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

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

(Abstarct)

BEKINGTON MYRBOH

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, MEGHALAYA, INDIA

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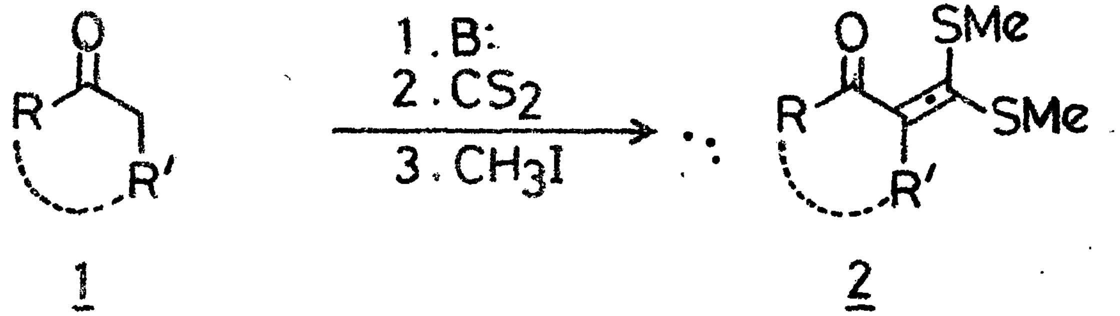
Chem
(Thesis)

The thesis is divided into two parts, the first part consisting, of four chapters, deals with the synthetic studies on polarized Keten S,S-acetals derived from various active methylene ketones of the general formula 1.

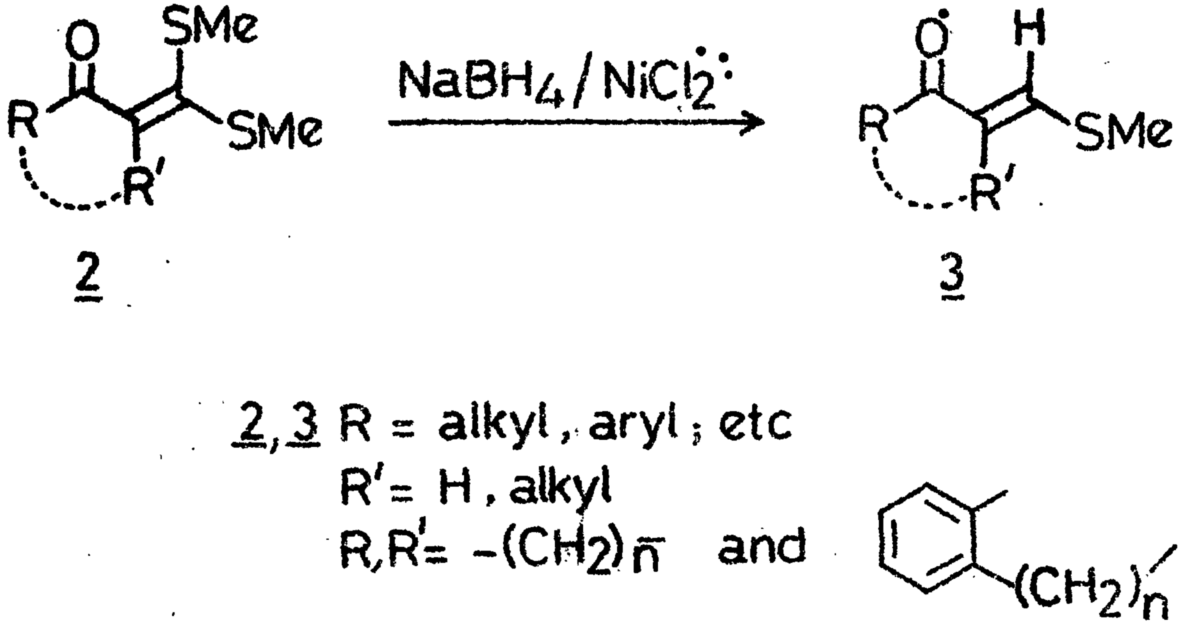
It has been well documented that a wide variety of active methylene compounds undergo facile condensation with carbon disulfide in the presence of two equivalents of base followed by subsequent alkylation to yield the corresponding polarised ketendithioacetals in good to excellent yields. Unlike the corresponding O,O-acetals, the S,S-acetals are stable under mild hydrolytic conditions and thus form an interesting class of useful synthetic intermediates. The synthetic applications of these acetals as useful intermediates for the construction of a wide variety of heterocyclic systems[1] have been discussed in the first chapter.

In the chapter II, a new general method for the synthesis of alkylthiomethylene ketones 3 by partial reductive demethylthiolation of 2 with sodium borohydride and nickel chloride[2] has been described. The yields of these methylthiomethylene ketones are generally in the range between 42-75%. The scope and generality of the



