SYNTHETIC AND MECHANISTIC INVESTIGATIONS ON OXOKETENE N,N- AND S,S- ACETALS

By

ABRAHAM THOMAS

DEPARTMENT OF CHEMISTRY

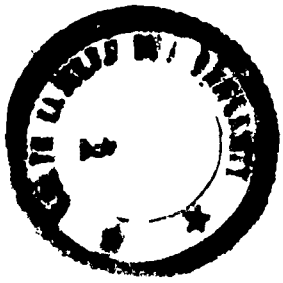
SCHOOL OF PHYSICAL SCIENCES

A THESIS

SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR

THE DEGREE OF

DOCTOR OF PHILOSOPHY



To

NORTH-EASTERN HILL UNIVERSITY

SHILLONG-793 001

MEGHALAYA (INDIA)

1989

Phone :
Grams : NEHU

North-Eastern Hill University

Bijni Complex
Bhagyakul, Shillong - 793003 (Meghalaya)

Professor H. Junjappa
Department of Chemistry

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

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

(H. JUNJAPPA)
SUPERVISOR

Phone :
Grams : NEHU

North-Eastern Hill University

Bijni Complex
Bhagyakul, Shillong - 793003 (Meghalaya)

Head
Department of Chemistry

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

Title	Course No.
1. Pericyclic Reactions	Chem - 624
2. Biosynthesis & Natural Products	Chem - 630
3. Medicinal Chemistry	Chem - 631
4. French Language	SPS - 601

(H. ILA)
Professor & Head
Head
Department of Chemistry
North-Eastern Hill University
Shillong — 793 003.

ACKNOWLEDGEMENTS

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

To list all the persons to whom I have become indebted through the years for their help, counsel and instruction is impossible. Nevertheless, my everlasting and never fading gratitude goes to all my colleagues and friends with whom I have been associated.

For providing excellent facilities, I thank the Directors and Technical staffs of RSIC, North-Eastern Hill University and Central Drug Research Institute, Lucknow. Grateful acknowledgement for financial support is made to the Council of Scientific and Industrial Research, New Delhi.

Special recognition and gratitude are due to Mrs. Rajamma Johns, Mrs. Florency Jose and Mr. P.N. Mazumdar for the help extended by them in processing this thesis.

Finally I would like to acknowledge the debt I owe to my family members for their support, patience and encouragement.

18/5/89

ABRAHAM THOMAS

C O N T E N T S

PREFACE

Extensive research has been carried out in this laboratory on the synthetic applications of polarized ketene dithioacetals, which are conveniently prepared from a variety of active methylene compounds in one pot reaction. The work described in this thesis has been carried out as a part of this ongoing research programme and highlights new transformation of oxoketene N,N- and S,S-acetals.

The thesis consists of five chapters. The first chapter gives a general introduction to polarized ketene dithioacetals and some of the recent transformations reported from this laboratory. The second chapter is divided into two parts. Part 1 deals with lead tetraacetate oxidation of N,N-acetals. In part II lead tetraacetate oxidation of S,S-acetals is described. Probable mechanism for the formation of various products is discussed.

In the third chapter, a detailed investigation on the reaction of Simmons-Smith reagent to various α-oxoketene dithioacetals is described. A new general approach to 3,4-substituted and annelated thiophenes is developed through a sulfonium ylid intermediate formed in the reaction.

A highly regioselective synthesis of pyrazolo[1,5-a]pyrimidines by the cyclocondensation of aminopyrazoles with various α-oxoketene dithioacetals is presented in chapter IV. In the last chapter, a novel heteroaromatic annelation approach for the synthesis of a large class of thiazolo[3,2-a] pyridinium tetrafluoroborate compounds is described.

Each chapter is divided into Introduction, Results and Discussion, Experimental and Conclusion. Relevant references have been included at the end of each chapter.

CHAPTER I

POLARIZED KETENE DITHIOACETALS: GENERAL INTRODUCTION

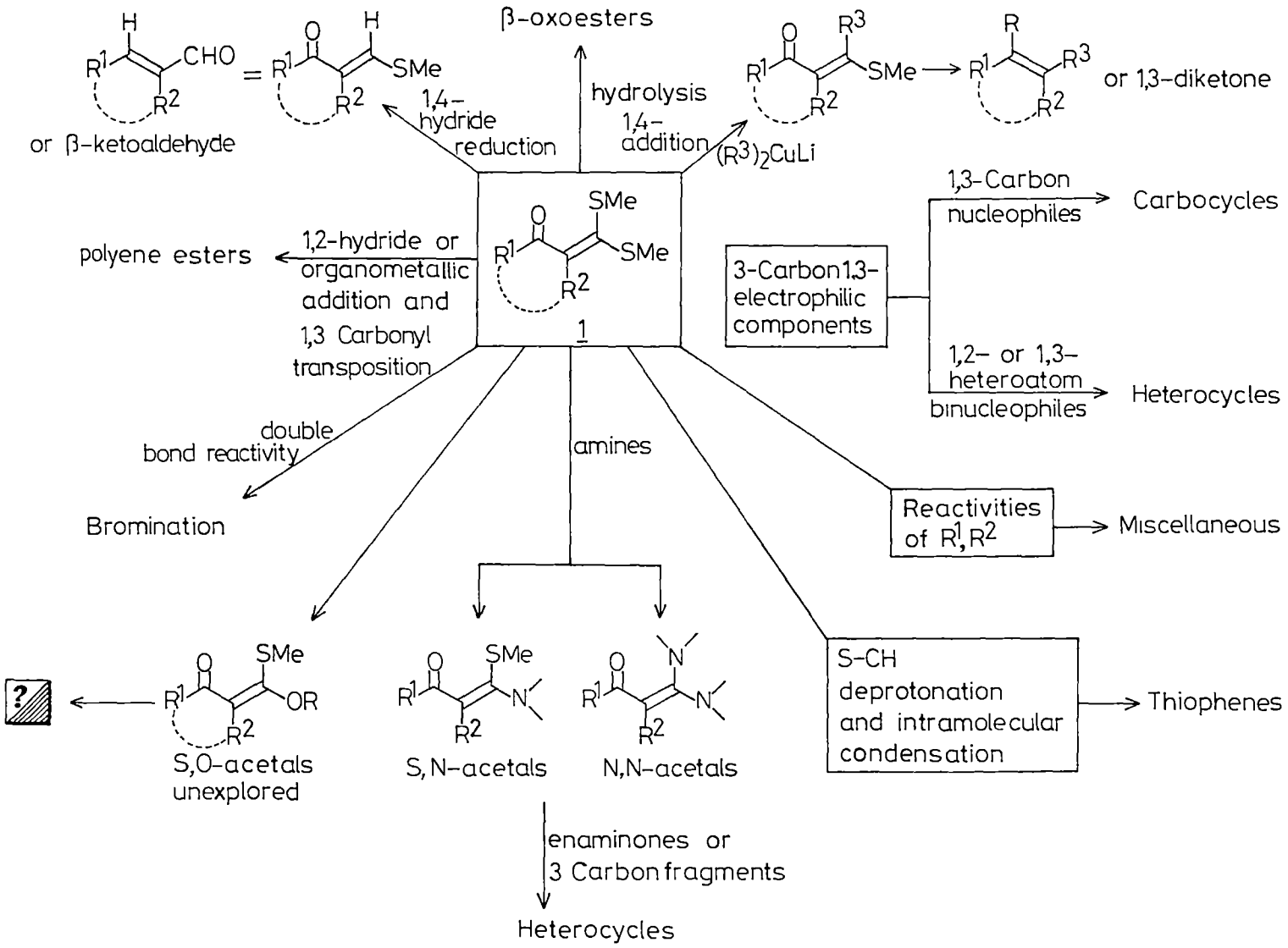
Polarized ketene dithioacetals have been recognized as useful building blocks in many synthetic operations[1]. These class of compounds can be conveniently prepared[2-10] by reacting any active methylene compound with two equivalents of base and carbon disulfide followed by alkylation. Various bases and reaction conditions have been employed depending on the nature of the active methylene compound. This chapter is devoted to a brief review and discussion on the chemistry of α-oxoketene dithioacetals in the context of the practical and potential application to organic synthesis.

The first synthesis of α-oxoketene dithioacetal was reported by Kelber and co-workers in 1910[11-13]. Much of the earlier work on oxoketene dithioacetals was confined to their preparation and properties, while little attention was paid for their synthetic utility. Later Thuillier and Vialle prepared these compounds in high yield in one pot reaction by reacting the active methylene ketone with carbon disulfide in the presence of sodium amylate followed by alkylation[2-5]. Subsequently these reaction conditions have been greatly improved using different bases and reaction conditions[6-10]. A large number of α-oxoketene dithioacetals have now been reported and their chemistry has been reviewed[1] by Dieter.

The oxoketene dithioacetals generally exhibit well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stored indefinitely without decomposition. The corresponding α-oxoketene O,O-acetals are moisture sensitive and undergo hydrolysis under mild conditions. The oxoketene dithioacetal is essentially a masked β-keto ester in which the ester functionality is protected as a ketene dithioacetal. Alternatively it may be viewed as an α,β-unsaturated ketone containing a highly functionalized β-carbon. They are versatile three carbon fragments with 1,3-electrophilic centres of differing electrophilicity. These intermediates possess considerable potential in the stereo- and regioselective construction of new bonds either by a 1,2-nucleophilic addition to carbonyl group or by 1,4-conjugate addition to the β-carbon of the enone system.

Also, oxoketene dithioacetals are primary precursors for the corresponding O,S-, N,S- and N,N-acetals. The preparation of O,S-acetal is accomplished through the displacement by an oxygen nucleophile of the sulfonium salt[14]. The N,S-acetal can be prepared by the displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol[15,16]. Alternately they can be prepared directly from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates followed by alkylation[17]. The oxoketene N,N-acetals can be prepared in high yield by displacing both the thiomethyl groups by amines in refluxing acetic acid[16,18]. The oxoketene S,S-, N,S-and N,N-acetals have been extensively used in this laboratory for the synthesis of both heterocyclic and carbocyclic compounds, while the chemistry of O,S-acetals remains unexplored.

Scheme 1 outlines various reactivity profiles of α-oxoketene dithioacetals of the general formula 1. Hydrides and organometallic reagents give 1,2-addition products typical of carbonyl function reactivity[19]. These additions can be directed in a 1,4-manner by suitably manipulating the reagent and reaction conditions[19-21]. Further transformations after the initial 1,2- or 1,4-additions are also reported[19]. The α-oxoketene dithioacetals possess typical 1,3-electrophilic centres. These intermediates react with 1,2- and 1,3-heteroatom binucleophiles to give 5- and 6-membered heterocyclic compounds, while 1,3-carbon binucleophiles give carbocyclic compounds. The enolate ion formed by the deprotonation (when R^1=alkyl) can undergo condensation with aldehydes to give α-enoylketene dithioacetals[2,22]. An allylic anion formation has been reported

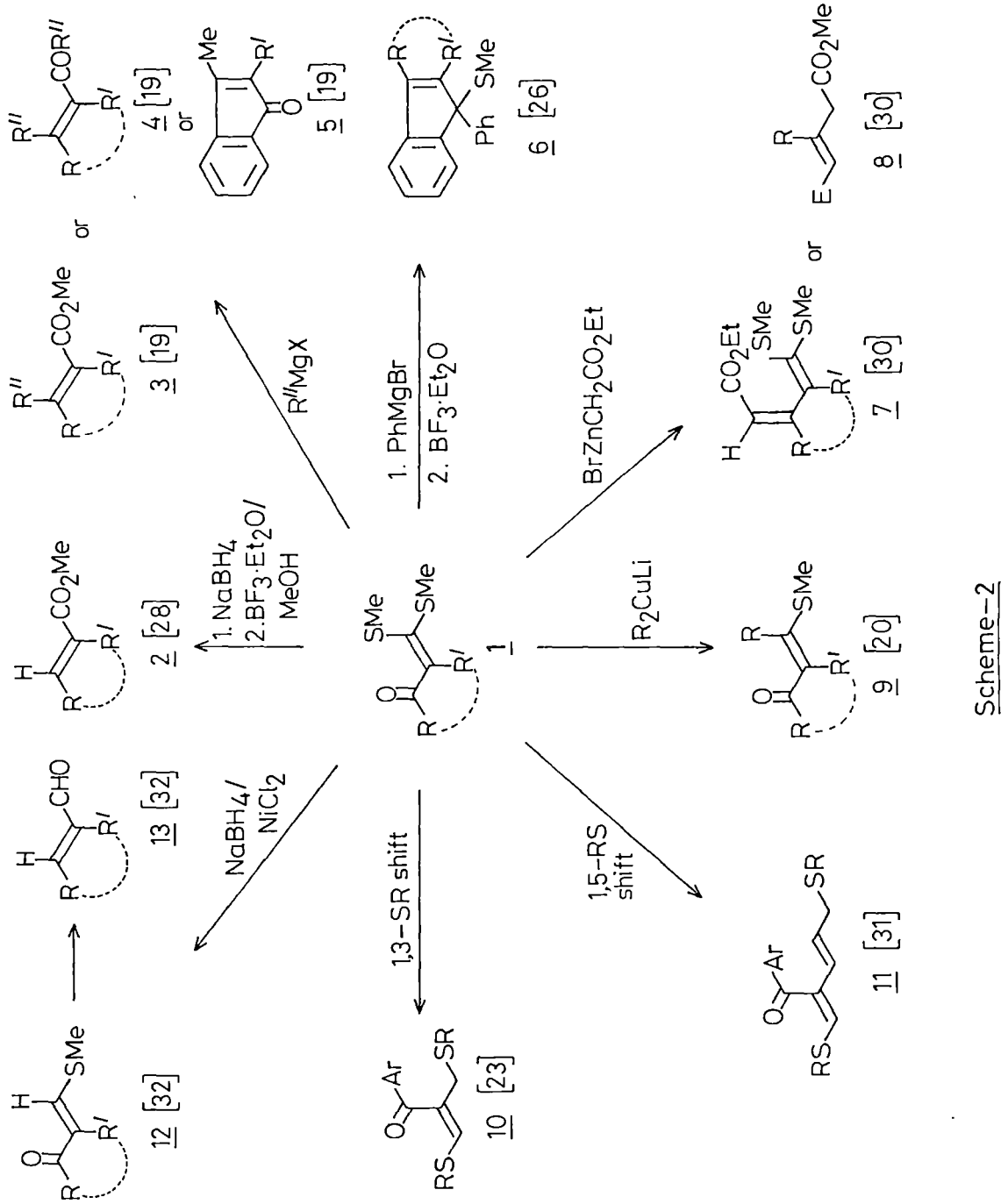

β-oxoesters
or β-ketoaldehyde
1,4-hydride reduction
hydrolysis
1,4-addition
$(R^3)_2CuLi$
or 1,3-diketone
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
polyene esters
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles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

Scheme-1

when R^2 is a methyl group, leading to rearranged products[23]. Also deprotonation on the thiomethyl group followed by intramolecular aldol type condensation to thiophene is also reported[24,25]. As discussed earlier they can be easily converted to oxoketene O,S- N,S- and N,N-acetals. The reactivity of the mercaptal double bond is also exploited with eletrophiles. Thus dithioacetals 1 (R^2=H) undergoes bromination at α-position with N-bromosuccinimide[26]. Thus, it is apparent that the oxoketene dithioacetals of general formula 1 constitute an important class of synthons with reactive electrophilic and nucleophilic centres distributed in various centres of its skeleton permitting reactions of great synthetic importance. Some of the selected transformations reported from this laboratory are briefly described in the following section.

The carbonyl group of α-oxoketene dithioacetals has been reported to undergo sodium borohydride reduction to give the corresponding carbinol acetals[27,28]. These carbinol acetals were shown to undergo smooth methanolysis in the presence of borontrifluoride etherate to afford α,β-unsaturated methyl esters 2[28] in high yields. The overall transformation is considered as homologation of active methylene ketones involving a 1,3-carbonyl transposition methodology.

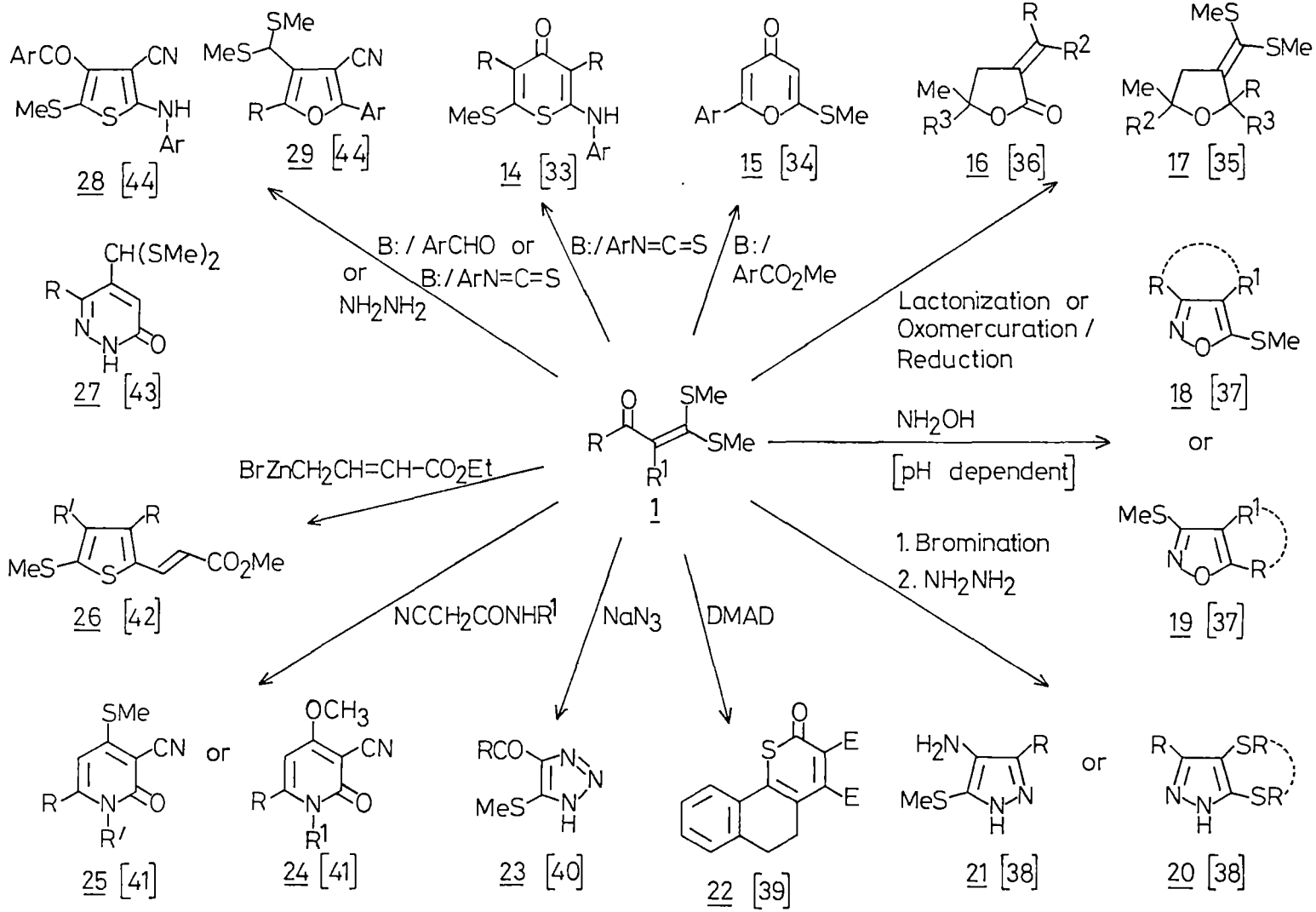
The Grignard and organolithium reagents undergo either regioselective 1,2-addition to afford the α-hydroxyketene dithioacetals or a sequential 1,4-and 1,2-additions to afford the β-hydroxyvinylsulfides[19-21]. The borontrifluoride etherate catalyzed solvolysis or the hydrolysis of these carbinols yield either β-substituted α,β-unsaturated esters 3



Scheme–2

or the corresponding ketone 4 (Scheme 2)[19] in good yields. However, when the R^1 is alkyl or aryl group the open chain cinnamates were not formed, instead the corresponding 2,3-disubstituted indenones 5 were formed[19]. The reaction of phenylmagnesium bromide followed by $BF_3.Et_2O$ treatment is reported to give the 1-methylthio-1-phenyl indane 6[29]. The Reformatsky reaction on dithioacetal 1 is reported to give the diene ester 7 and the β,γ-unsaturated ester 8[30]. Dieter and co-workers have reported the chemo- and stereoselective addition of organocuprates to dithioacetals 1[20,21]. Thus, organocuprates are shown to undergo conjugate addition to give β-alkylthio-β-substituted α,β-unsaturated ketones. In another study from this laboratory, base catalyzed rearrangement of α-oxoketene dithioacetals derived from propiophenones are reported[23]. The 2-alkylthiomethylacrylophenones 10 are formed by a 1,3-RS shift. A base assisted 1,5-RS shift to the diene 11 is also reported[31]. The α-oxoketene dithioacetals were also shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthio-alkenyl ketones 12[32]. These intermediates are hydrolysed to the α,β-unsaturated aldehydes 13[32] (Scheme 2).

The α-oxoketene dithioacetals have been extensively explored in this laboratory for the construction of various substituted and fused five and six membered heterocyclics[33-44]. Some of the selected transformations developed recently are shown in Scheme 3. From these transformations it is apparent that α-oxoketene dithioacetals with wide functional group variation and many easily accessible reagents and reaction intermediates manifest various possibilities leading to diverse product range.

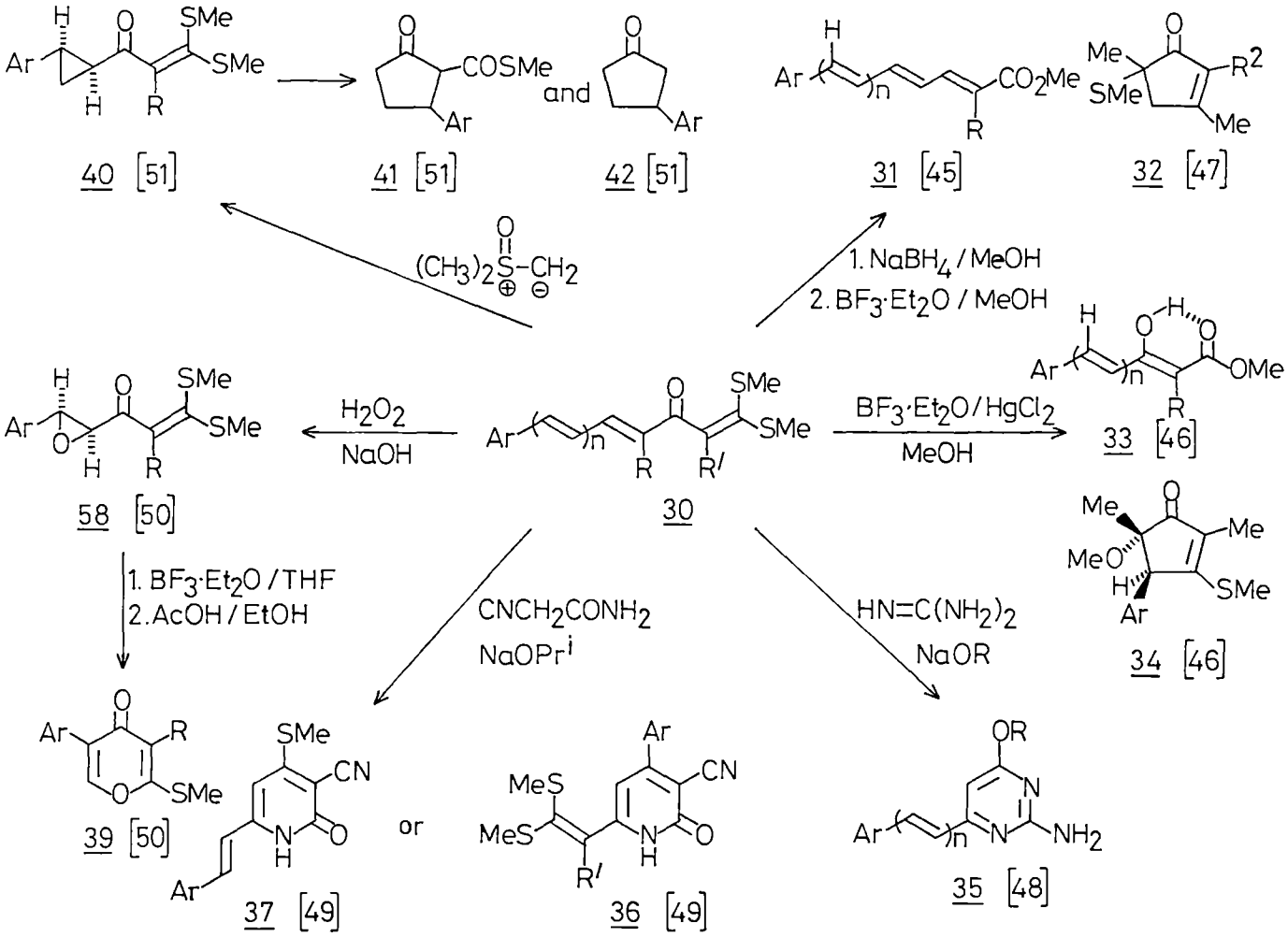

28 [44]
29 [44]
14 [33]
15 [34]
16 [36]
17 [35]
27 [43]
B: / ArCHO or
or B:/ArN=C=S
NH2NH2
B:/ArN=C=S
B:/
ArCO2Me
Lactonization or
Oxomercuration /
Reduction
18 [37]
NH2OH
[pH dependent]
or
1
BrZnCH2CH=CH-CO2Et
26 [42]
1. Bromination
2. NH2NH2
19 [37]
NCCH2CONHR1
NaN3
DMAD
25 [41]
24 [41]
23 [40]
22 [39]
21 [38]
or
20 [38]

Scheme-3

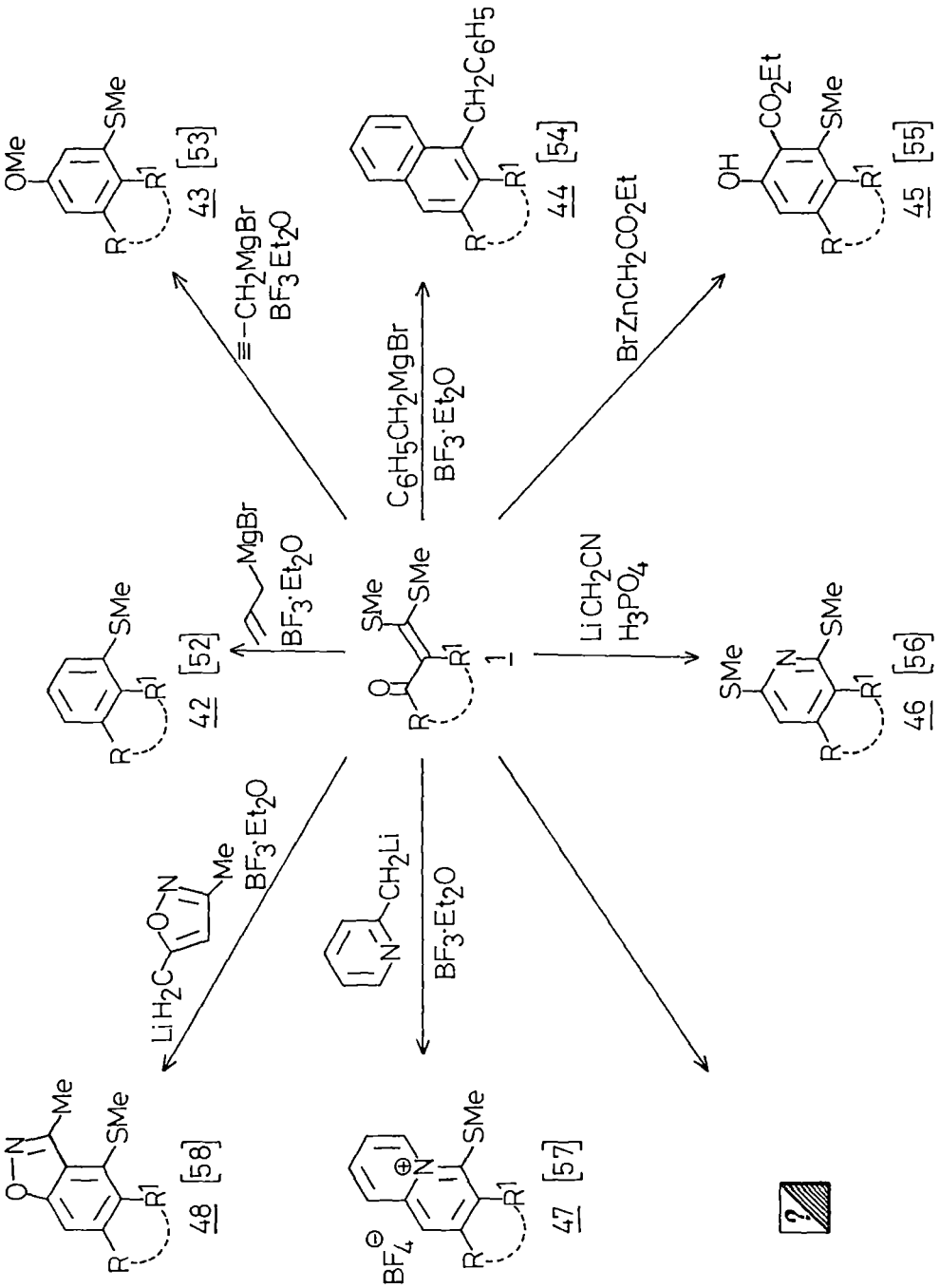
Various transformations developed based on α-cinnamoyl and 5-aryl-2,4-pentadienoylketene dithioacetals are outlined in Scheme 4. A general method for the synthesis of polyene esters 31[22,45] have been reported by 1,2-reduction followed by methanolysis in the presence of borontrifluoride etherate. In Hg(II) assisted hydrolysis the corresponding γ,δ-unsaturated β-keto esters are formed[46]. In the case of 2,4-disubstituted ($R=R^1=CH_3$) the corresponding cyclopentenenones 32 and 34 are formed in both reaction conditions[46,47]. Styryl pyrimidines 35, pyridones 36 and 37 were also synthesised using these intermediates[48,49]. The cinnamoylketene dithioacetals 30 have been reported to undergo regioselective cyclopropanation and epoxidation at the styryl double bond[50,51]. The intermediates 38 and 40 were further exploited for the synthesis of pyrones 39 and cyclopentanones 41 and 42 respectively[50,51].

The synthetic outcome of the aromatic annelation approach via α-oxoketene dithioacetals developed in this laboratory is depicted in Scheme 5. Allylmagnesium bromide has been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetals in high yield, which on $BF_3.Et_2O$ assisted cationic cyclization yield the substituted and fused benzene derivatives 42[52]. The approach is extended for the synthesis of other benzenoids 43, 44 and 45[53-55]. The method is further shown to be extremely versatile and found general application for the synthesis of pyridines 46[56], quinolizinium salts 47[57] and 1,2-benzisoxazoles 48[58].

In the present study, it was proposed to undertake some of the transformations based on α-oxoketene N,N- and S,S-acetals. Although ketene


40 [51]
41 [51]
and
42 [51]
31 [45]
32 [47]
1. NaBH4 / MeOH
2. BF3·Et2O / MeOH
(CH3)2S-CH2
H2O2
NaOH
30
BF3·Et2O / HgCl2
MeOH
33 [46]
58 [50]
1. BF3·Et2O / THF
2. AcOH / EtOH
CNCH2CONH2
NaOPr^i
HN=C(NH2)2
NaOR
34 [46]
39 [50]
or
37 [49]
36 [49]
35 [48]

Scheme-4

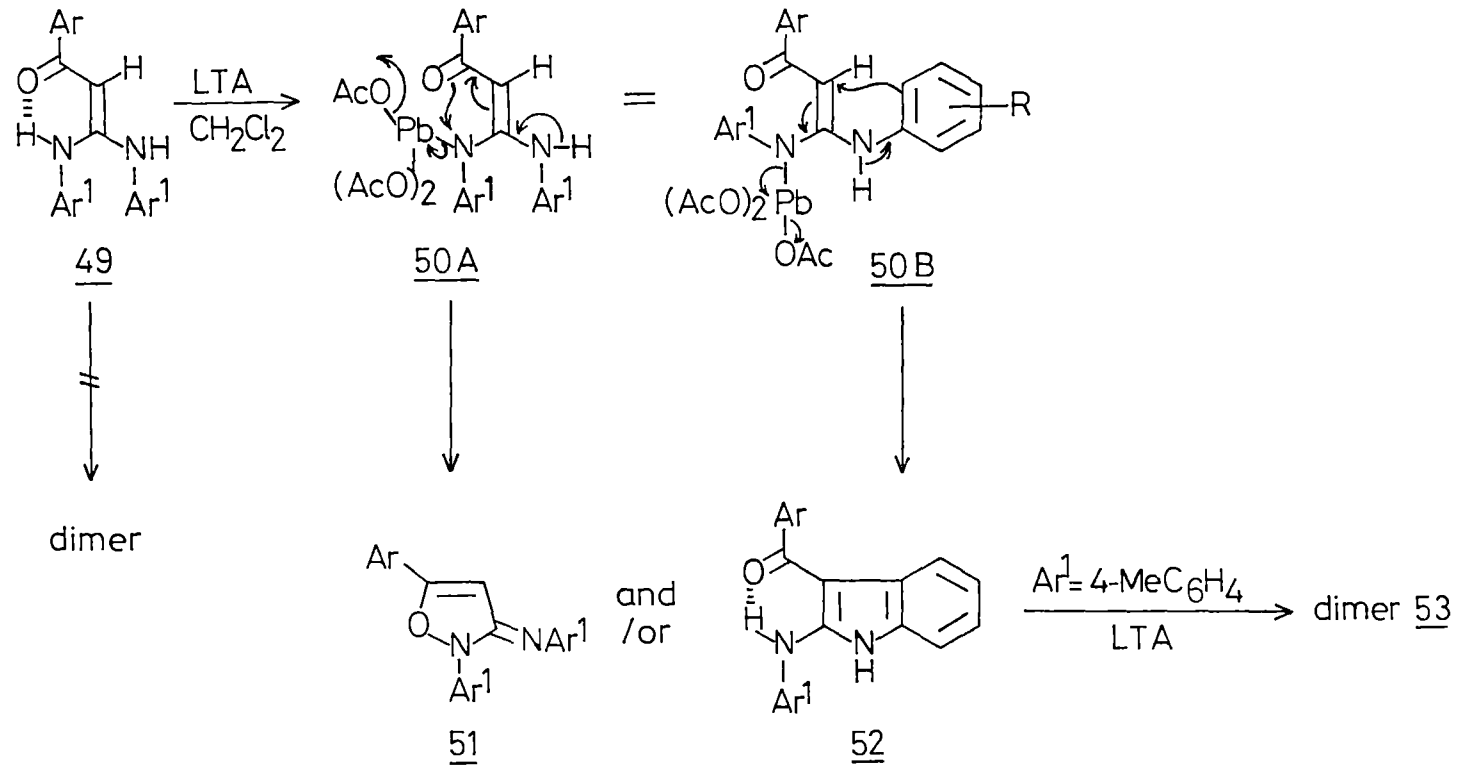

OMe
SMe
R
R1
43 [53]
≡-CH2MgBr
BF3 Et2O
CH2C6H5
44 [54]
C6H5CH2MgBr
BF3·Et2O
OH
CO2Et
45 [55]
BrZnCH2CO2Et
MgBr
BF3·Et2O
42 [52]
SMe
O
1
LiCH2CN
H3PO4
46 [56]
LiH2C
Me
BF3·Et2O
CH2Li
BF3·Et2O
48 [58]
47 [57]
BF4⊖
?

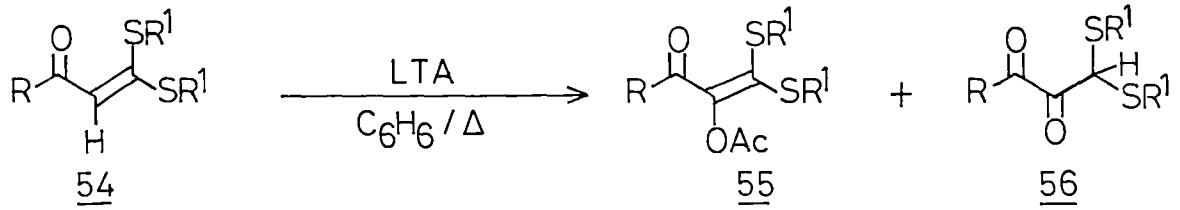
Scheme-5

N,S-acetals have been extensively sutided[59-71], the corresponding N,N-acetals remains less attended[59,72,73]. In the second chapter, the N,N-acetals 49 are shown to give isoxazolines 51 and indoles 52 in varying yields on oxidation with lead tetraacetate (Scheme 6)[18]. Typical reaction of the enaminone moiety of the N,N-acetal towards electrophilic lead (IV) acetate is exploited in this reaction. The detailed mechanistic pathways for the formation of various products and the factors governing the course of reaction are discussed in detail. In the oxidation of dithioacetals 54 the reactivity of the double bond is realised. Thus, dithioacetal 54 was oxidised with LTA in benzene to give the acetates 55 and the diketones 56 in good yields.

In chapter 3, the reaction of Simmons-Smith reagent ($Zn-Cu/CH_2I_2$) with various α-oxoketene dithioacetals is described[74]. A new general method for the synthesis of 3,4-substituted and fused thiophenes is developed (Scheme 7). The probable mechanism of the described transformation apparently involves the carbenoid methylene addition to one of the sulfur atoms of 1 to yield the sulfonium ylid 55 which on intramolecular aldol type condensation and subsequent demethylation of the S-methylthiophenium salts 56 afford the thiophenes 57. The approach utilizes the reactivity of the thiomethyl group. The products 58 and 59 arising from the reactivity of the double bond was not formed in the reaction suggesting the regioselectivity of the carbenoid addition.

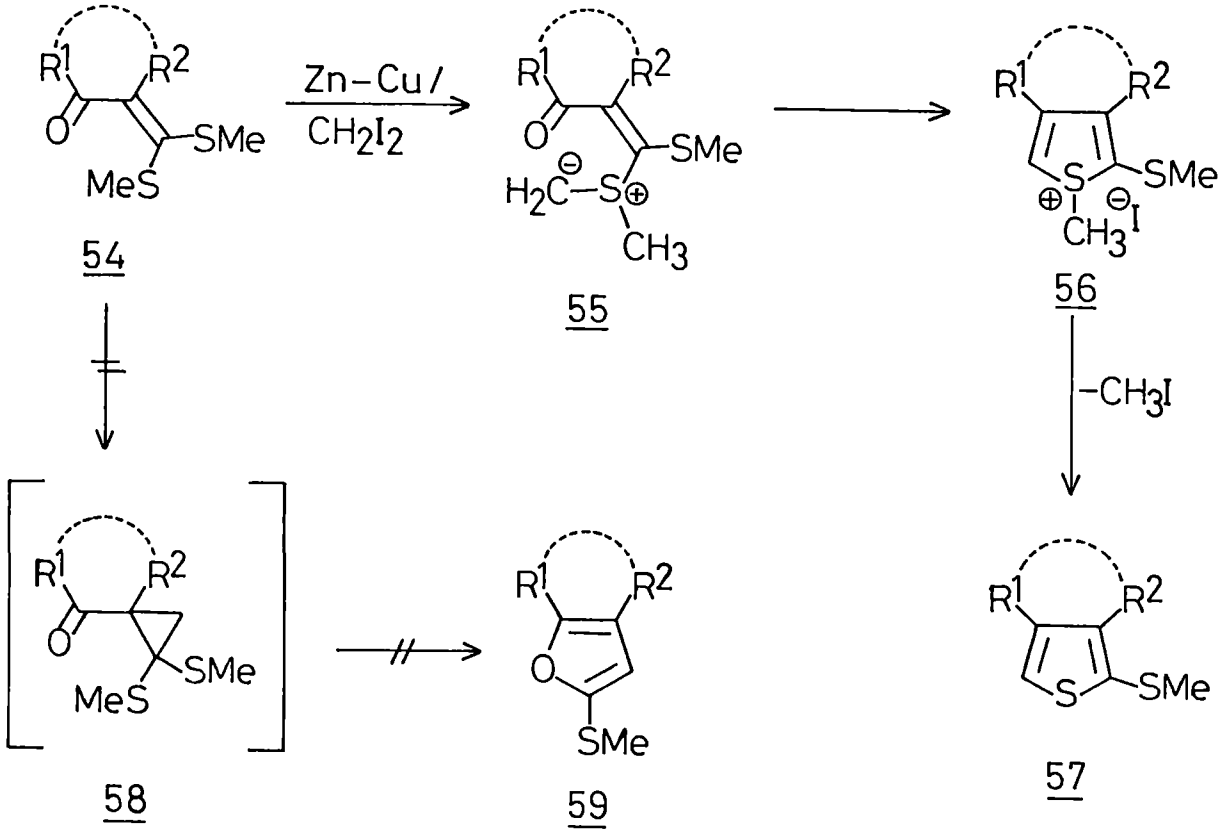
A highly regioselective cyclocondensation of α-oxoketene dithioacetals with aminopyrazoles is described in chapter IV. Thus, various substituted,





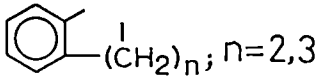
R=Substituted aryl, Me; R^1=Me, Et

Scheme-6



54–57 R^1 = aryl, alkyl, Ar(CH=CH-)$_n$; n=1,2,3

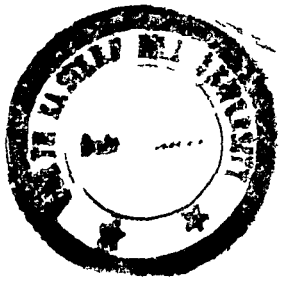
R^2 = H, alkyl

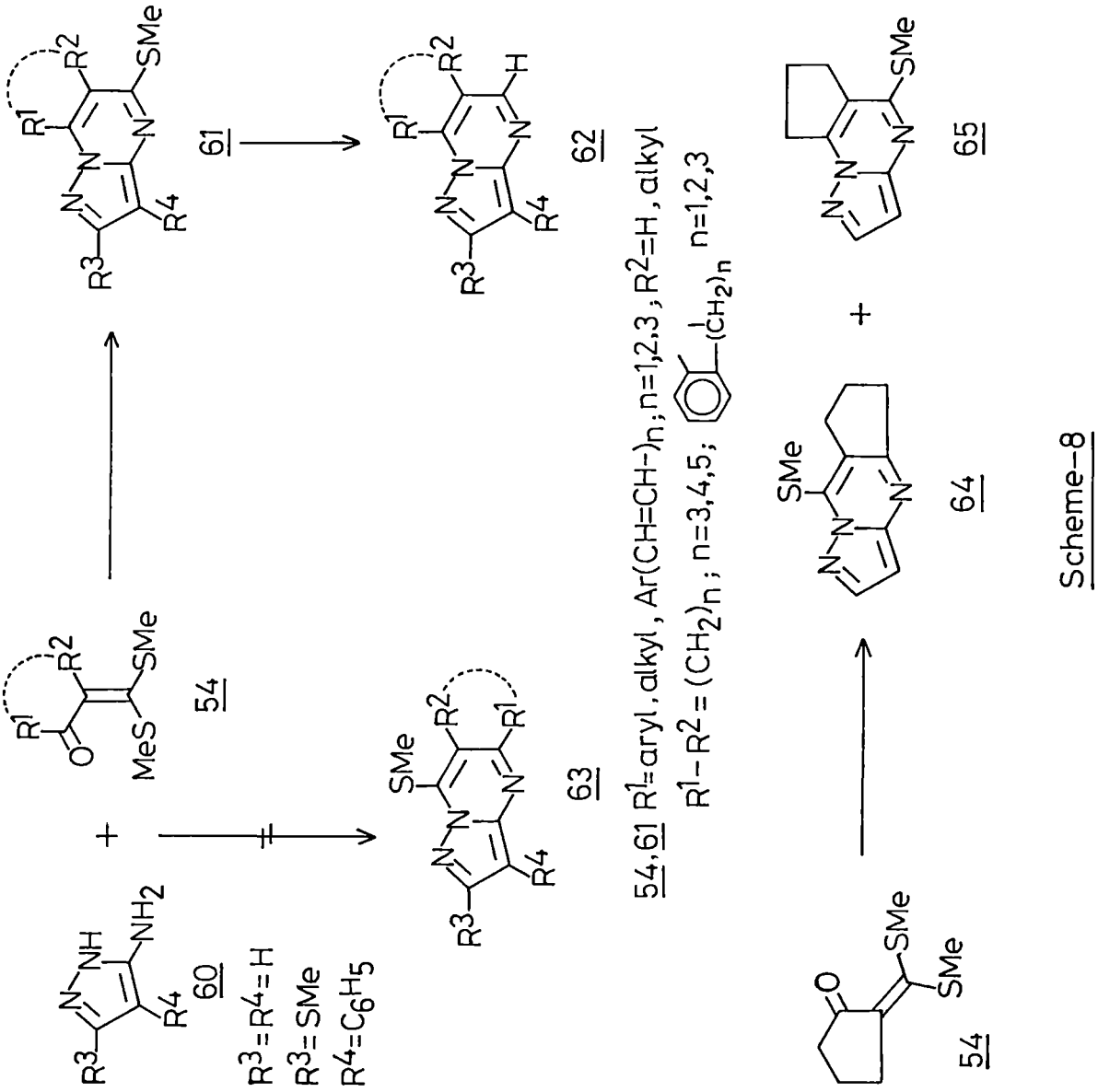
R^1–R^2 = $(CH_2)_n$; n= 4,5;  ; n=2,3

Scheme-7

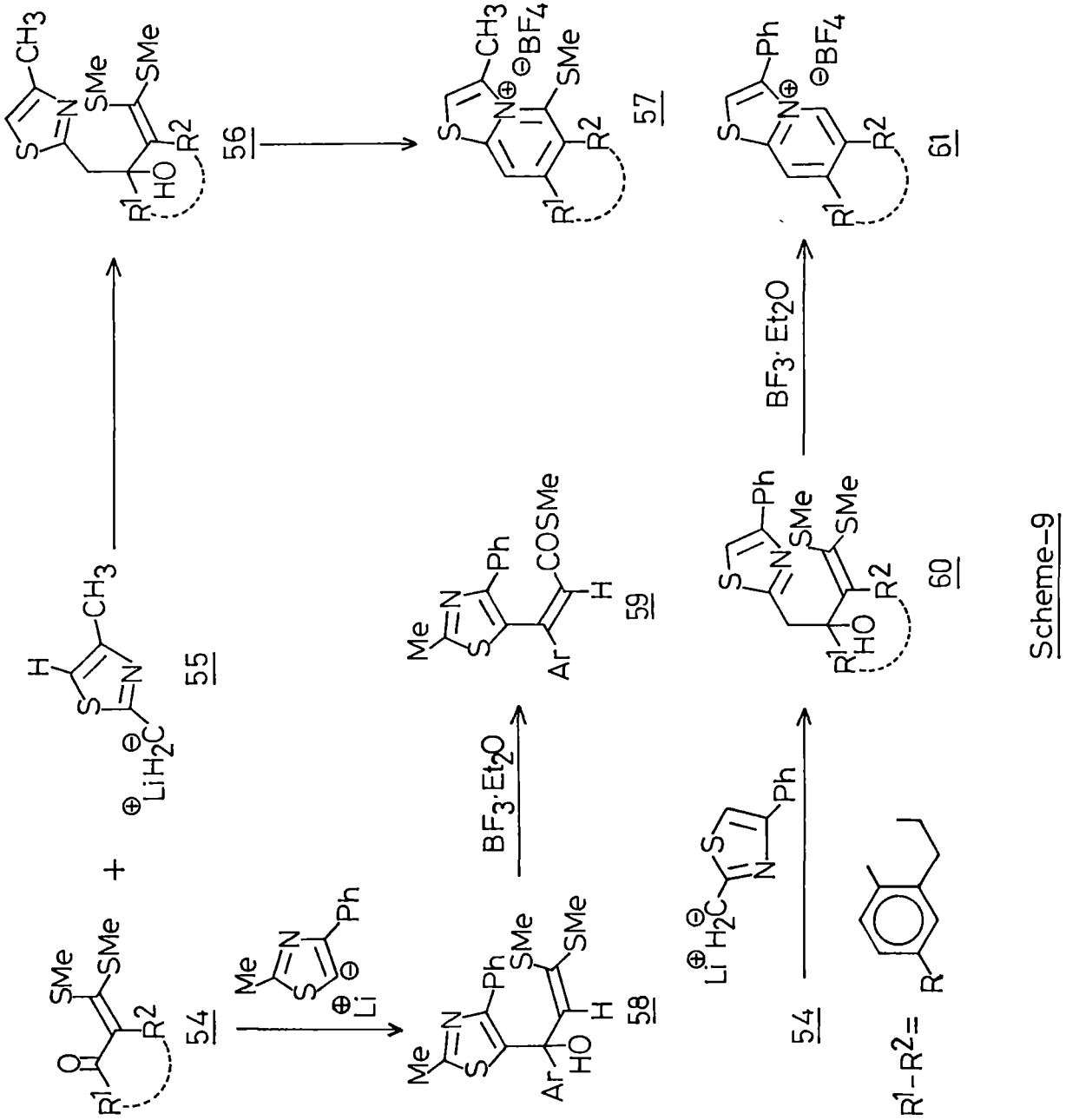
fused polyenyl pyrazolo[1,5-a]pyrimidines 61 are synthesized by the reaction of 1,3-heteronucleophilic aminopyrazole 60 with 1,3-electrophilic oxoketene dithioacetal 54 (Scheme 8). Although two regioisomers are possible in this reaction, only one isomer is formed in all cases with one exception. The dithioacetal derived from cyclopentanone gave the linearly and angularly fused pyrazolopyrimidines 64 and 65. The 5-methylthio and 2,5-bis(methylthio)pyrazolopyrimidines are desulfurized to the sulfur free compounds 62. The regioisomers were assigned on the basis of ^{1}H and ^{13}C n.m.r. spectral data.

In the last chapter, the heteroaromatic annelation methodology is described for the synthesis of thiazolo[3,2-a]pyridinium tetrafluoroborate compounds (Scheme 9). The initial 1,2-adduct 56 formed by the reaction of 2-lithiomethylthiazoles 55 with α-oxoketene dithioacetals 54 has been shown to undergo cycloaromatisation through the participation of the imino group of the thiazole ring to yield the thiazolo[3,2-a]pyridinium compounds in moderate to good yields. The preliminary study on the lithiation and reaction of the 2-methyl-4-phenyl thiazole is also described. The scope and limitation of this new approach developed is discussed in the chapter.




60
R3=R4=H
R3=SMe
R4=C6H5
54
63
61
62
54,61 R1=aryl, alkyl, Ar(CH=CH-)n; n=1,2,3; R2=H, alkyl
R1-R2=(CH2)n; n=3,4,5;
n=1,2,3
54
64
65

Scheme-8



Scheme-9

REFERENCES

1. For a review see R.K. Dieter, Tetrahedron, 42, 3029 (1986).
2. A Thuillier, J. Vialle, Bull. Soc. Chim.Fr.,2187 (1962).
3. A. Thuillier, J. Vialle, Bull. Soc. Chim.Fr. 2194 (1962).
4. M. Saquet, A. Thuillier, Bull. Soc. Chim. Fr., 1582 (1966).
5. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr.,1398 (1959).
6. R. Gompper, R.R. Schmidt, E. Kutter, Liebigs Ann. Chem. 684, 37 (1965).
7. E.J. Corey, R.H.K. Chen, Tetrahedron Lett.,3817 (1973).
8. I. Shahat, Y. Sasson, Tetrahedron Lett., 4207 (1973).
9. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 1779 (1976).
10. R.K. Dieter, J. Org. Chem., 46, 5031 (1981).
11. C. Kelber, Chem. Ber., 43, 1252 (1910).
12. C. Kelber, A. Schwarz, Chem. Ber.,44, 1693 (1911).
13. C. Kelber, A. Schwarz, Chem. Ber., 45, 137 (1912).
14. R. Spitzner, M. Menzel, W. Schroth, Synthesis, 206 (1982).
15. R. Gompper, H. Schaefer, Chem. Ber.,100, 591 (1967).
16. D. Borrmann, in Houben-Weyl, Methoden der Organischen Chemie, 4th Edn., E. Muller, Ed., Vol.VII/4, Georg Thieme Verlag, Stuttgart, 421 (1968).
17. W.D. Rudorf, A. Schierhorn, M. Augustin, Tetrahedron, 35, 551 (1979).
18. A. Thomas, J.N. Vishwakarma, H.Ila, H. Junjappa, Tetrahedron, 44, 1667 (1988).
19. G. Singh, M.L. Purkayastha, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I, 1289 (1985).
20. R.K. Dieter, L.A. Silks, J.R. Fishpaugh, M.E. Kastner, J. Amer. Chem. Soc., 107, 4679 (1985).

21. R.K. Dieter, J.R. Fishpaugh, L.A. Silks, Tetrahedron Lett., 23, 3751 (1982).

22. B. Myrboh, C.V. Asokan, H.Ila, H. Junjappa, Synthesis, 50 (1984).

23. S. Apparao, A. Rahman, H. Ila, H. Junjappa, Tetrahedron Lett., 23, 971 (1982).

24. J.P. Marino, J.L. Kostusyk, Tetrahedron Lett.,20, 2489 (1979).

25. J.P. Marino, J.L. Iostusyk, Tetrahedron Lett., 20, 2493 (1979).

26. G. Singh, H. Ila, H. Junjappa, Synthesis, 165 (1985).

27. M. Saquet, A. Thuillier, Bull. Soc. Chim. Fr.,3969 (1966).

28. B. Myrboh, H. Ila, H. Junjappa, J. Org. Chem., 48, 5327 (1983).

29. G.Singh, H. Ila, H. Junjappa, Synthesis, 744 (1986).

30. S. Apparao, A. Dutta, H. Ila, H. Junjappa, Synthesis, 169 (1985).

31. S. Apparao,S.S. Bhattacharjee, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I., 641 (1985).

32. B. Myrboh, L.W. Singh, H. Ila, H. Junjappa, Synthesis, 307 (1982).

33. L.W. Singh, H. Ila, H. Junjappa, Synthesis, 531 (1985).

34. L.W. Singh, H. Ila, H. Junjappa, Synthesis, 873 (1987).

35. A. Datta, S. Bhattacharjee, H. Ila, H. Junjappa, Synthesis, 725 (1988).

36. A. Datta, H. Ila, H. Junjappa, Tetrahedron, 43, 5367 (1987).

37. M.L. Purkayastha, H. Ila, H. Junjappa, Synthesis, 000 (1989).

38. G. Singh, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I., 1945 (1987).

39. J.N. Vishwakarma, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I, 1099 (1983).

40. R.T. Chakrasali, H. Ila, H. Junjappa, Synthesis, 453 (1988).

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

42. A. Datta, H. Ila, H. Junjappa, Synthesis, 556 (1988).

43. L.W. Singh, H. Ila, H. Junjappa, Synthesis, 89 (1988).

44. L.W. Singh, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I., 2365 (1988).

45. C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 163 (1985).

46. C.V. Asokan, S. Bhattacharjee, H. Ila, H. Junjappa, Synthesis, 281 (1988).

47. C.V. Asokan, H. Ila, H. Junjappa, Tetrahedron Lett.,26, 1087 (1985).

48. L.W. Singh, A.K. Gupta, H. Ila, H. Junjappa, Synthesis, 516 (1984).

49. L.W. Singh, H. Ila, H. Junjappa, Indian J. of Chemistry, 26B, 607 (1987).

50. B. Deb, C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 893 (1987).

51. B. Deb, C.V. Asokan, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 2111 (1988).

52. G.Singh, H. Ila, H. Junjappa, Tetrahedron Lett.,25, 5095 (1984).

53. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett.,1459 (1987).

54. M.P. Balu, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett.,27, 117 (1986).

55. A. Datta, H. Ila, H. Junjappa, Tetrahedron Lett.,29, 497 (1988).

56. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 6633 (1988).

57. M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett.,28, 3023 (1987).

58. M.P. Balu, D. Pooranchand, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 501 (1988).

59. A. Kumar, V. Aggarwal, H. Ila, H. Junjappa, Synthesis, 748 (1980).

60. V. Aggarwal, H. Ila, H. Junjappa, Synthesis, 65 (1982).

61. V. Aggarwal, G. Singh, H. Ila, H. Junjappa, Synthesis, 214 (1982).

62. S.S. Bhattacharjee, H. Ila, H. Junjappa, Synthesis, 410 (1983).

63. A. Rahman, H. Ila, H. Junjappa, Synthesis, 250 (1984).

64. A. Rahman, J.N. Vishwakarma, R.D. Yadav, H. Ila, H. Junjappa, Synthesis, 247 (1984).

65. A. Rahman, H. Ila, H. Junjappa, J. Chem. Soc. Chem. Commun., 430 (1984).

66. D. Pooranchand, H. Ila, H. Junjappa, Synthesis, 547 (1987).

67. J.N. Vishwakarma, A. Thomas, S. Apparao, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I, 169 (1988).

68. R.T. Chakrasali, H. Ila, H. Junjappa, Synthesis, 87 (1988).

69. A. Datta, H. Ila, H. Junjappa, Synthesis, 248 (1988).

70. A.K. Gupta, H. Ila, H. Junjappa, Synthesis, 284 (1988).

71. R.T. Chakrasali, H. Ila, H. Junjappa, Synthesis, 851 (1988).

72. V. Aggarwal, A. Kumar, H. Ila, H. Junjappa, Synthesis, 157 (1981).

73. V. Aggarwal, H. Ila, H. Junjappa, Synthesis, 147 (1983).

74. A. Thomas, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett.,000 (1989).

CHAPTER II

STUDIES ON LEAD TETRAACETATE OXIDATION OF α-OXOKETENE N,N- AND S,S-ACETALS*

II.1 LEAD TETRAACETATE OXIDATION OF α-OXOKETENE N,N-ACETALS

II.1.1 INTRODUCTION

Lead tetraacetate (LTA) is a versatile oxidising agent which has been widely used in organic synthesis. Its reactions generally involves the reduction of Pb(IV) to Pb(II) and the variety of pathways by which this can occur include both ionic and free radical mechanism. Acetoxylation, glycol cleavage, oxidative dehydrogenation, cyclisation, rearrangements and decarboxylation are some of the common reactions of LTA reported in the literature. Amines, amides and various nitrogen

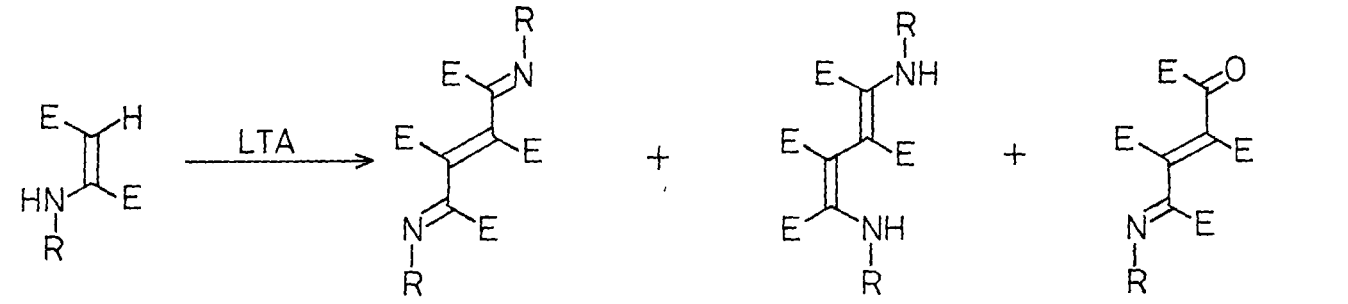
---

* A. Thomas, J.N. Vishwakarma, S. Apparao, H. Ila, H. Junjappa, Tetrahedron, 44, 1667 (1988).

compounds show a fascinating diversity of behaviour on oxidation with this reagent. Several excellent reviews are available dealing with these reactions[1-4]. Aylward has reviewed the reactions of organic nitrogen compounds in general and substituted azomethines with LTA[5]. Butler has reviewed LTA oxidation on specialized topics like oximes[6], hydrazones[7] and heteroallylic[8] systems. Also, a comparative study of the behaviour of isoelectronic Hg(II), Tl(III) and Pb(IV) acetates on organic nitrogen compounds[9] is also reviewed by the same author.

This section gives a brief account of the recent literature available on the LTA oxidation of imines, enamines and enaminoesters which are relevant to the present study. Extensive studies on the LTA oxidation of imines, enamines and compounds capable of undergoing imine-enamine tautomerism have been reported by Rindone and coworkers[10-14]. The oxidation in these reactions proceed by various pathways depending on the nature of the substrate.

