PART A : SYNTHETIC STUDIES ON POLARIZED KETOKETEN-S,S-ACETALS

PART B : SYNTHETIC STUDIES ON LEAD (IV) ACETATE OXIDATIONS

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

DOCTOR OF PHILOSOPHY

To

NORTH-EASTERN HILL UNIVERSITY
SHILLONG, MEGHALAYA, INDIA

MAY, 1983

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C E R T I F I C A T E

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

Date: 28th May, 1983.

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This is to certify that Mr. Bekington Myrboh has completed the following pre-Ph.D. courses as prescribed by this University satisfactorily:-

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A C K N O W L E D G M E N T S

The research work described in this thesis was carried out in the Department of Chemistry, North-Eastern Hill University, Shillong, under the supervision of Dr. H. Junjappa, Professor of Chemistry. I take this opportunity to thank him for suggesting the problem and for his able guidance throughout the course of this investigation. I am also grateful to Dr. (Mrs.) H. Ila, Reader, Department of Chemistry, NEHU, who had spared no effort in giving valuable help and inspiration all throughout this investigation.

I further extend my thanks to the Directors of Central Drug Research Institute, Lucknow, Regional Research Laboratory, Jorhat and Bose Institute, Calcutta, for providing the spectral and analytical service required in this investigation. Thanks are also due to my colleagues for the cooperation they had extended and the spirit of camaraderie they had shown.

To my parents, to whom I shall forever remain in debt, I take this opportunity to express my gratitude.

BEKINGTON MYRBOH

C O N T E N T S

PREFACE

In the first four chapters, a systematic investigational study was undertaken to exploit the polarized keten S,S-acetals as useful intermediates for the development of newer synthetic methods leading to the synthesis of alkylthiomethylene ketones, α,β-unsaturated esters and aldehydes and alkadienoic esters.

In the first chapter, the synthetic applications of these acetals as useful intermediates for the construction of a wide variety of heterocyclic systems have been discussed.

In the second chapter, a new general method for the synthesis of alkylthiomethylene ketones by partial reductive demethylthiolation of the acetals with sodium borohydride and nickel chloride is described. The method is general and can be extended for the synthesis of a number of alkylthiomethylene ketones with wide structural variations.

In the third chapter these ketoketen S,S-acetals have been successfully used as intermediates for the synthesis of α,β-unsaturated O-methyl and S-methyl esters and aldehydes. An application of this method for the

preparation of intermediates used in the synthesis of anthracyclinones has been presented.

In the next chapter, the above method has been extended to the synthesis of 5-aryl 2,4-pentadienoates. The generality of the method has been described.

The last two chapters deal with the synthetic application of lead (IV) acetate oxidation.

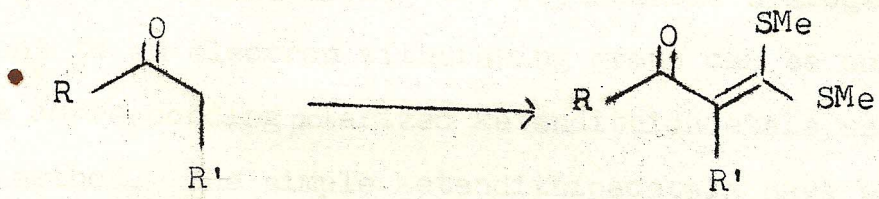
In the fifth chapter, a facile method for the conversion of the acetophenones to the corresponding methyl arylacetates has been developed. The method has been shown to be quite useful and general.

In the last chapter, the method has been successfully extended for the synthesis of alkynoic and allenic esters starting from appropriate pyrazolones respectively. The scope and generality of the method has been described by using pyrazolones with different substituents.