1,2 R = alkyl, aryl, etc
R' = H, alkyl, aryl,
R,R' = $-(CH_2)_n-$

Scheme 1

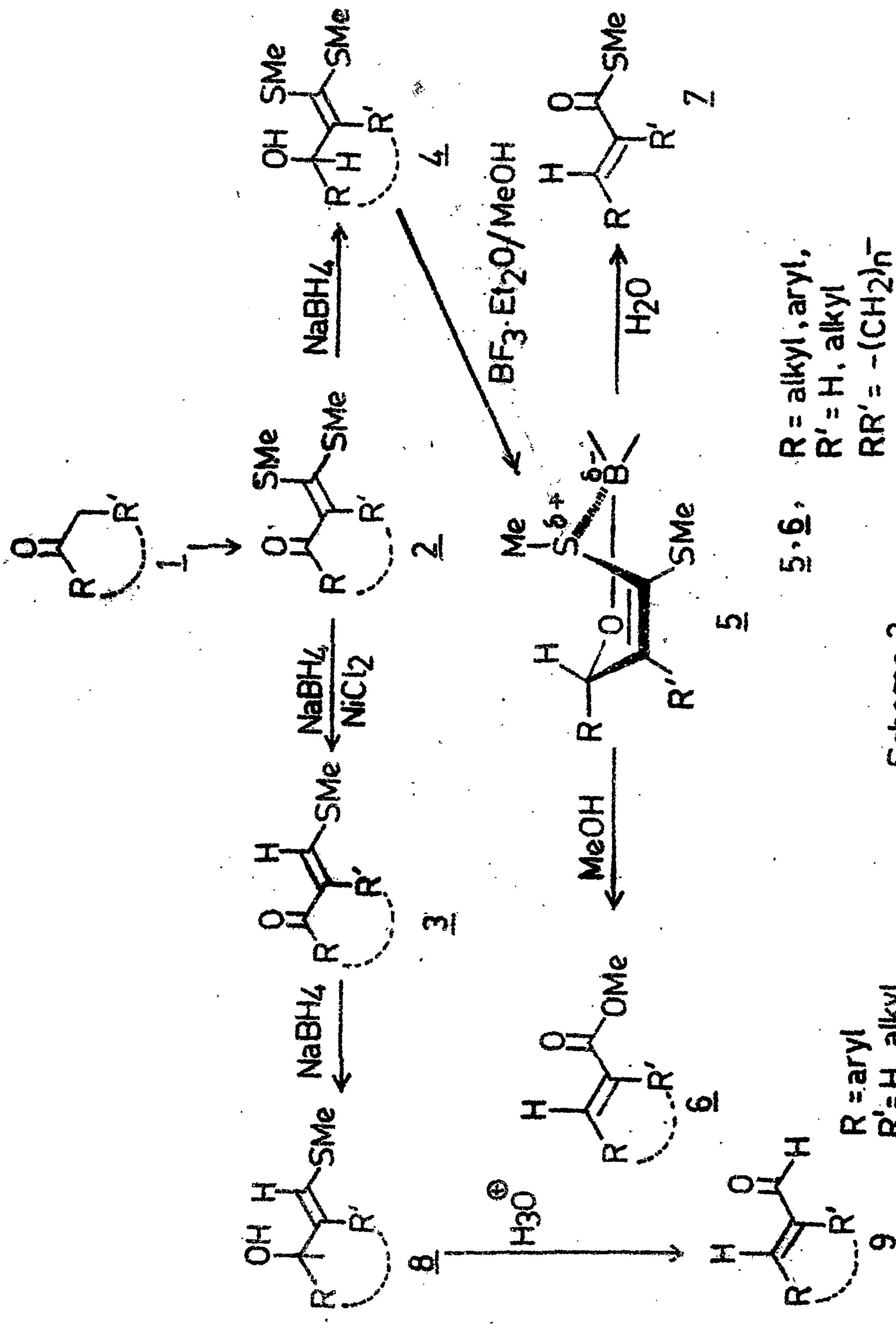


2, 3 R = alkyl, aryl; etc
R′ = H, alkyl
R,R′ = –(CH$_2$)$_n$– and

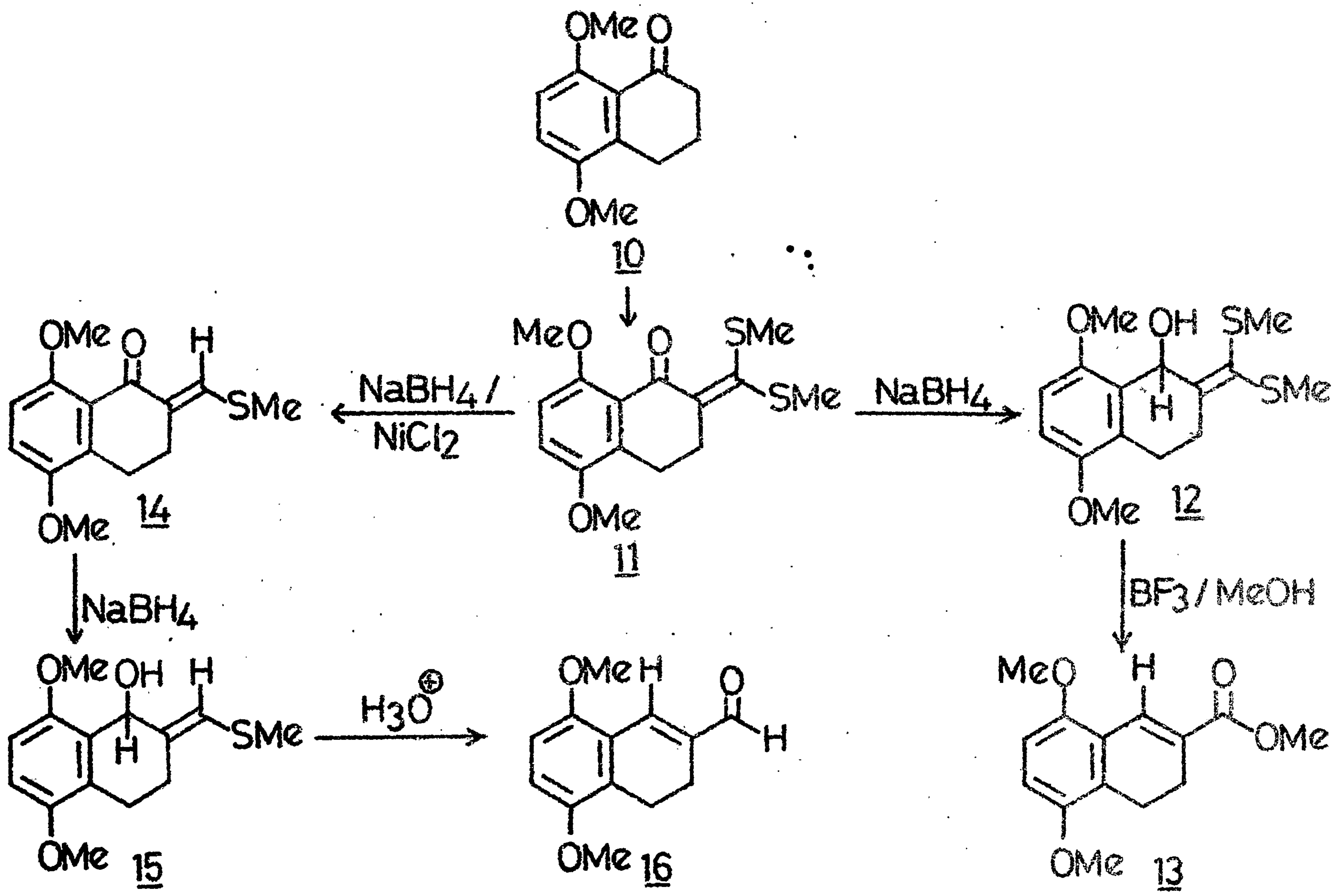
Scheme 2

method have been shown by choosing 2 with wide structural variations. The structural assignments and the stereoelectronic features of the thiomethylene ketones have been fully established on the basis of their spectral and analytical data.

In chapter III, a new general method for the conversion of ketones of the general formula 1 to the α,β-unsaturated esters 6 (Scheme 3) has been developed, using 2 as intermediates.[3] Thus, the dithioacetals 2 were subjected to 1,2-reduction using sodium borohydride to give the corresponding carbinols 4 in quantitative yields, which were shown to undergo facile methanolysis in the presence of boron trifluoride etherate to give the corresponding α,β-unsaturated methyl esters 6, in excellent yields. The esters 6 thus obtained exhibited high stereoselectivity and regiospecificity as assigned by their NMR spectral data. The dithioacetal carbinols 4 were further shown to undergo partial hydrolysis in the presence of boron trifluoride etherate and water to give the corresponding S-methyl esters 7 (Scheme 3) in high yields. These experiments were also extended to the alkylthiomethylene ketones 3 followed by hydrolysis to yield the corresponding α,β-unsaturated aldehydes 9 (Scheme 3). A probable mechanism involving cyclic twist-


1
2
3
4
5
6
7
8
9
NaBH4
NaBH4 NiCl2
NaBH4
BF3·Et2O/MeOH
MeOH
H2O
H3O⊕
SMe
OMe
B
δ+
δ−
5,6, R = alkyl, aryl, R' = H, alkyl RR' = -(CH2)n-
R = aryl R' = H, alkyl

Scheme 3


OMe
O
OMe
10
MeO
O
SMe
SMe
OMe
11
NaBH4 /
NiCl2
NaBH4
OMe
OH
SMe
H
SMe
OMe
12
BF3 / MeOH
MeO
H
O
OMe
OMe
13
OMe
O
H
SMe
OMe
14
NaBH4
OMe
OH
H
H
SMe
OMe
15
H3O⊕
OMe
H
O
H
OMe
16

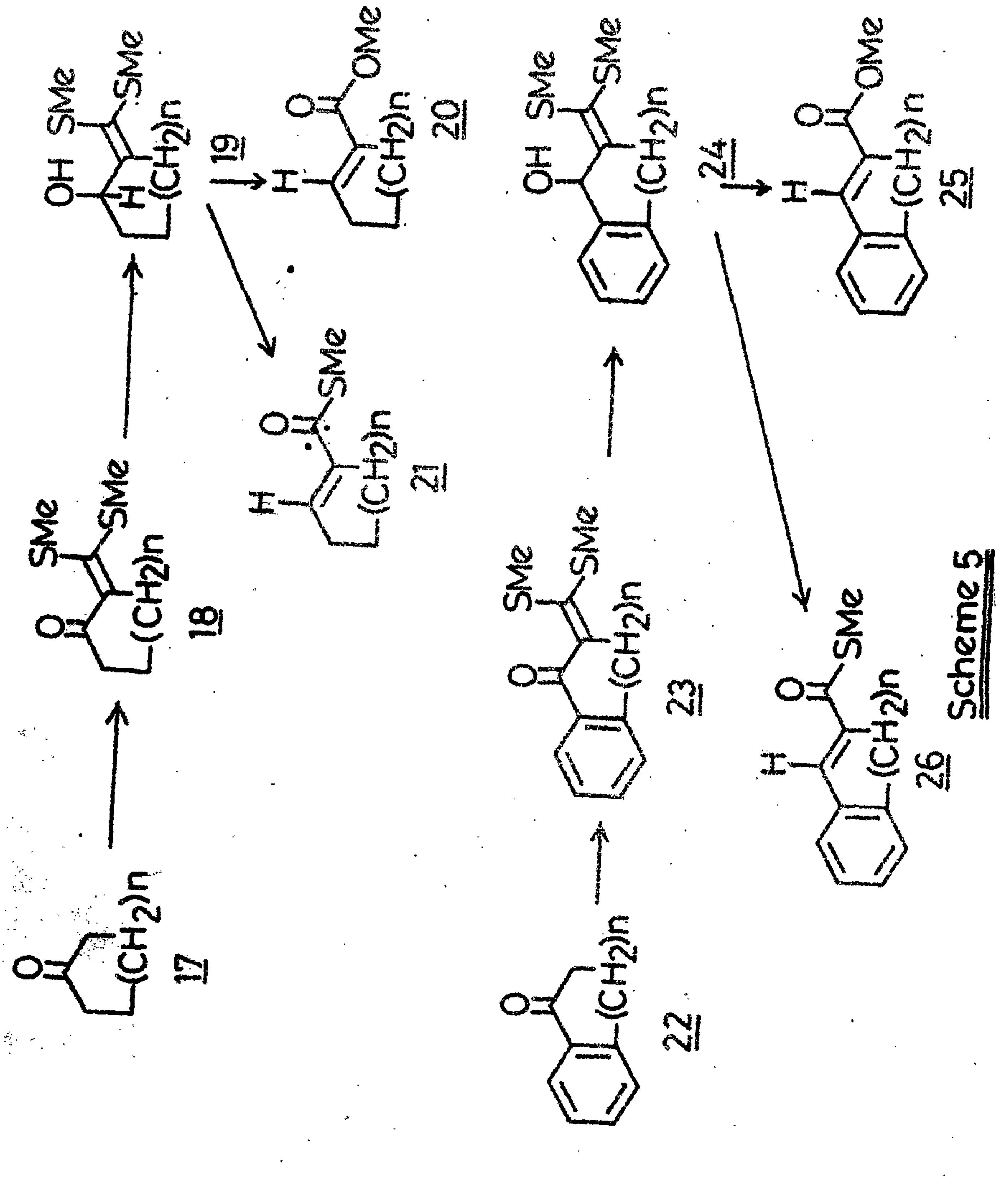
Scheme 4

boat intermediate 5 has been suggested for the conversion of 4 to the esters 6 or 7.

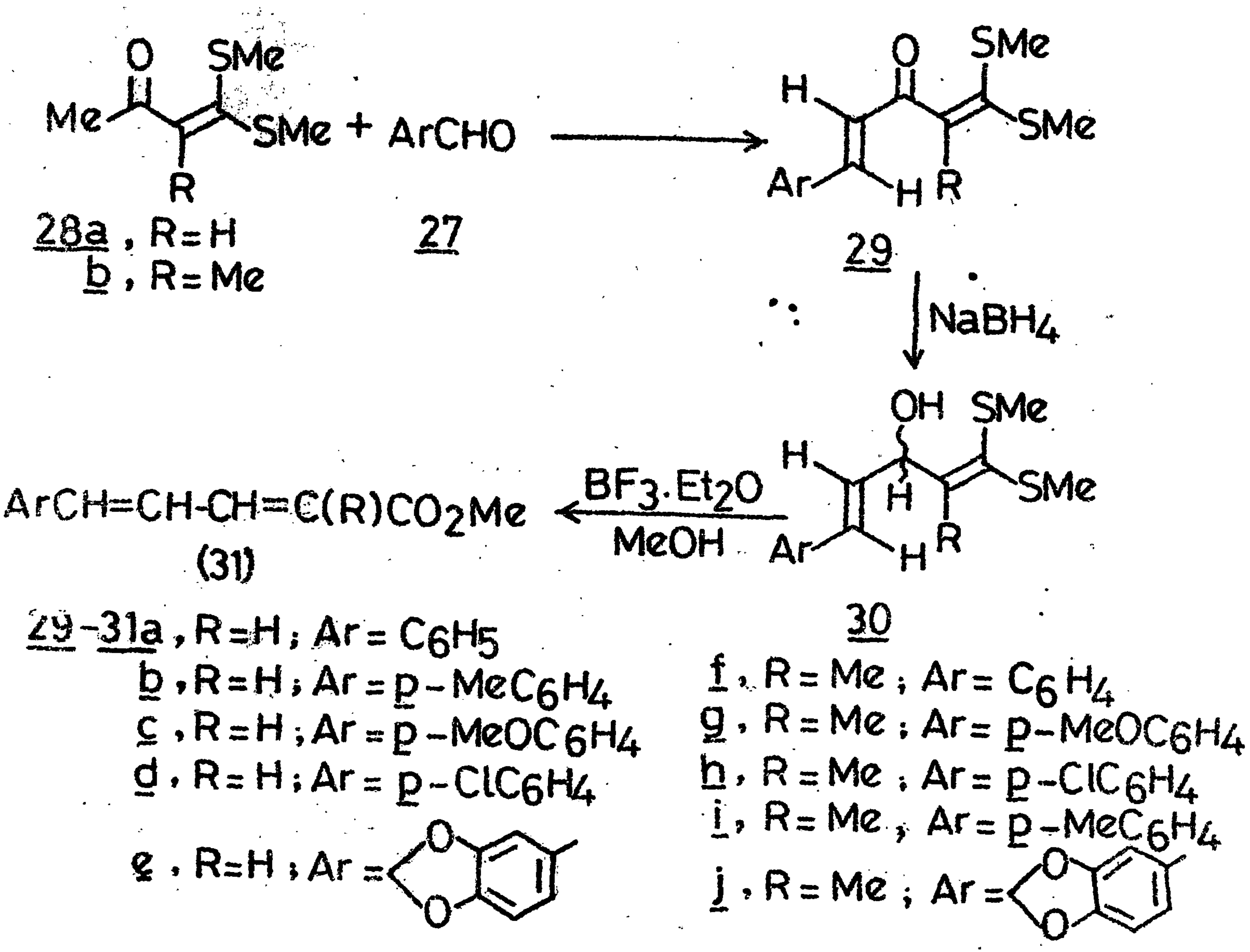
In Scheme 4, an application of this method for the preparation of 13 and 16 which are used as intermediates in the synthesis of anthracyclinones has been presented. The cyclic ketones of general formula 17 and 22 (Scheme 5) have been similarly converted to the corresponding O-and S-methyl esters under identical conditions.

