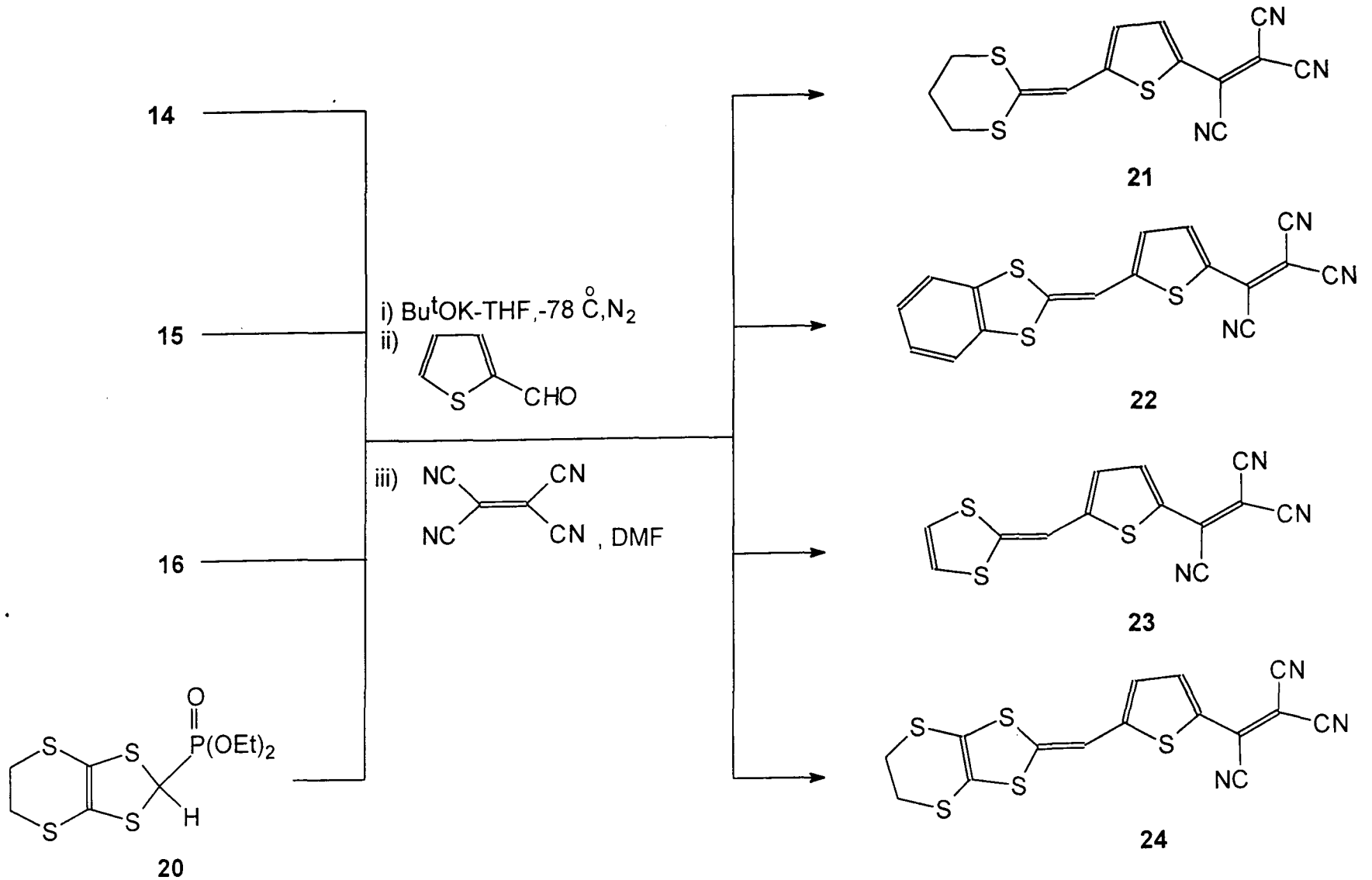
Scheme -2

polythiophenes **13**. These product molecules being attached with electron donor and electron acceptor groups have displayed good NLO properties.

Rao and co-workers[10] developed a series of thiophene derived NLO chromophores with dithiolyldinemethyl donor groups with tricyanovinyl and nitro aceptor terminals. These molecule had high β values with good thermal stability . 5-nitro thiophene -2- aldehyde was condensed with the Wittig reagents **14, 15, 16** to afford the corresponding nitroaldehydes **17, 18, 19** (Scheme-3). The other thiophene analogues with tricyano groups **21- 24** were similarly prepared from **14,15,16** and **20** by first condensing with thiophene 2-aldehyde followed by reaction with tetracyanoethylene in DMF.(Scheme-4) The electronic spectra of these compounds were recorded to compare their intramolecular charge transfer properties. The tricyano vinyl derivaties **21-24** displayed a red shift charge transfer band as compared to the nitroderivatives **17, 18** and **19**. These results proved that a stronger electron withdrawing group displays a greater ability to shift bands in the longer wavelength region. Also the second


S
PPh3Cl
S
H
14
O
P(OEt)2
S
S
H
15
O
P(OEt)2
S
S
H
16
i) ButOK-THF, -78° C
ii)
OHC
S
NO2
S
S
NO2
17
S
S
S
NO2
18
S
S
S
NO2
19

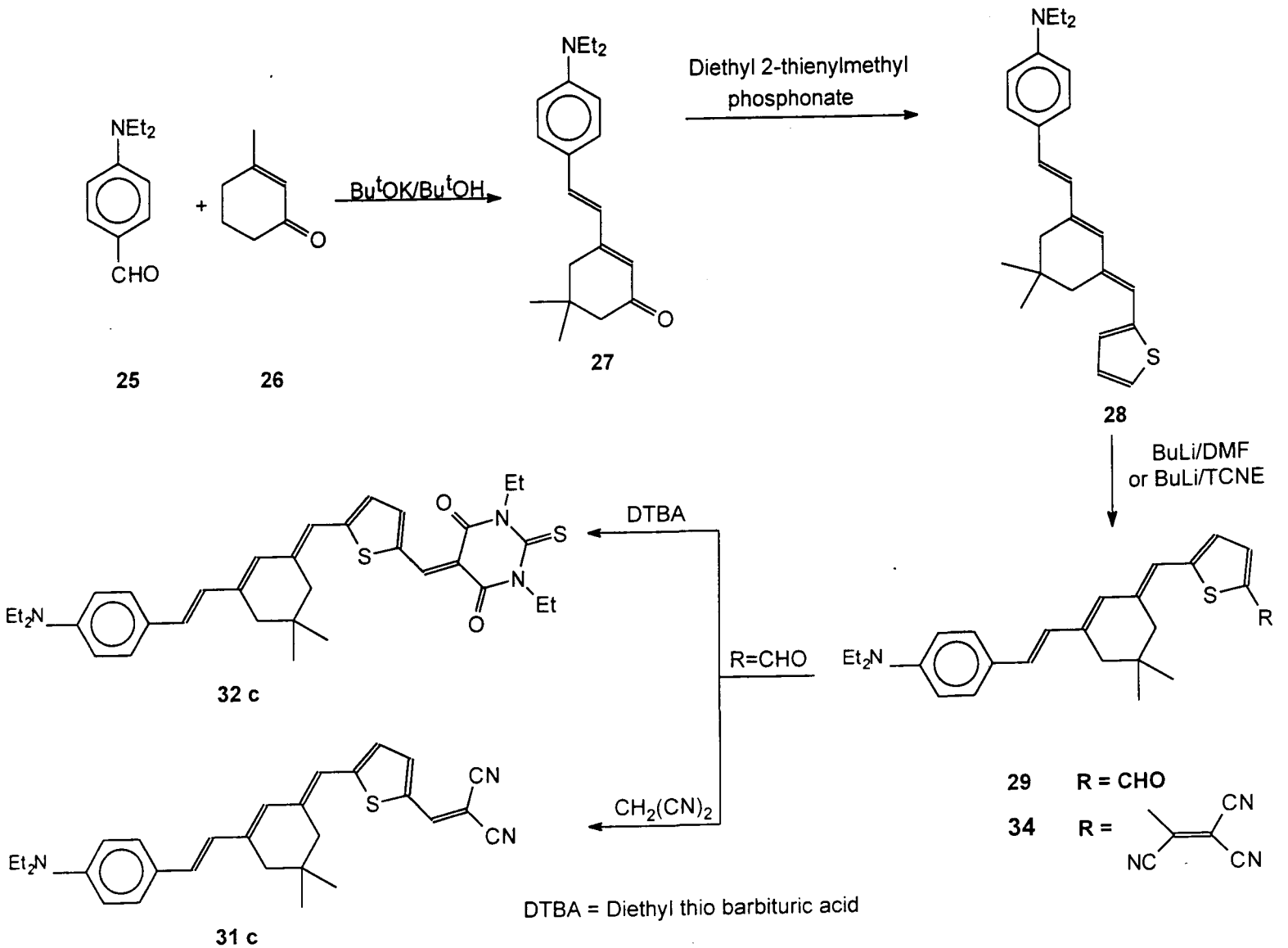
Scheme-3


14
15
16
20
i) ButOK-THF,-78 °C,N2
ii)
CHO
iii)
NC
CN
NC
CN
, DMF
O
P(OEt)2
H
21
22
23
24

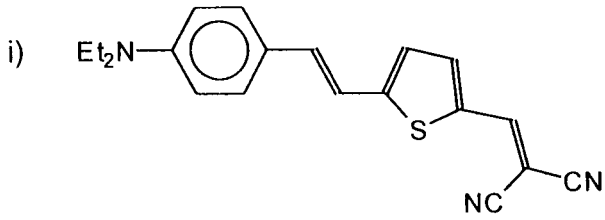
Scheme-4

order polarizability of the tricyanovinyl derivatives were substantially higher than the corresponding nitro compounds. Comparison of $\beta\mu$ values and λ_{max} peaks of the derivatives revealed that the combination of the dithiolylidinemethyl donor groups with tricyanovinyl acceptor groups provides a very efficient mechanism to enhance molecular non-linearity and charge transfer properties despite minimum conjucation bridge.

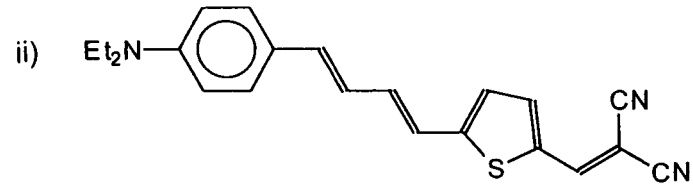
Chiang-Fong-Shu and co-workers[11] have developed a synthesis of second order NLO chromophores (Scheme-5) with increased non-linearity and thermal stability by applying a configurational lock to their trans geometry. Thus **27** was prepared with trans geometry, by applying a Knoevenegal condensation of 4-N,N-diethylamino benzyldehyde **25** with isophorone **26** in the presence of t-BuOK and t-BuOH. The compound **28** was prepared by a Wittig-Horner condensation of 2-thienylmethyl phosphonate with t-BuOK in THF. It was then treated with n-BuLi and reacted with tetracyanoethylene(TCNE) to yield the tricyanovinyl derivative **29b** (Tables 1,2).Thus a strongly electron withdrawing group was introduced on the thiophene ring. The


NEt2
CHO
25
26
Bu^tOK/Bu^tOH
27
Diethyl 2-thienylmethyl phosphonate
28
BuLi/DMF or BuLi/TCNE
DTBA
R=CHO
CH2(CN)2
Et2N
S
R
29 R = CHO
34 R =
CN
NC
32 c
31 c
DTBA = Diethyl thio barbituric acid

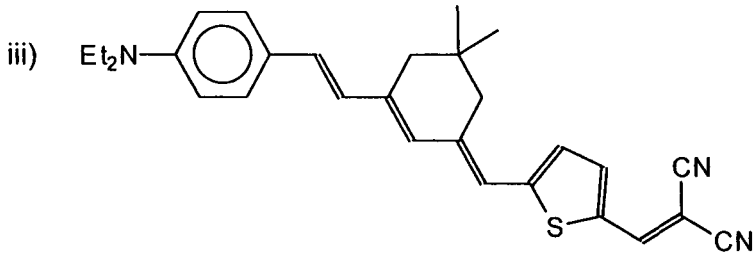
Scheme - 5

i) 

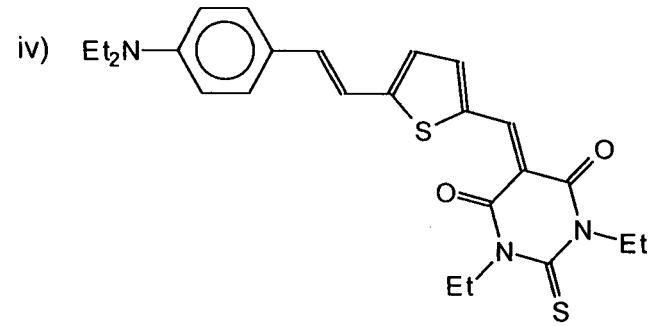
31a

ii) 

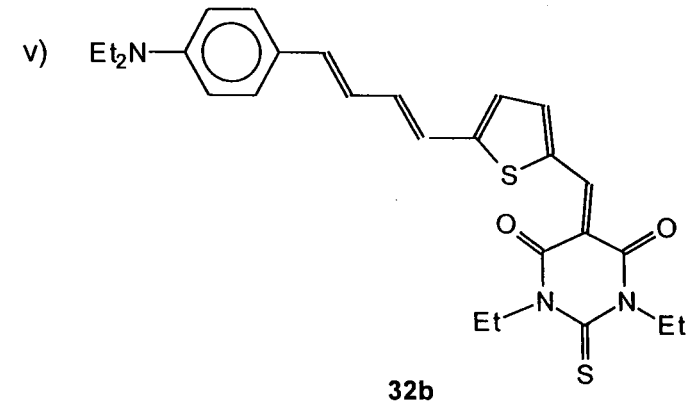
31b

iii) 

31c

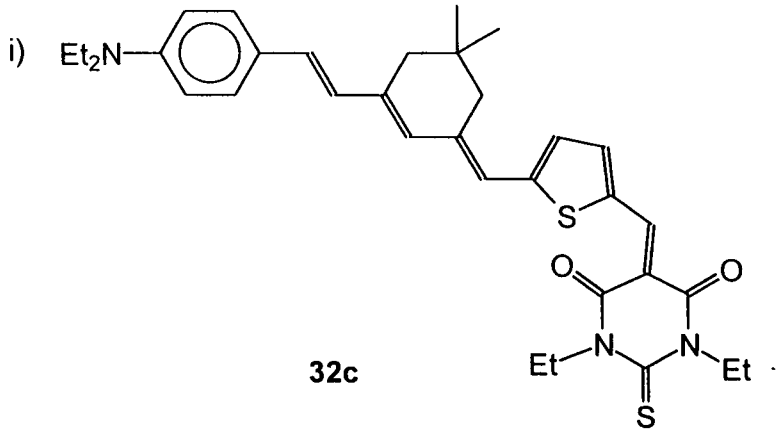
iv) 

32a

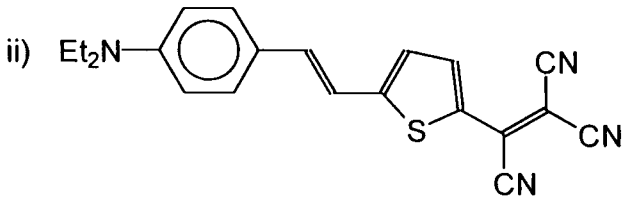
v) 

32b

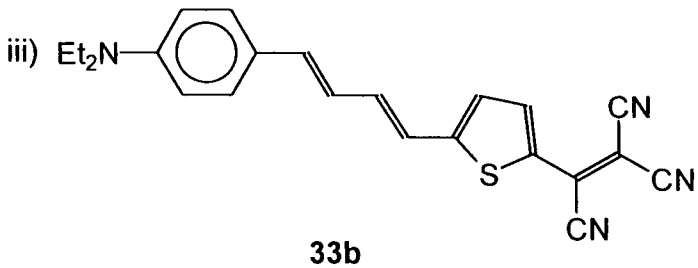
Table - 1

i) 

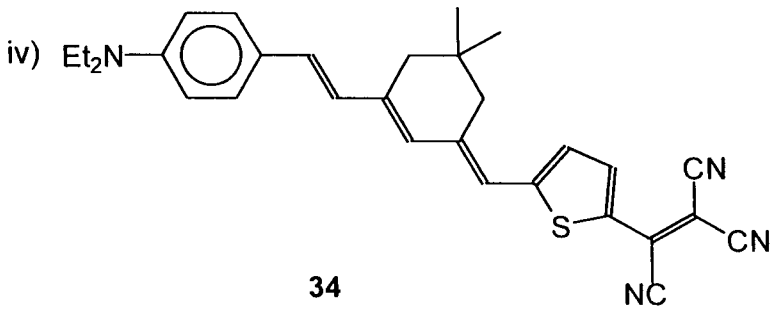
32c

ii) 

33a

iii) 

33b

iv) 

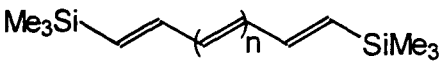
34

Table-2

metallated species derived from **28** was also reacted with DMF to introduce the aldehyde function in **29a**, which was then condensed with diethyl thiobarbituric acid to yield the corresponding barbitiurate **32c**. The aldehyde when condensed with malanonitrile gave the dicyano vinyl compound **31c.**

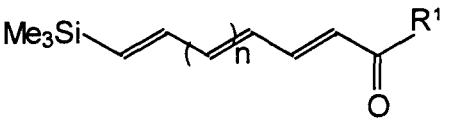
The II order hyperpolarisibility of these compounds were determined by electric field induced second harmonic generation (EFISH). It has been found that bridged configurational properties have resulted in inducting useful properties of molecular non-linearity.

Babudri et al,[11] developed a new method for the synthesis of conjugated polyenes containing upto eight double bonds with exclusive E configuration (Scheme-6). Both the terminals of these polyenes have electron withdrawing carbonyl groups in contrast to the preceding examples which contained donor-acceptor substituents. They have taken π-systems, **35a-c** with E-configuration, with trimethyl silyl group on both sides . The silyl group is replaced by a benzoyl group in an $AlCl_3$ assisted coupling reaction. The reaction afforded **36a** and **36b**



R^1COCl / $AlCl_3$

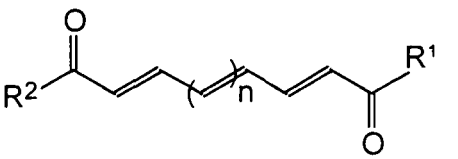
CH_2Cl_2 / 0 °C



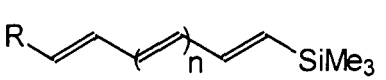
35 a n = 0
b n = 1
c n = 2

36 a n = 0
b n = 1

R^2COCl /$AlCl_3$ / CH_2Cl_2

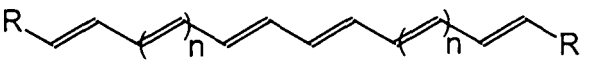


37 a n = 0
b n = 1



$PdCl_2/CuCl_2/LiCl/MeOH$

or $PdCl_2L_2/CuCl/LiCl/HMPA$



39 a - g

38 a	R =PhCO	n = 0
b	R =PhCO	n = 1
c	R =$PhCH_2CO$	n = 1
d	R =4-$CH_3C_6H_4CH_2CO$	n = 1
e	R =4-n-$C_{10}H_{21}C_6H_4CH_2CO$	n = 2
f	R =PhCO	n = 2
g	R =Ph	n = 0

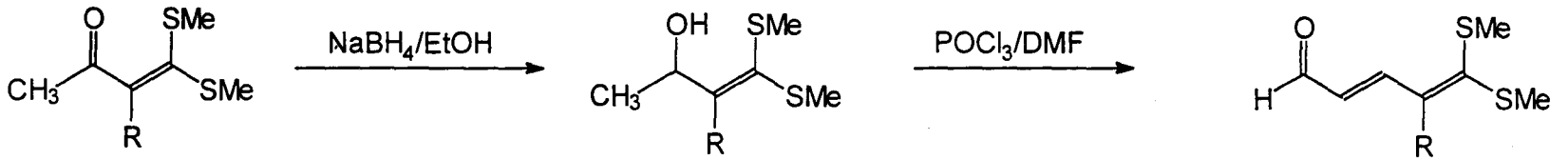
Scheme-6

which on repetion of previous step yielded the dicarbonyl polyene **37a**. Various carbonyl compounds were then similarily coupled to afford **39 a-g** .The influence upto 2 substituents with the same electronic effects on the nonlinear optical properties have been recently recognised. These results show that not only push-pull polyenes but also symmetrically substituted polyenes were suitable for providing molecules with large NLO coefficients. Thus the diketo polyenes are among the first group containing electron withdrawing groups on both terminals whose properties as NLO chromophores are still to be assessed.

In the preceding section we have described a short review on a select group of molecular types with donor-acceptor terminals and their effect on absorbance spectrum as potential charge transfer members. These data of electronic spectra are generally utilised to recognise the NLO property of these molecules which when tested separately confirmed their β values.

RESULTS AND DISCUSSION:

In the present investigation, it was contemplated that the mercapto functionality can be placed in one end of the conjugated polyenes as an electron donor group. The previous workers have demonstrated that the dithio group in conjucation with the polyenes is an effective electron donor functionality. Extensive work has been done in our laboratory to develop polyenealdehydes and polyenemercaptals using α-oxoketene dithioacetals as 3-carbon fragment in an iterative homelogation sequence through carbonyl transpositions[8]. The electronic push-pull nature of these polyenes, with the aldehyde function at one end and the bismethylthio function at the other end, can be further enhanced by substituting the aldehyde function with a variety of greater electron withdrawing substituents. A class of push-pull polyenes with potential opto-electronic properties will then be at hand. We have indeed achieved this goal and the chemistry of these compounds is essentially developed on the aldehydes as shown in schemes 7,8,9. In scheme 7, the key intermediate diene aldehydes **42-a,b** were prepared according to our earlier method[8] in 59% and 70% yields respectively.

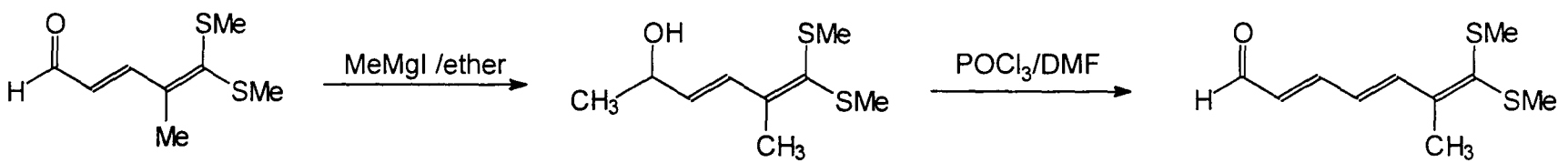


40 a R = H
b R = CH_3

41 a,b

42 a R = H 59%
b R =Me 70%

Scheme -7



42

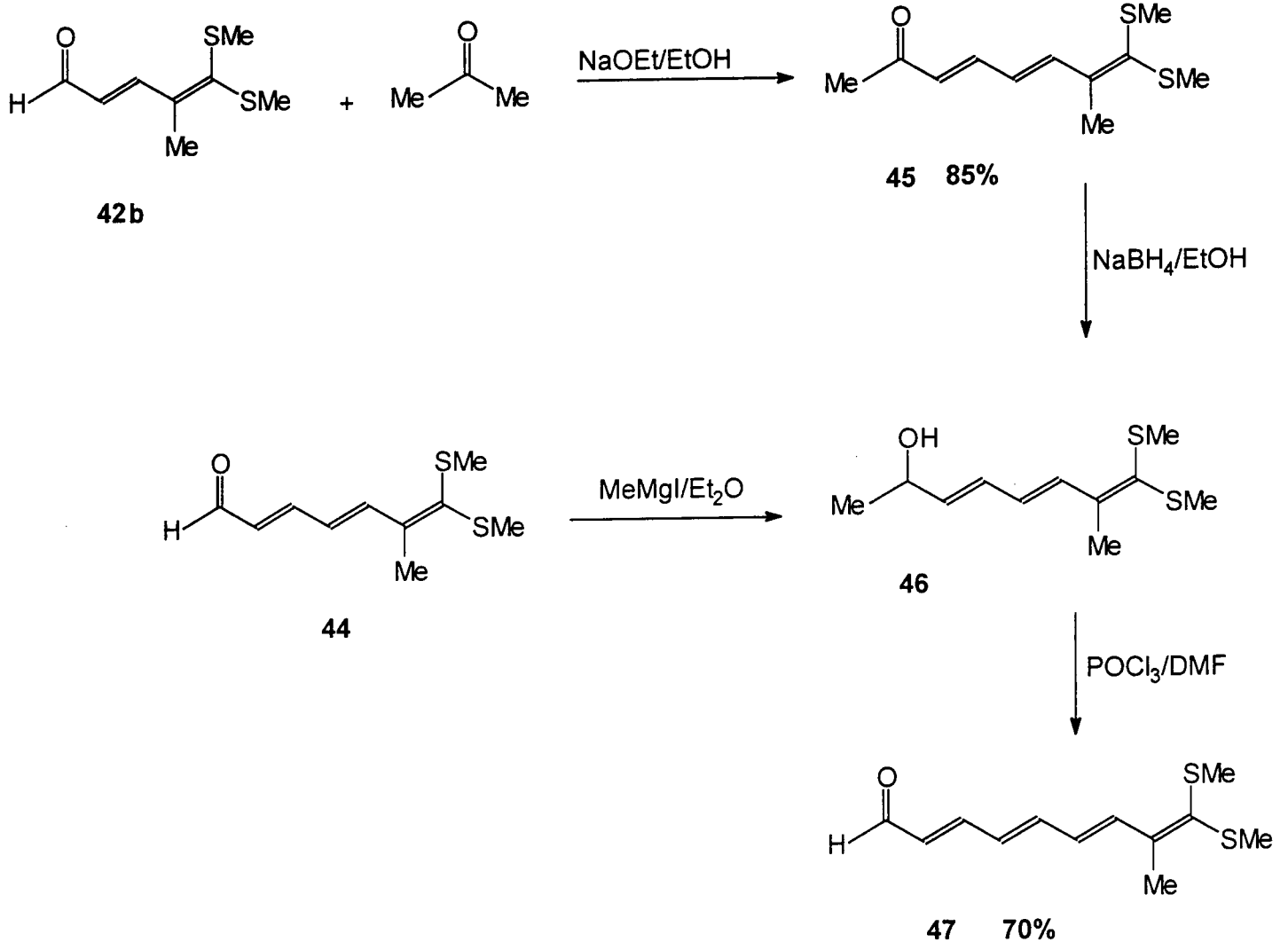
43

44 80%

Scheme -8

Thus acetone mercaptal **40a** was reduced with $NaBH_4$ in dry ethanol to afford the corresponding carbinol acetal **41a** in quantitative yield. The carbinol acetal was then subjected to Vilsmeier-Haack formylation ($POCl_3$/DMF) to afford the desired dienealdehydes **42a** in 59% yield. Similarly, the mercaptal derived from ethyl methyl ketone **40b** was transformed into α-methyl dienealdehyde **42b** in 70% yield under similar reaction conditions. The trienealdehyde **44** (Scheme-8) was also prepared in 80% yield. Thus the dienealdehyde **42b** was treated with methyl magnesium iodide in ether to afford the corresponding methyl carbinol acetal **43** which on $POCl_3$/DMF treatment yielded the corresponding trienealdehyde **44** in 80% yield.

The required tetraenealdehyde **47** (Scheme-9) was prepared by the two methods described in scheme-9. Thus the dienealdehyde **42b** was condensed with acetone in the presence of sodium methoxide in methanol at 0°C to afford the corresponding condensation product **45** in 85% yield. The ketone was then reduced by $NaBH_4$ in ethanol to afford the corresponding carbinolacetal in quantitative yield. Alternatively this carbinol **46** could be prepared from **44** . Thus treatment with methyl

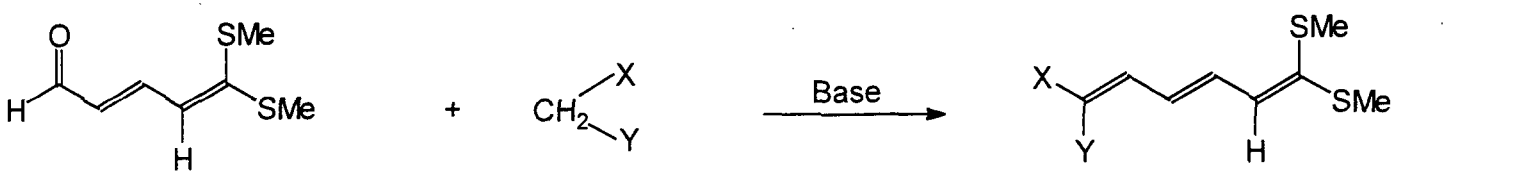

O
SMe
H
SMe
Me
42b
+
O
Me
Me
NaOEt/EtOH
O
SMe
Me
SMe
Me
45 85%
NaBH4/EtOH
OH
SMe
Me
SMe
Me
46
MeMgI/Et2O
O
SMe
H
SMe
Me
44
POCl3/DMF
O
SMe
H
SMe
Me
47 70%

Scheme - 9

magensium iodide afforded the corresponding carbinol acetal **46** in quantitative yield. Both the carbinols from different routes were identical (superimposable IR). It was then subjected to DMF/$POCl_3$ reaction to afford the corresponding tetraenealdehyde **47** in 70% yield.

In the next phase of experiments the four aldehydes thus prepared **42a**, **42b**, **44**, **47** were condensed with various active methylene compounds. The dienealdehyde **42a** was first reacted with diethyl malonate in the presence of piperidine at room temperature with stirring to yield after work up the corresponding hexatriene **43a** in 90%.(Scheme-10) The structure of **48a** was confirmed from its analytical and spectral data.

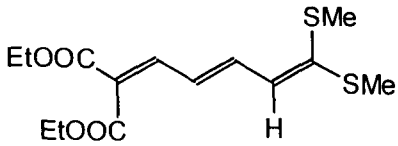
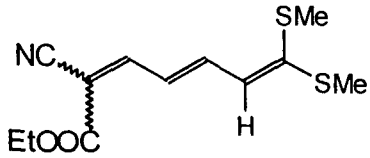
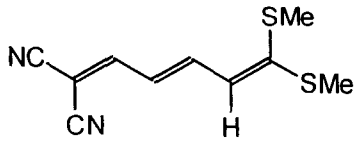
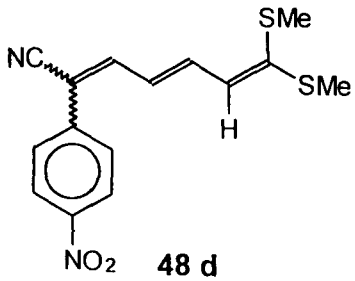
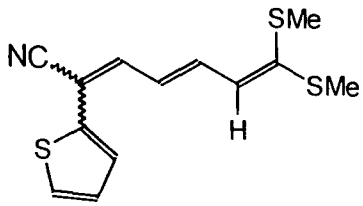
Ethylcyanoacetate similarly reacted with **42a** to afford the corresponding ethyl carboxylate **48b** in 87% yield. Then malanonitrile and p-nitro phenylacetonitrile were similarly reacted with **42a** to afford the corresponding dicyano and p-nitro phenylcyano condensed products **48c,d** in 80% and 88% yields. Similarly thiophene acetonitrile was condensed with **42a** using K_2CO_3 as base in acetone to afford **48e** in



42 a

48 a X = Y = COOEt
b X= CN Y= COOEt
c X= Y = CN
d X= CN Y = p-$NO_2C_6H_4$
e X= CN Y = 2- thienyl

Scheme - 10

S.No	PRODUCT	BASE	YIELD (%)	$\varepsilon_{max} \times 10^4$ λ_{max} (nm)
1	 48 a	i	90	1.32 (375)
2	 48 b	i	87	6.65 (409)
3	 48 c	i	80	6.57 (411)
4	 48 d	i	90	3.34 (430)
5	 48 e	ii	65	5.40 (411)

Base : i - Piperidine(cat) / EtOH

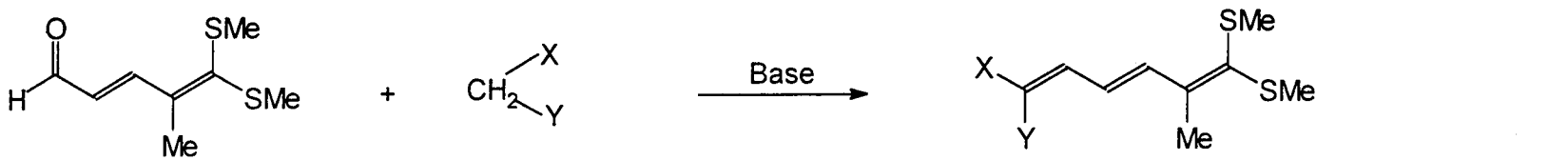
ii - K_2CO_3 / Acetone

Table - 3

65% yield. All the condensed products **48 a-e** were in full confirmity with their analytical and spectral data.

