

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

ABSTRACT

By

BALU M. P.

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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

To



NORTH-EASTERN HILL UNIVERSITY

SHILLONG - 793001

INDIA

1989



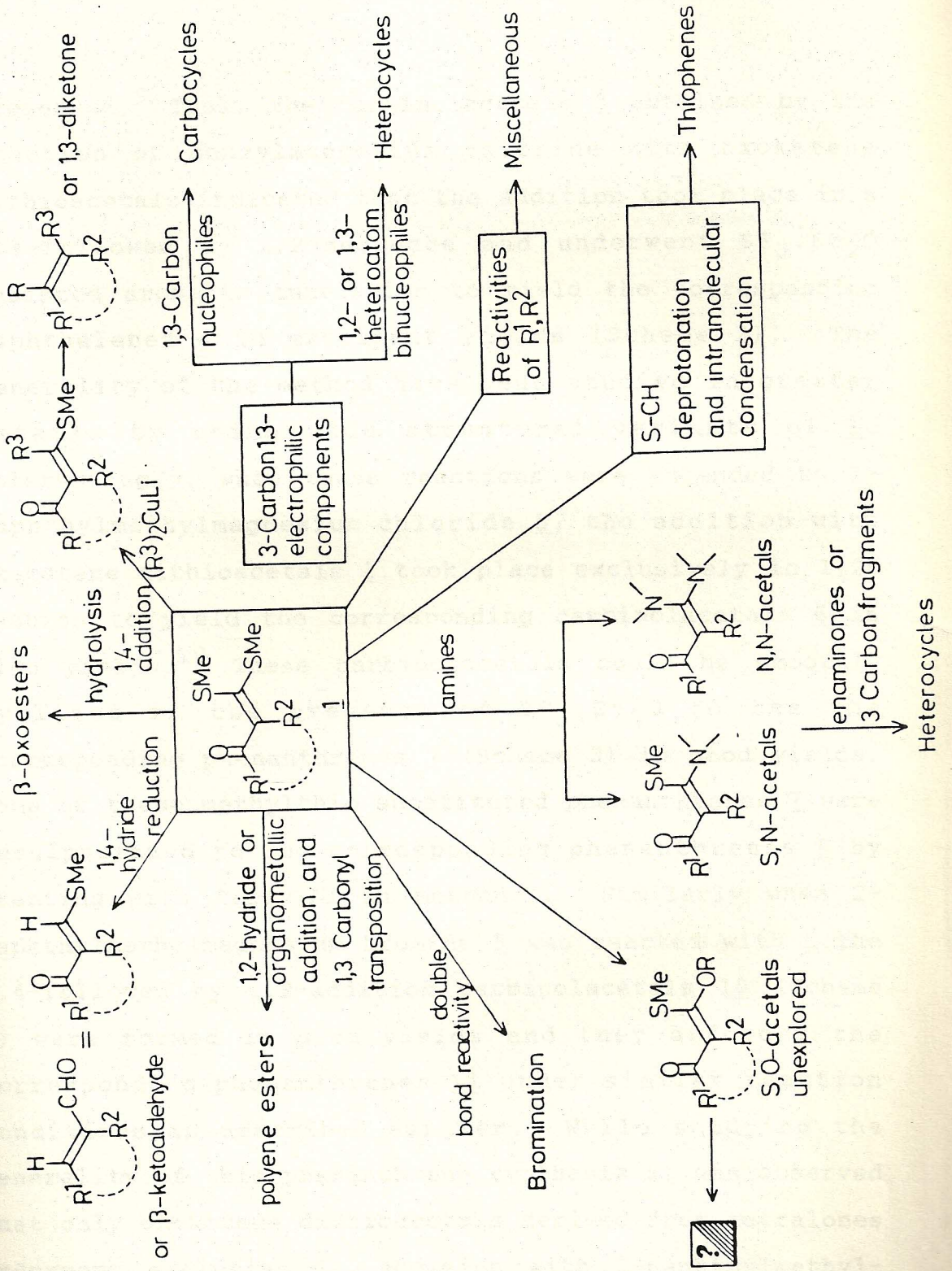
The α -oxoketene dithioacetals of the general formula 1 are among the simplest synthetic intermediates, which can be prepared by reacting any active methylene compound with two equivalents of base and carbon disulfide followed by alkylation. The first synthesis of α -oxoketene dithioacetals was reported by Kelber in 1910.¹ After the initial synthesis, for more than half a century the synthetic potential of these class of compounds remained unexplored. Later Thuillier and co-workers prepared these compounds in high yields in one pot reaction directly from ketones using sodium t-amylate as base and two equivalents of alkyl halide.² Subsequently these reaction conditions have been greatly improved using different bases and reaction conditions.^{3,4} A large number of oxoketene dithioacetals have now been reported and their chemistry has been reviewed.⁵