The method has also been extended in chapter IV, to the synthesis of methyl 5-aryl 2,4-pentadienoates 31 (Scheme 6). Thus various substituted benzaldehydes were condensed with the mercaptals 28a and 28b, when the corresponding ketones 29 were obtained in excellent yields. The ketones 29 were subsequently subjected to 1,2-reduction to give the corresponding carbinols 30 in nearly quantitative yields. The carbinols 30 were subjected to methanolysis in presence of boron trifluoride etherate, without isolation, to yield the diene esters 31a-j in 60-75% overall yields.

The second part of the thesis deals with the synthetic application of lead (IV) acetate oxidation. Thus in chapter V, a facile method for the conversion of the acetophenones 32 to the corresponding methyl arylacetate



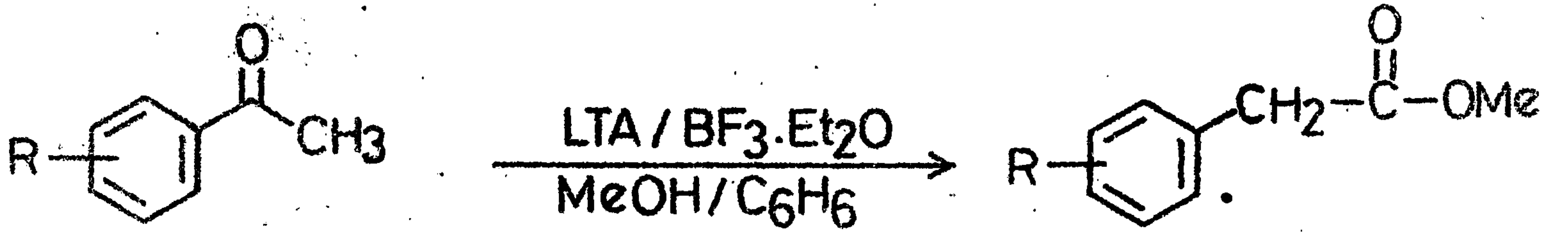
Scheme 5


28a, R=H
b, R=Me
27
+ ArCHO
29
NaBH4
30
BF3.Et2O
MeOH
ArCH=CH-CH=C(R)CO2Me
(31)
29-31a, R=H; Ar=C6H5
b, R=H; Ar=p-MeC6H4
c, R=H; Ar=p-MeOC6H4
d, R=H; Ar=p-ClC6H4
e, R=H; Ar=
f, R=Me; Ar=C6H4
g, R=Me; Ar=p-MeOC6H4
h, R=Me; Ar=p-ClC6H4
i, R=Me; Ar=p-MeC6H4
j, R=Me; Ar=

Scheme 6

33 in high yields has been developed[4] (Scheme 7). The conversion is achieved by treating 32 with lead (IV) acetate in the presence of boron trifluoride etherate and methanol at room temperature. Extension of this method to desoxybenzoin 34, methyl naphthyl ketone (36) and methylthienylketone (38) yielded the corresponding esters 35, 37 and 39 in excellent yields (Scheme 8). The advantages of this method over that of Willgerodt-Kindler reaction as well as that of thallium (III) nitrate method is discussed.

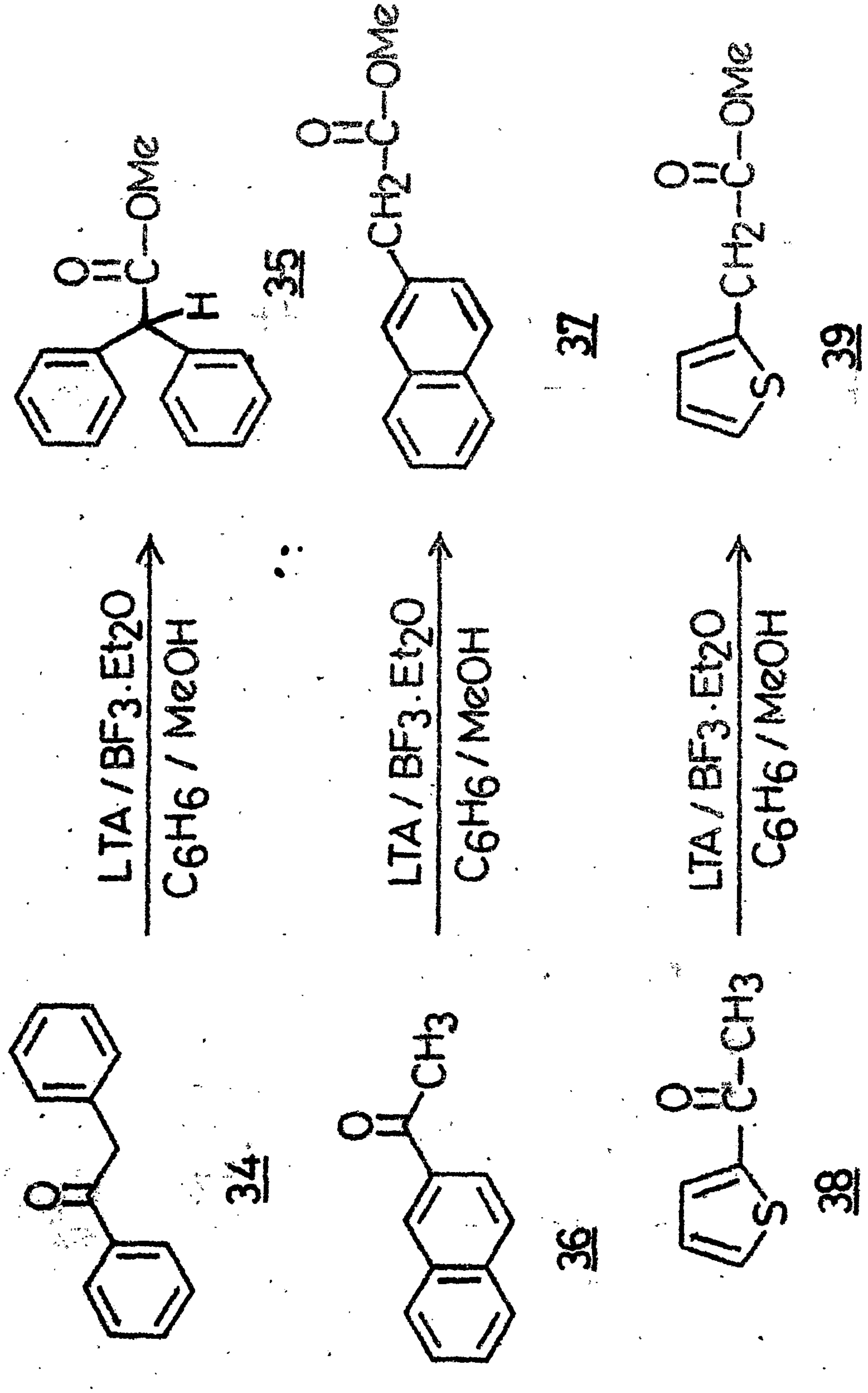
The lead (IV) acetate oxidation studies have also been successfully extended for the synthesis of alkynoic and allenic esters 41 and 43 (Scheme 9 and 10) starting from the appropriate pyrazolones 40 and 45 respectively.[5] The scope and generality of the method has been described by using pyrazolones with different substituents (Scheme 9 and 10).



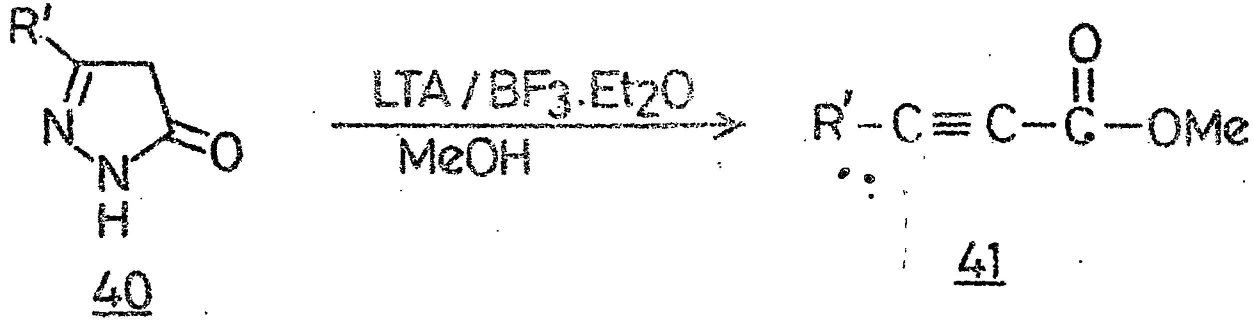
32 33

32, 33a, R = H
b, R = p–Me
c, R = p–MeO
d, R = m–MeO
e, R = p–Cl
f, R = p–Br
g, R = 2, 4 –dichloro
h, R = p–NO$_2$

Scheme 7

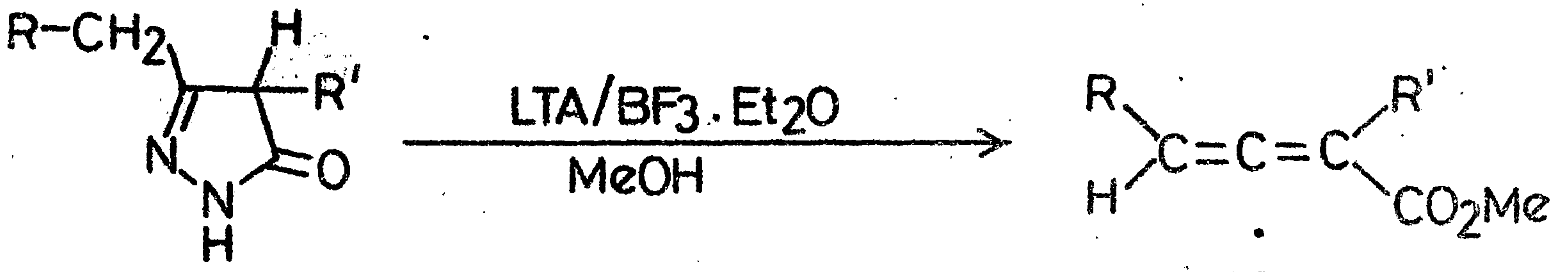


Scheme8



40, 41a , $R' = C_6H_5$
b , $R' =$ p-CH_3-C_6H_4
c , $R' =$ p-Cl-C_6H_4
d , $R' = CH_3$
e , $R' =$ n-C_4H_9
f , $R' =$ n-C_5H_{11}

Scheme 9



42 **43**

42, **43a**, R = H ; $R' = CH_3$
b, R = H ; $R' = C_2H_5$
c, R = H ; R' = *n*−C_3H_7
d, R = H ; R' = *n*−C_4H_9
e, R = H ; R' = *n*−C_5H_{11}
f, R = H ; R' = *n*−C_6H_{13}
g, R = H ; R' = *n*−$C_{10}H_{21}$
h, $R = CH_3$; $R' = CH_3$
i, $R = C_2H_5$; $R' = C_2H_5$

Scheme 10

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MAY, 1983

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Grams: NEHU

Dr. H. Junjappa
Professor

CERTIFICATE

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:-

1. Advance Concept in Physical Chemistry
2. Molecular Orbital and Valence Bond Theory
3. Advance Inorganic Chemistry
4. Highlights in Organic Chemistry

Head
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(Prof. T.S.B. Narasaraju)

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

BEKINGTON MYRBOH

CONTENTS

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.