CHAPTER I

POLARISED KETEN-S,S-ACETALS: GENERAL INTRODUCTION

The Ketoketendithioacetals 2 are among the simplest synthetic intermediates, which can be prepared by simple preparative routes using wide range of active methylene ketones.[1-3] They are either liquids with well defined boiling points or solids with sharp melting points, which can



1 2

R = alkyl, aryl, etc

R' = H, alkyl, aryl

RR' = $-(CH_2)_n-$

Scheme 1

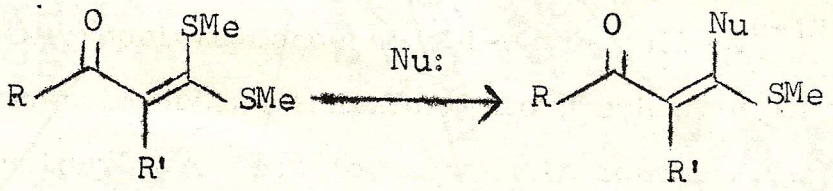
be purified by conventional purification methods. They are stable at room temperature and can be stored indefinitely, which will remain unchanged under both mild acidic and alkaline conditions. On the other hand, the corresponding O,O-acetals[4] are prepared by methods involving more than one step and are moisture sensitive. Consequently, they can

not be prepared and stored under ordinary conditions, since they suffer rapid hydrolytic cleavage in the presence of moisture. Therefore, the methods using active methylene compounds as starting materials cannot be extended to the preparation of O,O-acetals, as is followed for the corresponding 2. On the other hand, 2 can be easily synthesized in one pot reaction by treating 1 with two equivalents of base, carbon disulphide and an alkyl halide sequentially in good to excellent yields. In principle any organic molecule having two replaceable hydrogen atoms adjacent to an electron withdrawing group can be converted to the corresponding polarized ketendithioacetals using the above method. The simple ketendithioacetals have been prepared by reacting Grignard[4] and other organometallic reagents[4] with carbon disulphide followed by alkylation, which are not considered in the present studies. Much of the chemistry of 2 was largely confined to their synthesis and the study of their physical properties[5], when a systematic investigation of their synthetic applications was initiated in our laboratory.

Among the structural variants of 2, the ketendithioacetals carrying the α-keto and α-cyano groups constitute an important group of 3-carbon fragments with pronounced 1,3-electrophilic centres. This property has

been successfully exploited to construct a variety of important class of heterocyclic compounds by reacting them with appropriate mono- and bi-nucleophiles.[6-12] Some of the most important transformations achieved in this laboratory have been formulated in Scheme 2, using polarized ketendithioacetals derived from various active methylene compounds.[6-14] These methods have been shown to be general for the construction of the corresponding heterocycles with liberal structural variations. The generality and the scope of these methods have been well established, chosing appropriate substrates.

The acetals 2 are known to undergo a facile displacement reaction with appropriate nucleophiles to give the corresponding mixed acetals 3 (Scheme 3) in good yields. Particularly, when the nucleophile is an amine, the