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

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

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

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



Scheme-1

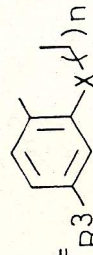
presented.⁹ Thus, the carbinolacetals 3 obtained by the reaction of benzylmagnesium chloride with oxoketene dithioacetals indicated that the addition took place in a 1,4-followed by 1,2-sequence and underwent $\text{BF}_3 \cdot \text{Et}_2\text{O}$ assisted aromatic annelation to yield the corresponding naphthalenes 4 in excellent yields (Scheme 2). The generality of the method have been studied in greater details by using wide structural variants of 1. Interestingly, when these reactions were extended to 1-naphthylmethylmagnesium chloride 5, the addition with oxoketene dithioacetals 1 took place exclusively in 1,2-fashion to yield the corresponding carbinolacetals 6 in high yields.¹⁰ These carbinolacetals could be smoothly cyclized in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to the the corresponding phenanthrenes 7 (Scheme 3) in good yields. Some of these methylthio substituted phenanthrenes 7 were desulphurized to the corresponding phenanthrenes 8 by treating with Raney-Ni in methanol. Similarly when 2-naphthylmethylmagnesium bromide 9 was reacted with 1, the 1,4-followed by 1,2-addition carbinolacetals 10 (Scheme 4) were formed in good yields and they afforded the corresponding phenanthrenes 11 under similar reaction conditions as described earlier. While studying the generality of this phenanthrene synthesis it was observed that only oxoketene dithioacetals derived from tetralones underwent exclusive 1,2-addition with 2-naphthylmethylmagnesium bromide. It appears that both steric and electronic factors play an important role in the



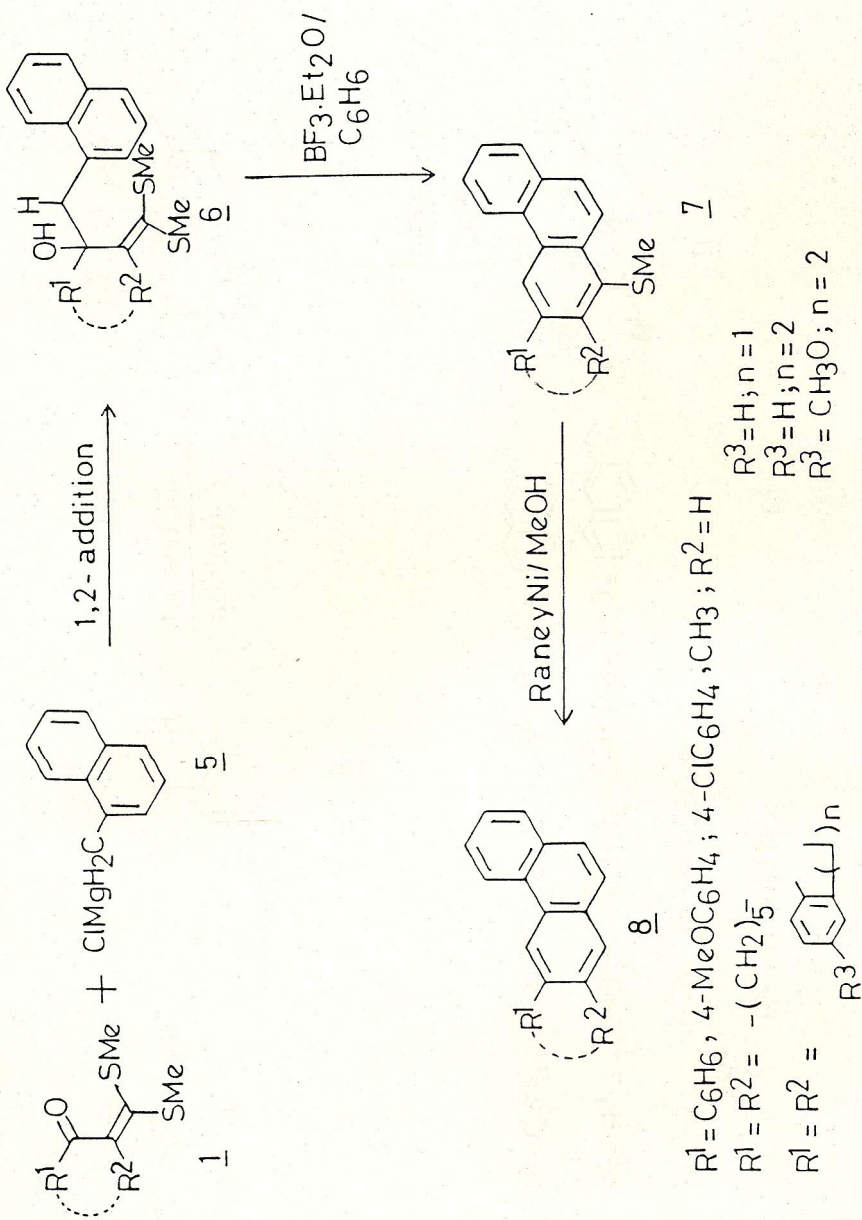
$R^1 = C_6H_5$, 4-MeOC $_6H_4$, 4-MeC $_6H_4$, 2-naphthyl; $R^2 = H$; 58-65 %