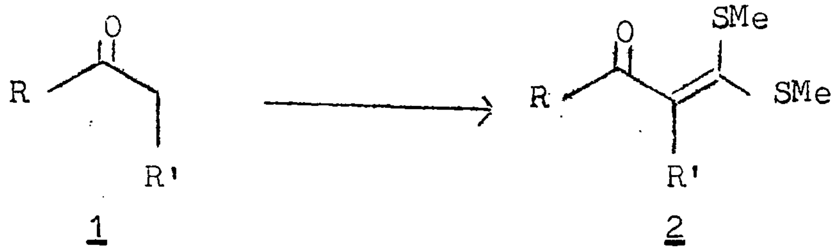
In the fifth chapter, a facile method for the conversion of the acetophenones to the corresponding methyl arylacetates has been developed. The method has been shown to be quite useful and general.

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 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



R = alkyl, aryl, etc

R'= H, alkyl, aryl

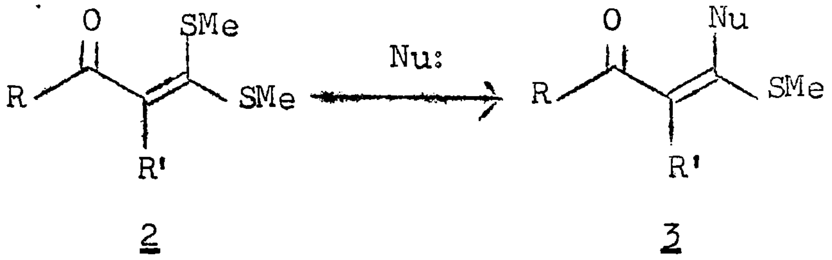
RR'= $-(CH_2)_n-$

Scheme 1

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

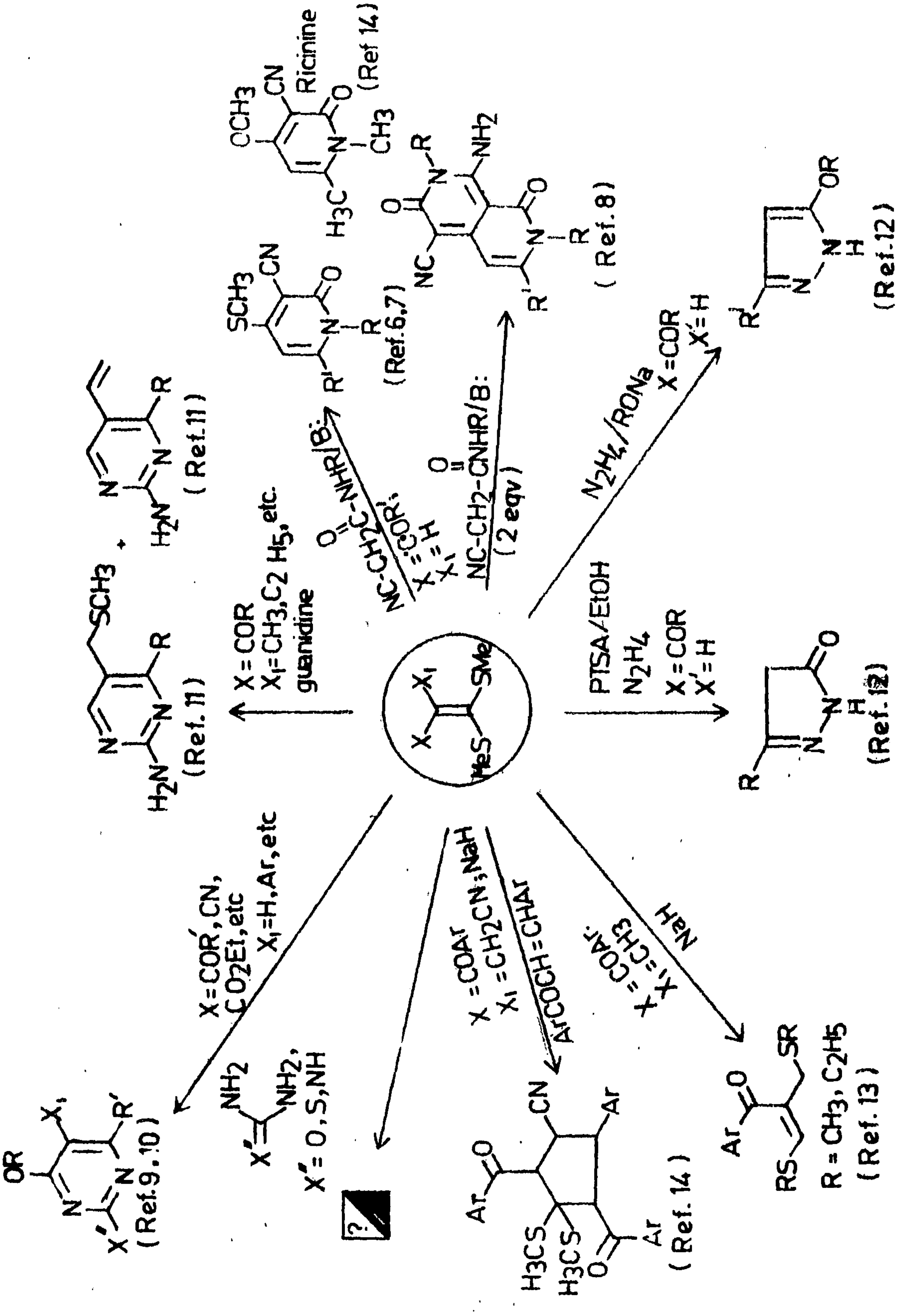


Nu: = amines

= active methylene compounds[15]

Scheme 3

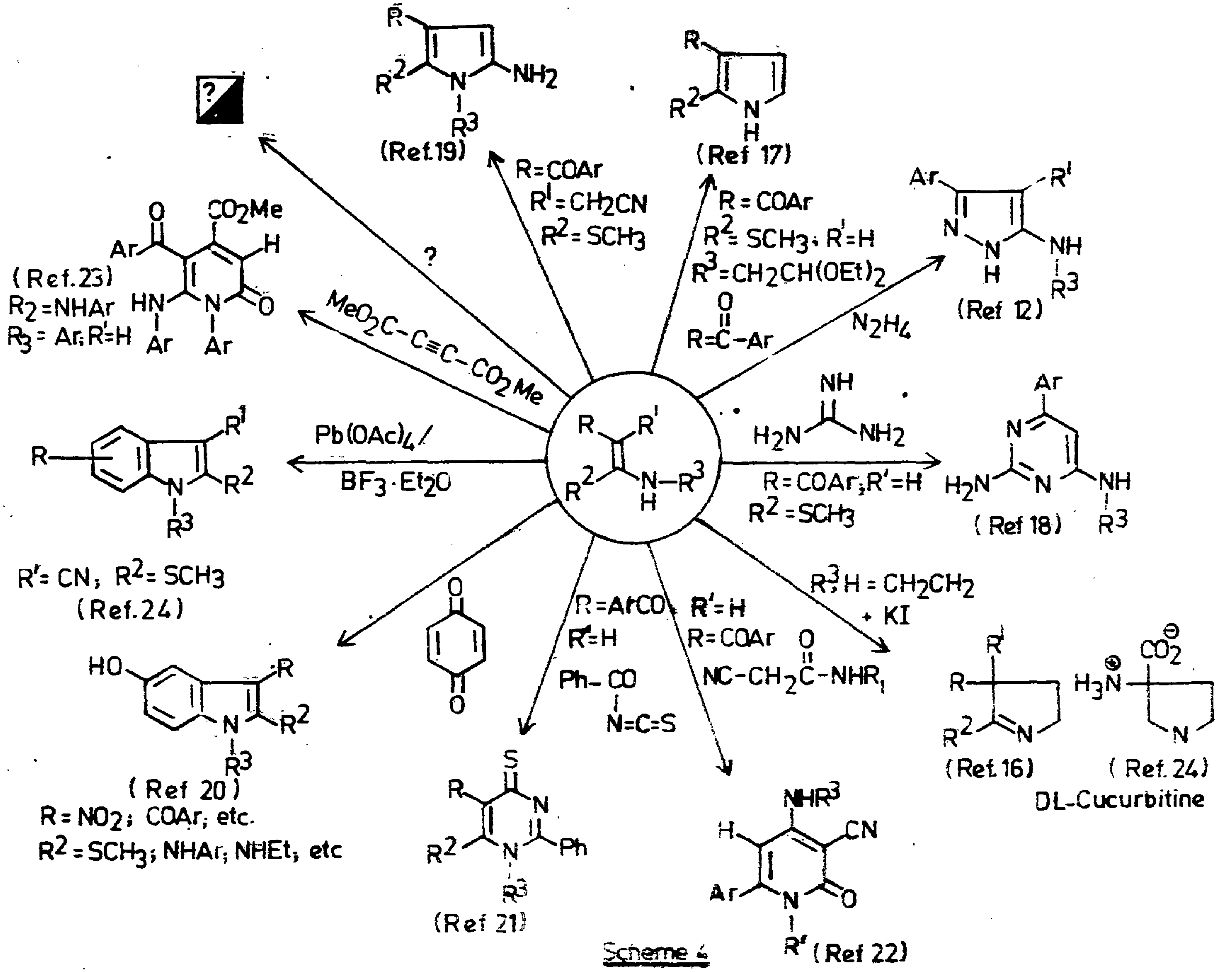
displacement can take place either to give the corresponding


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

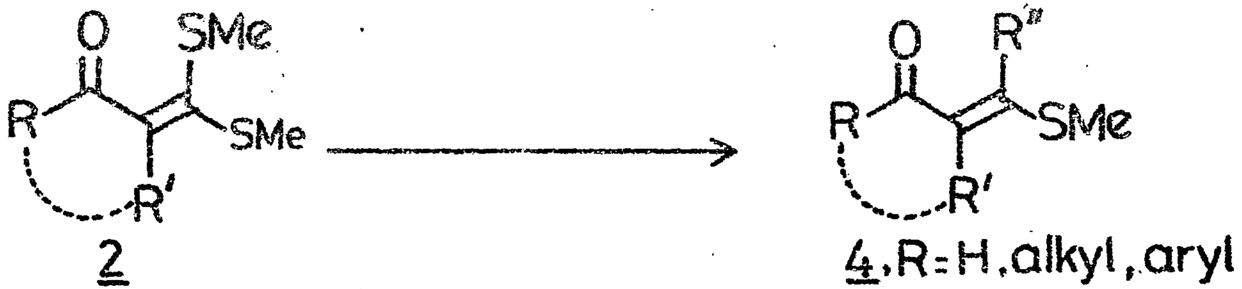
Scheme 2

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.