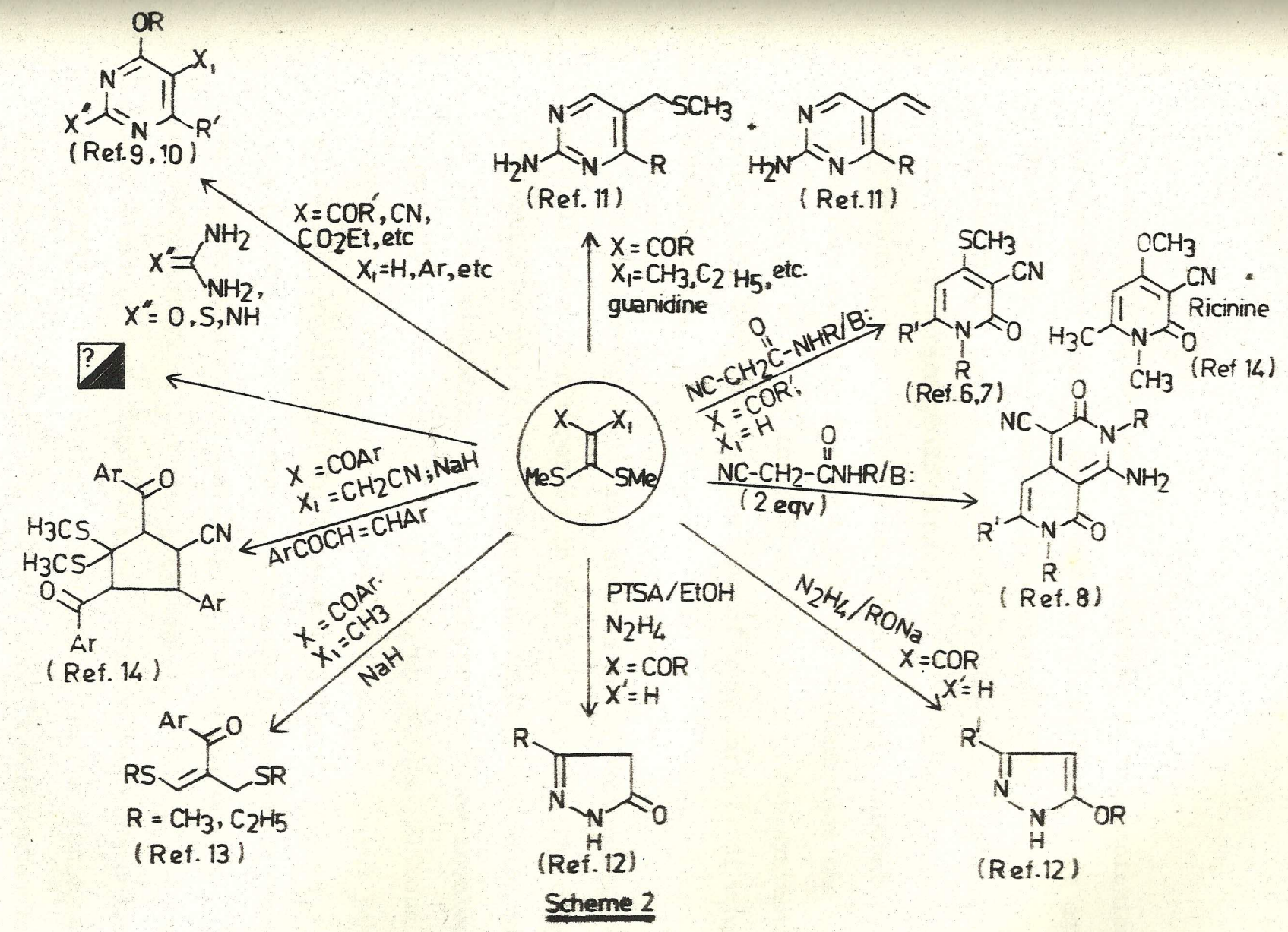
2 3

Nu: = amines

= active methylene compounds[15]