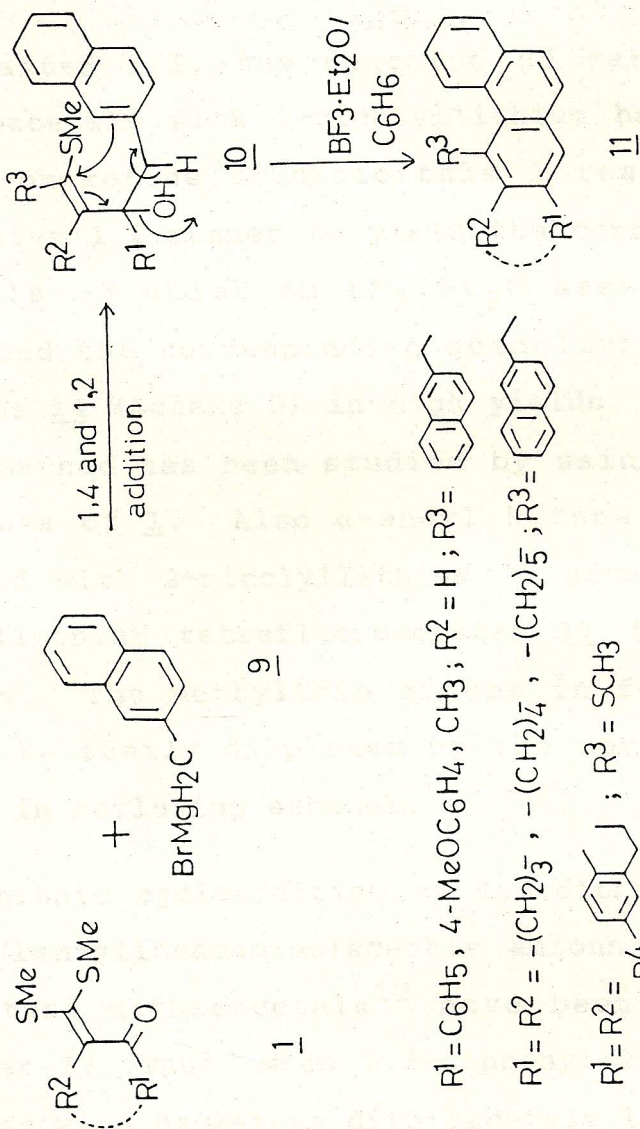
$R^1 = R^2 = -(CH_2)_n$; 81 %

$R^1 = R^2 =$  n $n=1$; 62 %
 $n=2$; 71 %

$R^1 = R^2 =$  n $R^3 = H; X = S; n=1$; 58 %
 $R^3 = Me; X = S; n=2$; 68 %
 $R^3 = H; X = O; n=2$; 67 %