In the second phase of experiments the dienealdehyde **42b** was similarily condensed with diethyl malonate, ethylcyanoacetate, malanonitrile and p-nitrophenylacetonitrile using pieridine in ethanol to afford the corresponding condensation products **48f-i** in 80-90% yields.(Scheme-11,Table4) Thiophene acetonitrile was condensed with **42b** using K_2CO_3/Acetone (**48e** 70%), while condensation with nitromethane and barbitiuric acid required NaOEt/EtOH.(**48k**,65%, **48l**,73%). Thus a high yield synthetic route to these compounds was achieved.

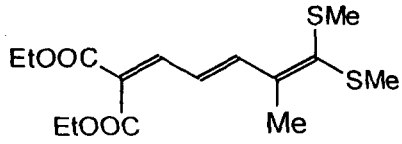
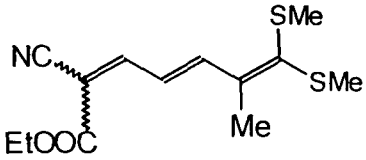
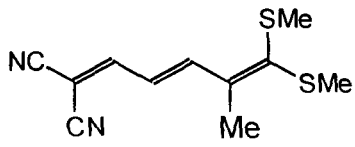
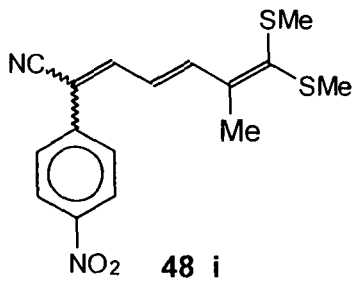
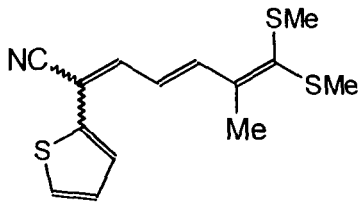
In the next phase of experiments the trienealdehyde **44** was condensed with two active methylene compounds. Thus ethylcyanoacetate was condensed with **44** in the presence of piperidine and ethanol to afford the corresponding tetraene **49a** in 73% yield.(Scheme-12)(Table-5).Then p-nitrophenyl acetonitrile were similarly condensed with **44** to afford the corresponding tetraene **49b** in



42 b

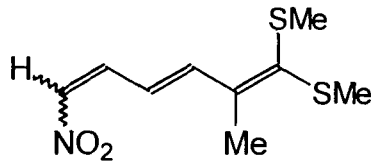
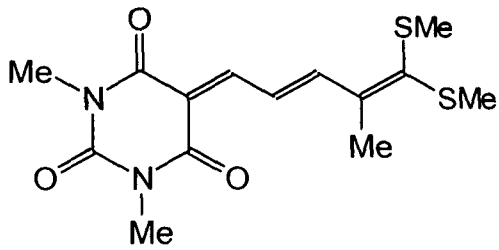
48 f X = Y = COOEt
g X = CN Y = COOEt
h X = Y = CN
i X = CN Y = p-$NO_2C_6H_4$
j X = CN Y = 2-thienyl
k X = H Y = NO_2
l X,Y = N,N, dimethyl -5-barbituryl

Scheme - 11

S.No	PRODUCT	BASE	YIELD (%)	$\varepsilon_{max} \times 10^4$ λ_{max} (nm)
1	 48 f	i	91	2.22 (374)
2	 48 g	i	88	2.12 (409)
3	 48 h	i	82	4.55 (417)
4	 48 i	i	87	3.02 (430)
5	 48 j	ii	70	4.57 (410)

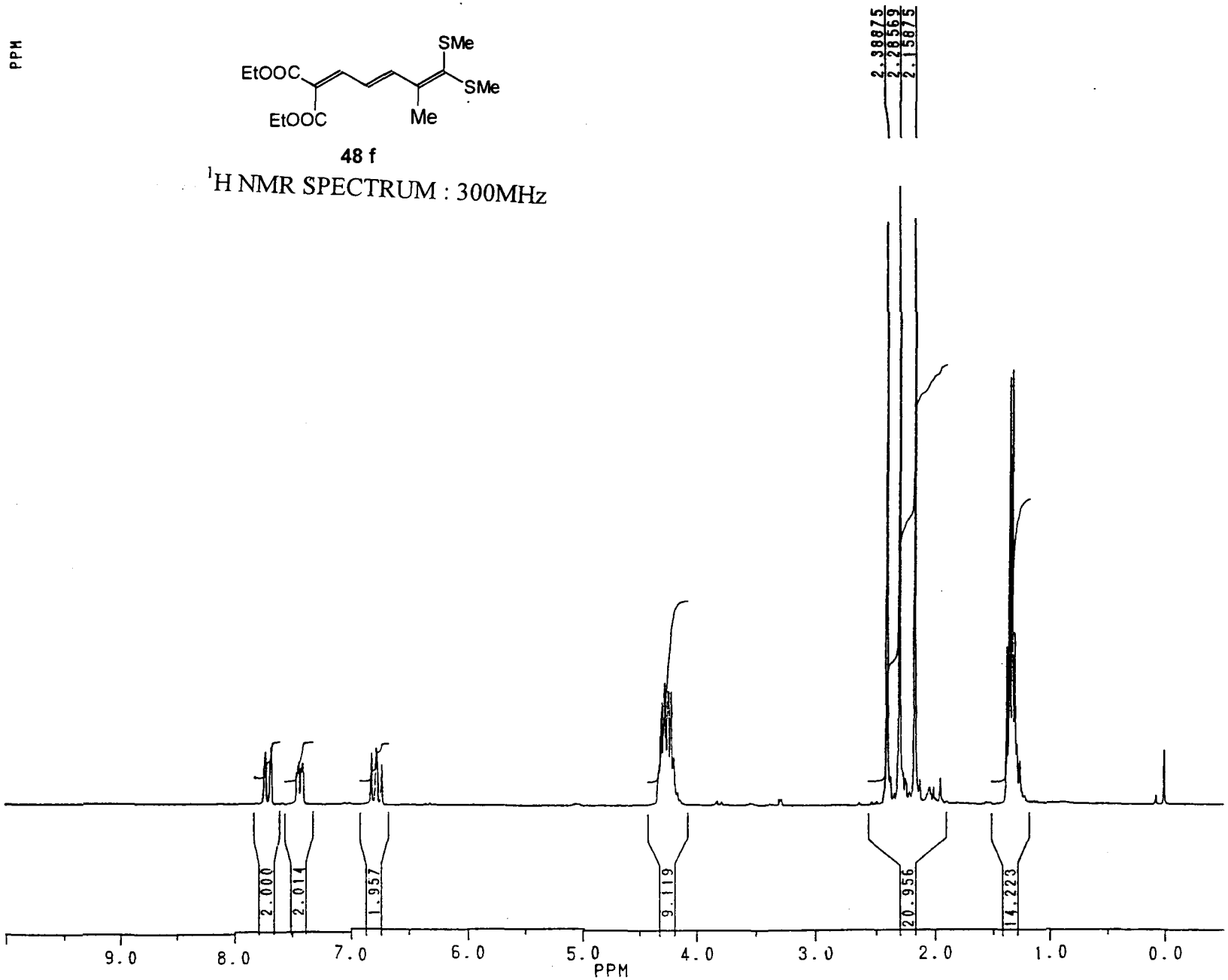
Base : i - Piperidine(cat) / EtOH
ii - K_2CO_3 / Acetone

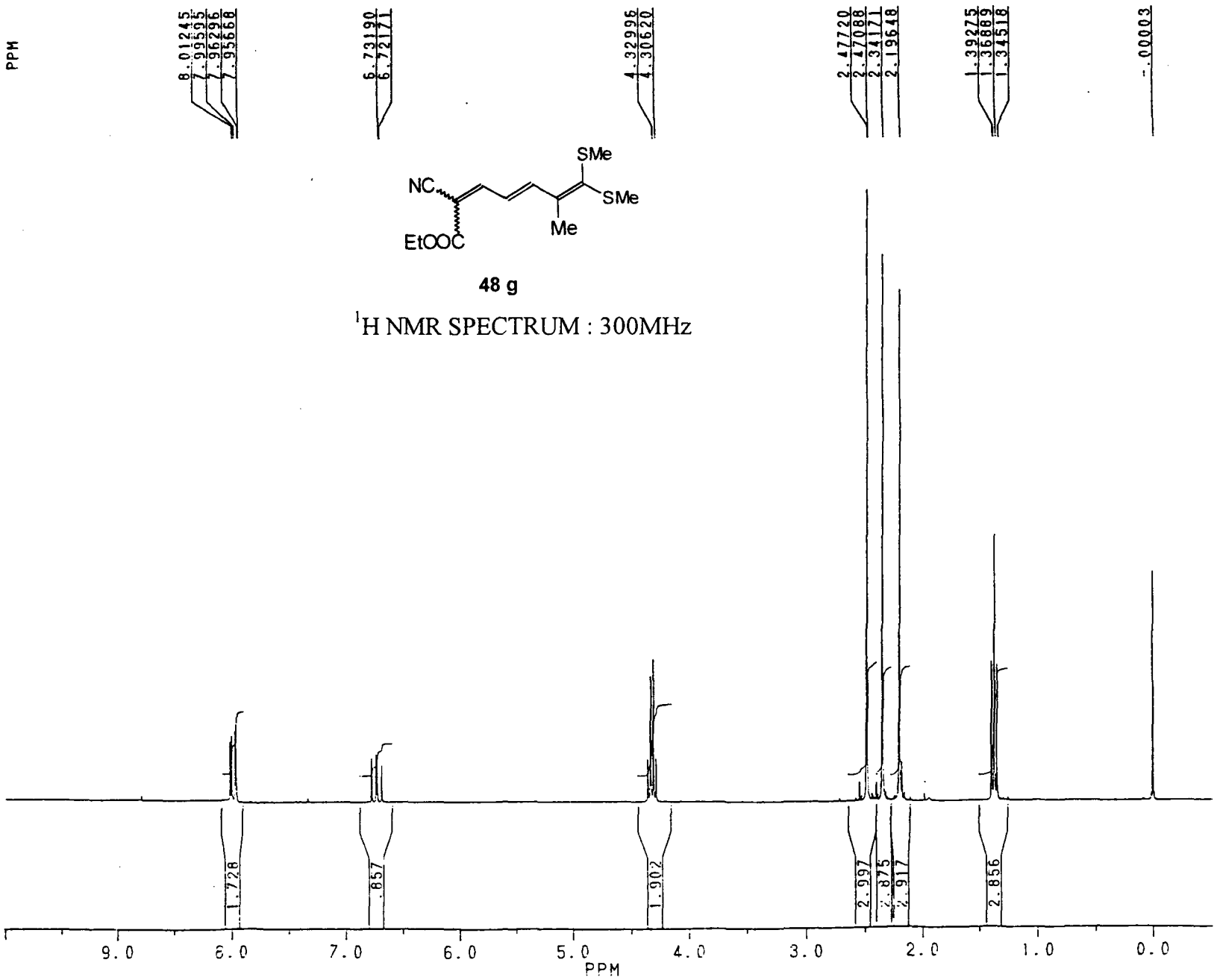
Table - 4

S.No	PRODUCT	BASE	YIELD(%)	$\varepsilon_{max} \times 10^4$ λ_{max} (nm)
6	 48 k	iii	65	1.88 (364)
7	 48 l	iii	73	2.50 (390)

Base : iii NaOEt /EtOH

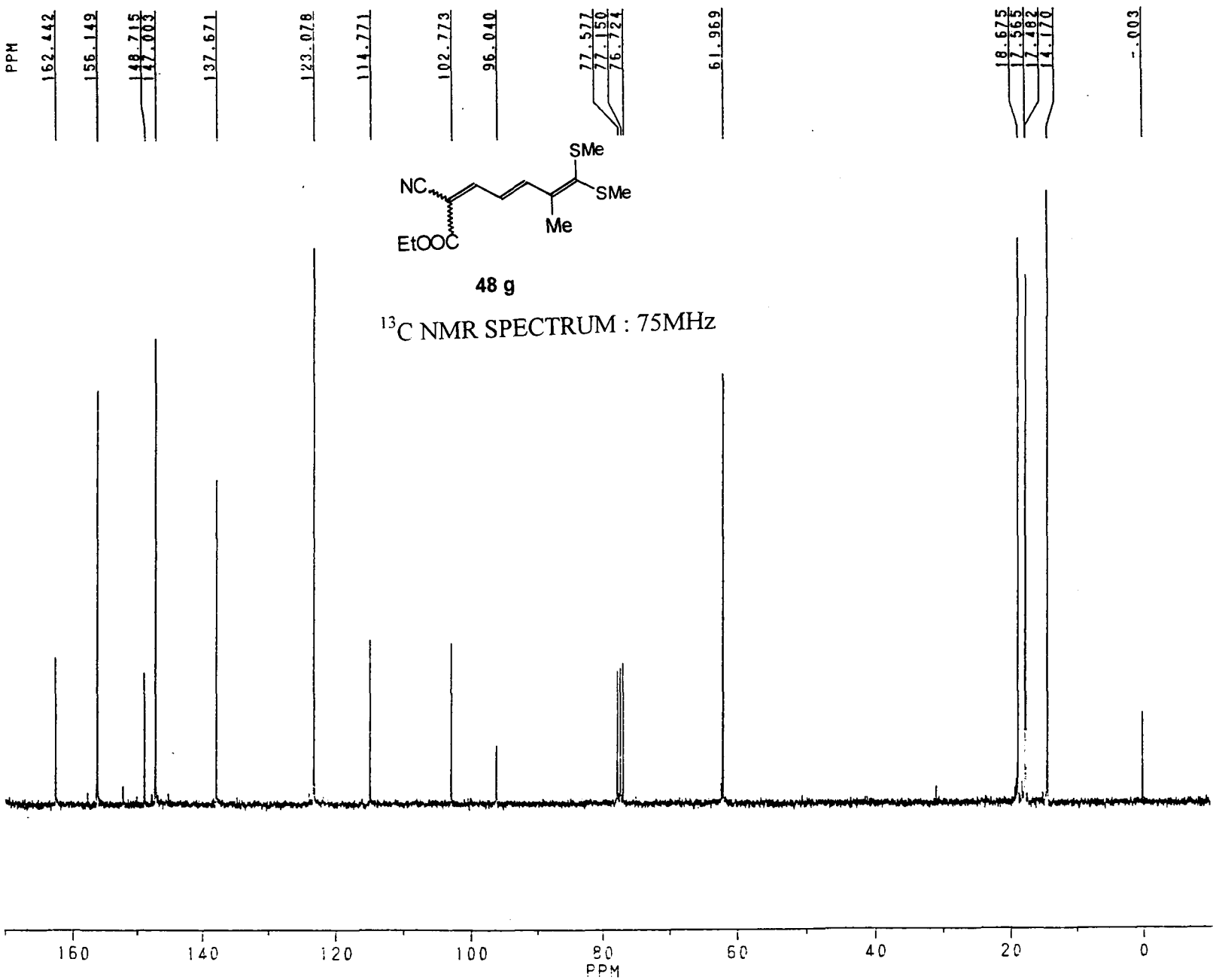
Table - 4 (contd)


PPM
EtOOC
SMe
SMe
EtOOC
Me
48 f
^{1}H NMR SPECTRUM : 300MHz
2.38875
2.28569
2.15875
2.000
2.014
1.957
9.119
20.956
14.223
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM



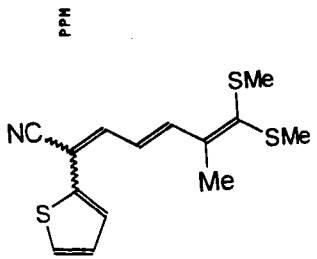
48 g

^{1}H NMR SPECTRUM : 300MHz



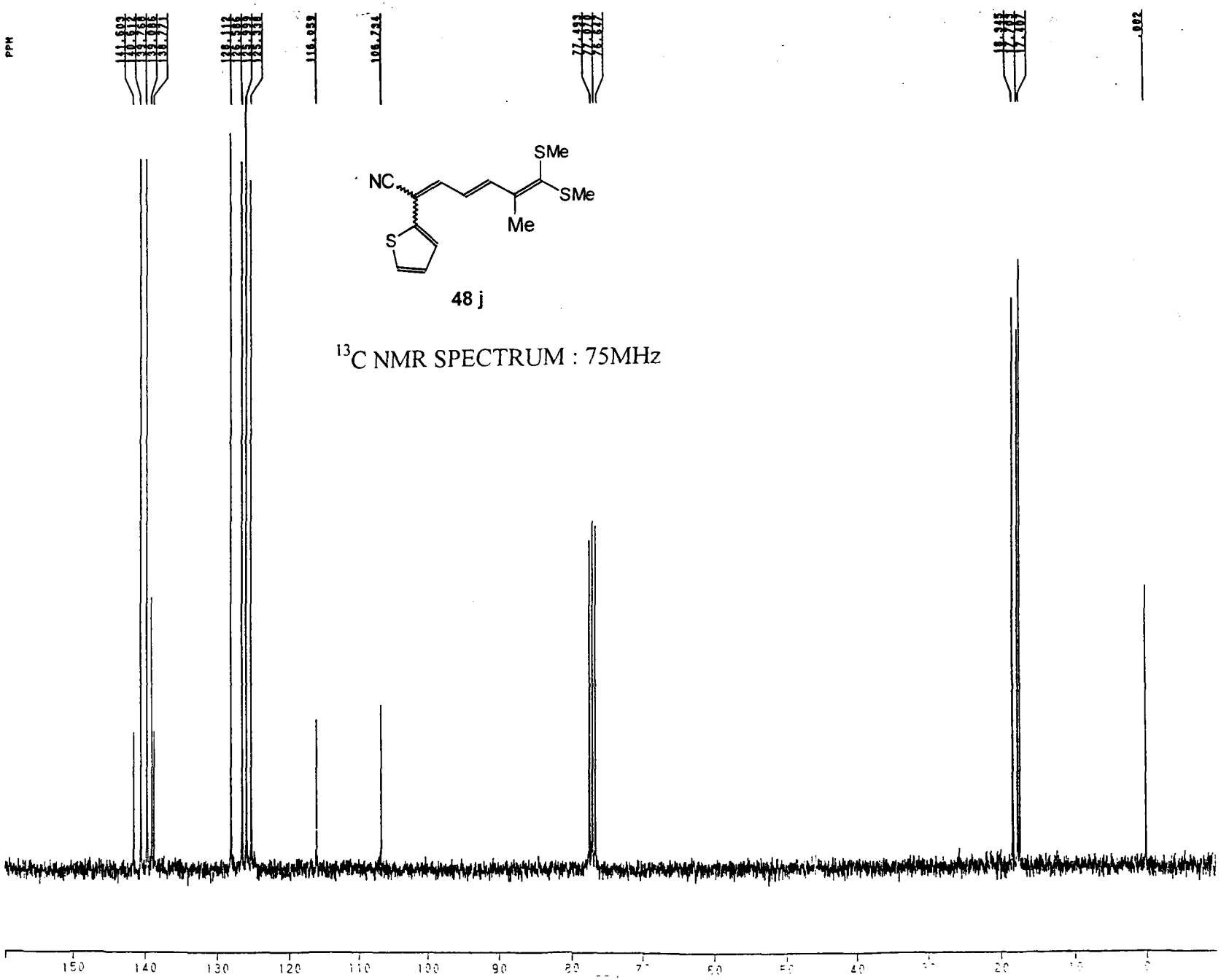
48 g

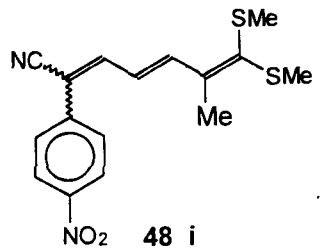
^{13}C NMR SPECTRUM : 75MHz



48 j

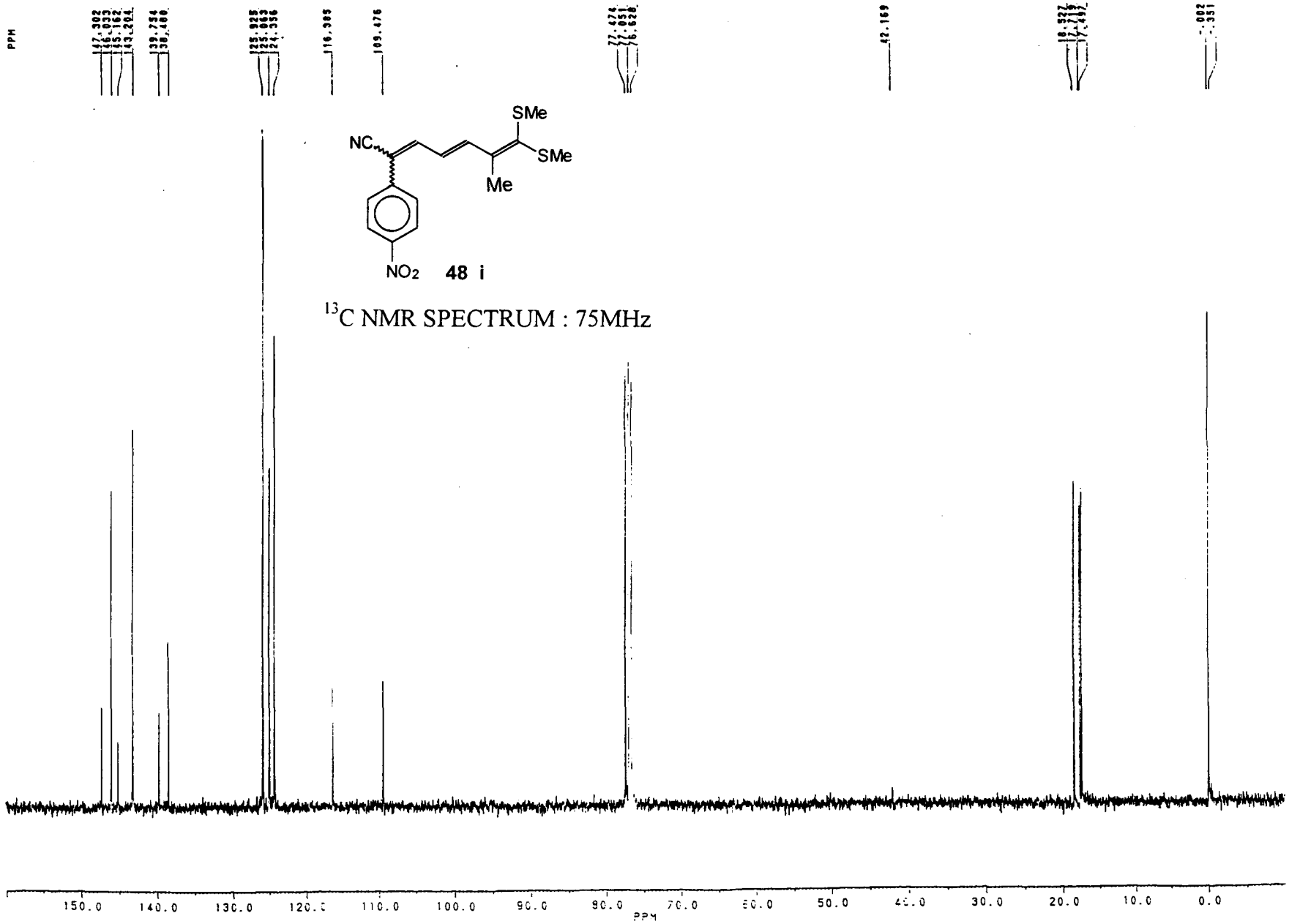
^{1}H NMR SPECTRUM : 300MHz

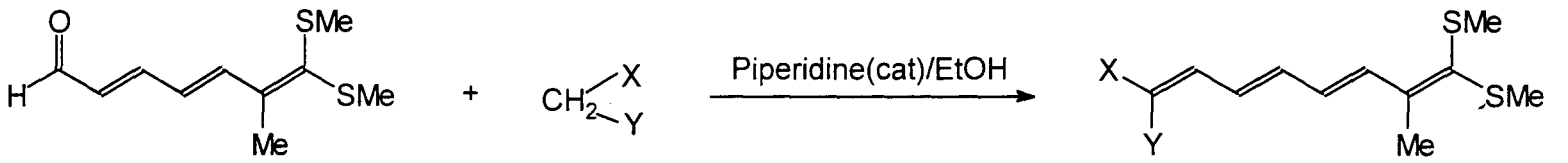

PPM
SMe
NC
SMe
Me
S
48 j
^{13}C NMR SPECTRUM : 75MHz
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



48 i

^{1}H NMR SPECTRUM : 300MHz


PPM
147.302
146.033
135.162
143.204
139.256
138.488
125.925
125.083
124.336
116.385
109.476
77.424
77.051
76.628
42.169
18.327
12.715
12.492
0.002
-0.351
SMe
NC
SMe
Me
NO2
48 i
13C NMR SPECTRUM : 75MHz
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
PPM



44

49 a X = CN Y = COOEt
b X = CN Y = p-$NO_2C_6H_4$

Scheme - 12

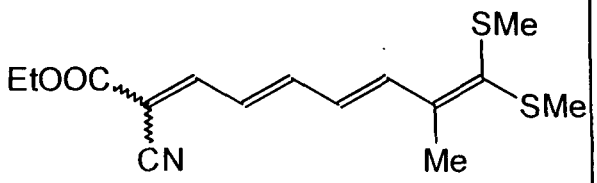
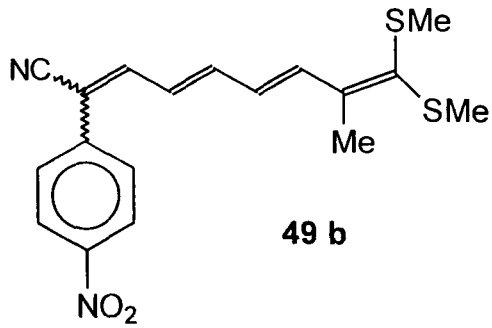
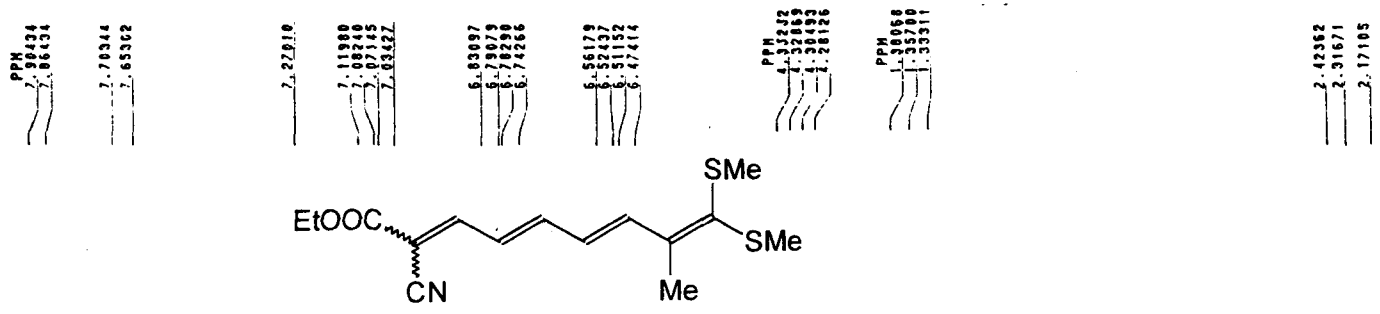
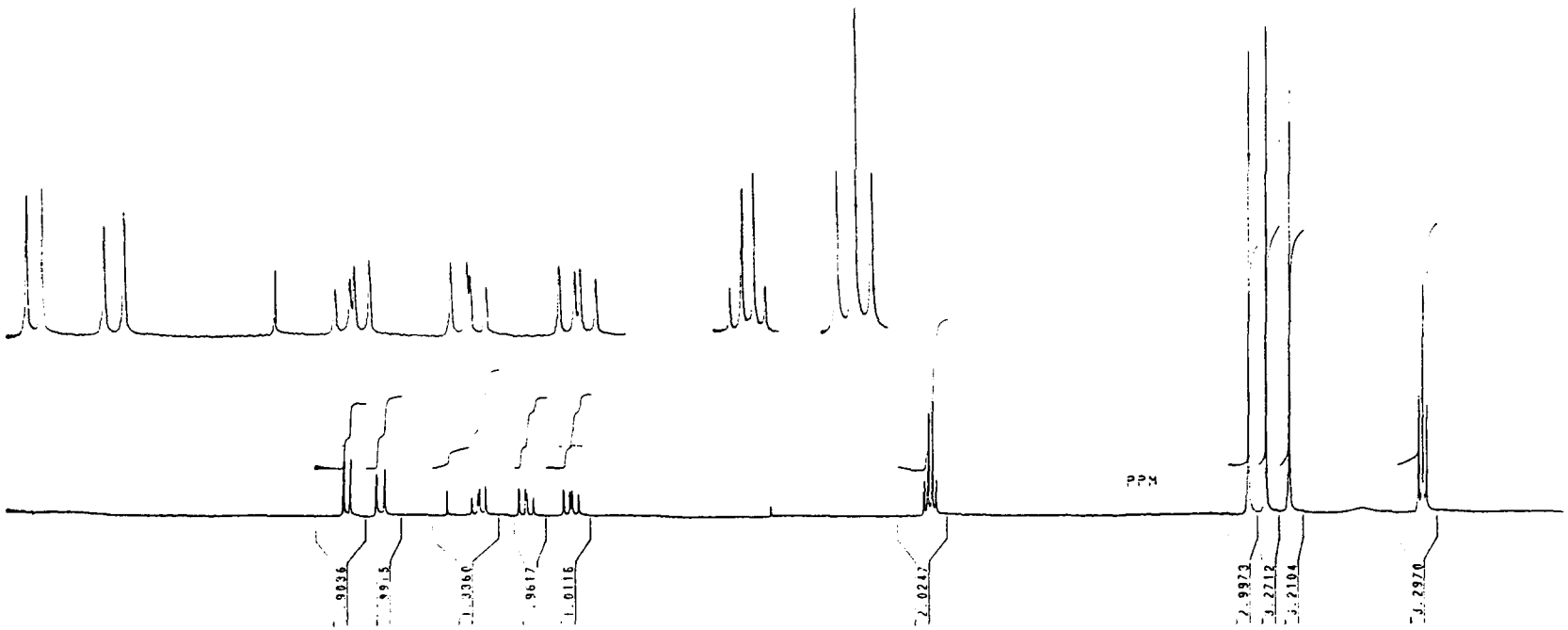
S.No	PRODUCT	YIELD (%)	$\varepsilon_{max} \times 10^4$ λ_{max} (nm)
1	 49 a	73	3.83 (432)
2	 49 b	78	2.69 (445)

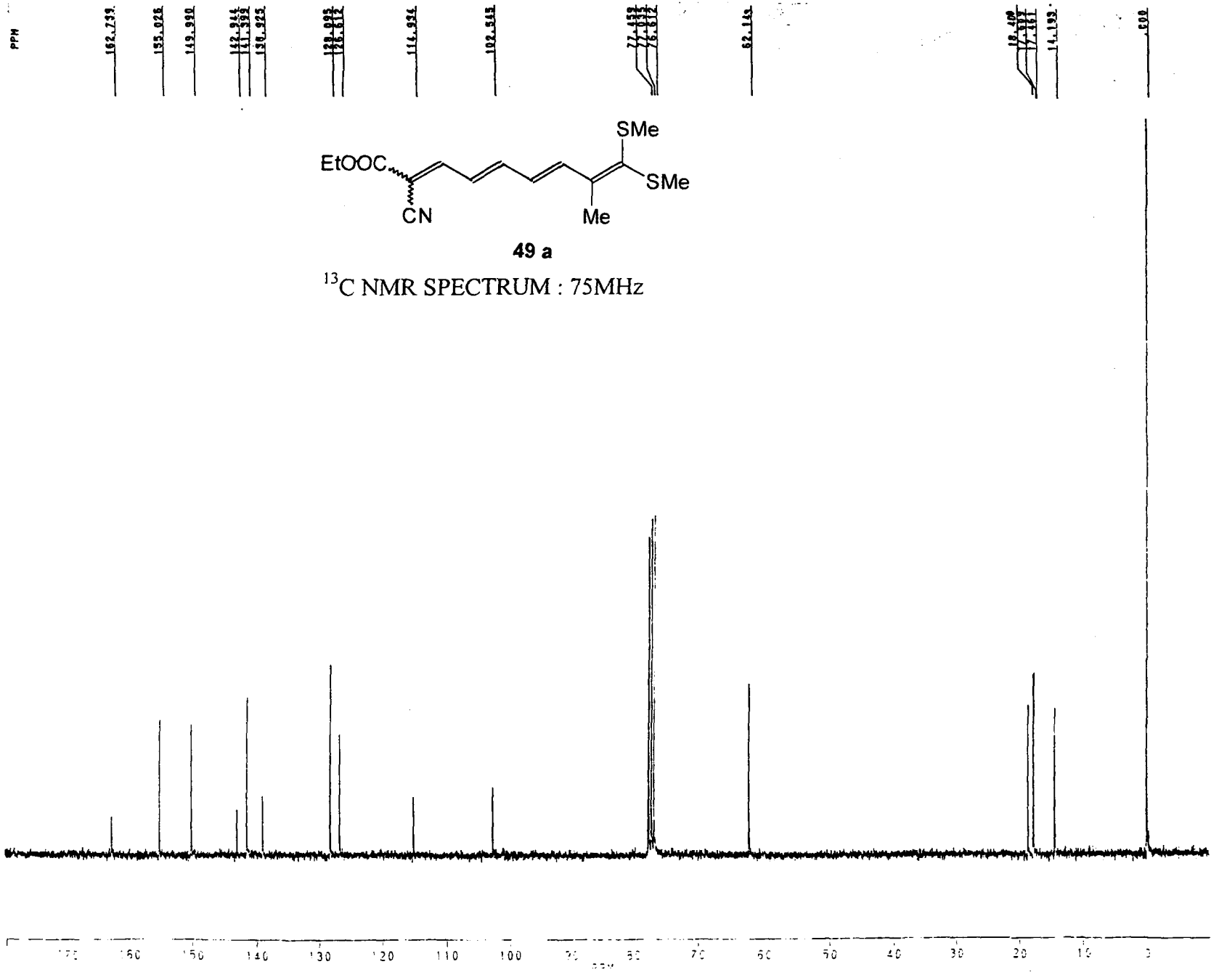
Table - 5



49 a

^{1}H NMR SPECTRUM : 300MHz





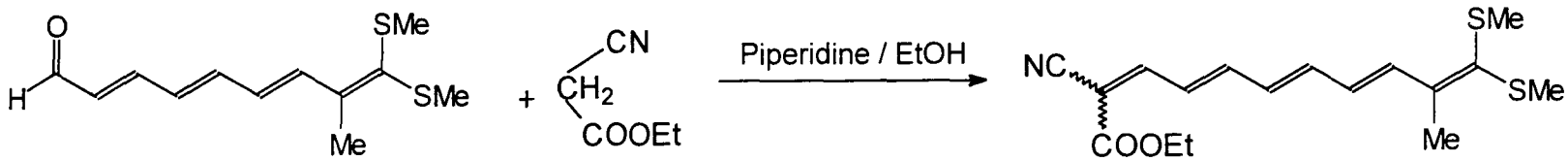
49 a

^{13}C NMR SPECTRUM : 75MHz

78% yield. The structure of both these compounds are in confirmity with their analytical and spectral data.