Scheme 3

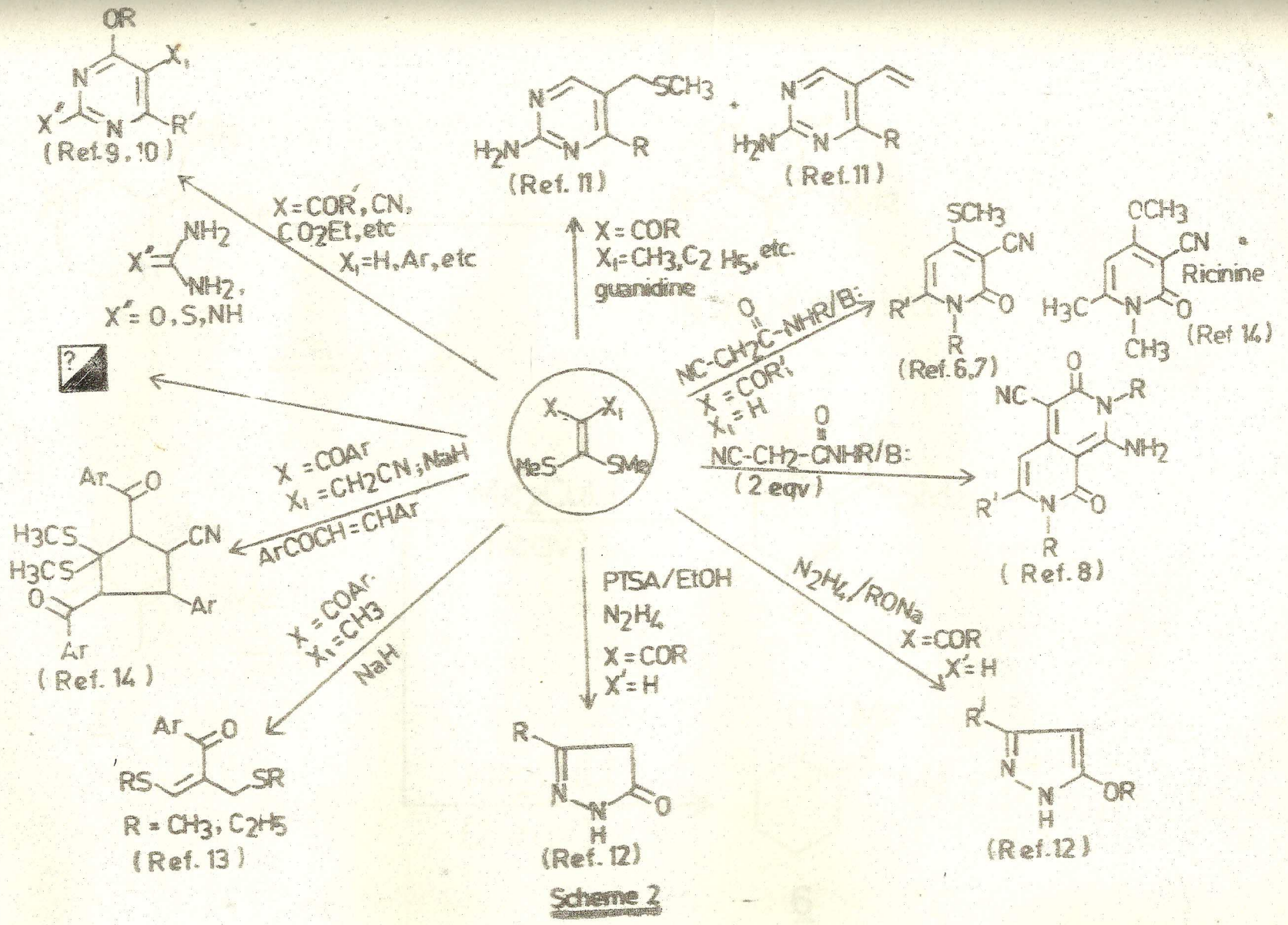
displacement can take place either to give the corresponding


OR
X1
X'
N
R'
(Ref.9,10)
X=COR', CN, CO2Et, etc
X1=H, Ar, etc
NH2
X''
NH2,
X''= O, S, NH
?
SCH3
H2N
R
(Ref. 11)
(Ref.11)
X = COR
X1= CH3, C2 H5, etc.
guanidine
O
NC-CH2C-NHR/B:
X = COR',
X1= H
SCH3
CN
OCH3
Ricinine
H3C
CH3
(Ref 14)
(Ref.6,7)
NC-CH2-CNHR/B:
(2 eqv)
NC
NH2
(Ref. 8)
X
X1
MeS
SMe
X =COAr
X1 =CH2CN; NaH
ArCOCH=CHAr
Ar
H3CS
CN
O
(Ref. 14)
X =COAr.
X1=CH3
NaH
RS
SR
R = CH3, C2H5
(Ref. 13)
PTSA/EtOH
N2H4
X = COR
X'= H
(Ref. 12)
N2H4/RONa
X=COR
X'= H
(Ref.12)