Scheme-2



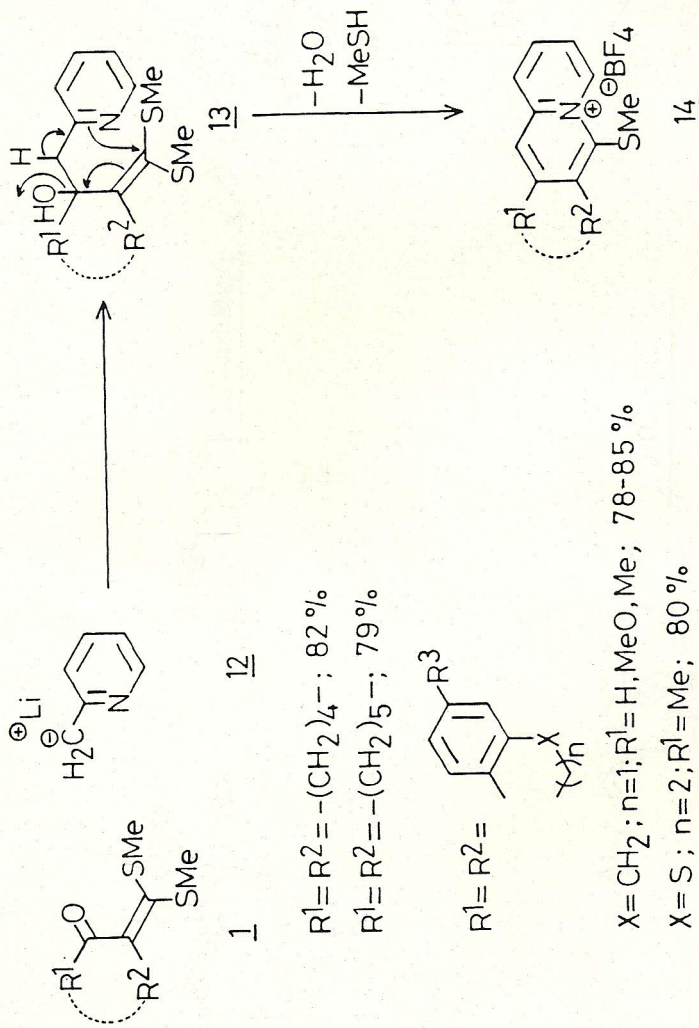


Scheme - 4

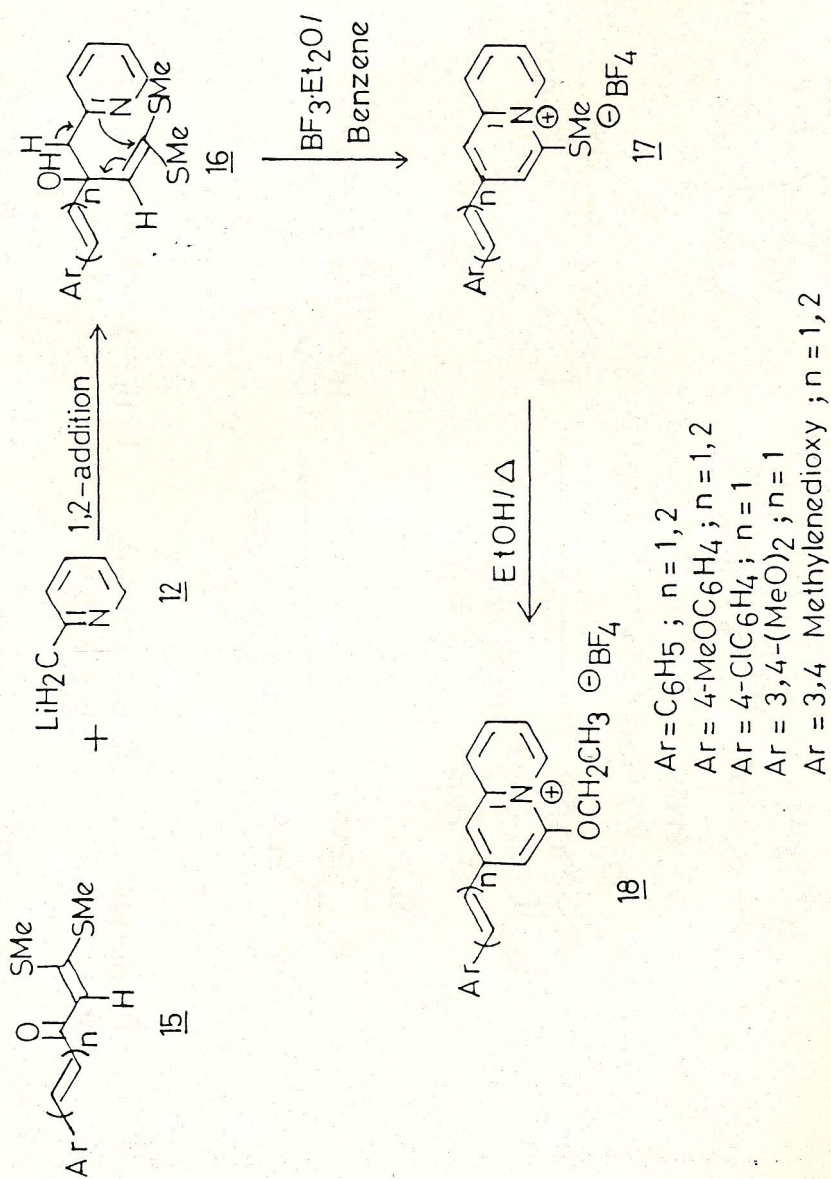
different reactivity patterns of benzyl, 1-naphthylmethyl- and 2-naphthylmethylmagnesium halides with α -oxoketene dithioacetals.