The enamines derived from the Michel addition of aniline and dimethylacetylene dicarboxylate is reported to give the pyrrole esters[15]. Later Vernon and coworkers carried out detailed investigation[16,17] on these enamine esters with different alkyl and aryl substituents and also in different reaction conditions. Thus, they have isolated six types of products (2-7) depending on the nature of the substituent (R) on the nitrogen and the experimental conditions employed (Scheme 1). Oxidation of N-methyl and N-ethyl aminofumarate 1 by LTA in dichloromethane containing trifluoroacetic acid at room temperature afforded the corresponding pyrrole ester 5, pyridone 6 and pyrrolopyrrole 7.

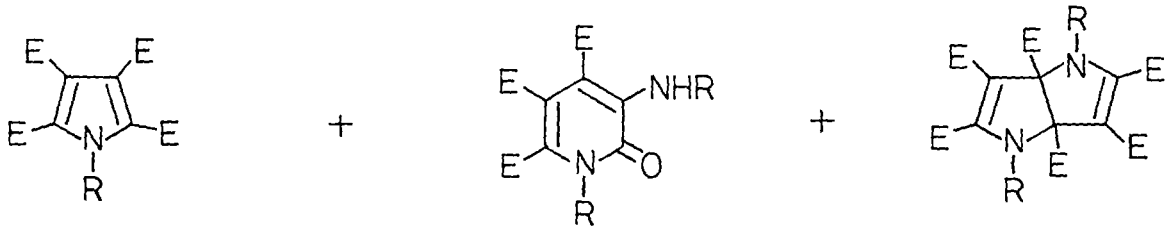


1

2, R=Pr^i, Bu^s, Bu^t
Cyclo-C_6H_{11}

3, R=Pr^i, Bu^t
Cyclo-C_6H_{11}

4, R=Cyclo-C_6H_{11}



5, R=Me, Et, Pr^i, C_6H_5
Cyclo-C_6H_{11}

6, R=Me, Et, Pr^i
Cyclo-C_6H_{11}

7, R=Me, Et

E=CO_2Me

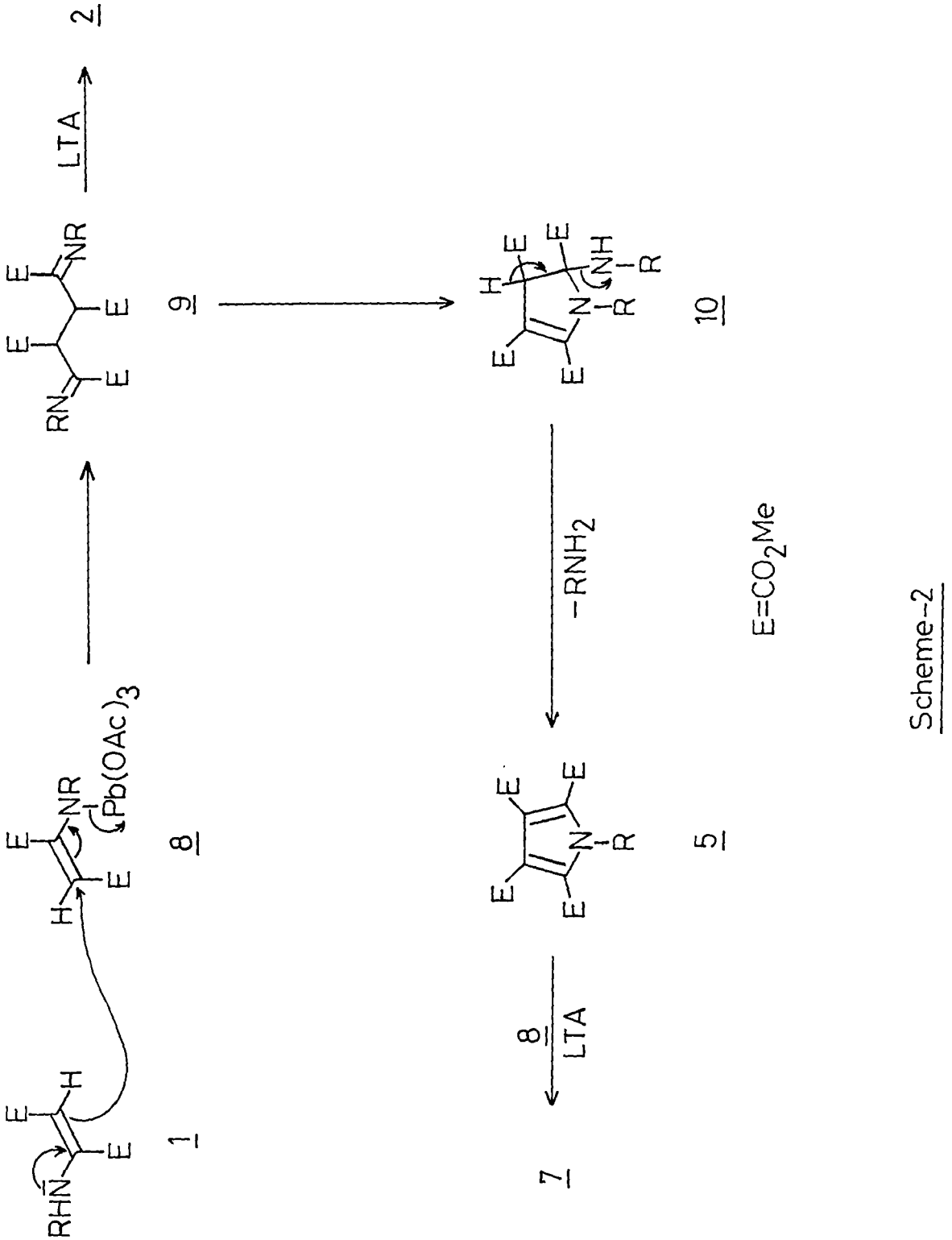
Scheme-1

Some of the other aminofumarates (R=Pr^i, cyclo-C_6H_{11}) also gave pyrrole ester 5 and pyridine 6 as shown in the scheme. Another set of dimeric heterocyclic polyesters were (2-4) formed when dimethyl N-cyclohexyl-aminofumarate was reacted with LTA in dichloromethane. Some other substituents (R=Pr^i, Bu^s, Bu^t) also gave dimeric oxidation products 2 and 3.

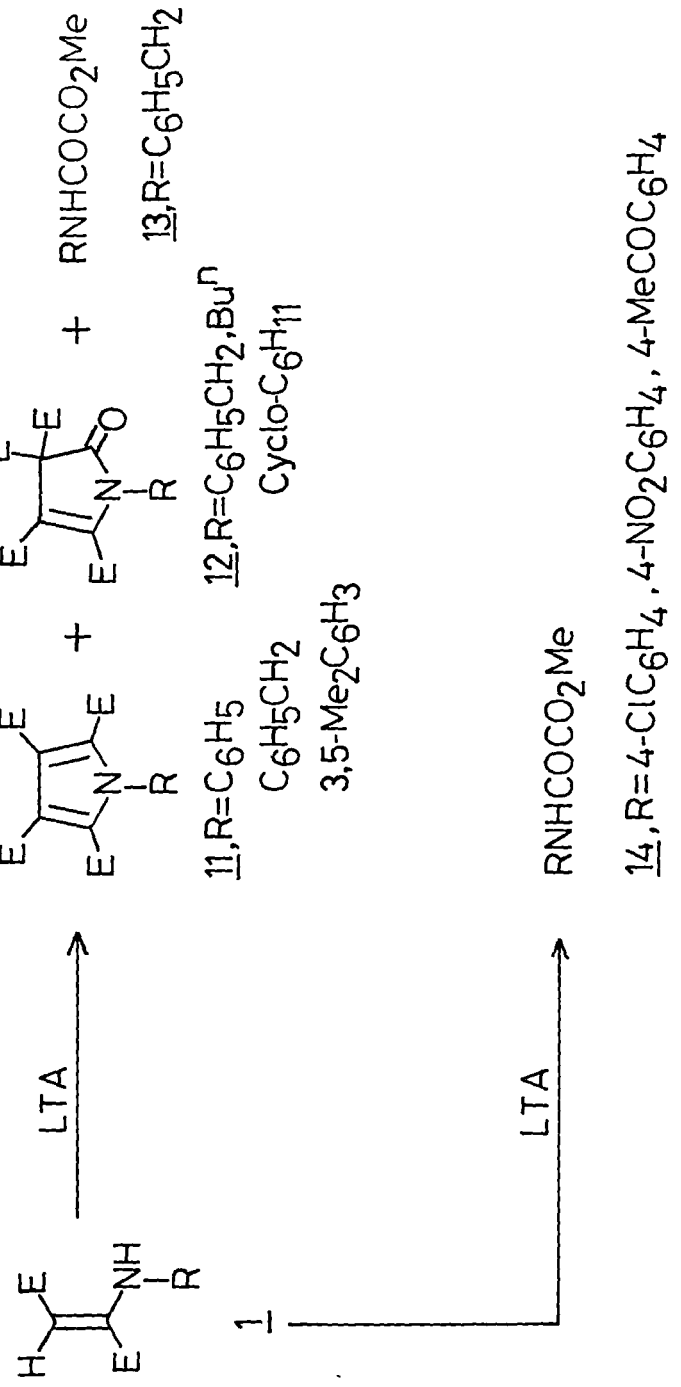
Enamines are ambident as nucleophiles and can react at the nitrogen or the β -carbon atom. The mechanism proposed for the transformation is through a plumbylated enamine adduct 8 which is attacked by the unchanged substrate 1 to give the diimine 9 which tautomerises to the bis-enamine 3. The bis-enamine is further oxidised by LTA to give the enediimine 2. The ketoester 4 is presumably formed from enediimine 2 by oxidative cleavage of one of the imino groups. The oxidative dimer 3 is the common intermediate for pyrrole ester 5 and pyridone 6 since they are independently isolated from dimer 3. The plumbylated enamine 8 couples with pyrrole 5 to give the pyrrolo[3,2-b]pyrrole 7 (Scheme 2).

Complimentary results are reported[18] by the same authors in an another publication. Oxidation of dimethyl N-benzylaminofumarate gave a mixture of pyrrole 11, pyrrolin-2-one 12 and oxamate 13. Analogus pyrroles and pyrrolinones were obtained from dimethyl 3,5-xylidinofumarate and cyclohexyl aminofumarate (Scheme 3). The anilinofumarates containing electron withdrawing substituents (R=4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$MeCOC_6H_4$) were less reactive towards LTA and gave only the corresponding oxanilate 14 in low yields (Scheme 3).

The authors have extended the same strategy for the synthesis of symmetrical dialkyl and diarylpyrroles[19]. The β-alkylamino crotonates 15 yielded the



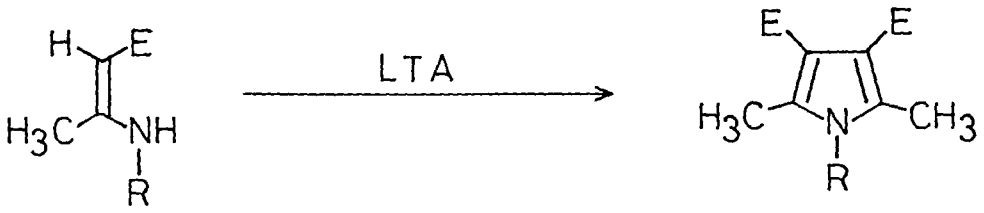
Scheme-2


LTA
LTA
1
11,R=C6H5
C6H5CH2
3,5-Me2C6H3
12,R=C6H5CH2,Bun
Cyclo-C6H11
13,R=C6H5CH2
RNHCOCO2Me
RNHCOCO2Me
14, R=4-ClC6H4, 4-NO2C6H4, 4-MeCOC6H4
E=CO2Me

Scheme-3

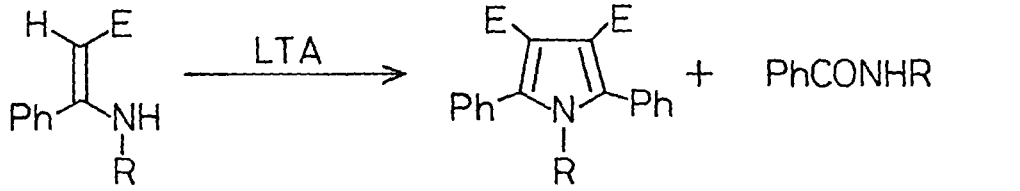
corresponding 2,5-dimethylpyrroles 16 in 20-40% yield on oxidation with LTA under nitrogen atmosphere (Scheme 4). The β-aminocinnamates 17 gave very low yields (10-20%) of the corresponding 2,5-diphenylpyrroles The low yields can be attributed to the steric hinderance due to bulky phenyl groups in 2,5-positions. However, the oxidation of 17 (R=$PhCH_2$, 4-ClC_6H_4) with LTA in air led to the corresponding amides 19 (Scheme 4).

The earlier studies[20] from this laboratory were undertaken to understand the behaviour of LTA towards ketene S,N-acetals derived from phenylacetonitriles, which posess typical enamine moiety. All the 3-anilino-3-methylthio-2-arylacrylonitriles 20 exist in the enamine form rather than the corresponding imino tautomer. Oxidation of these intermediates with LTA in CH_2Cl_2 gave products which are important from synthetic and mechanistic point of view. The course of the reaction is greatly dependant on the nature of the substituents in the aryl ring. The S,N-acetal 20 with electron donating groups in para position (20b-d) on oxidation with LTA in dichloromethane gave the iminoacetate 21b-d and the dimeric product 22a-c. The iminoacetate 21b-e were cyclised to the indoles 23b-e in the presence of borontrifluoride diethylether. However, the S,N-acetal 20a derived from phenylacetonitrile did not gave the dimeric product 22 but yielded the indole 23a directly along with the stable acetate 21a. In an analogus reaction condition, the 4-chloro S,N-acetal 20e gave the iminoacetate 21e,indole 23e and the dimeric product 22e in varying yields. The S,N-acetal 20d derived from trimethoxyphenylacetonitrile (R^1=R^2=R^3=OMe) gave the quinonemethide 24 in low yield besides other products (Scheme 5).



15 16, 20-40 %

15 16 R=Me, Bu^{i}, $C_6H_5CH_2$, Cyclo-C_7H_{13}, 4-ClC_6H_4

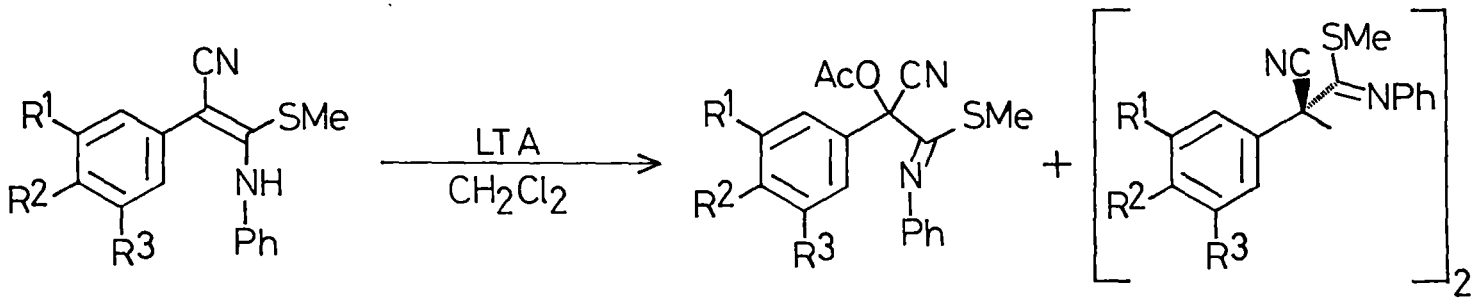


17 18 10-20 % 19, R=$C_6H_5CH_2$, 4-ClC_6H_4

17, 18, R=Me, i-Pr, $C_6H_5CH_2$, 4-ClC_6H_4

E=CO_2Me

Scheme-4

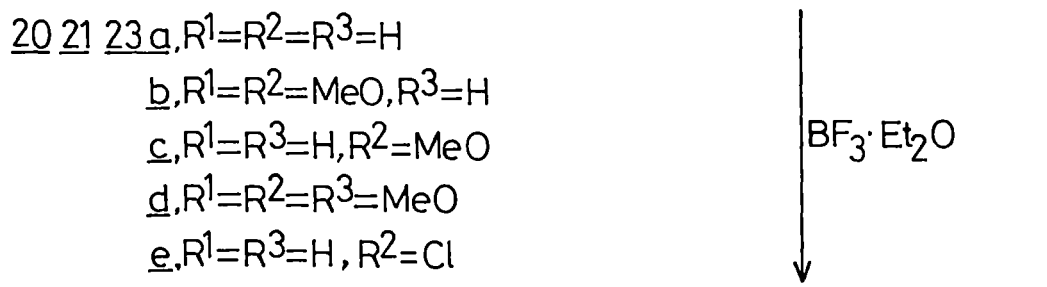


20

21a–e

22a, $R^1=R^2=MeO$, $R^3=H$
b, $R^1=R^3=H$, $R^2=MeO$
c, $R^1=R^2=R^3=MeO$
d, $R^1=R^3=H$, $R^2=Cl$

20 21 23a, $R^1=R^2=R^3=H$
b, $R^1=R^2=MeO$, $R^3=H$
c, $R^1=R^3=H$, $R^2=MeO$
d, $R^1=R^2=R^3=MeO$
e, $R^1=R^3=H$, $R^2=Cl$



23a–e

24 $R^1=R^2=OMe$

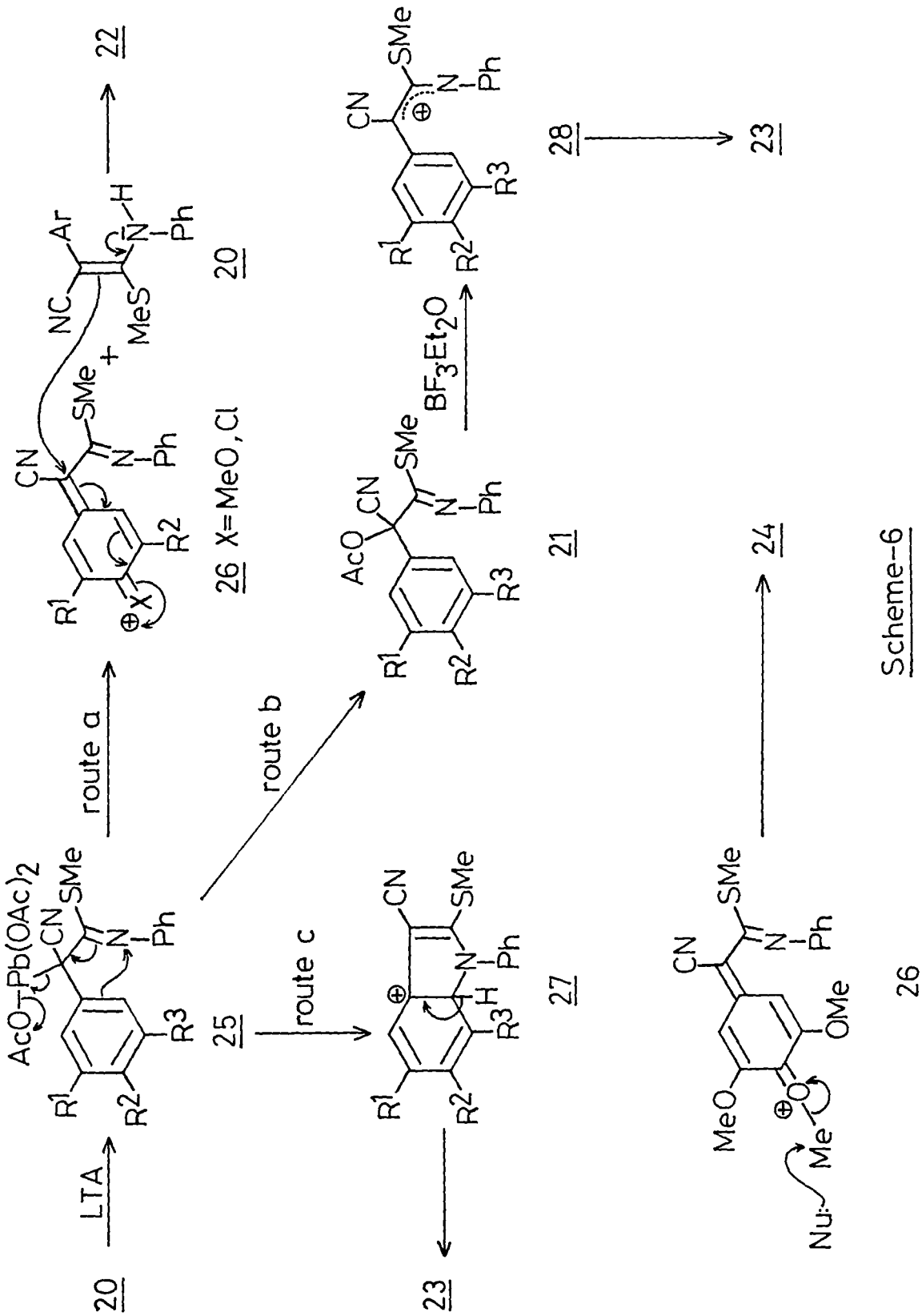
Scheme-5

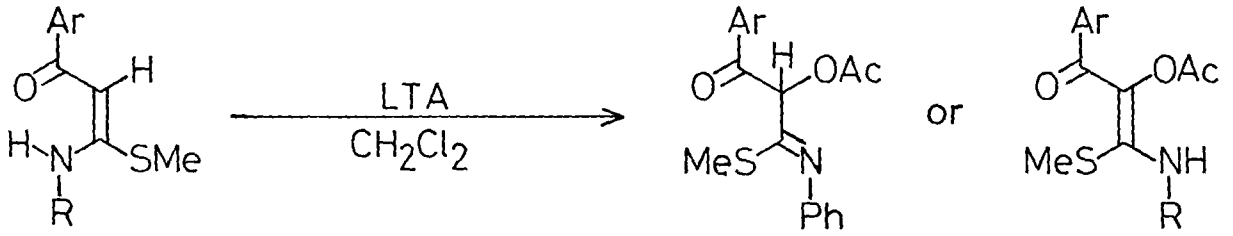
The probable mechanistic pathways for the formation of various products are shown in Scheme 6. The initially formed C-plumbylated adduct 25 appears to be the common intermediate from which compounds 21, 22 and 23 could be derived as shown in the Scheme. The quinonemethide 24 is plausibly formed by the demethylation of the iminoacetate 21 through the intermediate 26.

Although LTA oxidations of imine, enamine and enaminoesters are known in the literature, there have been no report on the oxidation of enaminones under similar reaction conditions. The S,N-acetals derived from acetophenones possess typical enaminone moiety and were considered of interest for LTA oxidation studies. Oxidation of some of these S,N-acetals have been reported[21] from this laboratory. The S,N-acetal 29 (R=Ph,$PhCH_2$) gave the α-acetoxy products 30 or 31a (Scheme 7). Oxidation of the corresponding S,N-ethylacetal with either one or two equivalents of LTA gave only the iminodiacetate 33 apparently derived by further oxidation of initially formed 31b. No cyclic or dimeric products were obtained from these reactions. The mechanism of formation of 30, 31a and 33 is shown in Scheme 7.

In continuation of these studies, it was considered of interest to see the behaviour of α-oxoketene N,N-acetals under LTA oxidation conditions. The N,N-acetals also possess an enaminone moiety with an additional anilino group attached to the β-carbon atom. Conceptually, this may lead to product range with different structural features and is also of interest to study the mechanism through which they are formed.

The previous studies[22] on these systems in this laboratory was only in the initial stage of its investigation and required further investigation


20
LTA
AcO-Pb(OAc)2
25
route a
route b
route c
22
26 X=MeO, Cl
20
21
BF3Et2O
28
23
27
23
24
26
Nu:
Me
Scheme-6



29a Ar=4-MeC_6H_4, R=C_6H_5

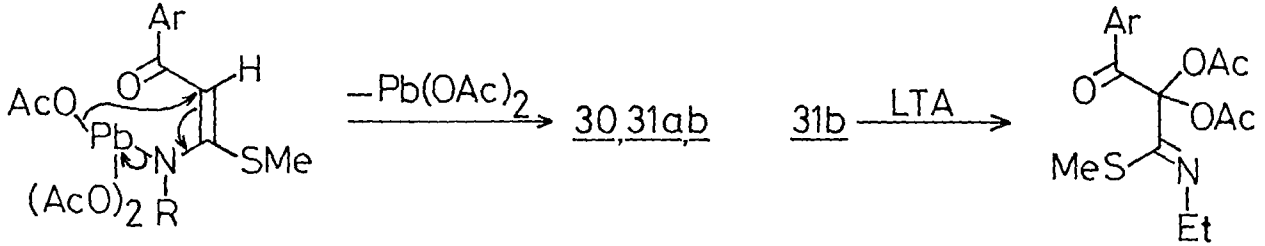
b Ar=4-MeC_6H_4, R=$C_6H_5CH_2$

c Ar=C_6H_5, R=Et

30 Ar=4-MeC_6H_4

31a Ar=4-MeC_6H_4, R=$C_6H_5CH_2$

b Ar=C_6H_5, R=Et



32

33

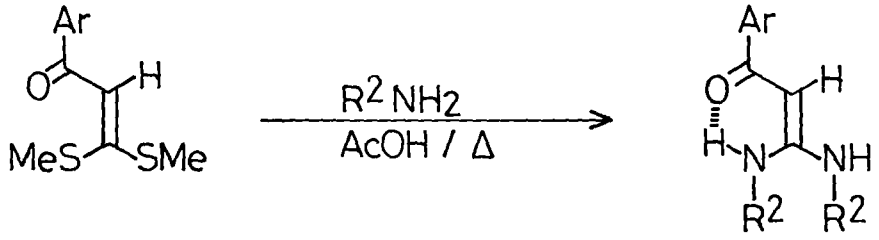
Scheme-7

to optimize the yields and to confirm the structures of products which were tentatively assigned. Only a few systems were studied and the structural assignment of the products isolated were subsequently found to be incorrect on the basis of ^{13}C n.m.r. spectral data. The new results of this studies have been discussed in the following section.

II.1.2 RESULTS AND DISCUSSION

The selected α-oxoketene N,N-acetals 35a-h required for the present study were prepared by the known reported procedure[23] by the direct displacement of both the thiomethyl groups in the α-oxoketene dithioacetal 34 by the respective arylamines (Scheme 8). The detailed procedure is given in the experimental section. The spectral and analytical data for all the previously unreported N,N-acetals 35a, 35c-h are also given in the experimental section. All the N,N-acetals 35a-h were found to exist in the intramolecular hydrogen bonded form 35 as displayed by the presence of low field signal between δ12.0-13.50 for the NH proton in their ^1H n.m.r. spectra. The other free NH proton appeared within the range of δ5.97-6.48 in ^1H n.m.r. spectra.

In a typical experiment, the N,N-acetal 35a was reacted with LTA in dichloromethane, work-up and column chromatography of the reaction mixture afforded a white crystalline solid (57%), which was characterised as 2-phenyl-3-(phenylimino)-5-(4-methylphenyl)-4-isoxazoline 37a on the basis of its spectral and analytical data. Thus 37a was analysed for $C_{22}H_{18}N_2O$ and exhibited molecular ion peak at m/z 326(100%) in its mass spectrum. Further structural proof for compound 37a was obtained from its ^1H and ^{13}C n.m.r. spectra. In its ^1H n.m.r. spectrum the signal due to CH_3 protons appeared at δ2.34. The signal due to the H-4 proton



34 35

35 a R^1= 4-MeC_6H_4 , R^2=C_6H_5

b R^1=R^2=C_6H_5

c R^1=C_6H_5 , R^2=4-BrC_6H_4

d R^1=C_6H_5 , R^2=3-MeC_6H_4

e R^1= C_6H_5 , R^2=4-MeC_6H_4

f R^1= C_6H_5 , R^2=2-MeC_6H_4

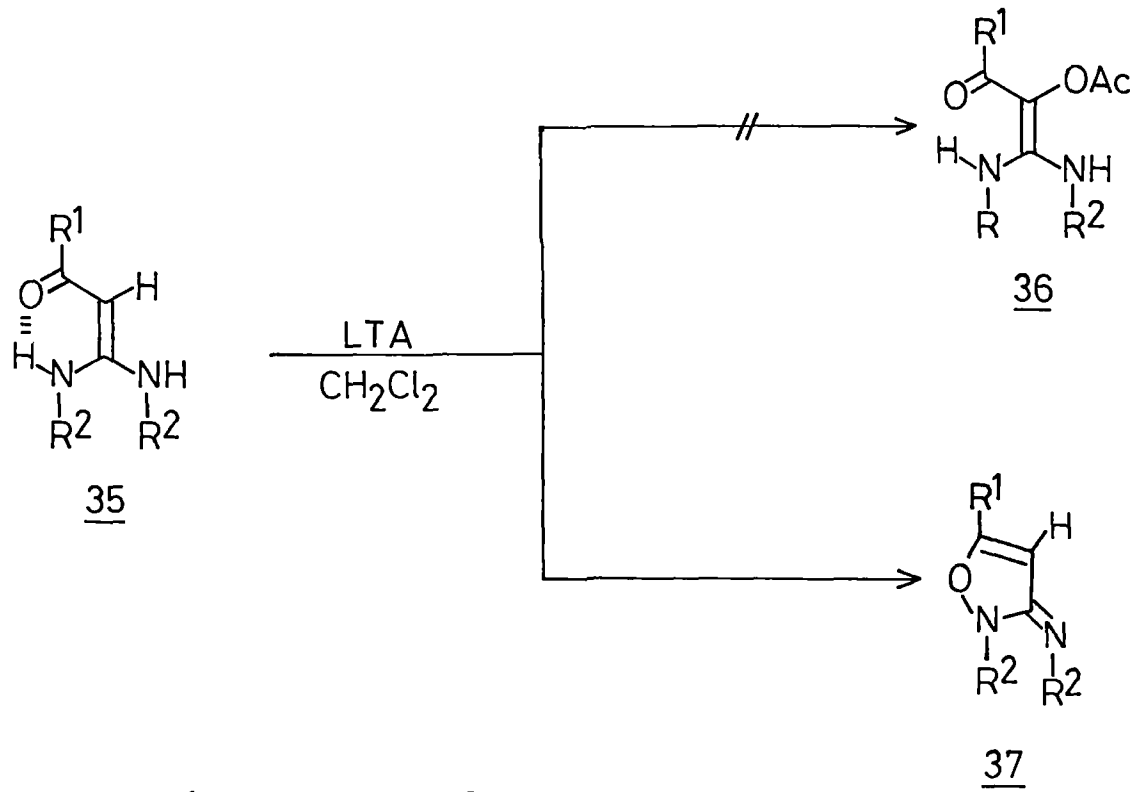
g R^1= 4-ClC_6H_4 , R^2=2-MeC_6H_4

h R^1= C_6H_4 , R^2=4-$MeOC_6H_4$

Scheme-8

of the isoxazoline ring was clearly separated from the aromatic protons and appeared at δ 6.92. The aromatic protons appeared as two multiplets between δ6.95-7.50(12H) and 7.74-7.90(2H). No NH proton could be traced in its ^{1}H n.m.r. spectrum. The ^{13}C n.m.r. spectrum of 37a showed clear absence of any carbonyl carbon signal in the range δ 180-200, while the signal due to the carbonyl carbon of the starting N,N-acetal 35a appeared at δ185.62. The other data in support of the assigned structure is given in the experimental. No other products including the α-acetoxy compound 36 could be isolated from the reaction in varying conditions. The other isoxazolines 37b-d were similarly obtained in 31-43% overall yield (Scheme 9). Considerable amount of tarry materials were formed in these reactions, even when the oxidations were carried out at lower temperature.

The reaction pathways were found to be not uniform in all the cases. The N,N-(4-methylphenyl)acetal 35e under similar reaction conditions afforded three more products besides the isoxazoline 37e (29%) along with small amounts of unreacted starting material 35e. These products were characterised as the indole 38a (9%), iminodiacetate 39 (8%) and the dimeric indole 40 (13%) on the basis of spectral and analytical data (Scheme 10). The compound 38a was analysed for molecular formula $C_{23}H_{20}N_2O$ and its mass spectrum exhibited molecular ion peak at m/z 340 (27%,M^+) and the base peak at 339 (100,M^+-1). Convincing structural proof was obtained from the ^{1}H and ^{13}C n.m.r. spectrum. Thus, in its ^{1}H n.m.r. spectrum the singlets at δ2.19(3H) and 2.36(3H) were assigned to the two methyl protons and the singlet at δ8.35 was assigned to indole NH proton. The aromatic protons appeared as a multiplet between δ6.57-7.66(12H).



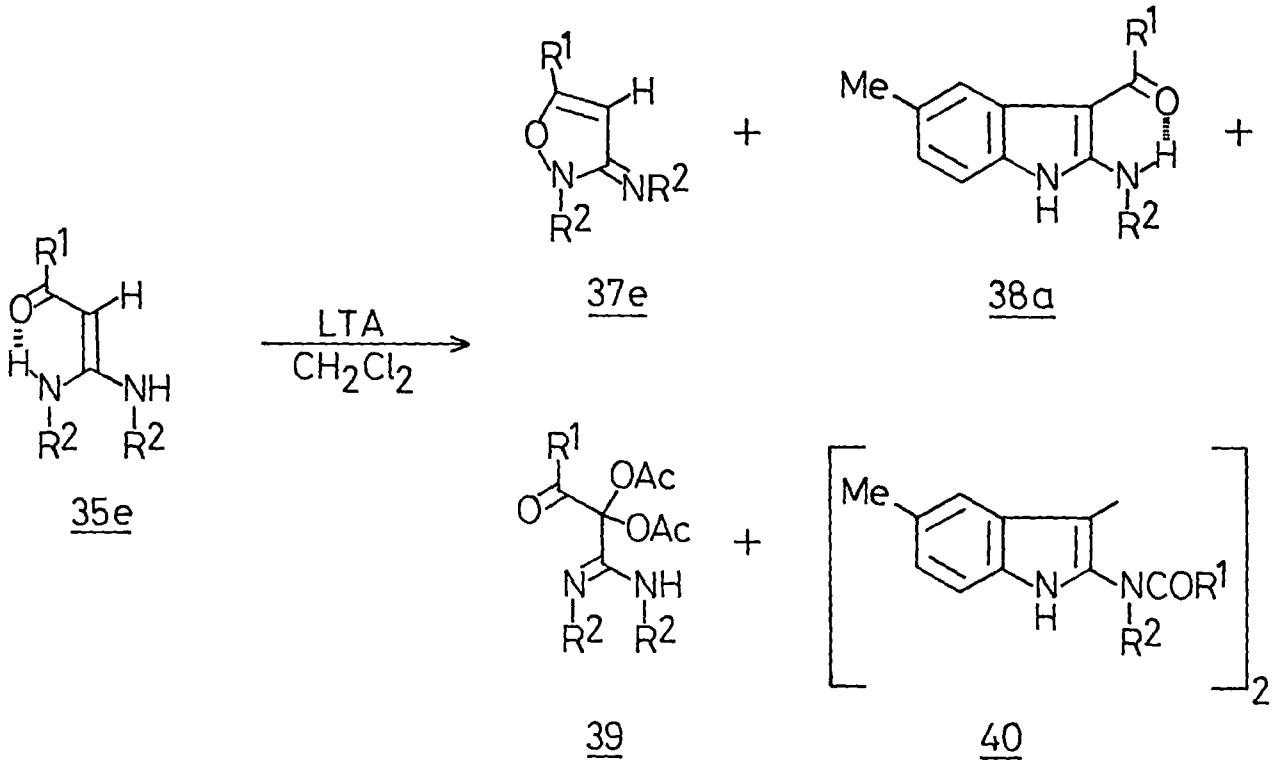
35,37 a $R^1 = 4\text{-}MeC_6H_4$, $R^2 = C_6H_5$

b $R^1 = R^2 = C_6H_5$

c $R^1 = C_6H_5$, $R^2 = 4\text{-}BrC_6H_4$

d $R^1 = C_6H_5$, $R^2 = 3\text{-}MeC_6H_4$

Scheme-9



35e,37e,38a,39,40 , $R^1=C_6H_5$; $R^2=4\text{-}MeC_6H_4$

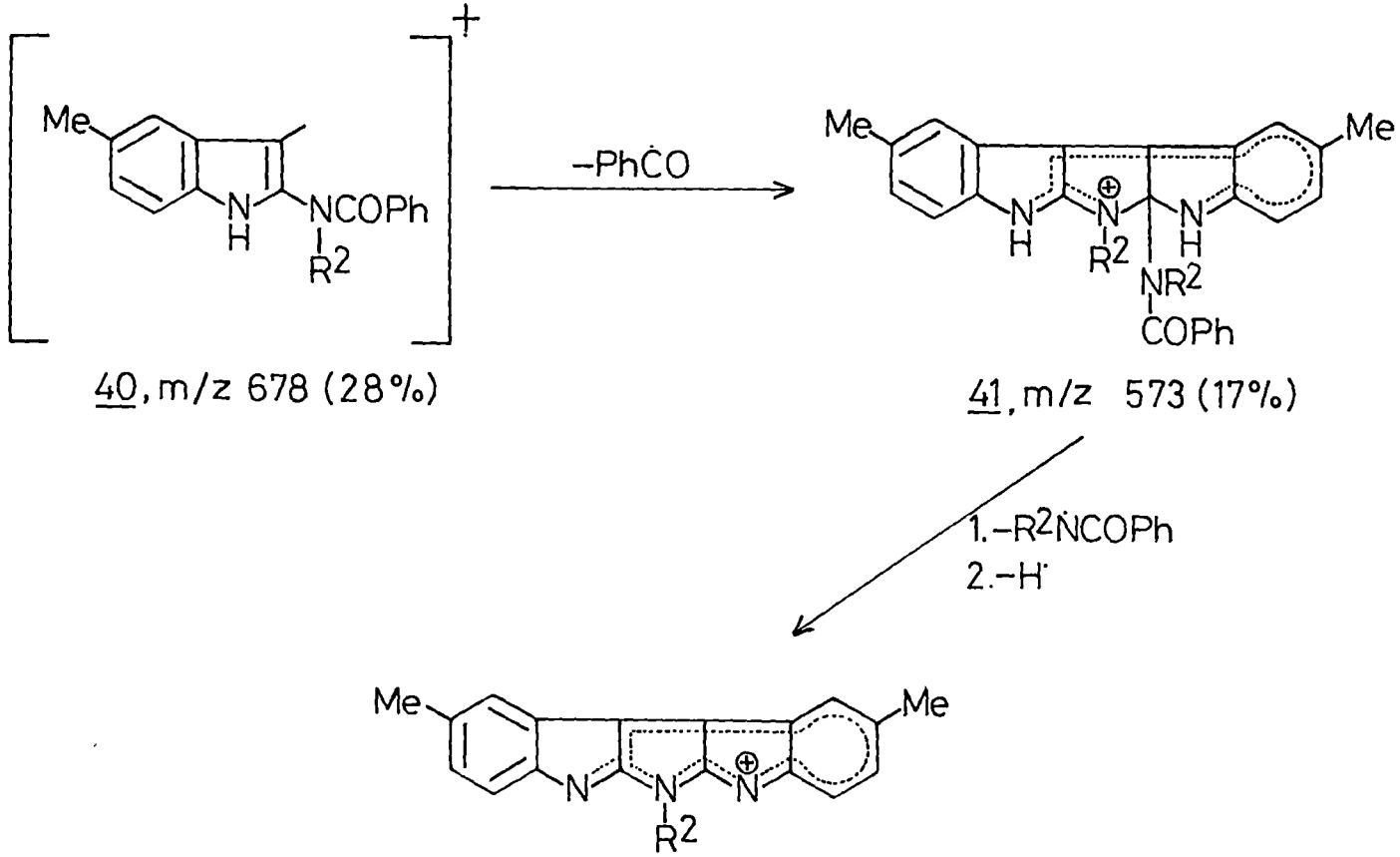
Scheme-10

The other hydrogen bonded NH appeared as a broad singlet at δ 10.69. The ^{13}C n.m.r. spectrum also fits in for the assigned structure. The carbonyl carbon appeared at δ190.69 and the other peak positions were also assigned and given in the experimental section. The structural assignment of the diacetate 39 was found to be relatively easy and is fully established on the basis of i.r., n.m.r. and analytical data.

The bisindole 40 was isolated as a high melting (315-316°C) colourless crystalline solid. Its ^{1}H and ^{13}C n.m.r. spectra were found to be similar to that of the indole 38a and showed it to be a symmetrical dimer. The presence of nine quaternary carbon signals and a peak at δ170 due to anilide carbonyl carbon in ^{13}C n.m.r. spectrum supports this assignment. Further proof was obtained from its mass spectral fragmentation (Scheme 11), which exhibit correct molecular ion peak at m/z 678 (28%), besides other peaks at m/z 573(17), 362(64) due to fragment ions 41 and 42.

The oxidation of N,N-(2-methylphenyl)acetals 35f and 35g under identical conditions gave the corresponding iminoisoxazolines 37f, 37g and the indoles 38b (27%), 38c (30%) in overall improved yields as compared to the N,N-acetal 37e (Scheme 12). The N,N-(4-methoxyphenyl)acetal 35h did not give any product in varying conditions and yielded only intractable tar.

A probable mechanism leading to the formation of various products is shown in Scheme 13. The N-plumbylated adduct 43 appears to be a common intermediate for the formation of isoxazolines 37 and indoles 38. Thus 43A is presumably attacked intramolecularly by carbonyl oxygen assisted by



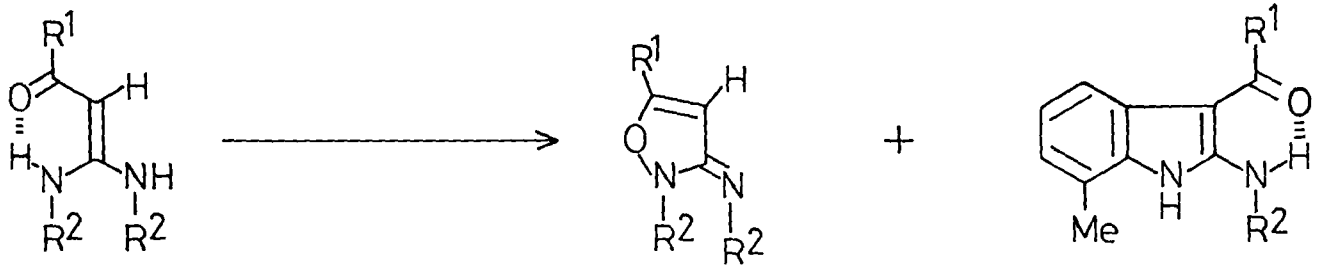
40, m/z 678 (28%)

41, m/z 573 (17%)

42, m/z 362 (64%)

40–42, R^2=4-MeC_6H_4

Scheme-11



35 f, g 37 f, g 38 b, c

35f, 37f, 38b $R^1 = C_6H_5$, $R^2 = 2\text{-}MeC_6H_4$

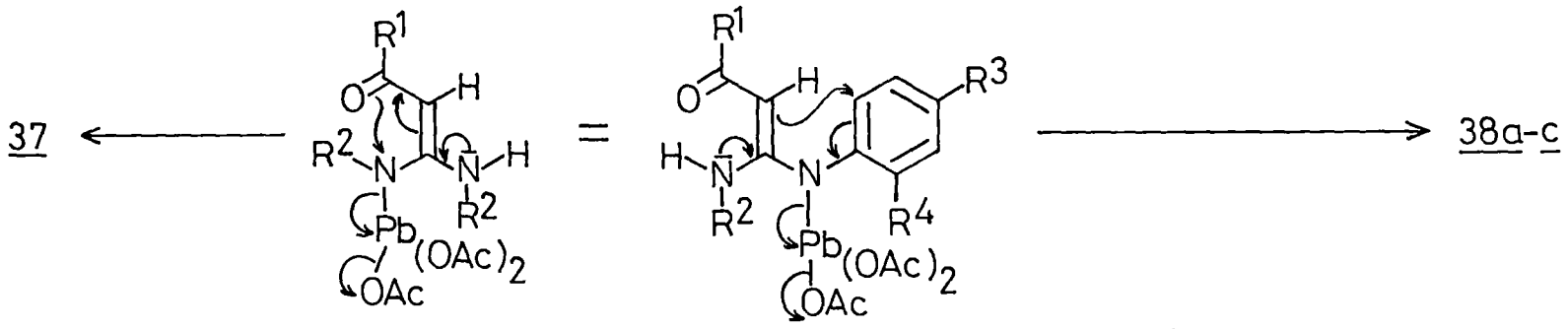
35g, 37g, 38c $R^1 = 4\text{-}ClC_6H_4$, $R^2 = 2\text{-}MeC_6H_4$

Scheme-12

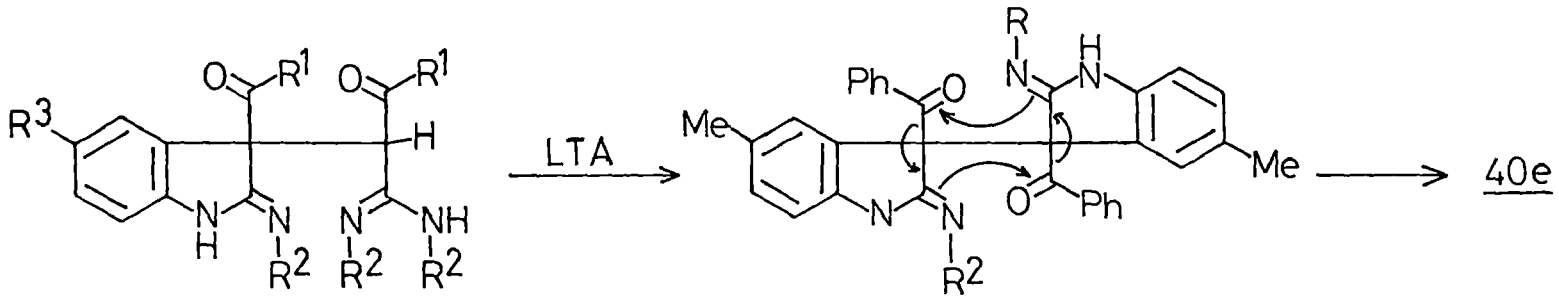
the lone pair of electrons of the other arylamino nitrogen leading to 3-aryliminoisoxazolines 37a-g. Alternatively, cyclization can take place through participation of the aromatic ring of one of the arylamino group of 43B yielding the indoles 38a-c . The overall increase in the yields of the oxidation products of 35f and 35g may be attributed to the steric crowding in the corresponding N-plumbylated adducts 43A or 43B. The dimer 40e appears to be formed either by the oxidative dimerisation of the indole 38a or by the nucleophilic attack of 38a on the N-plumbylated adduct 43A at the α-carbon atom leading to the intermediate 44. This intermediate can undergo further oxidative cyclization to give the intermediate 45, which on subsequent aromatization by intramolecular benzoyl group migration yields the indole dimer 40 (Scheme 13). The iminoacetate 39e is formed as a minor product by α-acetoxilation of 35e. In another reaction the oxidation of 35e was carried out with two equivalents of LTA under identical conditions, when the dimer 40 was formed in improved yield, while no starting N,N-acetal 35e was detected in the reaction mixture. This observation partially supports the proposed mechanism. The distinctly different behaviour of N,N-acetal 35e may be attributed to the presence of electron donating 4-methyl group in the arylamine moiety.

II.1.3 CONCLUSION

The above results have convincingly demonstrated the fascinating behaviour of N,N-acetals towards lead tetraacetate. Also the method offers an opportunity for the synthesis of molecules otherwise unattainable by the reported transformations. The substituents in the arylamino group plays a crucial role in determining the course of oxidation. Similar



43 A 43 B



44 45

Scheme–13

substituent effects were observed by Vernon and coworkers in their LTA oxidation studies of aminofumarates which are discussed in the introduction.

II.2 STUDIES ON LEAD TETRAACETATE OXIDATION OF α-OXOKETENE S,S-ACETALS

II.2.1 INTRODUCTION

While abundant literature is available for the LTA oxidation of organic nitrogen compounds, there have been a few examples dealing with the LTA oxidation of organic sulfur compounds. The present discussion summarises some of the relevant literature reports dealing with the LTA oxidation of organic sulfur compounds.

Thiols are highly reactive towards LTA and they are dimerised to the disulphides under mild conditions[24]. The dimerisation has been explained in terms of heterolysis of the specious $RS-Pb(OAc)_3$ to RS^+, OAC^- and $Pb(OAc)_2$ with subsequent attack by the cation on the parent thiol. Thioethers are oxidised by LTA to give the sulfoxide but other competing reactions are usually observed in the presence of oxidizable functional groups[25]. For example, dibenzyl sulfide was converted to the sulfoxide on treatment with LTA in acetic acid while prolonged reaction in benzene gave acetoxylation of the benzyl group. Aromatic and aliphatic disulfides with LTA in chloroform/methanol generally give the methylsulfinate esters[26-28]. Thiones are oxidised by LTA to give the oxothiocarbonyl compounds[29] or can undergo desulphurisation to give the corresponding carbonyl function[29], depending on the nature of the thione and the reaction conditions.

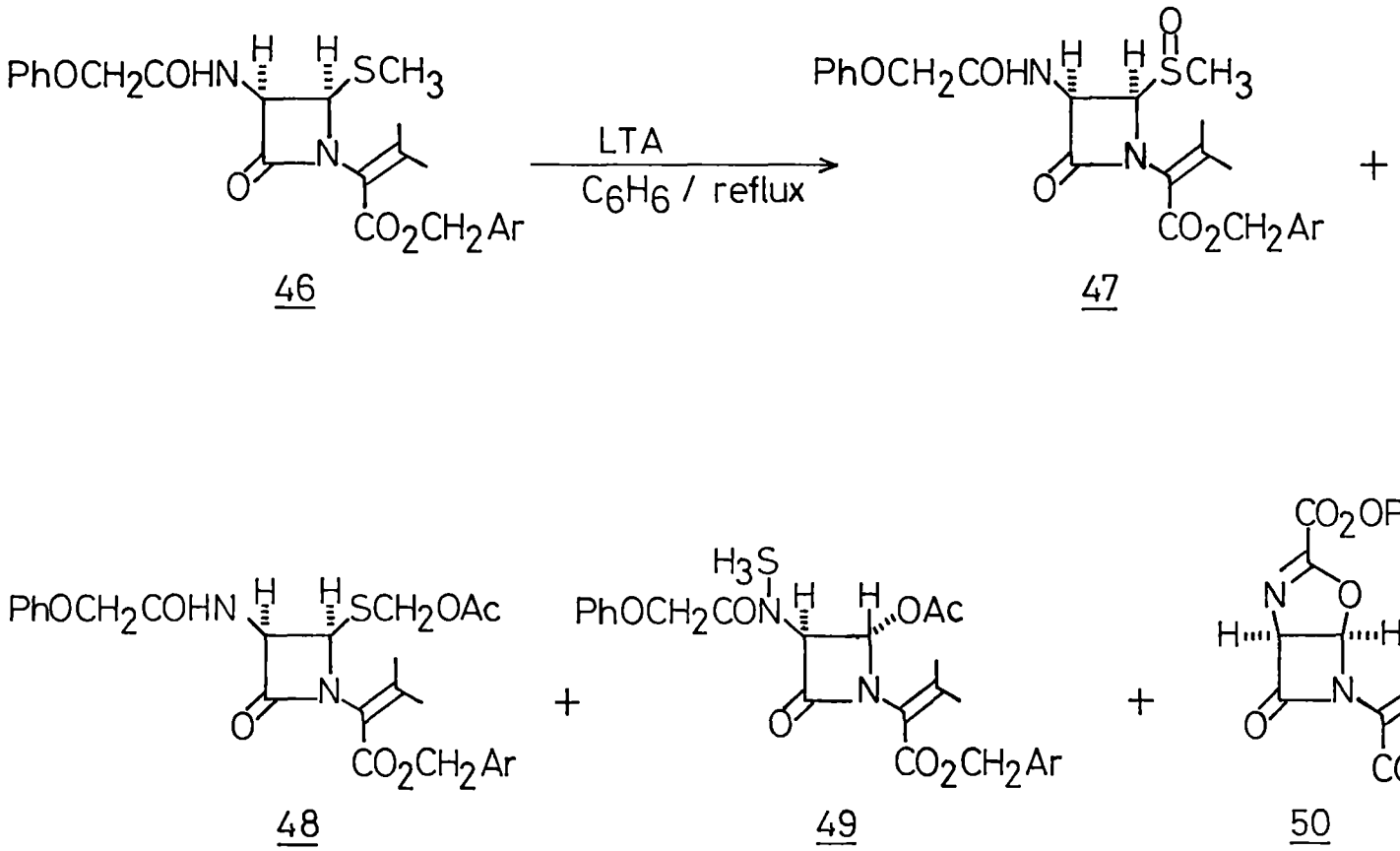
Another example related to the present study is the cleavage of dialkyl mercaptals by LTA[30]. The dialkylmercaptals of the aldehydo-sugar gave

the aldehyde diacetate and the dialkyl sulfide. This involves the acetolysis of the dialkylmercaptal to give the diacetate and alkyl-mercaptan R-SH, which being subsequently dimerised to the disulfide.

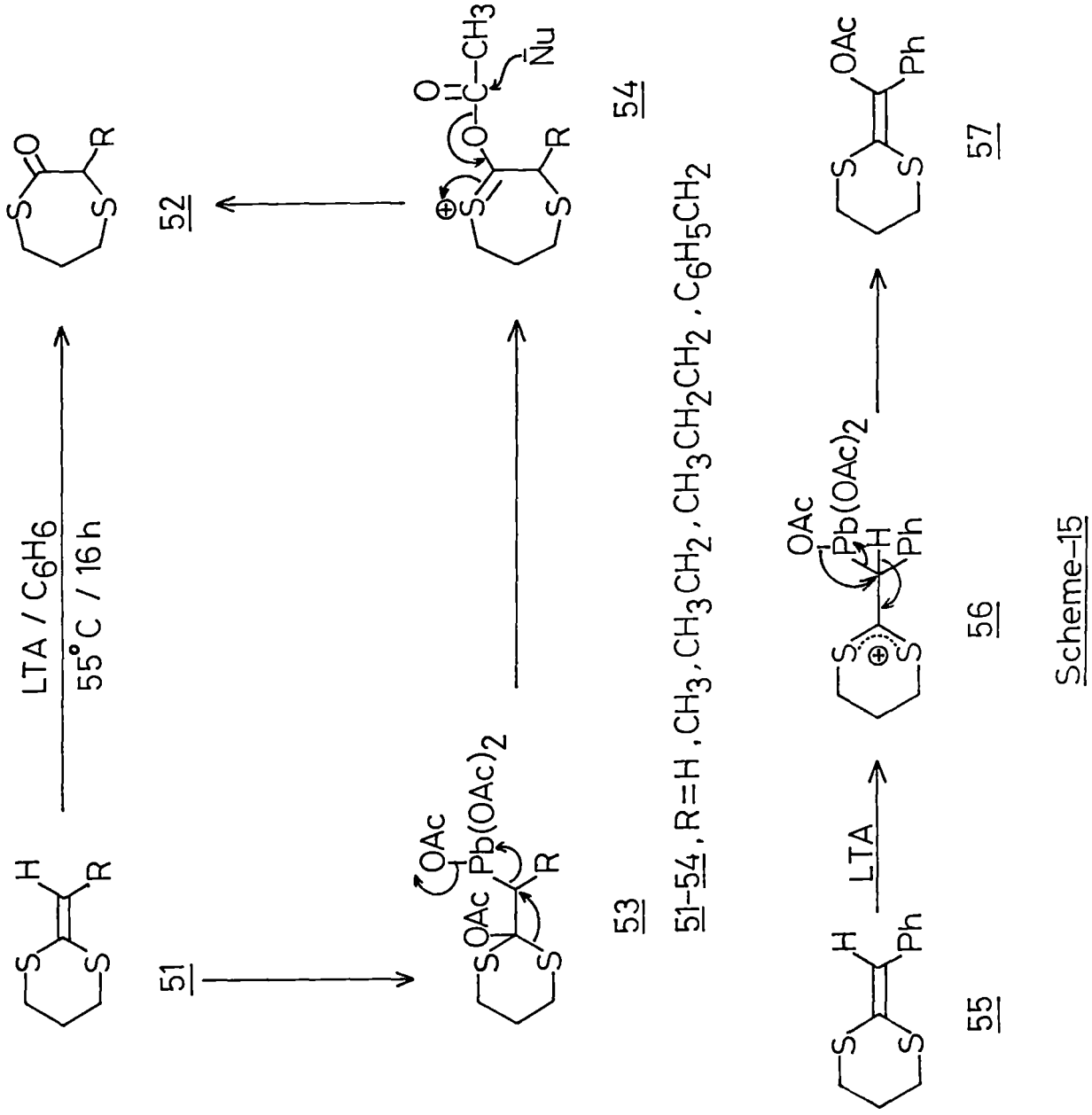
Nayler and coworkers have studied the LTA oxidation of 4-methylthio-azitidinone ester 46. They have shown that LTA attacks 4-methylthio azitidinone at the sulfur and adjacent carbon atoms leading to various products[31]. *Treatment of azitidinone 46 with LTA in refluxing benzene* for 15 minutes gave the products which were identified as sulfoxide 47, acetoxymethylthio azitidinone 48 formed by the acetoxylation of the alkyl sulfur group, the acetoxy N-methylthio compound 49 formed by the migration of the alkylthio group and the oxazoline 50 (Scheme 14).

Hiroi and Sato have studied the LTA oxidation of a few simple ketene dithioacetals i.e. 2-alkylidene and arylidene 1,3-dithianes 51 and 55[32]. Thus the 2-alkylidene 1,3-dithianes 51 on oxidation with LTA in benzene gave the 3-alkyl-1,4-dithiepan-2-ones 52 by an oxidative ring expansion reaction (Scheme 15). The reaction of 2-benzylidene-1,3-dithiane 55 did not provide the ring expanded compound, instead gave 2-(α-acetoxy-benzylidene)-1,3-dithiane 57. The mechanism for the formation of these products is also given in the same Scheme.

As illustrated by the limited number of examples available in the literature, the LTA oxidation of organic sulfur compound, leads to mixture of products depending on substrate structure and reaction conditions. The observed competing reactions in these cases makes the method synthetically less promising, obviously leading to limited number of studies in this direction.


PhOCH2COHN
SCH3
LTA
C6H6 / reflux
CO2CH2Ar
46
47
SCH2OAc
H3S
OAc
CO2OPh
48
49
50

Scheme–14


LTA / C6H6
55°C / 16 h
51
52
53
54
55
56
57
LTA
51-54, R=H, CH3, CH3CH2, CH3CH2CH2, C6H5CH2

Scheme-15

The α-oxoketene N,N-acetals as shown in earlier section gave interesting results on oxidation with LTA. This prompted investigation on its sulfur analogue i.e. α-oxoketene S,S-acetal under similar oxidation conditions. The results of this study is discussed in the following section.

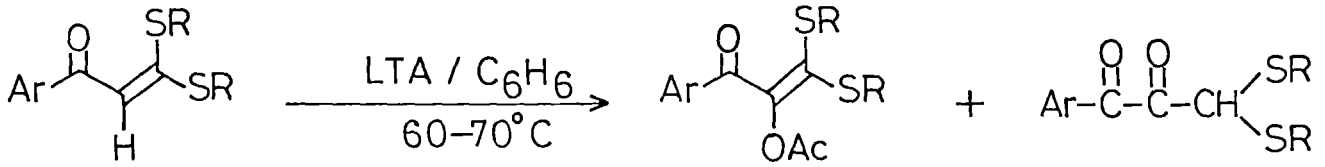
II.2.2 RESULTS AND DISCUSSION

The selected ketene dithioacetals 34a-e required in the present study were prepared according to the reported procedure[33] and is given in the experimental section. The cinnamoylketene dithioacetal 62 is also prepared by the reported procedure and is given in the experimental section of Chapter III. The references for the preparation of all these ketene dithioacetals are given in Chapter III. The structures of all dithioacetals 34a-e and 62 were confirmed by comparison of their spectral and analytical data with those of reported values.