Tetraenealdehyde **47** was then condensed with ethylcyanoacetate as described before to afford the corresponding pentaene acetate **50** in 58% yield (Scheme-13,Table-6) whose structure was confirmed by its analytical and spectral data.

The geometry of all the polyenes synthesised were assigned as *all trans* based on the *all trans* geometry of the polyene aldehydes[8].The compounds thus formed were then measured for their optical and electrical properties with a view to assess them as NLO chromophores. The UV-Vis spectra of all the polyenes were studied in dioxane at 25° and their ε_{max} and λ_{max} values are shown in tables 4-6. The compounds displayed broad and intense absorption in the region characteristic of internal charge transfer. On comparing the spectra of polyenes **48b**,**48g**,**49a**, and **50** as well as **48c**,**48i** and **49b**, it is evident that each series displayes a bathochromic effect with successively increasing conjucation.



47 **50**

Scheme - 13

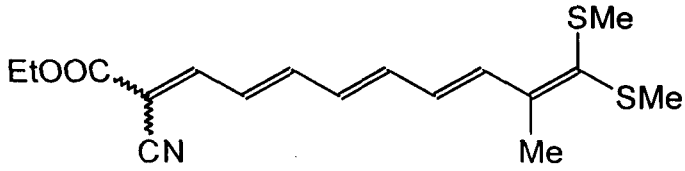
S.No	PRODUCT	YIELD (%)	$\varepsilon_{max} \times 10^4$ λ_{max} (nm)
1	 51 a	58	4.22 (443)

Table - 6

The trienes **48i** and **48l** were considered for measurement of electrical properties. Their β values were measured by the Rayleigh scattering method in methanol at 1062 nm. The barbitiurate **48i** gave a value of $88x10^{-30}$ e.s.u., while the p-nitro phenyl derivative **48l** measured $272x10^{-30}$ e.s.u. and they are comparable with those reported in the literature[13]. It must be mentioned here that considerble number of literature reports contain β values as derived from βμ measurements, obtained by Electic Field Induced Second Harmonic Generation (EFISH) method. The ground state dipole moment of the trienes **48i** and **48l** were 7~8D and therefore they are encouraging for NLO activity.

In summary we have achieved an efficient synthesis of novel push-pull donor-acceptor polyenes, some of which are promising NLO chromophores. Efforts to further enhance the scope of this strategy to synthesize a wider range of useful polyenes are in progress.

References:

1) Singer, K.D.; Sohn, J.E.; King, L.A.; Gordon, H.M.; Katz, H.E.; Dirk, C.W. *J.Opt. Soc. Am. B.* **1989**,*6*, 1339.

2) For the use of thiophene in donor-acceptor compounds, see

a) Rao, V.P.; Jen, A.K.Y.;Wong, K.Y.; Drost, K.J. *Tetrahedron. Lett.* **1993**, *34*, 1747.

b) Jen, A.K.Y.; Rao, V.P.; Wong, K.Y.; Drost, K.J. *J. Chem. Soc. Chem. Commun.* **1993,** 90.

c) Rao, V.P.; Jen, A.K.Y.; Wong, K.Y.; Drost, K.J. *J. Chem. Soc. Chem. Commun.* **1993**, 1118.

d) Wong, K.Y.; Jen, A.K.Y.; Rao, V.P. *Phys. Rev. A* **1994,** *49*, 3077

e) Wong, K.Y.; Jen, A.K.Y.; Rao V.P.; Drost. K.J. *J. Chem. Phys.* **1994,** *100*,6818.

f) Jen, A.K.Y.; Wong, K.Y.; Rao, V.P.; Drost, K.Y.; Cai, J. *J. Elect. Mater.***1994**, *23*, 653.

g) Rao, V.P.; Wong, K.Y.; Jen, A.K.Y.; Drost, K.Y. *J. Chem. Mater.* **1994**, *6*, 2210.

h) Drost, K.J.; Jen, A.K.Y.; Rao, V.P. *Chem. Technol.* **1995**, *25*, 16

l) Jen, A.K.Y.; Rao, V.P.; Chandrasekhar, J. *A.C.S. Symp. Series* **1995,** *601,* 147.

3) For the use of thiazole in donor-acceptor compounds, see: Dirk, C.W.; Katz, H.E.; Schilling, M.L.; King, L.A. *Chem. Mater*, **1990**, *2*, 700.

4) For the use of furan in donor-acceptor compounds, see

a) Cheng, L.T.; Tam, W.; Marder, S.R.; Stiegman, A.E.; Rikken, G.; Sprangler, C.W. *J. Phys. Chem.* **1991**, *95*, 10631.

b) Rao, V.P.; Cai,Y.; Jen, A.K.Y. *J. Chem. Soc. Chem. Commun.* **1994**, 1689.

5) Desce, M.B.; Ledoux, I.; Lehn, J.M.; Malthete, J.; Zyss, J. *J.C.S. Chem. Commun.* **1988**, 737.

6) Rao,V.P.; Jen, A.K.Y .J.C.S.Chem.Commun. 1994, 1689.

For a review on α-oxoketene dithioacetals see

7a) Junjappa,H.; Ila,H.; Asokan,C.V.*Tetrahedron*, **1990**, *31*, 5423

b) Dieter,R.K.; *Tetrahedron,* **1990**, *31*,1766.

c) Yokoyama,M.; Togo,M.; Kondo,S. *Sulfur.Rep.* **1990**, *10*, 23.

8) Chandrasekharam,M.; Asokan, C.V.;Junjappa,H.; Ila, H.*Tetrahedron Lett.* 1990, *31*, 1766

9) Mignani, G.; Leising; Meyrueix, R.; Samson, H. *Tetrahedron. Lett.* **1990**, *33*, 4743.

10) Jen, A.K.Y.; Rao, V.P.; Drost, K.J.; Wong, K.Y.; Cava, M.P. *J.C.S. Chem.* Commun. **1994**, 2057.

11) Shu, C.F.; Tsai, W.J.; Chen, J.Y. Jen, A.K.Y.; Zhang, Y.; Chen, T.A. *J.C.S. Chem. Commun.*, **1996**, 2279.

12) Babudri, F.; Cicciomessere, A.R.; Fanniola, G.M.; Fiandanese, V.; Marchese, G.; Musio, R.; Naso, F.; Sciacovelli, O. *J. Org. Chem.* **1997**, *62*, 3291.

13) Singer, K.D.; Sohn, J.E.; King, L.A.; Gordon, H.M.; Katz, H.E.; Dirk, C.W. *J. Am.Chem.Soc.* **1987**,*109*, 6561.

Experimental Section

General: The general experimental details were the same as those described in chapter 2. The UV-Vis experiments were done in dioxane at 25°C on a Beckmann DU-650 spectrophotometer.

Chemicals and Reagents: Diethyl ether was dried over sodium, while Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl. DMF was dried over calcium hydride while phosphorous oxychloride was purchased from Merck and used as such. Acetone, ethylmethyl ketone and Diethyl malonate were purchased from S.D fine chemicals and used as such. Nitromethane was purchased from spectro-chem and used as such. Ethyl cyanoacetate, malanonitrile thiophene-2-acetonitrile, and 1,3 dimethyl urea were purchased from Aldrich and used as such.

General Method for the preparation of a-oxoketene dithioacetals (40a,40b):

A mixture of ketone (0.2 mol) and carbon disulphide (12.5 ml, 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 room temperature for 5-6 hours. Neutral dimethyl sulphate (20 ml, 0.2 mol) was gradually added with stirring at 0°C and left to stir at room temperature for 8 hours. The reaction mixture was poured over ammonium chloride solution (250 ml) and the layers were seperated. The aqueous layer was extracted with benzene (2x100 ml) and the combined benzene extracts were washed with water (3x200 ml) dried over fused $CaCl_2$ and evaporated to give crude dithioacetals which were further purified by recrystallization (**40a**) or by distillation under reduced pressure (**40b**). The physical and spectral data were compared with that of the reported values.

General procedure for preparation of carbinols by $NaBH_4$ reduction.

To a solution of a-oxoketene dithioacetal (0.01 mol) in absolute ethanol, (60 ml) excess sodium borohydride (0.76g, 0.02 mol) was added portion-wise and the reaction mixture was then refluxed for 1.5 hours (monitored by TLC). The excess solvent is removed under reduced pressure. The reaction mixture is then poured over saturated NH_4Cl

solution (150 ml), extracted with chloroform, (2x100 ml), washed with water (2x75 ml), dried over anhydrous Na_2SO_4 and evaporated to give the carbinols in nearly quantitative yields which were used as such for the next step.

General procedure for preparation of methyl carbinol by Grignard reaction.

The Grignard reagent is first prepared. To a stirred suspension magnesium (1g), in dry ether (25 ml), a few drops of CH_3I and a crystal of iodine is added. Then the remainder of CH_3I (1.2ml, 0.02 ml) in dry ether (25 ml) is added and stirred for 30 minutes . The reaction mixture is then diluted with dry THF (50 ml) and the carbinol (20 mmol) in dry THF (50 ml) is added dropwise at 0°C. The reaction mixture is then allowed to stir for 4 hours. It is then poured into saturated NH_4Cl solution (200 ml), extracted with chloroform, (2x100 ml), washed with water (2x50 ml), dried over anhydrous Na_2SO_4 and then concentrated to give the carbinols in nearly quantitative yields and were used as such for the next step.

General Procedure for formylation of carbinols:

The Vils meir reagent is first prepared. $POCl_3$ (9.3 ml, 0.1mol) is added dropwise to dry DMF (15 ml,excess) at 0°C. The carbinol(0.05 mol) in dry DMF (25 ml)is added dropwise at 0°C. It is then allowed to warm to room temperature and stirring is continued for 6 hours. It is then poured over crushed ice, neutralised with K_2CO_3, extracted with chloroform (2x100ml), washed with water (2x100 ml), dried over anhydrous Na_2SO_4 and then concentrated. The crude polyene aldehydes are then purified by column chromotography over silica gel using hexane ethyl acetate (99:1) as eluent.

5,5-bis(methyl thio)-2,4-pentadienal (42a):

brown viscous liquid; yield 5.1g(59%); IR (CCl_4) 1670, 1592 cm^{-1}; ^1H NMR (300MHz, CCl_4) 2.40 (s,3H,SCH_3), 2.41 (s,3H,SCH_3), 5.98 (dd, 1H, J = 16 Hz, 8 Hz, H-2), 6.30 (d, 1H, J=12Hz, H-4), 7.47 (dd, 1H, J = 16 Hz, 12Hz, H-3), 9.52 (d, 1H, J = 8 Hz, CHO). (Anal. Calcd. for $C_7H_{10}OS_2$ 174.29, C, 48.24 %; H, 5.78%, Found C, 48.39%; H, 5.55%)

5,5-Bis(Methylthio)-4-methyl-2,4-pentadienal (42b):

Orange viscous liquid; yield 6.6g(70%) IR (neat): 1660, 1590 cm^{-1};^1H NMR (300MHz, CCl_4) 2.11 (s, 3H, SCH_3), 2.33 (s, 3H, SCH_3), 2.42 (s, 3H, SCH_3), 6.11 (dd, 1H, J = 16 Hz, 8Hz, H-2), 8.06 (d, 1H, J = 16Hz, H-3), 9.58 (d, 1H, J = 8 Hz,CHO). MS m/z 188 (M^+, 5%) ,(141,100%) (Anal. Calcd. for $C_8H_{12}OS_2$ 188.31; C, 51.03%; H, 6.42%, Found C, 51.20%, H, 6.63%).

7,7- -Bis(methylthio)-6-methyl-2,4,6-heptatrienal(44):

Orange viscous liquid; yield 8.6g(80%); IR (neat) 1670, 1600 cm^{-1}; ^1H NMR (300MHz, CCl_4) 2.14 (s, 3H, SCH_3), 2.33 (s, SH, SCH_3), 2.37 (s, 3H, SCH_3), 6.10 (dd, 1H, J= 16Hz, 8Hz, H-2), 6.41 (dd, 1H, J= 16Hz, 12Hz, H-4), 7.06 (dd, 1H, J = 16Hz, 12 Hz, H-3), 7.62 (d, 1H, J = 16 Hz, H-5), 9.52 (d, 1H, J = 8 Hz, CHO) : MS m/z 214 (M^+, 12%), (192,39%) (Anal. Calcd. for C_{10} $H_{14}OS_2$ 214.35; C, 56.03%, H, 6.58%; Found C, 56.21%, H, 6.71%).

9,9-Bis(methylthio)-8-methyl-2,4-6,8-nonatetraenal (47):

Reddish brown liquid; yield 8.4g(70%); IR (neat) 1675, 1612, 1585 cm^{-1}; ^1H NMR (300MHz, CCl_4) 2.11 (s, 3H, CH_3), 2.25 (s, 3H, SCH_3), 2.34

(s, 3H, SCH_3), 5.98 (dd, 1H, J = 15 Hz, 8 Hz, H-2), 6.23-7.21 (m, 4H, olefinic), 7.42 (d, 1H, J = 15 Hz), 9.49 (d, 1H, J = 8Hz, CHO); MS m/z 240 (M^+, 100%) (Anal. Calcd for $C_{12}H_{16}OS_2$ 240.38; C, 59.96%; H,6.71%; Found: C, 60.15%, H, 6.89%).

Preparation of 8, 8 - Bis (methylthio) - 7 - methyl - 3,5,7, - octatriene - 2 - one (45):

To a well stirred and cooled solution of sodium methoxide (0.54g, 10 mmol) in methanol (20 ml), mixture of dienaldehyde **42b** (0.94g, 0.005 mol) and acetone (0.4 ml, 5 mmol) in methanol (5 ml) was added dropwise and the mixture was stirred at room tempeature for 6-8 hours. The reaction mixture was diluted with water, extracted with chloroform (2x75 ml), washed with water (2x50 ml), dried over anhydrous Na_2SO_4 and concentrated. Coloumn chromatography over silica gel using hexane: ethylacetate (1:99) yielded a reddish brown semisolid.

8,8-Bis(methylthio)-7-methyl-3,5,7,-octatriene-2-one (45):

Reddish brown solid; low melting; yield 0.97g (85%) IR (CCl_4): 1658, 1600, 1580 cm^{-1}; ^1H NMR (300MHz, CCl_4) 2.09 (s,3H, CH_3), 2.11 (s, 3H, CH_3), 2.25 (s, 3H, SCH_3), 2.35 (s,3H, SCH_3), 6.09 (d, 1H, J = 15 Hz, H-3), 6.31 (dd, 1H, J = 11 Hz, 15 Hz, H-5), 7.19 (dd, 1H, J = 11 Hz H-4), 7.57 (d, 1H, J = 15 Hz, H-6); MS m/z 228 (M^+, 9%).(213, 29%) (Anal. calcd. for $C_{11}H_{16}OS_2$ 228.38; C, 57.85%, H, 7.06%; Found C, 57.90%, H, 7.21%).

General procedure for condensation using piperidine:

To a mixture of the polyene aldehyde (**42a**, **42b**, **44** or **47**) (5 mmol) and the active methylene compound (5 mmol) in ethanol (20 ml) at 0°C, 3 drops of piperidine are added at 0°C and left to stir for 2 hours (monitored by TLC). The excess ethanol is removed by distillation at reduced pressure and the residue is then poured into water (50 ml), extracted with chloroform (2x75 ml), washed with water, dried over anhydrous Na_2SO_4 and concentrated. Coluomn chromatography over silica gel using hexane: ethyl acetate (98:2) yielded pure polyenes.

Ethyl-6,6-bis(methylthio) 1,3,5-hexatrienedicarboxylate (48a):

Orange liquid, yield 1.42g (90%) ; IR (neat): 1703, 1596, 1576, 1170, 1152 cm^{-1} ;^{1}H NMR (300MHz, CCl_4): 1.29 - 1.37 (m, 6H, $OCH_2\underline{CH_3}$), 2.39 (s, 6H,SCH_3), 4.18 - 4.31 (m,4H,$OCH_2\underline{CH_3}$), 6.33 (d, 1H, J=11Hz), 6.60 - 6.70 (m,1H), 7.19-7.25(m,1H), 7.38(d,1H,J=11Hz) ; ^{13}C NMR (75MHz,$CDCl_3$)14.11,16.28,17.18,60.09,124.18,125.89,127.09,138.87, 144.29, 144.59, 163.46, 164.04 ; MS m/z 316: (M^+,32%) (255, 100%). (Anal. calcd. for $C_{14}H_{20}O_4S_2$ 316.44; C, 53.14 %, H, 6.37%, Found C, 53.01%, H, 6.53%); UV-Vis (Dioxane) $\varepsilon_{max} = 1.32x10^4$, $\lambda_{max} = 375nm$

Ethyl -6,6- bis (methylthio)-1-cyano-1,3,5- hexatriene-1- carboxylate (48b):

deep red needles, mp. 78-79°C, ($CHCl_3$/ether): yield 1.2g (87%); IR (KBr): 2211, 1700, 1566, 1170 cm^{-1}; ^{1}H NMR (300MHz, CCl_4): 1.36 (t, 3H, CH_3, J = 7Hz), 2.5 (s, 6H, SCH_3), 4.32 (q, 2H, CH_2, J = 7 Hz), 6.45 (d, 1H, J = 10 Hz, olefinic), 6.6-6.9 (m, 1H, olefinic), 7.45-77 (m, 1H, olefinic), 7.95 (d, 1H, J = 10 Hz, olefinic): MS m/z 269 (M^+, 66.3%), (208, 94%),(69, 100%) (Anal. Calcd. for $C_{12}H_{15}NO_2S_2$: 269.39; C, 53.50 %, H,5.61 %,N, 5.20 %. Found C, 53.71 %, H,5.76 %, N, 5.01%); UV-Vis (Dioxane) $\varepsilon_{max} = 6.65x10^4$, $\lambda_{max} = 409$ nm

6,6-Bis(methylthio)-1,1-dicyano-1,3,5-hexatriene (48c):

deep red flakes; m.p 102-103°C (ether/hexane); yield 0.89g (80%); IR (KBr):2218, 1570,1193,cm^{-1}; ^1H NMR (90MHz, CCl_4) 2.5 (s,6H,SCH_3), 6.2- 6.8 (m,2H),7.35-7.7 (m,2H), MS m/z 222 (M^+,38.4%), (207,56.1), (45,100); (Anal calcd. for $C_{10}H_{10}N_2S_2$:222.34. C,54.02% H, 4.53% N,12.60% .Found C, 54.30%, H, 4.36%, N,12.45%); UV-Vis (Dioxane) $\varepsilon_{max} = 6.57x10^4$, $\lambda_{max} = 411nm$

6,6-Bis(methylthio)-1-cyano-1-p-nitrophenyl-1,3,5-hexatriene (48d):

deep red cubes; m.p. 162-163°C, ($CHCl_3$/ether); yield 1.40g (88%) IR (KBr): 2206, 1558, 1512, 1496, 1480 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) 2.46 (s, 6H, SCH_3),6.38 (d, 1H, J = 11Hz, olefinic), 6.78-6.87 (m, 1H, olefinic), 7.36-7.53 (m, 2H, olefinic), 7.71-7.75 (m, 2H, arom), 8.23-8.27 (m, 2H, arom); ^{13}C NMR (75MHz, $CDCl_3$) 16.74, 17.51, 108.82, 116.49, 124.38, 124.88, 125.83,126.26, 139.60, 139.80, 145.34, 147.24, 148.25;(Anal. Calcd. for $C_{15}H_{14}N_2OS_2$, 318.42; C, 56.58%, H, 4.43%, N, 8.80%, Found C, 56.72%, H, 4.56%, N, 8.98%); UV-Vis (Dioxane) $\varepsilon_{max} = 3.34x10^4$, $\lambda_{max} = 430$ nm

Ethyl -6, 6- bis (methylthio) -5- methyl -1, 3, 5- hexatriene -1, 1- dicarboxylate (48f):

Orange liquid, yield 1.50g (91%); IR (CCl_4), 1706, 1598, 1237, 1212 cm^{-1}, ^1H NMR (300MHz, CCl_4):1.27-1.36(m, 6H,$OCH_2\underline{C}H_3$), 2.16(s, 6H, CH_3),2.29(s,3H,CH_3), 2.39(s,3H,CH_3), 4.10-4.30(m,$OCH_2\underline{C}H_3$), 6.75(m, 1H),7.42(m, 1H),7.70(m,1H); ^{13}C NMR(75MHz, CCl_4) 14.13, 16.99, 17.53, 17.99, 60.40,124.11, 124.31, 138.67, 142.13, 142.62, 145.53, 163.84, 164.31; (Anal. Calcd. for $C_{15}H_{22}O_4S_2$; C, 54.52%, H, 6.71%, Found C, 54.68%, H,6.59 %); UV-Vis (Dioxane) $\varepsilon_{max} = 2.21 \times 10^4$, λ_{max} = 374 nm.

Ethyl -6,6- bis (methylthio) -1- cyano- 5 -methyl - 1,1,3,5- hexatriene- 1- carboxylate (48g):

Orange needles; m.p. 63-64°C (ether:hexane); Yield 1.25g (88%); IR (KBr) 2220, 1713, 1577, 1488, 1171cm^{-1} ; ^1H NMR (300MHz, $CDCl_3$) 1.36 (t, 3H, J = 7 Hz, CH_3), 2.19 (s, 3H, CH_3), 2.34 (s, 3H, SCH_3), 2.47 (s, 3H, SCH_3), 4.29 (q, 2H, CH_2, J = 7 Hz), 6.73 (dd, 1H, J = 9Hz,3Hz, olefinic), 7.95-8.01 (m, 2H, olefinic); ^{13}C ($CDCl_3$): 14.17, 17.48, 17.56,

61.96, 102.77, 114.77, 123.07, 137.67, 147, 148.71, 156.14, 162.44; MS m/z 283 (M^+, 93.8%) (268,100%),(240, 64.7%);(Anal. Calcd. for $C_{13}H_{17}NO_2S$ 283.41 C, 55.09%, H, 6.05 %, N, 4.94%; Found C, 55.21%, H, 6.17 %, N, 4.71%); UV-Vis (Dioxane) $\varepsilon_{max} = 2.12x10^4$, $\lambda_{max} = 409$ nm

6,6- Bis(methylthio)- 1,1-dicyano-5-methyl-1,3,5- hexatriene (48h):

dark red cubes, m.p. 93-94°C (ether:hexane) : yield 0.97g (82%). IR (KBr) 2220, 1570, 1184 cm^{-1}, ^1H NMR (75MHz, CCl_4): 2.2 (s,3H,CH_3), 2.35 (s,3H,SCH_3), 2.5 (s, 3H, SCH_3), 6.6- 6.9 (m,1H, olefinic), 7.6 (d,1H, J= 18Hz), 8.0 (d, 1H, J= 18Hz); (Anal. Calcd for $C_{11}H_{12}N_2S_2$ 236.38 ; C, 55.90%, H, 5.12%, N, 11.85% ; Found C, 55.12 %, H, 5.03%);UV-Vis (Dioxane) $\varepsilon_{max} = 4.55x10^4$; $\lambda_{max} = 417$ nm

6,6- Bis(methylthio) -1- cyano -5- methyl -1- p-nitrophenyl -1,3,5 hexatriene (48I):

Deep red cubes ; m.p. 162-163°C ($CHCl_3$: Ether); Yield: 2.0g (87%); IR (KBr) 2213, 1575, 1514 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$):2.23 (s, 3H, CH_3), 2.34 (s,3H,SCH_3), 2.46 (s,3H,SCH_3), 6.88 (dd, 1H, J= 9Hz,

3.5Hz), 7.58 (dd,1H, J=11Hz, 0.6Hz), 7.74-7.78 (m,2H), 7.86- 7.91 (m,1H); 8.24- 8.27 (m,2H); ^{13}C NMR (75 MHz, $CDCl_3$): 17.49, 17,71, 18.52, 109.47, 116.38, 124.35, 125.06, 125.92, 138.48, 139.75, 143.20, 145.16, 146.03, 147.30; (Anal.Calcd for $C_{16}H_{16}N_2O_2S_2$. 332.45; C, 57.81%, H, 4.85%, N, 8.43; Found: C, 57.92 %, H, 4.71%, N, 8.30%); UV-Vis (Dioxane) $\varepsilon_{max} = 3.02x10^4$; $\lambda_{max} = 430$ nm ; $\beta = 272x10^{-30}$ e.s.u. (methanol)

Ethyl -8, 8- Bis (Methylthio) -1- cyano- 1, 3 ,5, 7- octatetraene -1-carboxylate (49a):

Red crystals m.p. 152-153°C; Yield 1.13g (73%); IR(KBr) 2213,1716,1588, 1548 cm^{-1}; ^1H NMR (300,MHz, $CDCl_3$) : 1.36 (t, 3H, J=7Hz,CH_3),2.17(s,3H,CH_3),2.31(s,3H,SCH_3),2.42(s,3H,SCH_3), 4.31 (q, 2H, J=7Hz, CH_2), 6.52(dd,1H, J= 4Hz,12Hz), 6.79 (dd, 1H, J= 2.5Hz , 12Hz), 7.08 (dd, 1H, J=3.3Hz, 11Hz), 7.68 (d, 1H, J= 7.5Hz), 7.88 (d, 1H, J= 12Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 14.19, 17.46, 17.61, 18.40, 62.14, 102.55, 114.93, 126.61, 128.09, 138.92, 141.39, 142.94, 149.99, 155.02, 162.74. (Anal. Calcd for $C_{15}H_{19}NO_2S_2$: 309.45; C, 58.22%, H,

6.19%, N,4.53%; Found C,58.07%, H, 6.31%, N, 4.66 %); UV-Vis (Dioxane) $\varepsilon_{max} = 3.83x10^4$; $\lambda_{max} = 432$ nm

8,8- Bis(methylthio) -1- cyano -7- methyl -1 - (p-nitrophenyl) - 1,3,5,7-octatetraene (49b):

Red Crystals; m.p.180-181°C; Yield 1.40g (78%); IR (KBr) 2206, 1588, 1528 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$), 2.19 (s,3H, CH_3), 2.32 (s,3H, SCH_3),2.41 (s, 3H, SCH_3),6.52-6.58 (m, 1H), 6.87- 7.01 (m, 2H), 7.45-7.63(m,2H), 7.74 (d, 2H, J- 9Hz,arom), 8.26(d, 2H, J= 9Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$), 17.44,17.65, 18.30, 109.27, 116.35, 124.38, 125.94, 128.35, 128.67, 139.29, 139.33, 139.75, 144.74, 145.65, 147.36, 148.29, 176.76,180.28;(Anal.Calcd for $C_{18}H_{18}N_2O2S_2$ 358.48; C, 60.31%, H,5.06 %, N, 7.81 %; Found C, 60.45%, H,5.25%, N,7.97%); UV-Vis (Dioxane) $\varepsilon_{max} = 2.69x10^4$; $\lambda_{max} = 445$nm

Ethyl-10,10-Bis(methylthio)-1-cyano- 9-methyl-l-1,3,5,7,9-pentaene-1- carboxylate (50):

red cubes; m.p.173-174°C; (hexane/ether); yield 1.0g(58%); IR (KBr) 2320, 2220, 1709, 1602 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) 1.35

(t,3H,J=7Hz, CH_2CH_3), 2.17(s, 3H, CH_3), 2.30 (s, 3H, SCH_3), 2.40 (s, 3H,SCH_3),4.31(q,2H,J=7Hz,OCH_3), 6.41-6.53(m,2H),6.68-6.83(m,2H), 6.93-7.02(m,1H), 7.53(d,1H,J=15Hz), 7.86(d,1H,J=12Hz); ^{13}C NMR (75MHz, $CDCl_3$)14.20,17.42,17.64,18.27,62.12, 102.60, 114.92, 126.35, 129.00, 131.20, 138.04, 139.60, 143.81, 148.89, 154.90, 162.71,180.30; Anal. Calcd for $C_{17}H_{21}NO_2S_2$ 335.49 ;C, 60.86%, H, 6.31%, N, 4.18%; Found C, 60.97%, H, 6.47%, N, 4.01%) ; Uv-Vis (Dioxane) ε_{max} = $4.2x10^4$; λ_{max} = 443nm

General procedure for condensation with thiophene-2-acetonitrile:

A mixture of anhydrous K_2CO_3 (5g), and thiophene-2-acetonitrile (0.53ml , 5m mol) in acetone (25ml) is stirred for 10 minutes. To this the dienealdehyde (**42a** or **42b**, 5 m mol) is acetone (10ml) is slowly added at 0°C. Stirring is continued for 2 hours (monitored by TLC). The excess solvent is distilled off at reduced pressure and the residue is diluted with 50 ml of water. It is then extracted with chloroform (2x 75ml) washed with water (2x50ml) , dried over anhydrous Na_2SO_4, and concentrated to yield crude products, which are purified by recrystalisation from ether: hexane.