In Chapter III, the reaction of various α -oxoketene dithioacetals with 2-picolyllithium has been described. The α -oxoketene dithioacetals 1 react with 12 in an exclusive 1,2-manner to yield the corresponding carbinol acetals 13 which on $\text{BF}_3 \cdot \text{Et}_2\text{O}$ assisted cyclization afforded the corresponding quinolizinium tetrafluoroborates 14 (Scheme 5) in high yields. The generality of this method has been studied by using wide structural variants of 1. Also α -enoyl ketene dithioacetals 15 reacted with 2-picolyllithium to give the corresponding quinolizinium tetrafluoroborates 17 (Scheme 6) in high yields. The methylthio groups in few of these salts could be easily displaced by the corresponding ethoxy group in refluxing ethanol.

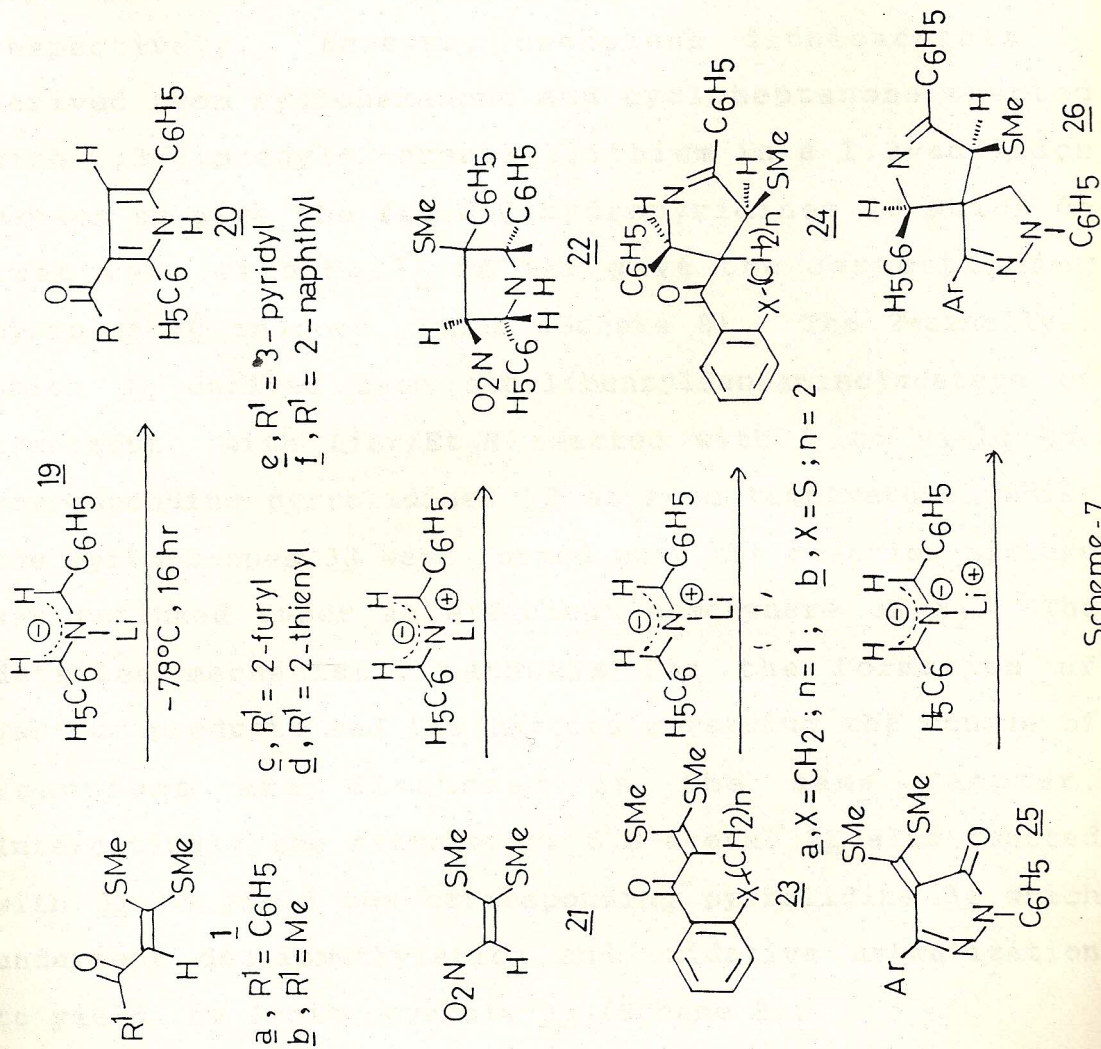
1,3-Anionic cycloaddition of 1,3-diphenyl-2-azaallyl and ethyl(benzylideneamino)acetate anions 19 and 31 with α -oxoketene dithioacetals¹² have been described in the Chapter IV. Thus, when 1,3-diphenyl-2-azaallyllithium 19 reacted with oxoketene dithioacetals 1, the corresponding pyrroles 20 (Scheme 7) were formed in good yields, apparently through [3+2] cycloaddition and subsequent elimination of methylthio group. However, with nitroketene dithioacetals 21 the corresponding pyrrole was not isolated, the fully saturated pyrrolidine 22 was