The α-oxoketene S,S-acetal 34a-c remained unchanged in a reaction similar to that is described for N,N-acetals i.e. LTA in dichloromethane. In an optimized condition, when the α-oxoketene dithioacetal 34a was reacted with LTA in dry benzene at 60-70°C for 15 hrs. usual work-up and silica gel column chromatography afforded two products. These products were characterised as 2-acetoxy-3,3-bis(methylthio)-1-phenyl-2-propen-1-one 58a and 3,3-bis(methylthio)-1-phenyl-propane-1,2-dione 59a formed in 54 and 26% yields respectively (Scheme 16). The i.r. spectrum (neat) of compound 58a exhibited characteristic absorption bands at 1760(ester CO) and 1656 (ArCO) cm^{-1}. The ^1H n.m.r. spectrum of 58a displayed signals at δ2.14(3H,s,SCH_3), 2.22(3H,s,SCH_3), 2.43(3H,s,$COCH_3$), 7.37-7.72(3H, m, ArH) and 7.90-8.19(2H,m,ArH). The structure of this compound is confirmed

by its mass spectrum which exhibited molecular ion peak at m/z 282(3%) and the peak at 239(5%) was assigned for the fragment ion formed by the loss of CH_3CO group. The base peak appeared at m/z 105(100%) due to C_6H_5CO fragment. The compound also gave satisfactory elemental analysis. The diketodithioacetal 59a was isolated as a viscous brown liquid and its i.r. spectrum showed characteristic bands at 1670 and 1690 cm^{-1} due to two carbonyl groups. In its ^1H n.m.r., the signals due to the SCH_3 groups appeared as a singlet at δ2.05. The signal due to the proton on the saturated carbon with bis(methylthio) group was merged with the SCH_3 signals. The aromatic protons appeared as a multiplet between δ7.19-7.43(3H,m) and 7.56-8.10(2H,m). The compound also gave satisfactory elemental analysis. The reaction was found to be general and the other dithioacetals 43b-d similarly gave the acetate 58b-d in 52-56% and the dione 59b-d in 25-30% overall yields (Scheme 16). The structure of the diketodithioacetals were also established by the ^{13}C n.m.r. spectrum of the dione 59c, which exhibited peaks at δ13.66(SCH_3), 73.85(CH), 129.00, 130.08(CH,ArH), 132.01, 140.19(C-1' and C-4', ArH), 190.06(CO), 192.03(CO). Also, in the ^1H n.m.r. spectrum of compound 5d, the proton on the saturated carbon atom was clearly separated from the S-ethyl protons and appeared as a singlet at δ2.09, fully supporting the structural assignment.

The dithioacetal 34e prepared from acetone also gave the acetate 58e and the diketone 59e in 53 and 28% yields respectively (Scheme 16). The structures were confirmed by its analytical and spectral data. Although active methylene ketones are known to undergo α-acetoxylation[34], no α-acetoxylated compound 60 was formed in isolable quantity (Scheme 16).



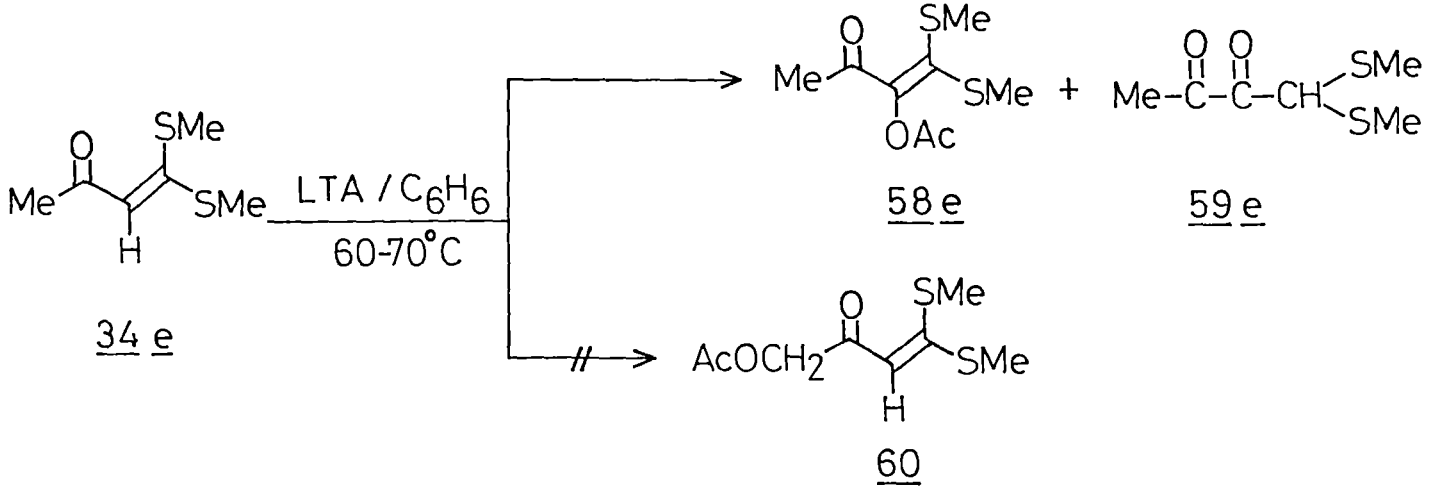
34 58 59

34, 58, 59 a Ar=C_6H_5, R=Me

b Ar=4-MeC_6H_4, R=Me

c Ar=4-ClC_6H_4, R=Me

d Ar=C_6H_5, R=Et



34 e 58 e 59 e 60

Scheme-16

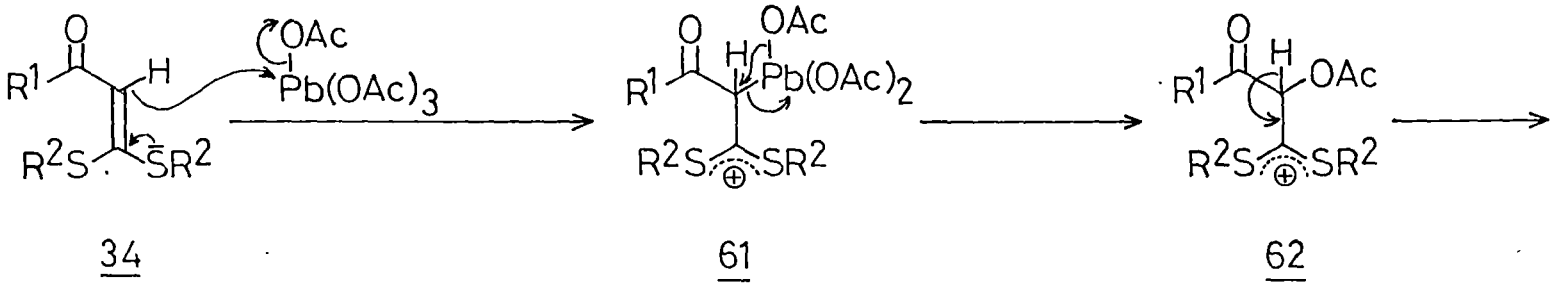
The probable mechanism for the overall transformation is given in Scheme 17. The sulfur assisted electrophilic attack of the Pb(IV) acetate on the double bond of dithioacetal 34 gives the C-plumbylated adduct 61 followed by acetate transfer gives the intermediate 62. This intermediate on proton loss gives the acetate 58. This acetate is cleaved to the diketone 59 through the intermediate 61.

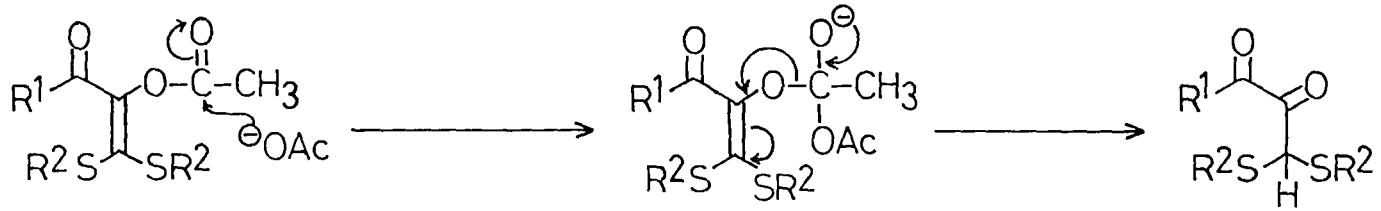
To examine the generality of the reaction, the cinnamoylketene dithioacetal 62 was subjected to LTA oxidation in the described conditions. The reaction afforded the acetate 63 and the diketone 64 in 31 and 53% yields respectively (Scheme 18). It is interesting to note that the styryl double bond is retained in the products and these intermediates can be used for the synthesis of functionalised olefins.

II.2.3 SUMMARY AND SCOPE OF THE REACTION

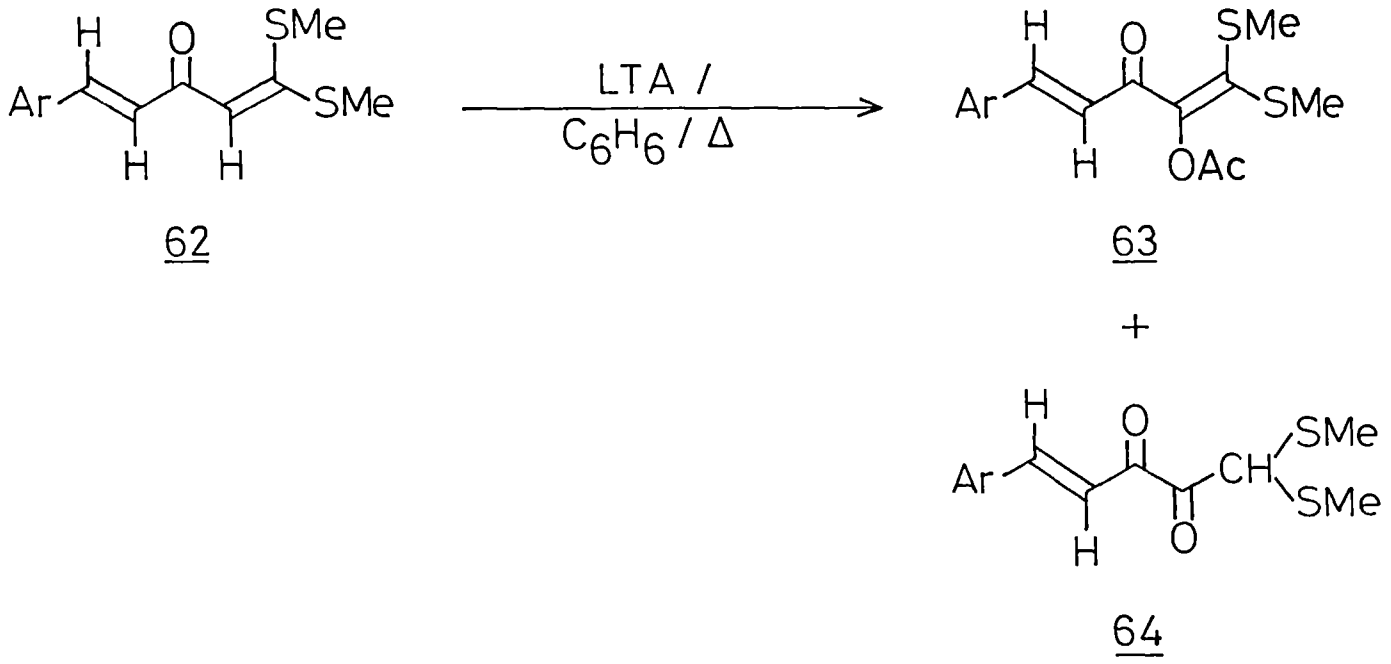
An attractive feature of the reaction is that the combined yield of the acetate and diketodithioacetal is excellent and the reaction is free from any other side reactions like thioacetal cleavage, sulfoxide formation and acetoxylation on the thiomethyl group as observed in the examples cited in the introduction of this section. Again, the acetate can be considered as the diketodithioacetal precursor, since it can be easily cleaved to the latter and the diketodithioacetal in turn is a masked α,β-diketoaldehyde precursor.

From the author's perspective, the dithioacetal moiety in diketodithioacetal compound can be converted into an acyl anion equivalent by deprotonation of the C-H proton. This can be alkylated or acylated and


R1
O
H
OAc
Pb(OAc)3
R2S
SR2
34
Pb(OAc)2
61
62


R1
O
O-C-CH3
OAc
R2S
SR2
58
61
59

Scheme-17



62

63

+

64

Scheme-18

subsequently dethioacetalized to the corresponding 1,2,3-trione or 1,2,3,4-tetraone. More work is in progress to realise these goals.

In conclusion, the method developed is of considerable synthetic importance and provides a two step route to diketoaldehyde precursors from active methyl ketones.

II.3 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 spectrometer in KBr unless specified. ^{1}H n.m.r. spectra were recorded on a Varian EM-390 (90 MHz) instrument in deutero-chloroform with tetramethylsilane as internal standard. Chemical shifts are expressed as δppm downfield from TMS. ^{13}C n.m.r. spectra were obtained on a Brucker WM-400 spectrometer. Mass spectra were recorded on Jel JMS D-300 spectrometer. Elemental analysis were obtained from Central Drug Research Institute, Lucknow, India.

Starting Materials

All ketones were available commercially and were purchased (Aldrich) and were used without purification. Aniline, o-toludine and m-toludine were distilled prior to use. p-Toludine, p-anisidine and p-bromoaniline were recrystallised (ethanol) before use. Reagent grade acetic acid and acetic anhydride were used for reactions. Dichloromethane was distilled over P_2O_5 and was stored over molecular sives (A°). Lead tetraacetate was prepared by reported procedure and was dried free of acetic acid prior to use.

General method for the preparation of α-oxoketene dithioacetals (34a-e):

A mixture of ketone (0.2 mol) and carbon disulphide (0.2 mol) was added dropwise to an ice cold and well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (200 ml) and the reaction mixture was allowed to stir at room temperature for 5-6 hrs. Acid free dimethyl sulphate (0.2 mol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stir at room temperature for 6-10 hr. The reaction mixture was poured over ammonium chloride solution (250 ml) and the layers were separated. The aqueous layer was extracted with benzene (100 ml) and the combined benzene extracts were washed with water (4x250 ml), dried (Na_2SO_4) and evaporated. Trituration of the oily residue with hexane gave the dithioacetals as yellow crystalline solid in good yields. The physical and spectral data were compared with that of reported values.

General method for the preparation of α-oxoketene N,N-acetals (35a-h) by displacement method:

A solution of the respective α-oxoketene S,S-acetal (0.01 mol) and the corresponding aniline (0.02 mol) in glacial acetic acid (25 ml) were refluxed with vigerous stirring for 6-12 hr. (monitored by t.l.c.). The major bulk of acetic acid was removed under reduced pressure and the residue was extracted into chloroform (50 ml). The chloroform layer was washed free of acetic acid, dried (Na_2SO_4) and evaporated to give crude N,N-acetals. The crude products were purified by column chromatography on silica gel using 5-10% ethylacetate in hexane as eluent. The physical and spectral data of the known α-oxoketene N,N-acetal 35b was compared with that of reported values[23] and the data of the unknown ones are reported below.

3,3-Bis(phenylamino)-1-(4-methylphenyl)-2-propen-1-one (35a) was isolated as yellow crystals (EtOAc-hexane), yield 72%; m.p. 156-157°C; ν_{max} 3244-3432, 1629, 1623 cm^{-1}; δ_H 2.32(3H,s,CH_3), 5.60(1H,s,vinylic), 6.38(1H, brs,NH), 6.62-7.51(12H,m,ArH), 7.52-7.85(2H,d,A_2B_2,ArH), 13.34(1H,brs, NH); δ_C 20.90(CH_3), 78.3(=CH), 123.96, 124.86, 126.00, 126.89, 128.05, 128.90, 129.51, 130.00(CH,ArH), 136.49, 137.40, 138.08, 139.94(quaternary C,ArH), 157.97(=CN_2), 185.62(CO). (Found: C,80.71; H,6.32; N,8.82. $C_{22}H_{20}N_2O$ requires: C,80.46; H,6.14; N,8.53%).

3,3-Bis(4-bromophenylamino)-1-phenyl-2-propen-1-one (35c) was isolated as yellow crystals (EtOAc-hexane), yield 74%; m.p. 172-173°C; ν_{max} 3215-3012, 1602 cm^{-1}; δ_H 5.55(1H,s,vinylic), 6.40(1H,brs,NH), 6.92-7.84(13H, m,ArH), 13.25(1H,brs,NH). (Found: C,53.67; H,3.71; N,6.22. $C_{21}H_{16}Br_2N_2O$ requires: C,53.42; H,3.42. N,5.93%).

3,3-Bis(3-methylphenylamino)-1-phenyl-2-propen-1-one (35d) was isolated as pale yellow crystals (EtOAc-hexane), yield 70%; m.p. 127-128°C; ν_{max} 3180, 3030, 1580 cm^{-1}; δ_H 2.33(6H,s,CH_3), 5.53(1H,s,vinylic), 6.48(1H,brs,NH), 6.90-7.48(11H,m,ArH), 7.66-7.86(2H,m,ArH), 13.37(1H, brs,NH). (Found: C,80.41; H,6.68; N,8.42. $C_{23}H_{22}N_2O$ requires: C,80.67; H,6.48; N,8.18%); m/z 342(19%,M^+), 236(62).

3,3-Bis(4-methylphenylamino)-1-phenyl-2-propen-1-one (35e) was isolated as yellow crystals (EtOAc-hexane), yield 76%; m.p. 132-133°C; ν_{max} 3243-3170, 1610 cm^{-1}; δ_H 2.26(3H,s,CH_3), 2.30(3H,s,CH_3), 5.39(1H,s,vinylic), 6.36(1H,brs,NH), 6.80-7.39(11H,m,ArH), 7.50-7.71(2H,m,ArH), 13.22(1H, brs,NH). (Found: C,80.39; H,6.62; N,8.40. $C_{23}H_{22}N_2O$ requires: C,80.67; H,6.48; N,8.18%).

3,3-Bis(2-methylphenylamino)-1-phenyl-2-propen-1-one (35f) was isolated as pale yellow crystals (EtOAc-hexane), yield 66%; m.p. 131-132°C; ν_{max} 3434, 3347, 1575, 1545 cm^{-1}; δ_H 2.23(3H,s,CH_3), 2.48(3H,s,CH_3), 5.26(1H,s,vinylic), 5.97(1H,s,NH), 7.13-7.40(11H,m,ArH), 7.66-7.48(2H, m,ArH), 13.25(1H,brs,NH). (Found: C,80.83; H,6.26; N,8.39. $C_{23}H_{22}N_2O$ requires: C,80.67; H,6.48; N,8.18%); m/z 342(12%,M^+), 236(37).

3,3-Bis(2-methylphenylamino)-1-(4-chlorophenyl)-2-propen-1-one (35g) was isolated as pale yellow crystals (EtOAc-hexane), yield 68%; m.p. 132-133°C; ν_{max} 3330-3040, 1575 cm^{-1}; δ_H 2.23(3H,s,CH_3), 2.47(3H,s,CH_3), 5.16(1H,s, vinylic), 5.98(1H,brs,NH), 7.10-7.37(11H,m,ArH), 7.55-7.66(2H,m,ArH), 13.18(1H,s,NH). (Found: C,73.54; H,5.90; N,7.71. $C_{23}H_{21}ClN_2O$ requires: C,73.30; H,5.62; N,7.43%); m/z 378(4%), 376(17,M^+), 272(11), 270(31).

3,3-Bis(4-methoxyphenylamino)-1-phenyl-2-propen-1-one (35h)was isolated as yellow crystals (EtOAc-hexane), yield 69%; m.p. 128-129°C; ν_{max} 3310, 3112, 1592 cm^{-1}; δ_H 3.79(6H,s,OCH_3), 5.34(1H,s,vinylic), 6.15(1H,brs,NH), 6.76-7.40(11H,m,ArH), 7.53-7.80(2H,m,ArH), 13.30(1H,brs,NH). (Found: C,73.51; H,5.70; N,7.72. $C_{23}H_{22}N_2O_3$ requires: C,73.78; H,5.92; N,7.48%).

General procedure for LTA oxidation of N,N-acetals (35a-h):

To a stirred and cooled (-10° to -15°C) suspension of lead tetraacetate (2.50g, 5.6 mmol) in dichloromethane (80 ml), the N,N-acetal (5 mmol) in dichloromethane (25 ml) was added during 5 minutes under nitrogen atmosphere. The reaction mixture was brought to room temperature during 0.5 hr. and further stirred for 2.5 hr. The precipitated lead diacetate was removed by filteration and the filterate was washed with water (2x200 ml),

dried (Na_2SO_4) and evaporated to give the crude products which were further purified by silica gel column chromatography using hexane-ethylacetate as eluent (20:1).

2-Phenyl-3-(phenylimino)-5-(4-methylphenyl)-4-isoxazoline (37a) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 57%; m.p. 107°C; ν_{max} 1681, 1658 cm^{-1}; δ_H 2.34(3H,s,CH_3); 6.92(1H,s,H-4), 6.95-7.50(12H, m,ArH), 7.74-7.90(2H,m,ArH), δ_C 21.22(CH_3), 108.68(d,C-4), 121.42, 122.22, 122.76, 123.34, 125.56, 128.64, 129.02, 129.39(CH,ArH), 124.38, 137.76, 137.96, 140.31(C-1' and C-4' of aryl), 146.30(C-4), 147.09(C-3). (Found: C,81.33; H,5.84; N,8.83. $C_{22}H_{18}N_2O$ requires: C,80.96; H,5.56; N,8.58%); m/z 326(100%,M^+).

2,5-Diphenyl-3-(phenylimino)-4-isoxazoline (37b) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 31%; m.p. 98°C; ν_{max} 1676, 1595 cm^{-1}; δ_H 7.10(1H,s,H-4), 7.13-7.69(13H,m,ArH), 7.70-8.15(2H,m,ArH); δ_C 109.58 (d,C-4), 121.66, 122.42, 122.93, 123.47, 125.68, 128.04, 128.82, 128.85, 129.16(CH, aromatic), 127.38, 136.97, 140.25(C-1' of phenyl), 146.56(C-5), 147.13(C-3). (Found: C,80.47; H,5.31; N,9.17. $C_{21}H_{16}N_2O$ requires: C,80.75; H,5.16; N,8.97%); m/z 312(100%,M^+).

2-(4-Bromophenyl)-3-(4-bromophenylimino)-5-phenyl-4-isoxazoline (37c) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 43%; m.p. 189-190°C; ν_{max} 1676, 1602 cm^{-1}; δ_H 7.11(1H,s,H-4), 7.16-7.58(11H,m, ArH), 7.65-7.71(2H,d,A_2B_2,ArH). (Found: C,53.92; H,3.21; N,6.28. $C_{21}H_{14}Br_2N_2O$ requires: C,53.65; H, 3.00; H,5.96%); m/z 472(49%), 470(99,M^+).

2-(3-Methylphenyl)-3-(3-methylphenylimino)-5-phenyl-4-isoxazoline (37d) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 43%; m.p.129°C;

ν_{max} 1670, 1590, 1578 cm^{-1}; δ_H 2.33(3H,s,CH_3), 2.36(3H,s,CH_3), 7.06 (1H,s,H-4), 6.73-7.45(11H,m,ArH), 7.48-7.63(2H,m,ArH). (Found: C,80.86; H,6.27; N,8.51. $C_{23}H_{20}N_2O$ requires: C,80.15; H,5.92; N,8.23%); m/z 340 (100%,M^+).

Oxidation of N,N-acetal (35e) according to the general procedure followed by column chromatography with increasing amounts of ethylacetate in hexane gave four products and the order of data of products described below is same as the elution order.

2-(4-Methylphenyl)-3-(4-methylphenylimino)-5-phenyl-4-isoxazoline (37e) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 29%; m.p. 136°C; ν_{max} 1666,1601 cm^{-1}; δ_H 2.29(6H,s,CH_3), 7.01(1H,s,H-4), 7.06-7.72 (13H,m,ArH). (Found: C,81.33; H,6.27; N,8.37. $C_{23}H_{20}N_2O$ requires: C,81.15; H,5.92; N,8.23%); m/z 340(100%,M^+).

N,N'-Bis(4-methylphenyl)-2,2-diacetoxy-3-oxo-3-phenylpropanamidine (39) was isolated as colourless solid (CH_2Cl_2-hexane), yield 8%; m.p. 165-166°C; ν_{max} 3432(br), 1778, 1748(ester CO), 1691(ArCO) cm^{-1}; δ_H 1.46 (3H,s,CH_3), 2.13(3H,s,CH_3), 2.29(3H,s,$COCH_3$), 2.30(3H,s,$COCH_3$), 6.83 (1H,s,NH), 7.01-7.72(13H,m,ArH). (Found: C,70.98; H,6.02; N,6.39. $C_{27}H_{26}N_2O_5$ requires: C,70.73; H,5.73; N,6.11%).

3-Benzoyl-5-methyl-2-(4-methylphenylamino)indole (38a) was isolated as yellow crystals (CH_2Cl_2-hexane), yield 10%; m.p. 171-172°C; ν_{max} 3490, 3300, 3160, 1624, 1602 cm^{-1}; δ_H 2.19(3H,s,CH_3), 2.36(3H,s,CH_3), 6.57-7.66(12H,m,ArH), 8.35(1H,s,indole NH), 10.69(1H,s,NH); δ_C 21.11(CH_3), 21.28(CH_3), 97.48(s,C-3), 109.82(d,C-7), 119.36, 121.58, 122.27, 122.50, 127.67, 130.12, 130.69(CH,ArH,indole C-4 and C-6), 128.79(s,C-8), 130.78,

130.98, 135.34(s,C-5), C-1' of benzoyl, C-4' of 4-$CH_3C_6H_4NH$), 135.44 (s,C-9), 142.26(s,C-1' of 4-$CH_3C_6H_4NH$), 152.71(s,C-2), 190.69(s,CO). (Found: C,81.37; H,6.28; N,8.50. $C_{23}H_{20}N_2O$ requires: C,81.51; H,5.92; N,8.23%); m/z 340(27%,M^+), 339(100), 338(93).

2,2'-Bis[N-benzoyl-N-(4-methylphenyl)amino]-5,5'-dimethyl-3,3'-biindole (40) was isolated as colourless crystals (EtOAc-hexane), yield 13%; m.p. 315-316°C(d); ν_{max} 3280(NH), 1642(anilidine CO) cm^{-1}; δ_H 1.97 (6H,s,CH_3), 2.12(6H,s,CH_3), 6.25-7.36(22H,m,ArH), 8.44(2H,brs,indole NH); δ_C (DMSO-d_6), 20.21, 21.05(CH_3), 101.53(s,C-3), 110.54(d,C-7), 119.20, 122.89, 126.32, 126.64, 127.44, 128.19, 128.47(d,CH,ArH and indole C-4 and C-6), 127.68(s,C-8), 129.49, 131.57, 133.82(s,C-5), C-1' of benzoyl, C-4' of 4-$CH_3C_6H_4NH$), 134.69(C-1' of 4-$CH_3C_6H_4NH$), 136.03(C-9), 139.46 (C-2), 170.70(NCO). (Found: C,81.62; H,5.91; N,8.53. $C_{46}H_{38}N_4O_2$ requires: C,81.39; H,5.64; N,8.25%); m/z 678(28%,M^+), 573(17), 362(64).

Oxidation of N,N-acetal (35f and 35g)by the general procedure followed by column chromatography gave the corresponding isoxazoline and the indole. The data is given below.

2-(2-Methylphenyl)-3-(2-methylphenylimino)-5-phenyl-4-isoxazoline (37f) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 43%; m.p. 130-131°C; ν_{max} 1677, 1592 cm^{-1}; δ_H 2.20(3H,s,CH_3), 2.43(3H,s,CH_3), 6.84(1H,s,H-4), 6.88-6.94(1H,m,ArH), 7.11-7.44(12H,m,ArH); δ_C 18.18, 18.42(CH_3), 112.13(d,C-4), 122.11, 122.18, 122.59, 125.96, 126.89, 127.46, 127.64, 128.63, 128.72, 130.02, 131.32(CH,ArH), 127.59, 131.38, 135.51(C-1' of phenyl, C-2' of 2-$CH_3C_6H_4NH$), 135.91, 139.89(C-1' of 2-$CH_3C_6H_4NH$), 145.44(C-5), 147.55(C-3). (Found: C,80.89; H,6.31; N,8.49. $C_{23}H_{20}N_2O$ requires: C,81.15; H,5.92; N,8.23%); m/z 340(100%,M^+).

3-Benzoyl-7-methyl-2-(2-methylphenylamino)indole (38b) was isolated as yellow crystals (CH_2Cl_2-hexane), yield 27%; m.p. 179-180°C; ν_{max} 3422, 1623, 1593 cm^{-1}; δ_H 2.34(3H,s,CH_3); 2.41(3H,s,CH_3), 6.67-6.83(3H,m,ArH), 7.15-7.54(7H,m,ArH), 7.67-7.72(2H,m,ArH), 8.15(1H,s,indole NH), 10.11 (1H,s,NH); δ_C 16.35, 17.94(CH_3), 97.86(s,C-3), 116.65(d,CH,ArH), 118.90 (s,C-7), 121.69, 121.71, 122.32, 125.75, 127.35, 127.56, 128.19, 130.09, 131.82(d,CH,ArH), 125.85(s,C-8), 131.82, 131.99(s,C-1' of PhCO and C-2' of 2-CH_3C_6H4NH), 136.56(s,C-9), 141.83(s,C-1' of 2-$CH_3C_6H_4NH$), 152.11 (s,C-2), 190.93(s,CO). (Found: C,81.41; H,6.23; N,8.51. $C_{23}H_{20}N_2O$ requires: C,81.15; H,5.92; N,8.23%); m/z 340(28%,M^+), 339(100), 338(92).

5-(4-Chlorophenyl)-2-(2-methylphenylimino)-4-isoxazoline (37g) was isolated as colourless crystals (CH_2Cl_2-hexane), yield 41%; m.p. 120°C; ν_{max} 1665, 1590 cm^{-1}; δ_H 2.16(3H,s,CH_3), 2.38(3H,s,CH_3), 6.75(1H,s,H-4), 6.80-7.38(12H,m,ArH). (Found: C,73.47; H,5.27; N,7.69. $C_{23}H_{19}ClN_2O$ requires: C,73.69; H,5.11; N,7.47%); m/z 376(6%), 374(31,M^+).

3-(4-Chlorobenzoyl-7-methyl-2-(2-methylphenylamino)indole (38c) was isolated as yellow crystals (CH_2Cl_2-hexane), yield 30%; m.p. 200-201°C; ν_{max} 3420, 1620, 1590 cm^{-1}; δ_H 2.30(3H,s,CH_3), 2.37(3H,s,CH_3), 6.60-6.90(3H,m,ArH), 7.12-7.73(8H,m,ArH), 8.20(1H,s,indole NH), 10.75(1H,s, NH). (Found: C,73.87; H,5.32; N,7.79. $C_{23}H_{19}ClN_2O$ requires: C,73.69; H,5.11; N,7.47%); m/z 376(23%), 374(100,M^+), 375(48), 374(74).

General procedure for LTA oxidation of S,S-acetals (34a-e and 62):

A solution of the α-oxoketene S,S-acetal (0.01 mol) in dry benzene (20 ml) was added to a suspension of lead tetraacetate (5.5g, 0.012 mol) in dry benzene (30 ml) and the mixture was maintained at 60-70°C with stirring for 6-12 hr. (monitored by t.l.c.). The reaction mixture was cooled

and a few drops of ethylene glycol was added to decompose any excess oxident present in the mixture. The precipitated lead diacetate was removed by filteration, and the benzene solution was washed with water (3x50 ml), dried (Na_2SO_4) and evaporated. The crude product thus obtained was purified by column chromatography on silica gel using ethyl acetate:hexane (1:20) as eluent.

2-Acetoxy-3,3-bis(methylthio)-1-phenyl-2-propen-1-one (58a) was isolated as viscous brown liquid, yield 54%; i.r. (neat): ν_{max} 1760(ester CO), 1656(ArCO) cm^{-1}; δ_H 2.14(3H,s,SCH_3), 2.22(3H,s,SCH_3), 2.43(3H,s,$COCH_3$), 7.37-7.72(3H,m,ArH), 7.90-8.19(2H,m,ArH). (Found: C,55.45; H,5.15. $C_{13}H_{14}O_3S_2$ requires: C,55.29; H,5.00%); m/z 282(3%,M^+), 239(5), 105(100).

3,3-Bis(methylthio)-1-phenylpropane-1,2-dione (59a) was isolated as viscous brown liquid, yield 26%; i.r. (neat): ν_{max} 1690, 1670 cm^{-1}; δ_H 2.05(7H,s,SCH_3 and CH), 7.19-7.43(3H,m,ArH), 7.56-8.10(2H,m,ArH). (Found: C,55.07; H,5.12. $C_{11}H_{12}O_2S_2$ requires: C,54.97; H,5.03%).

2-Acetoxy-3,3-bis(methylthio)-1-(4-methylphenyl)-2-propen-1-one (58b) was isolated as viscous brown liquid, yield 56%; i.r.(neat): ν_{max} 1761 (ester CO), 1650(ArCO) cm^{-1}; δ_H 2.19(3H,s,SCH_3), 2.24(3H,s,SCH_3), 2.43 (6H,brs,$COCH_3$ and CH_3 phenyl), 7.27(2H,d,J=9.0Hz,A_2B_2ArH), 7.90(2H,d, J=9.0Hz,A_2B_2,ArH). (Found: C,56.60; H,5.22. $C_{14}H_{16}O_3S_2$ requires: C,56.73; H,5.44%); m/z 296(5%,M^+), 253(6), 119(100).

3,3-Bis(methylthio)-1-(4-methylphenyl)propane-1,2-dione (59b) was isolated as brown semisolid, yield 25%; i.r.(neat): ν_{max} 1682, 1162 cm^{-1}; δ_H 2.10 (7H,s,SCH_3 and CH), 2.39(3H,s,CH_3), 7.23(2H,d,J=8.5Hz,A_2B_2,ArH), 7.76 (2H,d,J=8.5Hz,A_2B_2,ArH). (Found: C,56.51; H,5.54. $C_{12}H_{14}O_2S_2$ requires: C,56.66; H,5.55%); m/z 254(2%,M^+), 119(100).

2-Acetoxy-3,3-bis(methylthio)-1-(4-chlorophenyl)-2-propen-1-one (58c) was isolated as viscous brown liquid, yield 55%; i.r.(neat): ν_{max} 1760 (ester CO), 1655(ArCO) cm^{-1}; δ_H 2.02(3H,s,SCH_3), 2.09(3H,s,SCH_3),2.28 (3H,s,$COCH_3$), 7.27(2H,d,J=9.0Hz,A_2B_2,ArH),7.67(2H,d,J=9.0Hz,A_2B_2,ArH). (Found: C,49.32; H,4.20. $C_{13}H_{13}ClO_3S_2$ requires: C,49.28; H,4.14%); m/z 317(2%,M^+), 274(24), 107(100).

3,3-Bis(methylthio)-1-(4-chlorophenyl)propane-1,2-dione (59c) was isolated as yellow crystals (hexane), yield 30%; m.p. 99-100°C; i.r.(neat): ν_{max} 1690, 1676 cm^{-1}; δ_H 2.27(7H,s,SCH_3 and CH), 7.53(2H,d,J=8.5Hz, A_2B_2,ArH), 7.95(2H,d,J=8.5Hz,A_2B_2,ArH); δ_C 13.66(SCH_3); 73.85(CH), 129.00, 130.08(CH,ArH), 132.01, 140.19(C-1' and C-4',ArH), 190.06, 192.03(CO). (Found: C,47.97; H,4.09. $C_{11}H_{11}ClO_2S_2$ requires: C,48.08; H,4.04%); m/z 276(2%), 274(3,M^+), 154(100).

2-Acetoxy-3,3-bis(ethylthio)-1-phenyl-2-propen-1-one (58d) was isolated as viscous brown liquid, yield 52%; i.r.(neat): ν_{max} 1766(ester CO), 1664(ArCO) cm^{-1}; δ_H 1.03(3H,t,J=7.0Hz,$CH_2\underline{CH_3}$), 1.28(3H,t,J=7.0Hz,$CH_2\underline{CH_3}$), 2.12(3H,s,$COCH_3$), 2.61(2H,q,J=7.0Hz,$\underline{CH_2}CH_3$), 2.82(2H,q,J=7.0Hz,$\underline{CH_2}CH_3$), 7.30-7.57(3H,m,ArH), 7.76-7.95(2H,m,ArH). (Found: C,58.20; H,6.01. $C_{15}H_{18}O_3S_2$ requires: C,58.04; H,5.84%); m/z 310(4%,M^+), 268(24,M^+-CH_3CO).

3,3-Bis(ethylthio)-1-phenylpropane-1,2-dione (59d) was isolated as viscous brown liquid, yield 25%; i.r.(neat): ν_{max} 1672, 1686 cm^{-1}; δ_H 0.84-1.53(6H,m,CH_3), 2.09(1H,s,CH), 2.35-3.04(4H,m,CH_2), 7.20-7.56 (3H,m,ArH), 7.71-8.13(2H,m,ArH). (Found: C,58.02; H,5.93. $C_{13}H_{16}O_2S_2$ requires: C,58.17; H,6.01%).

2-Acetoxy-1,1-bis(methylthio)-1-butene-3-one (58e) was isolated as yellow liquid, yield 53%; i.r.(neat): ν_{max} 1769(ester CO), 1689(CH_3CO) cm^{-1}; δ_H 2.13(3H,s,SCH_3), 2.27(3H,s,SCH_3), 2.36(3H,s,$COCH_3$), 2.43(3H,s,CH_3). (Found: C,43.60; H,5.32. $C_8H_{12}O_3S_2$ requires: C,43.61; H,5.49%).

1,1-Bis(methylthio)butane-2,3-dione (59e) was isolated as yellow liquid, yield 28%; i.r.(neat): ν_{max} 1711, 1690 cm^{-1}; δ_H 2.06(7H,s,SCH_3 and CH), 2.45(3H,s,CH_3). (Found: C,40.54; H,5.60. $C_6H_{10}O_2S_2$ requires: C,40.42; H,5.62%).

2-Acetoxy-1,1-bis(methylthio)-5-phenyl-1,4-pentadiene-3-one (63) was isolated as viscous yellow liquid, yield 31%; i.r.(neat): ν_{max} 1772, 1645, 1607 cm^{-1}; δ_H 2.27(3H,s,SCH_3), 2.32(3H,s,SCH_3), 2.35(3H,s,$COCH_3$), 6.98(1H,d,J=17Hz), 7.15-7.66(6H,m,ArH and vinylic). (Found: C,58.55; H,5.32. $C_{15}H_{16}O_3S_2$ requires: C,58.41; H,5.23%).

1,1-Bis(methylthio)-5-phenyl-4-pentene-2,3-dione (64) was isolated as viscous yellow liquid, yield 53%; i.r.(neat): ν_{max} 1685, 1671, 1598 cm^{-1}; δ_H 2.16(7H,s,SCH_3 and CH), 7.05(1H,d,J=17Hz,olefinic), 7.27-7.74(6H,m, ArH and vinylic). (Found: C,58.49; H,5.39. $C_{13}H_{14}O_2S_2$ requires: C,58.62; H,5.30%); m/z 265(1%,M^+-1), 218(2).

REFERENCES

1. R. Criegee in 'Oxidation in Organic Chemistry'; K.B. Wilberg Ed., Academic Press, New York, Part A, p.277 (1965).
2. R.N. Butler in Synthetic Reagents-3, p. 277 (1977).
3. G.M. Rubotton in 'Oxidation in Organic Chemistry'; W.S. Trahanovsky, Ed., Academic Press, New York, Part D, p.1, 1982.
4. R.S. Atkinson in 'Azides and Nitrenes', E.F.U. Scriven, Academic Press, Orlando, Florida, Ch. 5, 1984.
5. J.B. Aylward, Quart. Rev., 25, 407 (1971).
6. R.N. Butler, Chem. Ind. (London), 523 (1972).
7. R.N. Butler, Chem. Ind. (London), 437 (1968).
8. R.N. Butler, Chem. Ind. (London), 499 (1976).
9. R.N. Butler, Chem. Rev., 84, 249 (1984).
10. B. Rindone, E. Santaniello, C.Scolastico, Tetrahedron Lett.,19 (1972).
11. F. Corbani, B. Rindone, C. Scolastico, Tetrahedron Lett.,2597 (1972).
12. A. Catto, F. Corbani, B. Rindone, C. Scolastico, Tetrahedron Lett., 2723 (1973).
13. F. Corbani, B. Rindone, C. Scolastico, Tetrahedron, 29, 3253 (1973).
14. F. Corbani, B. Rindone, C. Scolastico, Tetrahedron, 31, 455 (1975).
15. S.K. Khetan, J.C.S. Chem. Comm.,917 (1972).
16. R.M. Carr, R.O.C. Norman, J.M. Vernon, J.C.S. Chem. Comm., 855 (1977).
17. R.M. Carr, .R.O.C. Norman, J.M. Vernon J.Chem. Soc. Perkin Trans.I, 156 (1980).
18. J.M. Vernon, R.M. Carr, M.A. Sukari, J. Chem. Res(S), 115 (1982); J. Chem. Res(M), 1310 (1982).
19. M.A. Sukari, J.M. Vernon, Tetrahedron, 39, 793 (1983).

20. J.N. Vishwakarma, A. Thomas, S. Apparao, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans. I, 169 (1988).

21. A. Thomas, J.N. Vishwakarma, S. Apparao, H. Ila, H. Junjappa, Tetrahedron, 44, 1667 (1988).

22. J.N. Vishwakarma, unpublished results.

23. A. Kumar, V. Aggarwal, H. Ila, H. Junjappa, Synthesis, 748 (1980).

24. L. Field, J.E. Lawson, J. Amer. Chem. Soc. 80, 838 (1958).

25. V.H. Bohme, H. Fischer, R. Frank, Justus Liebigs Ann. Chem. 563, 54 (1949); 43: 7409c.

26. L.Field, J.M. Locke, C.B. Hoelzel, J.E. Lawson, J. Org. Chem., 27, 3313 (1962).

27. L. Field, C.B. Hoelzel, J.M. Locke, J. Amer. Chem. Soc., 84, 847 (1962).

28. L. Field, C.B. Hoelzel, J.M. Locke, J.E.Lawson, J. Amer. Chem. Soc. 1256 (1961).

29. T.J. Adley, A.K.M. Anisuzzaman, L.N. Owen, J. Chem. Soc.(C),807 (1967).

30. E.J. Bourne, W.M. Corbett, M. Stacey, R. Stephens, Chem. and Ind. 106 (1954).

31. E.G. Brain, A.J. Eglington, J.H.C. Nayler, M.J. Pearson, R. Southgate, J. Chem. Soc. Chem. Comm., 229 (1972).

32. H. Hiroi, S. Sato, Chemistry Letters, 923 (1979).

33. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2187 (1962).

34. K. Ichikawa, Y. Yamaguchi, J. Chem. Soc. Japan, 73, 415 (1952); 47; 10474d.

CHAPTER III

SIMMONS-SMITH REACTION ON α-OXOKETENE DITHIOACETALS: A NOVEL ROUTE TO 3-, 3,4-SUBSTITUTED AND ANNELATED THIOPHENES*.

III.1 INTRODUCTION

The reaction of an olefin with organozinc reagent prepared from methylene iodide and zinc-copper couple to afford the corresponding cyclopropane is generally termed as Simmons-Smith reaction, which was discovered by these chemists in 1950[1,2]. The cyclopropane formation is stereospecific with regard to the stereochemistry of the olefin and the reaction is usually free from undesirable side reactions. The method is of particular use, since it can be adopted for large scale preparations. The structure of the reagent and the mechanism of methylene transfer is not yet known with certainty.

---

* A. Thomas, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett.000 (1989).

The reagent, presumably the iodomethylzinc iodide is usually termed as carbenoid, which has been suggested for the description of intermediates which exhibits reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species.

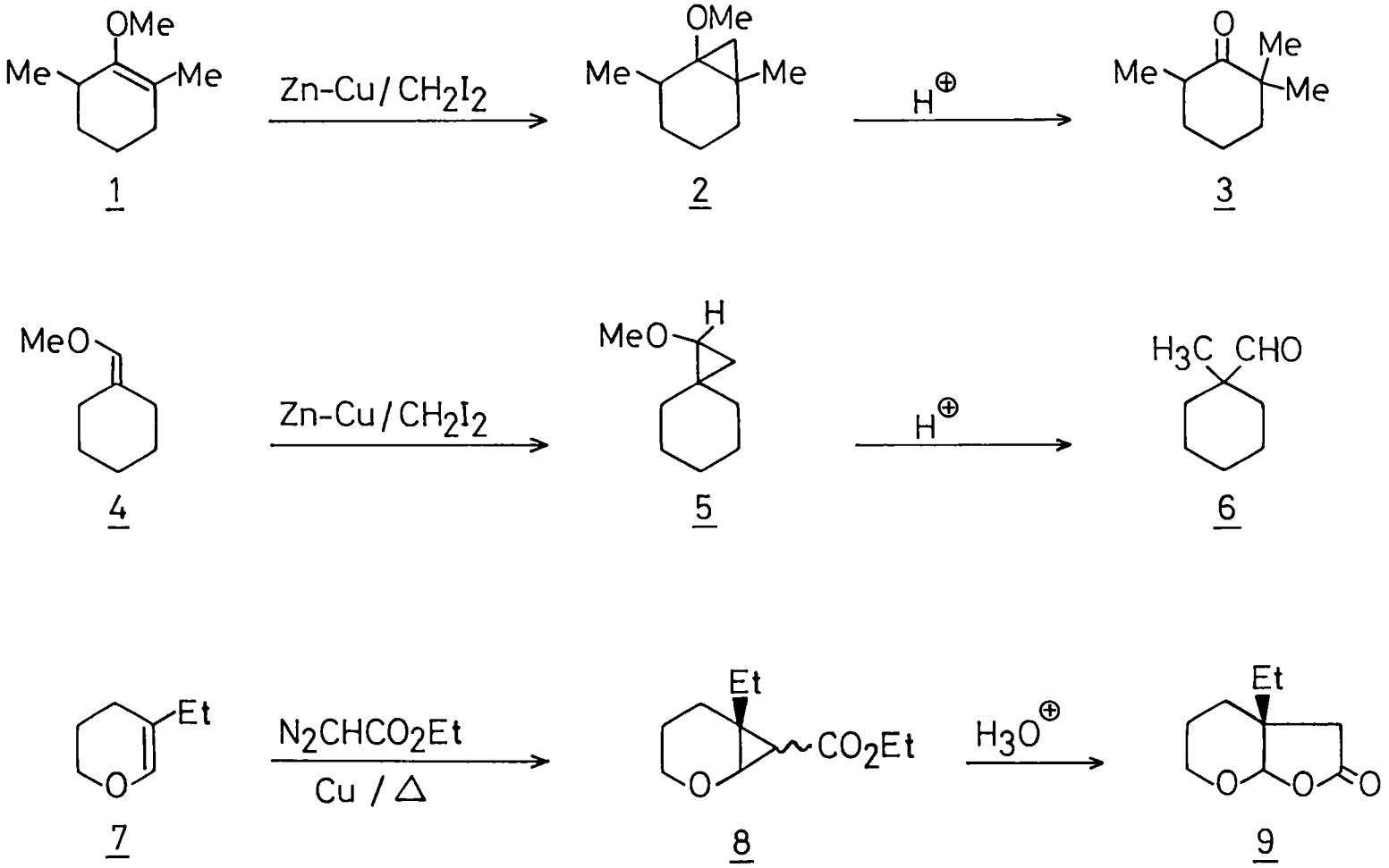
Alkenes substituted with usual functional groups at sites remote from the double bond generally undergo cyclopropanation without difficulty. Conjugated dienes react readily with the zinc reagent to form mono- and di-adducts stereospecifically, whose ratio can often be controlled. Substituents like halogens, alkoxy group, esters, primary and secondary amines, carbonyl, ketals and sulphones do not interfere in the cyclopropanation[2]. The zinc reagent behaves as a weak electrophile towards the double bond and the reactivity of the double bond increases with electron donating substituents, while electron withdrawing substituents deactivate the process. If the functional group can coordinate with the zinc reagent, methylene transfer in such cases may be accelerated even with electron withdrawing groups. Cyclopropanation occurs with high stereochemical control in allylic and homoallylic alcohols due to the coordination of the reagent with oxygen function[3-5]. α,β-Unsaturated ketones are known to undergo cyclopropanation[6] to form the cyclopropyl ketones, but the success of the reaction depends on the substrate structure. Some of the doubly α,β-unsaturated ketones are known to give mono- and di-adducts depending on the amount of the reagent used[7].

Since heteroatoms adjacent to the double bond do not interfere with cyclopropanation, Wenkert and coworkers have extensively studied the cyclopropanation of oxyolefins[8]. They have made use of Simmons-Smith

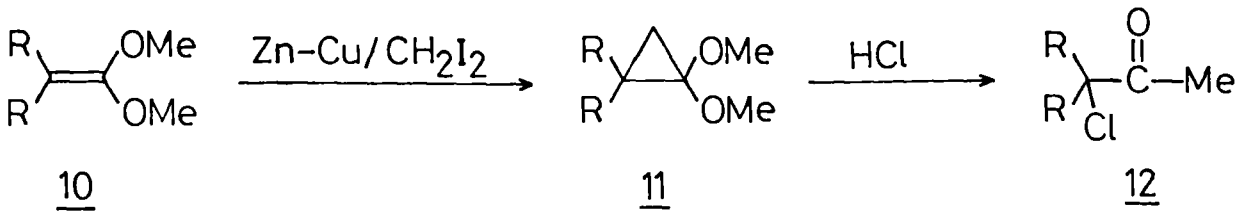
reaction as well as other methods of cyclopropanation to prepare the oxycyclopropane derivatives. These oxygenated cyclopropanes are shown to be useful intermediates in general organochemical reactions and complex natural product synthesis. Thus, enolethers 1 and 4 underwent facile cyclopropanation under Simmons-Smith reaction condition to give the cyclopropyl ethers 2 and 5, which on acid induced cleavage gave the α-methylated ketone 3 and the aldehyde 6 respectively[9]. Similarly cyclopropane 8 with donor-acceptor functionalities was prepared by the copper assisted reaction of the diazoacetate with the cyclic enolether 7. The cyclopropane 8 in acidic condition was cleaved and cyclized to the fused lactone 9[8] (Scheme 1).

The ketene O,O-acetals of the general formula 10 are also known to give the stable cyclopropanone acetals 11 which with hydrochloric acid yielded 3-chloro-3-methyl-2-butanone 12 ($R=CH_3$)[9,10]. Similarly enamine 13 was converted to the 1-aminobicyclic alkane 14[11], and cleaved to 15. Reaction of phenylvinyl sulfone 16 with zinc reagent prepared from iodomethylbenzoate and zinc-copper couple to give cyclopropyl phenyl sulfone 17 represents an example of sulfur compound undergoing cyclopropanation under the described conditions[12] (Scheme 2).

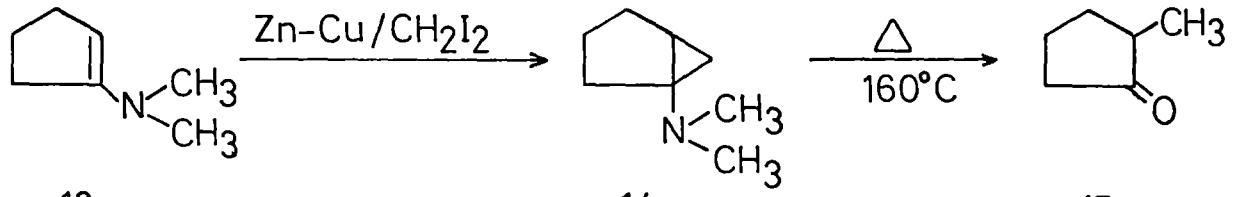
From these selected examples described above, despite the fact that Simmons-Smith reaction is not affected adversely by oxygen and nitrogen substituents and even by the presence of sulfones, there have been no example of olefins with divalent sulfur substituents such as vinyl sulfides, ketene S,S-acetals, β,β-bis(alkylthio)α,β-unsaturated enones studied under Simmons-Smith reaction condition. One reason for the lack of example in this area could be attributed to the facile


OMe
Me
Me
Zn-Cu / CH2I2
OMe
Me
Me
H⊕
O
Me
Me
Me
1
2
3
MeO
Zn-Cu / CH2I2
MeO
H
H⊕
H3C
CHO
4
5
6
Et
O
N2CHCO2Et
Cu / Δ
Et
O
CO2Et
H3O⊕
Et
O
O
O
7
8
9

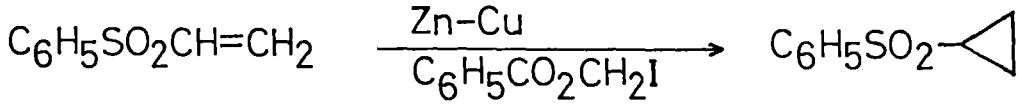
Scheme-1



10 11 12



13 14 15



16 17

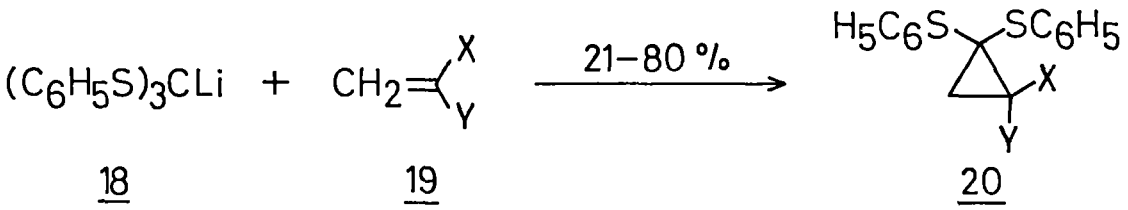
Scheme-2

formation of sulfur ylids by electrophilic addition of carbenes and carbenoids to the divalent sulfur. The carbenoid nature of the Simmons-Smith reagent may lead to products other than cyclopropanation.

The author's search was therefore directed towards examples of carbene/carbenoid intermediates and their behaviour towards ketene S,S-acetals and some of the related compounds. Such examples would throw light on the behaviour of sulfur compounds towards Simmons-Smith reagent.

Although Simmons-Smith reaction has been successfully applied to vinyl sulfone 16 (Scheme 2), to make the corresponding cyclopropane 17, the clear absence of vinyl sulfides or ketene S,S-acetals under these reaction conditions certainly leads to the speculation of ambident behaviour of the reagent to these intermediates. However Seebach has successfully added a carbenoid generated from trisphenylmercaptomethyl-lithium 18 to ketene dithioacetal 19 to afford the corresponding cyclopropane 20[13], which is one of the rare examples of construction of cyclopropane ring on olefin containing a divalent sulfur, through carbenoid addition. Subsequently it was shown that addition of lithio derivative of phenyl trimethylsilylmethyl sulfide 21[14] to ketene dithioacetals 22 yield the silylcyclopropane 23 (Scheme 3).

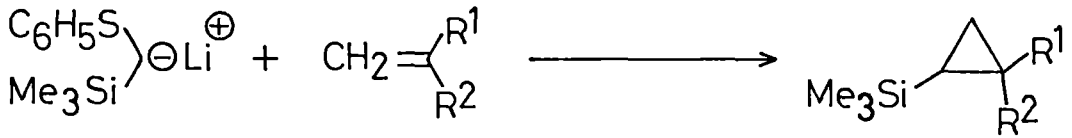
However, there have been larger number of examples where the divalent sulfur preferentially attacks the carbene to yield the sulfur ylid[15] rather than the cyclopropane. In fact this is one of the general methods of preparation of sulfur ylids[15]. Some examples involving participation of divalent sulfur with electrophilic carbenes to give the sulfur ylid and the products arising thereof have been illustrated



18 19 20

X=Y= OMe ; X= Y= SMe ; X=Y = SC_6H_5

X–Y = –S-$(CH_2)_3$-S– ; X=C_6H_5 , Y= morpholino



21 22 23

R^1=R^2=C_6H_5 ; R^1=R^2=SCH_3 ; R^1=R^2=SC_6H_5

R^1–R^2=-S-$(CH_2)_3$-S- ; R^1=SCH_3 , R^2=SC_6H_5

Scheme-3

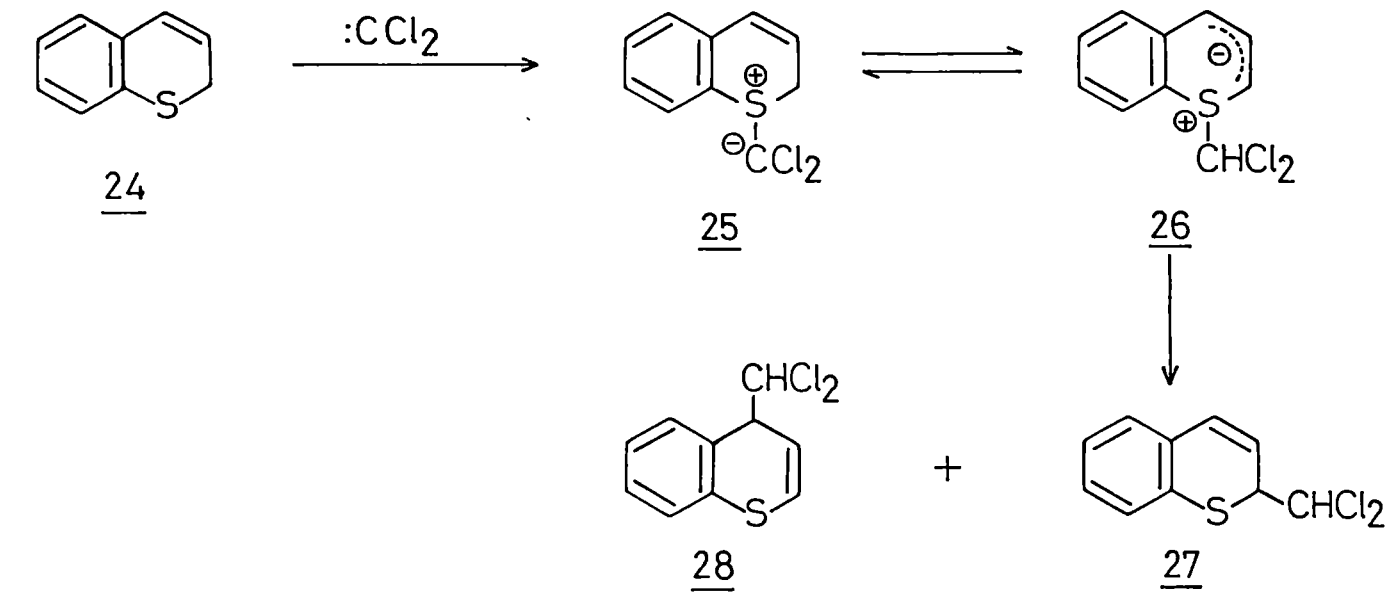
in the following section.

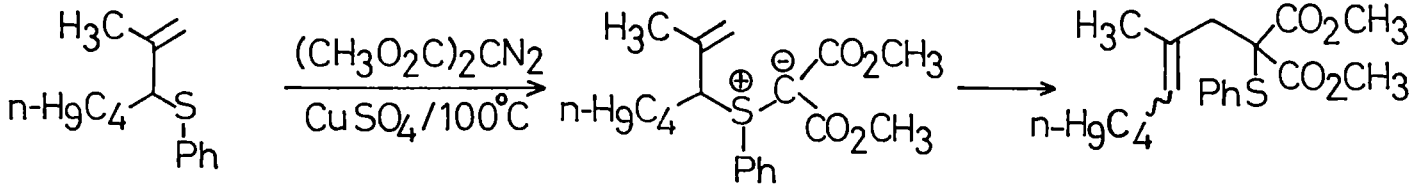
Thus, generating dichlorocarbene in the presence of 2H-1-benzothiopyran 24 produced the insertion products 27 and 28 explicable on the basis of an ylid intermediate 26 through 25[16,17]. Similarly the carbenoid derived from diazoacetate in thermal and photolylic conditions preferentially attacked by sulfur rather than the double bond, in the allyl sulfide 29 to give the ylid intermediate 30 which on [2,3]sigmatropic rearrangement gave isomeric 31[18,19] (Scheme 4). Another interesting example reported by Yoshimato and coworkers is the skeletal conversion of cephalosporin 32 to penicillin 34. This can be explained by the [2,3]-sigmatropic rearrangement of the intermediate cyclic allyl sulfonium ylid 33 formed by the carbene insertion to divalent sulfur[20] (Scheme 5).

Kametani and coworkers have exploited this unique property of sulfur as an efficient trap for carbenoid for the synthesis of some naturally occuring pyrrolizidine alkaloids. The key step involves the intramolecular carbenoid displacement (ICD) reaction of the diazo-sulfide to give the ylid 36, which on ring opening following by ring closure gives the product 38[21] (Scheme 6).

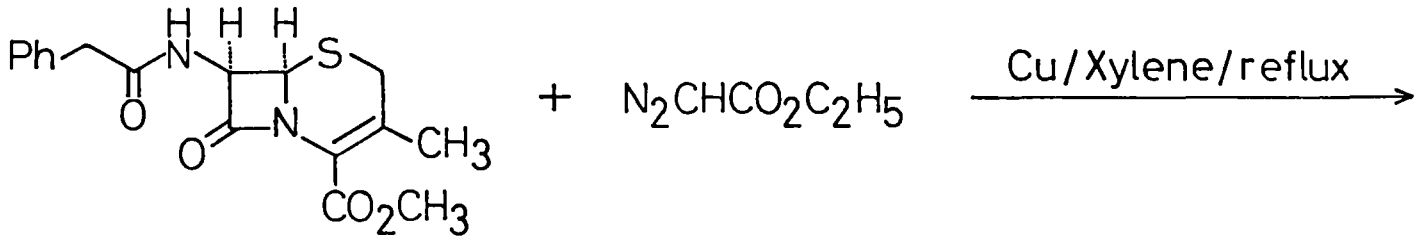
It is apparent from the above examples, that sulfur in its divalent state react with carbene/carbenoids to form the corresponding sulfonium ylid. Dialkyl sulfide is known to be four times more reactive than an olefin towards carbene[22]. Even dibenzothiophene in which the lone pair of sulfur is highly delocalized is an efficient trap for carbene[22].