6,6,- Bis (methylthio) -1 -cyano-1(2-thienyl)-1,3,5- hexatriene (48e):

Yellow needles,m.p.78-79°C (Hexane:ether) IR(KBr) 2361,1548,1246 cm^{-1};^1H NMR(300MHz, $CDCl_3$) 2.418(s,3H,SCH_3), 2.422(s,3H,SCH_3), 6.37(d,J=11Hz,1H),6.67-6.77(m,1H),7.01-7.05(m,1H),7.10-7.27(m,5H); ^{13}C NMR(75MHz, $CDCl_3$) 16.72, 17.67, 106.24,116.16,125.95, 126.52, 126.77,128.15,136.31,138.79,140.02,144.21;MS (m/z) 279 (M^+ 56.2%), 69 (100%);(Anal Calcd. For $C_{13}H_{13}NS_3$ 279.45 ; C, 55.88%, H, 4.69%, N, 5.01%; Found C, 55.79%, H, 4.81%, N, 5.18%); UV-Vis (Dioxane) $\varepsilon_{max} = 5.40x10^4$; $\lambda_{max} = 411$ nm

6,6-Bis (methylthio) -1- cyano -1- thienyl -5- methyl-1,3,5-hexatriene (48j):

Yellow needles: m.p.67-68°C(ether: hexane); Yield 0.9g(70%); IR (KBr) 2362,2206,1655,1582cm^{-1}; ^1H NMR(300MHz,$CDCl_3$)2.21(s,3H, SCH_3),2.31(s,3H,SCH_3);2.41(s,3H,SCH_3),6.78(dd,1H, J=11.3Hz, 15Hz), 7.01-7.05(m,1H),7.18 (d, 1H, J=11.3Hz), 7.25-7.27(m,2H),7.68 (d, 1H, J=15Hz); ^{13}C NMR (75MHz, $CDCl_3$):17.41,17.70,18.35,106.73,116.06, 125.34, 126.00, 126.59, 128.11, 138.77, 139.08, 139.77, 140.61, 141.60. (Anal. Calcd for $C_{14}H_{15}NS_3$:293.48; C, 57.30%, H, 5.15%,

N,4.77%;Found:C, 57.45%, H,5.29%, N,4.61%); UV-Vis (Dioxane) $\varepsilon_{max} = 4.57x10^4$, $\lambda_{max} = 410$ nm

Procedure for condensation using Sodium ethoxide/ethanol as base :

The solution of dienealdehyde **42b** (1g, 5mmol) and the active methylene compound(5mmol) in ethanol (25 ml) is added to a solution of sodium ethoxide(10 mmol) in ethanol [prepared from 10 mmol of sodium and 25 ml of ethanol] at 0°C and left to stir for 2 hours (monitored by TLC). The ethanol is distilled off at low pressure and the residue is quenched in water. It is extracted with $CHCl_3$ (2x50 ml) ,washed with water(2x30ml), dried over anhydrous Na_2SO_4 and concentrated. The crude residue is then purified by column chromatography over silica gel using hexane:ethyl acetate (99:1) as eluent.

6,6-Bis(methylthio)-5-methyl-1-nitro-1,3,5-hexatriene(48k) :

yellow liquid; yield 0.75g(73%); IR (CCl_4) 1609,1508,1332,1161 cm^{-1}; ^1H NMR(300MHz, $CDCl_3$) 2.15(s,3H,CH_3),2.31(s,3H,SCH_3),2.41(s,3H, SCH_3),2.43(dd,1H,J=11.7H,15.1Hz),7.09(d,1H,J=13.1Hz),7.63-7.72 (m, 1H),7.80(d,1H,J=15.2Hz); ^{13}CNMR(75MHz, $CDCl_3$)16.92,17.29, 17.91,

121.00, 138.05, 138.28, 138.47, 143.48; MS m/z 231(M^+,25.6%), (111, 100); (Anal .Calcd for $C_9H_{13}NO_2S_2$ 231.34; C, 46.73%, H, 5.66%;Found C, 46.86%, H,5.79%, N, 5.91%); UV-Vis (Dioxane) ε_{max} = 1.88x10^4, λ_{max} = 364 nm

1,3- Dimetyl -5 [5'-bis (methylthio) -penta -2',4'- dienylidene] barbitiuric acid (48l):

dark red crystals; m.p.128°C;($CHCl_3$/ether); yield 73%; IR(KBr) 1650, 1555,1545cm^{-1}, ^{1}H NMR(300MHz, $CDCl_3$)2.22(s,3H,SCH_3),2.34(s, 3H, SCH_3), 2.48(s,3H,SCH_3), 3.34(s,3H,NCH_3),8.01(dd,1H,J=15,15Hz),8.14 (d, 1H, J=15 Hz) 8.19(d,1H,J=12Hz); (Anal. Calcd for $C_{14}H_{18}N_2O_3S_2$ 326.44 ;C, 51.51%, H, 5.56%, N, 8.58%; Found C, 51.39%, H, 5.72%, N, 8.73%); UV-Vis (Dioxane)ε_{max} = 2.5 x10^4; λmax = 401 nm; β = 88x10^{-30}e.s.u. (methanol)

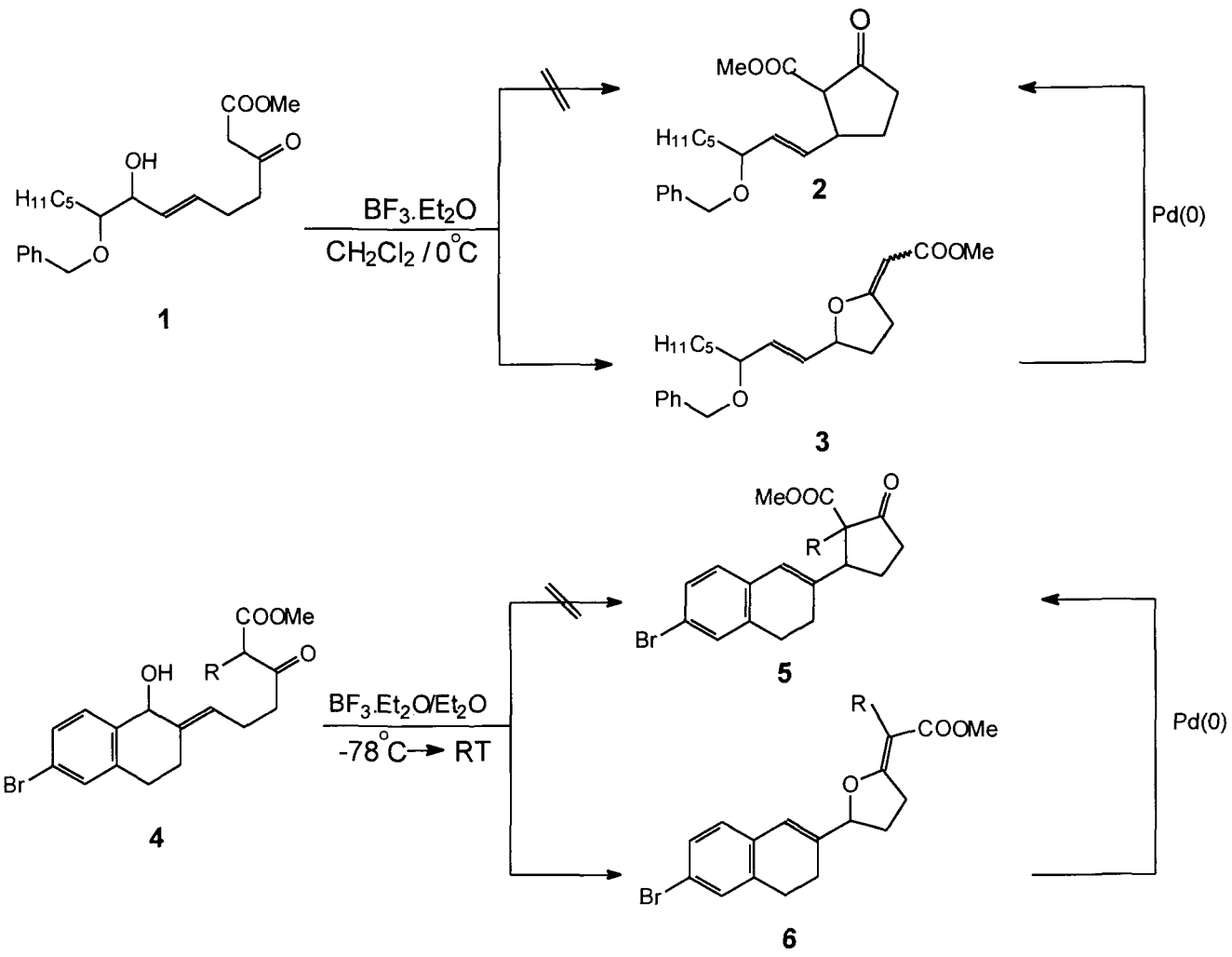
CHAPTER FOUR

REARRANGEMENT STUDIES OF HETEROARYL SUBSTITUTED CYCLOPROPYL KETONES FROM α-OXOKETENE DITHIOACETALS: A NOVEL TANDEM CARBOCATIONIC APPROACH FOR THE SYNTHESIS OF HETERO ARYL FUSED DIQUINANE SYSTEMS

Much attention is being paid in recent years to develop the chemistry of cyclopentanoids and their condensed diquinane variants, since several terpenoids containing this carbocyclic frame work have been isolated from natural sources.[1-8] Therefore many synthetic approaches have been developed for the synthesis of cyclopentanoids involving inter and intramolecular rearrangements. Many attempts have been made to develop methods similar to the well known Diels-Alder reaction using one carbon equivalents of dienophiles without apparent success. There have been many other approaches for cyclopentane

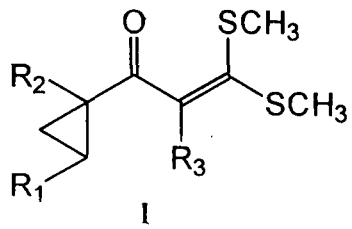
annelation with great success and they have been reviewed in recent years.[9-25] The application of classical reactions such as Dieckmann condensation, Aldol condensation, Friedel-Crafts reaction etc. for the construction of five membered carbocyclic systems have not been as successful as the construction of six membered carbocyclic systems.[9,10] The common approaches involving the cyclization of the enolate anion of γ-haloketonenes and their corresponding β-keto esters generally led to the preferred alkylidene tetrahydrofurans rather than cyclopentanoids.[10]

Trost and co-workers [9,30-32] did initial contribution towards the development of efficient methodology for the synthesis of cyclopentanoids. Thus the alkylidene tetrahydrofuran **3** (Scheme-1), an undesirable product from **1**, was shown to undergo Pd(0) catalysed rearrangement to afford the corresponding cyclopentanoids **2**. The preferred O-alkylation process to afford the tetrahydrofurans was later attributed to stereo electronic factors associated with 5-membered ring.[26-29] Though subsequently the transformation of **3** to **2** circumvented these limitations, no serious studies were reported


COOMe
O
OH
H11C5
Ph
O
1
BF3.Et2O
CH2Cl2 / 0°C
MeOOC
O
H11C5
Ph
O
2
COOMe
O
H11C5
Ph
O
3
Pd(0)
COOMe
R
O
OH
Br
4
BF3.Et2O/Et2O
-78°C→ RT
MeOOC
R
O
Br
5
R
COOMe
O
Br
6
Pd(0)

Scheme - 1

however prior to ours to block enolate functionality by modifying the precursor β -keto esters, so that the desired C-alkylation process is favoured over the O-alkylation process. As an illustration of this successful approach, we developed a series of bismethylthio alkyl fused cyclopropyl ketones **I**

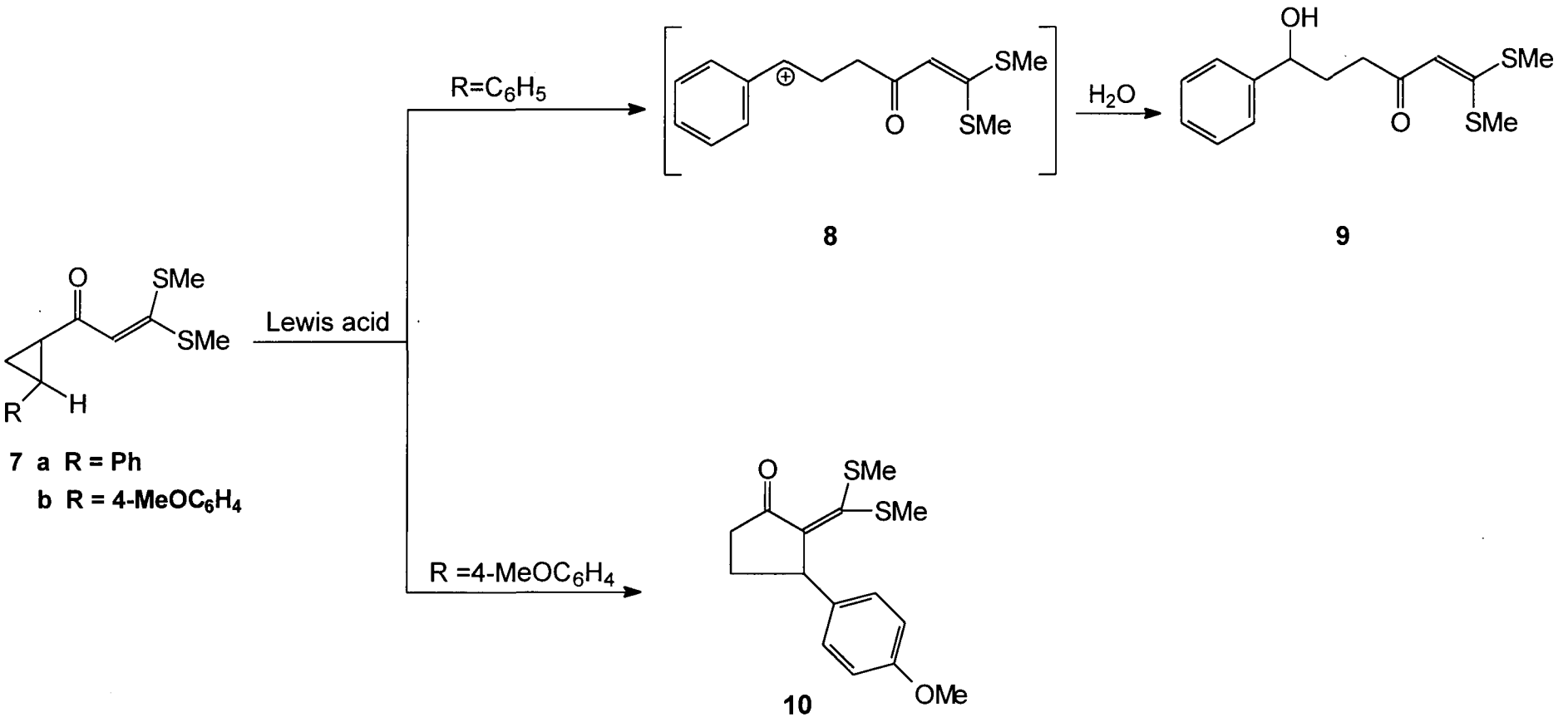


I

where the β-keto ester component is masked by the mercapto double bond, and then subjected them to acid catalysed ring opening. The bis(methylthio) methylene group was expected to undergo intramolecular π participation with the developing carbocation during ring opening and thus lead to cyclopentanones, rather than furan derivatives. This objective was successfully realised when the cyclopropyl ketones of the general formula **I** underwent an interesting rearrangement on treatment with a variety of Lewis acids to yield cyclopentanones. These results were published in a series of communications.[36-38,41,42,47,49]

Cyclopropyl ketones derived from -cinnamoyl ketene

dithioacetals were first considered[36,37] for examination of their tendency to undergo the rearrangement. When **7a** (R=Ph) was treated with $BF_3.Et_2O$ in nitromethane, the product obtained was found to be the open chain carbinol **9**.(Scheme-2) This proved that the rearrangement goes through an intermediate carbocation **8**, which on trapping by water yields the carbinol **9**. Apparently the formation of the C-C bond demands that there should be no external nucleophile in the reaction medium, failing which only simple open chain systems can be obtained. However, when the cyclopropyl ring carried an activated aryl group containing 4-MeO group(**7b**), the rearrangement of **7b** under H_3PO_4/HCOOH conditions did indeed lead to the formation of the cyclopentanone ketene dithioacetal **10** in excellent yield. The intramolecular C-C bond formation seems to be spontaneous only when the phenyl ring contained an activating group. Apparently an unsubstituted benzene ring did not provide the intermediate carbocation, the required stability. Hence in subsequent studies electron rich substituents, namely aryl rings containing one or more MeO groups were incorporated on the cyclopropane ring to facilitate this rearrangement. Thus when p-methoxy phenyl group was present on the



8

9

7 a R = Ph

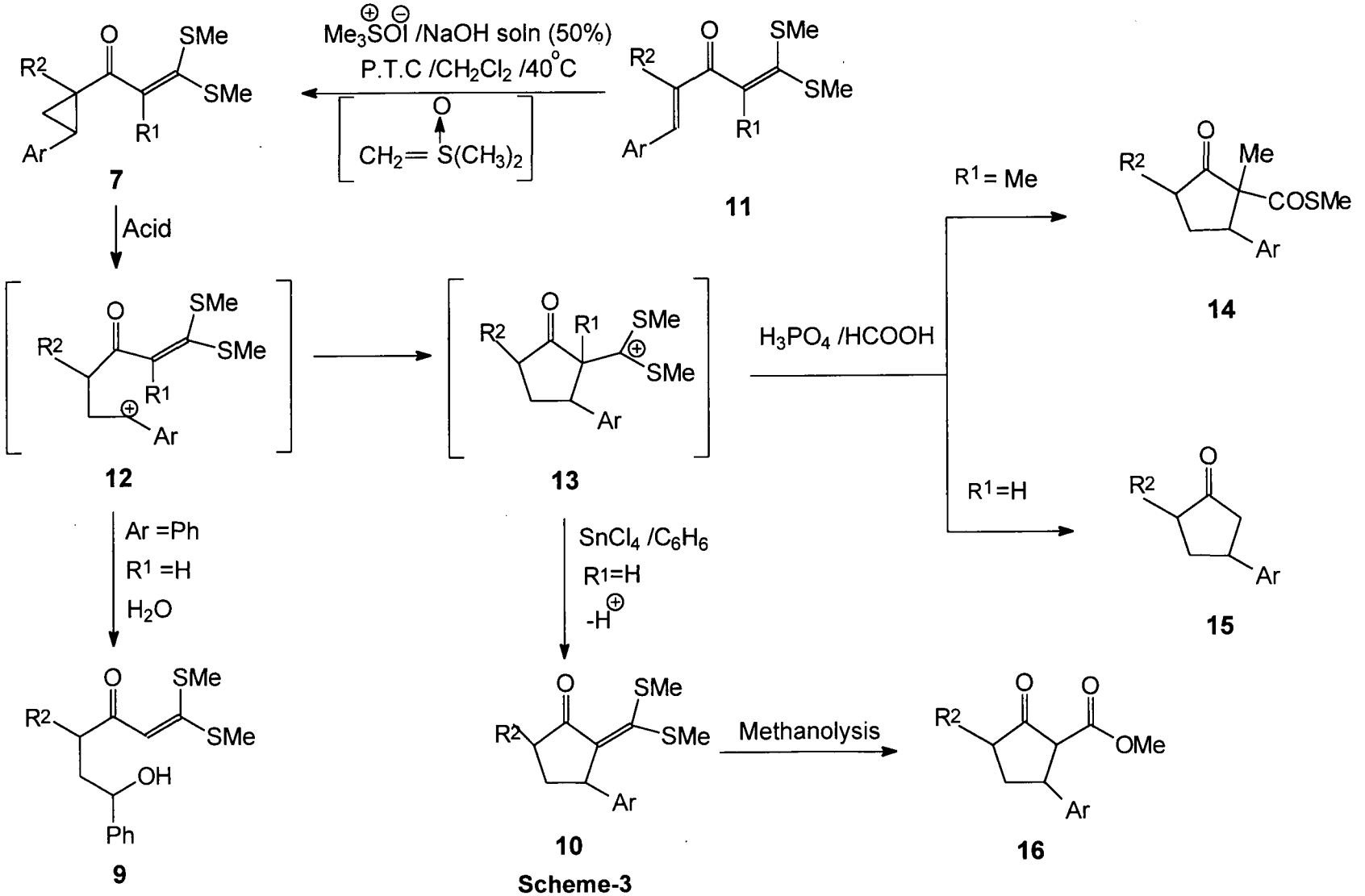
b R = 4-MeOC$_6$H$_4$

10

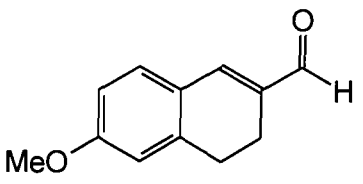
Scheme -2

cyclopropane ring the acid assisted rearrangement in H_3PO_4/HCOOH lead to the formation of cyclopentanones either **14** or **15**.(Scheme-3) If the mercapto double bond carried a methyl group as an α substituent then the carbocation **13** underwent hydrolysis to afford **14.** On the other hand, when R^1=H the carbocation **13** underwent hydrolysis and loss of COSMe group to afford cyclopentanone **15.** Interestingly the same carbocation under $SnCl_4/C_6H_6$ conditions underwent proton loss to afford the cyclopentanone mercaptal **10** in excellent yields. This mercaptal was subsequently subjected to methanolysis to regenerate the carbomethoxy group from its bismethylthiomercaptal functionality.

An interesting synthetic application of this methodology is for the preparation of 11-oxo steroid precursor **20**[38,40] and is formulated in Schemes-4,5. Thus dihydro naphthalene aldehyde **17** was condensed with mercaptals derived from either acetone **18a** or ethyl methyl ketone **18b** to afford the α,β unsaturated enones **19a,b** in excellent yields. The enones were then subjected to cyclopropanation using dimethyl-oxosulphonium methylide in the presence of phase transfer catalyst[39] to afford the corresponding cyclopropyl ketones **7c**, and **7d** respectively in good yields. The cyclopropyl ketone **7c** on treatment with $SnCl_4/C_6H_6$ at

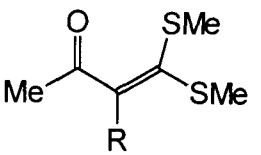

Me3SOI /NaOH soln (50%)
P.T.C /CH2Cl2 /40°C
CH2= S(CH3)2
7
11
Acid
12
13
H3PO4 /HCOOH
R1 = Me
14
R1=H
15
Ar =Ph
R1 =H
H2O
9
SnCl4 /C6H6
R1=H
-H
10
Methanolysis
16

Scheme-3



17

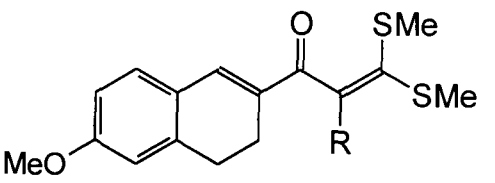
+



18 a R = H

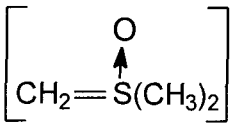
b R =Me

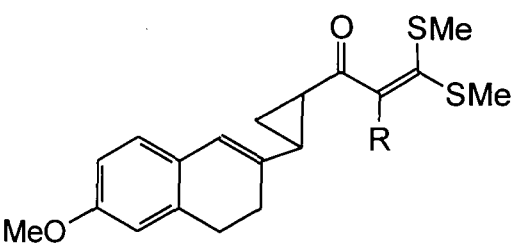
NaOEt/EtOH



19 a R =H

b R = Me

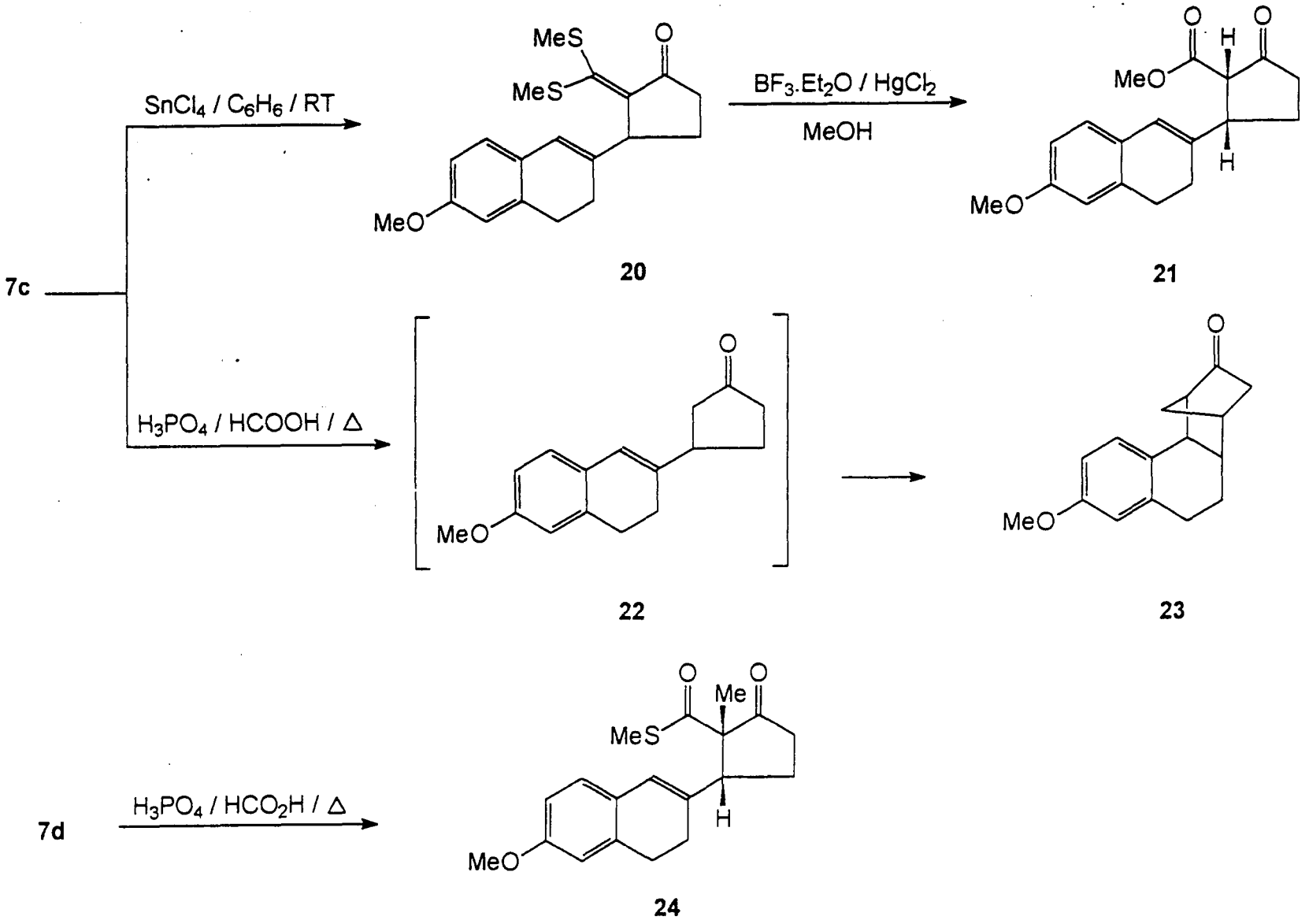




7 c R = H

d R = Me

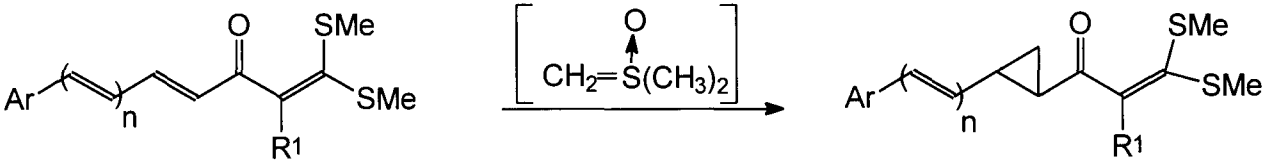
Scheme - 4


7c
SnCl4 / C6H6 / RT
MeS
MeS
O
MeO
20
BF3.Et2O / HgCl2
MeOH
O
H
O
MeO
H
MeO
21
H3PO4 / HCOOH / Δ
O
MeO
22
O
MeO
23
7d
H3PO4 / HCO2H / Δ
O
Me
O
MeS
H
MeO
24

Scheme- 5

room temperature yielded the cyclopentanone ketene dithioacetal **20** (Scheme-5). This on subsequent methanolysis using $BF_3.Et_2O/HgCl_2$ in MeOH yielded the 11-oxosteroid precursor **21** as a single trans product. However, the H_3PO_4/HCOOH treatment of **7c** resulted in the bicyclic ketone **23** presumably via the substituted cyclopentanone **22,** involving the tetralin double bond The cyclopropylketone **7d**, when subjected to H_3PO_4/HCOOH treatment yielded the expected thioester **24** as a single trans product.

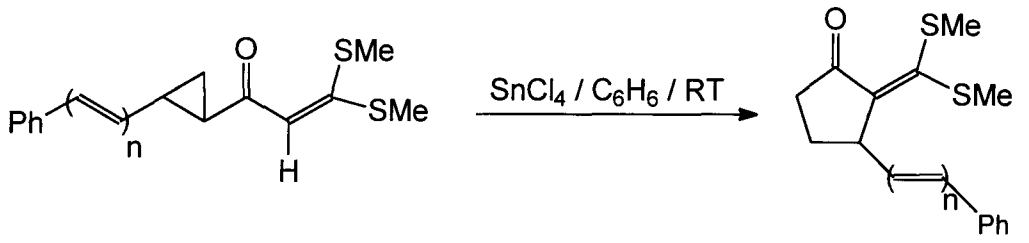
It was further considered of interest to incorporate an olefinic bridge between the aryl ring and the cyclopropyl ring and study the behaviour of these stryl and dienylaryl cyclopropylketones towards various acids. The desired cyclopropyl ketones **26a-g** were readily prepared from the respective enones **25a-g** by the earlier mentioned method in excellent yields (Scheme-6). When **26a** (Ar=Ph,n=1)was treated with $SnCl_4$ in C_6H_6 at RT, the cyclopentanone ketene dithioacetal **27a** was formed in good yield (Scheme-7). Apparently the intermmediate carbocation undergoes only proton loss, leaving both the ene and mercapto double bond unaffected. Similarly **26e** (where n = 2)



25 a-g **26 a-g**

25,26 **a** **Ar=C_6H_5,R^1=H,n=1**
b **Ar=C_6H_5,R^1=Me,n=1**
c **Ar=4-MeOC_6H_4,R^1=Me,n=1**
d **Ar=3,4-$(MeO)_2C_6H_3$,R^1=H,n=1**
e **Ar=C_6H_5,R^1=H,n=2**
f **Ar=4-MeOC_6H_4,R^1=H,n=1**
g **Ar=4-MeOC_6H_4,R^1=H,n=2**

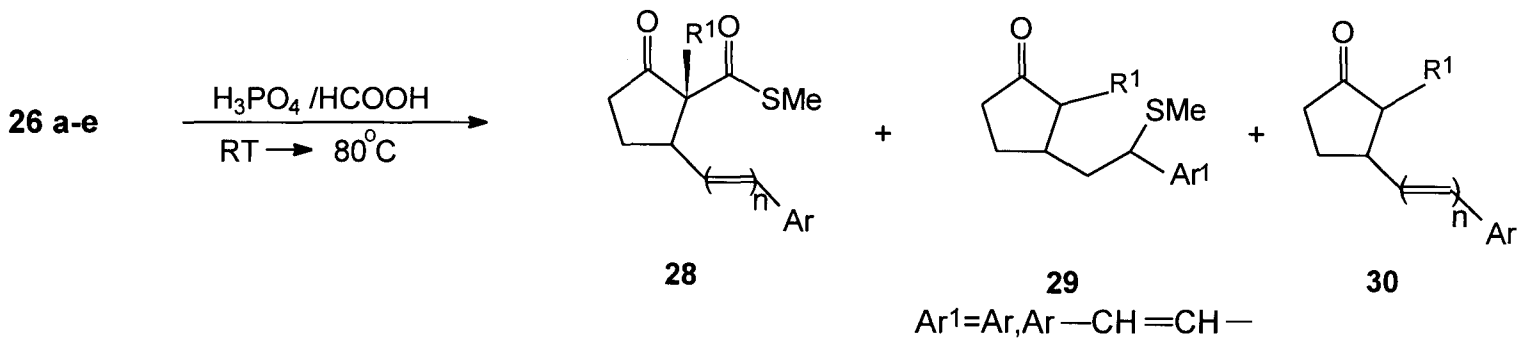
Scheme - 6



26a n = 1
e n = 2

27a n =1
b n = 2

Scheme- 7



28

29

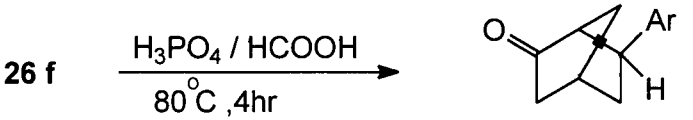
Ar1=Ar,Ar—CH=CH—

30

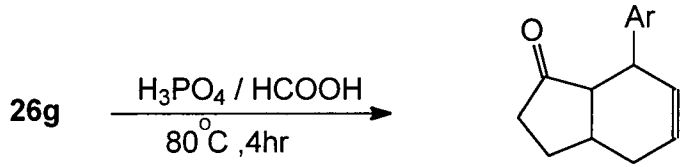
Scheme-8

yielded **27b** in good yield. However when the cyclopropylketones **26a-e** were subjected to H_3PO_4/HCOOH conditions,the reactions yielded the three different cyclopentanone products **28,29** and **30** (Scheme-8). The abundance of each depended upon the temperature and duration of the reaction times. In the product **28**, the ester arose due to hydrolysis of the bismethyl(thio) functionality, which is in accord with our earlier observation. The formation of **29** can be easily explained that the expelled MeSH group attackes the protonated double bond with concomittant loss of CO_2 under the reaction conditions. The cyclopentanone **30** results from the expulsion of MeSH group form **29**. However the cyclopropyl ketone **26f** (R=H, n =1) yielded the bicyclic ketone **31** while **26g** (R=H,n=2) yielded the annulated cyclopentanone **32** (Scheme-9).