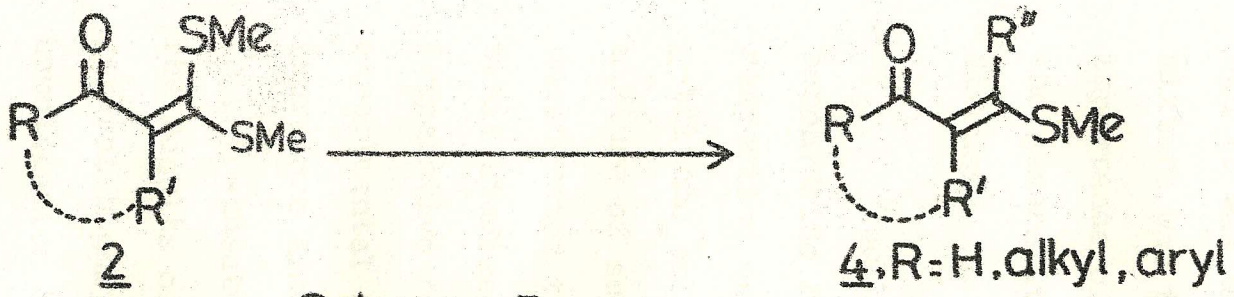
Scheme 2

S,N-acetal or its N,N-acetal depending on the stoichiometry of the amine used or the reaction conditions. Here again the S,N- and N,N-acetals have been proved to be synthetically useful substrates for the construction of a variety of heterocyclic rings.[12,16-24] Some of the important general methods developed in this laboratory have been formulated in Scheme 4. It is evident that the keten-S,S- and S,N- and N,N-acetals have great synthetic potentials for the construction of wide variety of novel heterocycles.

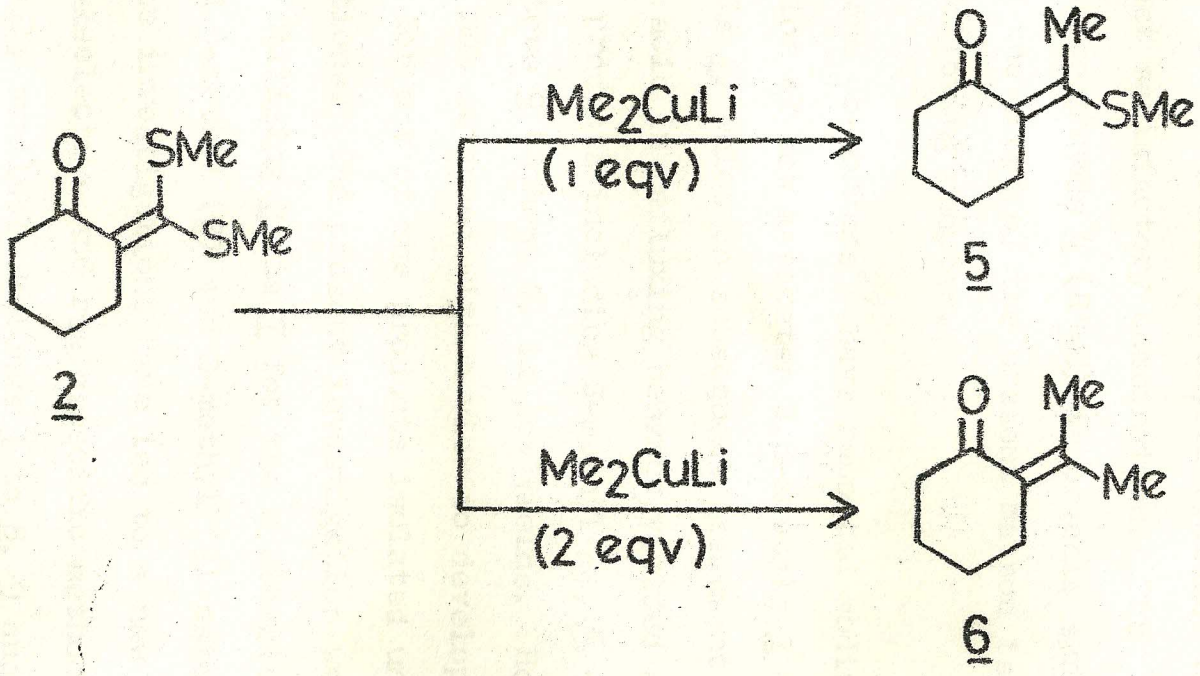
Recently, reductive studies on ketoketendithioacetals have been reported in the literature. The only reference on the partial reductive dealkylthiolation of 2 to the corresponding alkylthiomethylene ketones involves electrolytic reduction[25] of 1 (R=C_6H_5; R'=H). Although a variety of reagents have been developed in recent years which add exclusively in 1,4-manner (Chapter II) to α,β-unsaturated ketones, there is no systematic study on similar transformations of 2 to the corresponding alkylthiomethylene ketones 4 (Scheme 5). Recently Corey[26] has observed that dimethylcopper lithium reagents undergo 1,4-addition to ketoketen S,S-acetal 2 (R=R'= $-(CH_2)_4-$) to give 5 and 6 respectively (Scheme 6). It was contemplated in the present studies to develop a convenient preparative