There have also been rare examples, where the sulfonium ylid undergoing intramolecular reaction with electrophilic carbon centres within the

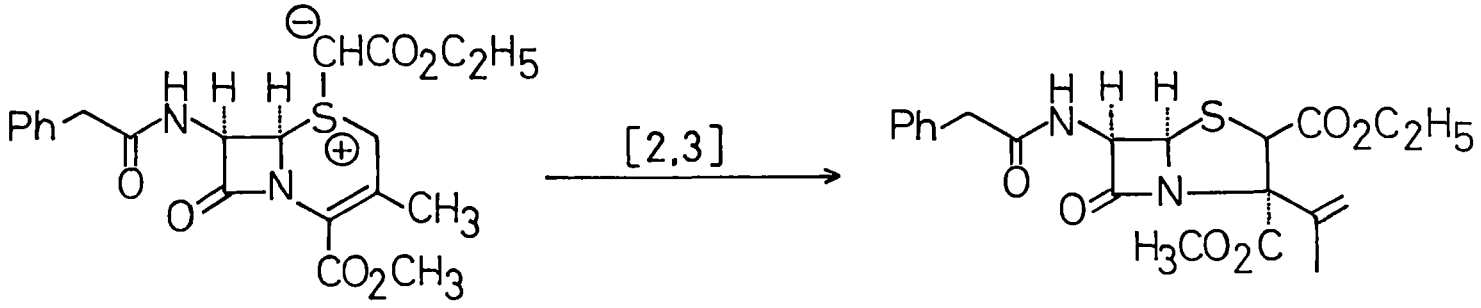

:CCl2
S
24
⊕S
⊖CCl2
25
⊖
⊕S
CHCl2
26
CHCl2
S
28
+
S
CHCl2
27


H3C
n-H9C4
S
Ph
29
(CH3O2C)2CN2
CuSO4/100°C
H3C
n-H9C4
⊕S
Ph
⊖C
CO2CH3
CO2CH3
30
H3C
n-H9C4
PhS
CO2CH3
CO2CH3
31

Scheme–4

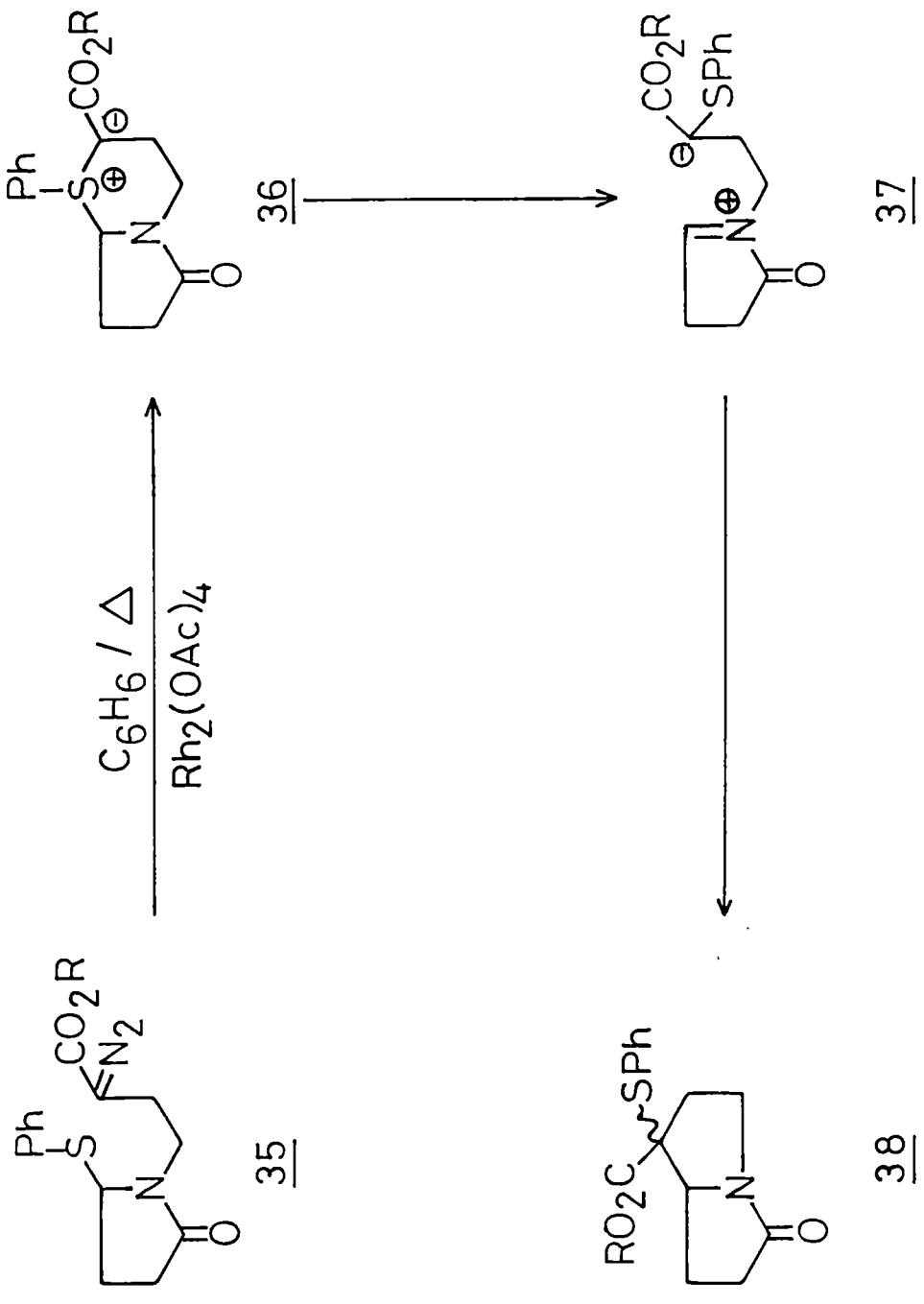


32



33 34

Scheme–5

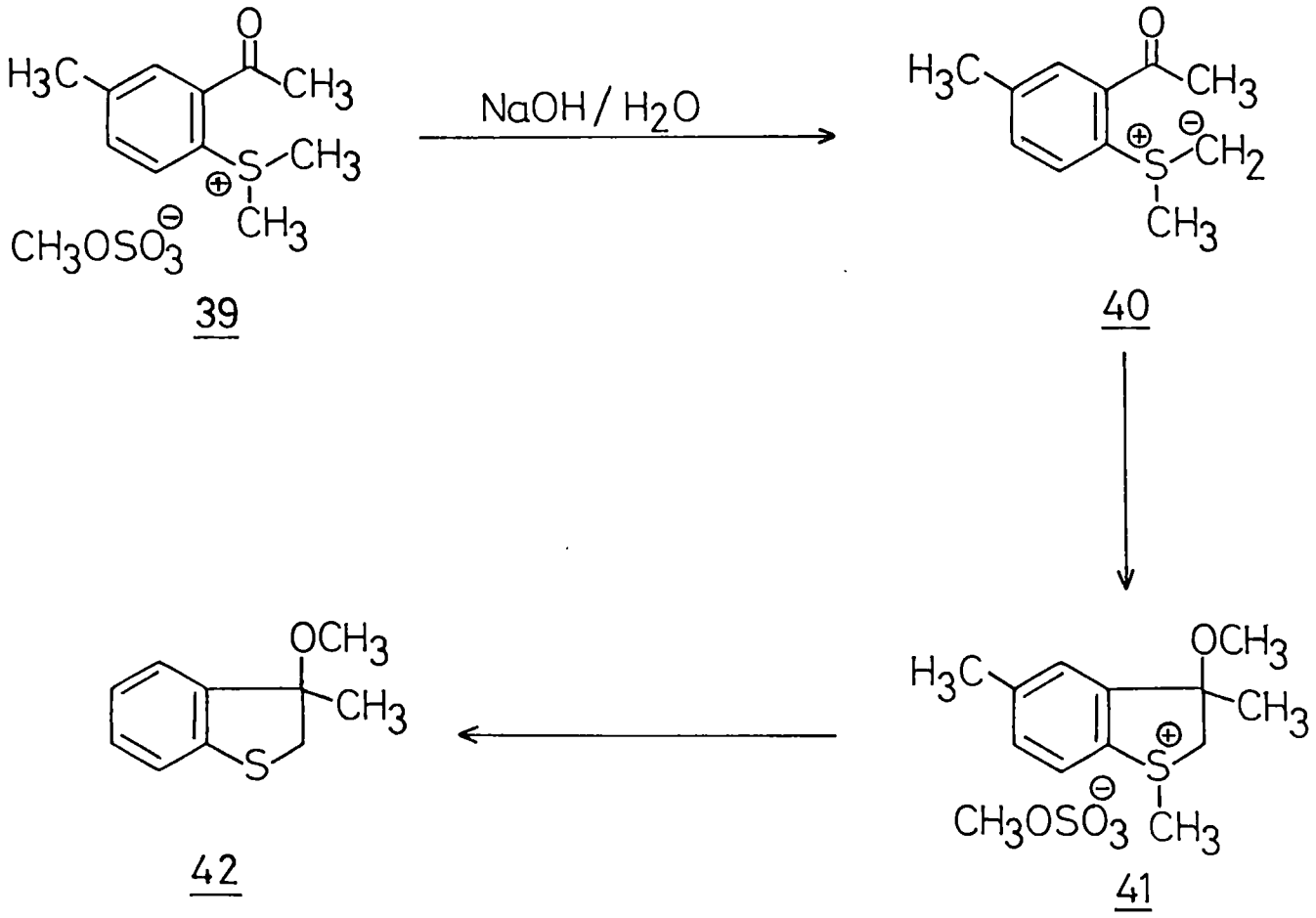

Ph
S
CO2R
N2
O
35
C6H6 / Δ
Rh2(OAc)4
Ph
S
CO2R
N
O
36
CO2R
SPh
N
O
37
RO2C
SPh
N
O
38

Scheme-6

molecule. The first and only example reported in the literature is the intramolecular aldol type condensation of the ylid 40 generated from the corresponding dimethyl (o-aceto-p-tolyl) sulfonium methylsulfonate 39, to give the intermediate 41 which on demethylation give the benzothiophene 42[23] (Scheme 7). There are a few examples, in which the more stabilized dimethylsulfoxonium methylide undergoing condensation with carbonyl group. Thus dimethylsulfoxonium methylide gives the intermediate ylid 44 by Michael addition on the acetylenic ketone 43, followed by thermal dehydration to generate the S-methylthiabenzene S-oxide 45[24]. Similarly 1,3-diketone 46 also underwent cyclocondensation with sulfoxonium methylide to give the annelated thiabenzene S-oxide 47[25] (Scheme 8).

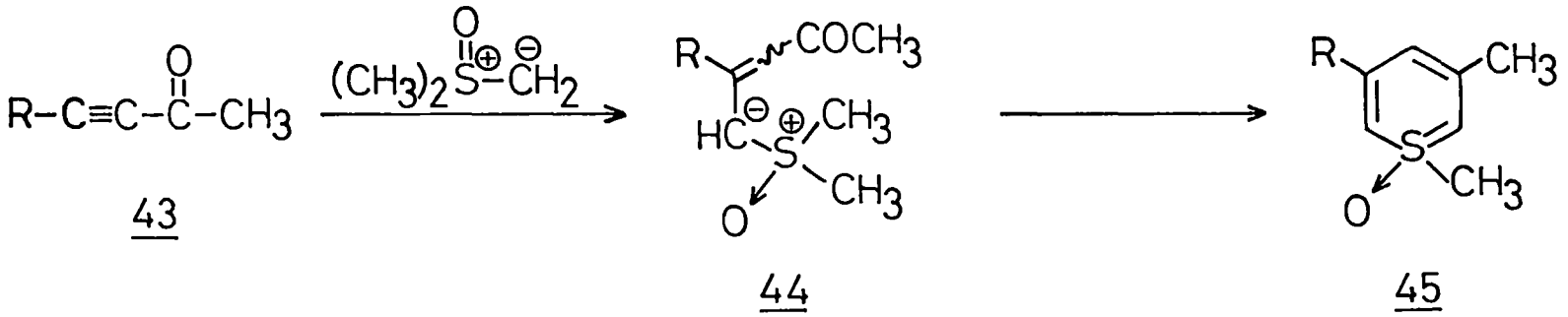
The following conclusions may be made on the basis of the illustrations described above.

1. Simmons-Smith reaction is not affected by usual oxygen and nitrogen functionalities and also by sulfone whereas the examples of Simmons-Smith reaction with vinyl sulfides, ketene S,S-acetals and polarised ketene S,S-acetals have not been reported.
2. The electrophilic carbenes and carbenoids react with divalent sulfur compounds to give the corresponding sulfur ylid. Whereas vinylethers, ketene O,O-acetals and enamines react with carbene to give cyclopropanes.
3. Carbene addition to ketene S,S-acetals to afford cyclopropanes have been studied and examples are very few (Scheme 3).
4. There have been a few examples of sulfoxonium methylide undergoing aldol condensation with carbonyl group. However, no report of

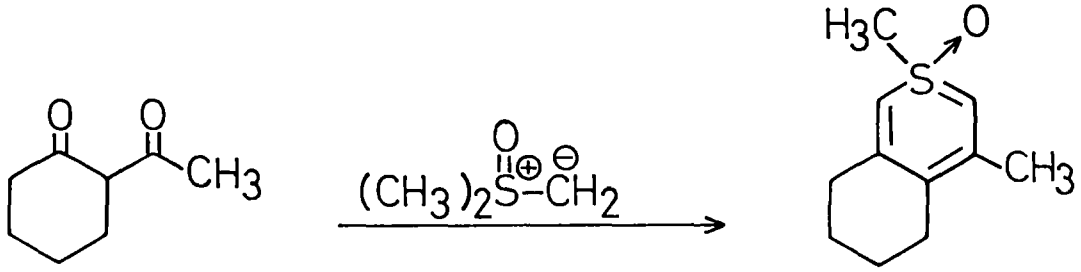


39 40 41 42

Scheme-7



43 44 45



46 47

Scheme–8

sulfonium ylid undergoing aldol type condensation with carbonyl group is available, while they are known to give the epoxy compounds[15,35,36] on reaction with carbonyl compounds.

In conclusion, it is of immense practical interest to see, how α-oxoketene S,S-acetal behave towards Simmons-Smith reagent, whether cyclopropanation on mercapto double bond or electrophilic attack on the thiomethyl sulfur to give the sulfur ylid and the products arising from it. In the examples given above, some of these questions related to the reaction of α-oxoketene dithioacetal towards Simmons-Smith reaction and other carbene/carbenoids, and possible intramolecular aldol type condensation of the sulfur ylids have been highlighted, so that the course of chemical events of the present investigation would be easily understood.

III.2 RESULTS AND DISCUSSION

This Chapter deals with the reaction of α-oxoketene dithioacetals under Simmons-Smith reaction condition, indeed leading to 2-methylthio-4-substituted and 3,4-disubstituted thiophenes. The formation of these thiophenes are rationalised on the basis of examples illustrated in the introduction. On the basis of structural characteristics of starting α-oxoketene dithioacetals and the corresponding distribution of substituents in the product thiophenes the presentation is divided into three parts.

III.2.1 SYNTHESIS OF 2-METHYLTHIO-4-SUBSTITUTED AND 2-METHYLTHIO-3,4-DISUBSTITUTED THIOPHENES

The selected α-oxoketene dithioacetals 48a-k required for the present investigation were prepared according to the known procedure[26-28] by reacting the respective active methylene ketones with two equivalent

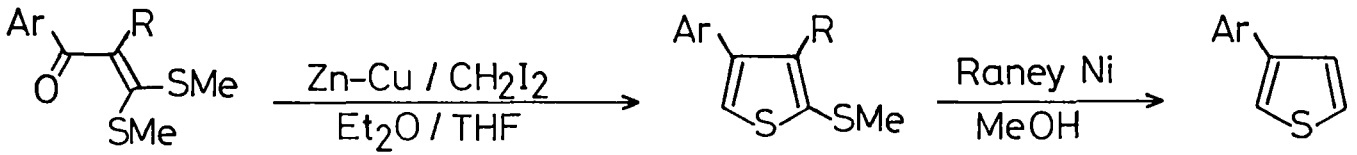
of base and carbondisulfide followed by alkylation. Authenticity of these compounds were confirmed by comparison of their spectral and analytical data with those of reported values.

In a typical experiment, the ketene dithioacetal 48a was reacted with Simmons-Smith reagent prepared from methylene iodide and zinc-copper couple in Et_2O/THF mixture (experimental) afforded a pale yellow solid, m.p. 42°C which was characterised as 2-methylthio-4-phenylthiophene 49a in 61% yield. The structure of 49a was fully established by its analytical and spectral data. Thus, compound 49a was analysed for $C_{11}H_{10}S_2$ and exhibited molecular ion peak at m/z 206(100%). The infrared spectrum showed clear absence of a carbonyl group. In its ^1H n.m.r. the signal at δ2.30 was assigned for thiomethyl protons. The phenyl and thiophene protons appeared as a multiplet between δ 7.10-7.59. The ^{13}C n.m.r. spectrum is also in full agreement with the assigned structure (experimental). Further structural proof was achieved by its independent synthesis[29,30] by the method report by Marino and Kostusyk*. Also careful desulphurisation of thiophene 49a gave the known thiophene 50a[31] (Scheme 9).

The high resolution (400 MHz) ^1H n.m.r. spectrum of thiophene 49b was found to be more useful for the assignment of substitution pattern in the thiophene ring. The signal due to C-3 and C-5 protons were found to be clearly separated from the phenyl protons. The signals at δ2.30 and 2.46 were assigned to CH_3 and SCH_3 protons, while the doublet at δ 7.13 (J=8.5Hz,2H) was assigned for phenyl protons. The signals due

---

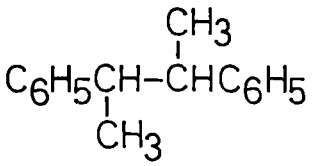
* The i.r. and n.m.r. spectra of 49a were superimposable with the product prepared by Marino's method, while the melting point reported (92°C) was found to be incorrect. The thiophene 49d showed same melting point (102-103°C) as reported.



48 49 50

48,49 a Ar=C_6H_5 ; R=H
b Ar=4-MeC_6H_4 ; R=H
c Ar=4-ClC_6H_4 , R=H
d Ar=4-MeOC_6H_4 ; R=H
e Ar=2-naphthyl ; R=H
f Ar=C_6H_5 ; R=CH_3
g Ar=C_6H_5 , R=C_2H_5
h Ar=C_6H_5 , R=n-C_3H_7
i Ar=4-ClC_6H_4 ; R=$C_6H_5CH_2$
j Ar=R=C_6H_5
k Ar=C_6H_5 ; R=CH_2=CH-CH_2

50 a Ar=C_6H_5
b Ar=4-MeC_6H_4
c Ar=4-ClC_6H_4



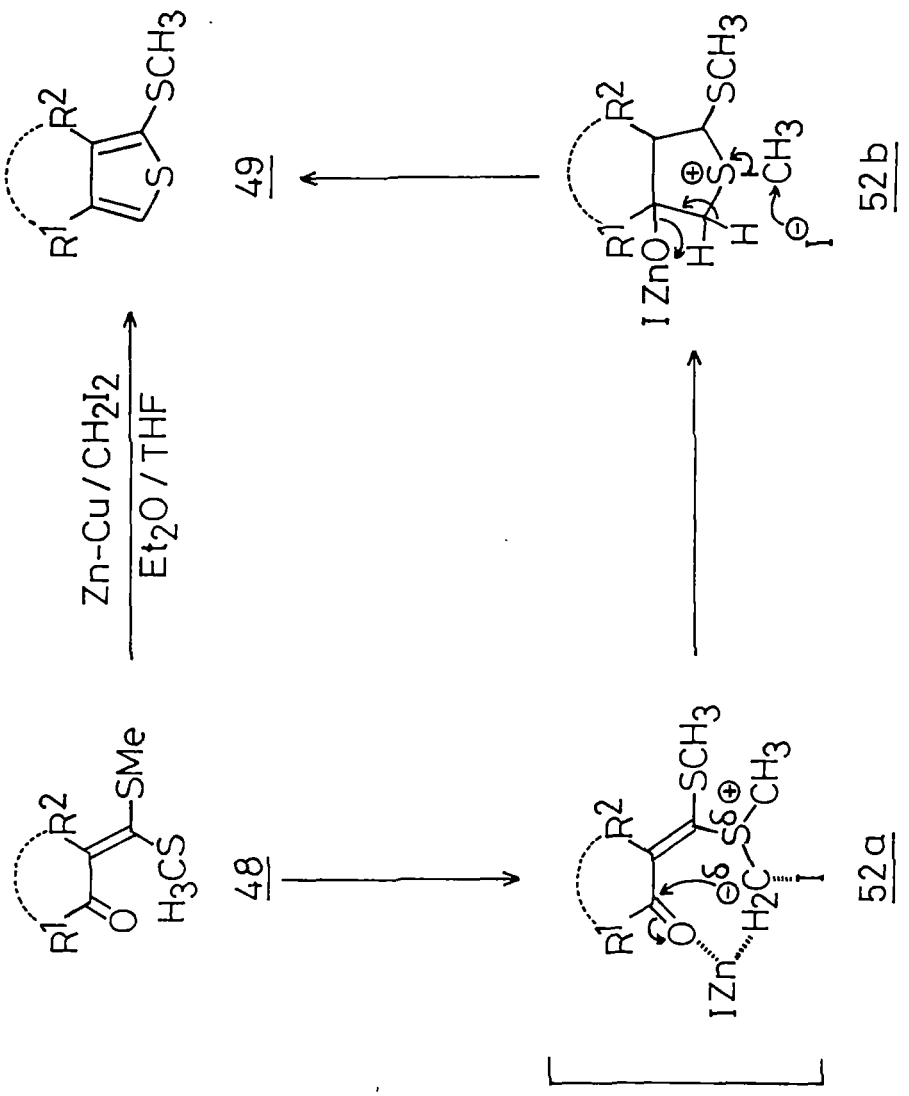
51

Scheme-9

to H-3 and H-5 protons appeared at δ7.27(J=1.5Hz) and 7.30(J=1.5Hz). The other phenyl protons appeared at δ7.39(J=8.5Hz,2H). The coupling value (J=1.5Hz) evidently fits for the long range coupling between H-3 and H-5 signals. The possibility of getting the other regioisomeric thiophene will be discussed later.

The probable mechanism for the above transformation apparently involves the carbenoid methylene insertion to one of the sulfur atoms of the α-oxoketene dithioacetal 48 to give the sulfonium ylid intermediate 52a which on intramolecular aldol type condensation assisted by coordination of zinc with carbonyl oxygen gives the S-methylthiophenium salt 52b. Subsequent demethylation of the intermediate 52b afforded the thiophene 49 (Scheme 10). The sequence seems to be valid in the light of examples given in the introduction.

The other speculative pathways the reaction can adopt is outlined in Scheme 11. Like O,O-acetals if the α-oxoketene dithioacetal 48 react with Simmons-Smith reagent it should in principle yield 2,2-bis(methylthio)-1-benzoyl cyclopropane 53 (R^2=H). This intermediate is expected to undergo facile ring cleavage due to the presence of donor-acceptor[32-34] functionalities in the vicinal carbon atoms. Thus the intermediate 53 can in principle give the furan 55 (path a), which was not observed in the reaction. Okazaki and coworkers have reported similar approach for the synthesis of furans from α-oxoketene dithioacetal through an epoxyketene dithioacetal intermediate[35,36]. The other possibility is the dethiomethylation of the intermediate 53 to give the α-oxodithioester 56 (path b) which can give thiophene 57 isomeric with observed thiophene 49. This possibility is ruled out on the basis of ^{1}H n.m.r. spectrum.

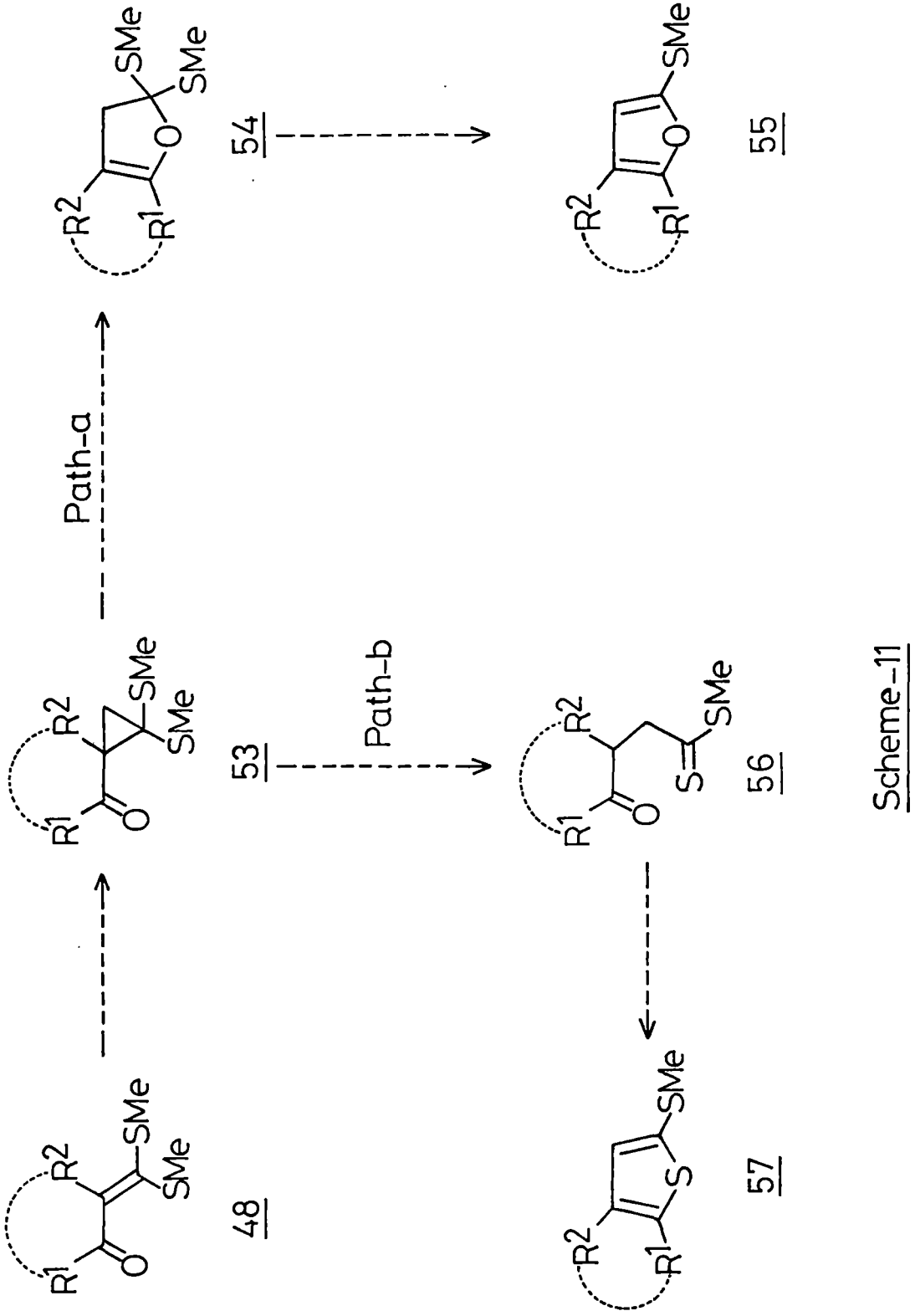


Scheme-10

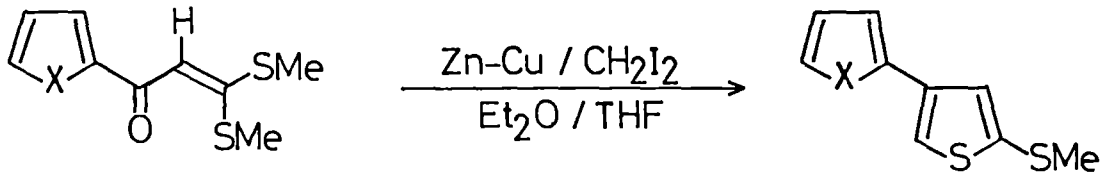
If the reaction follows path b (Scheme 11), ∝-oxoketene dithioacetal 48b should give regioisomeric 2-methylthio-5-(4-methylphenyl)thiophene. The coupling constant for C-3 and C-4 protons in this thiophene is expected to be around 3.5-4.5Hz [37a], whereas the observed value is only 1.5Hz. Thus, the possibility of the 5-regioisomer is ruled out. Therefore the structure of thiophenes 49 is conclusively established and mechanism proposed in Scheme 12 appropriately fits in.

The other ∝-oxoketene dithioacetals 48c-k were also transformed to the corresponding thiophenes 49c-k in 54-67% overall yield (Scheme 9). The structure of all these thiophenes were fully established by their analytical and spectral data, described in the experimental section. Another interesting observation is that an isolated double bond in 48k is carried over to the 3-position in the product thiophene 49k without being participating in Simmons-Smith reaction.

Although thiophene ring is known to rupture by Raney Nickel[38a], the thiophenes 49a-c were successfully dethiomethylated to the corresponding arylthiophenes 50a-c by using W-2 Raney Nickel in methanol at room temperature in 51-57% overall yield. Under similar reaction conditions thiophene 49j underwent reductive desulphurisation to give 2,3-diphenylbutane 51 in 72% yield. The thiophene ring in 49j could not be retained even by W-1 Raney Nickel[39]. Similarly ∝-oxoketene dithioacetals 58a and 58b derived from 2-acetylfuran and 2-acetylthiophene underwent thiophene formation to give 2-methylthio-4-(2-furyl) and 4-(2-thienyl) thiophenes 59a and 59b in 58 and 63% yields respectively (Scheme12). The structural assignment was fully established by analytical and spectral

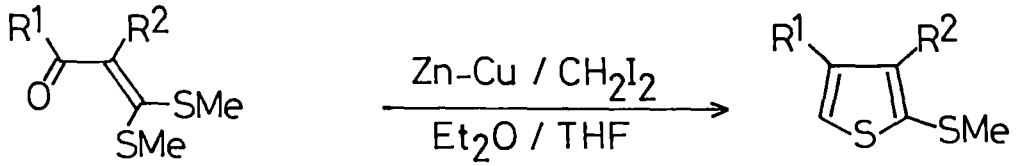


Scheme-11



58 59

58, 59 a X=O
b X=S



60 61

60, 61 a $R^1=CH_3$, $R^2=H$
b $R^1=R^2=CH_3$
c $R^1=C_2H_5$, $R^2=CH_3$
d $R^1=CH_3$, $R^2=n\text{-}C_4H_9$

Scheme-12

data and are given in the experimental.

The reaction was extended to α-oxoketene dithioacetals prepared from aliphatic ketones. Thus, α-oxoketene dithioacetals 60a-d smoothly reacted under Simmons-Smith reaction condition to yield the corresponding thiophenes 61a-d in 53-62% overall yield (Scheme 12). Compound 61a was isolated as a colourless liquid. In its ^{1}H n.m.r. spectrum the two thiophene protons (H-3 and H-5) appeared as a broad singlet at δ6.80. The H-5 thiophene protons in 61b, 61c and 61d appeared as broad singlets at δ6.80, 6.81 and 6.82 respectively. Spectral and analytical data are given in the experimental.

III.2.2 SYNTHESIS OF 2-METHYLTHIO-3,4-ANNELATED THIOPHENES

In the previous section, the reactivity of α-oxoketene dithioacetals derived from alkyl and aryl ketones towards Simmons-Smith reagent have been presented. In this section various cyclic α-oxoketene dithioacetals have been investigated with a view of extending the present methodology for the synthesis of 3,4-annelated thiophenes. The literature methods available for the synthesis of 3,4-fused thiophenes are scanty and suffers from lack of generality[30,38b]. Considering the fact that a number of cyclic ketones can be converted to the corresponding dithioacetals, the method should be promising for the synthesis of these class of thiophenes.

The representative cyclic α-oxoketene dithioacetals 62a,b, 64a,b, 66 and 68 were prepared according to the reported method[28] and characteised by comparison of their physical and spectral data with those of reported values. Thus 62a derived from cyclohexanone was reacted with methylene

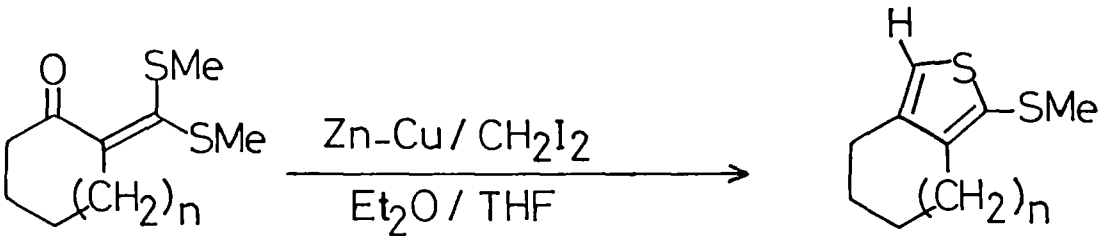
iodide and zinc-copper couple in identical condition yielded a colourless oily liquid, characterised as 2-methylthiocyclohexa[c]thiophene 63a (65%). In its ^{1}H n.m.r. spectrum the characteristic H-5 signal of thiophene ring appeared as a singlet at δ6.76 which supplements other proofs for structural assignment. Similarly 63b was obtained from 62b in identical conditions (Scheme 13).

The method was found to be equally efficient when extended to dithioacetals derived from benzocyclic ketones. Thus thiophenes 65a and 65b were formed in 57 and 60% yields respectively from the corresponding dithioacetals 64a and 64b (Scheme 13). The reaction was also extended to dithioacetals 66 and 68 prepared from benzothiepinone and benzoxepinone, and was readily converted to the thiophenes 67 and 69 in 61 and 62% yield (Scheme 14). Analytical and spectral data are given in the experimental. The method may also find use in introducing other hetero atoms in the main skeleton.

However, the method was found to be inefficient for thiophene annelation on five membered rings. Thus dithioacetals derived from cyclopentanone and indanone failed to give the annelated thiophenes, and no tractable product could be isolated from the reaction mixture.

III.2.3 SYNTHESIS OF 2-METHYLTHIO-4-ENYL/CYCLOPROPYL/CYCLOPROPYLENYL-3-UNSUBSTITUTED/ALKYLTHIOPHENES

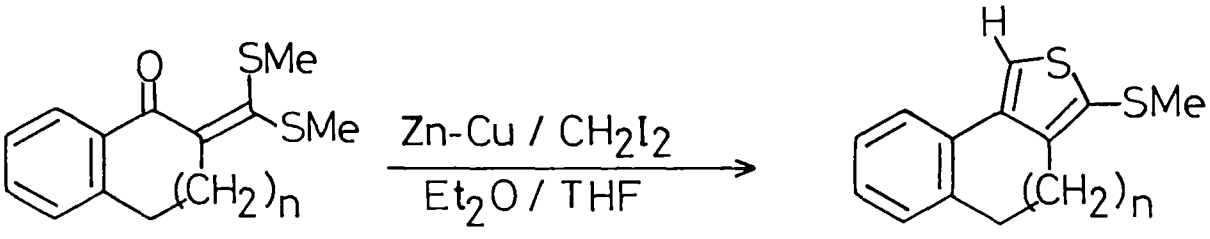
In the earlier sections the successful conversion of α-oxoketene dithioacetals derived from various alkyl, aryl and cyclic ketones to the corresponding thiophenes are described. Further, it was considered of interest to modify the substrate structure by replacing the alkyl



62 63

62,63 a n=1

b n=2

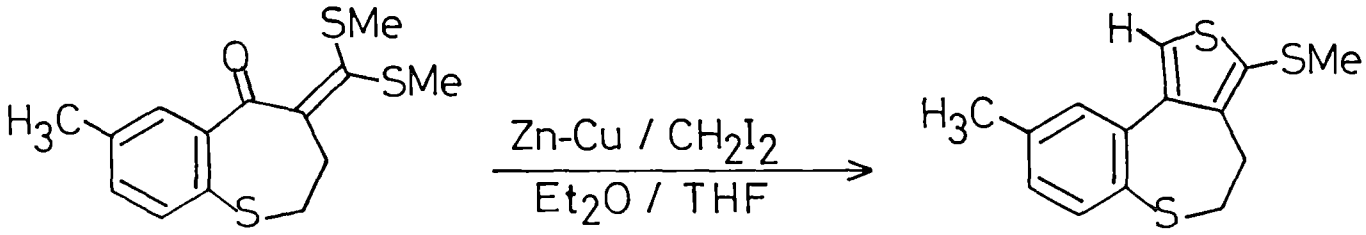


64 65

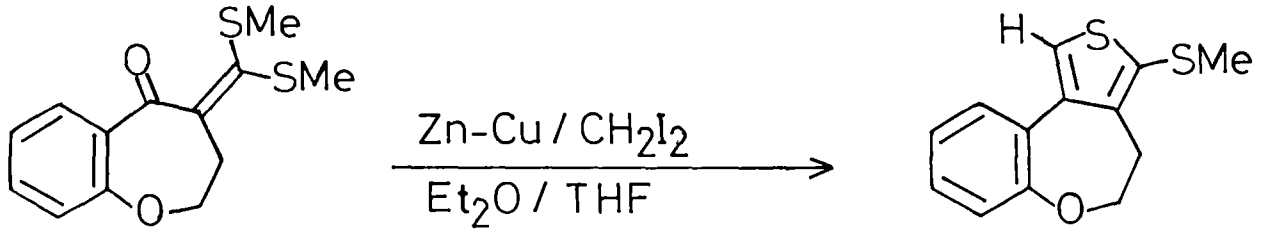
64,65 a n=1

b n=2

Scheme-13



66 67



68 69

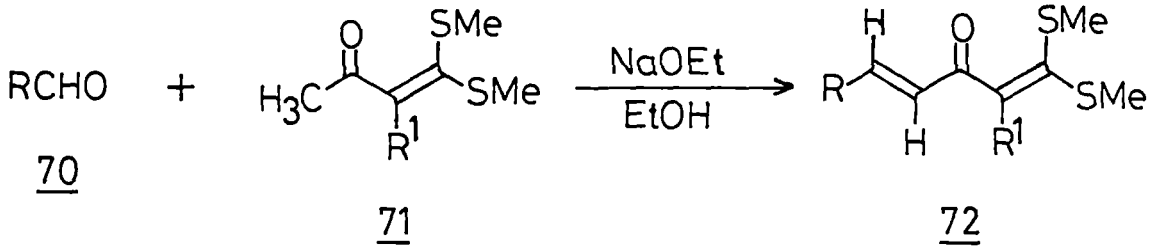
Scheme-14

and aryl substituents by a styryl moiety. The importance of this substrate stems from the fact that α,β-unsaturated ketones are known to undergo cyclopropanation[6] under Simmons-Smith reaction, therefore the reaction can give an idea about the degree of selectivity of the reagent towards sulfide sulfur in presence of a double bond in the same molecule.

The cinnamoyl ketene dithioacetals 72a-g selected for the study were prepared by published methods[40,41] by condensing suitable acylketene dithioacetals with benzaldehydes 70 using two equivalents of sodium ethoxide in ethanol (see table). Detailed procedure is given in the experimental section.

The cinnamoyl ketene dithioacetal 72a was reacted with the zinc reagent prepared from methylene iodide and zinc-copper couple under the described conditions yielded a white crystalline solid m.p. 58-59 °C which was characterised as 2-methylthio-4-styrylthiophene 73a formed in 58% yield. Analytical and spectral data are in complete agreement with the assigned structure and is given in the experimental section. The presence of an additional double bond did not interfere in the thiophene formation showing the regiospecific nature of carbenoid addition. Under identical conditions cinnamoylketene dithioacetals 72b-g gave the styrylthiophenes 73b-g in 59-68% overall yield (Scheme 15). Structure of all these compounds were confirmed by spectral and analytical data described in the experimental. Styrylthiophenes are of particular interest since they are known to be excellent dienes in cycloaddition reactions[42-45].

With the above results, the reaction was extended to 5-aryl-2,4-pentadienoyl ketene dithioacetals 72h-m prepared by condensation of acylketene



72 a R=C_6H_5 ; R^1 =H

b R=4-ClC_6H_4 ; R^1=H

c R=3,4-methylenedioxy C_6H_3 ; R^1=H

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

e R=C_6H_5 ; R^1=CH_3

f R=4-MeOC_6H_4 ; R^1=CH_3

g R=3,4-methylenedioxy C_6H_3 ; R^1=CH_3

h R=C_6H_5CH=CH– ; R^1=H

i R=4-MeOC_6H_4CH=CH– ; R^1=H

j R=3,4-methylenedioxy C_6H_3CH=CH– ; R^1=H

k R=C_6H_5CH=CH– ; R^1=CH_3

l R=3,4-methylenedioxy C_6H_3CH=CH– ; R^1=CH_3

m R=4-MeOC_6H_4CH=CH– R^1=n-C_4H_9

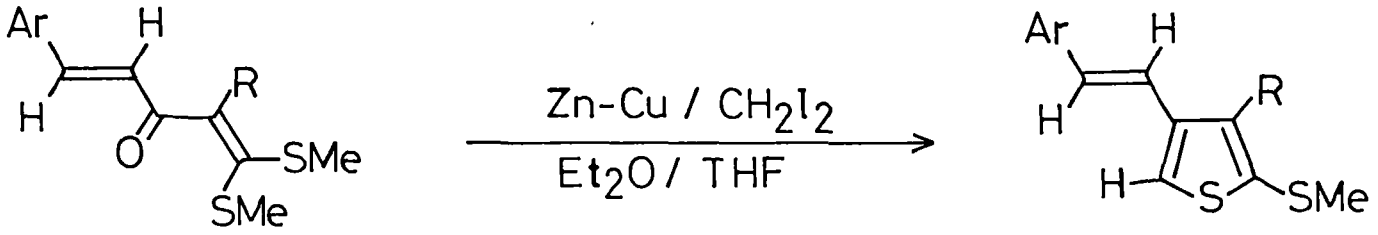
n R=$C_6H_5(CH$=CH$)_2$– ; R^1=H

o R=3,4-methylenedioxy $C_6H_3(CH$=CH$)_2$– ; R^1 =H

p R=3,4-methylenedioxy $C_6H_3(CH$=CH$)_2$– ; R^1 =CH_3

q R=4-MeOC_6H_4 ; R^1 =H

Table



72 a-g

73 a-g

72,73 a Ar = C_6H_5 ; R = H

b Ar = 4-ClC_6H_4 ; R = H

c Ar = 3,4-methylenedioxy C_6H_3 ; R = H

d Ar = 2-ClC_6H_4 ; R = H

e Ar = C_6H_5 ; R = CH_3

f Ar = 4-$MeOC_6H_4$; R = CH_3

g Ar = 3,4-methylenedioxy C_6H_3 ; R = CH_3

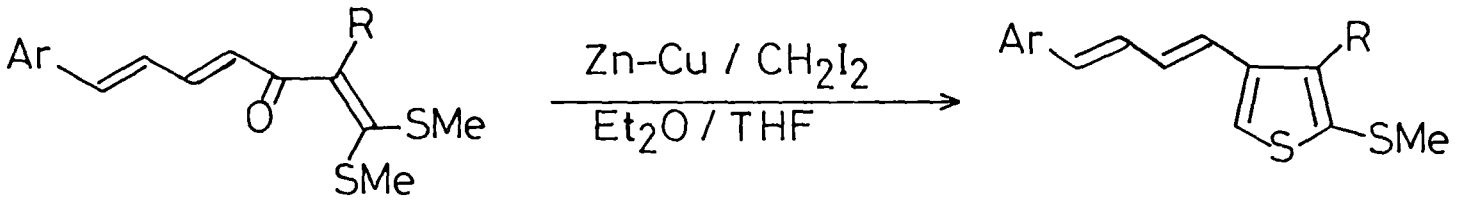
Scheme-15

dithioacetals with suitable cinnamaldehyde following the same procedure given in the experimental. Structure of all the known products were confirmed by comparison with that of reported data and the data for the unknown compound 72m is given in the experimental section.

These systems are of special interest, since they carry a diene moiety in conjugation with carbonyl group and should give product thiophenes with a diene skeleton retained in the 4-position. Thiophenes with 1,3-butadienyl side chain in 2- and 3-position is known to give interesting results under photolysis[46], and no general route is available in the literature for the synthesis of these class of thiophenes.

Thus 4-aryl-2,4-pentadienoylketene dithioacetals 72h-m under described transformation yielded the 4-(4-aryl-1,3-butadienyl) thiophenes 73h-m in 60-67% overall yield (Scheme 16). Analytical and spectral evidence in support of the assigned structure is given in the experimental section.

The cinnamoylketene dithioacetal 75a and 5-aryl-2,4-pentadienoylketene dithioacetal 75b prepared by condensing the respective aldehyde with 1,1-bis(methylthio)2-methylpentane-3-one needs special comment as it can lead to methyl substitution at 3-position of thiophene ring and also in the side chain double bond. The dithioacetals 75a and 75b yielded the thiophene 76a and 76b in 61 and 58% yield (Scheme 17). ^{1}H n.m.r. spectra of thiophene 75a and 75b showed broad singlets for side chain methyl groups at δ 2.21 and 2.10 due to allylic coupling. Other spectral and analytical values are given in the experimental. The thiophene 76a underwent complete reductive desulphurization by W-2 Raney Nickel in methanol at room temperature to give the saturated hydrocarbon 77 (Scheme 17).



72 h-m

73 h-m

72,73 h Ar=C_6H_5 , R=H

i Ar=4-$MeOC_6H_4$, R=H

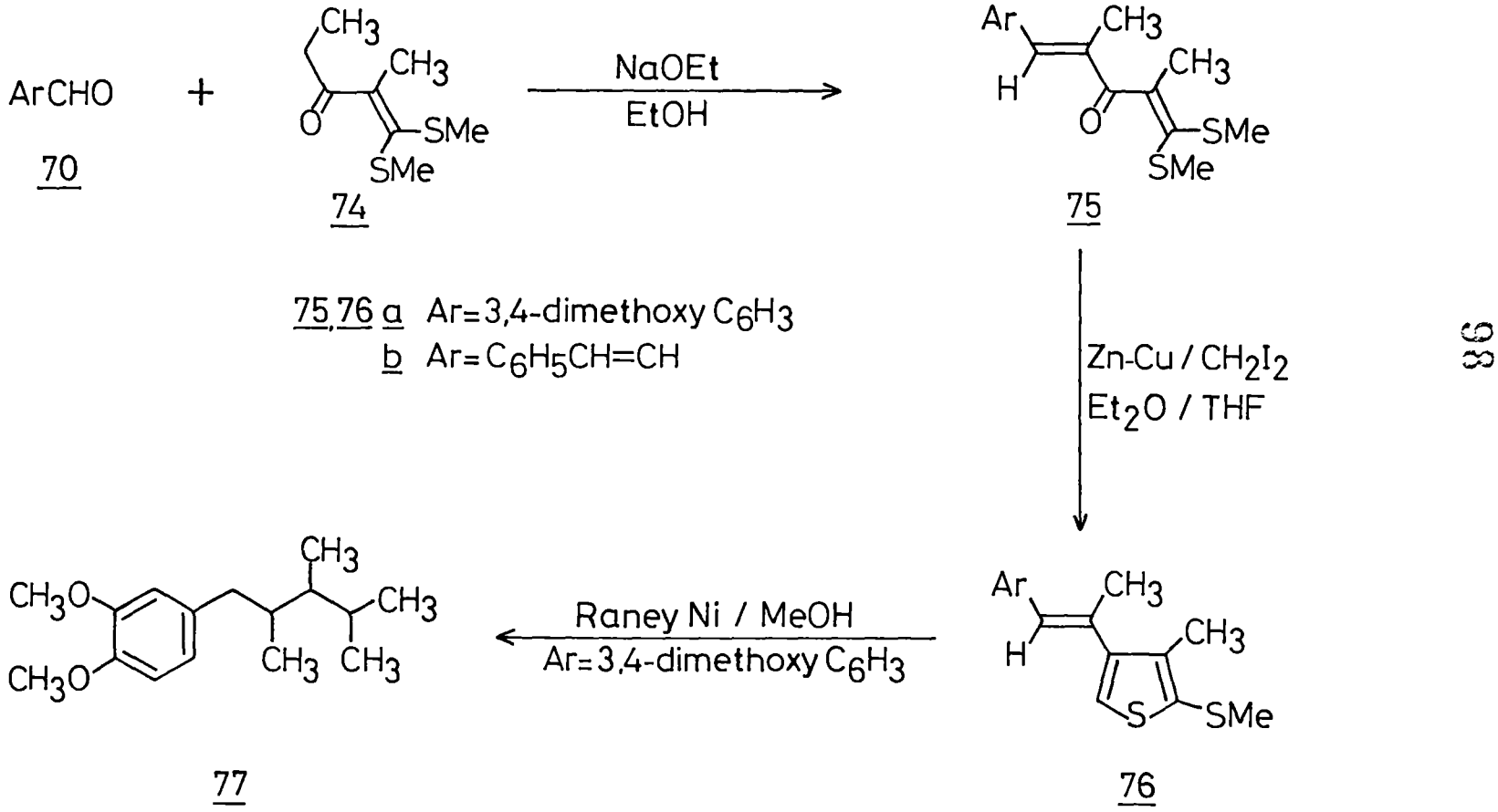
j Ar=3,4-methylenedioxy C_6H_3 , R=H

k Ar=C_6H_5 , R=CH_3

l Ar=3,4-methylenedioxy C_6H_3 , R=CH_3

m Ar=4-$MeOC_6H_4$, R=n-C_4H_9

Scheme-16



75,76 a Ar=3,4-dimethoxy C_6H_3

b Ar=$C_6H_5CH=CH$

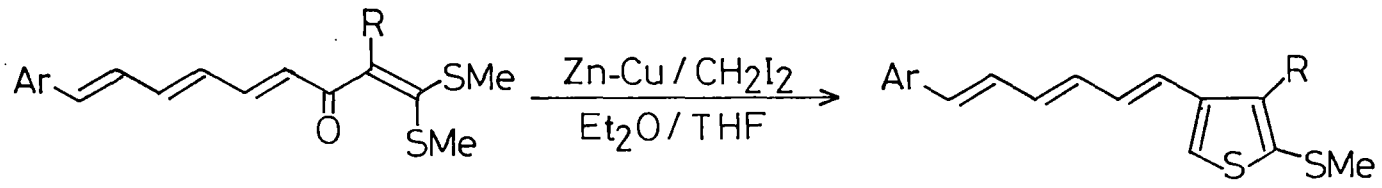
Scheme-17

Spectral and analytical data in support of the structure of compound 77 is given in experimental section.

In this stage of the study, it is almost convincingly proved that the method can be adapted for the synthesis of thiophenes with 4-polyenyl side chain, if the dithioacetal with suitable polyene side chain is available. This requirement is partially met in 7-aryl-2,4,6-hepta-trienoylketene dithioacetals 72n-p. These new compounds were synthesized by the careful condensation of the respective 5-aryl-2,4-pentadienals with acylketene dithioacetals by the method reported in the experimental section. The diene aldehydes are prepared by following the Vilsmeier-Haack route as reported by Krishna Rao and coworkers[47]. Dithioacetals 72n-p were obtained in 81-85% overall yield and showed satisfactory spectral and analytical data, described in the experimental section.

Thus, dithioacetals 72n-p were subjected to Simmons-Smith reaction following the general procedure, work-up and column chromatography on silica gel gave the expected 4-(6-aryl-1,3,5-hexatrienyl) thiophene 73n-p in 68-70% overall yield (Scheme 18). In the high resolution (400 MHz) ^{1}H n.m.r. spectrum of 73n the signals due to thiophene ring protons were clearly separated and appeared as broad singlets at 7.09 (H-3) and 7.20(H-5), while part of the olefinic protons appeared as a multiplet. Other spectral and analytical evidence in support of the assigned structure is given in the experimental. Also thiophene 73o and 73p showed satisfactory spectral and analytical data (experimental).

The thiophenes 73n and 73p underwent complete reductive desulphurisation in Raney Nickel/methanol at room temperature to give the long chain



72 n-p

73 n-p

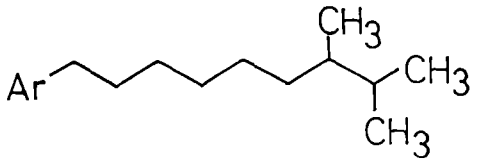
72, 73 n Ar=C_6H_5 ; R=H

o Ar=3,4-methylenedioxy C_6H_3; R=H

p Ar=3,4-methylenedioxy C_6H_3 ; R=H

Raney Ni

MeOH / r.t.



78

78 a Ar=C_6H_5 ; R^1=H

b Ar=3,4-methylenedioxy C_6H_3 ; R^1=CH_3

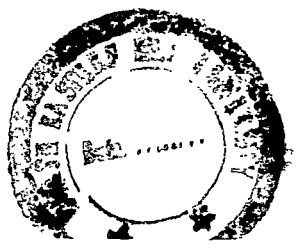
Scheme-18

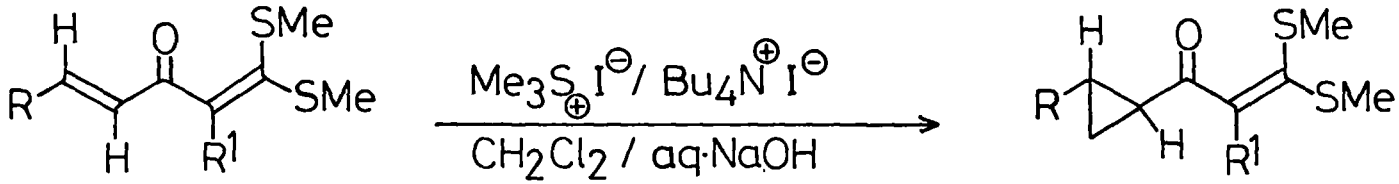
hydrocarbon 78a and 78b in 70 and 71% yield. Spectral and analytical data are given in the experimental.

Finally, the substrates selected for the study were α-oxoketene dithioacetals with a preconstructed cyclopropane ring and cyclopropane ring with enyl and dienyl side chain adjacent to the carbonyl group. These intermediates are prepared in excellent yield by the method recently developed in this laboratory[48]. Regiospecific cyclopropanation is achieved by the reaction of the respective enoylketene dithioacetals with dimethylsulfoxonium methylide under phase transfer condition[49]. Detailed procedure is given in the experimental section. All the cyclopropyl ketones 79a-e selected for the study were prepared by the above method from the corresponding enoylketene dithioacetals 72a,g,g,h and 72n in 82-93% overall yield (Scheme 19). Structural assignment is fully established on the basis of spectral and analytical data given in the experimental section.

Compound 79d and 79e claims special attention in terms of structural features. In compound 79d the double bond is no more in conjugation with the carbonyl group and can behave as an isolated double bond and in 79e an isolated diene fragment is present in similar status. These structural features makes them interesting substrates to study in Simmons-Smith reaction condition in view of understanding the degree of selectivity of the carbenoid addition.

In an analogous manner cyclopropyl ketene dithioacetals 79a-c were subjected to Simmons-Smith reaction, usual work up and column chromatography gave the cyclopropyl thiophenes 80a-c in 57-61% overall yield.





72 79

72a,79a R=C_6H_5, R^1=H

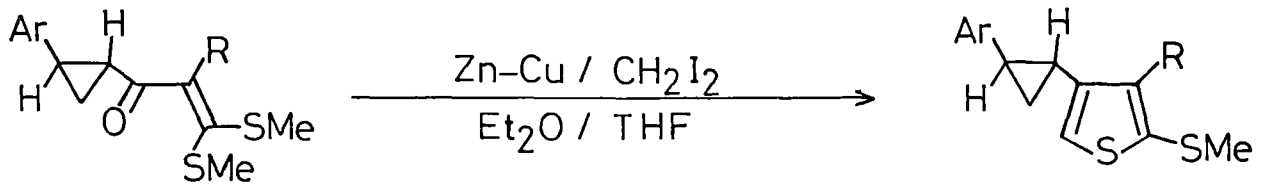
72g,79b R=4-MeOC_6H_4, R^1=H

72g,79c R=3,4-methylenedioxy C_6H_3, R^1=CH_3

72h,79d R=C_6H_5CH=CH–, R^1=H

72n,79e R=C_6H_5CH=CH–CH=CH–, R^1=H

Scheme-19



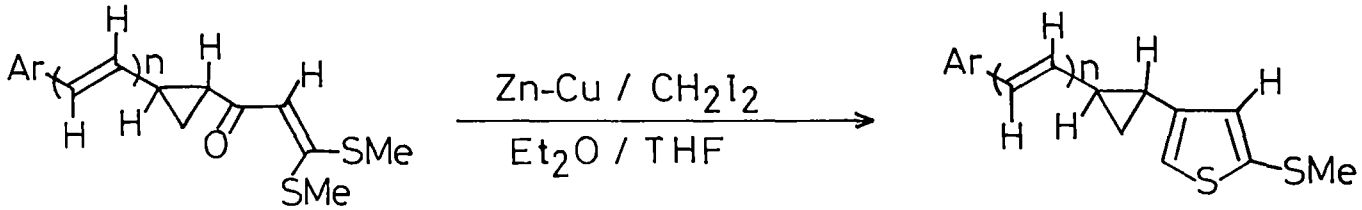
79 a-c

80 a-c

79,80 a Ar = C_6H_5 , R=H

b Ar = 4-$MeOC_6H_4$, R=H

c Ar = 3,4-methylenedioxy C_6H_3 , R=CH_3



79 d,e

80 d,e

79,80 d Ar= C_6H_5 ; n=1

e Ar= C_6H_5 ; n=2

Scheme-20

^{1}H n.m.r. spectra of 80a-c unambiguously showed the presence of cyclopropane ring. Similarly 79d and 79c were also transformed to the corresponding cyclopropyl thiophenes 80d and 80e in 54 and 56% yield (Scheme 20). Although yields are comparitively low, the double bonds attached to the cyclopropane ring remained unaffected which is evident from their ^{1}H n.m.r. spectra. Spectral and analytical data in support of the assigned structure is given in the experimental section.

III.3 CONCLUSION

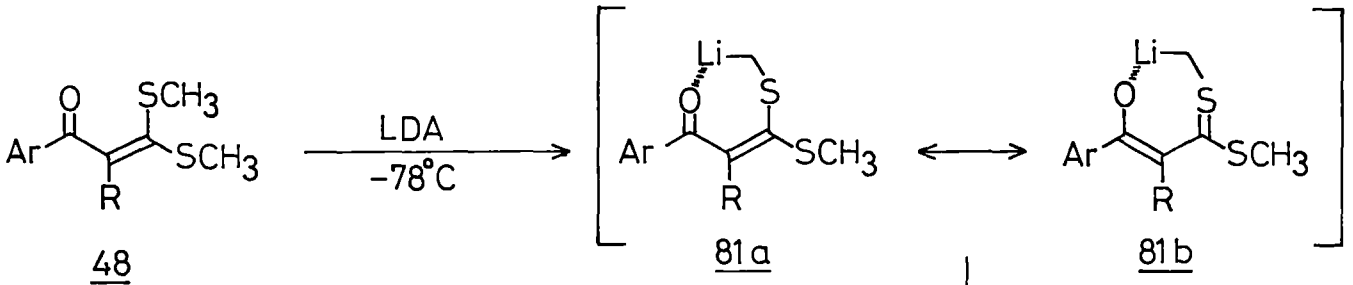
It is the experience of the author that the methodology developed for the thiophene synthesis described above via oxoketene dithioacetal is of considerable synthetic value. Evidently this is mainly due to the fact that a wide variety of α-oxoketene dithioacetals can be prepared from various class of active methylene ketones. Also another class of dithioacetals can be prepared by condensing the acylketene dithioacetals with various aldehydes. Another important factor is that the reaction can tolerate any structural variation on the α-oxoketene dithioacetal moiety.

By suitable manipulation of the substrate structure, thiophenes substituted at 3-position or 3,4-position can be obtained besides 3,4-annelated ones. Despite abundant literature on thiophene synthesis most of the methods are leading to 2- or 2,5-disubstituted thiophenes. Only very few methods are reported in the literature for the synthesis of 3- or 3,4-disubstituted thiophenes[30,37b, 38b].

An interesting and qualitatively similar approach reported in the literature is due to Marino and Kostusyk[30] using the same intermediates

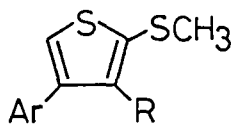
(Scheme 21). The reaction involves selective deprotonation of the thiomethyl group cis to carbonyl group to give the stabilised anion 81, which undergoes cyclisation to give thiophenes 49. However, the method suffers from many serious drawbacks such as (1) The reported yields are very poor (22-42%) and only in one case the yield recorded is 55%. (2) The method fails for all acylketene dithioacetals i.e. it cannot be used for the synthesis of any 4-alkyl or 3,4-dialkyl thiophenes. This is due to the preferential formation of enolate ion rather than S-methyl deprotonation. Structural limitations for 3,4-annelated thiophenes are also evident from the representative cyclic α-oxoketene dithioacetal 84 selected in their study. The method cannot be used for the synthesis of 4-enylthiophene due to vinylic deprotonation. (3) The substituent at α-position cannot be a methyl group due to allylic anion formation, although higher alkyl chains are tolerated. Thus, a methyl group cannot be introduced in the 3-position of thiophene ring.