These rearrangement studies were then extended to the cyclopropyl carbinols[41]**33** obtained from the corresponding ketones **7,26** by either NaBH4 reduction or addition of alkyl Grignard reagents. When carbinols **33** obtained by $NaBH_4$ reduction or addition of alkyl Grigard reagents to aryl substituted cyclopropyl ketones **7** were subjected to

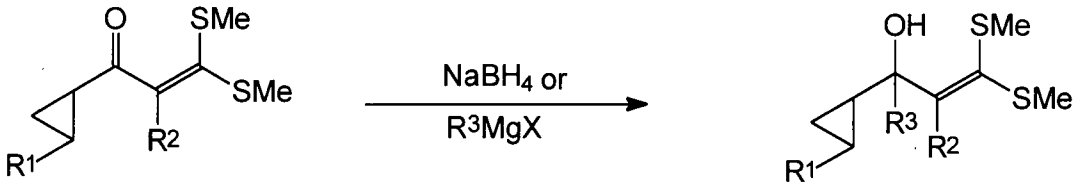


31



32

Scheme - 9



33

7 R_1 = aryl

26 R_1 = styryl,dienyl aryl

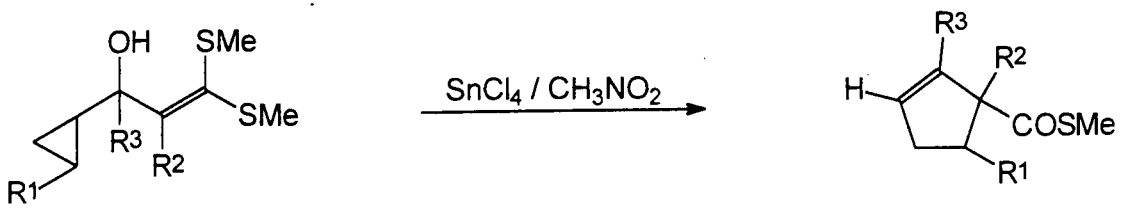
R_3 = H (from $NaBH_4$ reduction)

R_3 = alkyl (from alkyl Grignard addition)

Scheme - 10

$SnCl_4$ in nitromethane, good yields of β,γ-unsaturated cyclopentene carbothioate **34** were obtained (Scheme-11). The ^1H and ^{13}C spectra of these products obtained indicated the formation of only one stereoisomer,probably trans. A significant success of this reaction condition was that the phenyl substituted cyclopropyl carbinol underwent smooth cyclisation to the cyclopentene. The parent cyclopropyl ketone itself had not undergone cyclisation under any condition and instead gave only open chain product (Scheme-2). However, when the carbinols obtained by MeMgI addition to **7** (where the cyclopropyl ring carries a methyl as well as 4MeO-C_6H_4 substituent), was exposed to $SnCl_4$ in CH_3NO_2, the product obtained was the biphenyl **35** and not the cyclopentane **34a** (Scheme-12). The steric repulsion that could arise between the two methyl groups in the intermediate carbocation favoured the 6-endo mode of cyclization rather than the 5-exo mode.

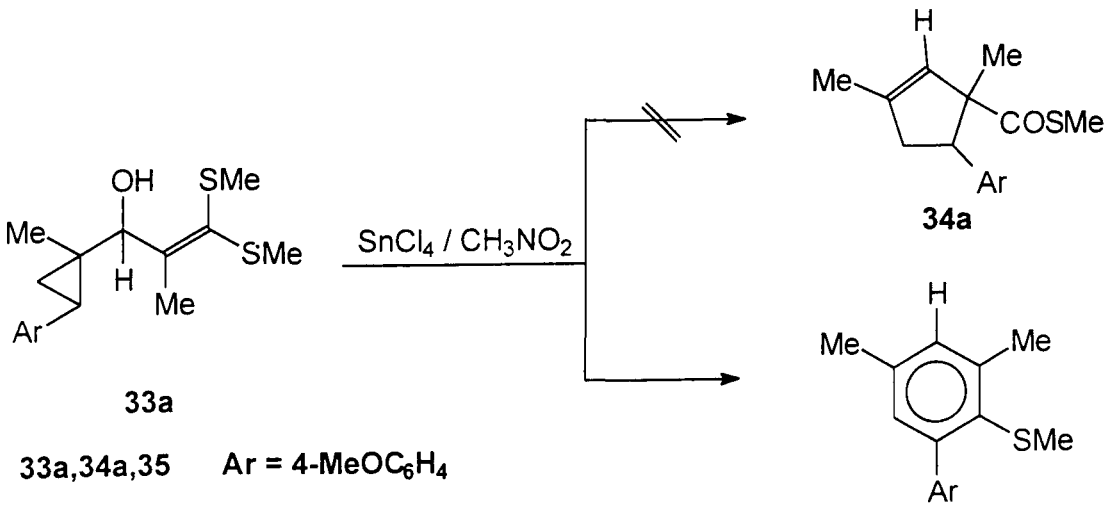
Attempts to obtain polyenes from the carbinols **33** obtained by $NaBH_4$ reduction succeeded when they were treated with pyridinium tosylate in refluxing CCl_4. Thus incorporation of aryl, stryl and dienylaryl groups on the cyclopropane ring successfully led to the



33 **R^1 = aryl**
R^2 = H,Me
R^3 = H,Me

34

Scheme - 11



33a

34a

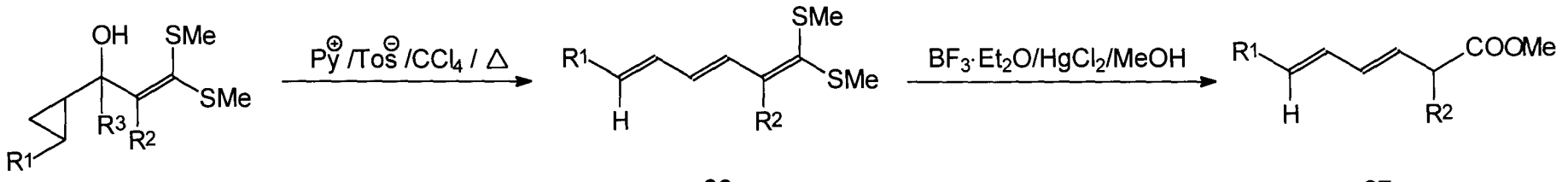
35

33a,34a,35 **Ar = 4-$MeOC_6H_4$**

Scheme - 12

formation of trienes**36a,** tetraenes **36b,** and pentaenes **36c** (Scheme-13). These polyenes on $BF_3.Et_2O/HgCl_2$ catalysed methanolysis yielded β,γ-unsturated diene esters **37a**, triene esters **37b** and tetraene esters **37c**. However, carbinols obtained by alkyl Grignard reagent addition (where R^2=H) did not lead to alkyl substituted polyenes. Instead cyclopentenes **38** with intact dithioacetyl functionality were obtained. (Scheme-14)

An elegant sequence for assembling cyclopent[a]indenes was acheived through, an interesting tandem carbocationic cyclisation of bis(methylthio)methylene arylcyclopropylketones **7** under Lewis acid conditions[42-46]. When the cyclopropyl ketone **7**, where R^1=H, was subjected to $SnCl_4$ in CH_3NO_2, the product obtained namely the cyclopentanone ketene dithioacetal **41** showed that the highly activated aromatic ring did not undergo electrophilic interaction with the sulphur stabilised cation **39** to afford the expected indenes **40** (Scheme-15). Despite the aromatic ring containing two oxygenated functional groups the expected C-C bond formation had failed to occur. The intermediate carbocation had probably undergone proton loss to afford the oxoketene dithioacetal, which we have observed in the past. It was contemplated that if R would be a methyl group, the possibility of proton loss would



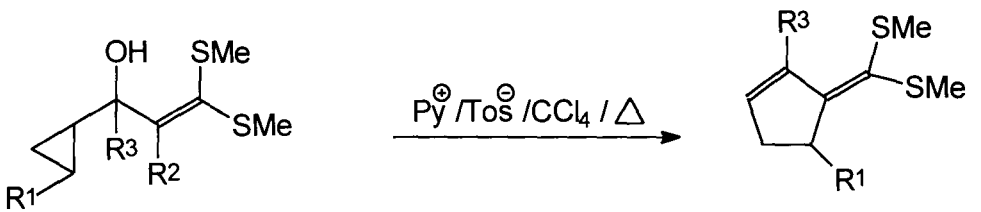
36

37

33 **R^1 = aryl,styryl,dienyl aryl**
R^2 = H, Me
R^3 = H

36,37 a R^1 = aryl
b R^1 = styryl
c R^1 = dienyl aryl

Scheme -13

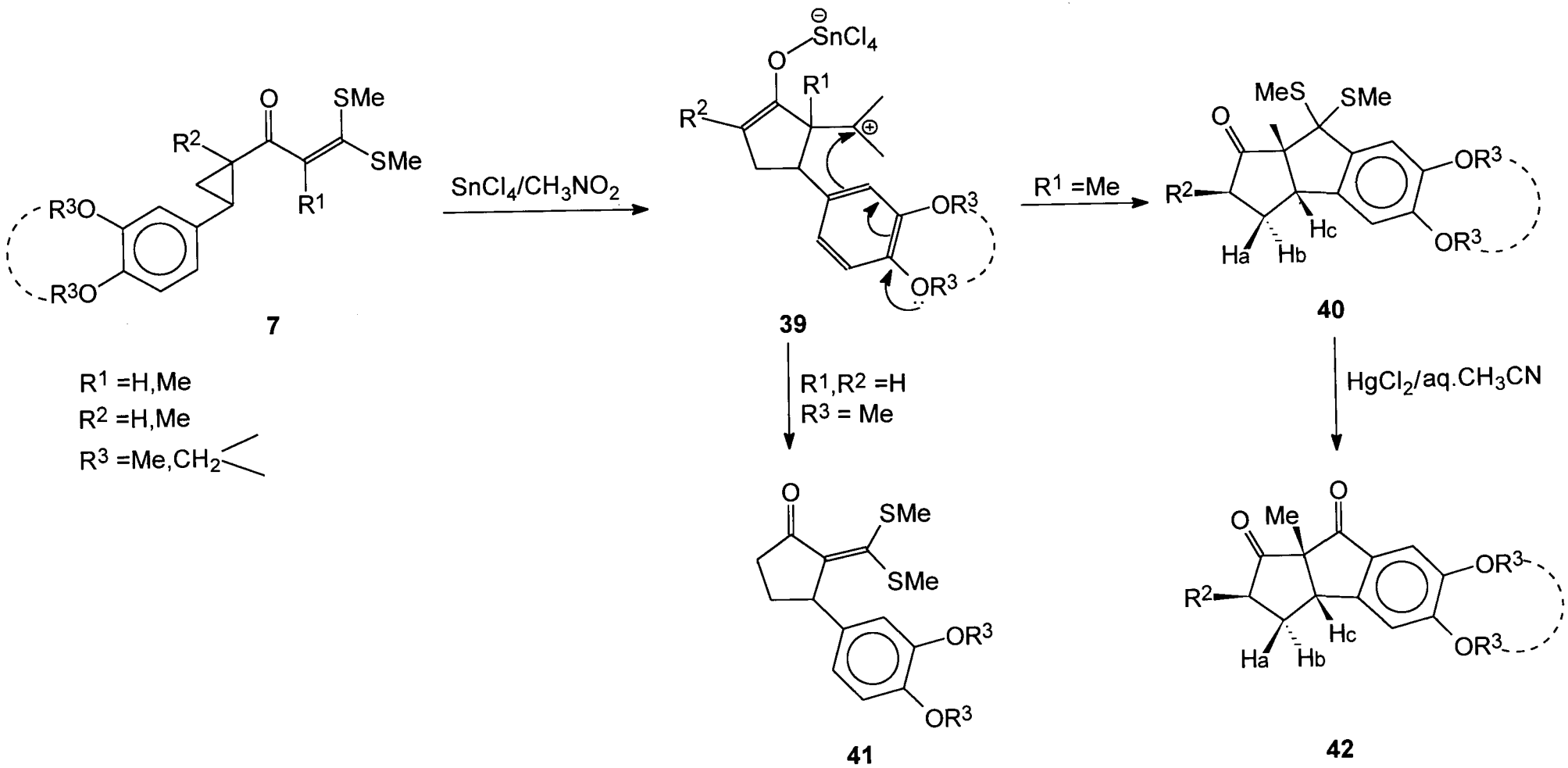


33

38

R^1 = Phenyl,aryl
R^2 = H
R^3 = alkyl

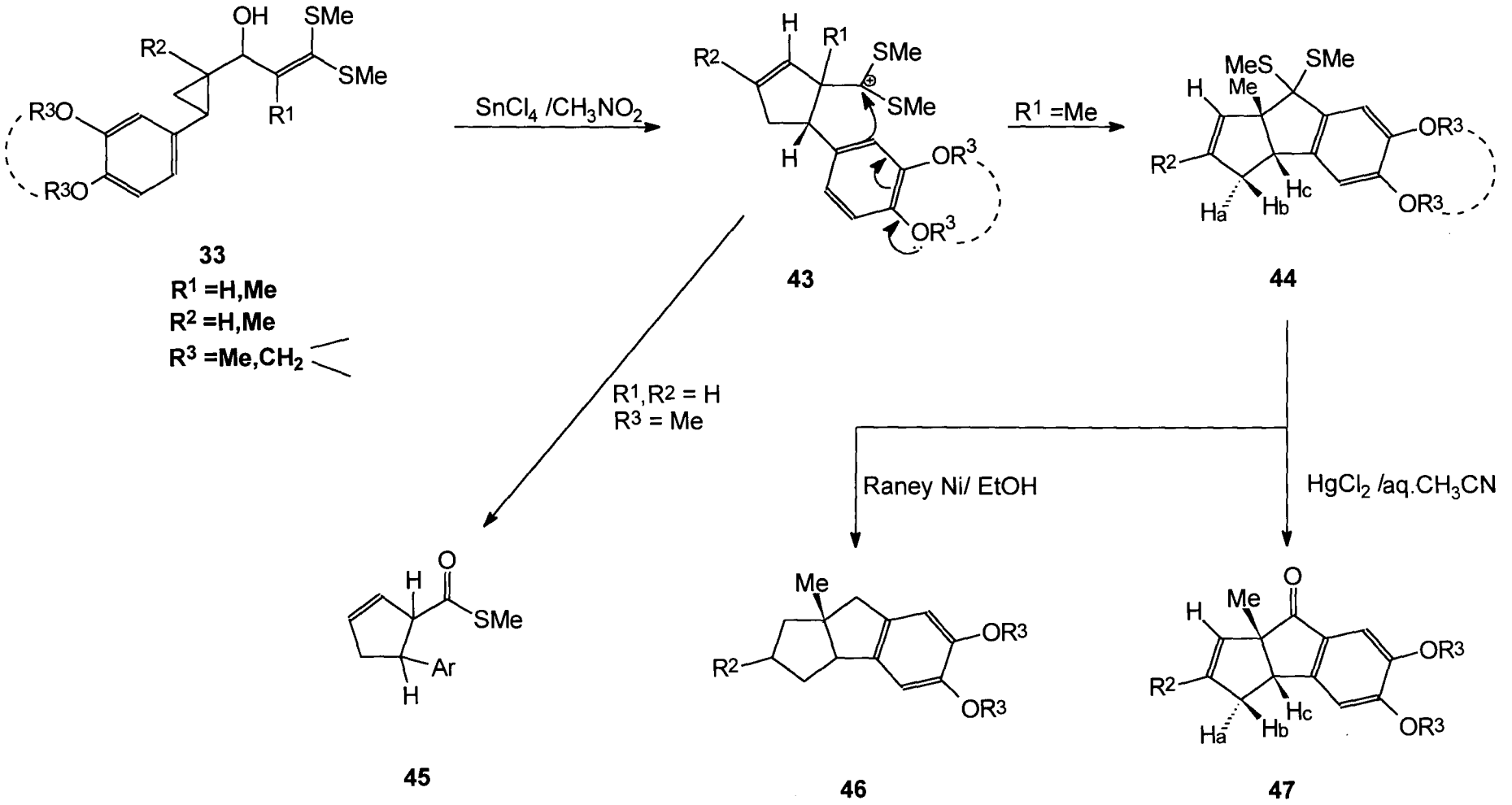
Scheme - 14


SnCl4/CH3NO2
R1 =Me
HgCl2/aq.CH3CN
R1,R2 =H
R3 = Me
7
39
40
41
42
R1 =H,Me
R2 =H,Me
R3 =Me,CH2

Scheme -15

be eliminated. We indeed observed the successful formation of the desired cyclopent[a] indene **40** in good yield, when **7** (R^1=Me) was treated with $SnCl_4$ in CH_3NO_2 . The desired intramolecular electrophilic substitution type reaction was thus accomplished. The thioketal group was hydrolysed with $HgCl_2$ in aqueous CH_3CN to yield the cyclopent[a]indeneone **42**. We could successfully extend this interesting tandem carbocationic rearrangement to the corresponding carbinols obtained by $NaBH_4$ reduction. Thus cyclopent[a]indenes **44** were formed in good yields from the carbinols by the action of $SnCl_4$ in nitromethane (Scheme-16). The ketals were then hydrolysed in the presence of $HgCl_2$ in aqueous CH_3CN medium to afford the corresponding indenones **47**. The ketal **44** was also subjected to Raney Ni desulfurisation to afford the sulphur free indene **46** in high yields. As observed earlier , aryl group participation was not detected when R^1=H . The product obtained was identified as the partially hydrolysed cyclopentanone **45.**

The cyclopropyl group carrying the styryl substituent as in **26** (Scheme-17), carrying a methyl group at α-position were subjected



33

R^1 =H,Me

R^2 =H,Me

R^3 =Me,CH_2

43

44

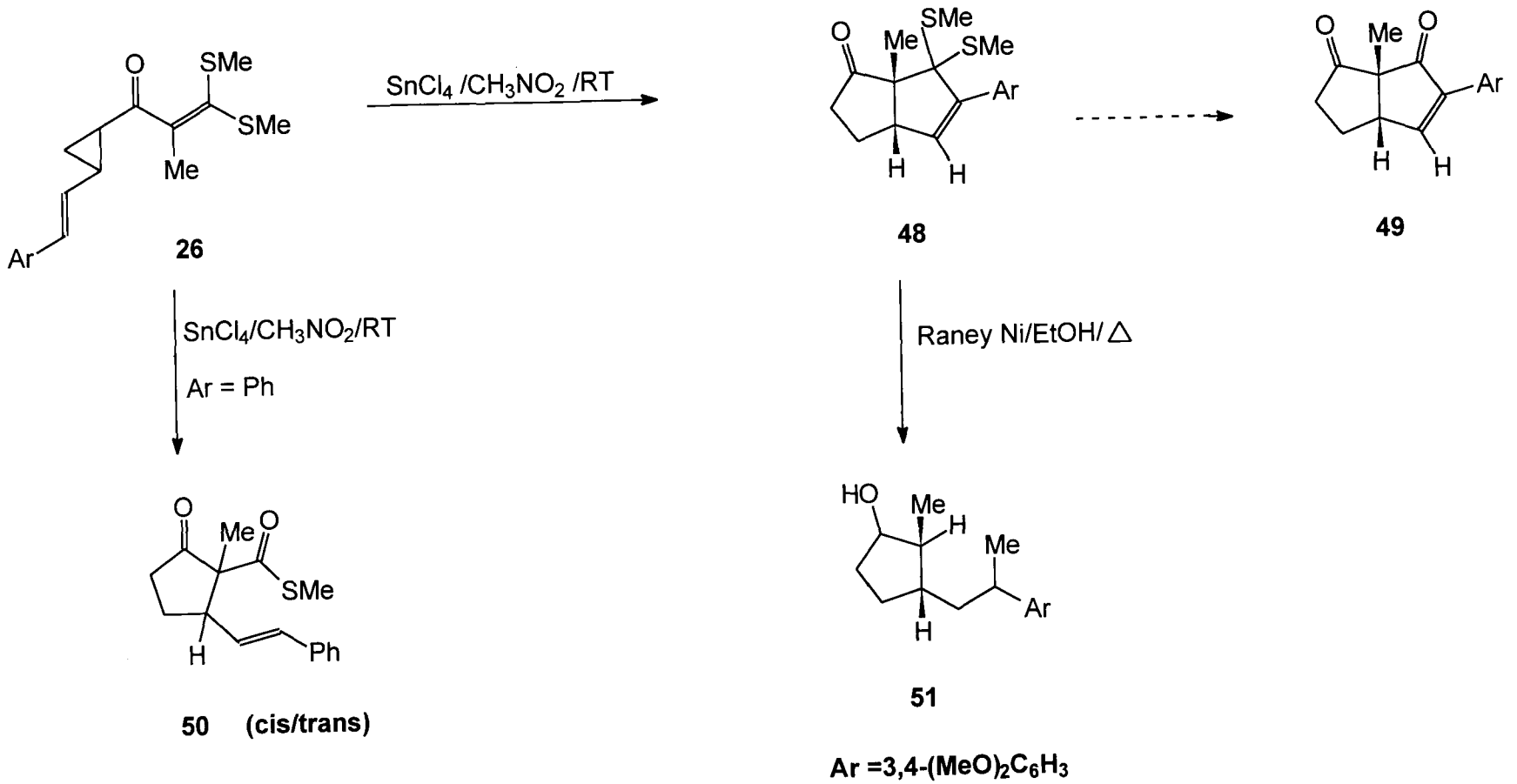
45

Ar = 3,4-$(MeO)_2C_6H_3$

46

47

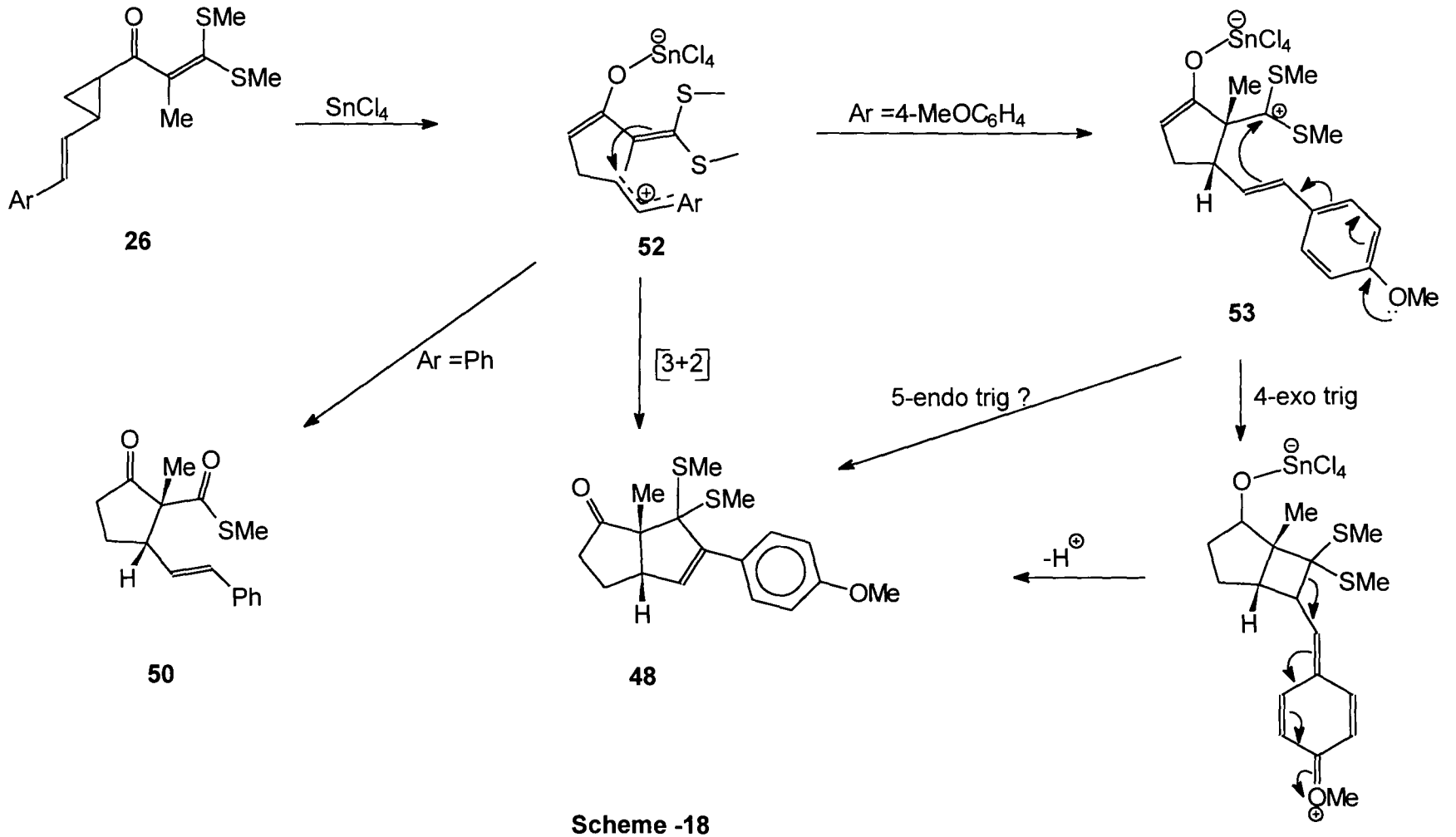
Scheme - 16


O
SMe
SMe
Me
Ar
26
SnCl4 /CH3NO2 /RT
SnCl4/CH3NO2/RT
Ar = Ph
O
Me
O
SMe
H
Ph
50 (cis/trans)
SMe
O
Me
SMe
Ar
H
H
48
Raney Ni/EtOH/△
HO
Me
H
Me
Ar
H
51
O
Me
O
Ar
H
H
49
Ar =3,4-(MeO)2C6H3

Scheme - 17

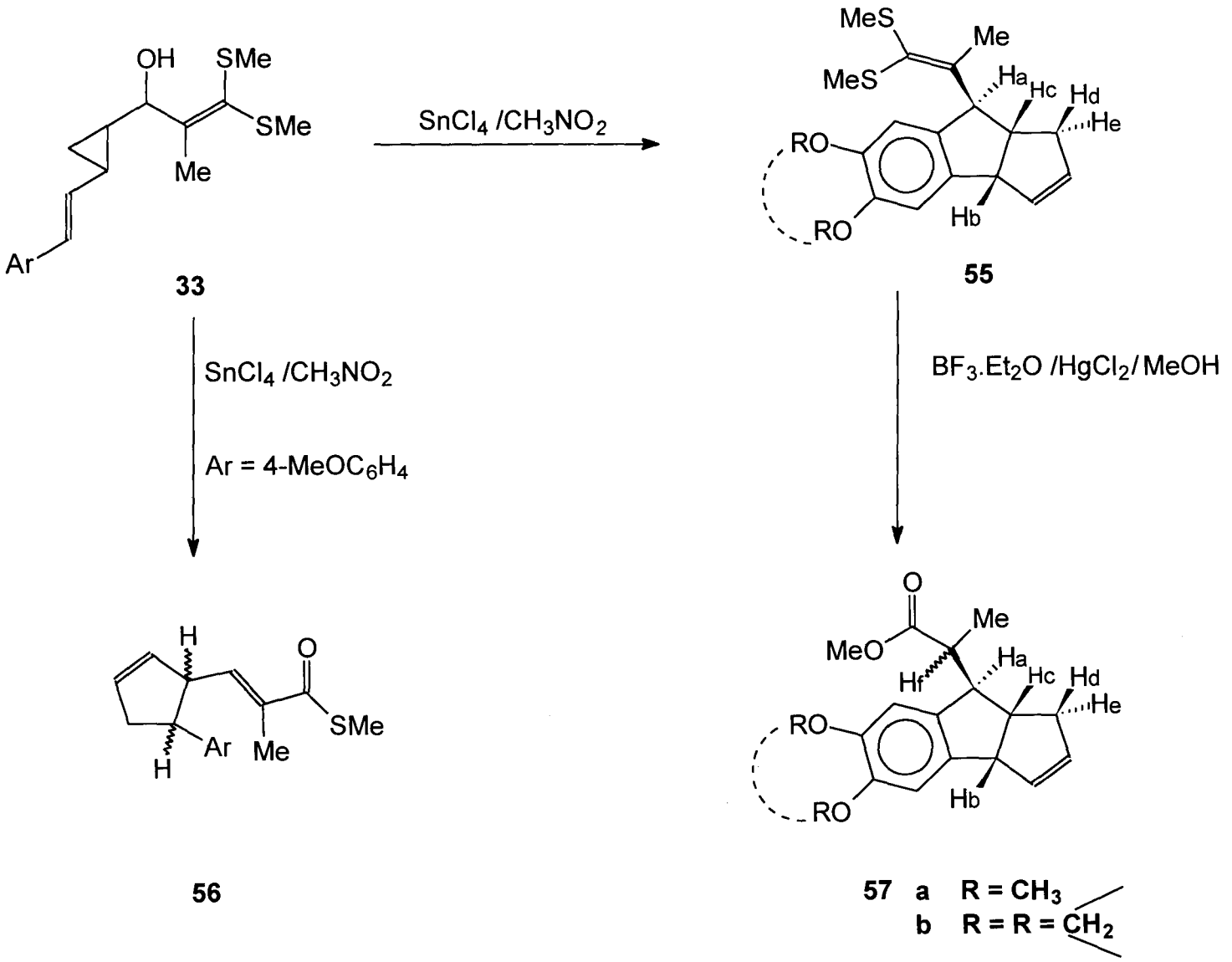
to $SnCl_4/CH_3NO_2$ and it was observed that the product was the corresponding bicycloocteneone **48**[47] indicating that the sulphur stabilised cation is trapped by the styryl double bond . This compound **48** however underwent cleavage to yield the open chain carbinol **51** when desulphurisation was attempted with Raney Ni in refluxing ethanol. The cyclopentanone carbothioate **50** was the sole product when the styryl double bond carried a phenyl group revealing that the carbocation was not attacked by the styryl double bond. It is quite likely that the carbocation **53** (Scheme-18) is trapped by the stryl double bond by an allowed 4-exo trig process to lead to the product **48** . However, an 5 endo trig process also cannot be ruled out, even though it is very unlikely.