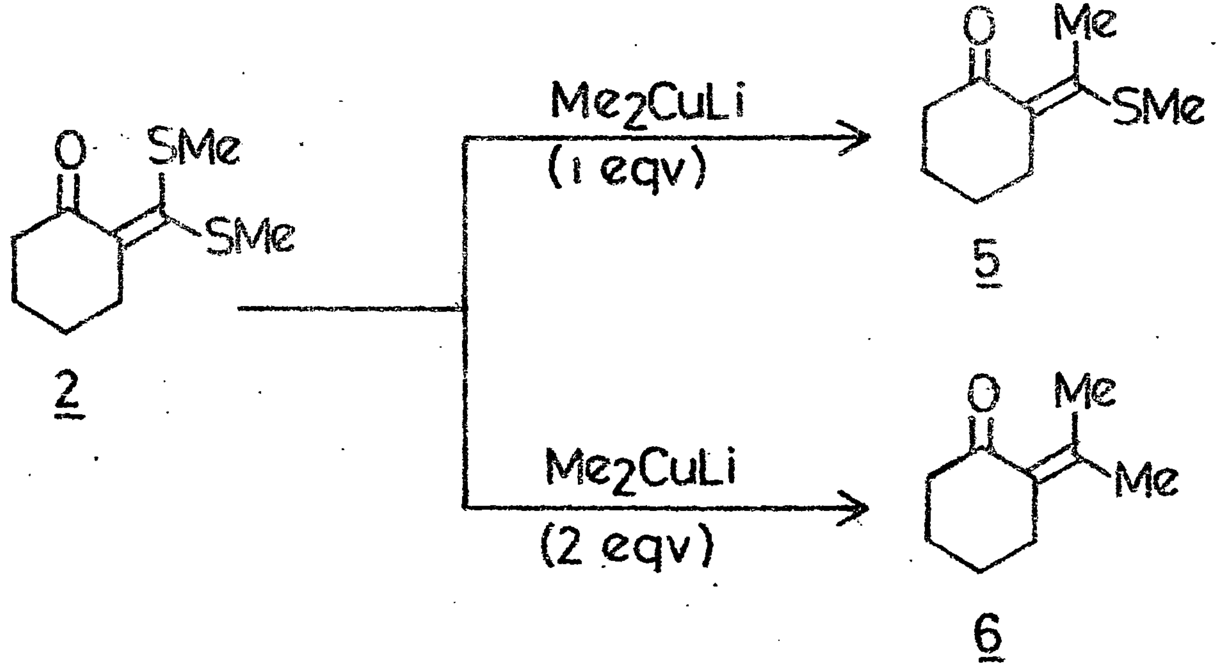
Recently, reductive studies on ketoketendithioacetals have been reported in the literature. The only reference on the partial reductive dealkylthiolation of 2 to the corresponding alkylthiomethylene ketones involves electrolytic reduction[25] of 1 ($R=C_6H_5$; $R'=H$). Although a variety of reagents have been developed in recent years which adds 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


?
R
R2
N
NH2
R3
(Ref.19)
R
R2
N
H
(Ref 17)
Ar
R'
N
N
H
NH
R3
(Ref 12)
R=COAr
R'=CH2CN
R2=SCH3
R=COAr
R2=SCH3; R'=H
R3=CH2CH(OEt)2
O
R=C-Ar
N2H4
?
O
CO2Me
Ar
H
(Ref.23)
R2=NHAr
R3=Ar; R'=H
HN
N
O
Ar
Ar
MeO2C-C≡C-CO2Me
NH
H2N
NH2
Ar
N
H2N
N
NH
R3
(Ref 18)
R=COAr; R'=H
R2=SCH3
R
R'
R2
N-R3
H
Pb(OAc)4/
BF3·Et2O
R
R1
R2
N
R3
R'=CN; R2=SCH3
(Ref.24)
R3H=CH2CH2
+ KI
R'
R
R2
N
(Ref.16)
H3N
CO2
N
(Ref.24)
DL-Cucurbitine
O
O
HO
R
R2
N
R3
(Ref 20)
R=NO2; COAr; etc.
R2=SCH3; NHAr; NHEt; etc
R=ArCO; R'=H
R'=H
Ph-CO
N=C=S
R=COAr
O
NC-CH2C-NHR1
S
R
N
R2
N
Ph
R3
(Ref 21)
NHR3
H
CN
Ar
N
O
R'
(Ref 22)

Scheme 4



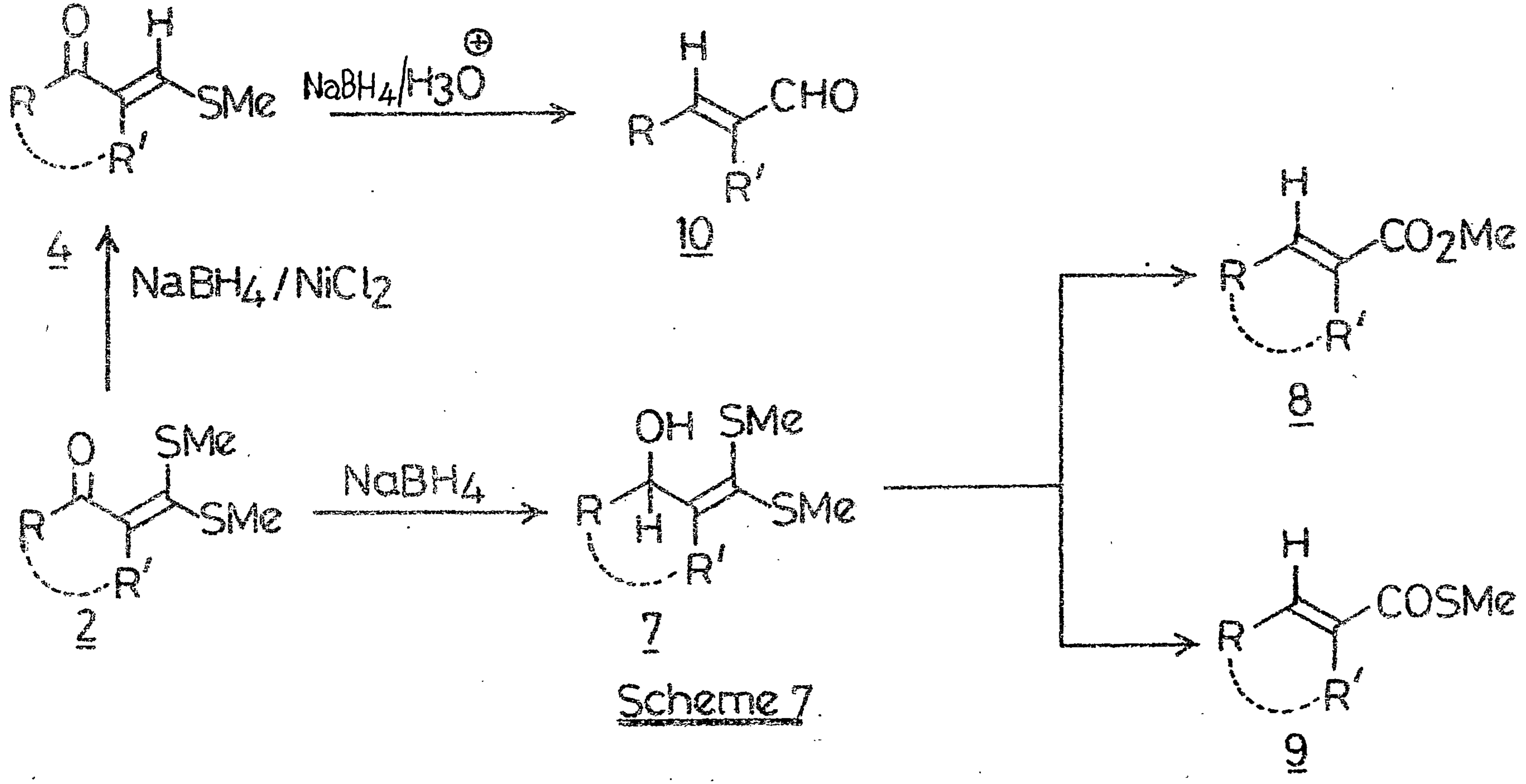
Scheme 5



Scheme 6

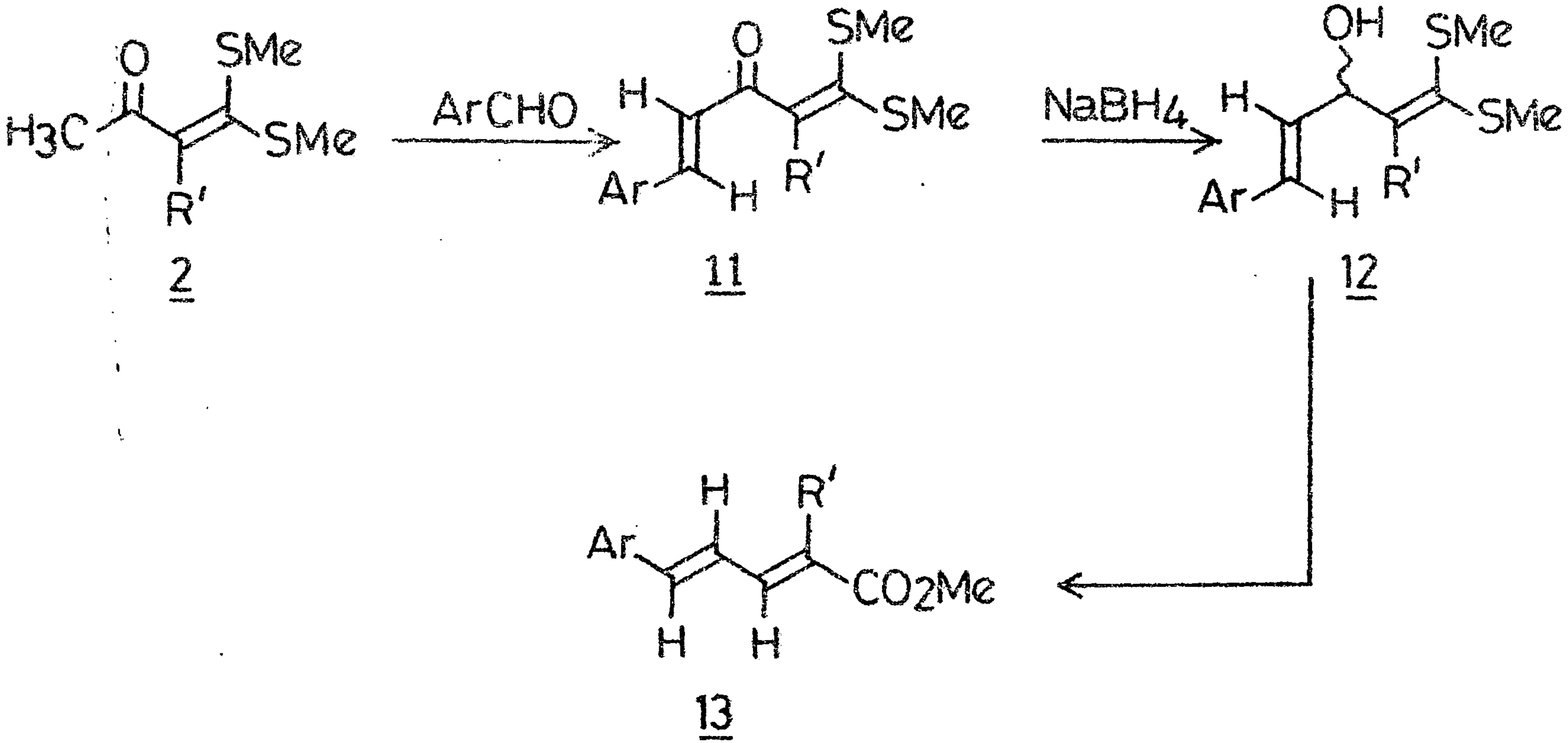
method for the conversion of 2 to 4 (R'=H). Several attempts using a mixture of sodium borohydride and transition metal halides were made to affect the conversion of 2 to 4 (R'=H) and it was found that the sodium borohydride/nickel chloride mixture was the most satisfactory combination. The importance 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-toluenesulfonic 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.