The methodology developed is of considerable synthetic importance and provides a simple two step route to not easily accessible 3- or 3,4-disubstituted thiophenes from a wide variety of commercially available active methyl and methylene ketones. Again the method distinguishes itself from other thiophene synthesis since it involves a facile intramolecular aldol type condensation of the sulphonium ylid intermediate resulting in ring closure. Although carbenes are known to add to sulfur to yield sulfur ylids, this represents the first report on their formation under Simmons-Smith reaction condition.

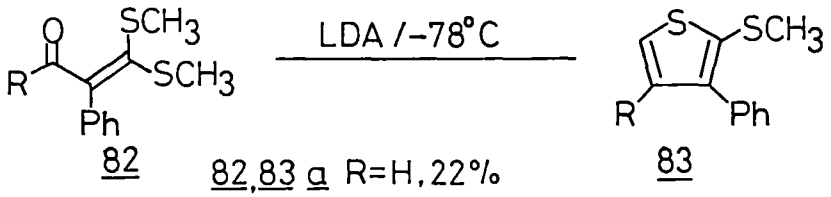


48 81a ⟷ 81b

Ar	R	yield %
C_6H_5	H	30
4-$MeOC_6H_4$	H	30
C_6H_5	Et	55
C_6H_5	MeO	42

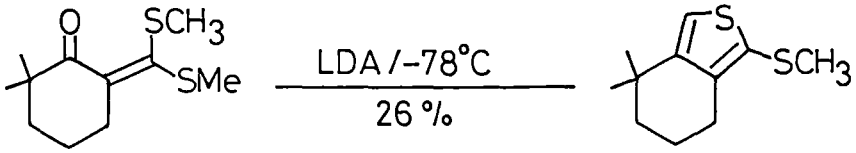


49



82 83

82,83 a R=H, 22%
b R=OCH_3, 38%



84 85

Scheme-21

III.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. I.r. spectra of crystalline compounds were determined for KBr discs and those of other compounds for thin films on a Perkin-Elmer 297 spectrophotometer. ^{1}H n.m.r. spectra were determined on a Varian EM-390 (90 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal standard unless otherwise indicated. Chemical shifts are expressed as δ(ppm) downfield from TMS. ^{13}C n.m.r. spectra were recorded on a Brucker WM-400 spectrometer. Mass spectra were obtained using a Jeol JMS D-300 spectrometer. Microanalysis were done at Central Drug Research Institute, Lucknow.

Starting Materials

Commercially available ketones were purchased (Aldrich) and were used as supplied. Other ketones were prepared by reported procedure. All liquid aldehydes were distilled free of acid before use. Some of the substituted cinnamaldehydes and higher homologues were prepared according to the reported procedure[47]. Zinc-copper couple was purchased (Ventron) and was dried at 120°C for 24 hr. prior to use. Methylene iodide was distilled before use. Diethyl ether and tetrahydrofuran were dried over sodium wire and distilled prior to use. All α-oxoketene dithioacetals 48a-j, 58a,b, 60a-d, 62a,b, 64a,b, 66 and 68 were prepared according to the general procedure described in Chapter II. The cinnamoyl ketene dithioacetals 72a-g, 72q, 75a, 5-aryl-2,4-pentadienoyl 72h-m, 75b and 7-aryl-2,4,6-heptatrienoyl 72n-p ketene dithioacetals were prepared as given below.

Condensation of α-acylketene dithioacetals with aldehydes: General procedure for the preparation of compounds (72a-q, 75a and 75b):

To a cooled and stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (0.06 mol) in ethanol (30 ml), a solution of the α-acylketene dithioacetal (0.03 mol) and the aldehyde (0.03 mol) in minimum ethanol was added dropwise over a period of 5 minutes. The reaction mixture was brought to room temperature over a period of 20 minutes and further stirred at room temperature for 4-5 hrs. The mixture was diluted with cold water (100 ml) and the solid separated out was filtered, washed with water (4x100 ml) and dried. The compounds 72a-l, 75a and 75b were previously reported[40,41] and the physical and spectral data were found to be in conformity with that of reported values. The data of unknown compounds 72m and 72n-p are given below.

1,1-Bis(methylthio)-2-(n-butyl)-7-(4-methoxyphenyl)-1,4,6-heptatriene-3-one (72m) was isolated as yellow crystalline solid (methanol), yield 78%; m.p. 60-61°C; ν_{max} 1600, 1506 cm^{-1}; δ_H 0.89(3H,distorted t,CH_3), 1.20(4H,m,CH_2), 2.22(3H,s,SCH_3), 2.43(3H,s,SCH_3), 2.44-2.73(2H,m,CH_2), 3.78(3H,s,OCH_3), 6.26(1H,d,J=16Hz,H-4), 6.69-6.93(5H,m,arom and olefinic), 7.34(2H,d,J=8.5Hz,A_2B_2,arom). (Found: C,66.18; H,7.30. $C_{20}H_{26}O_2S_2$ requires: C,66.26; H,7.23%); m/z 362(2%,M^+), 347(100).

1,1-Bis(methylthio)-9-phenyl-1,4,6,8-nonatetraene-3-one (72n) was isolated as brown solid (methanol), yield 82%; m.p. 142-143°C; ν_{max} 1619, 1550, 1458 cm^{-1}; δ_H 2.48(6H,s,SCH_3), 6.10(1H,s,H-2), 6.27(1H,d,J=16Hz, H-4), 6.39-7.90(5H,m,olefinic), 7.16-7.53(5H,m,arom). (Found: C,67.26; H,6.11. $C_{17}H_{18}OS_2$ requires: C,67.51; H,6.00%).

1,1-Bis(methylthio)-9-(3,4-methylenedioxyphenyl)-1,4,6,8-nonatetraene-3-one (72o) was isolated as brown solid (methanol), yield 85%; m.p. 149-150°C; ν_{max} 1610, 1594, 1512 cm^{-1}; δ_H 2.49(6H,s,SCH_3), 5.97(2H,s,CH_2); 6.14(1H,s,H-2), 6.23(1H,d,J=16Hz,H-4), 6.60-7.03(6H,m,arom and olefinic), 7.15-7.49(2H,m,arom). (Found: C,62.38; H,5.19. $C_{18}H_{18}O_3S_2$ requires: C,62.40; H,5.24%).

1,1-Bis(methylthio)-2-methyl-9-(3,4-methylenedioxyphenyl-1,4,6,8-nonatetraene-3-one (72p) was isolated as brown solid (methanol), yield 81%; m.p. 110-111°C; ν_{max} 1638, 1583, 1560 cm^{-1}; δ_H 2.13(3H,s,SCH_3), 2.24(3H,s,SCH_3), 2.36(3H,s,CH_3), 5.97(2H,s,CH_2), 6.29(1H,d,J=16Hz, H-4), 6.49-7.30(8H,m,arom and olefinic). (Found: C,63.46; H,5.71. $C_{19}H_{20}O_3S_2$ requires: C,63.30; H,5.59%).

Cyclopropanation of α-enoyldithioacetals using DMSY: General procedure for the preparation of cyclopropylketene dithioacetals (79a-e):

A solution of 50% aqueous NaOH solution (50 ml) was introduced beneath a solution of the substrate (0.01 mol) and the phase transfer catalyst (TBAI)(0.013 mol) in dichloromethane (50 ml). Trimethylsulfoxonium iodide (0.011 mol) was added and the mixture is maintained at 45-50°C with vigerous stirring for 16-24 hr. (monitored by t.l.c.). The layers were separated and the organic layer was evaporated. The residue was diluted with EtOAc and the precipitated catalyst was removed by filteration. The ethyl acetate solution was evaporated and chromatographed over silica gel column using 5% EtOAc-hexane as eluent.

3,3-Bis(methylthio)-1-(2-phenylcyclopropyl)-2-propen-1-one (79a) was isolated as pale yellow solid (CH_2Cl_2-hexane), yield 90%; m.p. 104°C;

ν_{max} 1620, 1479 cm^{-1}; δ_H 1.21-1.45(1H,m,CH_2 cyclopropyl), 1.61-1.86 (1H,m,CH_2 cyclopropyl), 1.99-2.23(1H,m,CH cyclopropyl), 2.43(3H,s, SCH_3), 2.50(3H,s,SCH_3), 2.36-2.66(1H,m,CH cyclopropyl, merged with SCH_3), 6.16(1H,s, vinylic), 7.00-7.33(5H,m,arom). (Found: C,63.49; H,6.02. $C_{14}H_{16}OS_2$ requires: C,63.60; H,6.10%); m/z 264(10%,M^+), 249(100).

3,3-Bis(methylthio)-1-[2-(4-methoxyphenyl)cyclopropyl]-2-propen-1-one (79b) was isolated as pale yellow solid (CH_2Cl_2-hexane), yield 92%; m.p. 96-97°C; ν_{max} 1621, 1492 cm^{-1}; δ_H 1.14-1.37(1H,m,CH_2 cyclopropyl), 1.52-1.80(1H,m,CH_2 cyclopropyl), 1.79-2.04(1H,m,CH cyclopropyl), 2.41(3H,s,SCH_3), 2.43(3H,s,SCH_3), 2.34-2.58(1H,m,CH cyclopropyl, merged with SCH_3), 3.75(3H,s,OCH_3), 6.16(1H,s,olefinic), 6.76(2H,d, J=9Hz,ArH), 7.00(2H,d,J=9Hz,ArH). (Found: C,65.02; H,5.76. $C_{15}H_{18}O_2S_2$ requires: C,65.18; H,5.84%); m/z 294(24%,M^+), 279(43).

3,3-Bis(methylthio)-2-methyl-1-[2-(3,4-methylenedioxyphenyl)cyclopropyl]-2-propen-1-one (79c) was isolated as viscous liquid, yield 91%; ν_{max} 1568, 1490, 1432 cm^{-1}; δ_H 1.16-1.39(1H,m,CH_2 cyclopropyl), 1.50-1.71 (1H,m,CH_2 cyclopropyl), 2.06(3H,s,SCH_3), 2.12(3H,s,SCH_3), 2.28(3H,s, CH_3), 1.99-2.59(2H,m,CH cyclopropyl, merged with SCH_3 and CH_3), 5.83(2H,s,CH_2), 6.50-6.66(3H,m,arom). (Found: C,59.73; H,5.68. $C_{16}H_{18}O_3S2$ requires: C,59.60; H,5.63%); m/z 322(12%,M^+), 307(77), 276(86).

3,3-Bis(methylthio)-1-(2-styrylcyclopropyl)-2-propen-1-one (79d) was isolated as pale yellow solid (CH_2Cl_2-hexane), yield 89%; m.p. 116-117°C; ν_{max} 1629, 1496 cm^{-1}; δ_H 0.89-1.20(1H,m,CH_2 cyclopropyl), 1.48-1.73 (1H,m,CH_2 cyclopropyl), 1.88-2.44(2H,m,CH cyclopropyl), 5.77(1H,dd,

J=16 and 8Hz,CH=CHAr), 6.30(1H,d,J=16Hz,CH=CHArH), 7.28(5H,m,arom). (Found: C,65.99; H,6.18. $C_{16}H_{18}OS_2$ requires: C,66.17; H,6.25%); m/z 290(8%,M^+), 275(36).

3,3-Bis(methylthio)-1-[2-(4-phenyl-1,3,-butadienyl)cyclopropyl]-2-propen-1-one (79e) was isolated as pale yellow solid (CH_2Cl_2-hexane), yield 86%; m.p. 122-123°C; ν_{max} 1626, 1471 cm^{-1}; δ_H 0.76-1.32(2H,m, CH_2 cyclopropyl), 1.49-1.72(1H,m,CH cyclopropyl), 1.86-2.18(1H,m, CH cyclopropyl), 2.42(6H,s,SCH_3), 5.37(1H,dd,J=16 and 8Hz,CH=CHAr), 6.13(1H,s,H-2), 6.21-6.63(3H,m,olefinic), 7.12-7.42(5H,m,arom). (Found: C,68.22; H,6.41. $C_{18}H_{20}OS_2$ requires: C,68.31; H,6.37%); m/z 316(2%,M^+), 301(3).

General procedure for Simmons-Smith reaction; synthesis of thiophenes: To a well stirred suspension of zinc-copper couple (4.0g) in dry ether (25 ml), under nitrogen atmosphere, a small crystal of iodine and CH_2I_2 (6.70g, 25 mmol) were added and the reaction mixture was refluxed for 45 minutes. A solution of the α-oxoketene dithioacetal (10 mmol) in dry THF (15 ml) was added and the reaction mixture was refluxed with stirring for 5-8 hr. (monitored by t.l.c.). The solvent was removed under reduced pressure and the residue was diluted with chloroform (150 ml) and water (200 ml). The reaction mixture was filtered and the residue was washed with chloroform. The chloroform layer was separated and washed with saturated NH_4Cl solution, water, dried (Na_2SO_4) and concentrated to give the crude thiophene which was purified by column chromatography over silica gel using hexane as eluent.

2-Methylthio-4-phenylthiophene (49a) was isolated as light yellow crystals (hexane), yield 61%; m.p. 42°C; ν_{max} 1597, 1482, 1443, 1300 cm^{-1}; δ_H 2.43 (3H,s,SCH_3), 7.10-7.59(7H,m,ArH+H-3and H-5); δ_C 21.32(SCH_3), 122.56(C-5), 130.02(C-3), 125.64, 126.64, 129.00(C-H arom), 135.35(C-1'), 138.28(C-2), 144.42(C-4). (Found: C,64.32; H,4.51. $C_{11}H_{10}S_2$ requires: C,64.03; H,4.88%); m/z 206(100%,M^+), 191(32), 147(23).

2-Methylthio-4-(4-methylphenyl)thiophene (49b) was isolated as light yellow crystals (hexane), yield 64%; m.p. 60-61°C; ν_{max} 1499, 1413, 1305 cm^{-1}; δ_H (400 MHz) 2.30(3H,s,SCH_3), 2.46(3H,s,CH_3), 7.13(2H,d,J=8.5Hz,ArH), 7.27(1H,d,J=1.5Hz,H-3), 7.30(1H,d,J=1.5Hz,H-5), 7.39(2H,d,J=8.5Hz,ArH); δ_C 21.49(SCH_3), 21.95(CH_3), 122.10(C-5), 130.26(C-3), 126.41, 129.76(C-H, ArH), 132.76, 136.86(C-1' and C-4' of aryl), 138.14(C-2), 142.58(C-4). (Found: C,65.20; H,5.41. $C_{12}H_{12}S_2$ requires: C,65.41; H,5.49%); m/z 220 (100%,M^+), 205(27), 161(21).

2-Methylthio-4-(4-chlorophenyl)thiophene (49c) was isolated as light yellow crystals (hexane), yield 65%; m.p. 64°C; ν_{max} 1596, 1485, 1356 cm^{-1}; δ_H 2.44(3H,s,SCH_3), 7.13-7.25(2H,m,thiophene H), 7.26-7.45(4H,m,arom); δ_C 21.88(SCH_3); 122.57(C-5), 129.51(C-3), 127.36, 128.29(CH arom), 133.01, 133.84(C-1' and C-4' of aryl), 138.63, 141.20(C-2 and C-4 of thiophene). (Found: C,54.76; H,3.80. $C_{11}H_9ClS_2$ requires: C,54.90; H,3.76%); m/z 242 and 240(45,100%,M^+).

2-Methylthio-4-(methoxyphenyl)thiophene (49d) was isolated as light yellow crystals (hexane), yield 62%; m.p. 102-103°C; ν_{max} 1601, 1529, 1498, 1410 cm^{-1}; δ_H (400 MHz) 2.51(3H,s,SCH_3), 3.77(3H,s,OCH_3), 6.79 (2H,d,J=8.5Hz,arom), 7.15(1H,d,J=1.5Hz,H-3), 7.21(1H,d,J=1.5Hz),7.38(2H,

d,J=8.5Hz,arom). (Found: C,61.12; H,5.20. $C_{12}H_{12}OS_2$ requires: C,60.98; H,5.12%); m/z 236(100%,M^+), 221(36), 177(10).

2-Methylthio-4(2-naphthyl)thiophene (49e) was isolated as colourless crystals (hexane), yield 67%; m.p. 70-71°C; ν_{max} 1591, 1490, 1410 cm^{-1}; δ_H 2.43(3H,s,SCH_3), 7.29-7.89(9H,m,arom). (Found: C,70.12; H,4.70. $C_{15}H_{12}S_2$ requires: C,70.27; H,4.72%); m/z 256(100%,M^+), 241(28),197(23).

3-Methyl-2-methylthio-4-phenylthiophene (49f) was isolated as light yellow liquid, yield 59%; ν_{max} 1599, 1576, 1484 cm^{-1}; δ_H 2.20(3H,s, SCH_3), 2.31(3H,s,CH_3), 7.05(1H,s,thiophene H), 7.26(5H,s,arom). (Found: C,65.22; H,5.38. $C_{12}H_{12}S_2$ requires: C,65.41; H,5.49%); m/z 220(100%,M^+), 205(35).

3-Ethyl-2-methylthio-4-phenylthiophene (49g) was isolated as light yellow liquid, yield 58%; ν_{max} 1598, 1574, 1482, 1440 cm^{-1}; δ_H 0.97 (3H,t,J=7Hz,$CH_2\underline{CH_3}$), 2.41(3H,s,SCH_3), 2.66(2H,q,J=7Hz,$\underline{CH_2}CH_3$), 7.09 (1H,s,thiophene H), 7.31(5H,s,arom). (Found: C,66.49; H,5.98. $C_{13}H_{14}S_2$ requires: C,66.62; H,6.02%); m/z 234(21%,M^+).

2-Methylthio-4-phenyl-3-(n-propyl)thiophene (49h) was isolated as light yellow liquid, yield 59%; ν_{max} 1595, 1573, 1520, 1487, 1440, 1360 cm^{-1}; δ_H 0.79(3H,t,J=7Hz,$CH_2CH_2\underline{CH_3}$), 1.30(2H,sext,J=7.0Hz, $CH_2\underline{CH_2}CH_3$), 2.42(3H,s,SCH_3), 2.66(2H,t,J=7.0Hz,$\underline{CH_2}CH_2CH_3$), 7.09(1H, s,thiophene H), 7.32(5H,s,arom). (Found: C,67.83; H,6.72. $C_{14}H_{16}S_2$ requires: C,67.69; H,6.49%); m/z 248(100%,M^+), 219(75), 172(49).

3-Benzyl-4-(4-chlorophenyl)-2-methylthiothiophene (49i) was isolated as viscous brown liquid, yield 58%; ν_{max} 1591, 1510, 1477, 1419 cm^{-1};

δ_H2.25(3H,s,SCH_3), 4.01(2H,s,$CH_2C_6H_5$),6.78-7.29(10H,m,ArH+thiophene H). (Found: C,65.21; H,4.52. $C_{18}H_{15}ClS_2$ requires: C,65.34; H,4.57%); m/z 332 and 330(100%,M^+).

3,4-Diphenyl-2-methylthiothiophene (49j) was isolated as colourless crystals (hexane), yield 54%; m.p. 99-100°C; ν_{max} 1598, 1479, 1435, 1428 cm^{-1}; δ_H 2.34(3H,s,SCH_3), 6.97-7.40(11H,m,ArH+thiophene H). (Found: C,72.19; H,4.92. $C_{17}H_{14}S_2$ requires: C,72.30; H,5.00%); m/z 282(100%,M^+), 267(29), 234(52).

3-Allyl-2-methylthio-4-phenylthiophene (49k) was isolated as light yellow liquid, yield 60%; ν_{max} 1599, 1490, 1443, 1425 cm^{-1}; δ_H 2.37 (3H,s,SCH_3), 3.39(2H,d,J=4.5Hz,$\underline{CH_2}$-CH=CH_2), 4.84-5.07(2H,m,CH_2-CH=$\underline{CH_2}$), 5.56-5.97(1H,m,CH_2-$\underline{CH}$=CH_2), 7.12(1H,s,thiophene H), 7.31(5H,s,arom). (Found: C,68.61; H,6.01. $C_{14}H_{14}S_2$ requires: C,68.25; H,5.72%); m/z 246(100%,M^+), 231(86).

4-(2-furyl)-2-methylthiothiophene (59a) was isolated as colourless liquid turning dark on keeping, yield 58%; ν_{max} 1600, 1520, 1474, 1418 cm^{-1}; δ_H 2.46(3H,s,SCH_3), 6.33(2H,brs,H-3' and H-5' furyl), 7.19(1H,brs,H-4' furyl), 7.36(2H,brs,H-3and H-5, thiophene). (Found: C,54.82; H,4.42. $C_9H_8OS_2$ requires: C,55.07; H,4.10%); m/z 196(100%,M^+).

2-Methylthio-4-(2-thienyl)thiophene (59b) was isolated as light yellow liquid, yield 63%; ν_{max} 1498, 1427, 1410 cm^{-1}; δ_H 2.47(3H,s,SCH_3), 6.87-7.28(5H,m,thiophene H). (Found: C,51.27; H,4.02. $C_9H_8S_3$ requires: C,50.90; H,3.80%); m/z 212(100%,M^+), 197(45), 153(58).

4-Methyl-2-methylthiothiophene (61a) was isolated as colourless volatile liquid, yield 53%; ν_{max} 1593, 1510, 1473, 1410 cm^{-1}; δ_H 2.20(3H,brs,CH_3),

2.41(3H,s,SCH_3), 6.80(2H,s,H-3 and H-5). (Found: C,50.21; H,5.83. $C_6H_8S_2$ requires:C,49.96; H,5.59%); m/z 144(100%,M^+).

3,4-Dimethyl-2-methylthiothiophene (61b) was isolated as light yellow liquid, yield 56%; ν_{max} 1430, 1380, 1363 cm^{-1}; δ_H 2.10(3H,s,3-CH_3), 2.13(3H,s,4-CH_3), 2.29(3H,s,SCH3), 6.80(1H,s,thiophene H). (Found: C,53.39; H,6.58. $C_7H_{10}S_2$ requires: C,53.11; H,6.37%); m/z 158(100%,M^+).

4-Ethyl-3-methyl-2-methylthiothiophene (61c) was isolated as light yellow liquid, yield 58%; ν_{max} 1599, 1458, 1428, 1376 cm^{-1}; δ_H 1.19 (3H,t,J=7.5Hz,$CH_2\underline{CH_3}$), 2.16(3H,s,CH_3), 2.29(3H,s,SCH_3), 2.48(2H,q, $\underline{CH_2}CH_3$), 6.81(1H,s,thiophene H). (Found: C,55.82; H,7.12. $C_8H_{12}S_2$ requires:C,55.76; H,7.02%); m/z 172(15%,M^+).

3-(n-Butyl)-4-methyl-2-methylthiothiophene (61d) was isolated as colourless liquid, yield 62%; ν_{max} 1440, 1379, 1309, 1179 cm^{-1}; δ_H 0.95(3H,distorted t,$(CH_2)_3\underline{CH_3}$), 1.23-1.54(4H,m,$CH_2(\underline{CH_2})_2CH_3$), 2.17(3H,s,$CH_3$), 2.36(3H,s,$SCH_3$), 2.61(2H,t,$\underline{CH_2}(CH_2)_2CH_3$), 6.82(1H, s,H-5). (Found: C,60.24; H,8.33. $C_{10}H_{16}S_2$ requires: C,59.95; H,8.05%); m/z 200(64%,M^+), 157(100).

2-Methylthiocyclohexa[c]thiophene (63a) was isolated as colourless liquid, yield 65%; ν_{max} 1543, 1437, 1388 cm^{-1}; δ_H 1.55-1.84(4H,m, CH_2), 2.34(3H,s,SCH_3), 2.60-2.82(4H,m,CH_2), 6.76(1H,s,thiophene H). (Found: C,58.90; H,6.83. $C_9H_{12}S_2$ requires: C,58.65; H,6.57%); m/z 184(100%,M^+), 169(42).

2-Methylthiocyclohepta[c]thiophene (63b) was isolated as colourless liquid, yield 62%; ν_{max} 1442, 1428, 1382, 1309 cm^{-1}; δ_H 1.43-1.90 (6H,m,CH_2), 2.30(3H,s,SCH_3), 2.57-2.89(4H,m,CH_2), 6.73(1H,s,thiophene H).

(Found:C,60.28; H,7.40. $C_{10}H_{14}S_2$ requires: C,60.56; H,7.11%); m/z 198(100%,M^+), 183(38).

2-Methylthio-3,4-dihydronaphtho[2,1-c]thiophene (63c) was isolated as viscous liquid, yield 57%; ν_{max} 1599, 1479, 1454, 1420 cm^{-1}; δ_H 2.32(3H,s,SCH_3), 2.79(4H,s,CH_2), 6.93-7.18(3H,m,arom), 7.28 (1H,s,thiophene H), 7.32-7.50(1H,m,arom). (Found: C,66.83; H,5.51. $C_{13}H_{12}S_2$ requires: C,67.19; H,5.21%); m/z 232(100%,M^+), 217(22).

2-Methylthio-4,5-dihydro-3H-benzocyclohepta[2,1-c]thiophene (65b) was isolated as viscous liquid, yield 60%; ν_{max} 1524, 1476, 1439, 1360 cm^{-1}; δ_H 1.83-2.24(2H,quint, CH_2), 2.31(3H,s,SCH_3), 2.38-2.71 (4H,m,CH_2), 7.00-7.24(5H,m,arom and thiophene H). (Found: C,68.52; H,5.91. $C_{14}H_{14}S2$ requires: C,68.25; H,5.73%); m/z 246(100%,M^+), 231(11).

2-Methylthio-3,4-dihydrobenzoxepino[2,1-c]thiophene (66) was isolated as viscous liquid, yield 61%; ν_{max} 1596, 1563, 1479, 1441 cm^{-1}; δ_H 2.27(3H,s,SCH_3), 2.89(2H,t,CH_2), 4.24(2H,t,CH_2), 6.78-7.18(3H, m,arom), 7.20(1H,s,thiophene H), 7.25-7.41(1H,m,arom).(Found: C,62.62; H,5.13. $C_{13}H_{12}OS_2$ requires: C,62.87; H,4.87%); m/z 248(100%,M^+), 233(44).

8-Methyl-2-methylthio-3,4-dihydrobenzothiepino[2,1-c]thiophene (69) was isolated as viscous brown semisolid, yield 62%; ν_{max} 1595, 1532, 1480, 1421 cm^{-1}; δ_H 2.32(3H,s,CH_3), 2.38(3H,s,SCH_3), 2.91-3.12(2H, m,CH_2), 3.21-3.39(2H,m,CH_2), 7.20-7.33(3H,m,arom and thiophene H), 7.53(1H,brs,arom). (Found: C,60.21; H,5.18. $C_{14}H_{14}S_3$ requires: C,60.39; H,5.07%); m/z 278(100%,M^+), 263(31).

2-Methylthio-4-styrylthiophene (73a) was isolated as light yellow crystalline solid (hexane), yield 58%; m.p. 58-59°C; ν_{max} 1600,1580, 1498, 1453, 1425 cm^{-1}; δ_H 2.48(3H,s,SCH_3), 6.88(2H,s,olefinic), 7.01-7.48(7H,m,ArH+thiophene H). (Found: C,67.28; H,5.33. $C_{13}H_{12}S_2$ requires: C,67.19; H,5.21%); m/z 232(86%,M^+), 184(100).

2-Methylthio-4-(4-chlorostyryl)thiophene (73b) was isolated as colourless crystalline solid (hexane), yield 68%; m.p. 79-80"C; ν_{max} 1585, 1481, 1403, 1391 cm^{-1}; δ_H 2.48(3H,s,SCH_3); 6.75-7.33(8H,m,arom+olefinic+ thiophene H). (Found: C,58.58; H,4.01. $C_{13}H_{11}ClS_2$ requires: C,58.52; H,4.16%); m/z 268 and 266(44,100%,M^+), 184(58).

2-Methylthio-4-(3,4-methylenedioxystyryl)thiophene (73c) was isolated as colourless crystalline solid (hexane), yield 63%; m.p. 65-66°C; ν_{max} 1598, 1510, 1495, 1479, 1440 cm^{-1}; δ_H 2.46(3H,s,SCH_3), 5.92 (2H,s,CH_2), 6.66-6.83(4H,m,arom and olefinic), 6.91-7.33(3H,m,ArH+ thiophene H). (Found: C,60.72; H,4.46. $C_{14}H_{12}O_2S_2$ requires: C,60.84; H,4.38%); m/z 276(100%,M^+); 228(84).

2-Methylthio-4-(2-chlorostyryl)thiophene (73d) was isolated as viscous yellow liquid, yield 66%; ν_{max} 1628, 1585, 1463, 1436 cm^{-1}; δ_H 2.49 (3H,s,SCH_3), 6.79-7.66(8H,m,ArH+ olefinic+thiophene H).(Found: C,58.41;H,3.99. $C_{13}H_{11}ClS_2$ requires: C,58.52; H,4.16%); m/z 268 and 266 (15,100%,M^+).

3-Methyl-2-methylthio-4-styrylthiophene (73e) was isolated as viscous liquid, yield 67%; ν_{max} 1592, 1488, 1440, 1372 cm^{-1}; δ_H 2.28(6H,s,CH_3 and SCH_3), 6.84(2H,brs,olefinic),6.94-7.43(6H,m,ArH+thiophene H). (Found: C,68.59; H,6.11. $C_{14}H_{14}S_2$ requires: C,68.25; H,5.73%); m/z 246(100%,M^+), 198(72).

3-Methyl-2-methylthio-4-(4-methoxystyryl)thiophene (73f) was isolated as light yellow solid (hexane), yield 68%; m.p. 85-86°C; ν_{max} 1591, 1560, 1498, 1426 cm^{-1}; δ_H 2.30(3H,s,CH_3), 2.32(3H,s,SCH_3), 6.67-6.83 (4H,m,ArH+olefinic), 7.16-7.38(3H,m,ArH+thiophene H). (Found: C,65.06; H,5.90. $C_{15}H_{16}OS_2$ requires: C,65.18; H,5.84%); m/z 276 (100%,M^+), 228(58).

3-Methyl-2-methylthio-4(3,4-methylenedioxystyryl)thiophene (73g) was isolated as light yellow solid (hexane), yield 64%; m.p. 55-56°C; ν_{max} 1591, 1490, 1479, 1436 cm^{-1}; δ_H 2.21(3H,s,CH_3), 2.23(3H,s,SCH_3), 5.88(2H,s,CH_2), 6.48-6.87(4H,m,arom and olefinic), 6.90(1H,s,thiophene H), 7.17(1H,s,arom). (Found: C,61.93; H,4.98. $C_{15}H_{14}O_2S_2$ requires: C,62.04; H,4.86%); m/z 290(100%,M^+), 242(86).

2-Methylthio-4(4-phenyl-1,3-butadienyl)thiophene(73h) was isolated as colourless crystalline solid (hexane), yield 65%; mp. 89-90°C; ν_{max} 1479, 1440, 1303 cm^{-1}; δ_H 2.47(3H,s,SCH_3), 6.50-6.80(4H,m,olefinic), 7.03-7.40(7H,m,ArH+thiophene H). (Found: C,69.80; H,5.58. $C_{15}H_{14}S_2$ requires: C,69.72; H,5.46%); m/z 258(100%,M^+), 210(77).

2-Methylthio-4-[4-(4-methoxyphenyl)-1,3-butadienyl]thiophene (73i) was isolated as light yellow crystalline solid (dichloromethane/hexane), yield 67%; m.p. 147-148°C; ν_{max} 1596, 1500, 1299, 1243 cm^{-1}; δ_H 2.47 (3H,s,SCH_3), 3.76(3H,s,OCH_3), 6.47-6.73(4H,m,olefinic),6.84(2H,d,J=8.5Hz, arom), 7.09(1H,brs,thiophene H), 7.22(1H,brs,thiophene H), 7.39(2H,d, J=8.5Hz,arom). (Found: C,66.53; H,5.67. $C_{16}H_{16}OS_2$ requires: C,66.63; H,5.59%); m/z 288(100%,M^+), 240(37).

2-Methylthio-4-[4-(3,4-methylenedioxyphenyl)-1,3-butadienyl]thiophene(73j) was isolated as light yellow crystalline solid (dichloromethane/hexane), yield 63%; m.p. 102°C; ν_{max} 1489, 1444, 1259 cm^{-1}; δ_H 2.49(3H,s,SCH_3), 5.93(2H,s,CH_2), 6.43-6.67(4H,m,olefinic), 6.72-6.83(2H,m,arom), 6.92 (1H,s,arom), 7.08(1H,brs,thiophene H), 7.19(1H,brs,thiophene H). (Found: C,63.49; H,4.52. $C_{16}H_{14}O_2S_2$ requires: C,63.55; H,4.67%); m/z 302(100%,M^+), 254(42).

3-Methyl-2-methylthio-(4-phenyl-1,3-butadienyl)thiophene (73k) was isolated as white crystalline solid (hexane), yield 62%; m.p. 98-99°C; ν_{max} 1584, 1489, 1479, 1426 cm^{-1}; δ_H 2.30(3H,s,CH_3), 2.35(3H,s,SCH_3), 6.59-6.99(4H,m,olefinic), 7.20-7.52(6H,m,ArH+thiophene H). (Found: C,70.52; H,5.99. $C_{16}H_{16}S_2$ requires: C,70.54; H,5.92%); m/z 272(100%,M^+), 224(73).

3-Methyl-2-methylthio-4-[4-(3,4-methylenedioxyphenyl)-1,3-butadienyl] thiophene (73l) was isolated as light yellow crystalline solid (hexane), yield 63%; m.p. 112°C; ν_{max} 1589, 1499, 1481, 1436, 1347 cm^{-1}; δ_H 2.28 (3H,s,CH_3), 2.35(3H,s,SCH_3), 5.91(2H,s,CH_2), 6.48-6.73(4H,m,olefinic), 6.80(2H,brs,arom), 7.94(1H,brs,arom), 7.27(1H,brs,thiophene H). (Found: C,64.61; H,5.19. $C_{17}H_{16}O_2S_2$ requires: C,64.52; H,5.10%); m/z 316(100%,M^+); 268(42).

3-n-Butyl-2-methylthio-4-[4-(4-methoxyphenyl)-1,3-butadienyl]thiophene (73m) was isolated as light yellow solid (hexane), yield 60%; m.p. 79-80°C; ν_{max} 1598, 1508, 1460, 1438 cm^{-1}; δ_H 0.95(3H,distorted t, CH_3), 1.25-1.62(4H,m,$CH_2(\underline{CH_2})_2CH_3$), 2.36(3H,s,$SCH_3$), 2.73(2H,t, $\underline{CH_2}(CH_2)_2CH_3$), 3.77(3H,s,$OCH_3$), 6.34-6.91(6H,m,arom and olefinic),

7.28-7.43(2H,m,arom), 7.30(1H,s,thiophene H). (Found: C,69.82; H,7.08. $C_{20}H_{24}OS_2$ requires: C,69.76; H,6.97%); m/z 344(100%,M^+).

3-Methyl-2-methylthio-4-[3-(3,4-dimethoxyphenyl)-2-propenyl]thiophene (76a) was isolated as colourless crystalline solid (hexane), yield 61%; m.p. 64-65°C; ν_{max} 1604, 1586, 1517, 1462, 1440 cm^{-1}; δ_H 2.21 (3H,brs,vinylic CH_3), 2.34(3H,s,3-CH_3), 2.42(3H,s,SCH_3), 3.94(6H, s,OCH_3), 6.49(1H,brs,arom), 6.94(3H,brs,arom and vinylic), 7.14(1H, s,thiophene H). (Found: C,63.80; H,6.32. $C_{17}H_{20}O_2S_2$ requires: C,63.71; H,6.29%); m/z 320(100%,M^+), 258(49).

3-Methyl-2-methylthio-4-(5-phenyl-2,4-pentadienyl)thiophene (76b) was isolated as viscous liquid, yield 58%; ν_{max} 1589, 1483, 1440, 1425, 1370, 1309 cm^{-1}; δ_H 2.10(3H,brs,CH_3), 2.24(3H,s,3-CH_3), 2.26(3H,s, SCH_3), 6.10-6.59(3H,m,olefinic), 6.88-7.39(6H,m,ArH+thiophene H). (Found: C,71.40; H,6.42. $C_{17}H_{18}S2$ requires: C,71.28; H,6.33%); m/z 286(100%,M^+), 238(39), 224(40).

2-Methylthio-4-(6-phenyl-1,3,5-hexatrienyl)thiophene (73n) was isolated as light yellow crystalline solid (dichloromethane/hexane), yield 69%; m.p. 133-134°C; ν_{max} 1612, 1580, 1479, 1439, 1410 cm^{-1}; δ_H (400 MHz), 2.46(3H,s,SCH_3), 6.40-6.52(3H,m,olefinic), 6.58(1H,d,J=12Hz,olefinic), 6.65(1H,dd,J=12 and 8.5Hz,olefinic), 6.85(1H,dd,J=12 and 8.5Hz,olefinic), 7.09(1H,brs,H-3), 7.20(1H,brs,H-5), 7.18-7.25(1H,m,merged with H-5 signal,arom), 7.31(2H,t,J=8.5Hz,arom), 7.40(2H,d,J=8.5Hz,arom).(Found: C,71.62; H,5.72. $C_{17}H_{16}S_2$ requires: C,71.78; H,5.67%); m/z 284(100%,M^+).

2-Methylthio-4-[6-(3,4-methylenedioxyphenyl)-1,3,5-hexatrienyl] thiophene (73o) was isolated as yellow crystalline solid (dichloromethane/

hexane), yield 68%; m.p. 142-143°C; ν_{max} 1628, 1509, 1498, 1451, 1260 cm^{-1}; δ_H 2.48(3H,s,SCH_3), 5.95(2H,s,CH_2), 6.24-6.63(6H,m,olefinic), 6.72-7.27(5H,m,ArH+thiophene H).(Found: C,65.69; H,4.82. $C_{18}H_{16}O_2S_2$ requires: C,65.82; H,4.91%); m/z 328(100%,M^+).

3-Methyl-2-methylthio-4-[6-(3,4-methylenedioxyphenyl)-1,3,5-hexatrienyl] thiophene (73p) was isolated as yellow crystalline solid (dichloromethane/ hexane), yield 70%; m.p. 109°C; ν_{max} 1601, 1480, 1435, 1352, 1251, 1235 cm^{-1}; δ_H 2.29(3H,s,CH_3), 2.36(3H,s,SCH_3), 5.92(2H,s,CH_2), 6.31-6.99(9H,m,olefinic and aromatic), 7.27(1H,s,thiophene H). (Found: C,66.72; H,5.21. $C_{19}H_{18}O_2S_2$ requires: C,66.63; H,5.30%); m/z 342(100%,M^+).

2-Methylthio-4-(2-phenyl)cyclopropylthiophene (80a) was isolated as viscous liquid, yield 57%; ν_{max} 1600, 1531, 1492, 1459, 1412 cm^{-1}; δ_H 1.24(2H,distorted t, J=7.0Hz,cyclopropyl CH_2), 2.00(2H,t,J=7.0Hz, cyclopropyl CH), 2.37(3H,s,SCH_3), 6.76(2H,brs,H-3 and H-5), 6.93-7.29 (5H,m,arom). (Found: C,68.56; H,6.07. $C_{14}H_{14}S_2$ requires: C,68.25; H,5.73%); m/z 246(100%,M^+).

2-Methylthio-4-[2-(4-methoxyphenyl)cyclopropyl]thiophene (80b) was isolated as light yellow viscous liquid, yield 59%; ν_{max} 1617, 1519, 1470, 1445 cm^{-1}; δ_H 1.16(2H,t,J=7.0Hz,cyclopropyl CH_2), 1.93(2H,t, J=7.0Hz,cyclopropyl CH), 2.37(3H,s,SCH_3), 3.62(3H,s,OCH_3), 6.59-6.76 (4H,m,aromatic,H-3 and H-5), 6.90(2H,d,J=8.5Hz,arom). (Found: C,65.09; H,5.91. $C_{15}H_{16}OS_2$ requires: C,65.18; H,5.84%); m/z 276(100%,M^+), 229(33).

3-Methyl-2-methylthio-4-[2-(3,4-methylenedioxyphenyl)cyclopropyl] thiophene (80c) was isolated as light yellow viscous liquid, yield 61%;

ν_{max} 1605, 1501, 1490, 1460, 1440 cm^{-1}; δ_H 1.17(2H,distorted t, J=7.0Hz,cyclopropyl CH_2), 1.83(2H,distorted t,J=7.0Hz,cyclopropyl CH), 2.22(3H,s,CH_3), 2.29(3H,s,SCH_3), 5.78(2H,s,CH_2), 6.50-6.54(3H,m,arom), 6.70(1H,s,H-5). (Found: C,63.46; H,5.62. $C_{16}H_{16}O_2S_2$ requires: C,63.13; H,5.30%); m/z 304(100%,M^+).

2-Methylthio-4-[2-(styryl)cyclopropyl]thiophene (80d) was isolated as viscous yellow liquid, yield 54%; ν_{max} 1640, 1597, 1530, 1487,1440, 1410 cm^{-1}; δ_H 0.92-1.21(2H,m,cyclopropyl CH_2), 1.45-1.91(2H,m,cyclopropyl CH), 2.31(3H,s,SCH_3), 5.64(1H,dd,J=16 and 7.5Hz,CH=CHAr), 6.31 (1H,d,J=16Hz,CH=CHAr), 6.63(1H,brs,H-3), 7.06(6H,brs,arom and H-5). (Found: C,70.84; H,6.23. $C_{16}H_{16}S_2$ requires: C,70.54; H,5.92%); m/z 272(100%,M^+), 225(22).

2-Methylthio-4-[2-(4-phenyl-1,3-butadienyl)cyclopropyl]thiophene (80e) was isolated as viscous yellow liquid, yield 56%; ν_{max} 1636, 1590, 1530, 1458, 1410 cm^{-1}; δ_H 0.80-1.23(2H,m,cyclopropyl CH_2), 1.37-1.89(2H,m, cyclopropyl CH), 2.31(3H,s,SCH_3), 5.27(1H,dd,J=16 and 7.5Hz,CH=CH-CH=CHAr), 5.95-6.63(3H,m,olefinic), 6.92(1H,s,H-3), 6.88-7.27(6H,m,arom and H-5). (Found: C,72.73; H,6.42. $C_{18}H_{18}S_2$ requires: C,72.44; H,6.08%); m/z 298(84%,M^+).

Desulphurisation of thiophenes (49a-c, 49j, 73n,p and 76a); General Procedure:

To a solution of methylthiothiophene (0.004 mol) in methanol (30 ml) was added Raney-Nickel (W-2) (ca.10 times by weight) and the mixture was stirred at room temperature for 3-5 hr. (monitored by t.l.c.). The reaction mixture was filtered and the residue was washed with hot

methanol (3x20 ml). The bulk of the methanol was removed under reduced pressure and chloroform (30 ml) was added. This solution was washed with water (2x50 ml), dried and evaporated. Analytically pure compounds were obtained by passing through short length silica gel column using pentane as eluent.

3-Phenylthiophene (50a) was isolated as colourless crystals (pentane), yield 52%; m.p. 89-90°C; ν_{max} 1589, 1482, 1440, 1192 cm^{-1}; δ_H 7.13-7.38(6H,m,ArH and thiophene H), 7.39-7.58(2H,m,ArH). (Found: C,75.12; H,5.10. $C_{10}H_8S$ requires: C,74.96; H,5.03%); m/z 160(100%,M^+), 115(49).

3-(4-Methylphenyl)thiophene (50b) was isolated colourless crystals (pentane), yield 58%; m.p. 108-109°C; ν_{max} 1499, 1370, 1305, 1193 cm^{-1}; δ_H 2.36(3H,s,CH_3), 7.17(2H,d,J=8.5Hz,A_2B_2,ArH), 7.36(3H,brs,thiophene H), 7.49(2H,d,J=8.5Hz,A_2B_2,ArH); δ_C 21.01(CH_3), 119.59, 125.92, 126.40(CH, thiophene), 126.34, 129.44(CH,ArH), 133.20(C-3,thiophene), 136.76, 142.42 (C-1' and C-4' ArH). (Found: C,75.86; H,5.84. $C_{11}H_{10}S$ requires: C,75.81; H,5.78%); m/z 174(100%,M^+).

3-(4-Chlorophenyl)thiophene (50c) was isolated as colourless crystals (pentane), yield 59%; m.p. 95-96°C; ν_{max} 1591, 1525, 1483, 1416, 1200 cm^{-1}; δ_H 7.20-7.50(7H,m,ArH). (Found: C,61.60; H,3.56. $C_{10}H_7ClS$ requires: C,61.69; H,3.62%); m/z 196, 194(39,100%,M^+).

2,3-Diphenylbutane (51) was isolated as colourless crystals (pentane), yield 62%; m.p. 125°C; ν_{max} 1599, 1488, 1444 cm^{-1}; δ_H 1.01(6H,d, J=6.0Hz,CH_3), 2.66-2.94(2H,m,$\underline{CH}CH_3$), 7.24(10H,brs,ArH). (Found: C,91.22; H,8.53. $C_{16}H_{18}$ requires: C,91.37; H,8.63%); m/z 210(22%,M^+), 105(100).

5-(3,4-Dimethoxyphenyl)-2,3,4-trimethylpentane (77) was isolated as colourless liquid; yield 72%; ν_{max} 1600, 1580, 1505, 1460, 1411 cm^{-1}; δ_H 0.67-1.17(9H,m,CH_3), 1.26-2.05(8H,m,CH_2,CH_3 and CH), 6.51-6.77 (3H,m,ArH). (Found: C,76.89; H,10.61. $C_{16}H_{26}O_2$ requires: C,76.75; H,10.47%); m/z 250(15%,M^+).

3-Methyl-9-phenylnonane (78a) was isolated as colourless liquid, yield 70%; ν_{max} 1601, 1545, 1490, 1450 cm^{-1}; δ_H 0.72-0.96(6H,m,CH_3), 1.11-1.73(12H,m,CH_2), 1.79-2.06(1H,m,CH), 2.56(2H,t,J=7.5Hz,benzylic CH_2), 7.10(5H,brs,ArH). (Found: C,88.21; H,12.15. $C_{16}H_{26}$ requires: C, 88, H,12%); m/z 218(51%,M^+).

2,3-Dimethyl-9-(3,4-methylenedioxyphenyl)nonane (78b) was isolated as colourless liquid, yield 71%; ν_{max} 1499, 1482, 1439, 1240 cm^{-1}; δ_H 0.70-1.04(6H,m,CH_3), 1.12-1.66(13H,m,CH_2 and CH_3), 1.77-2.20(2H, m,CH), 2.48(2H,t,J=7.5Hz,benzylic CH_2), 5.84(2H,s,CH_2), 6.51-6.64 (3H,m,ArH). (Found: C,78.11; H,10.23. $C_{18}H_{28}O_2$ requires: C,78.21; H,10.21%); m/z 276(39%,M^+).

REFERENCES

1. H.E. Simmons, R.D. Smith, J. Amer. Chem. Soc., 80, 5323 (1958).
2. H.E. Simmons, T.L. Cairns, S.A. Vladuchick, C.M. Hoiness in Organic Reactions, 20, 1973, Chapt. 1.
3. S. Winstein, J. Sonnenberg, L. de Uries, J. Amer. Chem. Soc., 81, 6523 (1959).
4. S.Winstein, J. Sonnenberg, J. Amer. Chem. Soc., 83, 3235 (1961).
5. E.J. Corey, R.L. Dawson, J. Amer. Chem. Soc., 85, 1782 (1963).
6. J.C. Limasset, P. Amice, J.M. Conia, Bull. Soc. Chim. Fr.,3981 (1969).
7. J.M. Conia, J.C. Limasset, Tetrahedron Lett., 3151 (1965).
8. E. Wenkert, Acc. Chem. Res., 13, 27 (1980).
9. E. Wenkert, R.A. Mueller, E.J. Reardon, Jr., S.S. Sathe, D.J. Scharf, G. Tosi, J. Amer. Chem. Soc., 92, 7428 (1970).
10. H.H. Wasserman, D.C. Clagett, Tetrahedron Lett., 341 (1964).
11. E.P. Blanchard, H.E. Simmons, J.S. Taylor, J. Org. Chem., 30, 4321 (1965).
12. G. Wittig, M. Jautelat, Justus Liebigs Ann. Chem., 702, 24 (1967).
13. D. Seebach, Chem. Ber., 105, 487 (1972).
14. E. Schaumann, C. Friese, C. Spanka, Synthesis, 1035 (1986).
15. B.M. Trost, L.S. Melvin, Jr., in Sulfur Ylides Emerging Synthetic Intermediates: Academic Press,1975.
16. W.E. Parham, R. Konros, J. Amer. Chem. Soc. 83, 4034 (1961).
17. W.E. Parham, S.H. Gwen, J. Org. Chem. 31, 1694 (1966).
18. W. Ando, S. Kondo, K. Nakayama, K. Ichibori, H. Kohoda, H. Yamato, I. Imai, S. Nakaido, T.Migita, J. Amer. Chem. Soc., 94, 3870 (1972).
19. W. Ando, M.Yamada, E. Matsuzaki, T. Migita, J. Org. Chem., 37, 3791 (1972).
20. M. Yoshimoto, S. Ishihara, E. Nakayama, N. Soma, Tetrahedron Lett., 2923 (1972).

21. T. Kametani, H. Yukawa, T. Honda, J. Chem. Soc. Perkin Trans.I, 833 (1988).

22. W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, T. Migita, J. Org. Chem., 37, 1721 (1972).

23. F. Krolipfeifer, H. Hartmann, F. Schmidt, Justus Liebigs Ann. Chem., 563, 15 (1949).

24. A.G. Hortman, R.L. Harris, J. Amer. Chem. Soc., 93, 2471 (1971).

25. B. Holt, J. Howard, P.A. Lowe, Tetrahedron Lett.4937 (1969).

26. A. Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2182 (1962).

27. S. Apparao, S.S. Bhattacharji, H. Ila, H. Junjappa, J. Chem. Soc. Perkin Trans.I, 641 (1985).

28. S.M.S. Chauhan, H. Junjappa, Tetrahedron, 32, 1779 (1976).

29. J.P. Marino, J.L. Kostusyk, Tetrahedron Lett.,2489 (1979).

30. J.P. Marino, J.L. Kostusyk, Tetrahedron Let.,2493 (1979).

31. H.Wynberg, H. Van Driel, J. Amer. Chem. Soc., 87, 3998 (1965).

32. H.U. Reissig, Tetrahedron Lett.,22, 2981 (1981), and references therein.

33. I.G. Tishchenko, O.G. Kulinkovich, Y.V. Glazkov, Zh. Org. Khim., 11, 581 (1975), Chem. Abst., 83, 28027 (1975).

34. O.G. Kulinkovich, I.G.Tishchenko, N.A. Roslik, I.V. Reznikov, Synthesis, 383 (1983).

35. R. Okazaki, Y. Negishi, N. Inamoto, J. Chem. Soc. Chem. Comm., 1055 (1982).

36. R. Okazaki, Y. Negishi, N. Inamoto, J. Org. Chem., 49, 3819 (1984).

37 E. Campaigne, in Comprehensive Heterocyclic Chemistry; C.W. Bird, G.W.H. Cheesemann, Eds: Pergamon Press Ltd. Oxoford, Vol.4, 1984; Part-3, (a) Chapt. 3.13, p.730-731; (b) Chapt. 3.15, p.863-934.

38. S. Gronowitz, in Thophene and its derivatives; Ed. John Wiley and Sons, New York, 1985; p. 475-554; (b) Chapt.1, p.1-213.

39. R.L.Augustine in Catalytic Hydrogenation: Techniques and Application in Organic Synthesis; New York, Marcel Dekker, 1965, p.27.

40. A.Thuillier, J. Vialle, Bull. Soc. Chim. Fr., 2187 (1962).

41. C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 163 (1985).

42. W.E. Noland, C.K. Lee, S.K. Bae, B.Y. Chung, C.S. Hahn, K.J. Kim, J. Org. Chem., 2488 (1983).

43. B. Abarca,R. Ballesteros, E. Enriquez, G. Jones,Tetrahedron., 41, 2435 (1985).

44. B. Abarca, R. Ballesteros, E. Enriquez, G. Jones, Tetrahedron, 43, 269 (1987).

45. B. Abarca, R. Ballesteros, C. Soriano, Tetrahedron, 43, 991 (1987).

46. C.C. Leznoff, W.Lilie, C. Manning, Can. J. Chem., 52, 132 (1974).

47. M.P. Reddy, G.S. Krishnarao, Synthesis, 815 (1980).

48. B. Deb, C.V. Asokan, H. Ila, H. Junjappa, Tetrahedron Lett. 29, 2111 (1988).

49. For a review: See, Yu. G. Gololobov, A.N. Nesmeyanov, V.P. Lysenko, I.E. Boldeskul, Tetrahedron, 43, 2609 (1987).

CHAPTER IV

REGIOSELECTIVE CYCLOCONDENSATION OF OXOKETENE DITHIOACETALS WITH 3-AMINOPYRAZOLES: A FACILE GENERAL ROUTE TO SUBSTITUTED AND FUSED PYRAZOLO[1,5-a]PYRIMIDINES.

IV.1 INTRODUCTION

Pyrazolo[1,5-a]pyrimidines are purine analogues and some of the derivatives of this ring system possess useful properties as antimetabolites in purine biochemical reactions[1-4]. Robins and coworkers have recently shown that derivatives of this ring system inhibits CAMP-Phosphodiesterase, the enzyme responsible for anxiety[5-7]. It is also reported that certain derivatives have antianxiety activity comparable to benzodiazepam. Pyrazolo[1,5-a]pyrimidines are potential drugs for the treatment fo Schistosomiasis[6]. Many other azolo[1,5-a]pyrimidines are also known to possess broad spectrum of biological activity[8-10].

These interesting biological activities led to the development of numerous approaches for the synthesis of these ring systems. The most general approach involves cyclocondensation of a suitable 1,3-binucleophilic aminoazole with various 1,3-electrophilic carbon fragments. The availability of a variety of substituted and fused aminoazoles and a number of 1,3-electrophilic fragments like 1,3-diketones, β-ketoesters, β-ketoaldehydes and its masked functionalities makes this approach very general. Enormous literature[11] is available on the chemistry of these compounds by making use of this approach and other methods[11] as well.

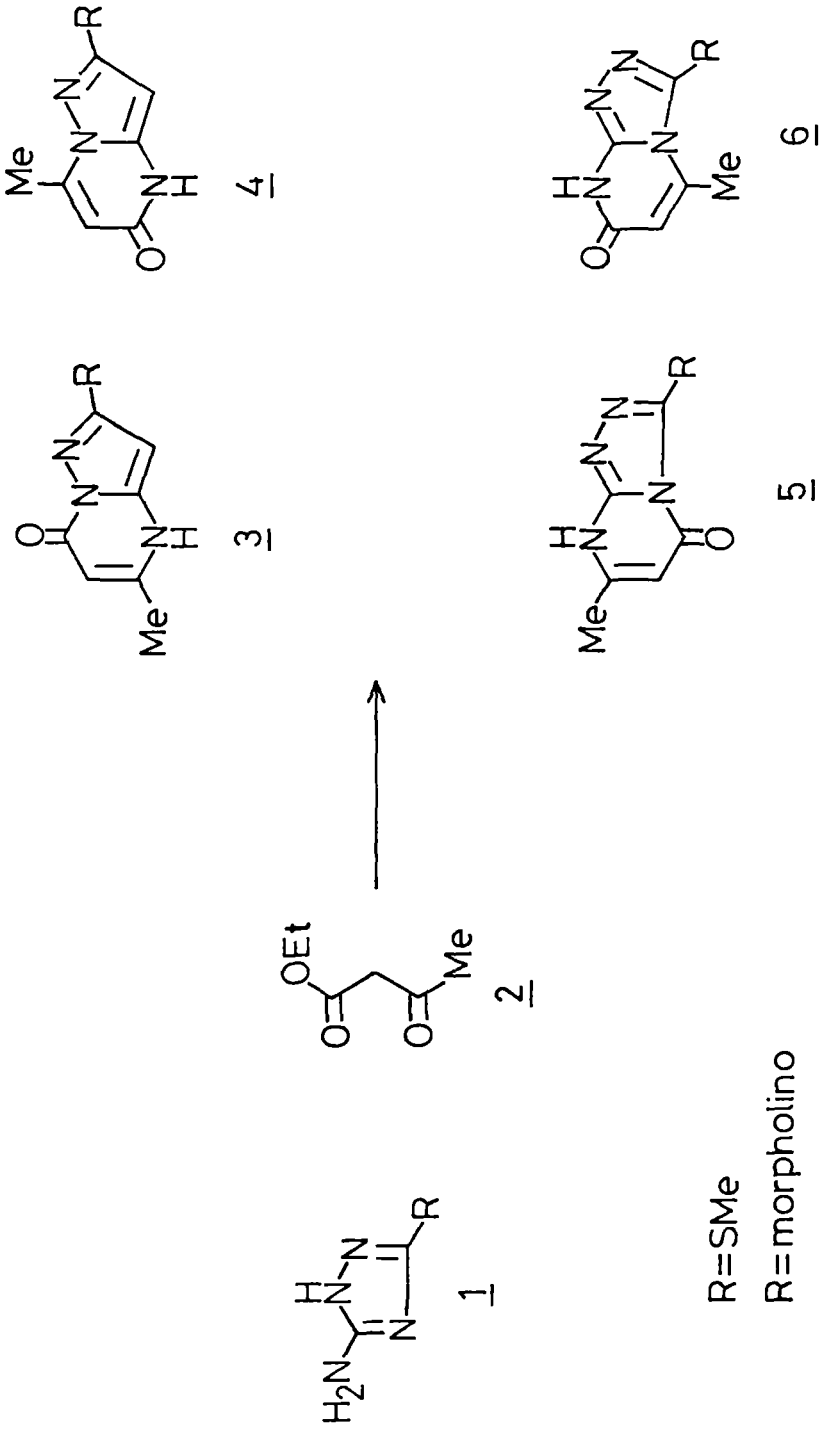
Despite the fact that the approach is very general, it suffers from the serious drawback that often regioisomeric mixtures of azolo[1,5-a]pyrimidines results in the case of unsymmetrical 1,3-electrophilic fragments or its equivalents. This leads to the reduced yield of the desired isomer and also the problem of separating it from other isomers. Besides, these methods do not offer much scope for substituent variation and structural modification because of the limited choice of β-dicarbonyl compounds available. The lack of regioselectivity in these reactions appears to stem from the competitive reactivity of the 1,3-electrophilic centres in the three carbon fragment. The reason for the competitive reactivity of the asymmetric binucleophile towards 1,3-electrophilic centres may be attributed to the poor discrimination of the electrophilicity of these centres.

In principle, it should, therefore, be possible to suitably modify the electrophilic centres in the three carbon components by appropriate

functional groups so that these centres are clearly recognized by the participating binucleophiles leading to single product isomer. It has been reported from this laboratory that the ambident binucleophile such as hydroxylamine reacts with α-oxoketene dithioacetals with high regioselectivity, which will be discussed later. It was therefore considered that the reactivity of α-oxoketene dithioacetals with aminoazoles might result in improved regioselectivity yielding only one regioisomer under a particular reaction condition. In the present study it has been observed that only one regioisomer is obtained with one exception. Some of the reactions involving aminoazoles and 1,3-electrophilic centres are reviewed in the following section.

The reaction of 3-substituted-5-amino-1,2,4-triazoles 1 with β-ketoesters 2 is reported[12] to give four regioisomers 3-6. These isomers are often difficult to distinguish due to the similarity of structural features. As a consequence, many of the early reports proposed incorrect structures. Reiter and coworkers have elucidated structures of isomeric triazolopyrimidinones 3-6 on the basis of u.v. and ^{13}C n.m.r. spectroscopy (Scheme 1)[12].