When the cyclopropyl carbinols **33** with styryl group were subjected to $SnCl_4$ in CH_3NO_2 they followed two pathways depending upon activation of aryl group.(Scheme-19) When Ar=3,4 MeOPh a stereospecific indene derivative **55** was formed ,which when subjected to $BF_3.Et_2O/HgCl_2$ methanolysis gave the corresponding methyl ester **57**. When Ar has only one methoxy group the carbinol yielded simple



26 **52** **53** **50** **48** **54**

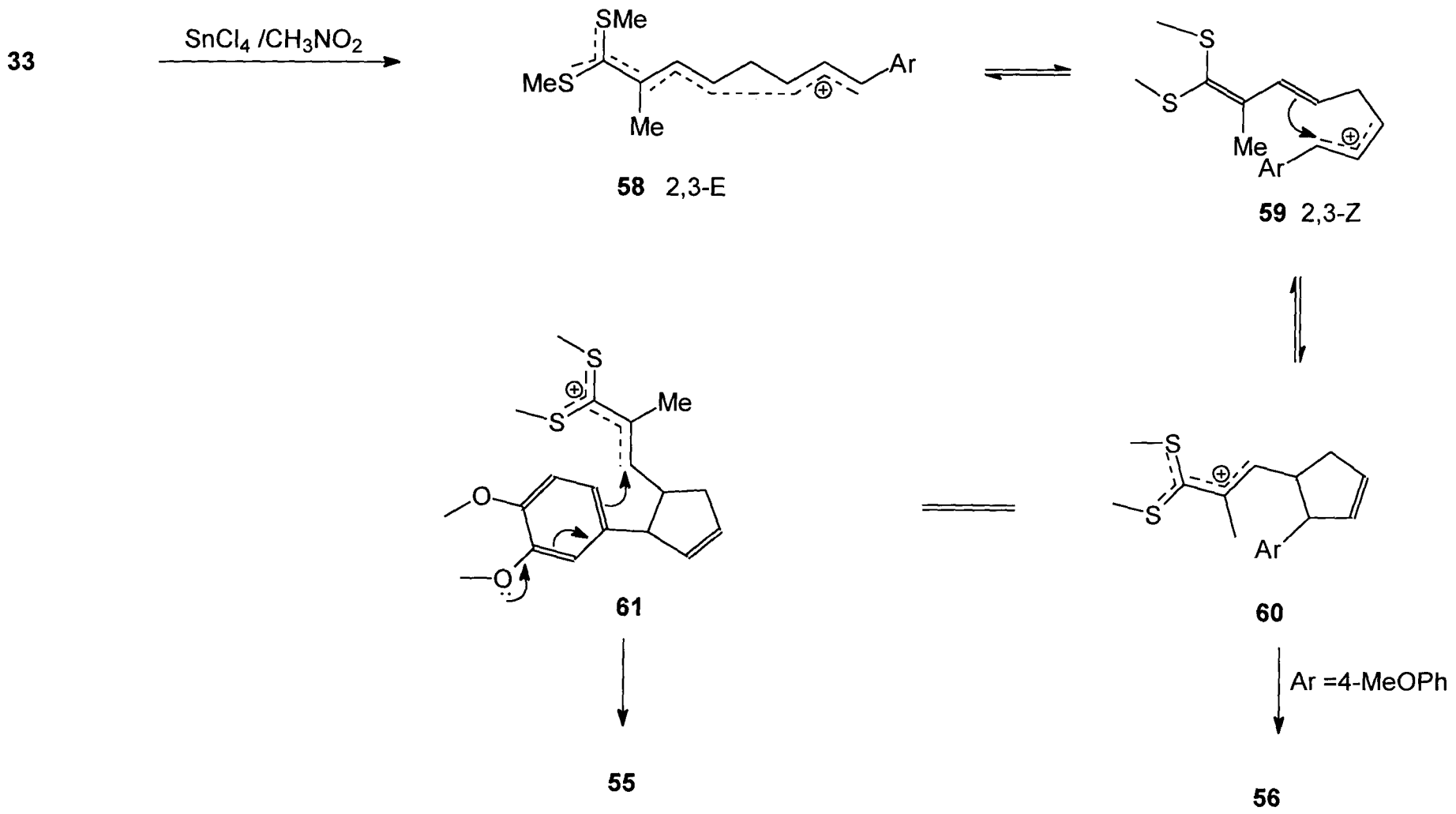
Scheme -18


OH
SMe
SMe
Me
Ar
33
SnCl4 /CH3NO2
MeS
MeS
Me
Ha
Hc
Hd
He
RO
RO
Hb
55
SnCl4 /CH3NO2
Ar = 4-MeOC6H4
BF3.Et2O /HgCl2/ MeOH
H
O
SMe
Ar
Me
H
56
O
Me
MeO
Hf
Ha
Hc
Hd
He
RO
RO
Hb
57 a R = CH3
b R = R = CH2

Scheme - 19

cyclopentanone derivative **56** with partial hydrolysis of the mercapto functionality under the described action conditions. The mechanism governing the formation is depicted in Scheme-20. The carbinol after cyclopropyl ring cleavage in the presence of $SnCl_4$, yields the highly stabilised homotrienylic cation **58** which appears to equilibrate to with the 2,3-Z isomer **59**. This cation **59** possesses the geometry favourable for cyclization by a 5-exotrig mode and probably forms the cyclopentane cation **60** which leads to the formation of the product **55** via cation **61**. The product **54**,arises out of the tandem cyclisation of the carbocation**60**.

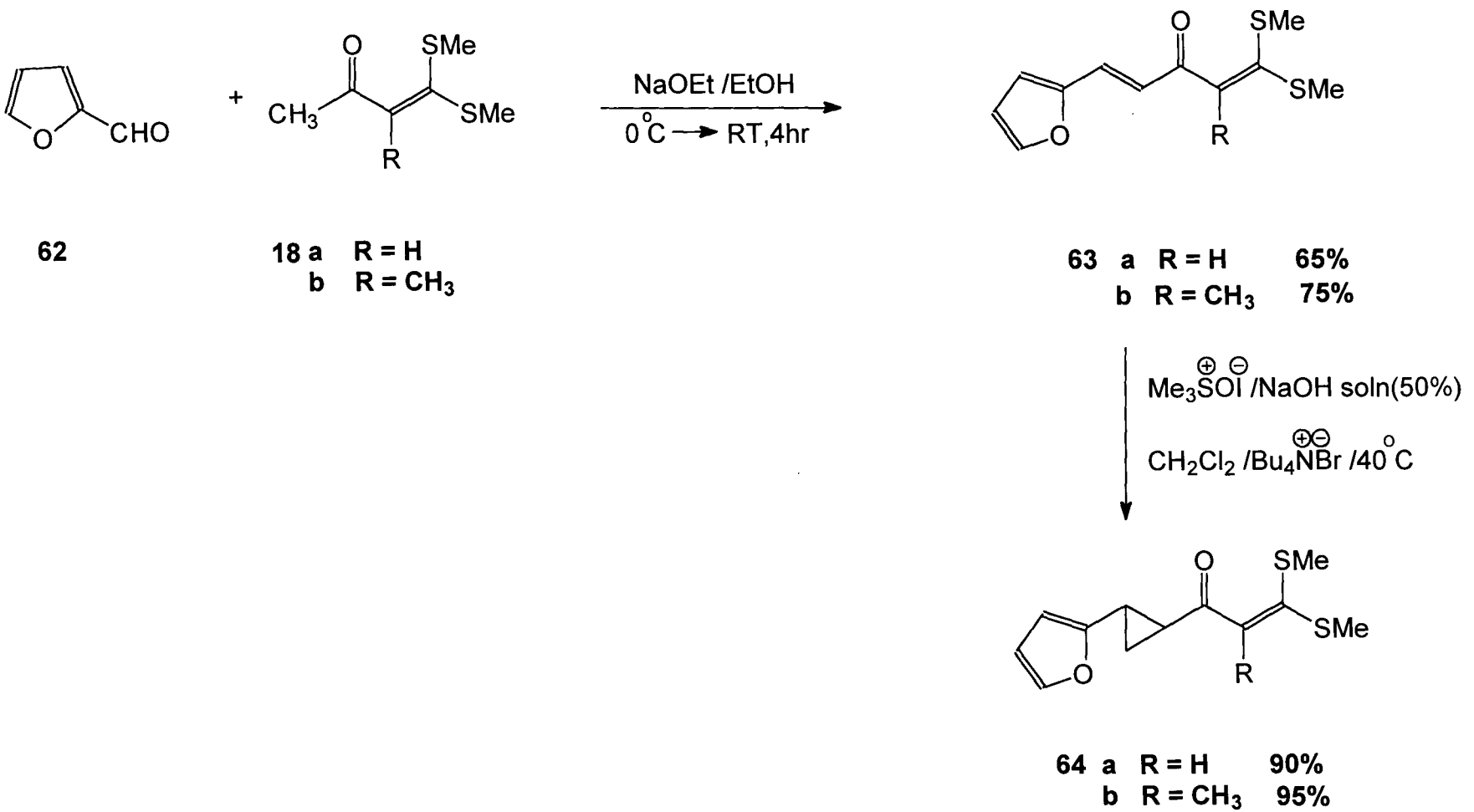
In the above examples we have briefly reviewed our studies on the cyclopropyl substituted α-oxo ketene dithioacetals and observed that the reaction is a two step protocol passing through an intermediate open chain carbocation which when stabilised by suitably activating alkoxy groups and proper reaction conditions yields cyclopentanoids in good yields. The α-methyl substituent plays a crucial part in their formation by eliminating the possibility of proton loss to form ketene dithioacetal and instead leads to partially hydrolysed


33
SnCl4 /CH3NO2
SMe
MeS
Me
Ar
58 2,3-E
S
S
Me
Ar
59 2,3-Z
S
S
Me
O
O
61
S
S
Ar
60
55
Ar =4-MeOPh
56

Scheme -20

methylthiocarbonyl group. The highly oxygenated aryl rings in these systems have given rise to a novel synthesis of cyclopent[a]indenes systems which are otherwise not easily accessible due to lack of appropriate methods. From these studies, it is apparent that in the place of an oxygenated aromatic ring,electron rich 5-membered heterocycles such as furan, thiophene and pyrrole would provide hetero aryl fused diquinane framework which will be of immense biological interest.

A preliminary examination of the Lewis acid catalysed rearrangement of furan substituted cyclopropyl ketones revealed the facile formation of furo bicyclooctane-5-one **66** and furyl substituted cyclopentanone-carbothioate **67**[48]. This success encouraged us to investigate the reaction in detail. The requisite starting materials were prepared according to the sequence depicted in scheme 23. Thus acetone mercaptal **18a** was condensed with furfural **62** in the presence of sodium methoxide to yield the corresponding enone **63a** in 65% yield. This was then cyclopropanated with dimethyl oxosulphonium methylide under P.T.C. conditions, to afford the corresponding furyl substituted cyclopropyl ketone **64a** in 90% yield. Similarly **63b**, the α- methyl substituted cyclopropyl ketone, was obtained in 95% yield (Scheme-



62

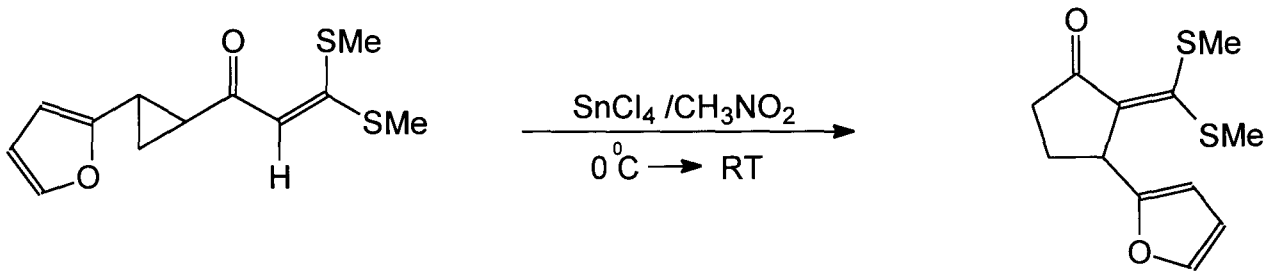
18 a R = H
b R = CH_3

63 a R = H 65%
b R = CH_3 75%

64 a R = H 90%
b R = CH_3 95%

Scheme - 21

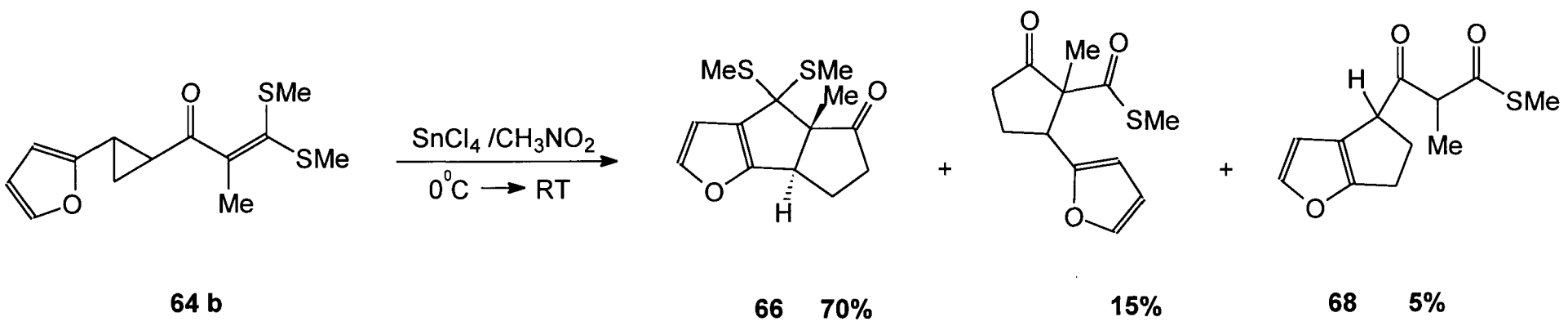
21)by following a parallel approach using the α oxoketene dithioacetal derived from ethyl methyl ketone. Their spectral and analytical data are in conformity with their assigned structure. When **64a**(where R=H) was exposed to $SnCl_4$ in nitromethane the reaction mixture on work-up after 8 hr, yielded the expected 3-furyl α-oxocyclopentane oxoketene dithioacetal **65** in 70% yield (Scheme-22).The cyclopropylketene **64b**, where R=Me, on treatment with $SnCl_4$ in nitromethane yielded a mixture of three products, namely the bismethyl thio substituted furo[b] bicyclopentane **66** (70%), furyl substituted cyclopentanone carbothioate **67** (15%) and the furocyclopentane substituted carbothioate **68** (5%). Their structures were assigned on the basis of their analytical and spectral data. The mechanism of the formation of these products is depicted in Scheme-24. The carbocation **69** formed after the ring opening of **64**, can in principle, lead to two different cyclisations. When it is trapped by the mercapto double bond, it leads to the cation **72,** which (when R=H) undergoes proton loss to yield **65**. Alternatively it can also form cation **73**, (when R=Me) depending on whether it undergoes hydrolysis or tandem cyclisation leads to **67** and **66** respectively. The cation **69** can also be trapped by the enolate double



64 a

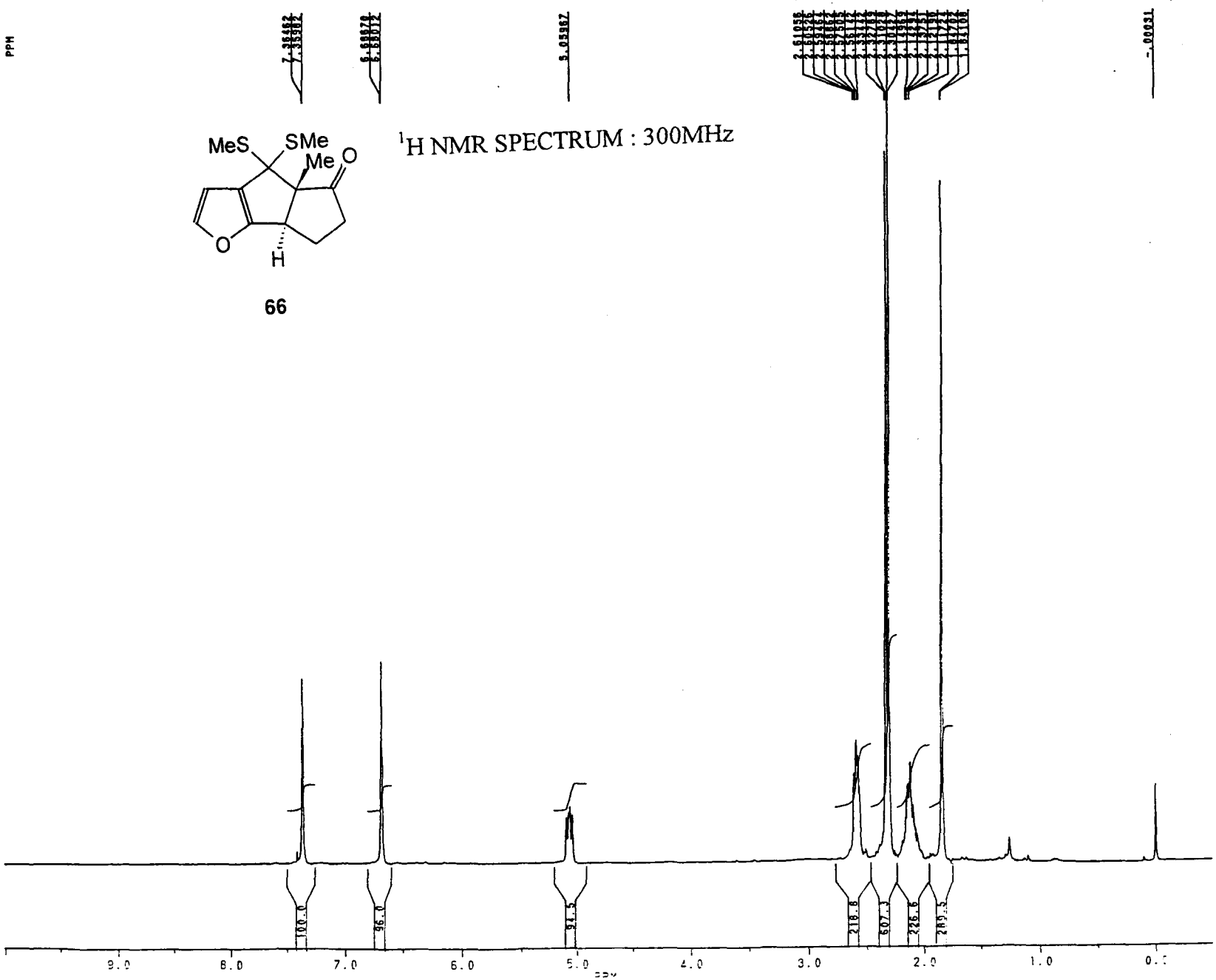
65 75%

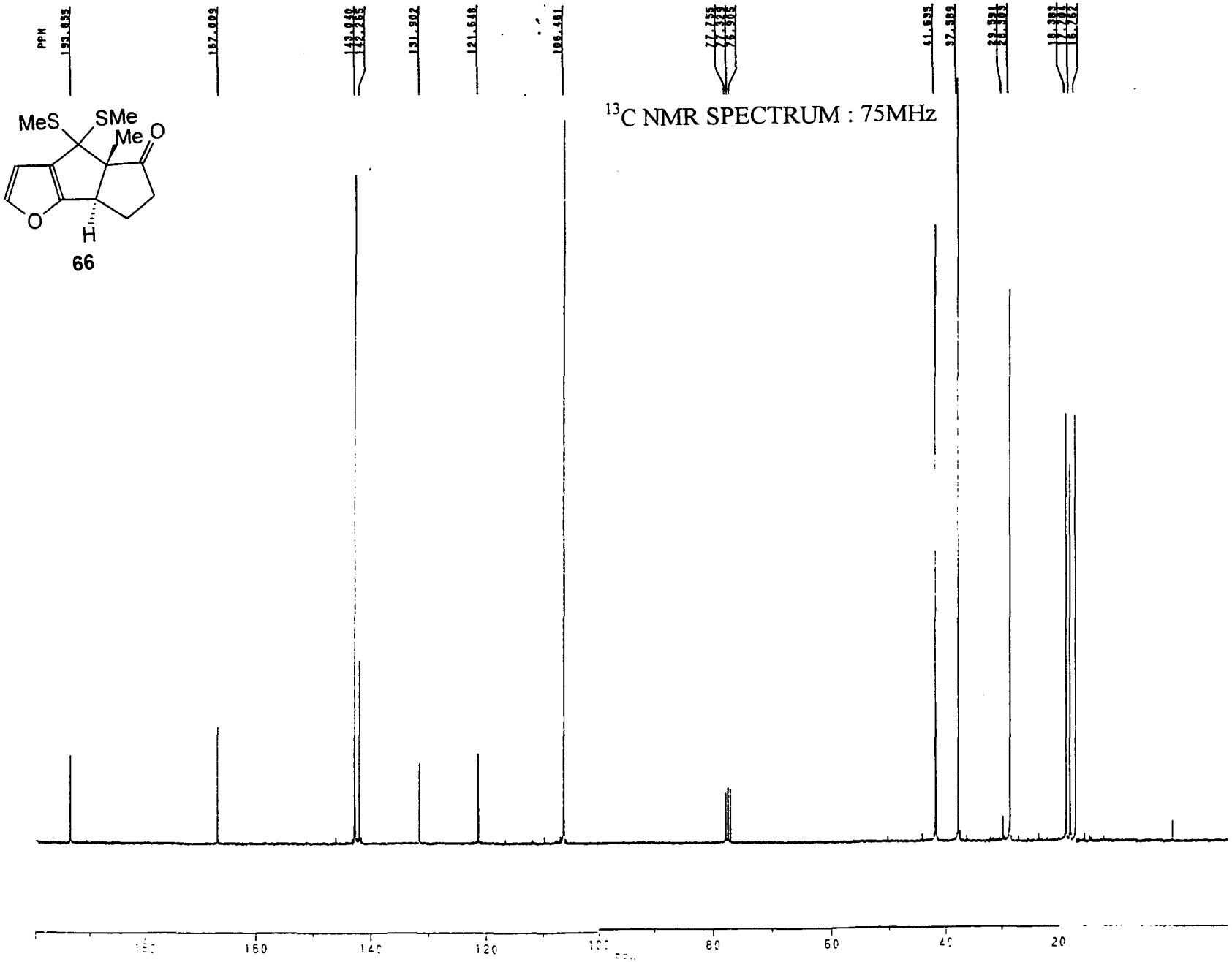
Scheme - 22

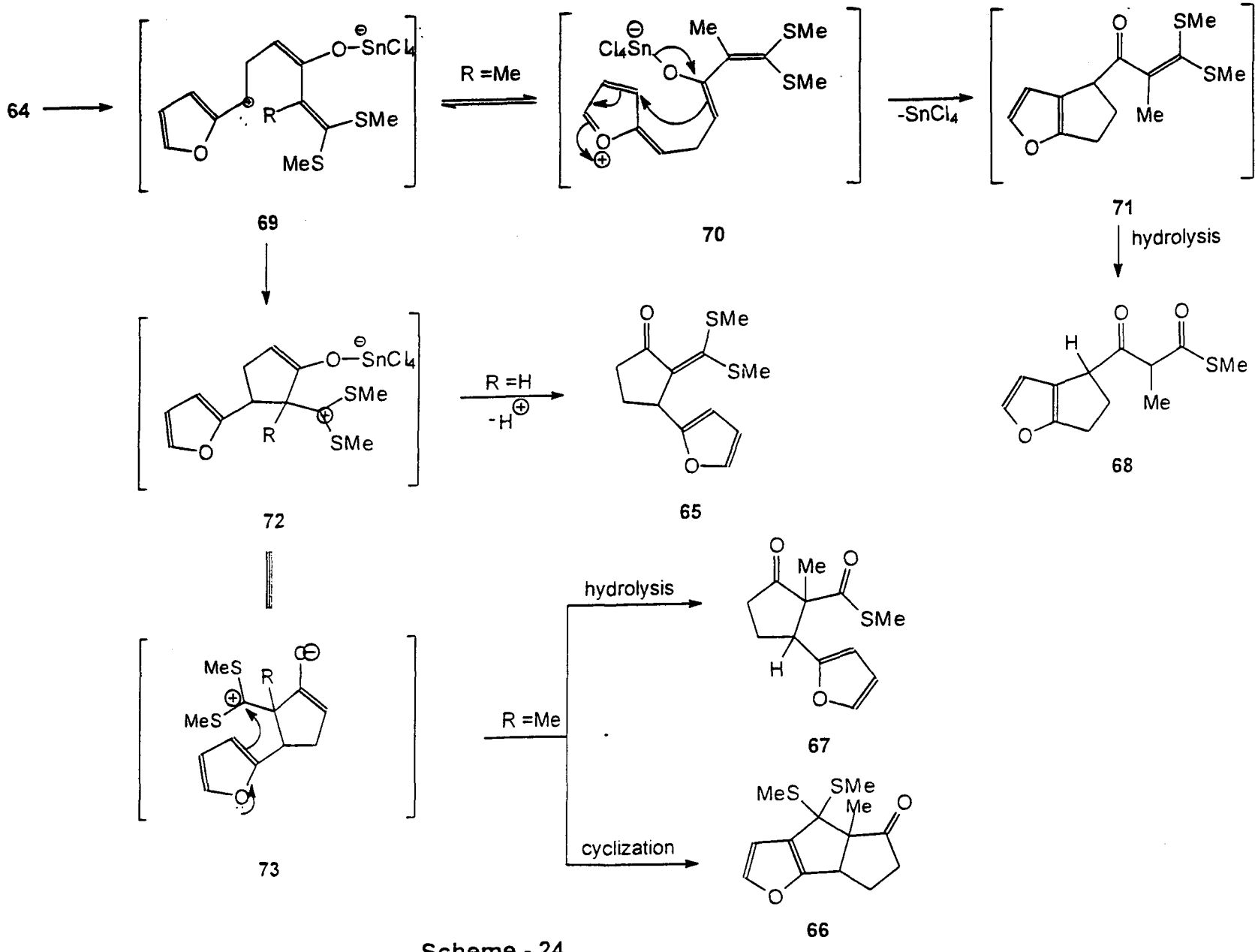


64 b **66 70%** **15%** **68 5%**

Scheme - 23


PPM
MeS
SMe
Me
O
O
H
66
^{1}H NMR SPECTRUM : 300MHz
100.0
96.0
91.5
218.8
607.3
226.6
289.5
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


MeS
SMe
Me
O
O
H
66
^{13}C NMR SPECTRUM : 75MHz
160
140
120
80
60
40
20

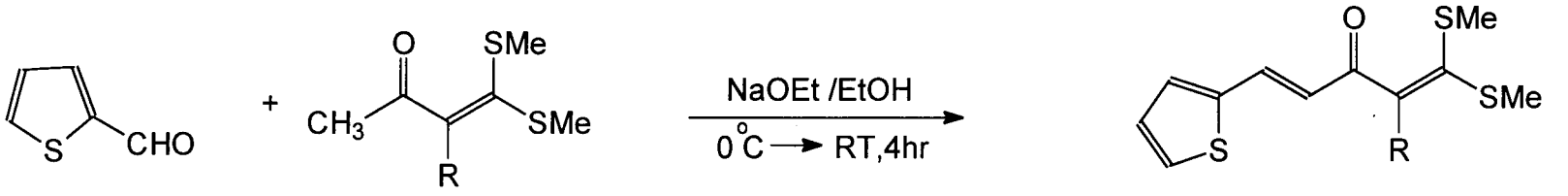

64
R =Me
-SnCl4
hydrolysis
69
70
71
68
72
65
R =H
-H
73
R =Me
hydrolysis
cyclization
67
66

Scheme - 24

bond to form the α-oxoketene dithioacetal **71** ,which is isolated as the carbothioate **68** as a result of hydrolysis.

The corresponding thiophene cyclopropyl ketone mecarptals **76a** and **76b** (Scheme-27) were prepared and examined further. Thus acetone mercaptal **18a** was condensed with thiophene-2-aldehyde **74** in the presence of NaOEt-EtOH to afford the corresponding enone **75a** in 67%, yield the structure of which was confirmed by its analytical and spectral data. Similarly, the α-oxoketene dithioacetal derived from ethyl methyl ketone was condensed with thienyl-2-aldehyde **74** in the presence of NaOEt/EtOH at 0°C yielding the corresponding enone **75b** in 73% yield whose structure was again established on the basis of analytical and spectral data. Both the enones **75a, 75b** were cyclopropanated by dimethyl oxosulphonium methylide to yield the corresponding cyclopropyl ketones in **76a,b** in 92% and 96% yields respectively (Scheme-25).

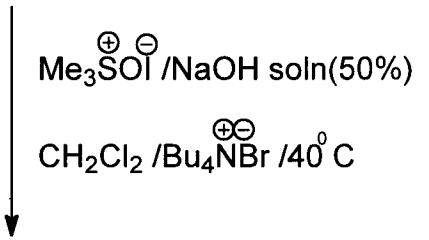
In a typical experiment the cyclopropyl ketone **76a** was treated with $SnCl_4$ in CH_3NO_2 as solvent and the reaction after workup

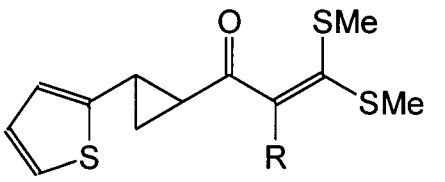


74

18 a R = H
b R = CH_3

75 a R =H 67%
b R =CH_3 73%



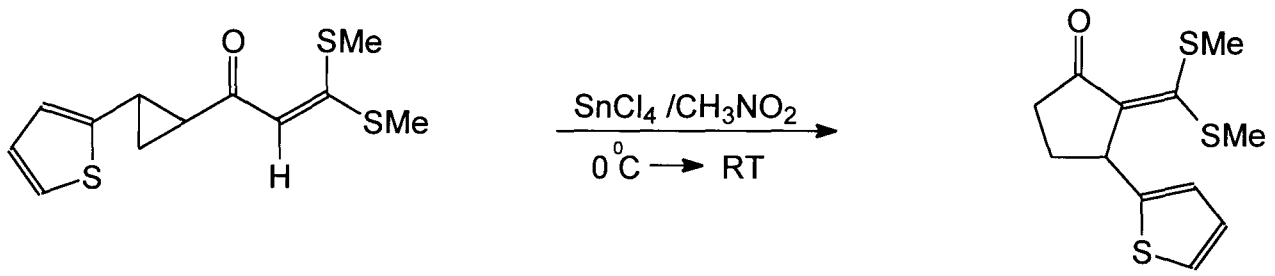


76 a R = H 92%
b R = CH_3 96%

Scheme - 25

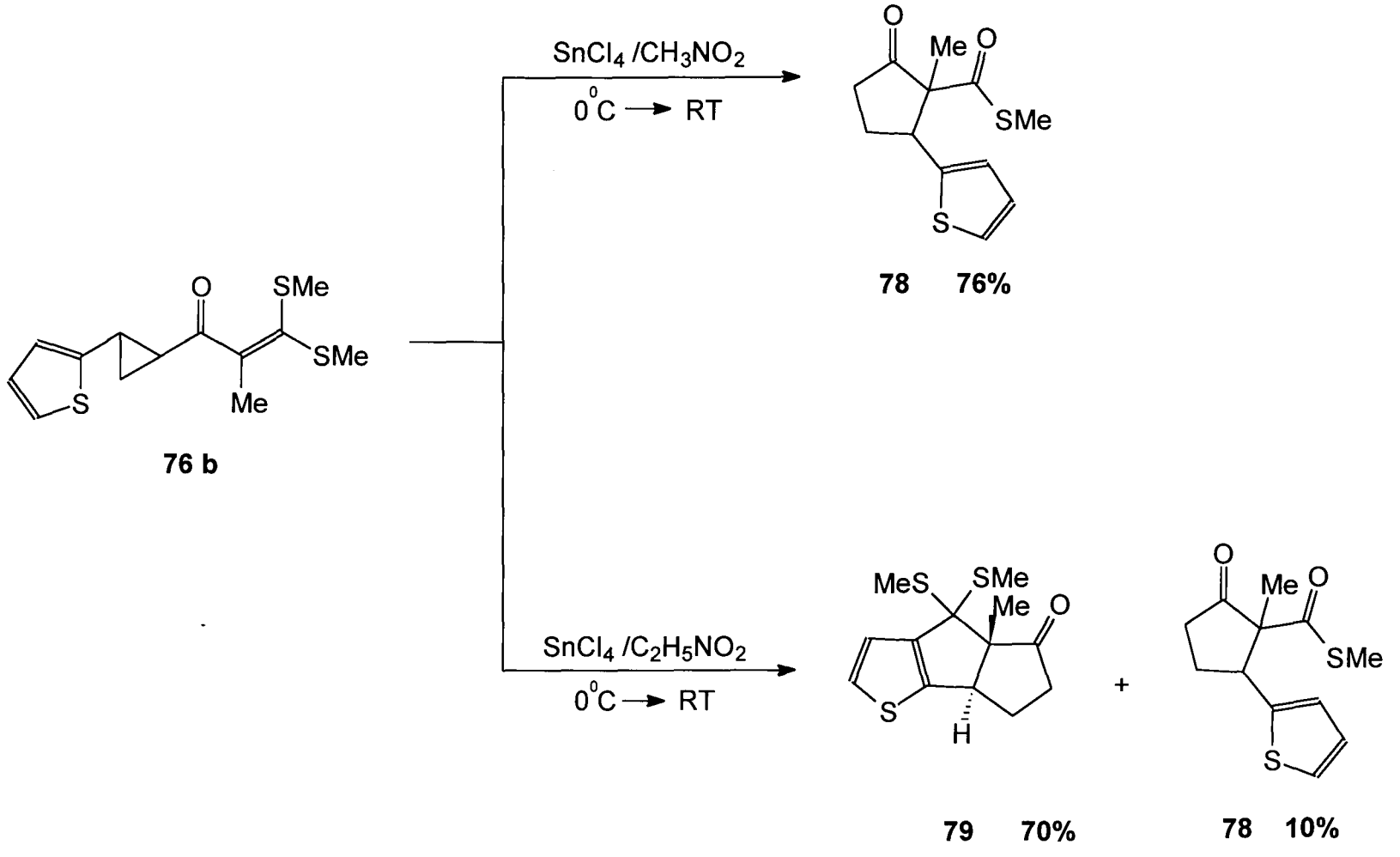
yielded the ketene dithioacetal **77** in 68% yield.(Scheme-26) The formation of this compound is greatly facilitated, as we have observed earlier, if the α-substituent is H.