Scheme-5

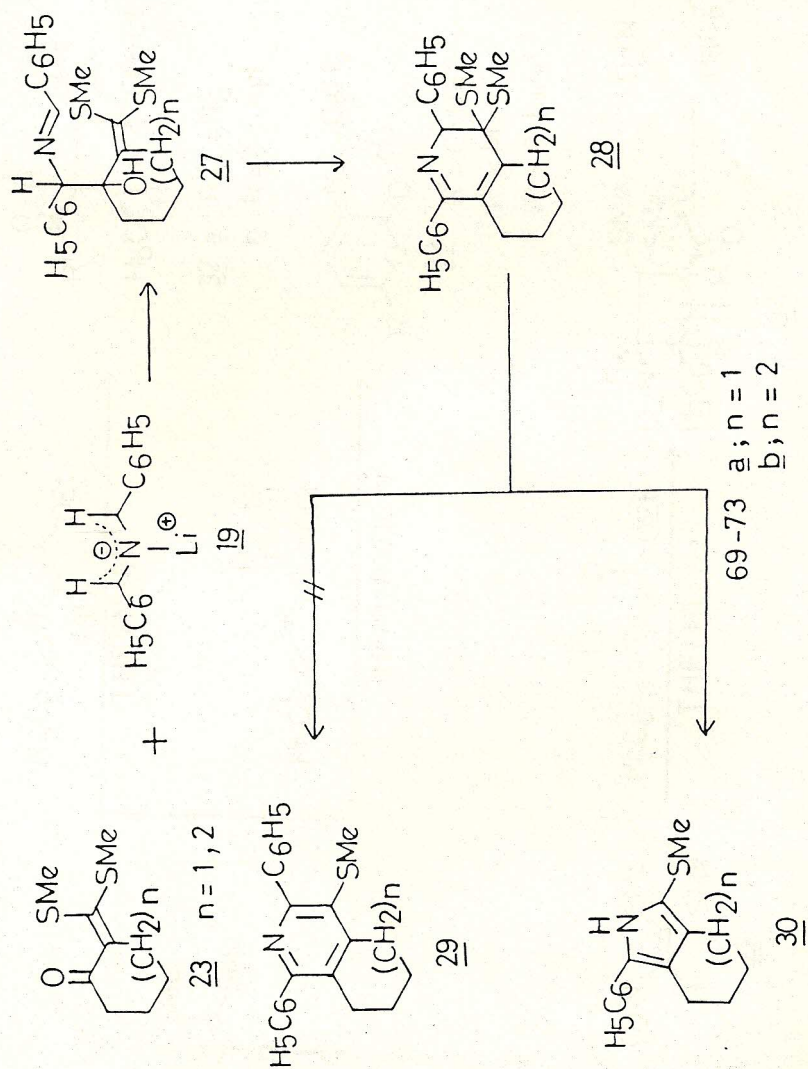


Scheme - 6

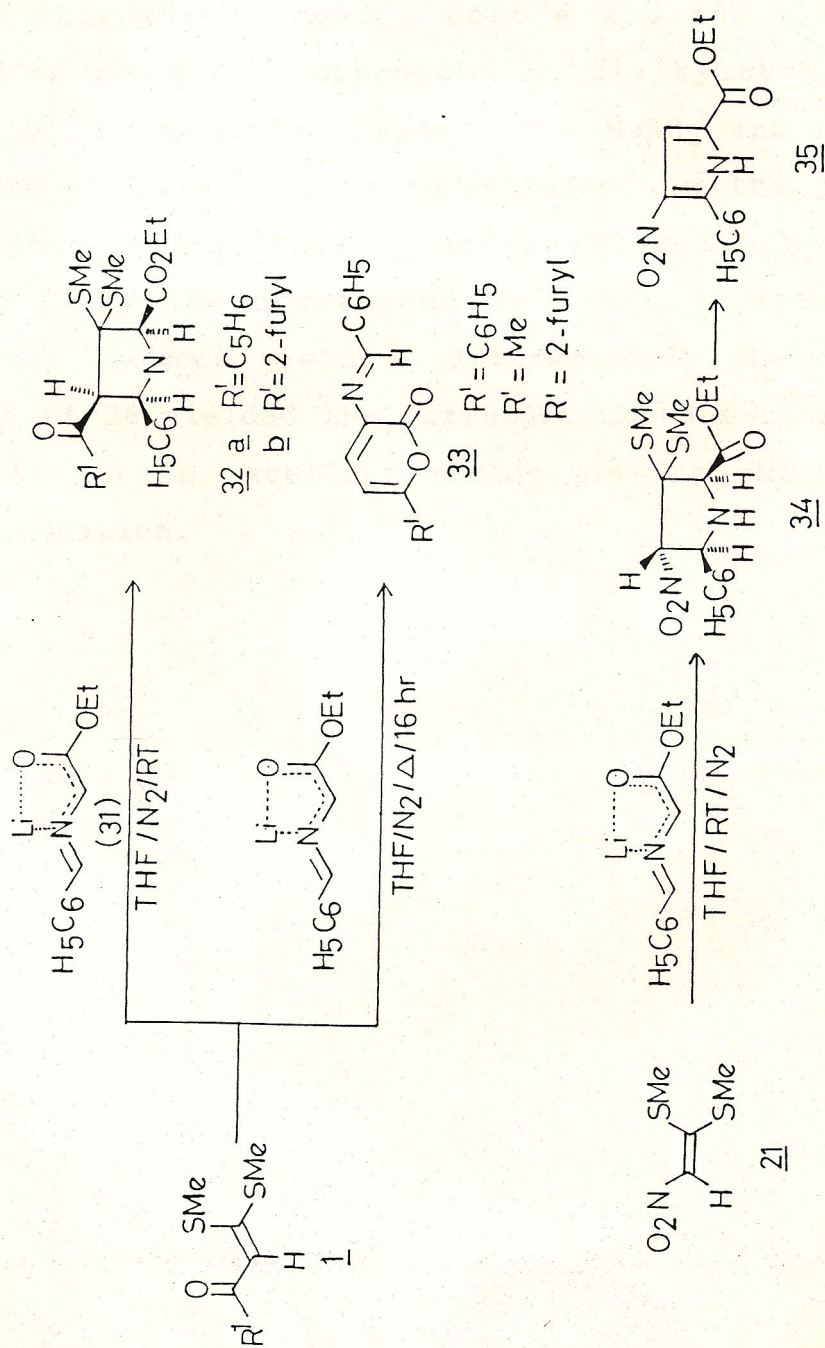


the only product obtained. The spiropyrrolines 24 and 26 were obtained in good yields by the reaction of 1,3-diphenyl-2-azaallyl anion 19 with 23 and 25 (Scheme 7) respectively. However, oxoketene dithioacetals 23 derived from cyclohexanone and cycloheptanone reacted with 1,3-diphenyl-2-azaallyllithium in a 1,2-addition manner to give the fused dihydropyridines 28 which on treatment with HgCl_2 in THF gave the corresponding pyrroles 30 in good yields (Scheme 8). The 2-azaallyl-anion 31 derived from ethyl(benzylideneamino)acetate by treatment with $\text{LiBr}/\text{Et}_3\text{N}$ reacted with 1 to yield the corresponding pyrrolidines 32 