Sykes and Bajwa have thoroughly investigated the synthesis of various azolo[a]pyrimidines by the condensation of various aminoazoles with β-ketoacetals and 2-hydroxymethylene cycloalkanones[13]. Structural elucidation of the regioisomers are done on the basis of ^{1}H and ^{13}C n.m.r. spectroscopy. Thus, the condensation of 4,4-dimethoxybutan-2-one 7 on reaction with 3-amino-1,2,4-triazole 8 resulted in the formation of 5-methyltriazolo[1,5-a]pyrimidine 9 accompanied by the


R
N
N
Me
NH
O
4
R
N
N
NH
O
Me
3
R
N
N
H
N
N
Me
O
5
R
N
N
H
N
N
O
Me
6
OEt
O
O
Me
2
R
N
N
H
N
N
H2N
1
R=SMe
R=morpholino

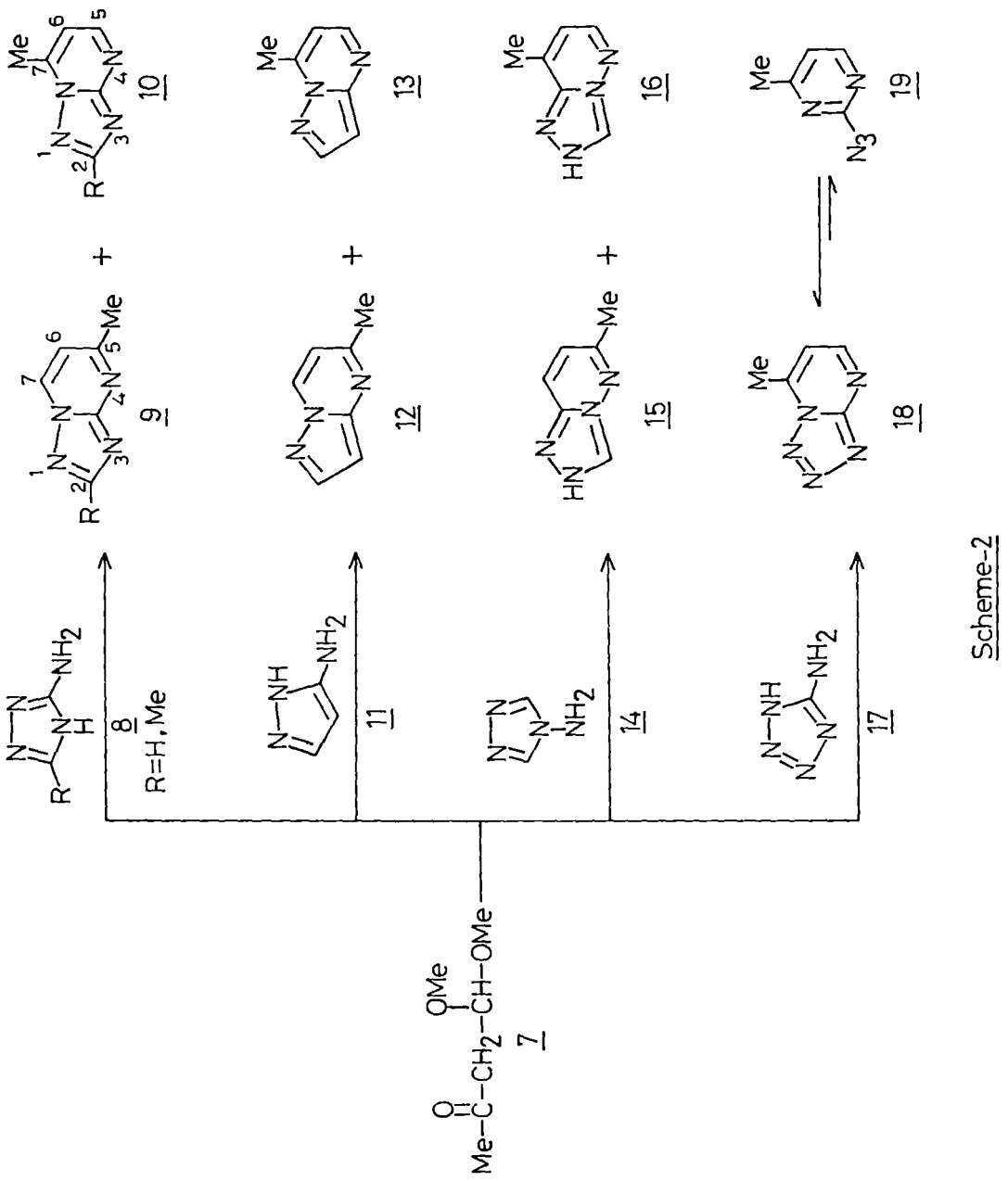
Scheme-1

isomeric 7-methyl compound 10. Similarly the aminopyrazole 11 and N-aminotriazole 14 afforded an isomeric mixture of pyrazolopyrimidines 12, 13 and triazolopyridazine 15 and 16 respectively. The reaction of 5-aminotetrazole 17 with β-ketoaldehyde-acetal 7 gave the 7-methyltetrazolopyrimidine 18 and the 5-methyl isomer is not formed in this reaction (Scheme 2).

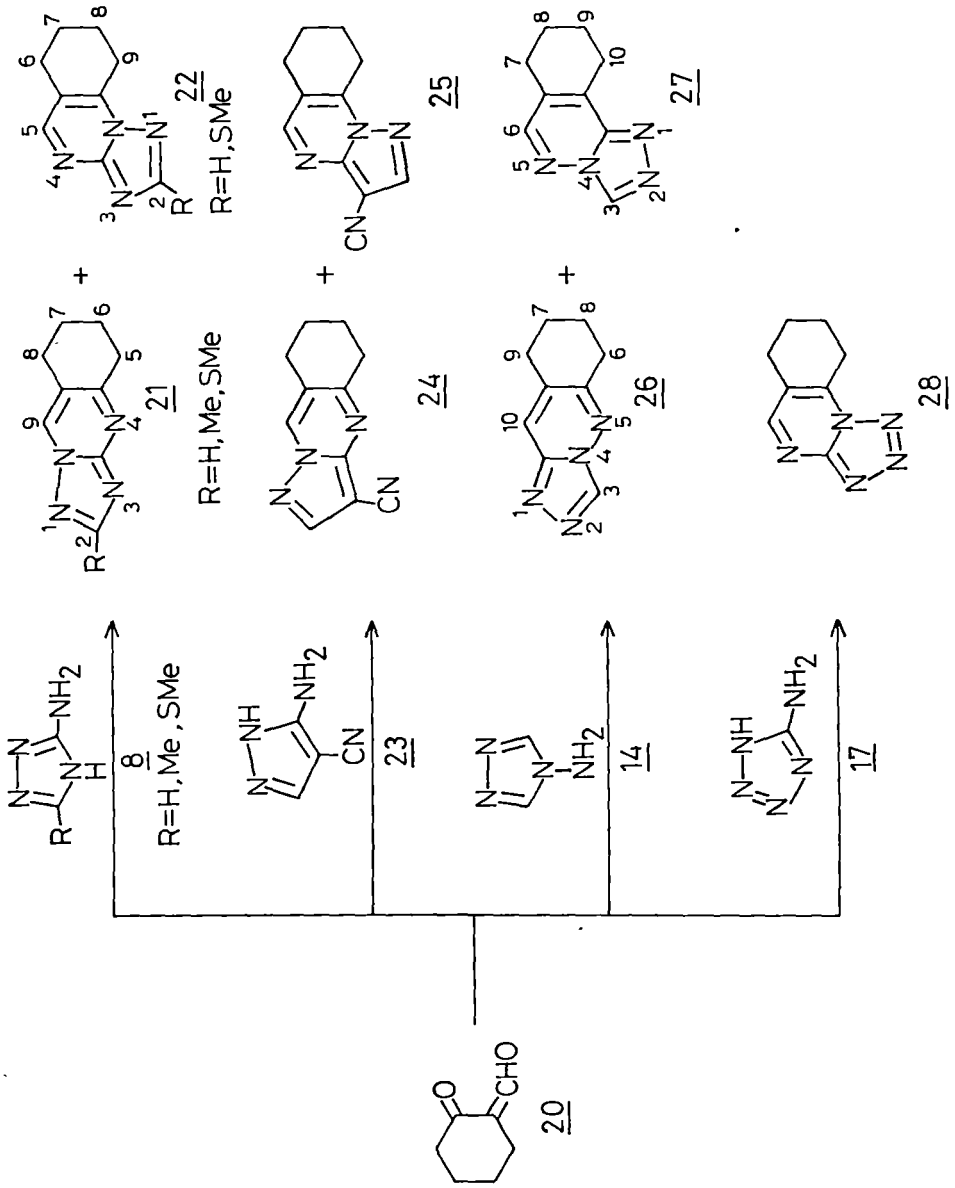
In an analogus reaction the aminoazoles condensed with the 2-hydroxymethylene cyclohexanone 20 to give linearly and angularly fused products. Thus, the aminotriazole 8 gave the 5,6-annelated triazolopyrimidine 21 and the 6,7-annelated triazolopyrimidine 22. The 4-cyano-5-aminopyrazole 23 and aminotriazole 14 similarly yielded isomeric pyrazolopyrimidine 24, 25 and 6,7-annelated triazolopyridazine 26 and 7,8-annelated pyridazine 27. As with the case of β-ketoaldehyde acetal 7 the hydroxymethylenecyclohexanone 20 with aminotetrazole 17 gave only one product, the angularly fused tetrazolopyrimidine 28 (Scheme 3).

The above illustrations clearly demonstrate that 1,3-electrophilic fragments like β-ketoaldehydeacetals and hydroxymethylenecycloalkanones show poor selectivity towards binucleophiles, apparantly making it less efficient in terms of preparative value.

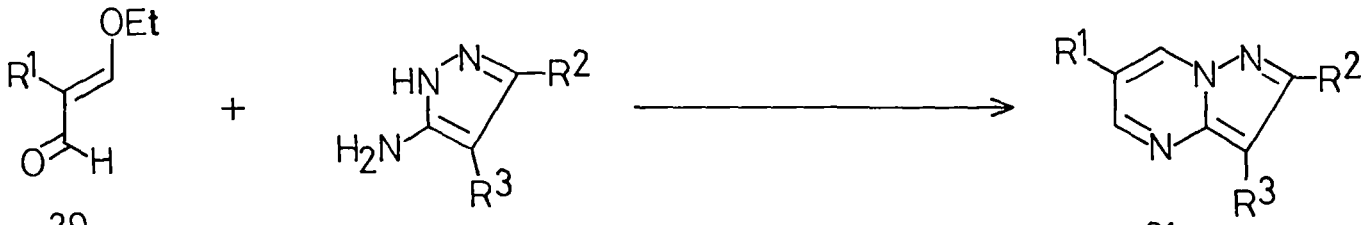
Muhmel and coworkers have studied the reactions of some acyclic and cyclic enolethers with substituted aminopyrazoles. Thus the reaction of 3-ethoxyacrolins 29 and 5-aminopyrazoles[14] 30 gave the pyrazolopyrimidines 31. Similarly the 5-formyl-3,4-dihydro-2H-pyran 31 and the aminopyrazole 30 in acetic acid afforded pyrazolopyrimidine 33 (Scheme 4). Unlike β-ketoaldehyde acetals the enolethers yielded



Scheme-2



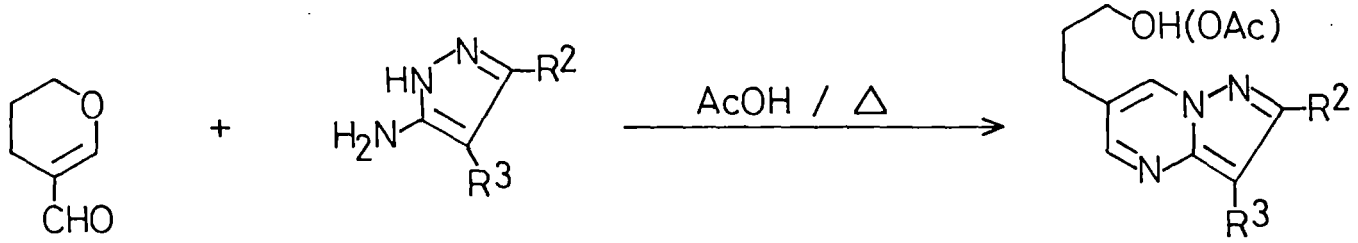
Scheme-3



29 30 31

R^1=Me, Et, n-Pr, n-C_4H_9, n-C_5H_{11}, R^2= R^3=H, R^2=Me, R^3=H

R^2=H, R^3=NO_2; R^2=Me, R^3= NO_2



32 30 33

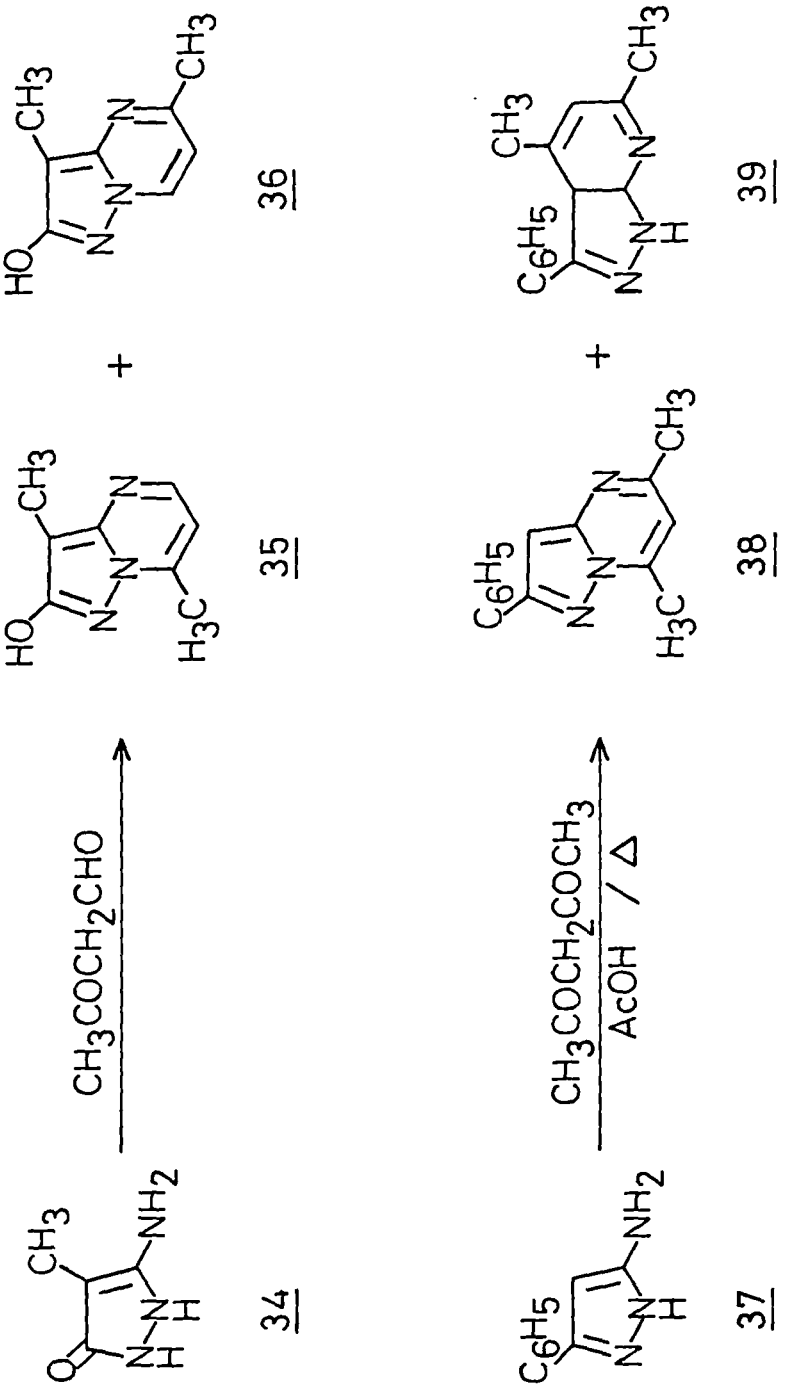
Scheme-4

only one regioisomer. However the moisture sensitive enolethers cannot always be prepared and stored indefinitely and therefore this approach for the synthesis of azolopyrimidines is less frequently used.

Haverbeke and coworkers have studied[15] the condensation of amino-pyrazolone 34 with β-ketoaldehydes. They have observed a regio-isomeric mixture of pyrazolopyrimidines 35 and 36 (Scheme 5). It may be noted that the reaction of pyrazolone 34 with an unsymmetrical diketone can lead to a maximum of four regioisomers depending on the direction of cyclisation. Joshi and coworkers have reported[16] the formation of pyrazolo[1,5-a]pyrimidine 38 and pyrazolo[3,4-b]pyridine 39 in the reaction of aminopyrazole 37 with acetylacetone in acetic acid (Scheme 5). They have synthesized some fluorinated pyrazole fused heterocyclic compounds to study their biological activity.

Elnagdi and coworkers have recently reported[17] the reaction of 5-amino-3-phenylpyrazole with various cinnamonotrile derivatives. Although many isomeric heterocyclic compounds are possible in these reactions, they have observed the formation of only pyrazolo[1,5-a]pyrimidine and pyrano[2,3-c]pyrazoles. Other isomeric structures were ruled out on the basis of i.r. and ^{1}H n.m.r. studies.

The literature covering several other earlier approaches for the synthesis pyrazolopyrimidines are cited in a review[18] by Greenhill. The reactions of 3-aminopyrazole with various esters and nitriles are discussed in the review. In most of these reports[19-27], a number of isomeric products are possible depending on the reaction conditions and direction of cyclisation. Many of the product structures were


CH3
NH2
O
NH
NH
34
CH3COCH2CHO
HO
CH3
CH3
N
N
N
36
+
HO
CH3
N
N
N
H3C
35
C6H5
NH2
NH
N
37
CH3COCH2COCH3
AcOH / Δ
C6H5
CH3
CH3
N
N
NH
39
+
C6H5
CH3
N
N
N
H3C
38

Scheme-5

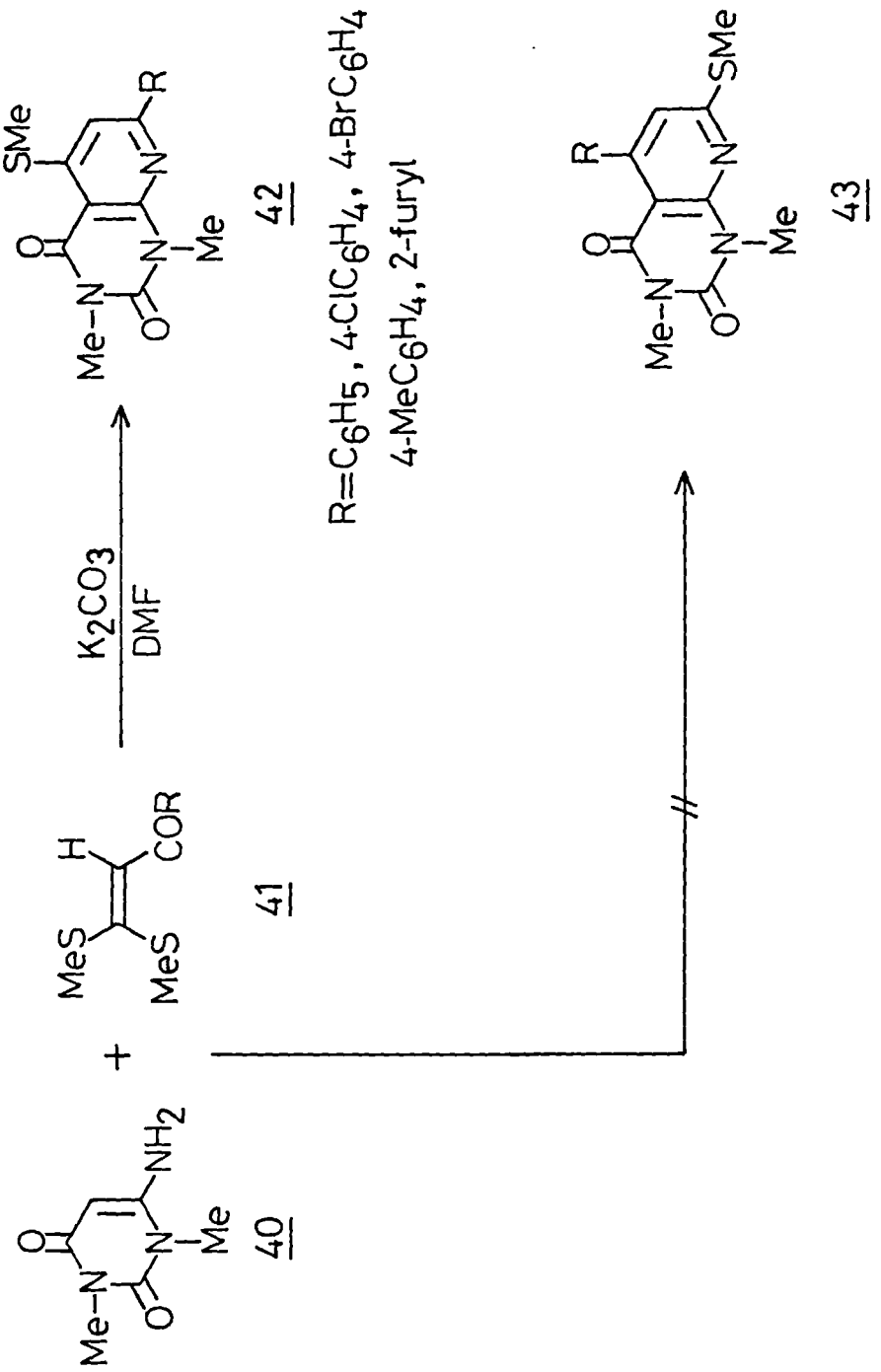
tentatively assigned without proper spectroscopic evidence.

From the above discussions it is evident that the major problem in the condensation of aminopyrazole with 1,3-electrophilic centres is due to the lack of regioselectivity in these reactions leading to two or more regioisomeric products. This is due to the poor discrimination of the 1,3-electrophilic centres by the ambident binucleophile in these reactions.

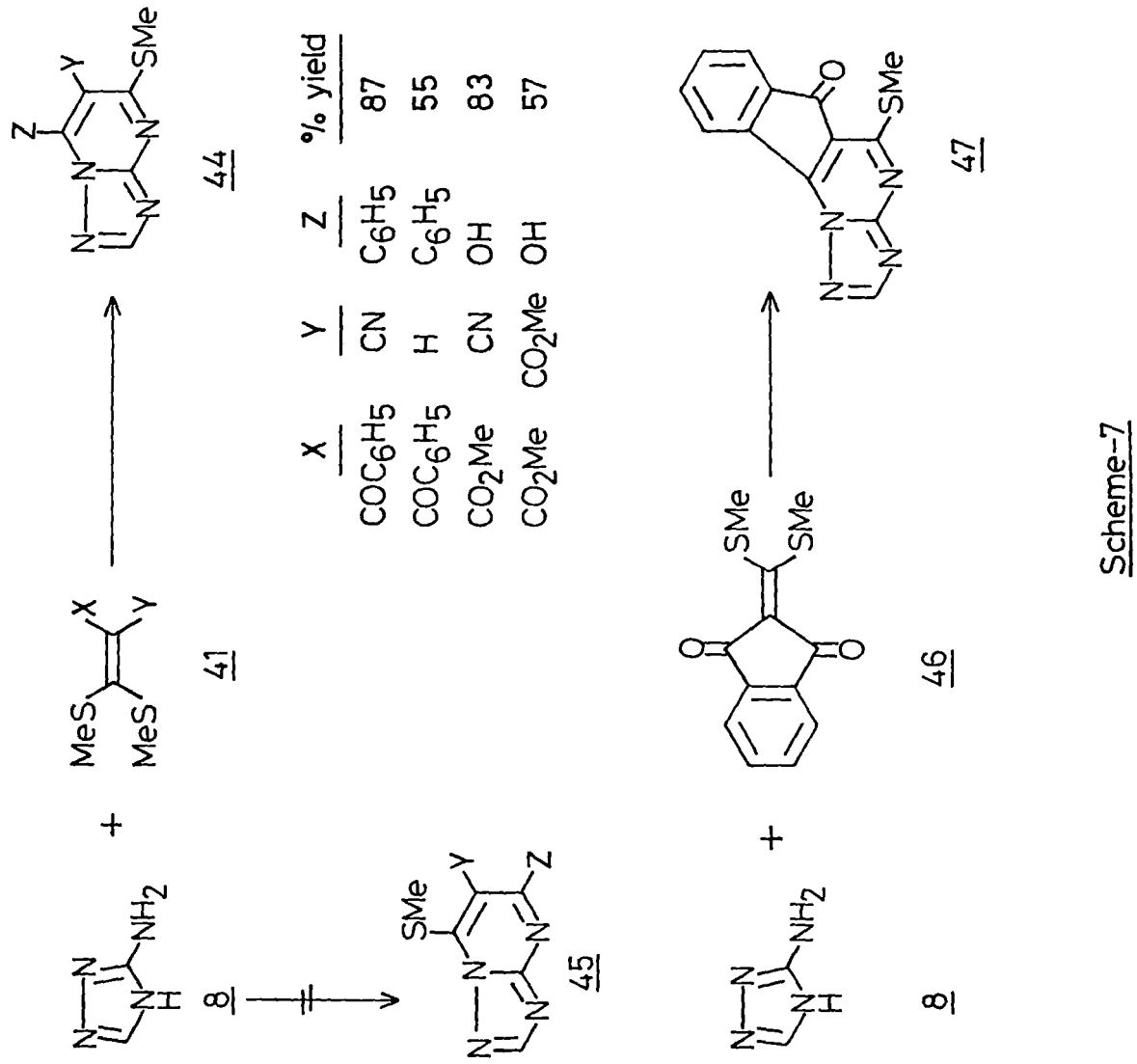
Tominaga and coworkers have reported[28] the reaction of 6-aminouracil with different ketene dithioacetals. Thus, the reaction of 6-amino-1,3-dimethyluracil 40 with α-oxoketene dithioacetal 41 in the presence of potassium carbonate in N,N-dimethylformamide yielded the 7-aryl-5-methylthiopyrido[2,3-d]pyrimidines 42 (Scheme 6). The other regioisomer 5-aryl-7-methylthiopyrido[2,3-d]pyrimidines 43 were not formed in the reaction (Scheme 6). Some other ketene dithioacetals like methyl-2-cyano-3,3-bis(methylthio)acrylate derived from methyl cyanoacetate gave the other regioisomer (7-methylthio) under identical conditions.

Tominaga and coworkers have observed similar regioselectivity in the reaction of ketene dithioacetals with aminotriazole[29]. Thus, the reaction of 3-aminotriazole 8 with ketene dithioacetals 41 afforded the 5-methylthiotriazolo[1,5-a]pyrimidines 44. The regioisomeric 7-methylthiotriazolo[1,5-a]pyrimidines 45 were not formed in the reaction (Scheme 7).

From this laboratory, a highly regioselective reaction of hydroxylamine with α-oxoketene dithioacetal has been reported[30] recently. Thus, the reaction of α-oxoketene dithioacetal 41 with hydroxylamine


SMe
R
O
N
Me-N
N
Me
O
42
R=C6H5, 4-ClC6H4, 4-BrC6H4
4-MeC6H4, 2-furyl
K2CO3
DMF
MeS
H
COR
MeS
41
+
NH2
Me-N
N
Me
O
40
R
SMe
43

Scheme-6


MeS
MeS
X
Y
41
8
SMe
Y
Z
45
Z
Y
SMe
44
X Y Z % yield
COC6H5 CN C6H5 87
COC6H5 H C6H5 55
CO2Me CN OH 83
CO2Me CO2Me OH 57
SMe
SMe
46
8
47
SMe

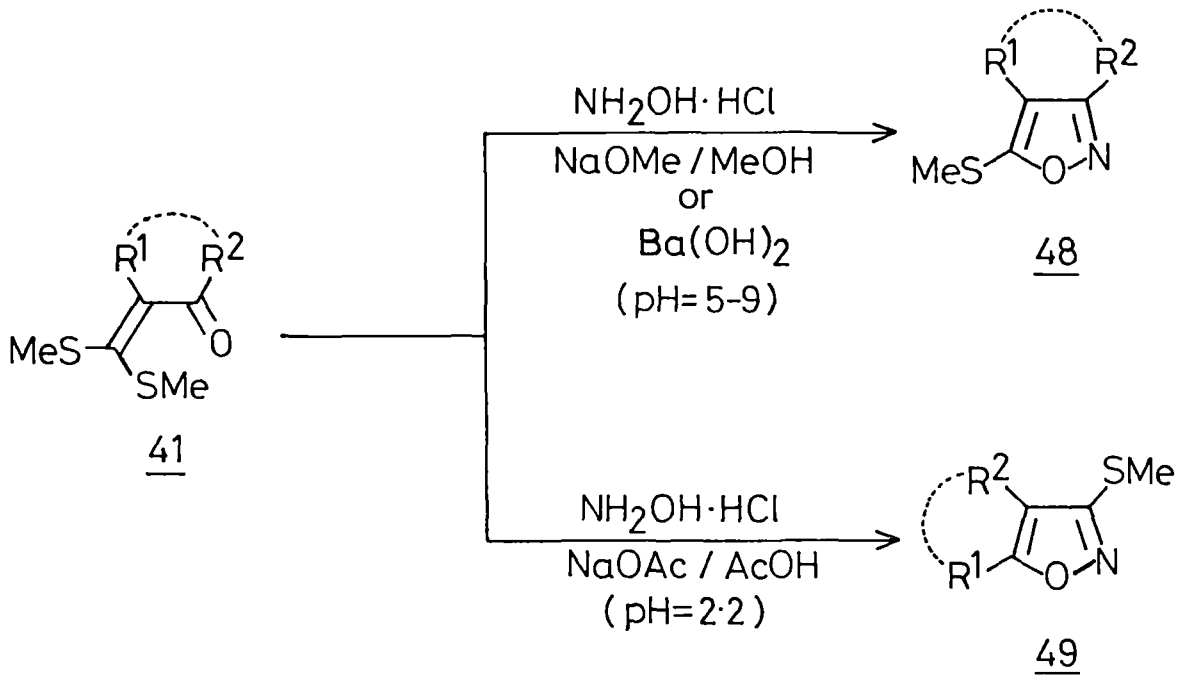
Scheme-7

in the presence of sodium methoxide in methanol (pH 5-9) gave 3-substituted-5-methylthioisoxazoles 48. The same reaction in the presence of sodium acetate in acetic acid (pH 2.2) afforded the 5-substituted 3-methylthioisoxazoles 49 (Scheme 8). Thus, by this method the desired regioisomeric isoxazoles were obtained simply by suitably changing the reaction conditions.

It was therefore contemplated that under a specific reaction condition, the condensation of aminopyrazole with α-oxoketene dithioacetals may lead to one regioisomeric pyrazolopyrimidine exclusively and also it may be possible to design a suitable reaction condition to get the other regioisomer. The results of this study are presented in the following section.

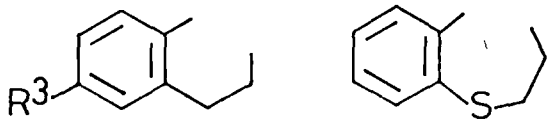
IV.2 RESULTS AND DISCUSSION

All the α-oxoketene dithioacetals 41a-j, 53a-g and 56a-j required for the present study were prepared according to the reported procedure. The detailed procedure for the preparation of 41a-j and 56a-j is given in Chapter II. The general procedure for the preparation of cinnamoylketene 53a-c, α-(5-aryl-2,4-pentadienoyl 53d,e and α-(7-aryl-2,4,6-heptatrienoylketene dithioacetals 53f-g is given in Chapter III. The structures of all these dithioacetals were confirmed by comparing their physical and spectral data with the reported values, while the hitherto unreported 53f was characterised by the spectral and analytical data (experimental). The detailed procedure for the preparation of 5-aminopyrazole 11 and 3-amino-4-phenyl-5-methylthiopyrazole 52 is given in the experimental section.



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

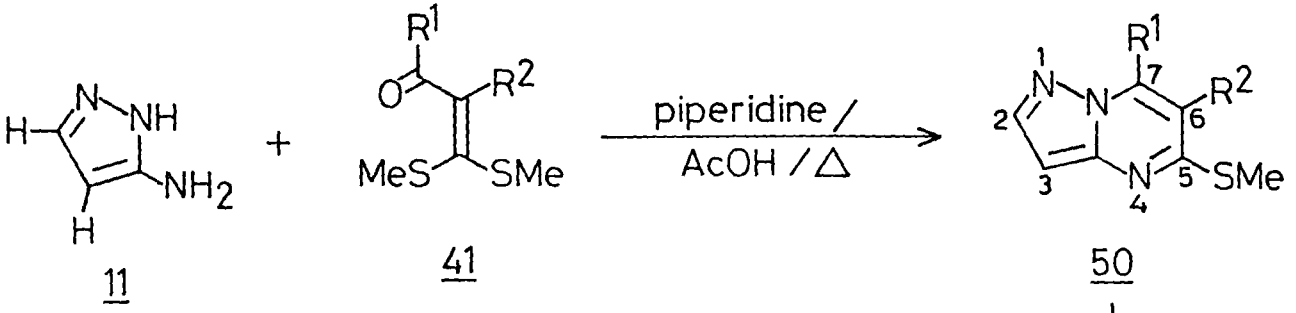
R^2=H

R^1= R^2= 

R^3=H, MeO

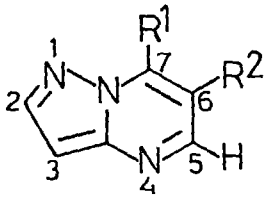
Scheme-8

Thus, in an optimized condition, the α-oxoketene dithioacetal 41a was reacted with the aminopyrazole 11 in aqueous acetic acid containing catalytic amount of piperidine at 110-115°C, usual work up and column chromatography yielded a single product which was characterized as 7-methyl-5-methylthiopyrazolo[1,5-a]pyrimidine 50a formed in 82% yield. The compound was fully characterized on the basis of analytical and spectral data. In its mass spectrum, it exhibited molecular ion peak at m/z 179(100%) and was analyzed for $C_8H_9N_3S$. In its ^1H n.m.r. spectrum the signal due to the 7-methyl protons appeared at δ 2.64 as a broad singlet due to allylic coupling with 6-H. This gives support for the assigned regioisomer, since in the other possible regioisomer (5-methyl-7-methylthiopyrazolopyrimidine) the methyl signal is expected to appear as a sharp singlet. The thiomethyl protons appeared as a singlet at δ 2.57 and the 6-H was present as a broad singlet at δ 6.48 due to allyl coupling with 7-Me protons. The 2-H and 3-H appeared as doublets at δ 8.00 and 6.49 with a vicinal coupling constant of 1.5 Hz. The ^{13}C chemical shift values of this compound was found to be in good agreement with the reported values of 7-methyl pyrazolo[1,5-a]pyrimidine 51a[13]. Further support in favour of the structure 50a is obtained by the dethiomethylation of this compound by Raney Nickel to the known[13] 7-methyl pyrazolo [1,5-a]pyrimidine 51a. This compound was isolated as colourless needles (68%) and showed melting point 61°C. The reported melting point of this compound is 59-60°C[13]. Also, the ^1H n.m.r. spectrum of this compound showed a broad singlet for the methyl protons and the coupling constant of 5-H and 6-H was found to be 4.5Hz which is in full agreement with the earlier reported values[13]. If the methyl



11 + 41 → 50

41,50 a R^1=Me; R^2=H
b R^1=4-ClC_6H_4; R^2=H
c R^1=2-thienyl; R^2=H
d R^1=2-furyl; R^2=H
e R^1=Et; R^2=Me
f R^1=C_6H_5; R^2=C_6H_5CO



51

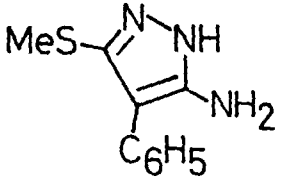
51 a R^1=Me; R^2=H
b R^1=2-furyl; R^2=H
c R^1=Et; R^2=Me

Scheme-9

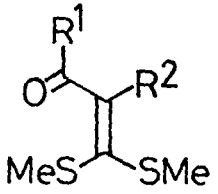
group is in the 5-position the coupling constant between 6-H and 7-H is expected to be around 7Hz. All these spectral data unequivocally prove the assigned regioisomeric structure 50a. Another important observation is that no trace of the other regioisomer could be isolated from the reaction mixture.

In an analogus reaction condition, the α-oxoketene dithioacetals 41b-e were reacted with aminopyrazole 11 to give the pyrazolopyrimidines 50b-e in 86-93% overall yields. The other 7-methylthio regioisomer was not formed in all these cases. The structures of all these compounds were established on the basis of analytical and spectral data. The compounds 50d and 50e were dethiomethylated by Raney Nickel to the corresponding sulfur free pyrazolopyrimidines 51d and 51e in 75 and 71% yield. The ^{1}H n.m.r. chemical shift values for the 5-H in 51d and 51e were in full agreement with the assigned regioisomer(experimental). In the ^{1}H n.m.r. spectrum of 51d, the 6-H signal appeared as a doublet at δ 7.28 with a vicinal coupling constant of 4.5Hz which supplements the assignment. The reaction of aminopyrazole 11 with ketene dithioacetal 41f[31] prepared from dibenzoyl methane was found to be sluggish and considerable amount of starting material was recovered even after prolonged refluxing (20 hr.) The spectral and analytical data of 50f was in full agreement with the assigned structure.

A few of the selected α-oxoketene dithioacetals (41a, 41g -j) were also reacted with 3-amino-4-phenyl-5-methylthiopyrazole 52 (Scheme 10) which was prepared by the reaction of 3,3-bismethylthio-2-phenylacrylonitrile[33] and hydrazine hydrate in refluxing ethanol (experimental).

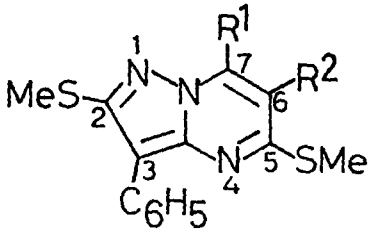


52



41

Piperidine / AcOH / △



50

41a,50g R^1=Me; R^2=H

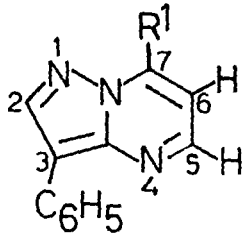
41g,50h R^1=4-MeOC_6H_4 ; R^2=H

41h,50i R^1=C_6H_5 ; R^2=H

41i,50j R^1=Me; R^2=n-C_4H_9

41j,50k R^1=C_6H_5 ; R^2=Me

Raney Ni / MeOH



51

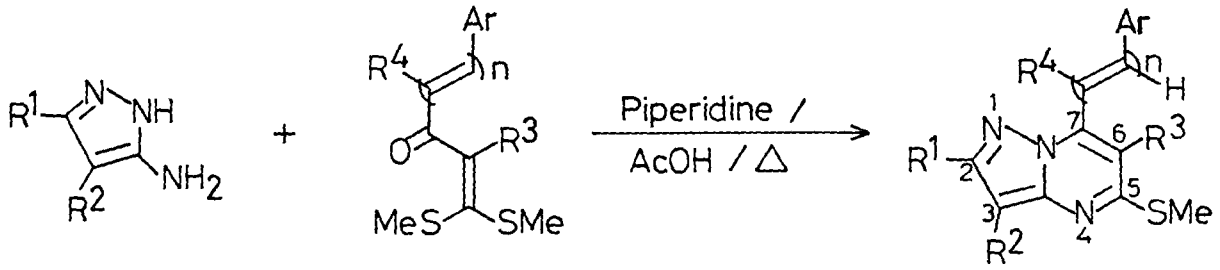
51g R^1=Me

h R^1=4-MeOC_6H_4

Scheme-10

The reaction of aminopyrazole 52 with dithioacetals 41a and 41g-j in the described conditions afforded the corresponding 2,5-bis(methylthio)-3-phenylpyrazolo[1,5-a]pyrimidines 50g-k in 78-93% overall yield. Only the 5-methylthio regioisomer is formed in all these cases, which was supported by the desulphurization of the selected pyrazolopyrimidines 50g and 50h. Thus, the dethiomethylation of 50g and 50h by Raney Nickel afforded the 3-phenylpyrazolopyrimidines 51g and 51h in 79 and 80% yields (Scheme 10). In the ^{1}H n.m.r. spectrum of 51g, the signal due to 7-methyl protons appeared as a broad singlet at δ 2.84 while the 6-H was present as a broad doublet (J=4.5Hz) at δ 6.80. The doublet due to the 5-H signal was merged with the 2-H signal and appeared as a multiplet between δ8.51-8.68, fully supporting the assigned regioisomeric structure 50g. Similarly, the structure of the regioisomer 51h was also established on the basis of ^{1}H n.m.r. spectrum which showed J=5,6 as 4.5Hz.

It was further considered of particular interest to examine the reaction of aminopyrazoles with α-cinnamoyl, 5-aryl 2,4-pentadienoyl and 7-aryl 2,4,6-heptatrienoylketene dithioacetals. This reaction should in principle give the 7-enylpyrazolo[1,5-a]pyrimidines. It is worth mentioning that, no styryl, dienyl and trienyl substituted pyrazolopyrimidines are reported in the literature. This may be attributed to the difficulty in obtaining appropriately functionalized 1,3-electrophilic compounds to react with aminopyrazoles. Thus,the reaction of cinnamoyl ketene dithioacetal 53a with aminopyrazole 52 afforded the 2,5-dimethylthio-7-(4-methoxystyryl)-3-phenylpyrazolo [1,5-a]pyrimidine 54a exclusively in 89% yield. The compound was



11,52 + 53 → 54

53,54 a R^1= SMe; R^2=C_6H_5; R^3=R^4=H; Ar= 4-MeOC_6H_4; n = 1

b R^1=R^2=R^4=H; R^3=Me; Ar = 3,4-methylenedioxyC_6H_3; n=1

c R^1=R^2=H; R^3=R^4=Me; Ar=3,4-$(MeO)_2C_6H_3$; n=1

d R^1=SMe; R^2=C_6H_5; R^3=R^4=H; Ar=C_6H_5; n=2

e R^1=R^2=R^4=H; R^3=Me; Ar=C_6H_5; n=2

f R^1=R^2=R^3=R^4=H; Ar= 4-MeOC_6H_5; n=3

g R^1= SMe; R^2=C_6H_5; R^3=R^4=H; Ar=C_6H_5; n=3

54 → 55

55 a Ar=4-MeOC_6H_4; n=1

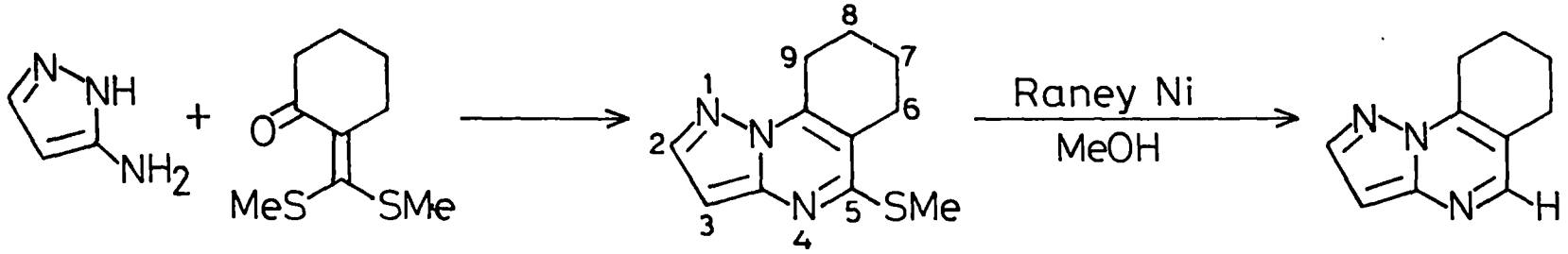
f Ar=C_6H_5; n=3

Scheme-11

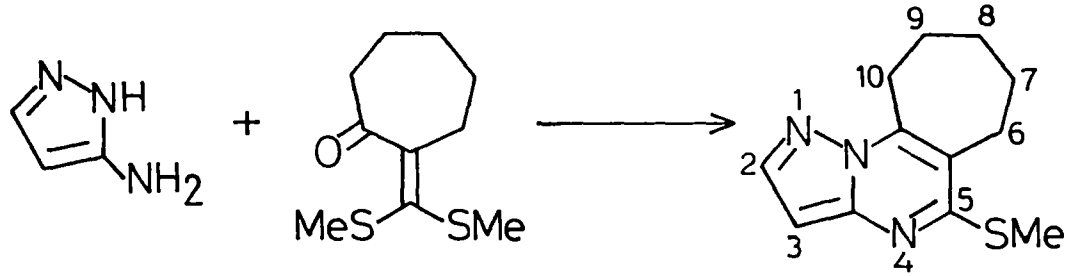
analysed for $C_{23}H_{21}N_3OS_2$ and its mass spectrum showed molecular ion peak at m/z 420(100%). Other spectral and analytical data in favour of the assigned structure is given in the experimental. The structure 54a is unambigously established by its dethiomethylation to pyrazolopyrimidine 55a. The dethiomethylation was accompanied by side chain saturation affording 7-[2-(4-methoxyphenyl)ethyl]-3-phenylpyrazolo[1,5-a]pyrimidine 55a. The observed coupling constant (J=4.5Hz) for 6-H confirms the regiochemical assignment. The other dithioacetals 53b-g were also smoothly condensed with aminopyrazole 11 or 52 to give the 7-enylpyrazolopyrimidines 54b-g in 78-87% overall yields. The product 54g also underwent a facile dethiomethylation and side chain saturation by W-2 Raney Nickel in methanol at room temperature to give 7-(6-phenyl-n-hexyl)-3-phenyl-pyrazolopyrimidine 55g (Scheme 11) in good yield.

The following section will focus on the reaction of aminopyrazoles with various α-oxoketene dithioacetals derived from cyclic, benzo-cyclic and benzoheterocyclic ketones. The known approach for the synthesis of 5,6- or 6,7-fused pyrazolo[1,5-a]pyrimidines involve the reaction of aminopyrazoles with 2-hydroxymethylenecycloalkanones. However the method is confined to the synthesis of only a few annelated pyrimidines and invariably results in regioisomeric mixture.

The cyclic α-oxoketene dithioacetals 56a-j were prepared by the reported method and their structures were fully established on the basis of spectral and analytical data. The condensation of dithio-acetal 56a with aminopyrazole 11 furnished the 5-methylthio-6,7,8,9-



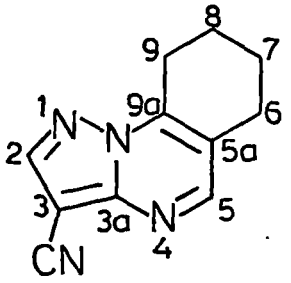
11 56 a 57 a 58 a



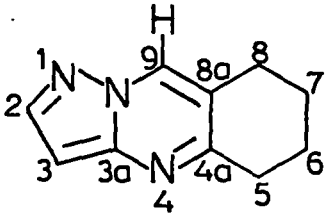
11 56 b 57 b

Scheme-12

tetrahydropyrazolo[1,5-a]quinazoline 57a in 81% yield. The structure of this compound is established on the basis of analytical and spectral data. The chemical shift values in the ^{13}C n.m.r. spectrum of 57a (experimental) was found to be in good agreement with that of the reported[13] 3-cyano analogue 57A. Further structural proof for 57a



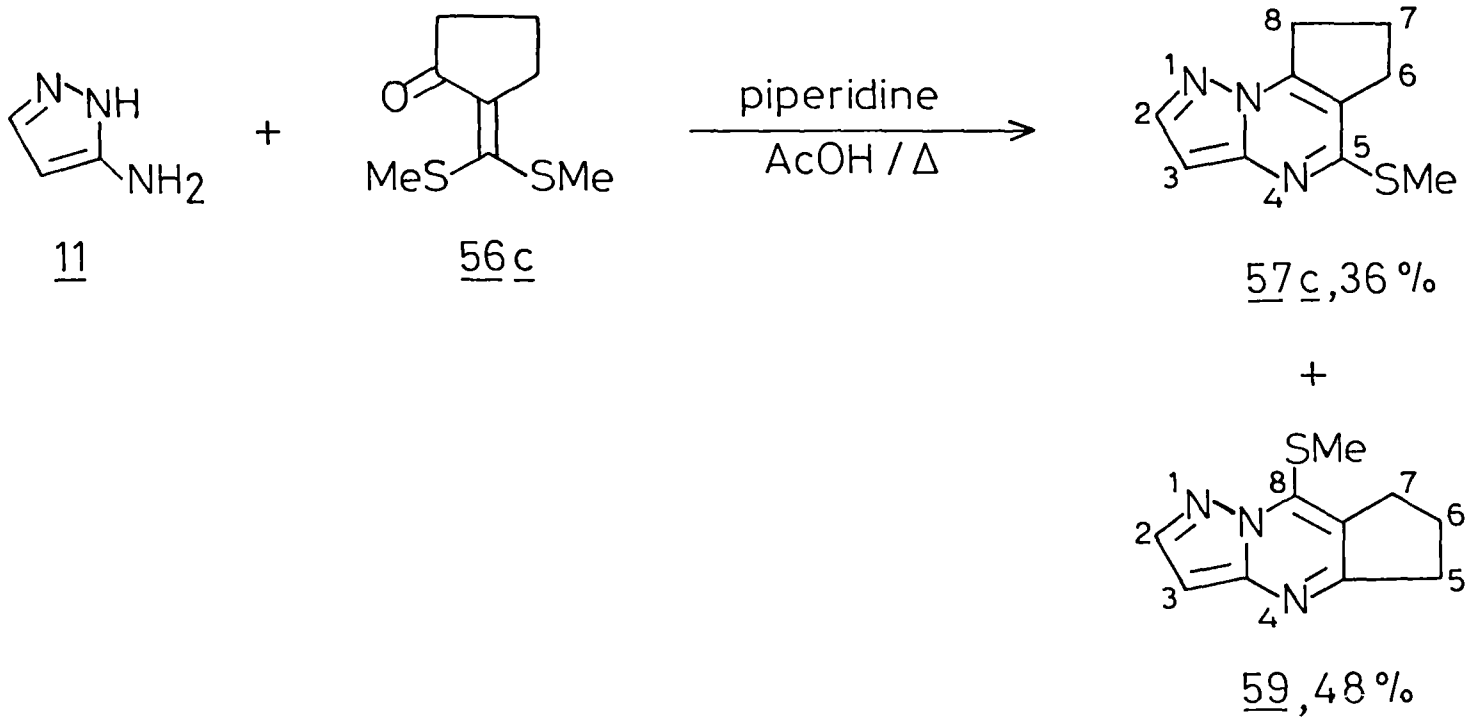
57A



58A

was obtained by its Raney Nickel dethiomethylation to 58a. In the ^{1}H n.m.r. spectrum of 58a the characteristic signal due to 5-H proton appeared as a sharp singlet at δ8.28 while in the alternative linearly fused 58A the proton on the C-9 is expected to appear as a broad singlet due to allylic coupling with C-8 methylene protons. Under identical conditions, the dithioacetal 56b prepared from cycloheptanone reacted with aminopyrazole 11 to afford the pyrazolopyrimidine 57b in 79% yield.

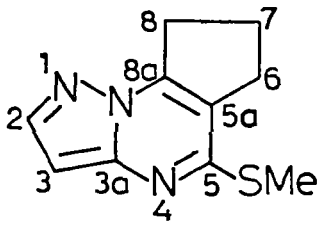
However, the dithioacetal 56c showed anomalous behaviour on reaction with aminopyrazole 11 under identical conditions. Usual work up and careful column chromatography of the reaction mixture yielded two products which were characterized as the angularly and linearly annelated pyrazolopyrimidines 57c and 59 formed in 36 and 48% yield. In the ^{1}H n.m.r. spectrum of 57c the signals due to the 6- and



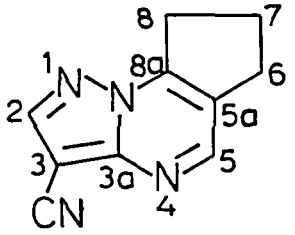
11 + 56 c → 57 c, 36 % + 59, 48 %

Scheme-13

8-methylene protons appeared as double triplets (J=6.5, 1.0Hz) at δ2.88 and 3.31 due to homoallylic coupling between the methylene protons, while compound 59 showed 5- and 7-methylene protons as partially overlapping sharp triplets.



57c

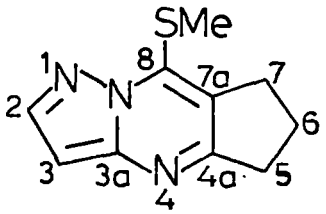


57C

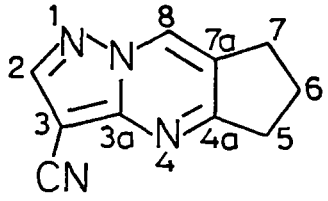
^{13}C n.m.r. chemical shift values

C-2	143.05	C-5	157.61	C-2	147.09	C-5	149.56
C-3	94.45	C-5a	120.02	C-3	82.18	C-5a	125.80
C-3a	148.93	C-9a	146.81	C-3a	148.68	C-8a	151.71

Additional clues to distinguish between the regioisomers were drawn by comparing the ^{13}C n.m.r. spectra of 57c and 59 with that of reported[13] 3-cyano analogues 57C and 59A.



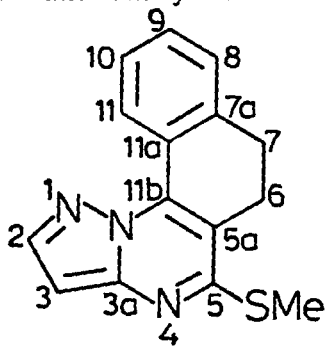
59



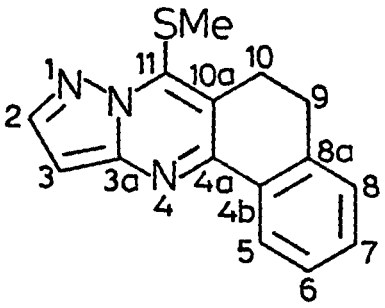
59A

C-2	143.20	C-4a	166.45	C-2	146.36	C-4a	173.41
C-3	95.59	C-7a	124.39	C-3	81.14	C-7a	126.25
C-3a	148.70	C-8	139.80	C-3a	149.62	C-8	130.19

The reaction was further extended for the synthesis of hitherto unknown benzocyclic and benzoheterocyclic pyrazolopyrimidines. Thus the condensation of dithioacetals 56d-h with aminopyrazole 11 or 52 yielded the corresponding benzocyclopyrazolo[1,5-a]pyrimidine 57d-h in 73-92% overall yield. Only one isomer is formed in all these cases and the structures were established on the basis of spectral and analytical data.

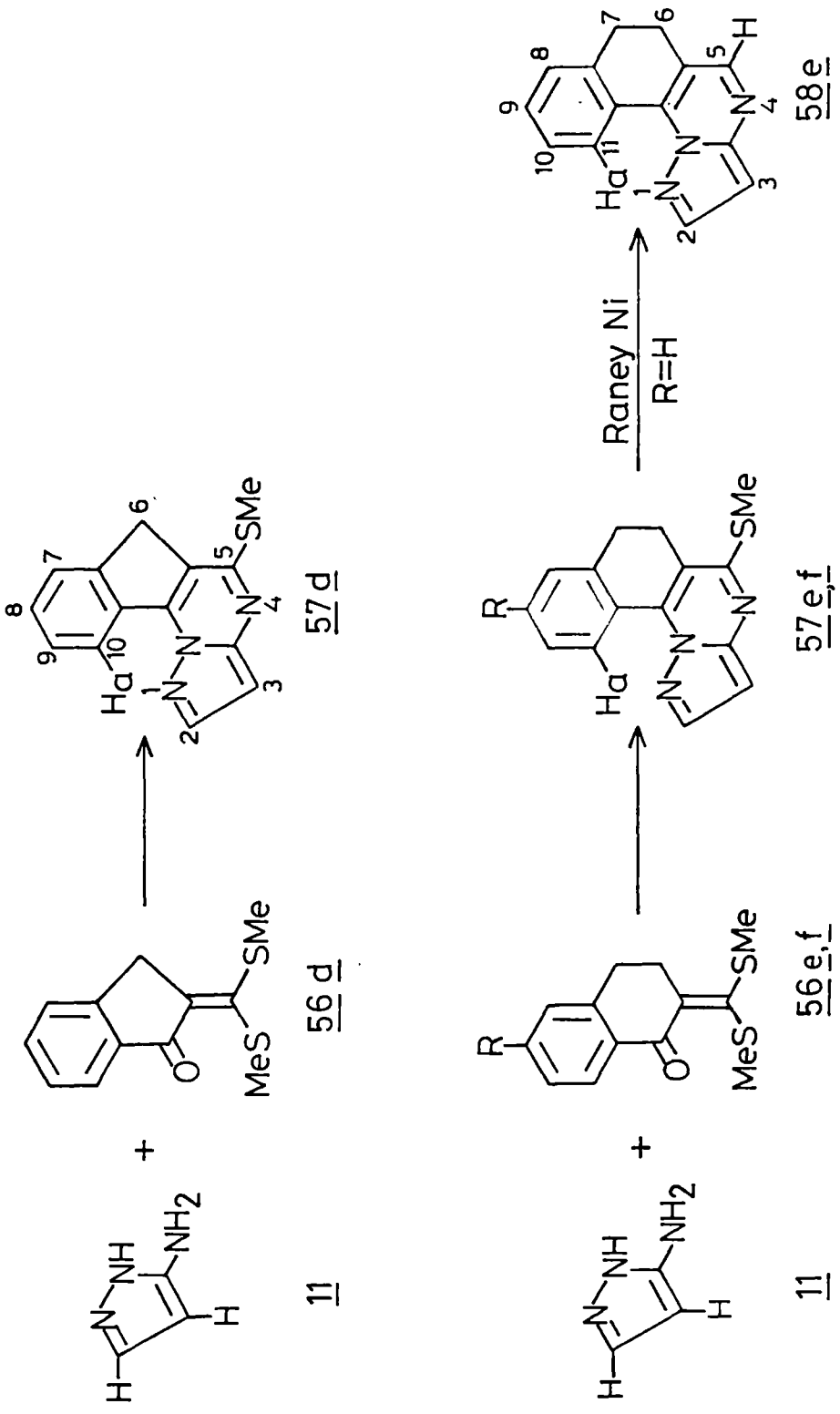


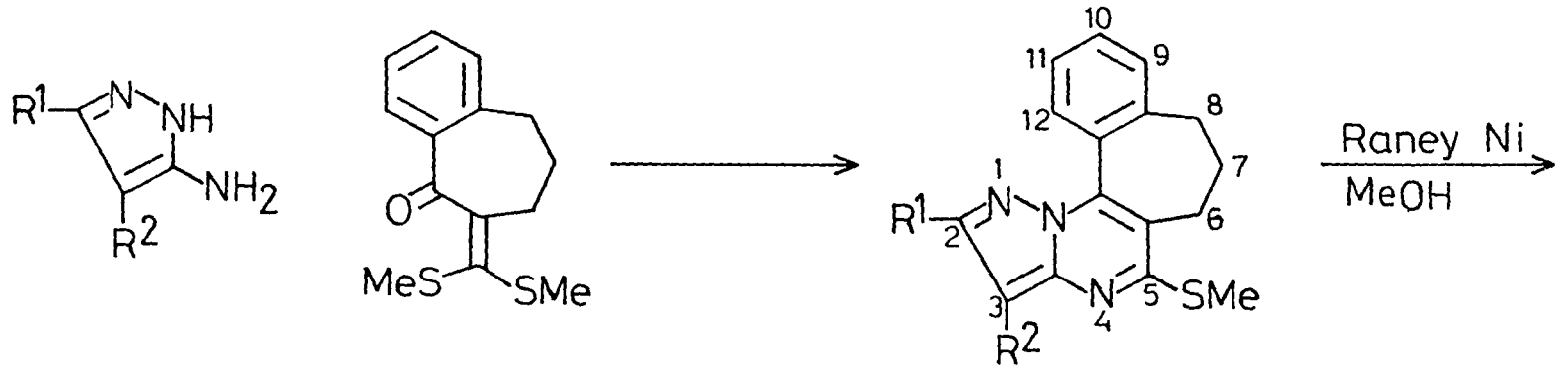
57e



57E

In the ^{13}C n.m.r. spectrum of compound 57e, the signal due to C-5 appeared at δ159 identical to the values observed in the other pyrazolopyrimidines 50a, 57a and 57c. On the otherhand in the linearly fused pyrazolopyrimidine 57E, the signal due to C-4a is expected to appear above δ 165[13]. The ^{1}H n.m.r. spectra of the desulphurised pyrazolopyrimidines 58e and 58h showed sharp singlets at δ8.37 and 8.56 respectively for C-5 protons showing the absence of any long range coupling which would be expected in the linearly fused regioisomer. The dithioacetals 56i and 56j derived from benzothiopyrone and benzothiepinone also afforded the pyrazolopyrimidine 57i and 57j in 86 and 82% yield on reaction with aminopyrazole 11 and 52 respectively. The spectral and analytical data of 57i and 57j were found to be in agreement with the assigned


11
56 d
57 d
56 e,f
57 e,f
56,57 e R=H
f R=MeO
Raney Ni
R=H
58 e
Scheme-14



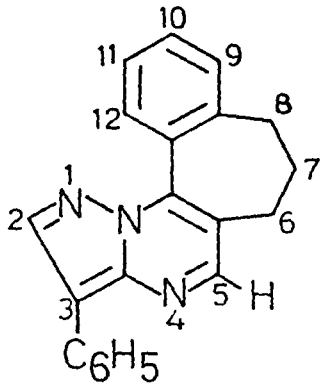
11, 52

56g

57

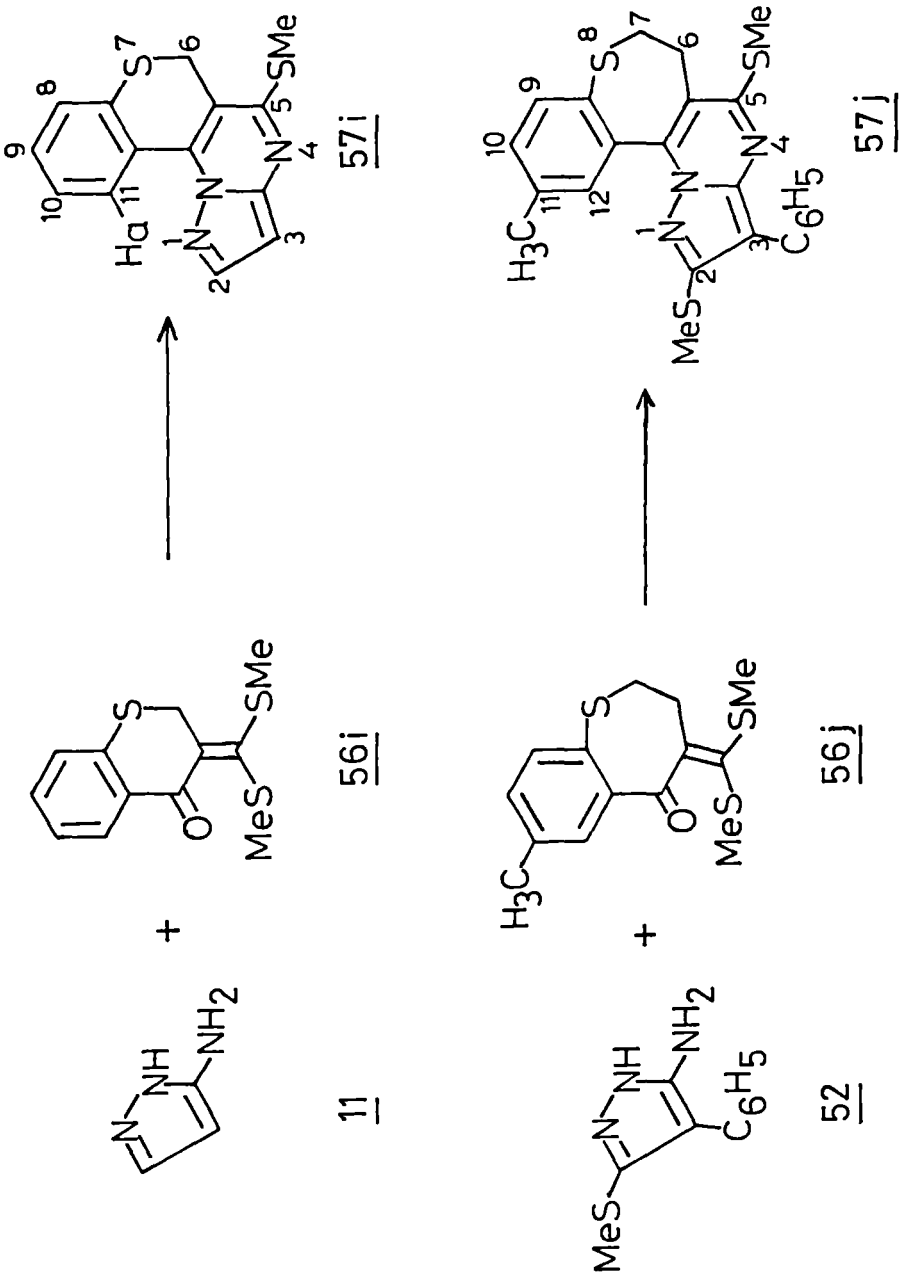
57g $R^1 = R^2 = H$

h R^1=SMe; $R^2 = C_6H_5$



58h

Scheme–15



Scheme-16

structure and is given in the experimental section. In the ^1H n.m.r. spectra of pyrazolopyrimidines 57d-f, 58e and 57i, the signal due to one of the aromatic protons (Ha) appeared at significantly low field (δ8.57-9.51) probably due to the deshielding effect of the pyrazole ring.