(Ref. 9, 10)
X = COR', CN, CO2Et, etc
X1 = H, Ar, etc
X' = O, S, NH
(Ref. 11)
(Ref. 11)
X = COR
X1 = CH3, C2H5, etc.
guanidine
(Ref. 6,7)
Ricinine
(Ref 14)
NC-CH2C-NHR/B:
X = COR'
X1 = H
NC-CH2-CNHR/B:
(2 eqv)
(Ref. 8)
X = COAr
X1 = CH2CN; NaH
ArCOCH=CHAr
(Ref. 14)
X = COAr
X1 = CH3
NaH
RS
SR
R = CH3, C2H5
(Ref. 13)
PTSA/EtOH
N2H4
X = COR
X' = H
(Ref. 12)
N2H4/RONa
X = COR
X' = H
(Ref. 12)

Scheme 2



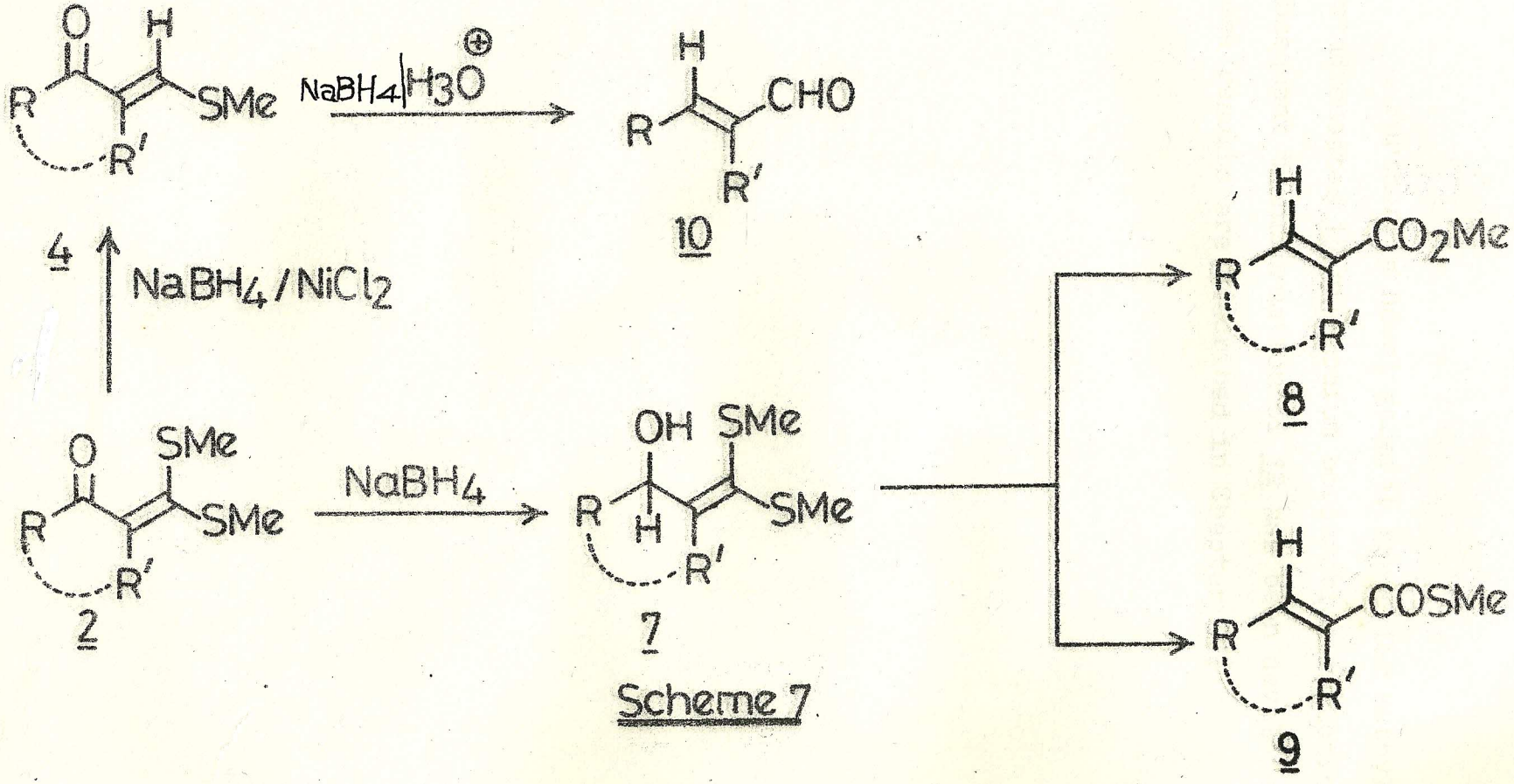
Scheme 5



Scheme 6

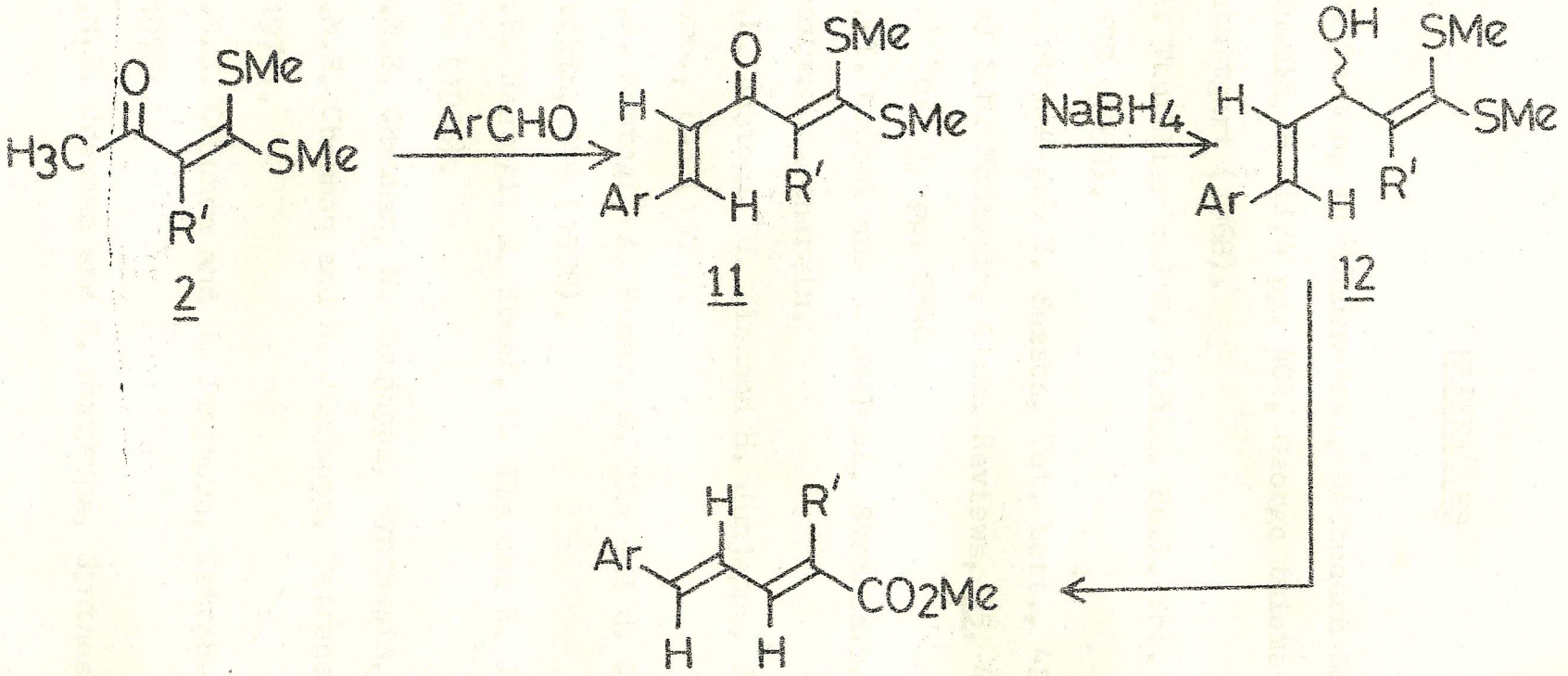
method for the conversion of 2 to 4 (R'=H). Several attempts using a mixture of sodium borohydride and transition metal halides were made to affect the conversion of 2 to 4 (R'=H) and it was found that the sodium borohydride/nickel chloride mixture was the most