However when **77b** as subjected to SnCl4 in nitromethane, the sole product obtained after work up was the thiophene substituted cyclopentanone carbothioate **78** in 76% yield.(Scheme-27).No trace of the tandem cyclised product was found. When the reaction was repeated using nitroethane as solvent, the desired tandem reaction product was obtained .Thus work up of the reaction mixture after 12 hrs yielded two products, namely the thieno[b] bicyclooctane **79** (72%) and the carbothiote **78** (10%).Their structures were confirmed on the basis of their analytical and spectral data. NOE irradiation experiments conducted on **79** indicated the relative geometry of the α- methyl group and the bridge head proton to be trans.However there was no trace of cyclopenta[b]thiophene derivative as observed in the case of furan. We propose a mechanism, parallel to the one proposed for the rearrangement of furyl substituted cyclopropyl ketones.(Scheme-28)

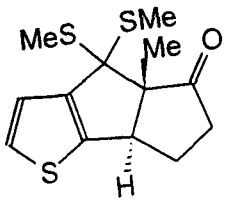


77 68%

Scheme - 26

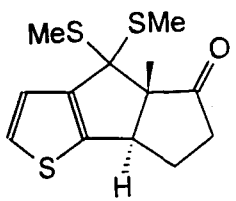


Scheme-27



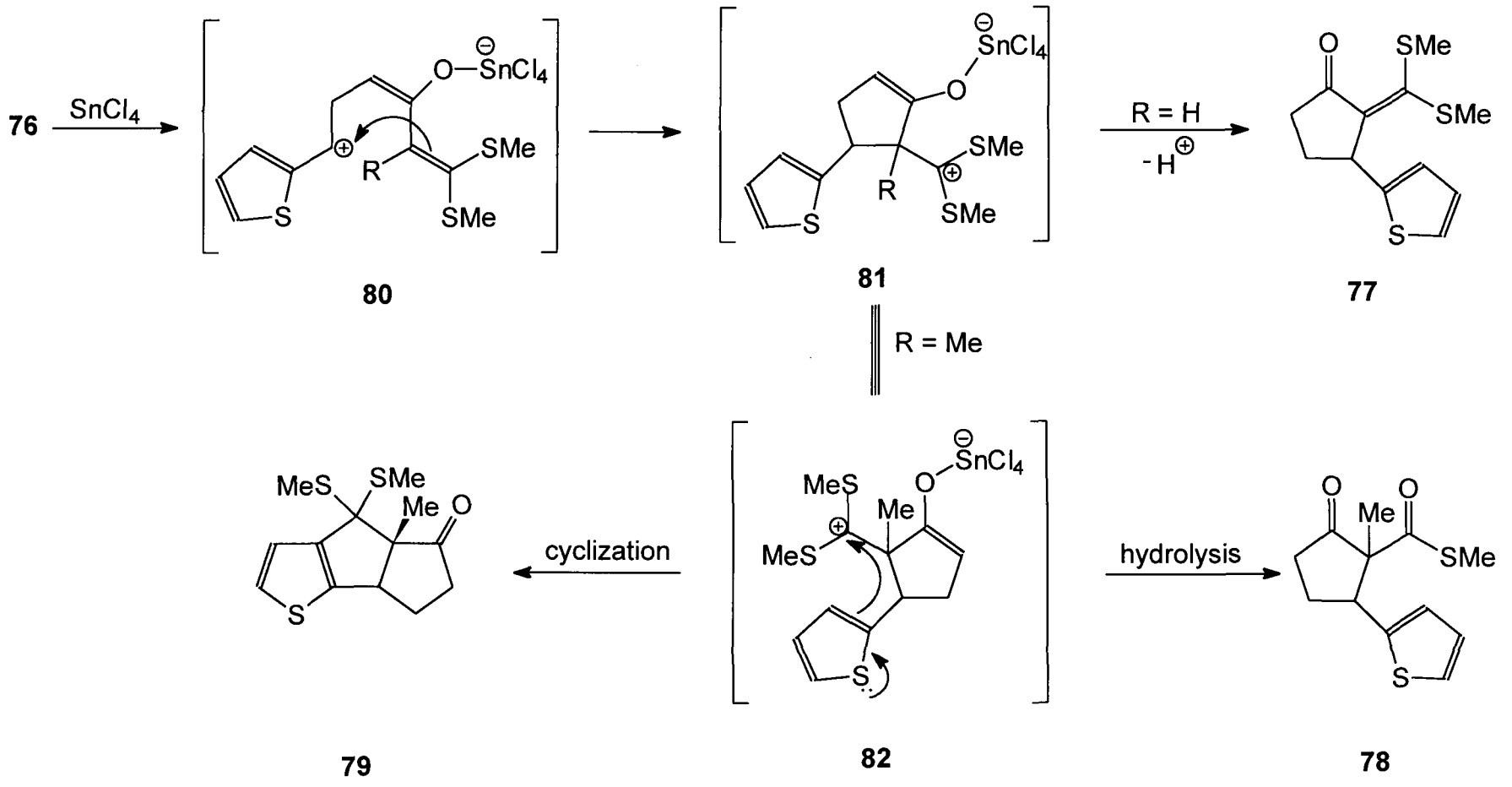
79

^{1}H NMR SPECTRUM : 300MHz



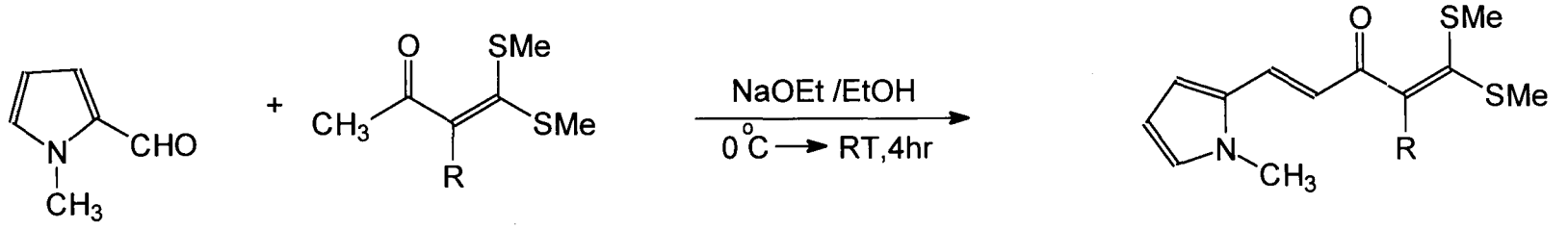
79

^{13}C NMR SPECTRUM : 75MHz


76
SnCl4
O—SnCl4
R
SMe
SMe
S
80
SnCl4
O
SMe
R
SMe
S
81
R = H
-H⊕
O
SMe
SMe
S
77
R = Me
MeS
SMe
Me
O
S
79
cyclization
MeS
SnCl4
O
Me
MeS
S
82
hydrolysis
O
O
Me
SMe
S
78

Scheme - 28

In continuation N-methyl pyrrole-2-aldehyde **83** was selected as next example for this investigation. Thus acetone mercaptal **18a** was smoothly condensed with **83** in the presence of NaOEt in ethanol to afford the corresponding enone **84a** in 67% yield. Similarly **84b** was obtained in an improved 81% yield from condensation of **18b** with **83** under the described reaction conditions (Scheme-29). In the next experiment when **84a** was subjected to cyclopropanation reaction under the similar conditions described earlier. The expected cyclopropane **85a** was not obtained and instead the product isolated was characterised as the cyclopentanone ketene dithioacetal **86** in 67% yield.(Scheme-30) Interestingly when the reaction pathway was followed by TLC (silca gel) roughly the cyclopropane intermediate was visible which however merged with that of **86** during work up. It was therefore not possible to isolate cyclopropyl ketone **85a** when pyrrole ring was attached to it. The presence of pyrrole ring seems to have attributed for the ring cleavage and cyclisation which is unprecedented in all the studies carried out in our laboratory. The structure of **86** was established by its analytical and spectral data.

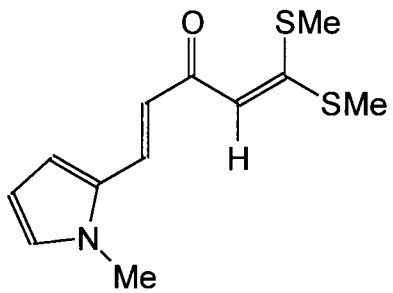


83

18 a R = H
b R = CH_3

84 a R = H 67%
b R = CH_3 81%

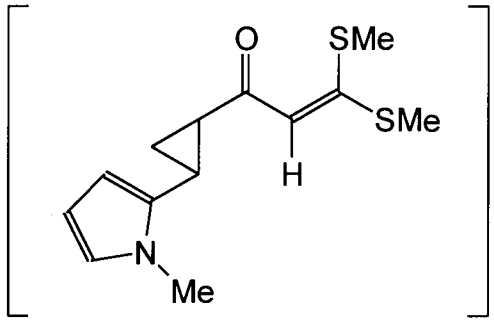
Scheme - 29



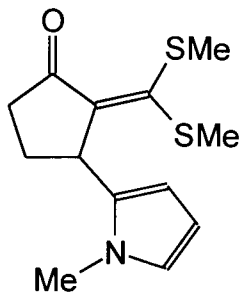
84 a

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ / NaOH soln (50%)

CH_2Cl_2 / $Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$ /40° C

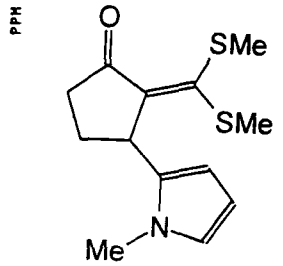


85 a



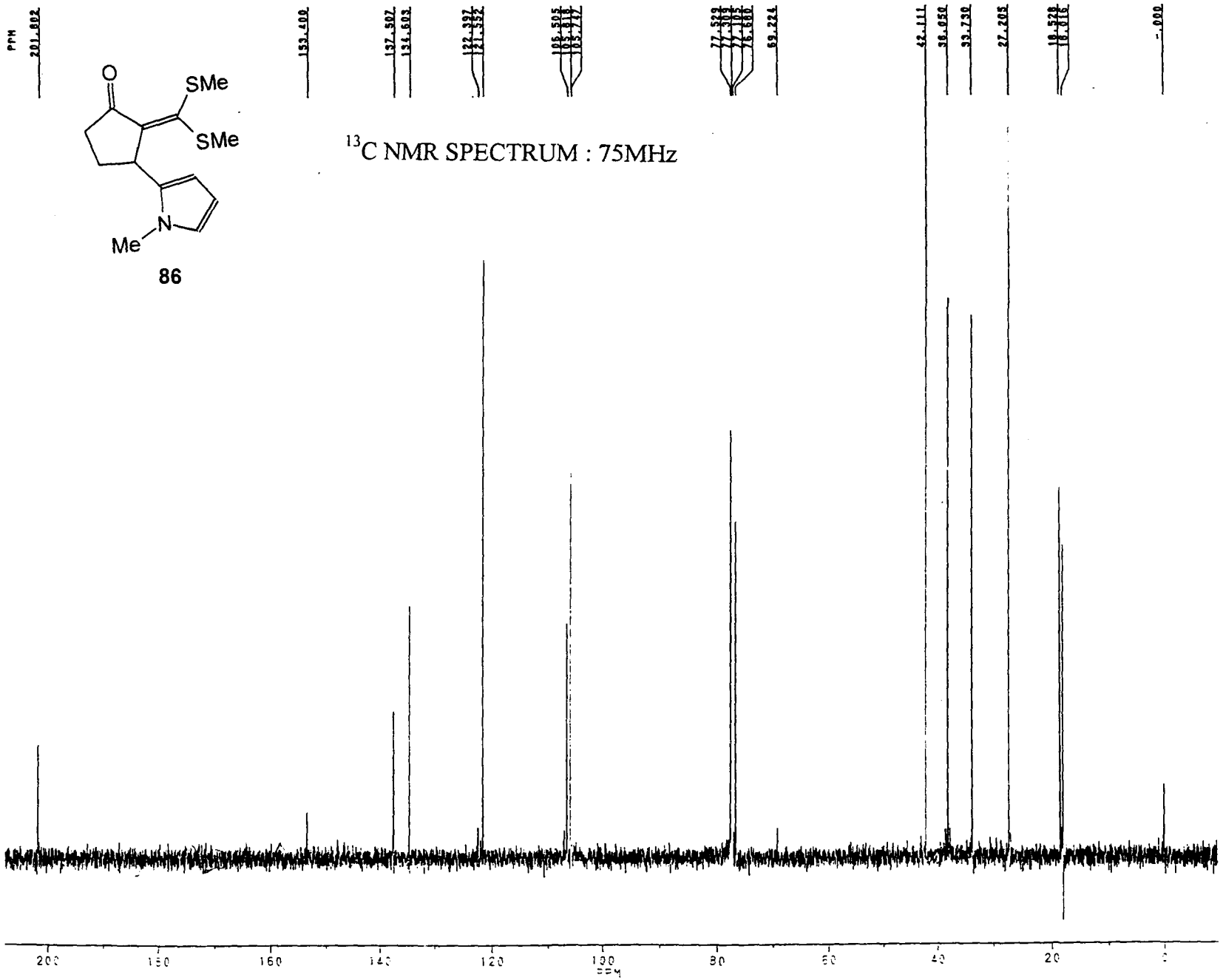
86 69%

Scheme - 30



86

^{1}H NMR SPECTRUM : 300MHz

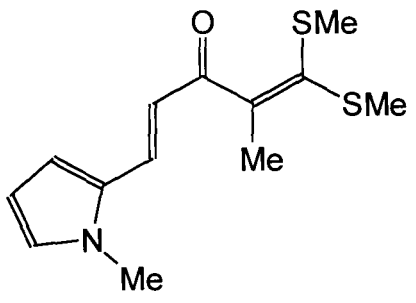


^{13}C NMR SPECTRUM : 75MHz

86

The reaction followed similar course when **84b** was (Scheme-31) attempted for cyclopropanation as described earlier. The reaction mixture after work up yielded partially hydrolysed cyclopentanone **87** in 73% yield without using any Lewis acid catalyst. The intermediacy of the cyclopropane was observed on TLC which during work up rearranged to **87**. The structure of **87** was deduced from its analytical and spectral data. The mechanism of formation the pyrrole substituted cyclopentanone is depicted in Scheme-32. The cyclopropyl ketones formed *in situ*, apparently undergoes a lone-pair assisted ring opening followed by cyclisation and hydrolysis to yield the cyclopentanones **86** and **87**.

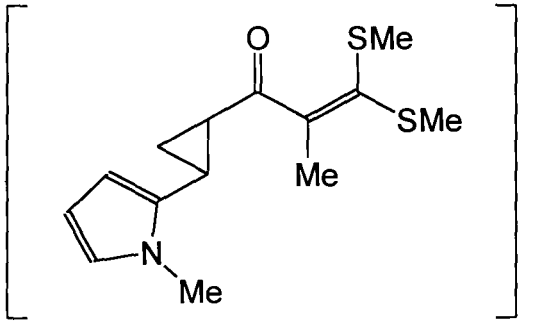
In the place of 5-membered heterocycles it was contemplated to examine the effect of indole ring. Thus indole-3-aldehyde **90** was condensed with acetone mercaptal **18a** in the presence of sodium ethoxide in ethanol to afford the corresponding enone **91a** in 61% yield.(Scheme-33) Similarly **91b** was obtained by condensing **90** with 18b under the described action conditions in 87% yield (Scheme-33). The structure of **91a** and **91b** were established by their analytical and spectral data. **91a** was subjected to cyclopropanation as described



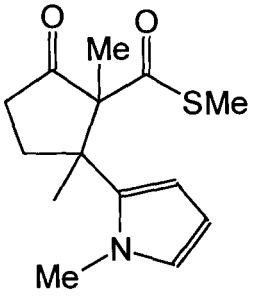
84 b

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ / NaOH soln (50%)

CH_2Cl_2/ $Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$ / 40 °C

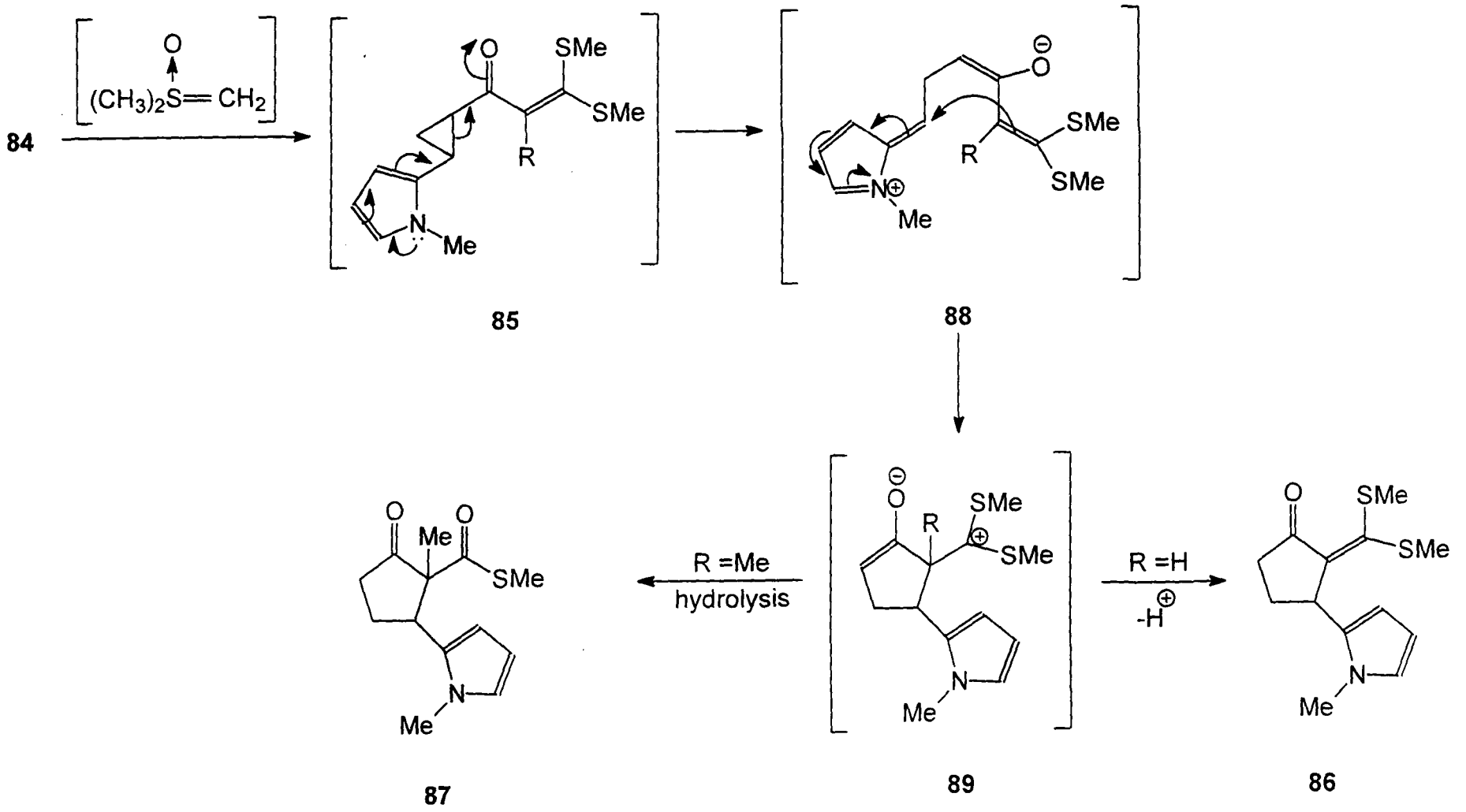


85 b

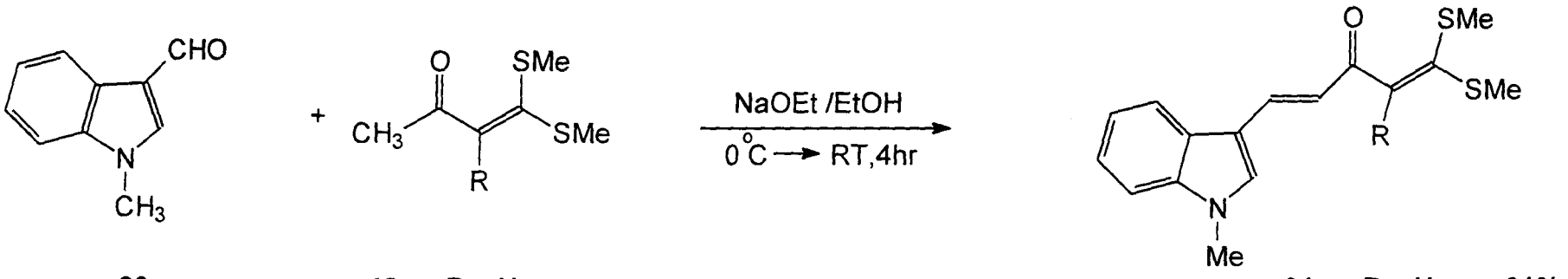


87 73%

Scheme - 31


84
(CH3)2S=CH2
O
SMe
SMe
R
N
Me
85
88
SMe
SMe
R
N
Me
R =Me
hydrolysis
R =H
-H
O
Me
SMe
N
Me
87
89
86

Scheme - 32



90

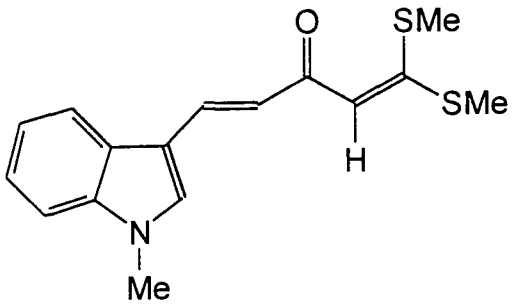
18 a R = H
b R = CH_3

91 a R = H **61%**
b R = CH_3 **81%**

Scheme - 33

earlier.(Scheme-34) The reaction after work up, however yielded directly the rearranged cyclopentanone mercaptal **93** in 63% yield. The structure was fully established from its spectral and analytical data. It was interesting to know that cyclopropane intermediate **92a** underwent so facile a transformation involving *in situ* cyclization to yield the cyclopentanone derivative **93**. The enone **91b** on subjected to cyclopropanation condition indeed followed the expected pathway for the compound **94** in 76% overall yield (Scheme-35). The structure of **94** was fully established by its analytical and data. The mechanism as depicted in Scheme 36 suggests a lone assisted ring opening followed by ring closure to yield the product cyclopentanones **93** and **94**.

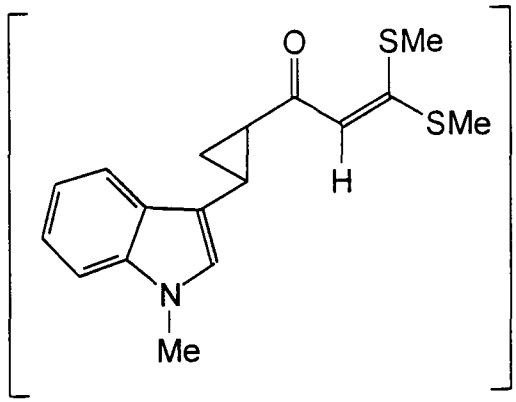
In conclusion we have examined the effect of 5-membered heterocycles like thiophene, pyrrole, and condensed pyrroles such as indoles in a bismethyl thio cyclopropyl ketone rearrangement study. The study indicated that the rearrangement followed the expected protocol in both the cases of furan and thiophene. In pyrrole the cyclopropanation process directly underwent *in situ* rearrangement under the reaction condition to yield the corresponding cyclopentanone



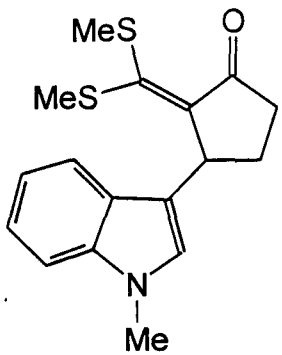
91 a

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ /NaOH soln (50%)

CH_2Cl_2 /$Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$/40° C

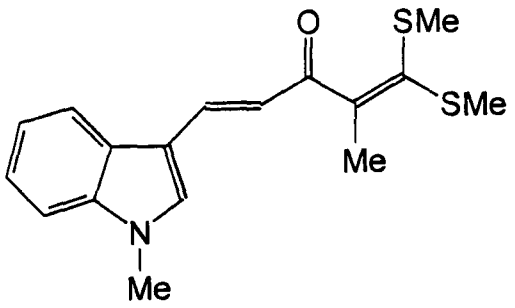


92 a



93 63%

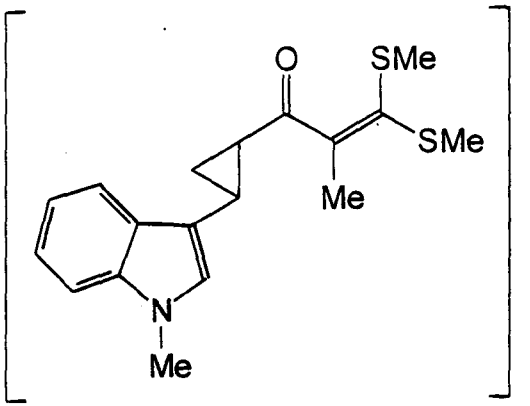
Scheme - 34



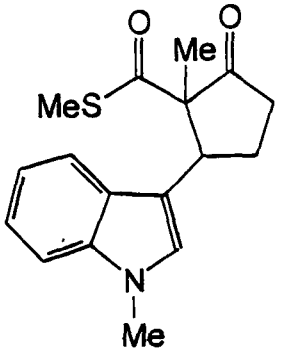
91 b

$Me_3\overset{\oplus}{S}O\overset{\ominus}{I}$ /NaOH soln (50%)

CH_2Cl_2 /$Bu_4\overset{\oplus}{N}\overset{\ominus}{Br}$/40° C

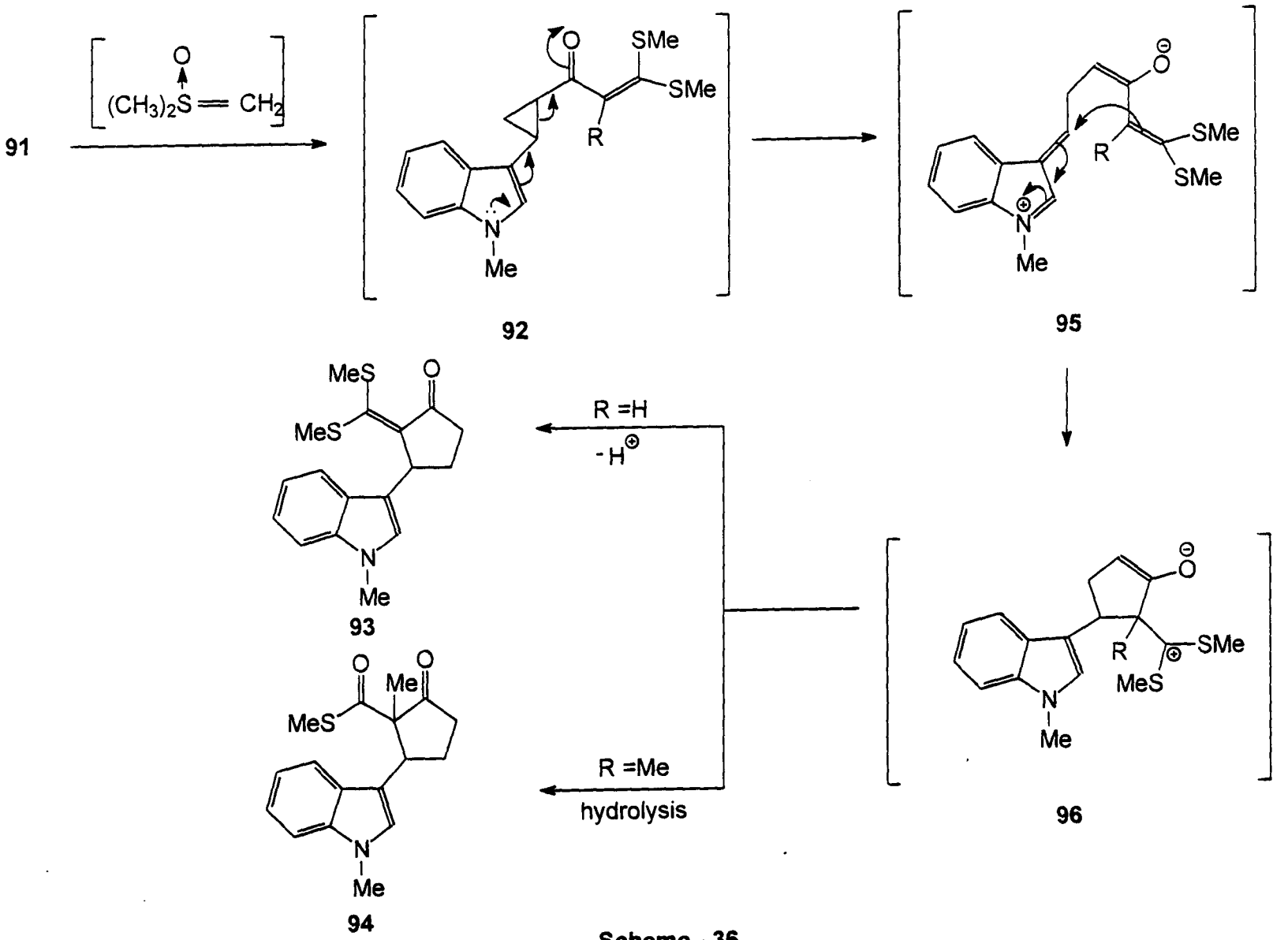


92 b



94 76%

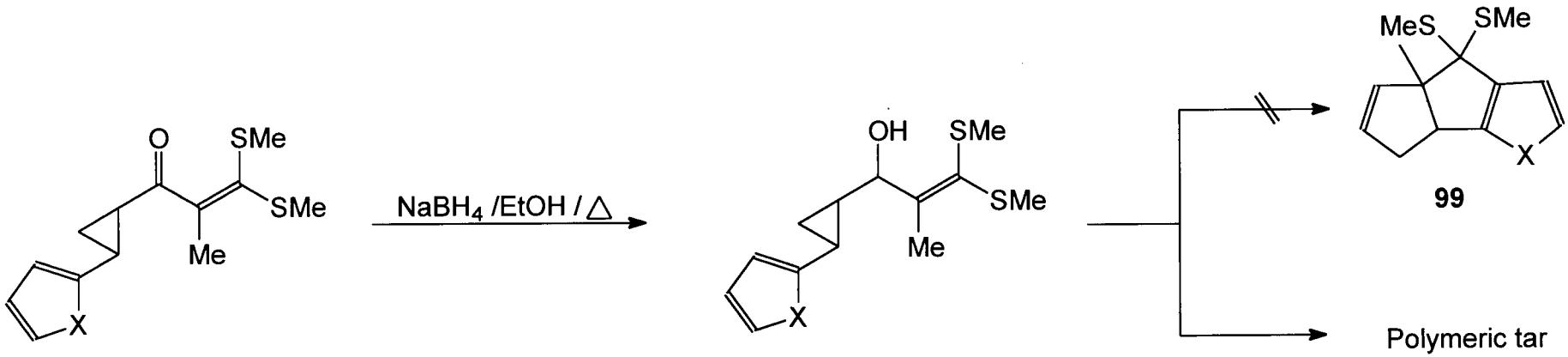
Scheme - 35


91
(CH3)2S = CH2
O
SMe
SMe
R
N
Me
92
95
R
SMe
SMe
MeS
O
MeS
R =H
- H⊕
93
Me
O
MeS
N
Me
94
R =Me
hydrolysis
96
R
SMe
MeS

Scheme - 36

and so there was no scope to study the effect of Lewis acids on the cyclopropyl ketones. However, since the pyrrolo bicyclooctanes could not be isolated even in traces it appears that a Lewis acid is necessary for the tandem ring closure. Similarly, indole directly yielded indole cyclopentanones.