IV.3 CONCLUSION

A simple and practical method have been developed for the synthesis of pyrazolo[1,5-a]pyrimidines via α-oxoketene dithioacetals. The method is remarkably efficient compared to the available literature methods and some of the attractive features are (1) the cycloconden-sation proceeds with high regioselectivity leading to only one regioisomer. (2) The method is highly efficient for the synthesis of many structural variants of pyrazolo[1,5-a]pyrimidine ring systems, since a large number of acyclic and cyclic α-oxoketene dithioacetals can be prepared from active methyl and methylene ketones. Also, a number of enoyl and polyenoyl ketene dithioacetals can be prepared and were shown to give pyrazolopyrimidines in high yield. (3) In many cases products were isolated directly in high yield and required little purification. The method should be promising for the synthesis of other azolo[1,5-a]pyrimidines.

IV.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run as KBr discs on a Perkin-Elmer model 297 spectrometer. ^1H n.m.r. spectra were recorded on a Varian EM-390 (90 MHz) and ^{13}C n.m.r. spectra on a

Brucker WM-400 spectrometer in deutrochloroform with tetramethylsilane as internal standard. Chemical shifts are given in δ units down field from TMS. Mass spectra were obtained on a Jeol JMS D-300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-RAPID instrument.

General experimental details for the preparation of α-oxoketene dithioacetal is given in Chapter II. All ketene dithioacetals (41a-j, 56a-j, were prepared using this procedure and were characterised by physical and spectral data. The α-cinnamoyl (53a-c), 5-aryl 2,4-pentadienyl (53d,e) and 7-aryl 2,4,6-heptatrienoyl (53f,g) ketene dithioacetals were achieved by the condensation of α-acylketene dithioacetals with aldehydes. The general procedure for the condensation reaction and the spectral and analytical data of the unknown trienoylketene dithioacetal 53g is given in Chapter III. The data of trienoylketene dithioacetal 53f is given in this section.

Commercially available 2-chloroacrylonitrile and phenylacetonitrile were purchased (Aldrich) and was reacted without purification. Hydrazinehydrate was used as a 55% solution in water.

Preparation of 5-aminopyrazole(11)[32]:

Hydrazinehydrate (55g, 1.1 mol) was added to a solution of K_2CO_3 (140g, 1 mol) in water (400 ml). To this vigerously stirred mixture was added dropwise 2-chloroacrylonitrile (87.5g, 1 mol) at 5-10°C (ice-salt cooling) under nitrogen atmosphere over a period of 1 hr. Stirring was continued for 1 hr. at room temperature and 1.5 hr. at 40-50°C and the mixture was left to stand over night. The mixture

was extracted many times with ethyl acetate (5-aminopyrazole is soluble in water) and distilled to remove the solvent. The crude oil thus obtained was distilled under reduced pressure to give the pure aminopyrazole 58g (70%).

3-Amino-4-phenyl-5-methylthiopyrazole (52):

A solution of 3,3-bis(methylthio)-2-phenylacrylonitrile[33] (22.1g, 0.1 mol) and hydrazinehydrate (5.5g, 0.1 mol) in ethanol (100 ml) was refluxed with stirring for 4-6 hr. (monitored by t.l.c.). The bulk solvent was evaporated and reaction mixture was poured into cold water (100 ml). The colourless crystalline solid separated was collected by filteration, and recrystallised from methanol to give 18.86g, (92%) of the product, m.p. 133-134°C; ν_{max} 3380-3010(br), 1600, 1570 cm^{-1}; δ_H 2.28(3H,s,SCH_3), 6.17(2H,brs,NH_2), 7.20-7.73 (6H,m,arom and NH). (Found: C,58.32; H,5.35; N,20.70. $C_{10}H_{11}N_3S$ requires: C,58.51; H,5.40; N,20.47%).

1,1-Bis(methylthio)-9-(4-methoxyphenyl)-1,4,6,8-nonatetraene-3-one (53f) was isolated as brown solid (methanol), yield 86%; m.p. 135-136°C; ν_{max} 1621, 1599, 1560, 1473 cm^{-1}; δ_H 2.47(6H,s,SCH_3), 3.79(3H,s,OCH_3), 6.12(1H,s,H-2), 6.27(1H,d,J=16Hz,H-4), 6.55-6.98 (6H,m,arom and olefinic), 7.17-7.30(3H,m,arom and olefinic). (Found: C,64.86; H,6.31. $C_{18}H_{20}O_2S_2$ requires: C,65.02; H,6.02%); m/z 332 (6%,M^+).

General procedure for the synthesis of pyrazolo[1,5-a]pyrimidines (50a-k, 54a-g, 57a-j and 59):

Method A: A mixture of the α-oxoketene dithioacetal (0.005 mol) and the aminopyrazole (0.005 mol) in a mixture of acetic acid (25 ml)

and water (7 ml) containing a drop of piperidine was heated at 110-115°C, with stirring for 6-12 hr. (monitored by t.l.c.). The reaction mixture was cooled and water (20 ml) was added and the precipitate which had separated was collected by filteration, washed free of acetic acid, and dried. Analytically pure compounds were obtained by recrystallisation from chloroform-hexane.

Method B: The condensation was carried out using the procedure described above. The reaction mixture was diluted with water (50 ml) and extracted with chloroform (3x25 ml), and the combined extracts were washed with water (2x100 ml), dried (Na_2SO_4) and evaporated. The resulting product was purified by silica gel column chromatography and recrystallised from suitable solvent.

7-Methyl-5-methylthiopyrazolo[1,5-a]pyrimidine (50a) was isolated by Method B (ethylacetate-hexane 1:20 as eluent) as colourless needles (82%), m.p. 88-89°C; ν_{max} 1620, 1545, 1501 cm^{-1}; δ_H 2.57 (3H,brs,CH_3), 6.48(1H,brs,H-6), 6.49(1H,d,J=1.5Hz,H-3), 8.00(1H, d,J=1.5Hz,H-2); δ_C 12.60(SCH_3), 16.73(CH_3), 95.02(C-3), 106.33 (C-6), 143.69(C-7), 143.89(C-2), 148.57(C-3a), 159.95(C-5). (Found: C,53.50; H,4.93; N,23.58. $C_8H_9N_3S$ requires:C,53.61; H,5.06; N,23.64%); m/z 179(100%,M^+).

7-(4-Chlorophenyl)-5-methylthiopyrazolo[1,5-a]pyrimidine (50b) was isolated by Method A as yellow crystals (93%), m.p. 183-184°C; ν_{max} 1605, 1544 cm^{-1}; δ_H 2.63(3H,s,SCH_3), 6.52(1H,d,J=1.5Hz,H-3), 6.64(1H,s,H-6), 7.47(2H,d,J=8.5Hz,A_2B_2,arom), 7.92(2H,d,J=8.5Hz, A_2B_2,arom), 8.02(1H,J=1.5Hz,H-2). (Found:C,56.49; H,3.52; N,15.29.

$C_{13}H_{10}ClN_3S$ requires: C,56.62; H,3.66; N,15.24%); m/z 274(100%,M^+), 276(35).

5-Methylthio-7-(2-thienyl)pyrazolo[1,5-a]pyrimidine (50c) was isolated by Method A as yellow crystals (89%), m.p. 103-104°C; ν_{max} 1597, 1533 cm^{-1}; δ_H 2.64(3H,s,SCH_3), 6.55(1H,d,J=1.5Hz,H-3), 7.03(1H,s,H-6), 7.23(1H,distorted t, J=5.0Hz,H-4'), 7.68(1H,d, J=4.5Hz,H-3'), 8.14(1H,d,J=1.5Hz,H-2), 8.25(1H,d,J=4.5Hz,H-5'). (Found: C,53.31; H,3.60; N,17.18. $C_{11}H_9N_3S_2$ requires: C,53.42; H,3.67; N,16.99%); m/z 247(100%,M^+).

5-Methylthio-7-(2-furyl)pyrazolo[1,5-a]pyrimidine (50d) was isolated by Method A as yellow needles (88%), m.p. 122-123°C; ν_{max} 1615, 1572, 1528 cm^{-1}; δ_H 2.62(3H,s,SCH_3), 6.36-6.73(2H,m,H-3 and H-4'), 7.12(1H,s,H-6), 7.63(1H,brs,H-3'), 7.93-8.23(2H,m,H-2 and H-5'). (Found: C,57.01; H,3.86; N,18.28. $C_{11}H_9N_3OS$ requires: C,57.12; H,3.92; N,18.17%); m/z 231 (100%,M^+).

7-Ethyl-6-methyl-5-methylthiopyrazolo[1,5-a]pyrimidine (50e) was isolated by Method B (ethyl acetate-hexane 1:20 as eluent) as pale yellow solid (86%), m.p. 95°C; ν_{max} 1616, 1536 cm^{-1}; δ_H 1.30(3H, t,J=7Hz,$CH_2\underline{CH_3}$), 2.23(3H,s,SCH_3), 2.58(3H,s,CH_3), 3.20(2H,q,J=7Hz, $\underline{CH_2}CH_3$), 6.46(1H,d,J=1.5Hz,H-3), 7.98(1H,d,J=1.5Hz,H-2). (Found: C,58.03; H,6.33; N,20.40. $C_{10}H_{13}N_3S$ requires: C,57.94; H,6.32; N,20.27%); m/z 207(100%,M^+).

6-Benzoyl-5-methylthio-7-phenylpyrazolo[1,5-a]pyrimidine (50f)

The reaction was found to be incomplete (t.l.c.) after refluxing for 20 hr. Column chromatography (ethylacetate-hexane 1:20) gave

compound 50f as colourless solid (76%), (on the basis of pure recovered starting material), m.p. 149-150°C; ν_{max} 1666, 1600, 1509 cm^{-1}; δ_H 2.58(3H,s,SCH_3), 6.57(1H,d,J=1.5Hz,H-3), 7.06-7.83 (10H,m,arom), 8.04(1H,d,J=1.5Hz,H-2). (Found: C,69.70; H,4.42; N,12.30. $C_{20}H_{15}N_3OS$ requires: C,69.70; H,4.38; N,12.17%); m/z 345(100%,M^+), 312(50).

General procedure for the reductive dethiomethylation of 5-methylthio and 2,5-bis(methylthio)pyrazolo[1,5-a]pyrimidines 50a,d,e, 50g,h, 54a,f, 57a, 57e and 57h):

A solution of the pyrazolopyrimidine (0.001 mol) in methanol (30-100 ml) depending on the solubility) was stirred at room temperature with aged (10 days) W-2 Rany Nickel (ca.15-20 times by weight) for 2-4 hr. (monitored by t.l.c.). The nickel was separated by filteration and the residue was washed with methanol. The methanol was evaporated and the product was extracted into chloroform (30 ml) and washed with water (2x30 ml), dried (Na_2SO_4), evaporated and recrystallised from suitable solvent or purified by passing through short length silica gel column.

7-Methylpyrazolo[1,5-a]pyrimidine (51a) was isolated as colourless needles (n-pentane), yield 68%; m.p. 61°C [lit. m.p. 59-60°C]; ν_{max} 1615, 1540 cm^{-1}; δ_H 2.81(3H,brs,CH_3), 6.70(1H,d,J=4.5Hz,H-6), 6.76(1H,d,J=1.5Hz, H-3), 8.24(1H,d,J=1.5Hz,H-2), 8.49(1H,d,J=4.5Hz,H-5). (Found: C,62.98; H,5.21; N,31.69. $C_7H_7N_3$ requires: C,63.14; H,5.30; N,31.56%); m/z 133(100%,M^+).

7-(2-Furyl)pyrazolo[1,5-a]pyrimidine (51d) was isolated as yellow crystals (chloroform-hexane), yield 75%; m.p. 111-112°C; ν_{max} 1615, 1563, 1515 cm^{-1}; δ_H 6.68(1H,dd,J=1.0 and 1.5Hz,H-4'), 7.28(1H,d, J=4.5Hz,H-6), 7.72(1H,d,J=1.9Hz,H-3'), 8.23(1H,d,J=1.5Hz,H-2), 8.28 (1H,d,J=1.5Hz,H-5'), 8.56(1H,d,J=4.5Hz,H-5). (Found: C,64.92; H,3.82; N,22.80. $C_{10}H_7N_3O$ requires: C,64.86; H,3.81; N,22.69%); m/z 185 (100%,M^+).

7-Ethyl-6-methylpyrazolo[1,5-a]pyrimidine (51e) was isolated as pale yellow crystals (hexane), yield 71%; m.p. 74°C; ν_{max} 1609, 1520 cm^{-1}; δ_H 1.33(3H,t,J=7.5Hz,$CH_2\underline{CH_3}$), 2.34(3H,s,CH_3), 3.19(2H,q,J=7.5Hz, $\underline{CH_2}CH_3$), 6.63(1H,d,J=1.5Hz,H-3), 8.09(1H,d,J=1.5Hz,H-2), 8.28(1H, s,H-5). (Found: C,67.23; H,7.01; N,26.20. $C_9H_{11}N_3$ requires: C,67.05; H,6.88; N,26.07%); m/z 162(100%,M^++1), 160(74).

2,5-Bis(methylthio)-7-methyl-3-phenylpyrazolo[1,5-a]pyrimidines (50g) was isolated by Method B (ethylacetate-hexane 1:10 as eluent)as yellow crystals (80%), m.p. 125-126°C; ν_{max} 1616, 1545 cm^{-1}; δ_H 2.57(3H,s, SCH_3), 2.62(3H,s,SCH_3), 2.65(3H,s,CH_3), 6.42(1H,s,H-6), 7.15-7.50 (3H,m,arom), 7.86-8.10(2H,m,arom). (Found: C,59.60; H,5.21; N,14.05. $C_{15}H_{15}N_3S_2$ requires: C,59.77; H,5.02; N,13.94%); m/z 301(100%,M^+), 254(73).

2,5-Bis(methylthio)-7-(4-methoxyphenyl)-3-phenylpyrazolo[1,5-a] pyrimidine (50h) was isolated by Method A as yellow crystals (93%), m.p. 198-199°C; ν_{max} 1595, 1547 cm^{-1}; δ_H 2.63(6H,s,SCH_3), 3.86(3H, s,OCH_3), 6.62(1H,s,H-6), 6.85-7.55(5H,m,arom), 7.82-8.15(4H,m,arom). (Found: C,63.95; H,4.92; N,10.80. $C_{21}H_{19}N_3OS_2$ requires: C,64.09; H,4.87; N,10.68%); m/z 394(100%,M^+), 347(60).

2,5-Bis(methylthio)-3,7-diphenylpyrazolo[1,5-a]pyrimidine (50i) was isolated by Method A as yellow crystals (92%), m.p. 178-179°C; ν_{max} 1590, 1540 cm^{-1}; δ_H 2.56(3H,s,SCH_3), 2.60(3H,s,SCH_3), 6.62 (1H,s,H-6), 7.16-7.56(6H,m,arom), 7.90-8.06(4H,m,arom). (Found: C,65.96; H,4.70; N,11.72. $C_{20}H_{17}N_3S_2$ requires: C,66.08; H,4.72; N,11.56%); m/z 363(32%,M^+), 316(31).

6-(n-Butyl)-2,5-dimethylthio-7-methyl-3-phenylpyrazolo[1,5-a] pyrimidine (50j) was isolated by Method B (ethylacetate-hexane 1:20 as eluent) as pale yellow crystals (78%), m.p. 112-113°C; ν_{max} 1602, 1538 cm^{-1}; δ_H 0.98(3H,t,J=6.5Hz,CH_3), 1.26-1.69(4H,m, CH_2), 2.56(3H,s,SCH_3), 2.64(3H,s,SCH_3), 2.66(3H,s,CH_3), 2.45-2.82 (2H,m,CH_2, merged with CH_3), 7.11-7.56(3H,m,arom), 7.95-8.13(2H, m,arom). (Found: C,63.96; H,6.60; N,11.88. $C_{19}H_{23}N_3S_2$ requires: C,63.83; H,6.48; N,11.75%); m/z 358(100%,M^+), 311(42).

2,5-Bis(methylthio)-3,7-diphenyl-6-methylpyrazolo[1,5-a]pyrimidine (50k) was isolated by Method A as yellow crystals (81%), m.p. 178-179°C; ν_{max} 1652, 1598 cm^{-1}; δ_H 2.12(3H,s,CH_3), 2.42(3H,s,SCH_3), 2.62(3H,s,SCH_3), 7.21-7.63(8H,m,arom), 7.92-8.15(2H,m,arom). (Found: C,66.98; H,5.20; N,11.29. $C_{21}H_{19}N_3S_2$ requires: C,66.81; H,5.07; N,11.13%); m/z 378(100%,M^+), 330(64).

7-Methyl-3-phenylpyrazolo[1,5-a]pyrimidine (51g) was isolated as yellow crystals (chloroform-hexane), yield 79%; m.p. 224-225°C; ν_{max} 1640, 1575 cm^{-1}; δ_H 2.84(3H,brs,CH_3), 6.80(1H,d,J=4.5Hz,H-6), 8.30(5H,brs,arom), 8.51-8.68(2H,m,H-2 and H-5). (Found: C,74.50; H,5.19; N,20.24. $C_{13}H_{14}N_3$ requires: C,74.62; H,5.30; N,20.08%); m/z 209(100%,M^+).

7-(4-methoxyphenyl)-3-phenylpyrazolo[1,5-a]pyrimidine (51h) was isolated as yellow crystals (chloroform-hexane), yield 80%; m.p. 201-202°C; ν_{max} 1503, 1549, 1400 cm^{-1}; δ_H 3.82(3H,s,OCH_3), 6.86 (1H,d,J=4.5Hz,H-6), 7.09(2H,d,J=8Hz,arom), 7.26-7.60(3H,m,arom), 7.99-8.16(4H,m,arom), 8.43(1H,s,H-2), 8.56(1H,d,J=4.5Hz,H-5). (Found: C,75.62; H,4.96; N,14.08. $C_{19}H_{15}N_3O$ requires: C,75.73; H,5.02; N,13.94%); m/z 301(100%,M^+).

2,5-Bis(methylthio)-7-(4-methoxystyryl)-3-phenylpyrazolo[1,5-a] pyrimidine (54a) was isolated by Method A as bright yellow crystals (89%); m.p. 164-165°C; ν_{max} 1604, 1588, 1534 cm^{-1}; δ_H 2.60(3H,s, SCH_3), 2.70(3H,s,SCH_3), 3.80(3H,s,OCH_3), 6.68(1H,s,H-6),6.90(2H,d, J=8.5Hz,arom), 7.24-8.10(9H,m,arom and olefinic). (Found: C,65.69; H,4.90; N,10.20. $C_{23}H_{21}N_3OS_2$ requires: C,65.84; H,5.03; N,10.02%); m/z 420(100%,M^+).

6-Methyl-5-methylthio-7-(3,4-methylenedioxystyryl)pyrazolo[1,5-a] pyrimidine (54b) was isolated by Method A as yellow crystals (84%); m.p. 181-182°C; ν_{max} 1624, 1580 cm^{-1}; δ_H 2.41(3H,s,CH_3), 2.60(3H, s,SCH_3), 5.96(2H,s,CH_2), 6.36(1H,d,J=1.5Hz,H-3), 6.73-7.38(4H,m, arom and olefinic), 7.94(1H,d,J=16Hz,olefinic), 7.96(1H,d,J=1.5Hz, H-2). (Found: C,62.60; H,4.66; N,13.02. $C_{17}H_{15}N_3O_2S$ requires: C,62.75; H,4.65; N,12.91%); m/z 325(100%,M^+).

7-[2-(3,4-Dimethoxyphenyl)-1-isopropenyl]-6-methyl-5-methylthio-pyrazolo[1,5-a]pyrimidine (54c) was isolated by Method B (ethylacetate-hexane 1:10 as eluent) as pale yellow crystals (78%); m.p. 130-131°C; ν_{max} 1600, 1510 cm^{-1}; δ_H 2.30(6H,brs,CH_3), 2.61(3H,s,SCH_3), 3.90(6H, s,OCH_3), 6.44(1H,d,J=1.5Hz,H-3), 6.55(1H,brs,arom), 6.72-7.02(3H,m,

arom and olefinic), 7.94(1H,d,J=1.5Hz,H-2). (Found: C,63.99; H,5.80; H,5.80; N,11.98. $C_{19}H_{21}N_3O_2S$ requires: C,64.20; H,5.96; N,11.82%); m/z 355(8%,M^+), 291(100).

2,5-Bis(methylthio)-3-phenyl-7-(4-phenyl-1,3-butadienyl)pyrazolo [1,5-a]pyrimidine (54d) was isolated by Method A as red crystals (86%); m.p. 190-191°C; ν_{max} 1602, 1538 cm^{-1}; δ_H 2.56(3H,s,SCH_3), 2.68(3H,s,SCH_3), 6.56(1H,s,H-6), 6.90-7.98(14H,m,arom and olefinic). (Found: C,69.48; H,5.26; N,10.27. $C_{24}H_{21}N_3S_2$ requires: C,69.36; H,5.09; N,10.11%); m/z 415(93%,M^+), 300(100).

6-Methyl-5-methylthio-7-(4-phenyl-1,3-butadienyl)pyrazolo[1,5-a] pyrimidine (54e) was isolated by Method A as red crystals (87%); m.p. 140-142°C; ν_{max} 1598, 1528 cm^{-1}; δ_H 2.38(3H,s,CH_3), 2.60(3H, SCH_3), 6.47(1H,d,J=1.5Hz,H-3), 6.80-7.09(3H,m,arom and olefinic), 7.19-7.60(5H,m,arom and olefinic), 8.02(1H,d,J=1.5Hz,H-2), 7.93-8.22(1H,m,arom). (Found: C,70.41; H,5.43; N,13.80. $C_{18}H_{17}N_3S$ requires: C,70.32; H,5.58; N,13.67%); m/z 307(100%,M^+).

5-Methylthio-7-[6-(4-methoxyphenyl)-1,3,5-hexatrienyl]pyrazolo[1,5-a] pyrimidine (54f) was isolated by Method A as red crystals (79%); m.p. 151-152°C; ν_{max} 1585, 1512 cm^{-1}; δ_H 2.58(3H,s,SCH_3), 3.76(3H,s,OCH_3), 6.42-7.95(13H,m,arom and olefinic). (Found: C,68.89; H,5.40; N,12.20. $C_{20}H_{19}N_3OS$ requires: C,68.74; H,5.48; N,12.03%); m/z 349(27%,M^+), 348(100).

2,5-Bis(methylthio)-3-phenyl-7-(6-phenyl-1,3,5-hexatrienylpyrazolo[1,5-a] pyrimidine (54g) was isolated by Method A as red crystals (80%);m.p. 181-182°C; ν_{max} 1575, 1530 cm^{-1}; δ_H 2.58(3H,s,SCH_3), 2.70(3H,s,SCH_3),

6.43-8.08(17H,m,arom and olefinic). (Found: C,70.59; H,5.38; N,9.60. $C_{26}H_{23}N_3S_2$ requires: C,70.71; H,5.25; N,9.52%); m/z 441(26%,M^+), 440(83).

7-[2-(4-methoxyphenyl)ethyl]-3-phenylpyrazolo[1,5-a]pyrimidine (55a) was isolated as yellow crystals (chloroform-hexane), yield 76%; m.p. 151-152°C; ν_{max} 1611, 1562, 1508 cm^{-1}; δ_H 3.13(2H,t,J=7Hz,CH_2), 3.45(2H,t,J=7Hz,CH_2), 3.72(3H,s,OCH_3), 6.58(1H,d,J=4.5Hz,H-6), 6.79 (2H,d,J=8Hz,A_2B_2,arom), 7.15(2H,d,J=8Hz,A_2B_2,arom), 7.29-7.62(3H,m, arom), 8.00-8.16(2H,m,arom), 8.40-8.53(2H,m,H-2 and H-5). (Found: C,76.68; H,6.00; N,12.89. $C_{21}H_{19}N_3O$ requires: C,76.57; H,5.81; N,12.76%); m/z 329(36%,M^+); 121(100).

7-(6-phenyl-n-hexyl)-3-phenylpyrazolo[1,5-a]pyrimidine (55f) was purified by silica gel column chromatography using ethylacetate-hexane (1:20) as eluent, pale yellow crystals (74%); m.p. 91-92°C; ν_{max} 1612, 1600, 1552, 1533 cm^{-1}; δ_H 1.31-2.06(8H,m,CH_2), 2.60(2H, t,J=7Hz,CH_2), 3.16(2H,t,J=7Hz,CH_2), 6.61(1H,d,J=4.5Hz,H-6), 7.10-7.58(8H,m,arom), 8.00-8.19(2H,m,arom), 8.42-8.59(2H,m,H-2 and H-5). (Found: C,81.21; H,7.06; N,11.99. $C_{24}H_{25}N_3$ requires:C,81.09; H,7.09; N,11.82%); m/z 355(68%,M^+), 209(100).

5-Methylthio-6,7,8,9-tetrahydropyrazolo[1,5-a]quinazoline (57a) was isolated by Method B (ethylacetate-hexane 1:20 as eluent) as colourless crystals (81%); m.p. 139-140°C; ν_{max} 1611, 1530 cm^{-1}; δ_H 1.62-1.95 (4H,m,H-7 and H-8), 2.54(3H,s,SCH_3), 2.28-2.66(2H,m,CH_2,merged with SCH_3), 2.80-3.16(2H,m,CH_2), 6.35(1H,d,J=1.5Hz,H-3), 7.86(1H,d,J=1.5Hz, H-2); δ_C 12.70(SCH_3), 20.88, 21.74, 23.16 (C-6, C-7, C-8 and C-9),

94.46(C-3), 114.65(C-5a), 141.52(C-9a), 143.05(C-2), 147.02(C-3a), 160.54(C-5). (Found: C,60.03; H,6.08; N,19.30. $C_{11}H_{13}N_3S$ requires: C,60.24; H,5.97; N,19.16%); m/z 219(11%,M^+), 186(100).

5-Methylthio-7,8,9,10-tetrahydro-6H-cyclohepta[e]pyrazolo[1,5-a] pyrimidine (57b) was isolated by Method B (ethylacetate-hexane 1:20 as eluent) as colourless crystals (79%); m.p. 121-182°C; ν_{max} 1617, 1538 cm^{-1}; δ_H 1.43-2.03(6H,m,CH_2), 2.56(3H,s,SCH_3), 2.66-2.96(2H,m, CH_2), 3.31-3.60(2H,m,CH_2), 6.43(1H,d,J=1.5Hz,H-3), 7.96(1H,d,J=1.5Hz, H-2). (Found: C,61.88; H;6.60; N,18.22. $C_{12}H_{15}N_3S$ requires: C,61.77; H,6.48; N,18.01%); m/z 233(100%,M^+), 200(87).

6,7,8,9-Tetrahydropyrazolo[1,5-a]quinazoline (58a) was isolated as colourless solid (n-hexane), yield 74%; m.p. 91-92 °C; ν_{max} 1618, 1517 cm^{-1}; δ_H 1.66-2.11(4H,m,CH_2), 2.75(2H,t,J=7Hz,CH_2), 3.10(2H,t,J=7Hz,CH_2), 6.64(1H,d,J=1.5Hz,H-3), 8.08(1H,d,J=1.5Hz,H-2), 8.28(1H,s,H-5). (Found: C,69.52; H,6.49; N,24.32. $C_{10}H_{11}N_3$ requires: C, 69.34; H, 6.40; N,24.26%); m/z 174(100%,M^++1), 172(28).

5-Methylthio-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (57c) was isolated by Method B (ethylacetate-hexane 1:30 as eluent) as colourless crystals (36%); m.p. 133-134°C; ν_{max} 1620, 1532 cm^{-1}; δ_H 2.27(2H,quintet, J=7Hz,CH_2), 2.61(3H,s,SCH_3), 2.88(2H,t,J=7Hz, CH_2), 3.31(2H,t,J=7Hz,CH_2), 6.44(1H,d,J=1.5Hz,H-3), 7.93(1H,d,J=1.5Hz, H-2); δ_C 12.13(SCH_3), 21.82, 28.84, 29.58(C-6, C-7 and C-8), 94.45 (C-3), 120.02(C-5a), 143.97(C-2), 146.81(C-8a), 148.93(C-3a), 157.62 (C-5). (Found: C,58.39; H,5.48; N,20.60. $C_{10}H_{11}N_3S$ requires: C,58.51; H,5.40; N,20.47%); m/z 205(99%,M^+), 172(91).

Further elution with increased amount of ethylacetate in hexane (1:20) gave the isomeric pyrazolopyrimidine 59.

8-Methylthio-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine (59) was isolated as colourless solid (48%); m.p. 103-104°C; ν_{max} 1603, 1500 cm^{-1}; δ_H 2.34(2H,quintet, J=7Hz,CH_2), 2.73(3H,s,SCH_3), 2.83-3.17 (4H,m,CH_2), 6.47(1H,d,J=1.5Hz,H-3), 7.97(1H,d,J=1.5Hz,H-2); δ_C 15.23 (SCH_3), 23.41, 28.93, 34.12(C-5, C-6 and C-7), 95.59(C-3), 124.40 (C-7a), 139.80(C-8), 143.20(C-2), 148.70(C-3a), 166.46(C-4a). (Found: C,58.42; H,5.48; N,20.52. $C_{10}H_{11}N_3S$ requires: C,58.51; H,5.40; N,20.47%); m/z 205(20%,M^+), 172(100).

5-Methylthio-6H-indeno[2,1-e]pyrazolo[1,5-a]pyrimidine (57d) was isolated by Method A as yellow crystals (92%); m.p. 150-151°C; ν_{max} 1600, 1532 cm^{-1}; δ_H 2.70(3H,s,SCH_3), 3.80(2H,s,CH_2), 6.56(1H,d,J=1.5Hz, H-3), 7.43-7.60(3H,m,arom), 8.12(1H,d,J=1.5Hz,H-2), 8.57-8.73(1H,m, arom). (Found: C,66.50; H,4.46; N,16.72. $C_{14}H_{11}N_3S$ requires: C,66.38; H,4.38; N,16.59%); m/z 253(100%,M^+), 220(66).

5-Methylthio-6,7-dihydronaphtho[2,1-e]pyrazolo[1,5-a]pyrimidine (57e) was isolated by Method A as yellow crystals (89%); m.p. 118-119°C; ν_{max} 1602, 1492 cm^{-1}; δ_H 2.60(3H,s,SCH_3), 2.83(4H,brs,CH_2), 6.50 (1H,d,J=1.5Hz,H-3), 7.13-7.54(3H,m,arom), 8.04(1H,d,J=1.5Hz,H-2), 9.23-9.46(1H,m,arom); δ_C 12.65(SCH_3), 22.44(CH_2), 28.05(CH_2), 94.43 (C-3), 114.89(C-5a),126.36, 127.11, 128.83, 129.96(CH,ArH), 126.56 (C-7a), 137.40(C-11a), 139.09(C-11b), 143.01(C-2), 149.04(C-3a), 159.25(C-5). (Found: C,67.50; H,5.15; N,15.76. $C_{15}H_{13}N_3S$ requires: C,67.39; H,4.90; N,15.72%); m/z 267(21%,M^+), 266(100), 233(58).

5-Methylthio-9-methoxy-6,7-dihydronaphtho[2,1-e]pyrazolo[1,5-a] pyrimidine (57f) was isolated by Method A as yellow crystals (90%); m.p. 172-173°C; ν_{max} 1605, 1486 cm^{-1}; δ_H 2.62(3H,s,SCH_3), 2.86(4H, brs,CH_2), 3.86(3H,s,OCH_3), 6.47(1H,d,J=1.5Hz,H-3), 6.73-7.01(2H,m, arom), 8.03(1H,d,J=1.5Hz,H-2), 9.36(1H,d,J=8Hz,arom). (Found: C,64.51; H,4.97; N,14.22. $C_{16}H_{15}N_3OS$ requires: C,64.62; H,5.08; N,14.13%); m/z 297(100%,M^+), 264(57).

6,7-dihydronaphtho[2,1-e]pyrazolo[1,5-a]pyrimidine (58e) was isolated as yellow crystals (n-hexane), yield 77%; m.p. 68-69°C; ν_{max} 1604, 1507 cm^{-1}; δ_H 2.89(4H,s,CH_2), 17.71(1H,d,J=1.5Hz,H-3), 7.22-7.47 (3H,m,arom), 8.17(1H,d,J=1.5Hz,H-2), 8.37(1H,s,H-5), 9.35-9.52(1H, m,arom). (Found: C,75.89; H,5.22; N,19.15. $C_{14}H_{11}N_3$ requires: C,76.00; H,5.01; N,18.99%); m/z 221(100%,M^+).

5-Methylthio-7,8-dihydro-6H-benzo-cyclohepta[2,1-e]pyrazolo[1,5-a] pyrimidine (57g) was isolated by Method B (ethylacetate-hexane 1:20 as eluent) as pale yellow crystals (73%); m.p. 151-152°C; ν_{max} 1607, 1594 cm^{-1}; δ_H 2.03-3.02(6H,m,CH_2), 2.62(3H,s,SCH_3), 6.52(1H,d,J=1.5Hz, H-3), 7.26-7.57(3H,m,arom), 8.00(1H,d,J=1.5Hz,H-2), 8.01-8.21(1H,m, arom). (Found: C, 68.19; H,5.25; N,15.15. $C_{16}H_{15}N_3S$ requires: C,68.30; H,5.37; N,14.93%); m/z 281(100%,M^+), 248(64).

2,5-Bis(methylthio)-3-phenyl-7,8-dihydro-6H-benzocyclohepta[2,1-e] pyrazolo[1,5-a]pyrimidine (57h) was isolated by Method A as yellow needles (75%); m.p. 157-158°C; ν_{max} 1602, 1588, 1500 cm^{-1}; δ_H 1.93-2.72(6H,m,CH_2), 2.55(3H,s,SCH_3), 2.62(3H,s,SCH_3), 7.10-7.56(6H,m,arom), 7.96-8.16(3H,m,arom). (Found: C,68.28; H,5.30; N,10.58. $C_{23}H_{21}N_3S_2$ requires: C,68.45; H,5.25; N,10.41%); m/z 404(100%,M^+), 357(52).

3-Phenyl-7,8-dihydro-6H-benzocyclohepta[2,1-e]pyrazolo[1,5-a]pyrimidine (58h) was obtained as yellow crystals (chloroform-hexane); yield 79%; m.p. 145-146°C; ν_{max} 1602, 1523 cm^{-1}; δ_H 2.13-2.82(6H,m,CH_2), 7.20-7.62 (6H,m,arom), 8.02-8.29(3H,m,arom), 8.47(1H,s,H-2), 8.56(1H,s,H-5). (Found: C,81.23; H,5.68; N,13.73. $C_{21}H_{17}N_3$ requires: C,81.00; H,5.50; N,13.50%); m/z 311(100%,M^+).

5-Methylthio-6H-benzothiapyrano[2,1-e]pyrazolo[1,5-a]pyrimidine (57i) was isolated by Method A as yellow needles (86%); m.p. 154-155°C; ν_{max} 1598, 1495 cm^{-1}; δ_H 2.65(3H,s,SCH_3), 3.86(2H,s,CH_2), 6.52(1H, d,J=1.5Hz,H-3), 7.14-7.60(3H,m,arom), 8.02(1H,d,J=1.5Hz,H-2), 8.85-9.21(1H,m,arom). (Found: C,58.80; H,3.99; N,14.94. $C_{14}H_{11}N_3S_2$ requires: C,58.92; H,3.89; N,14.72%); m/z 285(21%,M^+), 284(84), 269(100).

2,5-Bis(methylthio)-11-methyl-3-phenyl-6,7-dihydrobenzothiepino[2,1-e] pyrazolo[1,5-a]pyrimidine(57j) was isolated by Method A as yellow crystals (82%); m.p. 232-233°C; ν_{max} 1595, 1518 cm^{-1}; δ_H 2.41(3H,s,CH_3),2.53 (3H,s,SCH_3), 2.64(3H,s,SCH_3), 2.73-3.72(4H,m,CH_2), 7.24-7.64(5H,m, arom), 7.93-8.15(3H,m,arom). (Found: C,63.20; H,4.75; N,9.72. $C_{23}H_{21}N_3S$ requires:C,63.41; H,4.86; N,9.65%); m/z 436(100%,M^+), 389(39).

REFERENCES

1. J.O. Alexandar, G.R. Wheeler, D.D. Hill, M.P. Morris, Biochem. Pharmacol., 881, 15 (1966).
2. G.B. Elion, S. Gallaham, H. Nathan, S. Bicher, R.W. Randles, G.H. Hitchings, Biochem. Pharmacol.,85, 12 (1963).
3. B.G. Hildick, G. Shaw, J. Chem. Soc.(C), 1610 (1971).
4. R.A. Earl, R.J. Pugmire, G.R. Revankar, L.B. Townsend, J. Org. Chem., 40, 1822 (1975).
5. H.E. Skipper, R.K. Robins, J.R. Thomson, C.C. Ching, R.W. Brockman, F.M: Schabel, Cancer Res., 17, 579 (1957).
6. H.E. Skipper, R.K. Robins, J.R. Thomson, Proc. Soc. Exptl. Biol. Med., 89, 594 (1955).
7. B. Bear, M. Chasin, D.E. Clody, J.R. Vogel, Z.P. Horovitz, Science, 428, 176 (1972).
8. E. Tenor, R. Ludwig, Pharmazie, 26, 534 (1971).
9. J.G. Buchanan, A. Stobie, R.H. Wightman, Can. J. Chem., 58, 2624 (1980).
10. G.A. Bhat, L.B. Townsend, J. Chem. Soc., Perkin Trans.I, 2387 (1981).
11. J.V. Greenhill, in Comprehensive Heterocyclic Chemistry., K.T. Potts Eds., Pergamon Press Ltd. Oxford 1984, Vol.5, Chapt.4.05, p.305-343.
12. J. Reiter, L. Pongó, P. Dyortsak, Tetrahedron, 43, 2497 (1987).
13. J.S. Bajwa, P.J. Sykes, J. Chem. Soc. Perkin Trans.I, 3085 (1979).
14. G. Muhmel, R. Hanke, E. Breitmaier, Synthesis, 673 (1982).
15. Y.V. Haverbeke, A. Maquestiau, J. J.V. Eynde, J. Heterocyclic Chem., 16, 773 (1979).
16. Ḱ.C. Joshi, V.N. Pathak, U. Garg, J. Heterocyclic Chem., 16, 1141 (1979).
17. H.A. Elfahham, F.M. Abdel-Galil, Y.R. Ibrahim, M.H. Elnagdi, J. Heterocyclic Chem. 19, 662 (1983).

18. J.V. Greenhill in Comprehensive Heterocyclic Chemistry., K.T. Potts, Eds., Pergamon Press Ltd., Oxford 1984, Vol.5, Chapt. 4.05, p.331-33.

19. Y. Makisumi, Chem. Pharm. Bull.,10, 620 (1962).

20. H. Reimlinger, M.A. Peiren, R. Merenyi, Chem. Ber.,103, 3252 (1970).

21. I. Hori, K. Saito, H. Midorikawa, Bull.Chem. Soc. Jpn. 43, 849 (1970).

22. V. Sprio, S. Plescia, J. Heterocyclic Chem. 9, 951 (1972).

23. A. Dornow, M. Siebrecht, Chem. Ber.,93, 1106 (1960).

24. H. Junek, I. Wrtilek, Monatsh. Chem., 100, 1250 (1969).

25. M.A. Khan, B.M. Lynch, J. Heterocyclic Chem. 7, 247 (1970).

26. E. Alczlde, J. de Mendoza, J.M. Garcia-Marquina, C. Almera, J. Elquero, J. Heterocyclic Chem., 11, 423 (1974).

27. K. Senga, T. Novinson, H.R. Wilson, R.K. Robins, J. Med. Chem., 24, 610 (1981).

28. Y. Tominaga, S. Kohra, H. Okuda, A. Ushirogochi, Y. Matsuda, G. Kobayashi, Chem. Pharm. Bull.,32, 122 (1984).

29. Y. Tominaga, S. Sakai, S.Kohra, J. Tsuka, Y. Matsuda, G. Kobayashi, Chem. Pharm. Bull.,33, 962 (1985).

30. M.L. Purkayastha, H. Ila, H. Junjappa, Synthesis, 000 (1989).

31. F. Eiden, H.D. Schweiger, Synthesis, 511 (1974).

32. G. Ege, P. Arnold, Angew. Chem. Int. Ed. Engl.,13, 206 (1974).

33. J. Sandstrom, I. Wennerbeck, Acta, Chem. Scand.,24, 1191 (1970).

CHAPTER V

CYCLOAROMATIZATION OF 2-LITHIOMETHYLTHIAZOLES WITH α-OXOKETENE DITHIOACETALS: SYNTHESIS OF SUBSTITUTED AND FUSED THIAZOLO[3,2-a]PYRIDINIUM COMPOUNDS

V.1 INTRODUCTION

Formation of carbon-carbon bond is one of the most fundamental reactions in organic synthesis. The synthesis of complex molecules from simple fragments would not be possible without this reaction. One of the most intensively studied synthetic methodlogies for the construction of new carbon-carbon bond is by the addition of an organometallic reagent to a suitable electrophilic carbon centre.

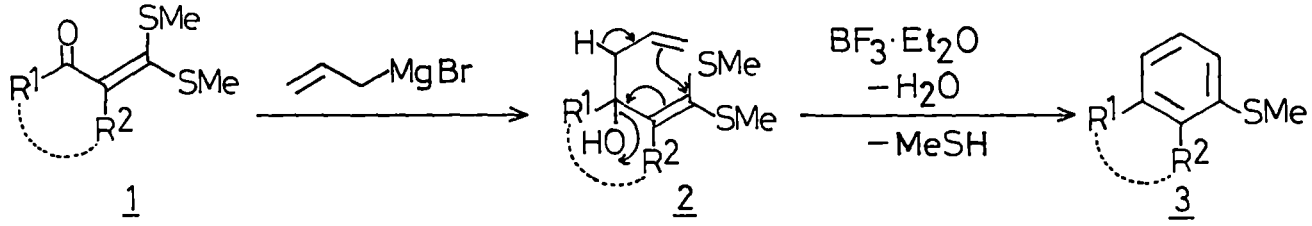
Oxoketene dithioacetals have been a subject of intense investigation in this laboratory and elsewhere for the chemo-, stereo- and regio-selective construction of new C-C bonds using organometallic reagents[1].

The new C-C bond can be formed either by a 1,2-nucleophilic addition to the keto carbonyl or 1,4-conjugate addition to the β-carbon of the enone system. The 1,2- and 1,4-nucleophilic addition reactions can be effected separately or sequentially by suitable selection of the nucleophilic reagents and appropriate reaction conditions. A number of organolithium and magnesium reagents have been shown to add to α-oxoketene dithioacetals in a 1,2-manner to give the alcohol acetals which are suitable for other transformations. A brief account of some of these reactions which are relevant to the present study is given in the following section.

The foregoing discussion is restricted to the reports on C-C bond forming reactions via α-oxoketene dithioacetals which ultimately results in ring forming reactions to afford aromatic and heteroaromatic systems. The general strategy involves 1,2-addition of a suitable carbon nucleophile to α-oxoketene dithioacetals to give the allyl alcohol which on subsequent Lewis acid assisted cationic cyclization to form six membered ring followed by aromatization. The overall reaction can generally be termed as aromatic annelation or cycloaromatization and many variations of this approach have been reported[2-10] in the literature. The other common methods for the construction of six membered rings consists of the union of two fragments, one with two atom fragment and other with four atom fragment (Diels-Alder reaction[11,12] and Robinson annelation[13]). The present method involving the union of two three atom fragments usually proceeds with high regiocontrol.

It is reported from this laboratory that the allylmagnesium bromide undergoes a 1,2-addition with α-oxoketene dithioacetals of general formula 1 to afford the corresponding alcohol acetals 2 in nearly quantitative yields. These carbinols in the presence of borontrifluoride etherate were cyclized to give the benzoannelated products 3[14]. The reaction appears to proceed through intramolecular π-participation of the allylic double bond to form a cationic species which on loss of proton and methylmercaptan yield the aromatized products 3 (Scheme 1). The reaction of allyl and crotyl magnesium bromide with cinnamoylketene dithioacetals 4 is also reported[15] to give the substituted stilbenes of the general formula 5 (Scheme 1). Subsequently, the reaction of benzylmagneisum bromide 6 with α-oxoketene dithioacetals has been reported[16]. The bulky benzylmagnesium bromide 6 underwent a 1,4-conjugate addition followed by a 1,2-addition to give carbinol 7 which in the presence of borontrifluoride etherate gave the naphthalene derivatives 8 (Scheme 2).

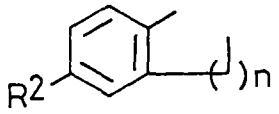
A benzoannelation approach for the synthesis of fused thioresorcinol dimethylethers is also reported[17] by the reaction of propargylmagnesium bromide with α-oxoketene dithioacetals 1 prepared from cyclic ketones. The cyclization proceeds by the intramolecular participation of the propargyl triple bond in the carbinol acetal 9 with concommitant attack of methanol on the incepient vinyl cation, followed by loss of methylmercaptan to yield the thioresorcinol dimethylethers 10 in good yields (Scheme 3).



1 2 3

$R^1=R^2=-(CH_2)_4-$; 74 %

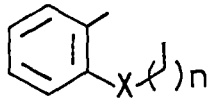
$R^1=R^2=-(CH_2)_3-$; 64 %



R^2=H; n=1 ; 54 %

R^2=H; n=2 ; 68 %

R^2=MeO; n=2 ; 67 %

$R^1=R^2=$ 

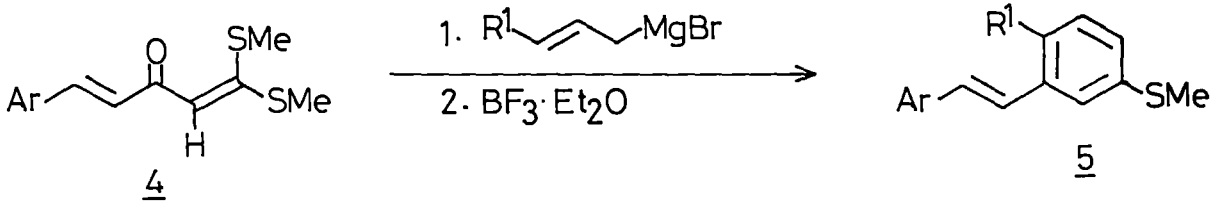
X=S; n=1 ; 59 %

X=S; n=2 ; 67 %

X=O; n=2 ; 64 %

$R^1=C_6H_5$, 4-$MeOC_6H_4$, 4-ClC_6H_4 ; R^2=H ; 40-45 %

R^1=Et ; R^2=Me ; 40 %

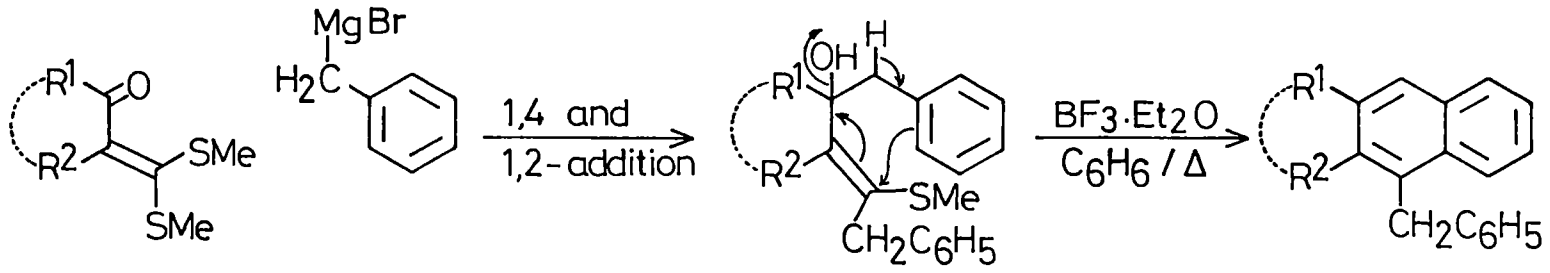


4 5

Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, m-$MeOC_6H_4$, 2-ClC_6H_4, 2,6-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$; R^1=H ; 53-68 %

Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4; R^1=Me ; 52-61 %

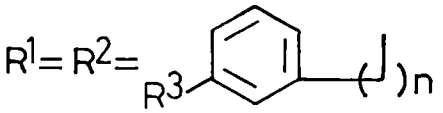
Scheme-1



1 6 7 8

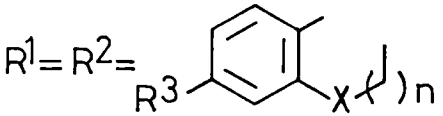
$R^1 = C_6H_5$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-naphthyl ; $R^2 = H$; 58–65 %

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



n=1 ; 62 %

n=2 ; 71 %

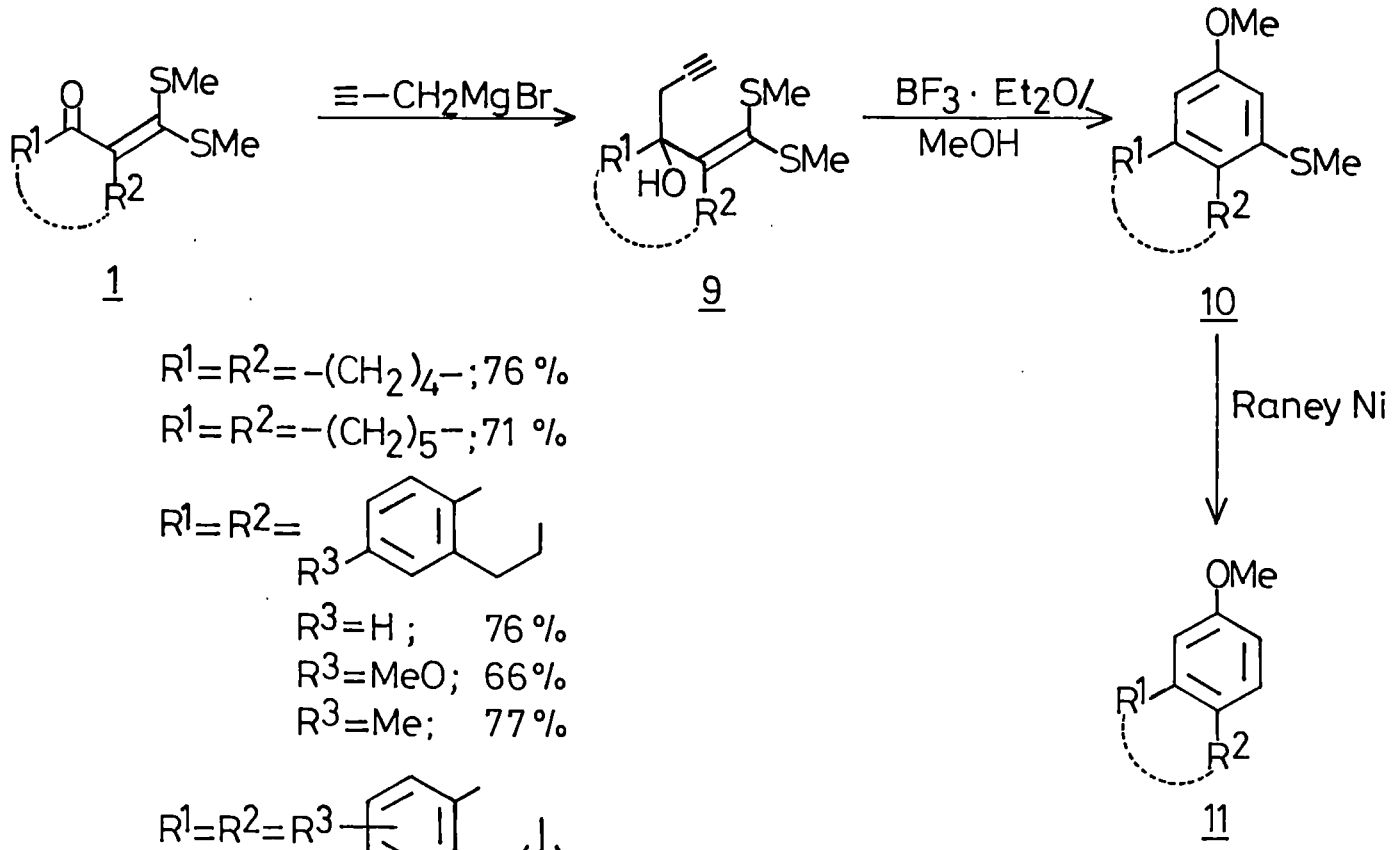


R^3= H ; X = S ; n = 1 ; 58 %

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

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

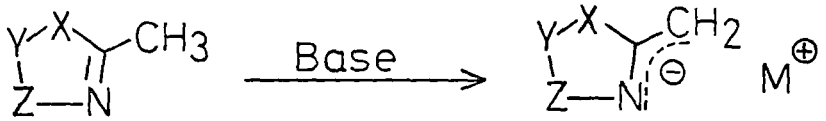
Scheme–2


SMe
O
R1
SMe
R2
1
≡—CH2MgBr
SMe
R1
HO
SMe
R2
9
BF3 · Et2O/
MeOH
OMe
R1
SMe
R2
10
Raney Ni
OMe
R1
R2
11
R1=R2=—(CH2)4—; 76 %
R1=R2=—(CH2)5—; 71 %
R1=R2=
R3
R3=H ; 76 %
R3=MeO; 66%
R3=Me; 77 %
R1=R2=R3
X
n
R3=H, Me; X=S, O ;
n=1,2 ; 68–81 %

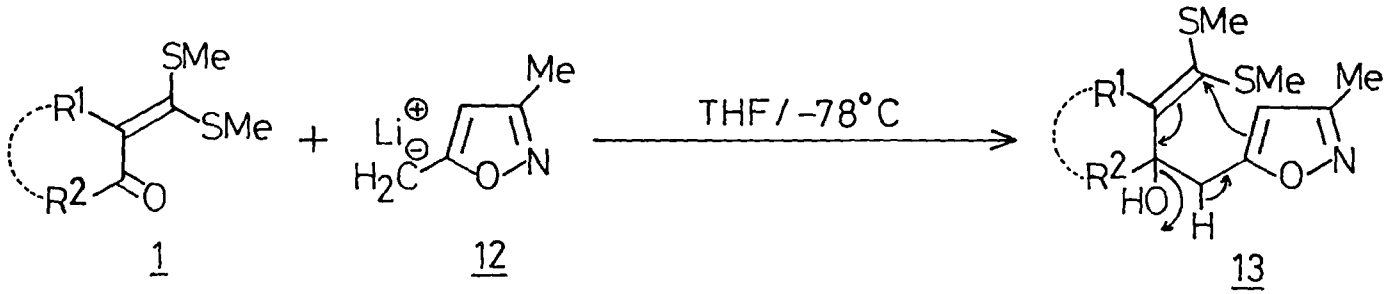
Scheme–3

The above strategy of aromatic annelation is also extended for the synthesis of fused five and six membered heteroaromatic compounds. Thus, 5-lithiomethyl-3-methylisoxazole 12 underwent an exclusive 1,2-addition to α-oxoketene dithioacetal to give the carbinol acetal 13. These carbinol acetals were cyclized to the corresponding 1,2-benzisoxazoles 14[18] in the presence of borontrifluoride etherate (Scheme 4). Another related example reported[19] is the reaction of 2-picolyllithium 15 with α-oxoketene dithioacetals resulting in the formation of substituted and fused quinolizinium ring systems. The 2-picolyllithium which bears an azaallyl moiety adds to dithioacetals 1 to give the alcohol acetals 16, which underwent cycloaromatization to the quinolizinium salts 17 through the participation of pyridine ring (Scheme 5).