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

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, 11–13, R' = H or Me

Scheme 8

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CHAPTER II

PARTIAL REDUCTIVE DEMETHYLTHIOLATION OF KETOKETEN-S,S-ACETALS WITH SODIUM BOROHYDRIDE/NICKEL CHLORIDE : A NEW GENERAL METHOD FOR 2-METHYLTHIO-1-ALKENYL KETONES*

II. 1. INTRODUCTION

The thioalkyl group in the α-ketoketendithioacetals 1 and the alkylthiomethylene ketones 2 provide unique opportunity for devising new reactions leading to the synthetically useful organic intermediates. Both structures 1 and 2 (Scheme 1) possess 1,3-electrophilic centres as shown by the broken arrows. The thioalkyl groups in these compounds are activated by the electron withdrawing group in the β-position and can thus undergo facile displacement reactions with a wide variety of nucleophiles resulting in the formation of the corresponding mixed acetals. Similarly, if 1 or 2 is reacted with a suitable binucleophile, they behave like efficient 3-carbon fragments yielding the corresponding heterocyclic systems (Chapter I). The thiomethylene ketones 2 are useful synthetic intermediates in organic synthesis, besides being used as effective protecting groups.[1-9] There have been many publications in recent years concerning their synthetic utility rather than methods of their preparation.

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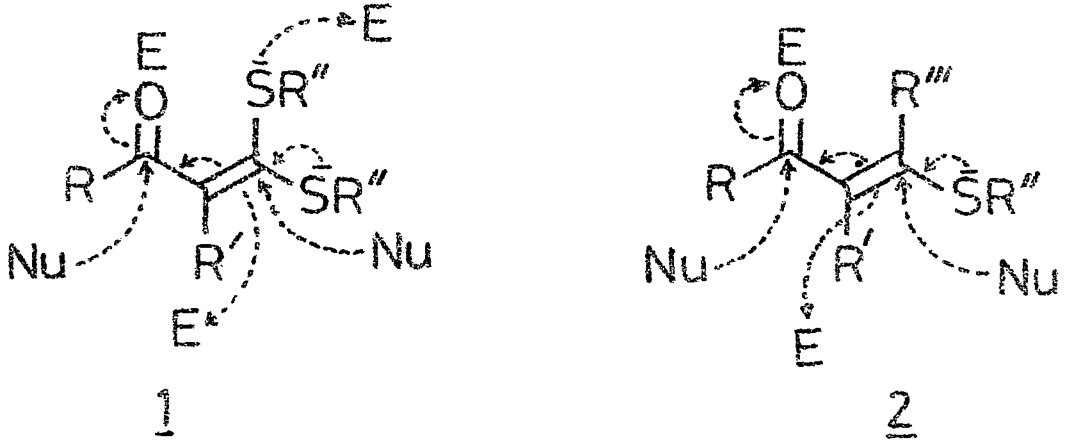


Scheme 1

In the course of our studies on ketoketendithioacetals, it was aimed at developing a method for the conversion of **1** to **2** (R'=H) by devising a route involving displacement of one of the thiomethyl groups by hydrogen. Such a method would provide a convenient synthetic entry to **2** from a wide variety of easily available active methylene compounds.

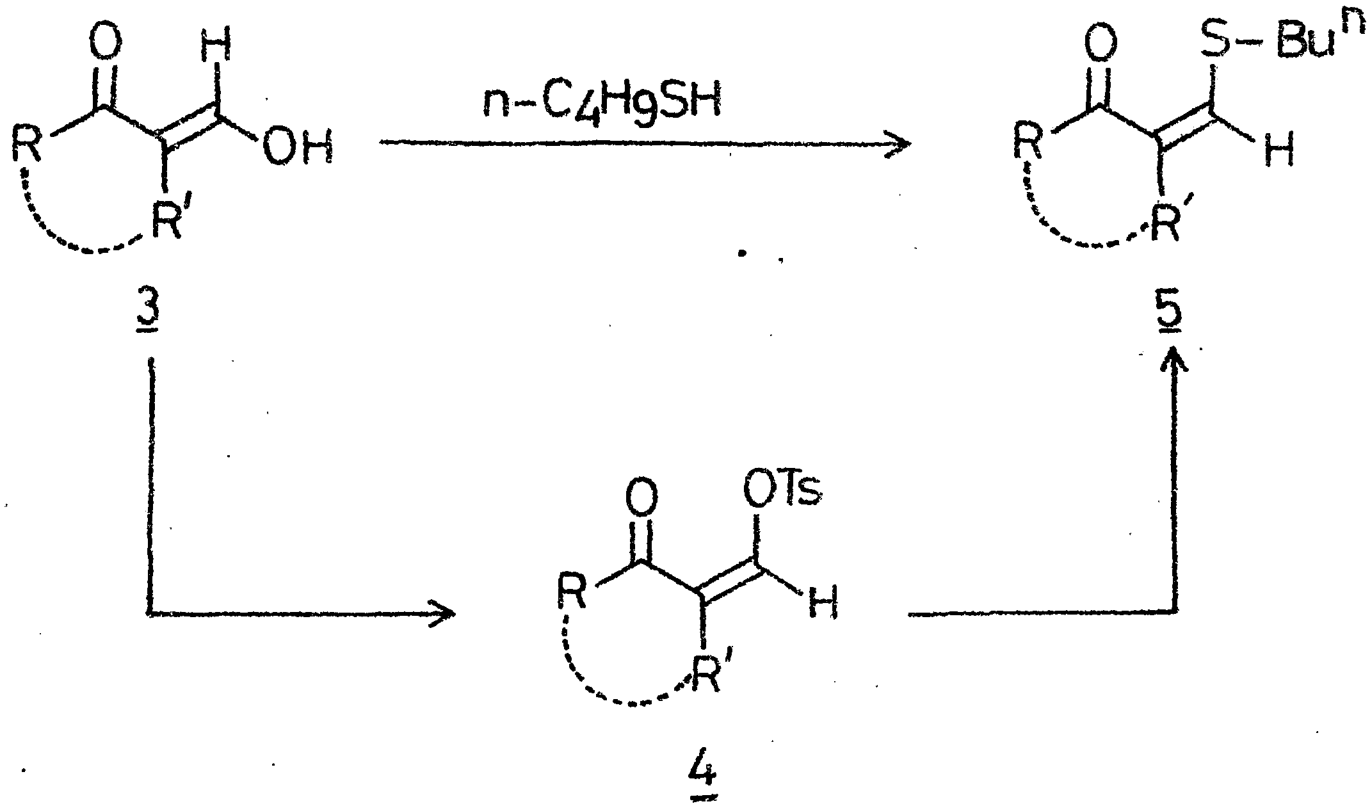
The reported methods for the preparation of alkylthiomethylene ketones are briefly discussed as follows:

II.1.1. Through Ireland's Formylation Method[1,10-12]

Ireland and co-workers have prepared the alkylthiomethylene ketones by reacting the active methylene ketones with ethyl formate to yield the corresponding formyl derivatives, which are subsequently converted into the corresponding thiomethylene ketones **5** either directly by reaction with *n*-butylmercaptan or through their tosylates (Scheme 2). This method has been used by these authors for the subsequent conversion of **5** to the corresponding α, β-unsaturated aldehydes.

II.1.2. Through 1,4-Addition of Alkyl/arylmercaptans to β-Ketoacetylenes[13-17]

β-Aroyl/acylacetylenes **6** undergo Michael addition with aryl/alkyl mercaptans in the presence of a mild base



Scheme 2

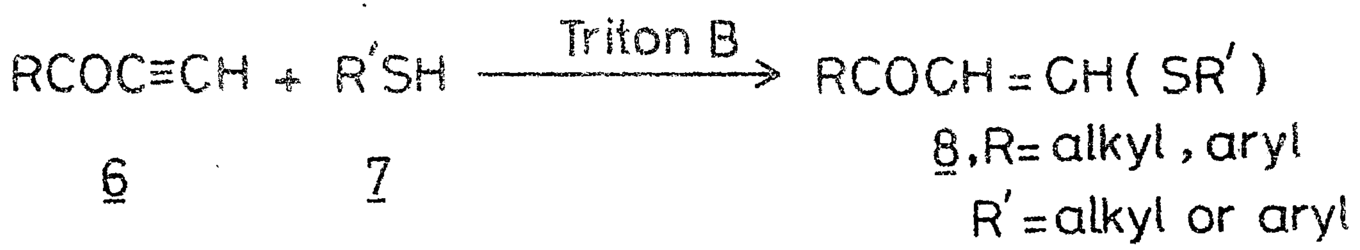
like Triton B (Scheme 3) to give the corresponding β-alkyl/arylthiomethylene ketones 8 in excellent yields. The method is quite frequently used for the preparation of 8.