at room temperature, while the pyran-2-ones 33 were formed when the reaction mixture was refluxed under an efficient atmosphere of N_2 . The detailed mechanistic pathways for the formation of various products and the factors governing the course of reactions are discussed in the same Chapter. Interestingly the nitroketene S,S-acetal 21 also reacted with 31 to yield the corresponding pyrrolidine 34 which underwent dethiomethylation and oxidative aromatization to yield the 4-nitropyrrole 35 (Scheme 9).

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



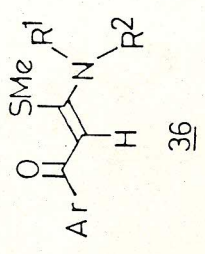
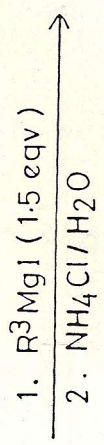
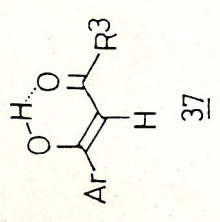
Scheme-8



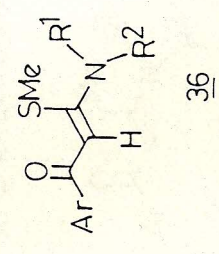
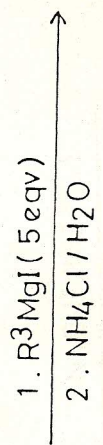
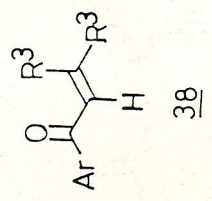
Scheme-9

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



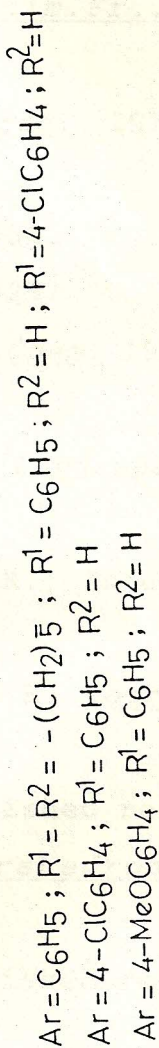
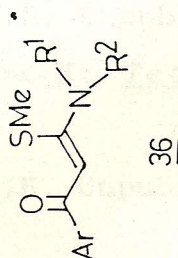
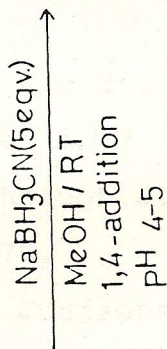
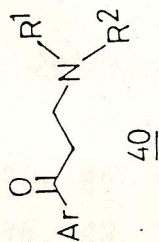
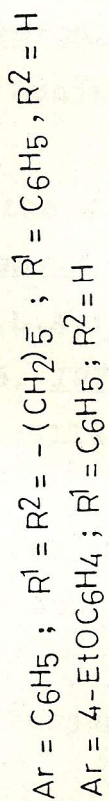
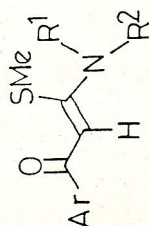
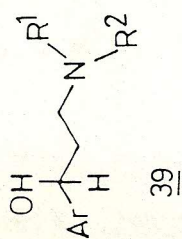


Ar = C₆H₅, 4-MeOC₆H₄; R¹ = R² = -(CH₂)₅⁻, Me;
R³ = Me, Et, n-pr, C₆H₅



Ar = C₆H₅; 4-MeOC₆H₄; R¹ = R² = -(CH₂)₅⁻; Me
R³ = Me, Et, n-Pr.

Scheme-10



REFERENCES

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

NEHU Library
Acc. No. 102320
Acc. by [Signature]
Date 7/10/91
Class by
Sub Heading by
Salarby
Transcribed by