As an extension of the above described strategy for the construction of aromatic and heteroaromatic ring systems (heteroaromatic annelation), it was considered of interest to explore the possibility of synthesizing other bridgehead aromatic nitrogen heterocycles using this approach. A nitrogen heterocycle with a methyl group on the carbon atom adjacent to the imino nitrogen can generate an azaallyl anion moiety by deprotonation with suitable base, provided competing sites are not present in the molecule. This structural requirement



is met in 2-methyl-4-substituted thiazoles which are selected for the

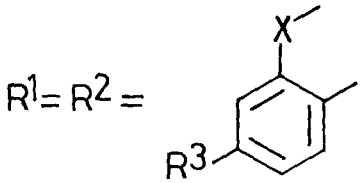


1 12 13

R^1=C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, Me, 2-furyl, 2-thienyl; R^2=H; 54-73 %

R^1=R^2=-$(CH_2)_n$-; n=4; 65 %

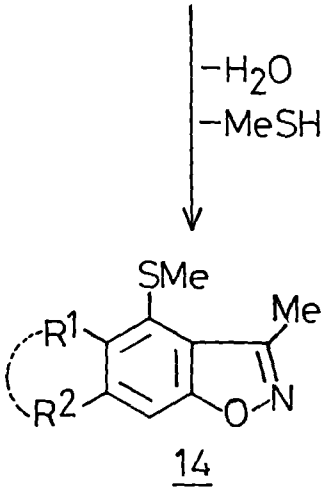
n=5; 67 %



R^3=H, X=CH_2; 57 %

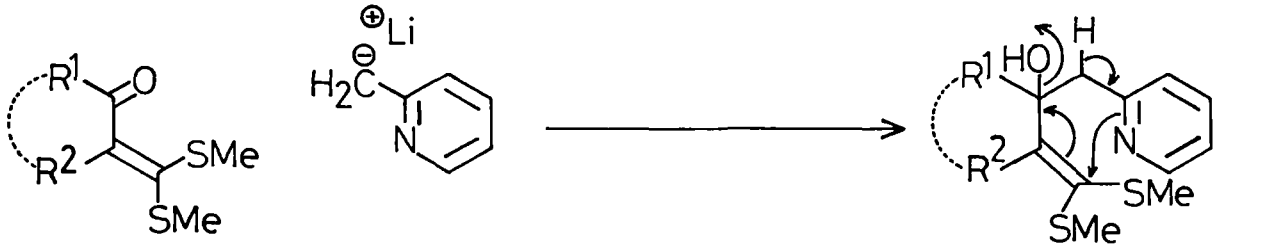
R^3=H, X=-$(CH_2)_2$-; 76 %

R^3=CH_3, X=S-$(CH_2)_2$-; 81 %



14

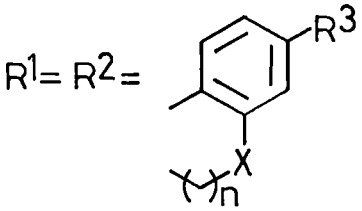
Scheme-4



1 15 16

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

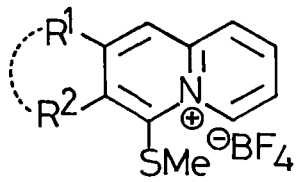
$R^1 = R^2 = -(CH_2)_5-$; 79 %



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

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

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



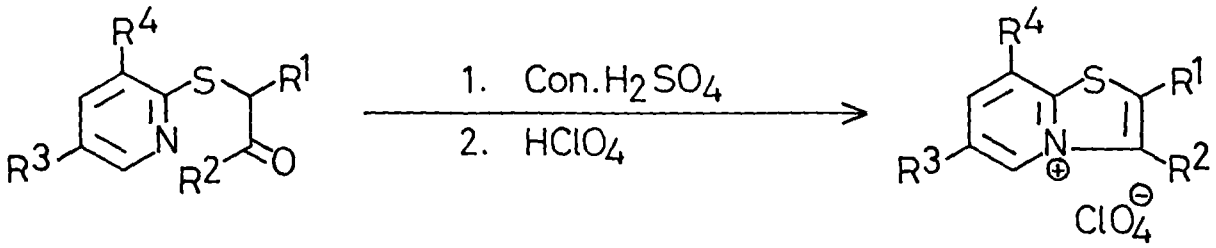
17

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

Scheme-5

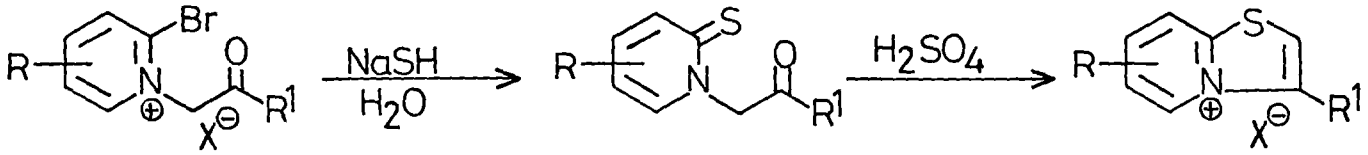
present study. The reaction of α-oxoketene dithioacetals with azaallyl anion generated from 2-methylthiazole should in principle lead to the formation of thiazolopyridines following the sequence described in the above examples. The reaction was found to be successful for the synthesis of thiazolo[3,2-a]pyridinium salts which are described in this chapter. The following section reviews some of the literature methods for the synthesis of these class of compounds.

The thiazolo[3,2-a]pyridine ring systems can in principle be synthesized from a preconstructed 2-thiopyridine or from a thiazole derivative. Most of the literature methods make use of a suitably substituted pyridine derivatives and the approaches starting from thiazole precursors are scanty. The first synthesis of thiazolopyridinium salts is accomplished by Bradsher and Lohr[20,21] starting from the corresponding pyridylsulfide 18 having a carbonyl function β - to the sulfide linkage. These sulfides can be prepared by the reaction of α-haloketones or α-haloacetals with 2-mercaptopyridine. The keto-sulfide 18 was treated with concentrated sulphuric acid to bring about the cyclization, which on perchloric acid treatment gave the thiazolo[3,2-a]pyridinium perchlorate 19 (Scheme 6). Alternatively, the cyclization can be effected in the opposite direction starting from a quaternized nitrogen intermediate as reported[22] by Blank and coworkers. Thus, 2-bromopyridines were quaternized with phenacyl bromide to produce the 2-bromopyridinium salt 20. These salts were converted to pyridine 2-thiones 21 by treatment with aqueous sodium hydrosulfide. The ring closure of pyridine-2-thiones 21 to the



18 19, 31–98 %

18,19 R^1=H, Me, COMe, C_6H_5;
R^2=H, Me, C_6H_5;
R^3=R^4=Cl, NO_2



20 21 22, 10–92 %

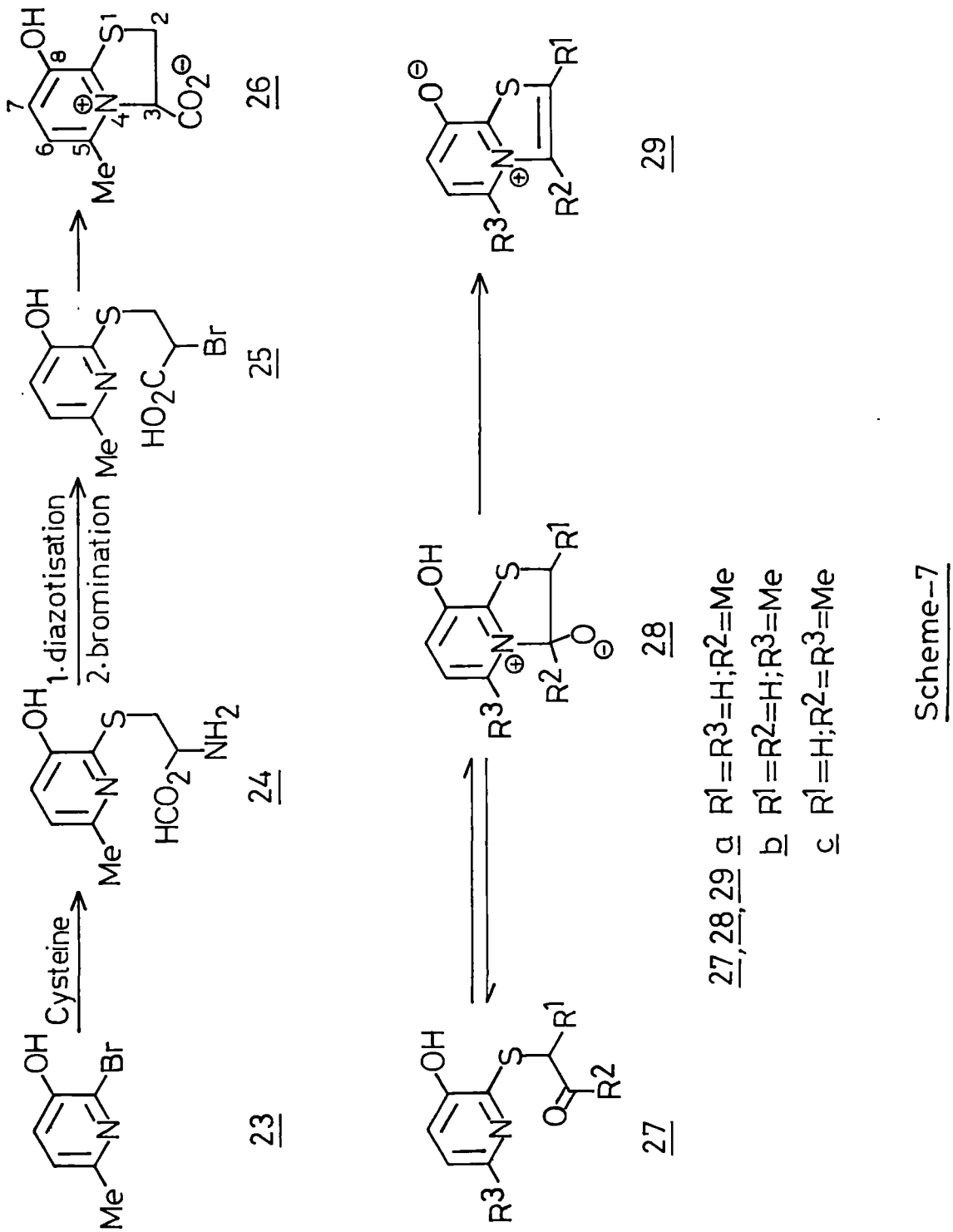
20-22 R=H, Me; R^1= C_6H_5, 4-BrC_6H_4, 3-$NO_2C_6H_4$, 4-$MeSO_2C_6H_4$, 3-$AcNHC_6H_4$

Scheme-6

thiazolopyridinium salts 22 is effected by concentrated sulphuric acid (Scheme 6).

Undheim and coworkers have extensively studied[23] dihydrothiazolo [3,2-a]pyridinium-9-olate systems and the literature on the chemistry of these compounds have been reviewed by the same authors[23]. The initial studies on thiazolo/dihydrothiazolo[3,2-a]pyridinium 8-olates and related systems were initiated by the isolation of strongly blue fluorescent substance from bovine liver hydrolysates. The substance was identified as 5-methyl-8-hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate 26[24]. This compound was synthesized[23] in 65% optical purity through the sequence of reactions shown in Scheme 7. The bromopyridine 23 was reacted with the (R)-cysteine to give the amino acid 24. The bromo compound 25 was prepared from the diazonium salt of the amino acid 24 with inversion of configuration. In basic conditions, the bromo compound 25 was cyclized stereospecifically to the optically active (S)-dihydrothiazolo[3,2-a]pyridinium-3-carboxylate 26.

The general method for the synthesis of thiazolo[3,2-a]pyridinium salts consists of an acid catalyzed cyclization of 2-(2-oxoethylthio) pyridines 27. The substituent effects[25] in the cyclization step is also studied by the same group of workers. The reaction is sensitive to the steric interference from the pyridine 6-substituent. Thus, the methylketone 27a and the corresponding aldehyde 27b cyclized to the pyridinium salt 29a and 29b in the presence of cold sulphuric acid, while the 6-methyl compound 27c required heating for cyclization to give 29c (Scheme 7).


Cysteine
1. diazotisation
2. bromination
23
24
25
26
27
28
29
27 28 29 a R1=R3=H;R2=Me
b R1=R2=H;R3=Me
c R1=H;R2=R3=Me

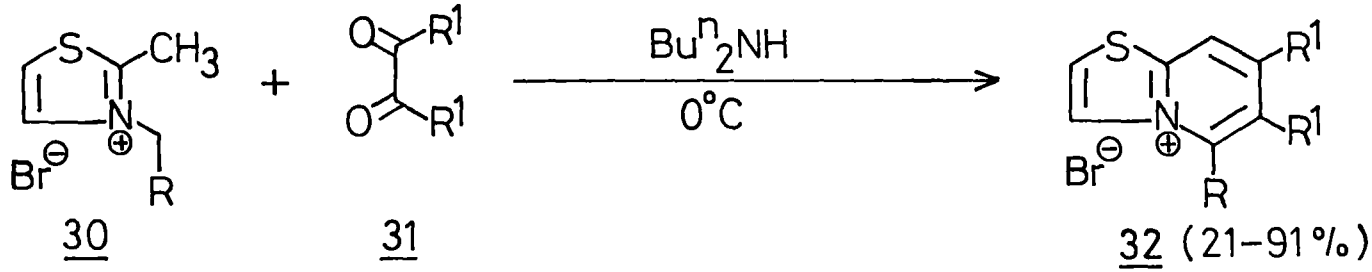
Scheme-7

In the following two examples given in the Scheme 8, the construction of thiazolopyridinium ring systems starts from a thiazole ring rather than pyridine ring. The base catalyzed condensation of N-substituted 2-methyl thiazolinium salt 30 with 1,2-diketones 31 affords the thiazolopyridinium salts 32[26]. Similarly, the thiazolopyridone 35 was prepared by the condensation of 2-cyanomethylthiazole 33 and ethylacetoacetate through the intermediate 34[27].

From the reviewed examples given above, it is evident that the synthesis of thiazolo[3,2-a]pyridinium salts makes use of preformed pyridine or a thiazole nucleus. Both the approaches are known and only a few reports are available making use of the latter approach. Also, both the approaches do not offer much scope for substituent variation in the pyridine ring. The following section describes the successful application of the aromatic annelation approach for the synthesis of these class of compounds.

V.2 RESULTS AND DISCUSSION

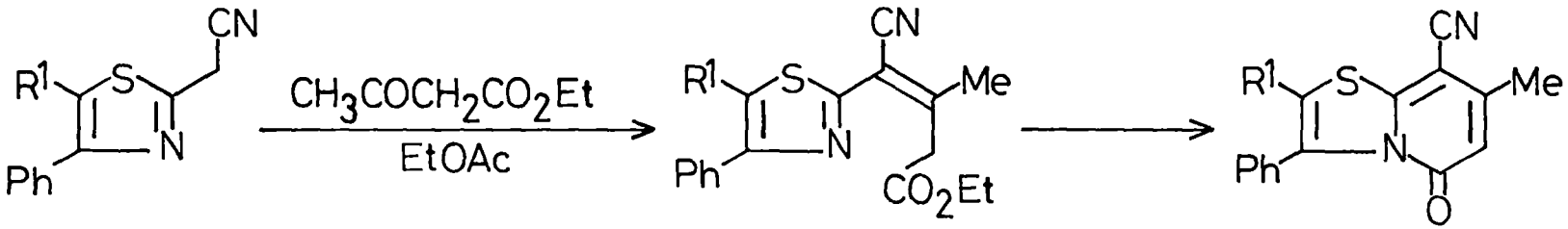
The required 2,4-dimethylthiazole and 2-methyl-4-phenylthiazole were prepared by a modified reported procedure[28] by the reaction of thioacetamide with chloroacetone or phenacyl bromide. The detailed procedure is given in the experimental section. The selected ketene dithioacetals 1a-g, 41a-e and 43a-c were prepared by the general procedure described in Chapter II. The procedure for the preparation of known cinnamoylketene dithioacetal is given in the experimental section of Chapter III. The authenticity of all these ketene dithioacetals is confirmed by comparison of their i.r. and n.m.r. spectral data with those of reported values.



30 31 32 (21–91%)

R=COC_6H_5, CN, $CO_2C_2H_5$

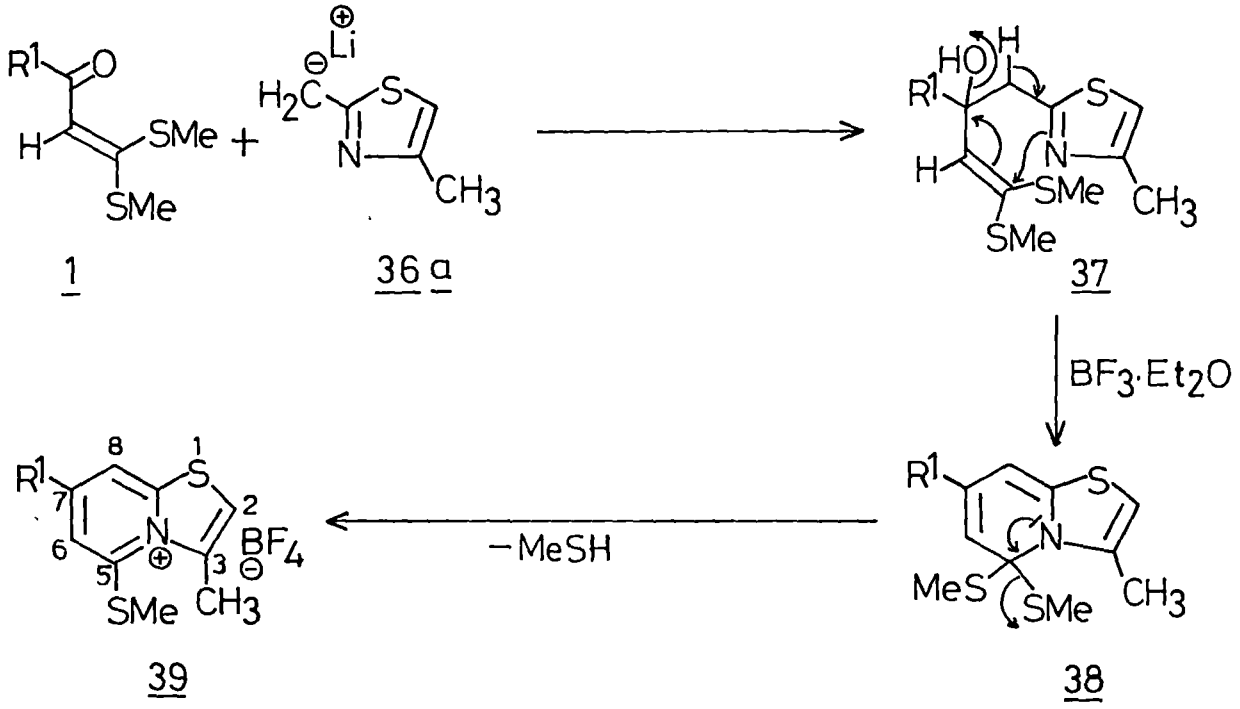
R^1=CH_3, C_6H_5, 2-furyl



33 34 35

Scheme-8

In an optimized reaction condition, the 2-lithiomethyl-4-methyl-thiazole 36a was generated by deprotonation at 2-methyl group by butyllithium in dry THF maintained at -78°C under an efficient atmosphere of nitrogen. The α-oxoketene dithioacetal 1a was added as a THF solution maintaining the same temperature. The usual work up of the reaction (experimental) afforded the alcohol acetal 37a in nearly quantitative yield. However, the alcohol 37a was found to be not stable enough for purification and characterization and was subjected as such to borontrifluoride-ether catalyzed cyclization in refluxing benzene. Work up of the reaction mixture afforded a pale yellow solid, which was characterised as 3-methyl 5-methylthio-7-phenylthiazolo[3,2-a]pyridinium tetrafluoroborate 39a formed in 55% yield. The structure of this compound is assigned on the basis of spectral and analytical data. The product 39a was analyzed for $C_{15}H_{14}NS_2BF_4$ and its mass spectrum displayed characteristic peaks at m/z 272 (34%, M^+-BF_4), 271(100%) and 256(62%), Infrared spectrum of this compound showed a broad band between 1020-1120 cm^{-1} which is characteristic of tetrafluoroborate salt. The ^1H n.m.r.(TFA) spectrum of 39a showed singlets at δ 2.92(3H) and 3.30(3H) due to methyl and methylthio protons respectively. The multiplet between δ 7.56-7.93 was assigned for seven aromatic protons and the singlet at δ 8.31 was assigned for 8-H proton. The other thiazolopyridines 39b-g were obtained by the same sequence by the reaction of 1b-g with 2-lithiomethylthiazole 36a in 61-68% overall yield (Scheme 9). Spectral and analytical data in support of the assigned structure is given in the experimental. The cinnamoylketene dithioacetal 4 was reacted with lithiomethylthiazole



1 36 a 37

38

39

1, 37–39 a $R^1=C_6H_5$ e R^1=2-furyl

b R^1=4-MeC_6H_4 f R^1=2-thienyl

c R^1=4-$MeOC_6H_4$ g R^1=Me

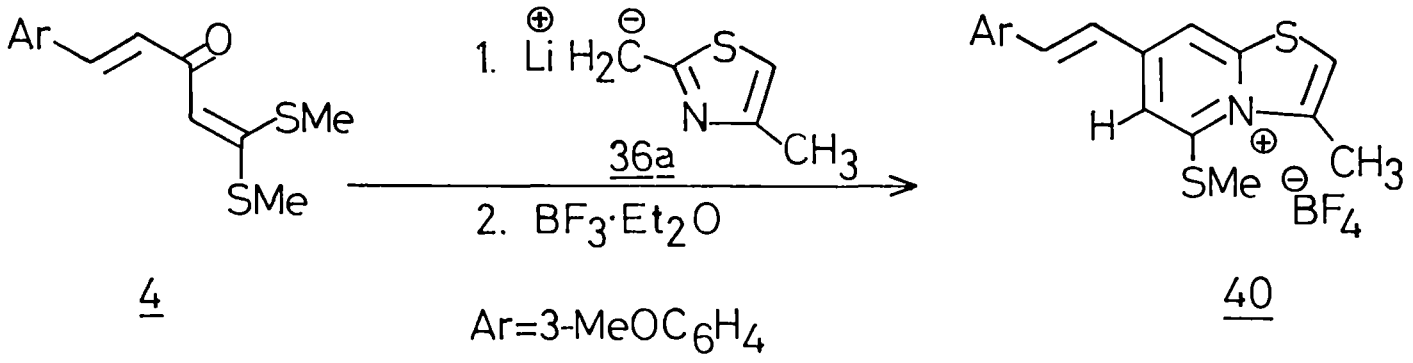
d R^1=2-naphthyl

Scheme–9

36a with a view to generalize the method for the synthesis of thiazolopyridines with 7-styryl substitution. Although alcohol acetal was formed in quantitative yield the cylcization was found to be sluggish leading to lower yield (42%) of 40. Spectral and analytical data is given in the experimental.

The reaction of 2-lithiomethylthiazole 36a with α-oxoketene dithioacetals derived from cyclic ketones were next investigated. Thus, treatment of dithioacetal 41a with lithiomethylthiazole 36a gave the alcohol acetal in good yield. However, subsequent cyclization of alcohol in the presence of $BF_3.Et_2O$ gave the tetrahydroisoquinolinium salt 42a in low yield (33%)(Scheme 10). The characteristic signals due to 2-H and 10-H protons appeared at δ6.56 and 6.81 in its ^1H n.m.r. spectrum. The other spectral and analytical data are given in the experimental. In an analogus reaction condition, the ketene dithioacetals 41b-d prepared from benzocyclic ketones gave the tetracyclic thiazolopyridinium salts 42b-d in 60-64% overall yield (Scheme 11). Interestingly the yields 42b-d were found to be reasonably good compared to that of the product 42a. The structures of 42b-d were fully established by spectral and analytical data (experimental). The ketene dithioacetal 41e derived from benzothiepinone also afforded the thaizolopyridinium salt 42e in 62% yield on reaction with 36a followed by $BF_3.Et_2O$ treatment. Spectral and analytical data of 42e are given in the experimental.

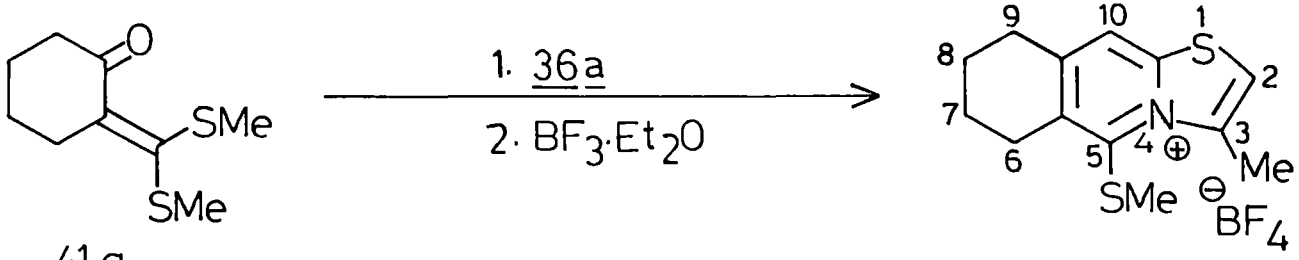
Despite its success as a general method for the synthesis of thiazolopyridinium salts, the method failed to give the products in the case of ketene dithioacetals 43a-c (Scheme 12). The enolacetals 44a-c were indeed formed in quantitative yield, which however failed to undergo



4

Ar=3-MeOC$_6$H$_4$

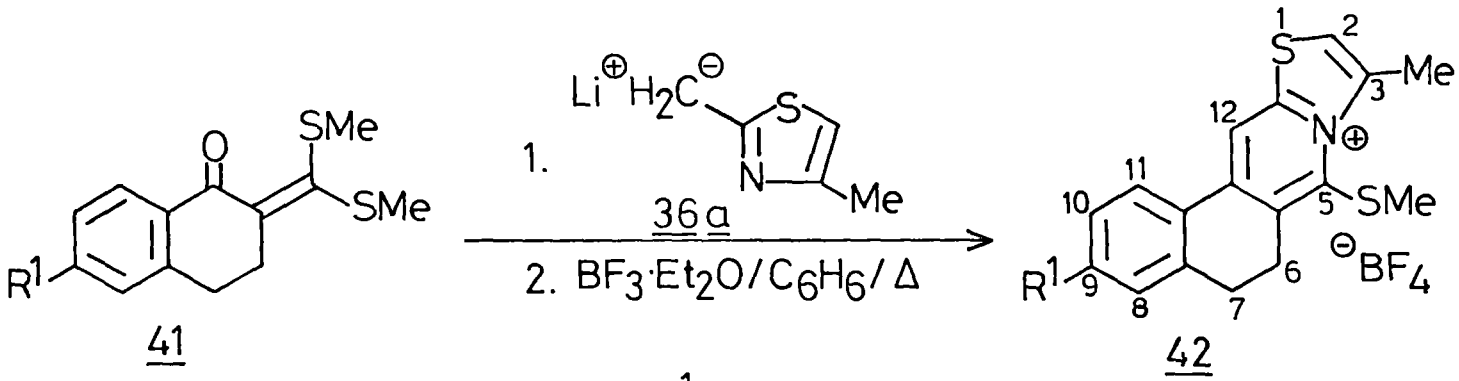
40



41 a

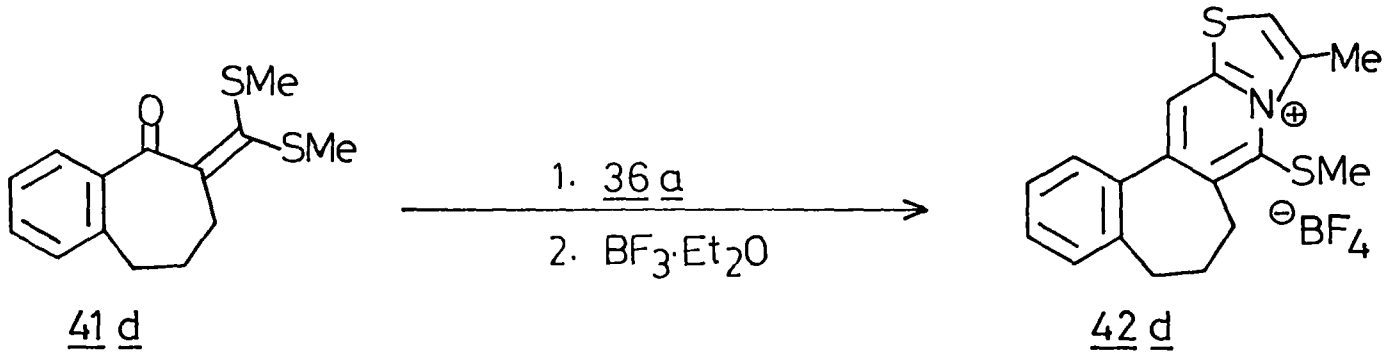
42 a

Scheme-10

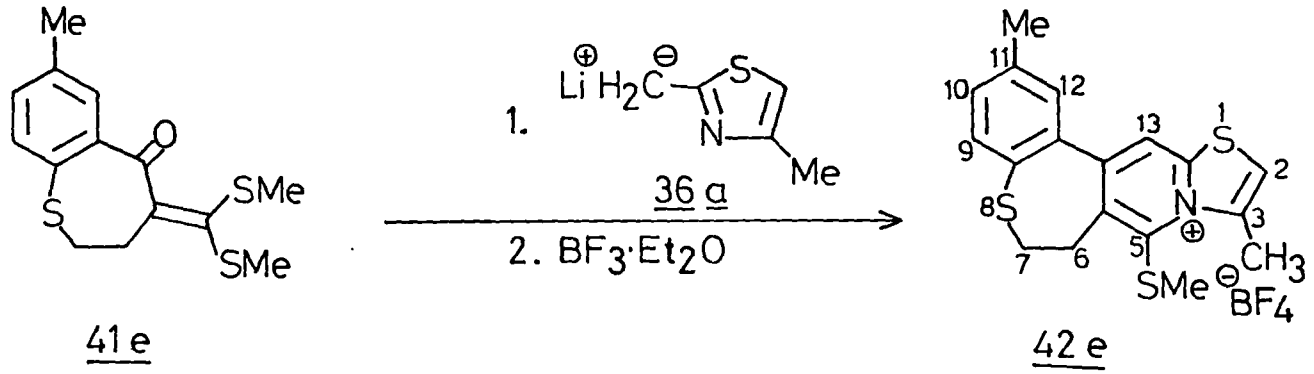


41,42 b R^1=H

c R^1=OMe

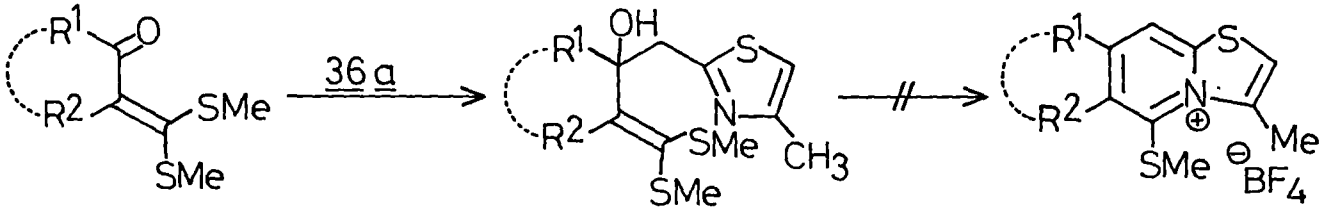


Scheme-11



41 e

42 e



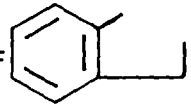
43

44

45

43, 44 a $R^1=R^2=Me$

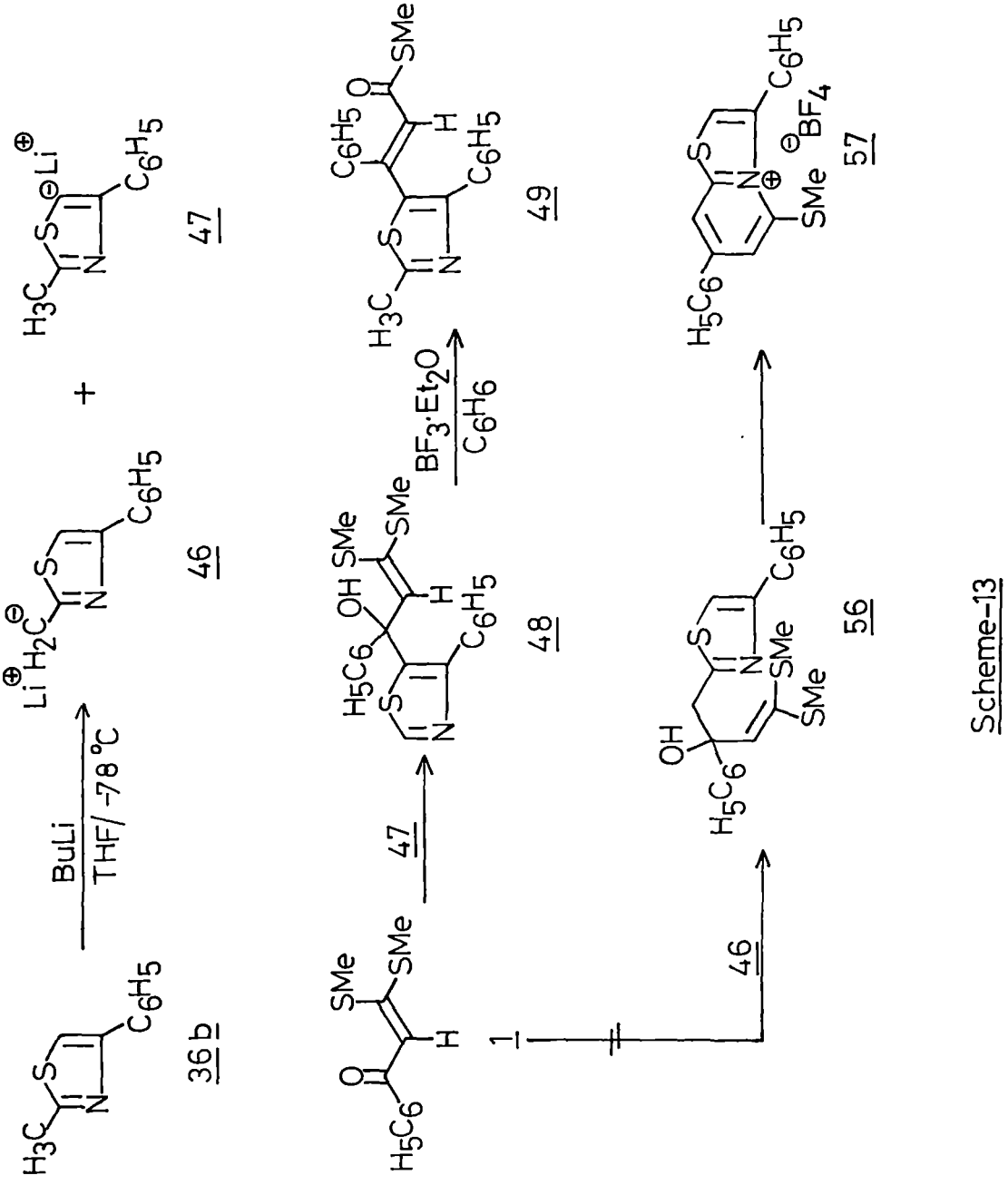
b $R^1=R^2=-(CH_2)_3-$

c $R^1=R^2=$ 

Scheme-12

cyclization to yield the thiazolopyridinium salts 45a-c. It appears that in the case of 44a the mercaptal double bond assumes an unfavourable geometry through rotation of carbon-carbon bond pushing the R^2 substituent towards the thiazole ring.

To check the efficacy and generality of the method, 2-methyl-4-phenylthiazole 36b was metallated and reacted with -oxoketene dithioacetals under the described conditions. Thus, lithiation of thiazole 36b with butyllithium at -78°C followed by reaction with dithioacetal 1 and $BF_3.Et_2O$ treatment afforded an yellow crystalline solid after usual work up and column chromatography. The compound was characterized as the thioester 49 on the basis of spectral and analytical data. Thus, the thioester 49 was analyzed for $C_{20}H_{17}NOS_2$ and exhibited molecular ion peak at m/z 305 (100%) in its mass spectrum. Its i.r. spectrum displayed characteristic band at 1656 cm^{-1} due to the thioester carbonyl group. In its ^1H n.m.r. spectrum ($CDCl_3$) the thiomethyl protons appeared as a singlet at δ 2.21(3H) and the signal due to 2-methyl protons of the thiazole ring was present at δ 2.69(s,3H). The signal due to the olefinic proton appeared at δ 6.70(s,1H) and the aromatic protons appeared as two multiplets between δ 7.12-7.46(8H) and 7.60 -7.74 (2H) confirming the structural assignment. Evidently the compound 49 is formed by the hydrolysis of the alcohol acetal 48 formed by the reaction of lithiated thiazole 47 with dithioacetal 1 (Scheme 13). The thiazolopyridinium salt 51 which can be formed by the reaction 2-lithiomethyl species 46 could not be isolated and considerable amount of thiazole 36b was isolated from the reaction mixture.

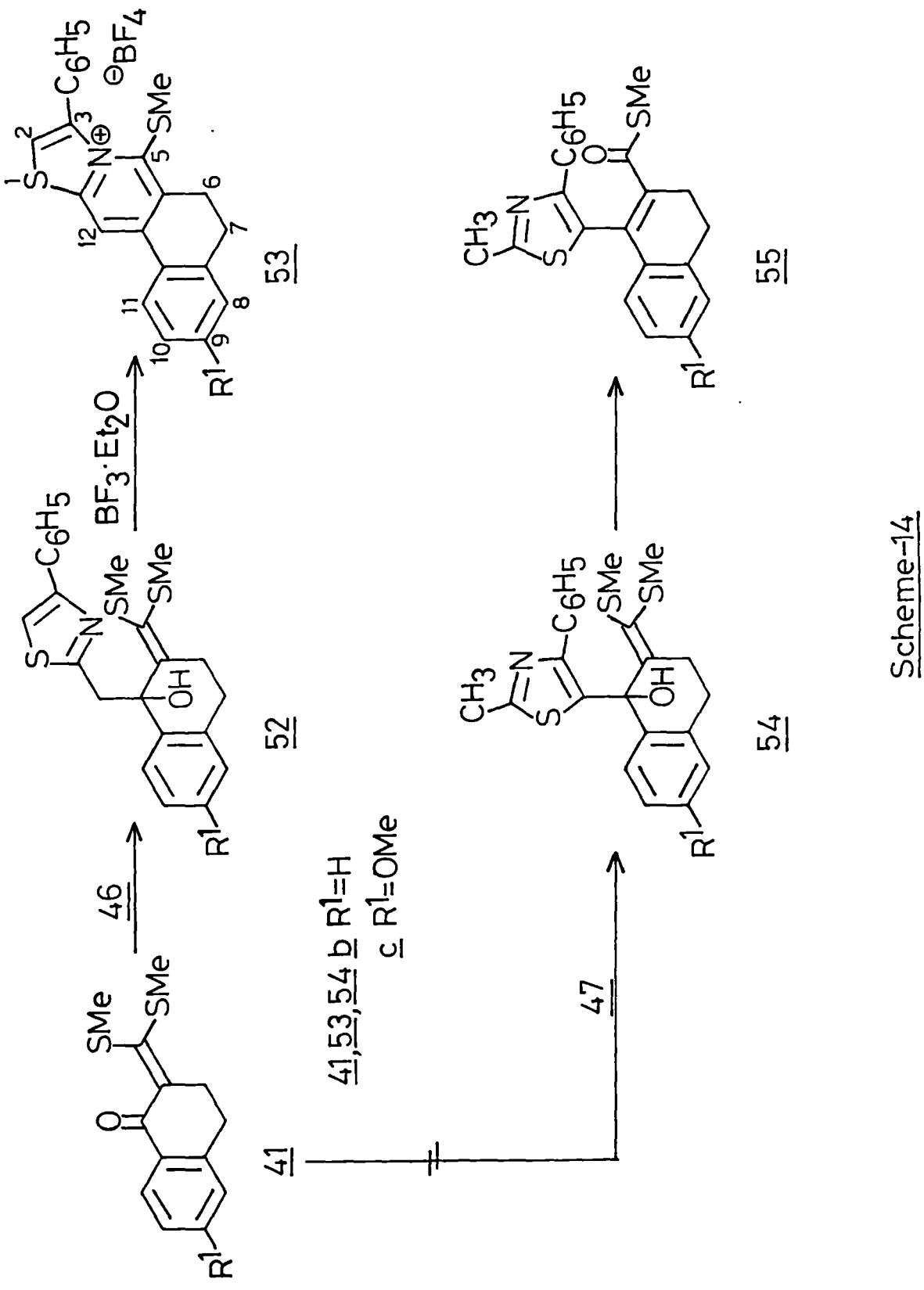


Scheme-13

The literature search at this stage revealed that the observed change in the behaviour of 2-methylthiazole by replacing the 4-methyl group with a phenyl group as in thiazole 36b is not unusual and Meyers and Knaus have made similar observations[29-31] in the lithiation of 2-methyl-4-phenylthiazole 36b. They observed that the lithiation of thiazole 36b takes place both at the 2-methyl and 5-position at low temperature. The lithio derivative 46 and 47 do not exchange hydrogen or metal and the products arising from 46 and 47 are the result of independent metallation of 2-methyl and 5-position in a kinetically controlled process. Although it is reported that both the specious 46 and 47) react independently only the product arising from the 5-lithiated thiazole 47 could be isolated on reaction with dithioacetal 1. Surprisingly, in an analogus reaction condition the dithioacetal 41b derived from tetralone gave the 3-phenyl thiazolopyridinium salt 53 in 43% yield (calculated on the basis of recovered thiazole 36b). The thioester 55 which can be formed by the reaction of 5-lithiated thiazole 47 could not be isolated from the reaction mixture (Scheme 14). The dithioacetal 41c also gave the thiazolopyridinium salt 53c through the alcohol 52c. The spectral and analytical data in favour of the thiazolopyridinium salts 53b and 53c are given in the experimental section. The reason for the difference in the reactivity of the acyclic and cyclic dithioacetals towards lithiated thiazoles 46 and 47 is difficult to explain and further work is in progress to understand this anomalous observation.

V.3 SUMMARY

A new general heteroaromatic annelation strategy has been developed



Scheme-14

for the synthesis of substituted and fused thiazolo[3,2-a]pyridinium salts. Annelation of a pyridine ring onto a thiazole ring is achieved by the generation and reaction of an azaallyl anion equivalent with α-oxoketene dithioacetals. The Lewis acid induced cyclization of the alcohol acetal can be considered as a special case of aromatic annelation in which the electrophilic attack occurs on an aromatic heterocyclic nitrogen atom rather than a carbon atom. Most of the reported methods make use of a preconstructed pyridine ring and have obvious limitation in introducing substitutions in the pyridine ring. A number of hitherto inaccessible thiazolo[3,2-a]pyridine fused polycyclic ring systems are synthesized by the present method. Despite its moderate yields in a few cases the method developed can be of choice for the construction of these ring systems.

V.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a Perkin-Elmer 297 spectrophotometer. N.m.r. spectra refer to those run on a Varian EM-390 (90 MHz) spectrometer using TMS as internal standard. Chemical shifts are expressed as δ ppm downfield from TMS. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. Elemental analysis were carried out on a Heraus CHN-O-RAPID instrument.

Starting Materials

Chloroacetone (90%, stabilized by 0.5% $CaCO_3$) was purchased (Aldrich) and was used without further purification. Phenacyl bromide was prepared according to the standard procedure. Thioacetamide was purchased (Loba Chemicals) and was used without purification. All

α -oxoketene dithioacetals were prepared by the earlier reported procedure and the structural assignment was confirmed by comparing the spectral data with the reported values.

2,4-Dimethylthiazole:

To a stirred suspension of thioacetamide (37.5g, 0.5 mol) in benzene (100 ml) was added chloroacetone (51g, 0.5 mol) in benzene (50 ml) over a period of 45 minutes. The reaction mixture was initally warmed to initiate the exothermic reaction. The mixture was further refluxed for 30 minutes, cooled and the upper benzene layer was removed by decantation. To the thiazolonium hydrochloride remained as solid mass was added cold 20% NaOH solution until the solution is alkaline. The upper thiazole layer was separated and the aqueous layer is extracted with ether (3x75 ml). The combined extracts were washed once with water (100 ml), dried (Na_2SO_4) and distilled. B.P. 143-145°C, yield 39.5g (70%).

2-Methyl-4-phenylthiazole (36b) was prepared by the above method using phenacyl bromide and thioacetamide, and was obtained as colourless crystals, yield 68%, m.p. 67°C.

Generation and reaction of 2-lithiomethylthiazoles with oxoketene dithioacetals; General Procedure:

To a stirred solution of freshly distilled 2,4-dimethylthiazole (1.70g, 0.15 mol) in dry THF (25 ml), butyllithium (0.015 mol) was added under an efficient atmosphere of nitrogen, maintaining the temperature at -78°C. The lithiation was indicated by the appearance of reddish brown colour. The solution is stirred for 15 min. at -78°C. The oxoketene dithioacetal (0.01 mol) was added as a THF (15-25 ml depending

on solubility) solution in one portion and further stirred for 1 hr., slowly warming the mixture to room temperature. The reaction mixture was poured into saturated ammonium chloride solution and the layers were separated. The aqueous layer was extracted with ether (2x50 ml) and the combined organic layer was washed with water (100 ml), dried (Na_2SO_4) and evaporated to give the crude alcohol in nearly quantitative yield.

General procedure for the cycloaromatization of hydroxy dithioacetals; Synthesis of thiazolo[3,2-a]pyridinium tetrafluoroborates 39a-g, 40, 42a-e, 53b, c:

To a solution of crude hydroxy dithioacetal (Ca.0.01 mol) in dry benzene (50 ml), borontrifluoride etherate (8 ml) was added and the reaction mixture was refluxed with stirring for 1.5 hr. The reaction mixture was cooled and the benzene layer was removed by decantation. The remaining residue was dissolved in minimum amount of ethylacetate and neutralized with saturated sodium bicarbonate solution. The solid separated was collected by filteration, washed with water (3x50 ml) and diethylether (2x20 ml). Analytically pure products were obtained by recrystallization from ethylacetate.

3-Methyl-5-methylthio-7-phenylthiazolo[3,2-a]pyridinium tetrafluoroborate (39a) was isolated as yellow solid (ethylacetate), yield 55%; m.p. 247-248°C; ν_{max} 1601, 1500, 1420, 1020-1119 (br) cm^{-1}; δ_H 2.91(3H,s, CH_3), 3.30(3H,s,SCH_3), 7.56-7.93(7H,m,arom), 8.31(1H,s,H-8). (Found: C,49.99; H,3.81; N,4.02. $C_{15}H_{14}NS_2BF_4$ requires: C,50.15; H,3.93; N,3.90%); m/z 272(34%,M^+-BF_4), 271(100), 256(62).

3-Methyl-5-methylthio-7-(4-methylphenyl)thiazolo[3,2-a]pyridinium tetrafluoroborate (39b) was isolated as yellow solid (ethylacetate), yield 58%; m.p.281-182°C; ν_{max} 1599, 1497, 1423, 1027-1115 (br) cm^{-1}; δ_H 2.48(3H,s,CH_3), 2.90(3H,s,CH_3), 3.30(3H,s,SCH_3), 7.33-7.82(6H,m, arom), 8.24(1H,s,H-8). (Found: C,51.61; H,4.40; N,3.88. $C_{16}H_{16}NS_2BF_4$ requires: C,51.49; H,4.32; N,3.75%); m/z 286(75%,M^+-BF_4), 285(74), 270(100).

3-Methyl-5-methylthio-7-(4-methoxyphenyl)thiazolo[3,2-a]pyridinium tetrafluoroborate (39c) was isolated as yellow solid (ethylacetate), yield 68%; m.p. 284-185°C; ν_{max} 1604, 1505, 1433, 1021-1122(br) cm^{-1}; δ_H 2.90(3H,s,CH_3), 3.29(3H,s,SCH_3), 4.00(3H,s,OCH_3), 7.27(2H,d,J=8.5Hz, arom), 7.61(1H,s,arom), 7.74(1H,s,arom), 7.89(2H,d,J=8.5Hz,arom), 8.30 (1H,s,H-8). (Found: C,49.21; H,4.03; N,3.71. $C_{16}H_{16}NOS_2BF_4$ requires: C,49.37; H,4.14; N,3.60%); m/z 302(33%,M^+-BF_4),301(55), 287(100).

3-Methyl-5-methylthio-7-(2-naphthyl)thiazolo[3,2-a]pyridinium tetrafluoroborate (39d) was isolated as yellow solid (ethylacetate), yield 60%; m.p. 312-13°C; ν_{max} 1601, 1491, 1434, 1030-1119(br) cm^{-1}; δ_H 2.88 (3H,s,CH_3), 3.20(3H,s,SCH_3), 7.44-7.68(5H,m,arom), 7.77-8.04(4H,m,arom), 8.22(1H,s,H-8). (Found: C,55.58; H,4.02; N,3.60. $C_{19}H_{16}NS_2BF_4$ requires: C,55.76; H,3.94; N,3.42%); m/z 322(24%,M^+-BF_4), 321(48), 306(84).

3-Methyl-5-methylthio-7-(2-furyl)thiazolo[3,2-a]pyridinium tetrafluoroborate (39e) was isolated as yellow solid (ethylacetate), yield 53%; m.p. 249-250°C; ν_{max} 1609, 1501, 1477, 1421, 1009-1122(br) cm^{-1}; δ_H 2.91 (3H,s,CH_3), 3.26(3H,s,SCH_3), 6.75(1H,brs,H-3' furyl), 7.41(1H,distorted t, H-4' furyl), 7.54(1H,s,arom), 7.70(1H,s,arom), 7.77(1H,d,H-5' furyl),

8.26(1H,s,H-8). (Found: C,44.80; H,3.53; N,4.22. $C_{13}H_{12}NOS_2BF_4$ requires: C,44.71; H,3.47; N,4.01%); m/z 262(42%,M^+-BF_4), 261(96), 246(100).

3-Methyl-5-methylthio-7-(2-thienyl)thiazolo[3,2-a]pyridinium tetrafluoroborate (39f) was isolated as yellow solid (ethylacetate), yield 57%); m.p. 273-74°C; ν_{max} 1600, 1493, 1433, 1416, 1026-1120(br) cm^{-1}; δ_H 2.90(3H,s,CH_3), 3.23(3H,s,SCH_3), 7.29(1H,t,J=4.5Hz,H-4' thienyl), 7.53(1H,s,arom), 7.67(1H,brs,arom), 7.76(1H,d,J=4.5Hz,H-3' thienyl), 7.88(1H,d,J=4.0Hz,H-5' thienyl), 8.22(1H,s,H-8). (Found: C,42.66; H,3.32; N,4.01. $C_{13}H_{12}NS_3BF_4$ requires: C,42.75; H,3.31; N,3.84%); m/z 278(37%,M^+-BF_4), 277(100), 262(97).

3-Methyl-5-methylthio-7-methylthiazolo[3,2-a]pyridinium tetrafluoroborate (39g) was isolated as colourless solid (ethylacetate), yield 51%; m.p. 154-155°C; ν_{max} 1609, 1515, 1457, 1440, 1422, 1025-1120(br) cm^{-1}; δ_H 2.65(3H,s,CH_3), 2.83(3H,s,CH_3), 3.23(3H,s,SCH_3), 7.44(1H,s,H-2), 7.59(1H,s,H-6), 7.97(1H,s,H-8). (Found: C,40.58; H,4.01; N,4.88. $C_{10}H_{12}NS_2BF_4$ requires: C,40.42; H,4.07; N,4.71%); m/z 210(44%,M^+-BF_4), 194(28).

3-Methyl-5-methylthio-7-(3-methoxystyryl)thiazolo[3,2-a]pyridinium tetrafluoroborate (40) was isolated as yellow solid (ethylacetate), yield 42%; m.p. 293-294°C; ν_{max} 1604, 1530, 1461, 1430, 1030-1125(br) cm^{-1}; δ_H 2.88(3H,s,CH_3), 3.20(3H,s,SCH_3), 3.98(3H,s,OCH_3), 6.97-7.71 (8H,m,arom and olefinic), 8.13(1H,brs,H-8). (Found: C,51.96; H,4.30; N,3.48. $C_{18}H_{18}NOS_2BF_4$ requires: C,52.06; H,4.37; N,3.37%); m/z 328 (2%,M^+-BF_4), 313(79), 312(44).

3-Methyl-5-methylthio-6,7,8,9-tetrahydrothiazolo[3,2-a]isoquinolinium tetrafluoroborate (42a) was isolated by silica gel column chromatography (ethylacetate:hexane 1:20 as eluent) as yellow solid, yield 33%; m.p. 56-58°C; ν_{max} 1596, 1573, 1516, 1415, 1011-1123(br) cm^{-1}; δ_H 1.60-1.90 (4H,m,CH_2), 2.40(3H,s,CH_3), 2.56-2.90(4H,m,CH_2), 3.20(3H,s,SCH_3), 6.56(1H,s,H-2), 6.81(1H,s,H-10). (Found: C,62.78; H,6.69; N,5.72. $C_{13}H_{16}NS_2$ requires: C,62.36; H,6.44; N,5.59%).

3-Methyl-5-methylthio-6,7-dihydrothiazolo[3,2-a]phenanthroquinolinium tetrafluoroborate (42b) was isolated as yellow solid (ethylacetate), yield 62%; m.p. 193-194°C; ν_{max} 1600, 1581, 1505, 1431, 1412, 1028-1125 (br) cm^{-1}; δ_H 2.57(3H,s,CH_3), 3.11(2H,t,J=7.0Hz,CH_2), 3.30(3H,s,SCH_3), 3.64(2H,t,J=7.0Hz,CH_2), 7.41-7.64(3H,m,arom), 7.77(1H,s,arom), 7.98 (1H,d,J=8.5Hz,arom), 8.69(1H,s,H-12). (Found: C,53.21; H,4.13; N,3.70. $C_{17}H_{16}NS_2BF_4$ requires: C,53.00; H,4.19; N,3.64%); m/z 283 [98%,M^+-(BF_4 and CH_3)], 250(44).

3-Methyl-5-methylthio-9-methoxy-6,7-dihydrothiazolo[3,2-a]phenanthroquinolinium tetrafluoroborate (42c) was isolated as yellow solid (ethylacetate), yield 64%; m.p. 278-279°C; ν_{max} 1590, 1577, 1511, 1430, 1412, 1020-1121(br) cm^{-1}; δ_H 2.56(3H,s,CH_3), 3.10(2H,t,J=7.0Hz,CH_2), 3.29(3H,s,SCH_3), 3.60(2H,t,J=7.0Hz,CH_2), 4.03(3H,s,OCH_3), 6.99-7.23 (2H,m,arom), 7.70(1H,s,arom), 7.97(1H,d,J=8.5Hz,arom), 8.57(1H,s,H-12). (Found: C,51.91; H,4.13; N,3.44. $C_{18}H_{18}NOS_2BF_4$ requires: C,52.06; H,4.37; N,3.37%); m/z 328(6%,M^+-BF_4), 313(100).

3-Methyl-5-methylthio-7,8-dihydro-6H-benzocyclohepta[2,1-d]thiazolo [3,2-a]pyridinium tetrafluoroborate (42d) was isolated as colourless

crystals (ethylacetate:hexane), yield 60%; m.p. 156-157°C; ν_{max} 1602, 1588, 1500, 1440, 1412, 1028-1116(br) cm^{-1}; δ_H 2.26-2.78(4H,m,CH_2), 2.57(3H,s,CH_3 merged with CH_2), 2.77-3.36(2H,m,CH_2), 3.29(3H,s,SCH_3, merged with CH_2), 7.25-7.62(4H,m,arom), 7.63(1H,s,arom), 8.13(1H,s, H-13). (Found: C,54.30; H,4.52; N,3.56. $C_{18}H_{18}NS_2BF_4$ requires: C,54.15; H,4.54; N,3.51%); m/z 312(2%,M^+-BF_4), 311(3), 297(12).

3-Methyl-11-methyl-5-methylthio-6,7-dihydrobenzothiepino[2,1-d] thiazolo[3,2-a]pyridinium tetrafluoroborate (42e) was isolated as yellow solid (ethylacetate), yield 62%; m.p. 239-240°C; ν_{max} 1598, 1576, 1433, 1411, 1389, 1030-1109(Br) cm^{-1}; δ_H 2.47(3H,s,CH_3), 2.57(3H,s, CH_3), 3.34(3H,s,SCH_3), 2.74-3.40(2H,m,CH_2 merged with SCH_3), 3.59-4.23(2H,m,CH_2), 7.50(2H,brs,arom), 7.59(1H,s,arom), 7.88(1H,brs,arom), 8.29(1H,s,H-13). (Found: C,50.11; H,4.30; N,3.38. $C_{18}H_{18}NS_3BF_4$ requires: C,50.12; H,4.21; N,3.25%); m/z 329[2%,M^+-(BF_4 and CH_3)], 314(22), 313 (100), 298(85).

3-[5-(2-methyl-4-phenyl)thiazolo]-S-methylthiocinnamate (49) was isolated as yellow crystals (CH_2Cl_2;hexane), yield 32%; m.p. 115-116°C; ν_{max} 1655, 1589 cm^{-1}; δ_H 2.20(3H,s,CH_3), 2.76(3H,s,SCH_3), 6.69(1H, s,vinylic), 7.11-7.46(8H,m,ArH), 7.60-7.74(2H,m,ArH). (Found: C,68.19; H,4.76; N,4.09. $C_{20}H_{17}NOS_2$ requires: C,68.34; H,4.88; N,3.99%); m/z 351(9%,M^+).

5-Methylthio-3-phenyl-6,7-dihydrothiazolo[3,2-a]phenanthroquinolinium tetrafluoroborate(53b) was isolated as yellow solid (ethylacetate), yield 43%; m.p. 254-255°C; ν_{max} 1589, 1510, 1410, 1027-1110(br) cm^{-1}; δ_H 2.15(3H,s,SCH_3), 3.06(2H,distorted t, CH_2), 3.46(2H,distorted t, CH_2), 7.34-7.71(7H,m,ArH), 7.82(1H,s,H-2), 7.90-8.09(2H,m,ArH),

8.70(1H,s,H-12). (Found: C,59.21; H,4.15; N,3.26. $C_{22}H_{18}NS_2BF_4$ requires: C,59.07; H,4.06; N,3.13%).

9-Methoxy-5-methylthio-3-phenyl-6,7-dihydrothiazolo[3,2-a]phenanthroquinolinium tetrafluoroborate (53c) was isolated as yellow solid (ethylacetate), yield 41%; m.p. 226-228°C; ν_{max} 1587, 1509, 1411, 1020-1101(br) cm^{-1}; δ_H 2.13(3H,s,SCH_3), 3.03(2H,distorted t, CH_2), 3.43(2H,distorted t, CH_2), 6.88-7.13(2H,m,ArH), 7.33-7.64(5H,m,ArH), 7.74(1H,s,H-2), 7.94(1H,d,J=8.5Hz,ArH), 8.54(1H,s,H-12). (Found: C,58.02; H,4.38. N, 3.20. $C_{23}H_{20}NOS_2BF_4$ requires: C,57.87; H,4.22; N,2.93%).

REFERENCES

1. For a review, see R.K. Dieter, Tetrahedron, 42, 3029 (1986).
2. P. Bamfield, P.E. Gordon, Chem. Soc. Rev., 13, 441 (1984).
3. T.H. Chan, P. Brownbridge, J. Chem. Soc. Chem. Comm., 578 (1979).
4. T.H. Chan, P. Brownbridge, J. Amer. Chem. Soc., 102, 3534 (1980).
5. M.A. Tius, Tetrahedron Lett., 22, 3335 (1981).
6. M.A. Tius, S. Ali, J. Org. Chem., 47, 3163 (1982).
7. M.A. Tius, A. Thurkauf, J.W. Truesdell, Tetrahedron Lett., 23, 2819 (1982).
8. M.A. Tius, A. Thurkauf, J.W. Truesdell, Tetrahedron Lett., 23, 2823 (1982).
9. M.A. Tius, A. Savariar, Synthesis, 467 (1983).
10. M.A. Tius, A. Thurkauf, J. Org. Chem., 48, 3839 (1983).
11. S. Danishefsky, C-F. Yan, R.K. Singh, R.B. Gammill, P.M. McCurry, Jr, N. Fritsch, J. Clardy, J. Amer. Chem. Soc., 101, 7001 (1979).
12. S. Danishefsky, T. Harayama, R.K. Singh, J. Amer. Chem, Soc., 101, 7008 (1979).
13. D.L. Boger, M.D. Mullican, J. Org. Chem., 45, 5002 (1980) and references therein.
14. G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett.,25, 5095 (1984).
15. C.V. Asokan, H. Ila, H. Junjappa, Synthesis, 284 (1987).
16. M.P. Balu, G. Singh, H. Ila, H. Junjappa, Tetrahedron Lett.,27, 117 (1986).
17. A.K. Gupta, H. Ila, H. Junjappa, Tetrahedron Lett., 28, 1459 (1987).
18. M.P. Balu, D. Pooranchand, H. Ila, H. Junjappa, Tetrahedron Lett., 29, 501 (1988).
19. M.P. Balu, H. Ila, H. Junjappa, Tetrahedron Lett., 28, 3023 (1987).
20. C.K. Bradsher, D.F. Lohr, Chem. Ind. (London), 1801 (1964).
21. C.K. Bradsher, D.F. Lohr, J. Heterocyclic Chem., 3, 27 (1966).

22. B. Blank, N.W. DiTullio, A.J. Krog, H.L. Saunders, J. Med. Chem., 21, 489 (1978).

23. For a review, see K. Undheim, Heterocyclics, 15, 1349 (1981).

24. P. Laland, J.O. Alvsaker, F. Haugli, J.Dedichen, S. Laland, N. Thorsdalen, Nature, 210, 917 (1966).

25. K. Undheim, K.R. Reistad, Acta. Chem. Scand. 24, 2956 (1970).

26. O. Westphal, A. Joos, Angew. Chem. Int. Ed. Engl. 8, 74 (1969).

27. H. Schaefer,K. Gewald, J. Prakt. Chem., 316, 684 (1974).

28. A.I. Vogel in 'A Text book of Practical Organic Chemistry' ELBS and Longman, Fourth Edition, P. 928 (1978).

29. A.I. Meyers, G.N. Knaus, J. Amer. Chem. Soc., 95, 3408 (1973).

30. G. Knaus, A.I. Meyers, J. Org. Chem.,39, 1189 (1974).

31. G. Knaus, A.I. Meyers, J. Org. Chem., 39, 1192 (1974).