II.1.3. Through Displacement Reaction of β-Chlorovinyl Ketones with Aryl Mercaptans[13,18]

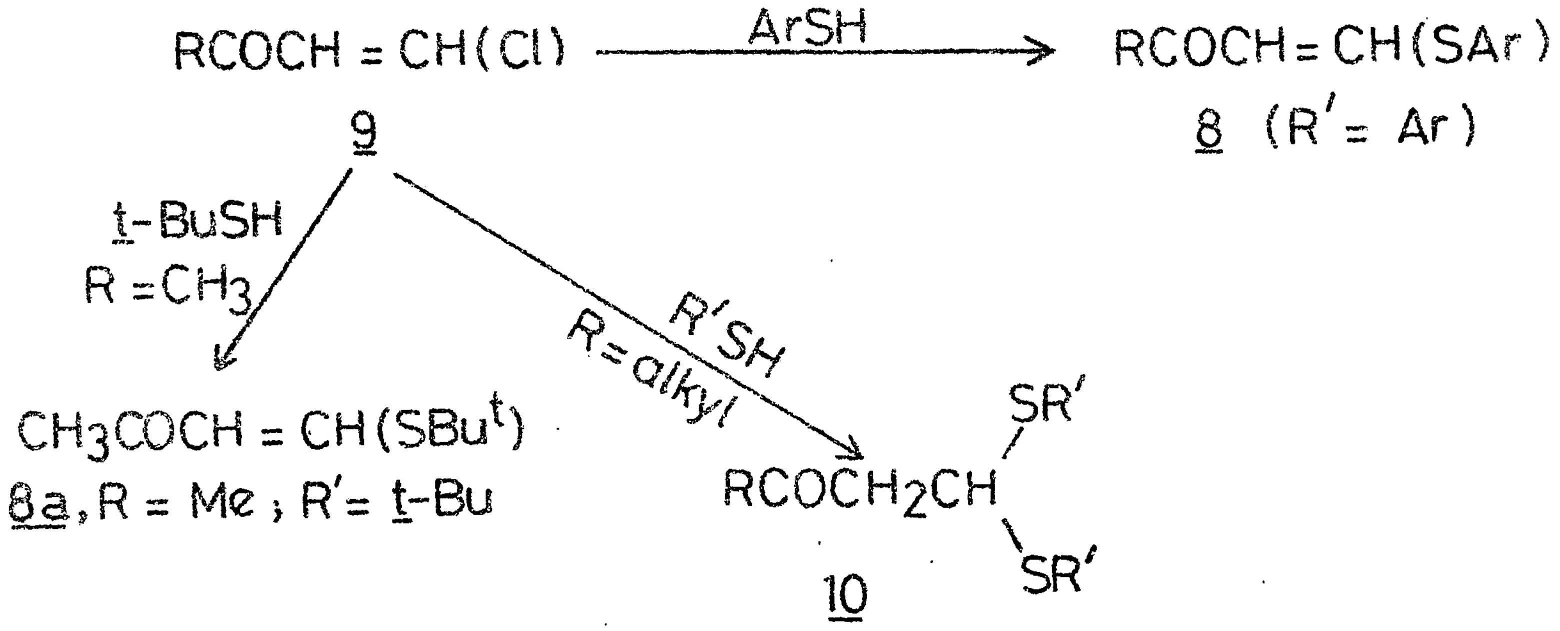
The β-chlorovinyl ketones 9 undergo displacement reaction with aryl mercaptans to give 8 (R'=Ar) in good yields. On the other hand the reaction of 9 with alkylmercaptan is reported to give the β-dithioacetals 10 (Scheme 4).[18] However, Akiyama[13] and co-workers have recently reported the preparation of β-t-butylthiomethyleneacetone 8 (R=Me; R'=t-Bu) by displacement reaction of 9 with t-butylmercaptan (Scheme 4).

II.1.4 Through Electrolytic Reduction of α-Ketoketen S,S-Acetals[19]

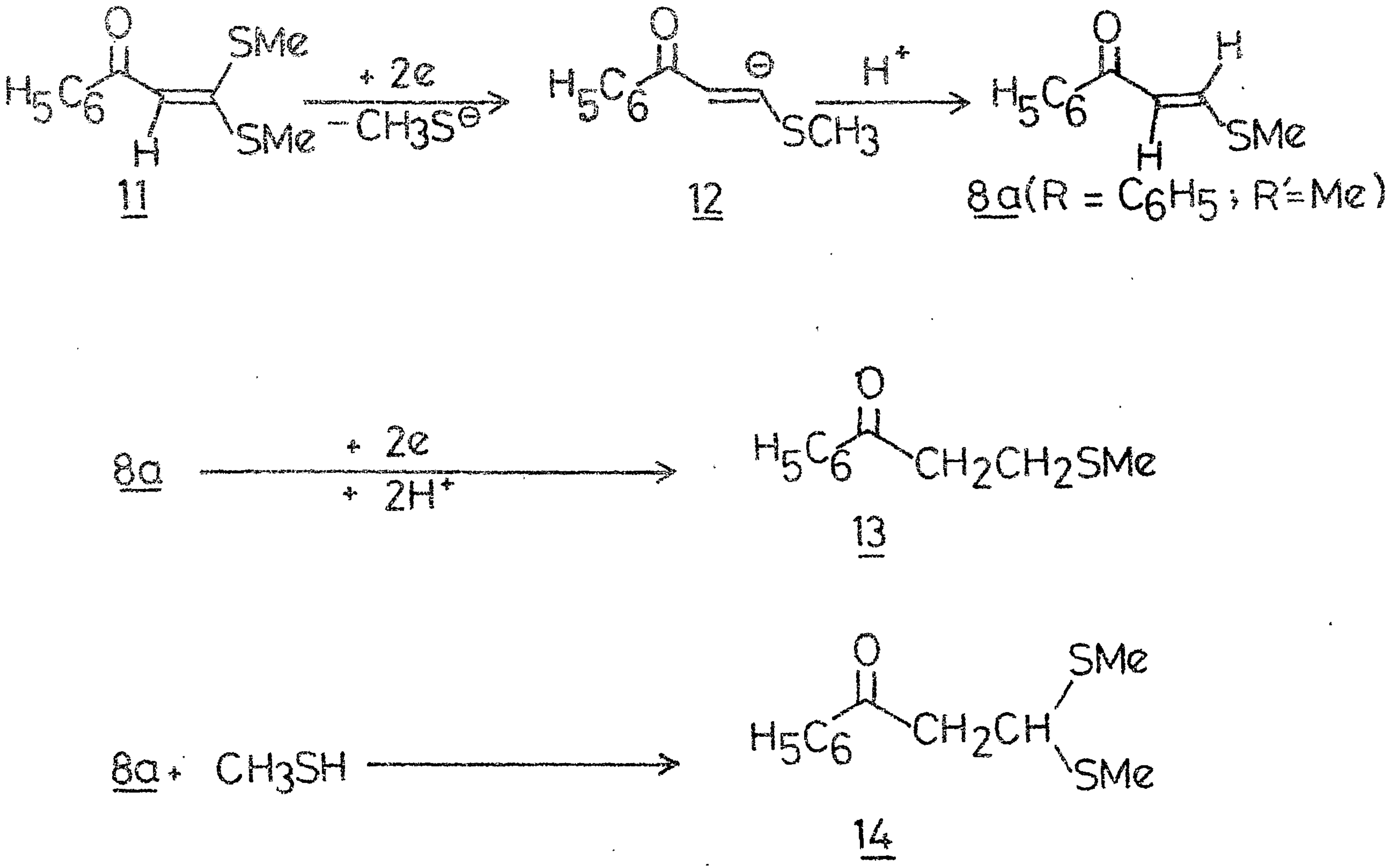
Rudorf and co-workers have reported the partial cleavage of the thiomethylene group under electrolytic reduction of 11, when the corresponding thiomethylene ketone 8a was formed in 64% yield (Scheme 5) through protonation of the intermediate carbanion 12. The authors however have not studied the generality of the reaction. The thiomethylene ketone 8a underwent further reduction to