satisfactory combination. The importance of these compounds 4 (R'=H) in organic synthesis, the generality and the scope of the present method is discussed in the following chapter.

Thuillier and co-workers[27] have reported sodium borohydride reduction of few ketoketen S,S-acetals 2 to the respective carbinols 7, which on subsequent treatment with p-toluene sulfonic acid in refluxing benzene, yielded a mixture of several products including S-methyl α,β-unsaturated thioesters 9 (Scheme 7) in low yields. However their studies were not intended with a view to developing preparative routes for any of the products isolated under experimental conditions. The present investigation was therefore aimed at utilizing 2 via 7 for the synthesis of α,β-unsaturated O-methyl (8) and S-methyl (9) esters. The results of these investigations have led to a new general highly stereoselective and regiospecific method for homologation of easily available ketones 1 to 8, 9 and 10 via 2 in excellent yields (Scheme 7). The scope and the generality of the method is presented in Chapter III.


O
H
R
SMe
R′
NaBH4/H3O⊕
H
CHO
R
R′
10
4
NaBH4/NiCl2
O
SMe
R
SMe
R′
2
NaBH4
OH
SMe
R
H
SMe
R′
7
H
CO2Me
R
R′
8
H
COSMe
R
R′
9

Scheme 7

Further, a novel general route for methyl 5-aryl-2,4-pentadienoates 13 via sodium borohydride reduction of 11 and subsequent transformation of 12 has been developed (Scheme 8). These results are described in Chapter IV.



2 11 12 13

2, 11–13, R' = H or Me

Scheme 8

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