Apart from these studies, the bismethyl thio cyclopropyl ketones **64b,76b** were also reduced to the carbinols **97,98** using sodium borohydride(Scheme-37).These in the presence of $SnCl_4$ in nitromethane did not yield the expected bicyclooctanes **99** . Instead the reaction mixture under the described condition resulted in intractable tar.



64 b X = O

76 b X = S

97 X = O

98 X = S

Scheme - 37

References:

1) Mitra, A. 'The Synthesis of Prostaglandins', John Wiley & Sons, New York, 1977.

2) Comer, F.W.; McCapra, F.; Qureshi, I.H.; Scott, A.I. *Tetrahedron*, **1967**, *23*, 4761.

3) Comer F.W.; Trotter, J.*J. Chem. Soc. B.* **1969,** 11.

4) Brown, N.M.D.; Cowley, D.*J. Alicyclic chemistry*, **1978**, *6*, 144.

5) Ono, M. *Syn. Org. Chem. Japan.* **1981**, 872.

6) Marino, J.P.; Kattermann, L.C. *J. Chem. Soc. Chem. Commun.* **1979,** 946.

7) Paquette, L.A.. *Topp. Curr. Chem.* **1984**, *119*, 1.

8) Paquette, L.A., Doberty, A.M. '*Polyquinane Chemistry: Syntheses and Reactions*; Springer-Verlag: Berlin, **1987.**

9) Trost, B.M.; *Chem. Soc. Rev.* **1982,** *11*, 141.

10) Ramaiah, M. *Synthesis*, **1984,** 529.

11) Paquette, L.A. *Aldrichim. Acta.* **1984**, *17*, 43.

12) Santelli-Rouvier, C.; Santelli M. *Synthesis, 1983*, 429.

13) Curran, D.P.; *Synthesis,* **1988**, *417*, 489.

14) Vandewalle, M.; Declereg, P. *Tetrahedron*, **1985**, *41*, 1767.

15) Trost, B.M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1

16) Trost, B.M. *Topp. Curr. Chem.* **1986**, *133*, 1.

17) Wong, H.N.C.; Lau, K.L.; K.F. *Topp. Curr. Chem.* **1986**, *133*, 83.

18) Salaun, T.R.Y. *Topp. Curr. Chem.* **1988**, *144*, 1.

19) Reissig, H.V. in *The Chemistry of the Cyclopropyl Group*; Rappoport, Z; Ed.; Wiley: Chichester, **1987**, part 1, Chapter 8.

20) Verhe, R.; Dekimpe, N.; in *The chemistry of the Cyclopropyl Group*; Rappoport, Z.; Wiley: Chichester, **1987**; Part 2; Chapter 9; Ibid.; parts 1 and 2.

21) Hudlicky, T.; Kitchan; T.M.; Naqvi, S.M. *Org React.* **1985**, *33*, 247.

22) Goldschmidt, Z.; Crammer, B.; *Chem. Soc. Rev.* **1988**, *17*, 229.

23) Hudlicky, T.; Rulin, F.; Lovelace, T.; Reed, J.N. in *Studies in Natural products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, Amsterdam, **1989**, Part-B, p-3.

24) Wony, H.N.C; Hon, M.,Y.; T.Sc.C.; Yip, Y.C; Tanki, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

25) Hudlicky, T.; Price, J.D. *Chem. Rev.* **1989**, *89*, 1467.

26) House, H.O.; Phillipps., W.V.; Sayer, T.S.B.; Yau,. C.C. *J. Org. Chem.* **1978**, *43*, 700.

27) Baldwin, J.E. *J. Chem. Soc. Chem. Comum.* **1976**, 734.

28) Baldwin, J.E.; Cutting, J. Dupont, W.; Kunse, L.; Silverman, L.; Thomas, R.C. *J. Chem. Soc. Chem. Comum.* **1976**, 736.

29) Baldwin, J.e.; Kruse, L.I. *J. Chem. Soc. Chem. Commun.* **1976**, 736.

30) Trost, B.M.; Jingheim, L.N. *J. Am. Chem. Soc.* **1980**, *102*; 7910.

31) Trost, B.M.; Runge, T.A. *J. Am. Chem. Soc.* **1981**, *103*, 7550.

32) Trost, B.M.; Range, T.A. *J. Am. Chem. Soc.* **1981**, *103*, 7559.

33) Junjappa,H.; ILa.H;Asokan,C.V.*Tetrahedron.***1990**,*46*,5423.

34) Dieter,R.K.*Tetrahedron.***1986**,*42*,3029.

35) Yokoyama,M.Togo,M.*S.Sulfur Rep.***1990**,*10*,23.

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

37) Deb, B; Ila, H.; Junjappa, H. *J. Chem. Res(S)* **1990**, 356; *J. Chem. Res.(M)* **1990**, 2728.

38) Patro, B.; Deb. B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1992**, *57*, 2257.

39) Merz, A.; Mark, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845.

40) Posner, G.H.; Chapdelaine, M.J.; Lentz, C.M. *J. Org. Chem.* **1979**, *44*, 3661.

41) Patro, B.; Deb, B.; Ila, H.; Junjappa, H. *Tetrahedron* **1994**, *50*, 255.

42) Patra, P.K.; Patro B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*,3951.

43) Lutz. F. Tietze. *Chem. Rev.* **1996**, 115

44) TandemOrganic Reactions. Ho, T.L. Wiley Interscience **1992.**

45) Mehta, G.; Srikrishna, A.*Chem Rev.* **1997**, 671.

46) Gupta, A.K.; Fu, X.; Synder, J.D.; Cook, J.M. *Tetrahedron*, **1991**, 3665

47) Pranab K. Patra.; V. Sriram; Ila, H.; Junjappa, H. *Tetrahedron* **1998**, *54*,531.

48) Patro,B. Ph.D Thesis.North Eastern Hill University

49) Satyanarayana, J.; Rao, M.V.B.; Ila, H.; Junjappa, H.; *Tetrahedron Lett.* **1996**, *37*, 3565.

50) Campaigne,E. and Archer,W.J.; *J.Am.Chem.Soc.***1953**, 989.

51) Silverstein,S.; Ryskiewiez, and Chaikin.; *J.Am.Chem.Soc.* **1954**, *76*,4485.

52) Org. Synth. Coll. Vol. IV pg 539.

53) Kuhn,R. and Trischmann,H.; *Ann.* **1958,** *611*, 570.

Experimental:

General: The general experimental were kept the same as described in chapter two.

Chemicals and Reagents: Freshly distilled furfuraldehyde was used. N- methyl pyrole was purchased from Aldrich and used as such. . Nitromethane and nitroethane were purchased from Spectro- chem and S.D. fine chemicals respectively and used as such. Stannic chloride was purchased from Spectro- chem and distilled before use. Thiophene-2-aldehyde[50], pyrole 2- aldehyde[51] and indole-3-aldehyde[52] were prepared according to reported procedures. The required α- oxoketene dithioacetals were prepared according to the procedure described in Chapter two. Trimethyl oxosulphonium Iodide was prepared by a modification of the reported procedure[53] and is given below:

Preparation of trimethyl oxosulphonium iodide:

To 14.2 ml (0.2 mol, 2 eq) of dry dimethyl sulphoxide, 6.2 ml (0.1 mol,1 eq) of CH_3I is added in 3 lots (3.1 ml each after 6 hours) and left to stir at 60°C. After a total 36 hours of stirring, the precipitated yellow

solid is filtered at the pump, washed with dichlromethane (30 ml). The solid is purified by recrystallisation from water to yield white crystals . m.p. 164-167°C (Lit. 165-169°C). Yield = 11 gm (50%).

General procedure for the preparation of heteroaryl substituted 1,4-pentadiene - 3- ones:

To a cooled and stirred solution of sodium ethoxide (0.06 mol) in ethanol (30 ml), a solution of α- oxoketene dithioacetal (0.03 mol) and the aldehyde (0.03 mol) in ethanol (25 ml) was added dropwise over a period of 5 minutes. The reaction mixture was allowed to warm to room temperautre and left stirring for 4-5 hours (monitored by TLC). The reaction mixture was then diluted with water and the solid that separated was filtered and dried at the pump. In the case, no solid separates out, the reaction mixture was extracted with chloroform (3 x 50 ml), washed with water (2 x 50 ml), dried over anhydrous sodium sulphate and evaporated to give crude products which on column chromatography on silicagel using hexane ethyl acetate (98:2) as eluent yielded pure products.

1,1,-Bis (methylthio) 5-(2-furyl)- 1,4- Pentadien-3 - one: (63a)

Viscous liquid ; Yield 6.6g(92%); IR (neat)2925, 1660, 1625, 1580cm^{-1}; ^1H NMR(300MHz, CCl_4) 2.40(s,3H,SCH_3),2.45(s,3H,SCH_3),6.16(s,1H, Hα),6.49(brs, 1H,CH-3), 6.66(brs, 1H,CH-4), 6.72(d,J=16Hz, 1H,=CH), 7.51(brs,1H,CH-5).(Anal.Calcd for $C_{11}H_{12}O_2S_2$ 240.35: C, 54.97%; H, 5.03% Found: C, 54.74%; H, 4.79%).

1,1- Bis (methylthio)-2-methyl-5-(2-furyl)-1,4-Pentadien-3-one:(63b)

Yellow crystals(hexane:ether); yield 6.8g(89%); m.p. 48-49°C; IR (KBr) 1675,1610,1580cm^{-1}; ^1H NMR(300MHz, CCl_4) 2.09(s,3H,CH_3), 2.27(s, 3H,SCH_3),2.36(s,3H,SCH_3),6.53(brs,1H,CH-3),6.69(brs,1H,CH-4),6.79 (d,J=16Hz,1H,=CH),7.27(d,J=16Hz,1H,=CH),7.57(brs,1H,CH-5);(Anal. Calcd. for $C_{12}H_{14}O_2S_2$ 254.37:C, 56.66%, H, 5.55%. Found : C, 56.82%; H, 5.69%).

1,1-Bis(methylthio)-5-(-2thienyl)-1,4-pentadiene-3-one (75a):

Yellow solid, low melting, yield 4.76g(67%);IR(CCl_4) 1743, 1682, 1608 cm^{-1}, ^1H NMR(90MHz, CCl_4),2.2(s,6H,SCH_3),6.1(s,1H),6.5(brs,1H), 7.0(d,1H,J=16Hz), 7.2-7.4 (m, 2H), 7.7 (d, 1H, J = 16 Hz). (Anal. Calcd. for $C_{11}H_{12}OS_3$ 256.41; C, 51.33%, H, 4.72%, Found: C, 51.17%, H,

4.53%.)

1,1-Bis(methylthio)-2-methyl-5(-2-thienyl)-1,4-pentadiene-3-one (75b):

yellow solid, low melting, yield g 5.9g (73%). IR (CCl_4). 1680, 1600, 1420 cm^{-1}, ^1H NMR(90MHz, CCl_4)2.1(s,3H,CH_3),2.2l(s,3H, SCH_3), 2.3 (s,3H, SCH_3),6.7(s,1H), 6.9-7.1(m 2H), 7.2-7.4(m,2H), 7.5 (brs, 1H); (Anal. Calcd. For $C_{12}H_{14}OS_3$, 270.44; C, 53.20%, H, 5.22%, Found C, 53.44%, H, 5.41%)

1,1-Bis(methylthio)-5(-2-(1-methyl)-pyrolyl)-1,4-pentadiene-3-one (84a):

Yellow solid, low melting, yield 5.0g (67%); IR (CCl_4): 1657, 1626, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), 2.49(s, 6H, SCH_3), 3.69 (s, 3H, N-CH_3), 6.13-6.17 (m, 2H), 6.58 (d, 1H, J = 16Hz), 6.67-6.75 (m, 2H), 7.60 (d,1H, J=16Hz); (Anal. Calcd. For $C_{12}H_{15}OS_2N$: 253.39,C ,56.88%, H, 5.97%, N, 5.53%, Found C, 56.61%, H, 5.81%, N, 5.76%.)

1,1-Bis(methylthio)-2-methyl-5(-2-(1-methyl)-pyrolyl)-1,4-pentadiene-3-one (84b):

Brown viscous liquid, yield 6.5g(81%); IR (CCl_4): 1635, 1600, 1474 cm^{-1};^{1}H NMR (90 MHz, CCl_4) 2.1(s,3H,CH_3), 2.3(s,3H, SCH_3), 2.4 (s, 3H, SCH_3), 3.8 (s, 3H, N-CH_3), 6.2 (brs, 1H, olefinic), 6.5-6.8, (m, 2H arom), 7.45 (d, 1H, 16 Hz). (Anal. Calcd. For $C_{13}H_{17}OS_2N$, 267.42, C, 58.39%, H, 6.41%, N, 5.24%, Found C, 58.53%, H, 6.59%, N, 5.40%)

1,1-Bis(methylthio)-5(-3-(1-methyl)-indolyl)-1,4-pentadiene-3-one (91a):

Yellow solid, m.p. 137-138°C (hexane/ether); yield 5.5g(61%); IR(KBr) 1622, 1521, 1373 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 2.50(s, 3H, SCH_3), 2.52 (s,3H, SCH_3), 3.79 (s, 3H, N-CH_3), 6.23 (s, 1H), 6.83 (d, 1H, J = 16 Hz), 7.25-7.48 (m, 4H), 7.9 (d, 1H, J = 16 Hz), 8.0 (d, 1H, J = 16Hz),^{13}C NMR (75 MHz, $CDCl_3$): 15.12 , 17.30, 33.18, 109.97, 112.93, 114.42, 120.74, 121.13, 122.52, 122.89, 126.17, 133.57, 135.19, 138.15, 162.58, 184.73, (Anal. Calcd. For $C_{16}H_{17}ONS_2$: 303.45, C, 63.33%, H, 5.65%, N, 4.62%. Found C, 63.51%, H, 5.82%, N, 4.41%.)

1,1,Bis(methylthio)-2-methyl -5- (-3-(1-methyl)-indolyl) -1,4-pentadiene-3-one (91b):

Yellow solid,m.p. 151-152°C, (hexane/ether); yield 9.5g (81%);IR(KBr)

1635, 1536, 1357 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) 2.20 (s,3H, CH_3), 2.23 (s,3H,SCH_3), 2.35 (S, 3H, SCH_3), 3.73 (s,3H,N-CH_3), 6.85 (d, 1H, J= 16 Hz), 7.27-7.32 (m, 4H), 7.65 (d, 1H, J = 16 Hz), 7.89 (d, 1H, J-6 Hz). (Anal. Calcd. For $C_{17}H_{19}ONS_2$: 317.47; C, 64.32%, H, 6.03%, N, 4.41%, Found C, 64.19%, H, 6.18%, N, 4.59%).

Procedure for cyclopropanation of enones:

A suspension of the appropriate enone (0.01mol), trimethyl sulphoxonium iodide(0.2.64g, 0.012mol), tetrabutyl ammonium bromide (3.6g,0.015 mol), in 50% NaOH ((w/v), 25 ml) and 75 ml of CH_2Cl_2 was stirred for 10-12 hours(monitored by TLC). The organic layer was seperated, concentrated and diluted with ethyl acetate to precipitate tetrabutyl ammonium bromide which was filtered off. The filtrate was concentrated to yield crude products which were purified by column chromatography over silica gel using hexane/ethyl acetate (99:1) as eluent.

1-[2-Bis(methylthio)methyleneacetyl]-2-(2-furyl) cyclopropane :(64)

Yellow viscous liquid; Yield 2.3g (90%);IR(neat)2950,1675, 1620 cm^{-1}; ^1H NMR (300MHz, $CCl_4/CDCl_3$)1.20-1.72(m,2H,CH_2), 2.0-2.66 (m,2H,

CH),2.40(s,6H,SCH_3),6.0(d,J=2.5Hz,1H,CH-3'),6.12-6.33(m,2H,CH-4' and Ha),7.20(brs, 1H,CH-5'); (Anal.Calcd.for $C_{12}H_{14}O_2S_2$ 254.37: C, 56.66%, H, 5.55%. Found :C, 56.85%; H, 5.67%)

1-[2-Bis(methylthio) methylene propanoyl--2-(2-furyl) cyclopropane:(64b)

Yellow viscous liquid; Yield 2.5g(95%) ; IR(neat)2950,1670,1600 cm^{-1}; ^1H NMR(300MHz,CCl_4)1.30-2.30(m,2H,CH_2),2.09(s,3H,SCH_3),2.19 (s, 3H,SCH_3), 2.33 (s,3H,SCH_3), 1.97-2.90 (m,H,Hα), 6.16(d, J=2.5Hz, 1H, H3'), 6.33(dd,J= 3,2.5 Hz,1H,CH-4),7.30(d,J=2Hz,1H,CH').(Anal.Calcd for $C_{13}H_{16}O_2S_2$ 268.40 : C, 58.18%; H, 6.01%, Found: C, 58.35%; H, 6.24%).

1-[2-Bis(methylthio)methylene acetyl]—2-(2-thienyl) cyclopropane (76a):

Yellow liquid, yield g(92 %); IR(CCl_4): 1734, 1671, 1602 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$), 1.31-1.33(m, 1H), 1.70-1.73 (m,1H), 2.14-2.16 (m,1H), 2.419 (s, 3H, SCH_3), 2.425 (S,3H,SCH_3), 2.42-2.44 (m, 1H), 6.19 (s, 1H, olefinic), 6.77-6.78 (m,2H), 6.84-6.87 (m, 2H), 7.02 (s, 1H),7.29(s, 1H) ;^{13}C NMR(75 MHz, $CDCl_3$)14.17, 16.49, 18.94, 23.15,

39.60, 112.16, 122.01, 122.84, 126.22, 144.70, 160.02, 190.93; (Anal. Calcd. for 270.44.41%, C, 51.53%,H, 4.72%,Found,C, 51.76, H, 4.49%)

1-[2-Bis)methylthio)methylene propanoyl)-2-(2-thienyl) cyclopropane (76b)

Yellow liquid, Yield 2.7g (96%), IR (CCl_4), 1760, 1680, 1620cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) 1.38-140 (m,1H), 1.77-1.80(m,1H), 2.10(s,3H, CH_3),2.33-2.35(m,1H),2.34(s,3H,SCH_3),2.70-2.73(m,1H), 6.79(brs,1H), 6.81-6.83(m,1H),7.00-7.02(m, 1H); ^{13}C NMR(75MHz, $CDCl_3$) 16.17, 17.17, 19.49, 20.31, 33.58, 122.53, 123.54, 126.46, 135.82, 144.60, 144.87, 201.88. M.S: m/z 284: (M^+, 1.1%), (268, 28.2%),(238, 30.4%), (83, 100%) (Anal. Calcd. For $C_{13}H_{16}OS_3$: 284.47 C, 54.89%, H, 5.67%, Found, C, 54.68%, H, 5.85%)

1,1-Bis (methylthio) methylene-3-(2-(-1methyl pyrrolyl) cyclopentanone:(86)

Brown viscous liquid; Yield 1.73g(65%);IR (CCl_4), 2815, 1650cm^{-1}, ^1H NMR (300MHz, $CDCl_3$),1.8-2.0 (m,1H, CH), 2.1-2.6 (m,2H, CH_2), 2.29 (s,3H, SCH_3), 2.49 (s,3H, SCH_3), 2.54-2.69 (m,1H, CH_2), 3.65 (s,3H, N-CH_3), 5.5 (d,1H, CH-8), 5.7 (m,1H, arom), 6.0 (m,1H, arom), 6.6 (m,1H,

arom);[13] C NMR ($CDCl_3$), 18.02, 18.53, 27.21, 33.73, 38.05, 42.11, 69.22, 105.75, 105.82, 106.51, 121.55, 122.84, 134.60, 137.51, 153.4, 201.80.(Anal.Calcd. for $C_{13}H_{15}OS_2N$ 267.42 C, 58.39%, H, 6.41% N, 5.24%; Found C, 58.56%, H, 6.72%, N, 5,11%)

S-methyl-2-methyl-3-(2-pyrrolyl)cyclopentanone-2- carbothioate (87):

Brown viscous liquid, Yield 1.8g (73%);IR (CCl_4): 1682, 1601, 1427 cm^{-1};^{1}H NMR (90 MHz, CCl_4).: 2.1 (s,3H,CH_3), 2.2-2.6 (m, 4H), 2.4 (S, 3H, SCH_3), 3.7 S, 3H, N-CH_3), 4.7 (brs 1H), 5.9 (brs, 1H arom), 6.1 (brs 1H, arom), 6.7 (brs, 1H, arom); (Anal. Calcd. For $C_{13}H_{17}O_2SN$: 251.35, C, 62.12%, H, 6.82%, N,5.57% Found C, 62.01%, H, 7.03%, N, 5.79%)

Bis(methylthio)methylene-3-(3-(1-methyl)-indolyl) cyclopentanone:(93)

Yellow solid, low melting,Yield 2.0g(63%);IR(KBr)1653, 1548,1397 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.12-2.27 (m,1H, CH_2), 2.27-2.32 (m,2H, CH_2), 2.28 (s, 3H, SCH_3), 2.43-2.52 (m,1H, CH_2), 2.48(s, 3H, SCH_3), 4.66 (brs,1H, CH), 6.50 9s, 1H, arom), 7.15-7.23 (m,3H, arom), 7.52-7.55 (m,1H, arom); ^{13}C NMR (75MHz, $CDCl_3$): 17.68, 18.68, 27.66, 32.36,

37.87,41.88, 109, 116.81, 118.76, 121.65, 125.42, 126.38, 137.38, 137.75, 151.12, 151.27;(Anal.Calcd. for $C_{17}H_{19}ONS_2$ 317.48 C, 64.32 H, 6.03%, N, 4.41%; Found C, 64.16, H, 6.20%, N, 4.57%)

S-Methyl -5(3-(1-methyl)- indolyl)-1- methyl-2-oxo cyclopentane carbothioate:(94)

Pale yellow flakes: m.p. 162°C($CHCl_3$/ether) yield 70%.IR (KBr): 3415, 1680, 1600 cm^{-1}, ^1H NMR ($CDCl_3$), 1.12(s,3H, CH_3), 32.12-2.23 (m,1H, CH_2), 2.30 (s,3H, SCH_3), 2.33-2.41 (m,1H, CH_2), 2.56-2.6 (m,2H, CH_2), 3.74 (s,3H, N-CH_3), 4.45-4.50 (m,1H, CH), 6.87 (s,1H, arom), 7.02 – 7.07 (m,1H, arom), 7.16-7.28 (mn,2H, arom), 7.43 (d, 1H, J= 4Hz, arom);^{13} C NMR ($CDCl_3$);12.15, 14.70,25.20,32.78, 38.17, 43.12, 67.38, 109.18, 112.25,119, 119.66, 121.76, 126.94, 127.67, 135.81, 202.01, 215.35;(Anal.Calcd for $C_{17}H_{19}O_2NS$ 301.41; C, 67.74%, H, 6.35%, N, 4.65%; Found C, 67.59%, H, 6.21%, N, 4.79%)

Procedure for $NaBH_4$ reduction :

To a solution of the cyclopropyl ketone(10 mmol) in absolute ethanol(40ml), excess of $NaBH_4$ (1.25g,40 mmol) was added and the

reaction mixture was refluxed for 2 hours(monitored by TLC). The excess ethanol was distilled off at reduced pressure and the residue was poured into crushed ice. Saturated $NaHCO_3$ solution (30 ml)was then added and the reaction mixture was extracted with $CHCl_3$(3x50ml), washed with brine (2x50 ml) and dried over anhydrous $NaSO_4$ and concentrated to yield a thick liquid which was used as such for the next step.

General procodure for rearangement of Cyclopropyl Ketones and carbinols with $SnCl_4$ in $CH_3NO_2/C_2H_5NO_2$:

To a cooled (0°C) solution of cyclopropyl ketone or carbinol(10 mmol) in nitromethane/nitroethane (15 ml), $SnCl_4$ (15 mmol,1.5 eq) was added and the reaction mixture was allowed to warm to room temperature. It is then stirred for 10 hours (monitored by TLC). The reaction mixture is then poured into saturated NH_4Cl solution(50 ml). It is then extracted with chloroform (3x50 ml) washed carefully with brine (2x 30 ml) and dried over anhydrous sodium sulphate and concentrated to yield crude products which on column chromatography on silicagel using hexane: ethyl acetate (99:1) yielded pure products.

Bis – (methylthio)methylene-3-(2- furyl) cyclopentanone:(65)

Yellow oil,Yield 1.9g(75%); IR (neat) 2695, 1755, 1610 cm^{-1}; ^1H NMR (300MHz, CCl_4) 2.0-2.27 (m, 4H, CH_2), 2.36 (s, 3H, SCH_3), 2.45(s, 3H, SCH_3), 4.54 (brs,1H,CH-5), 5.97 (brs,1H,H-4), 6.27 (brs,1H,CH-3), 7.42 (brs, 1H, CH-3);(Anal. Calcd for $C_{12}H_{14}S_2O_2$ 254.37: C, 56.66%, H, 5.55%. Found: C, 56.97%, H, 5.89%)

4,4-Bis (methylthio)-4a- methyl furobicyclooctane-5-one:(66)

Colourless low melting solid; Yield 1.9g(70%); IR(neat)2925,1705cm^{-1}; ^1H NMR(300MHz, Ccl_4)1.78 (s,3H,CH_3), 2.02-2.11(2H,m,CH_2), 2.25 (s,3H,SCH_3),2.28(s,3H,SCH_3),2.50-2.57(m,2H,CH_2),5.58(dd,J=6,2.5Hz, 1H,CH_3), 6.63 (d,J=1.5Hz,1H,CH-4), 7.24 (d,J=0.7Hz,1H,CH-5); (Anal. Calcd. for $C_{13}H_{16}O_2S_2$ 268.40: C, 58.17%, H, 6.01. Found: C, 58.46%; H, 6,32%)

(E)S-methyl-5-(2-furyl)-1-methyl-2-oxocyclopentane carbothioate:(78)

Viscous liquid; Yield 0.4g(15%); IR(neat); 2875, 1745, 1680, 1610cm^{-1}; ^1H NMR(300MHz, CCl_4)1.03(s,3H,CH_3),1.94-2.66(m,4H,CH_2), 2.30 (s,

3H,SCH_3),4.0-4.30(m,1H,CH-furyl),6.16(d,J=3Hz,1H,H-4),6.36(dd,J=3, 2.5Hz, 1H, H-3), 7.62 (d, 1H, J=2Hz,H-5); (Anal. Calcd. for $C_{12}H_{14}O_3S$ 238.31: C, 60.48%, H, 5.92%; Found C, 60.79%, H.6.23%)

S–Methyl-1[1-(cyclopenta[b]furan)1-yl]1-oxo-2-methyl-3-carbothioate: (68)

Pale red flakes; low melting solid; Yield 0.1g(5%);IR(CCl_4)1680, 1650,1610cm^{-1};^{1}H NMR($CDCl_3$)1.21(d,3H,CH_3,J=7Hz),1.35(d,3H,CH_3, J=7Hz),2.00-2.15(m,3H),2.16-2.30(m,3H),2.33 (s,3H,SCH3), 2.35(s,3H, SCH3), 2.36-2.65(m,4H), 3.05-3.15(m,1H), 3.27-3.42(m,2H), 3.51-3.58 (m,1H)6.68(brs,2H)7.35-7.38(m,2H); ^{13}C NMR(75MHz,$CDCl_3$): 11..64, 11.69, 13.62, 16.33, 24.94, 26.27, 35.83, 37.17, 37.33, 37.46, 48.77, 49.68, 106.62, 121.51, 121.76, 143.03, 143.12, 167.13, 180.30, 194.02, 201.89.(Anal.calcd. for $C_{12}H_{14}O_3S$ 238.31; C, 60.48%, H, 5.92% Found C, 60.63%, H, 5.75%)

Bis (methylthio)methylene-3-(-2-thienyl) cyclopentanone:(77)

Brown viscous liquid; Yield 1.8g(68%); IR 1686,1547,1376 cm^{-1} ; ^{1}H NMR(300MHz, CDCl3) 2.08-2.1(m,1H), 2.25-2.55(m,3H), 2.33(s,3H,

SCH_3), 2.49(s,3H,SCH_3), 4.72(d,1H,6Hz), 6.74–6.76(m,1H,arom), 6.87-6.90(m,1H, arom), 7.11-7.14(m,1H, arom);(Anal.Calcd.for $C_{12}H_{14}OS_3$ 270.44: C, 53.20% H, 5.22%; Found C, 53.39%, H,5.43%)

S-Methyl-2-methyl-3-(2-thienyl)cyclopentanone-2-carbothioate :(78)

Brown liquid; Yield 1.9g(76%); IR (CCl_4), 2850, 1730, 1670, 1600cm^{-1}; ^1H NMR(300MHz, $CDCl_3$) 1.08(s,3H,CH_3), 1.16(s,3H,CH_3), 2.02-2.54 (m,8H, CH_2), 2.17 (s,3H, S CH_3), 2.33 (s,3H, SCH_3), 4.38 –4.4 (m,1H, CH), 4.56-4.62 (m,1H, CH), 6.79-6.909 (m,1H, arom), 6.91-6.94 (m,1H, arom), 7.12-7.15 (m,1H, arom), ^{13}C NMR ($CDCl_3$); 11.78, 14.63, 15.39, 18.97, 25.48, 30.05, 37.35, 29.09, 45.25, 45.36, 67.36, 123.86, 124.89, 125.72,126.55,127.41,141.42,145.19,162.87,172,199.15, 211.61 (Anal. Calcd. for $C_{12}H_{14}O_2S_2$ 254.37 : C, 56.66%, H, 5.55%; Found C, 56.81%, H, 5.79%)

4,4- Bis (methylthio)-4a methyl thienobicycloctane-5-one:(79)

Palered flakes, low melting solid; Yield 2.0g(70%);IR 1680, 1650, 1610cm^{-1};^1H NMR(300MHz, $CDCl_3$)1.93 (s,3H, CH_3), 2.12-2.22 (m,2H, CH_2),2.32(s,3H, SCH_3),2.35(s,3H, SCH_3), 2.26-2.68 (m,2H, CH_2), 5.17-

5.23 (m,1H,CH), 7.08-7.13 (m,1H, arom), 7.39-7.49 (m,1H, arom);[13] C NMR(75MHz, $CDCl_3$) 16.84, 17.98, 18.25, 29.45, 37.99, 43.84, 123.79, 125.01, 132.29, 137.05, 144.27, 158.85, 192.44.

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9. LIST OF PUBLICATION: one

Lewis acid assisted Tandem carbocationic Ring opening and Cyclisations of α-[Bis(methylthio)methylene]ethyl-2-styryl cyclopropylketones and carbinols: Novel approach to Bicyclo[3.3.0]octene and cyclopent[a]indene frameworks

Pranab. K. Patra, V. Sriram, H. Ila, and H. Junjappa, *Tetrahedron*, 1998, *54*,531.