Scheme 3



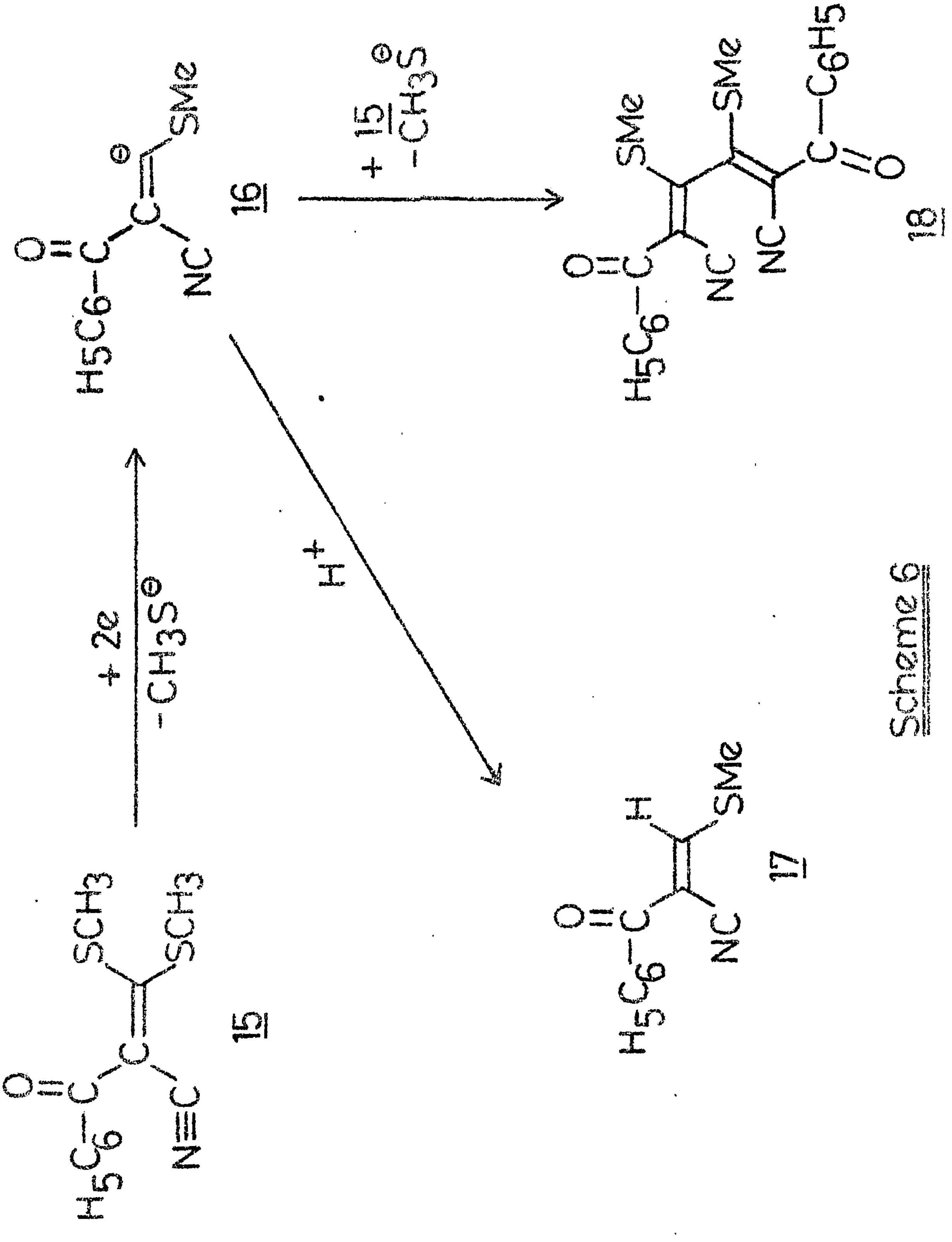
Scheme 4



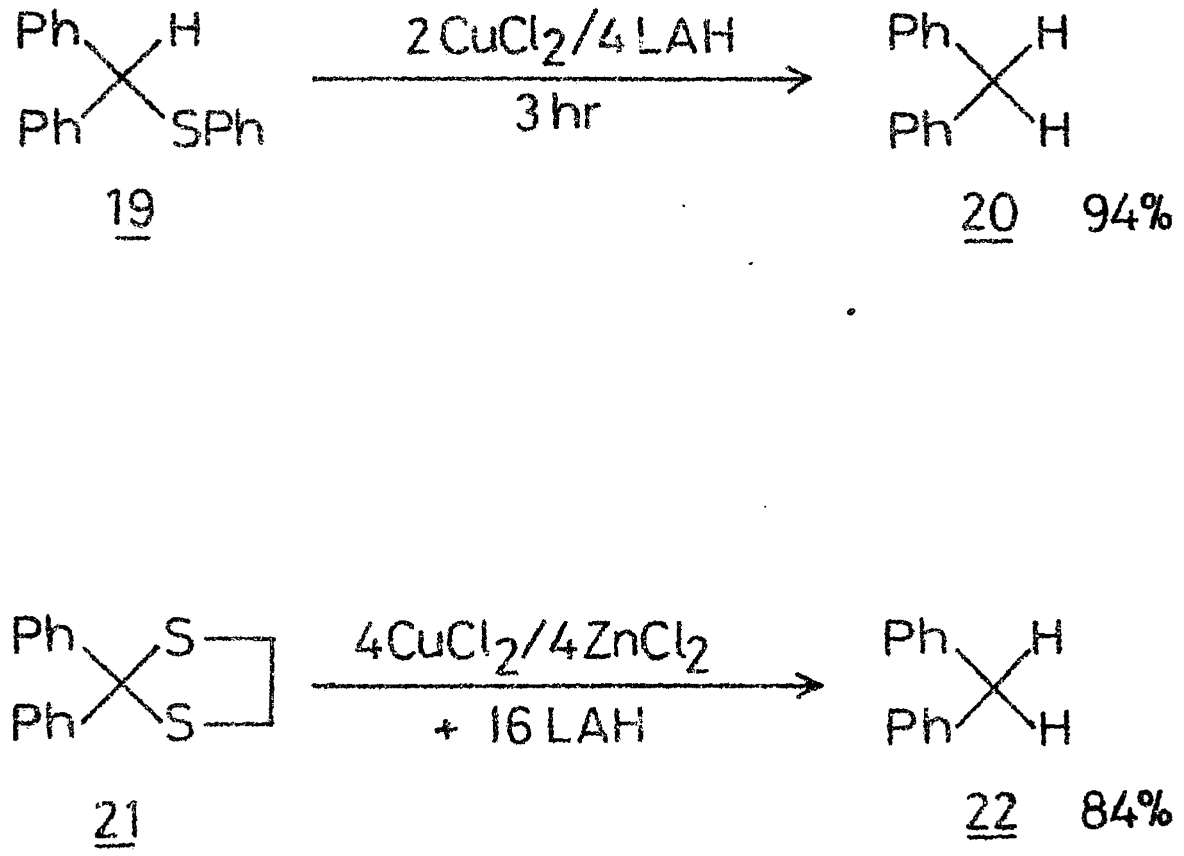
Scheme 5

give the corresponding saturated ketone 13 as well as the saturated dithioacetal 14 through Michael addition of the methylmercaptan on 8a. They further extended these reduction studies to 15, when they obtained 17 and 18 as formulated in Scheme 6.

Although the sulphides and thioacetals are not generally attacked by sodium borohydride[20] or lithium alluminium hydride, the application of these hydrides in combination with transition metal halides have been frequently used in organic synthesis to cleave the carbon sulphur bond selectively in recent years. Thus the saturated sulphide 19 (Scheme 7) is reported to undergo facile carbon-sulphur bond cleavage[21] in the presence of lithium aluminium hydride and copper (II) chloride to give the corresponding hydrocarbon 20 (Scheme 7) in 94% yield. Similarly 21 underwent complete reduction in the presence of lithium aluminium hydride and either copper (II) chloride or zinc (II) chloride to give the corresponding hydrocarbon 22 in 84% yield.[21] It has been suggested that the coordination of sulphur in 19 and 21 with copper (II) ion polarises the C-S bond and thus making it more susceptible to nucleophilic attack by hydride ion.[22] Similarly the course of reduction of 23 and 27 with sodium borohydride is changed in the presence of transition metal halides. Thus 23 undergoes 1,2-reduction with sodium

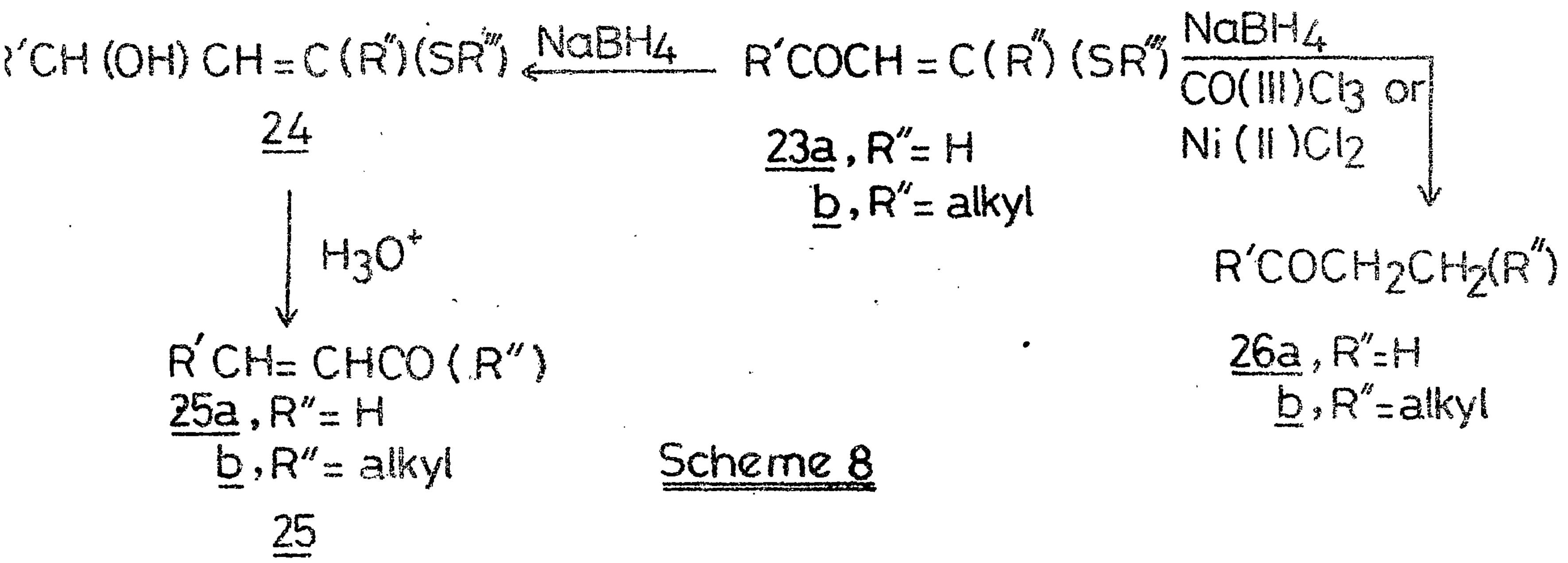


Scheme 6

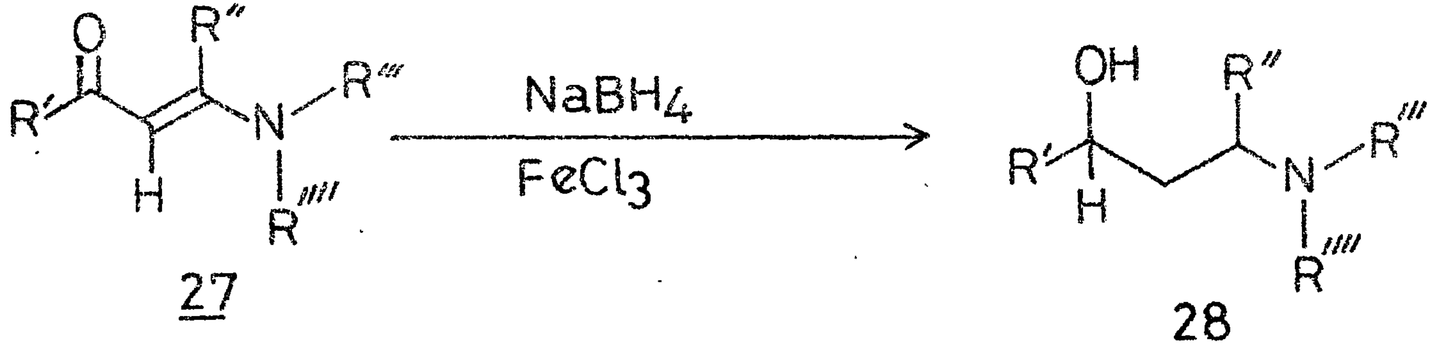

Ph
H
Ph
SPh
19
2 CuCl2/4 LAH
3 hr
Ph
H
Ph
H
20
94%
Ph
S
Ph
S
21
4CuCl2/4ZnCl2
+ 16 LAH
Ph
H
Ph
H
22
84%

Scheme 7

borohydride to give the carbinols 24 which on acid hydrolysis, were subsequently converted to the α,β-unsaturated aldehydes or ketones 25.[9-13,23,24] On the other hand, 23 yields products 26 via 1,4-reduction, regioselectively in the presence of sodium borohydride and cobalt (III) chloride or nickel (II) chloride[25] (Scheme 8). Similarly the β-dialkylaminoenone 27 also undergoes 1,4-reduction together with 1,2-reduction in the presence of sodium borohydride and ferric chloride (Scheme 9).[26-28] Brown[29] has studied the catalytic role of these transition metal halides in combination with sodium borohydride. These halides are shown to react rapidly with sodium borohydride in solution to give dark suspensions or precipitates, which are considered to be probably borides. Among the borides thus studied, the nickel boride has been extensively used for selective hydrogenation,[29-35] and as desulphurisation[36-40] catalyst, which has been found to be as active as Raney-nickel. Although the composition of the black material obtained by the reaction of borohydride with nickel (II) salts corresponds closely to Ni_2B, the X-ray powder defraction have shown it to be amorphous.[41] It has been suggested[36] that borohydride reduces the nickel (II) ion, which catalyses the hydrolysis of borohydride thus generating a large amount of hydrogen gas in the presence of finely divided nickel. The nickel so obtained has hydrogen adsorbed on its surface which is capable of reducing



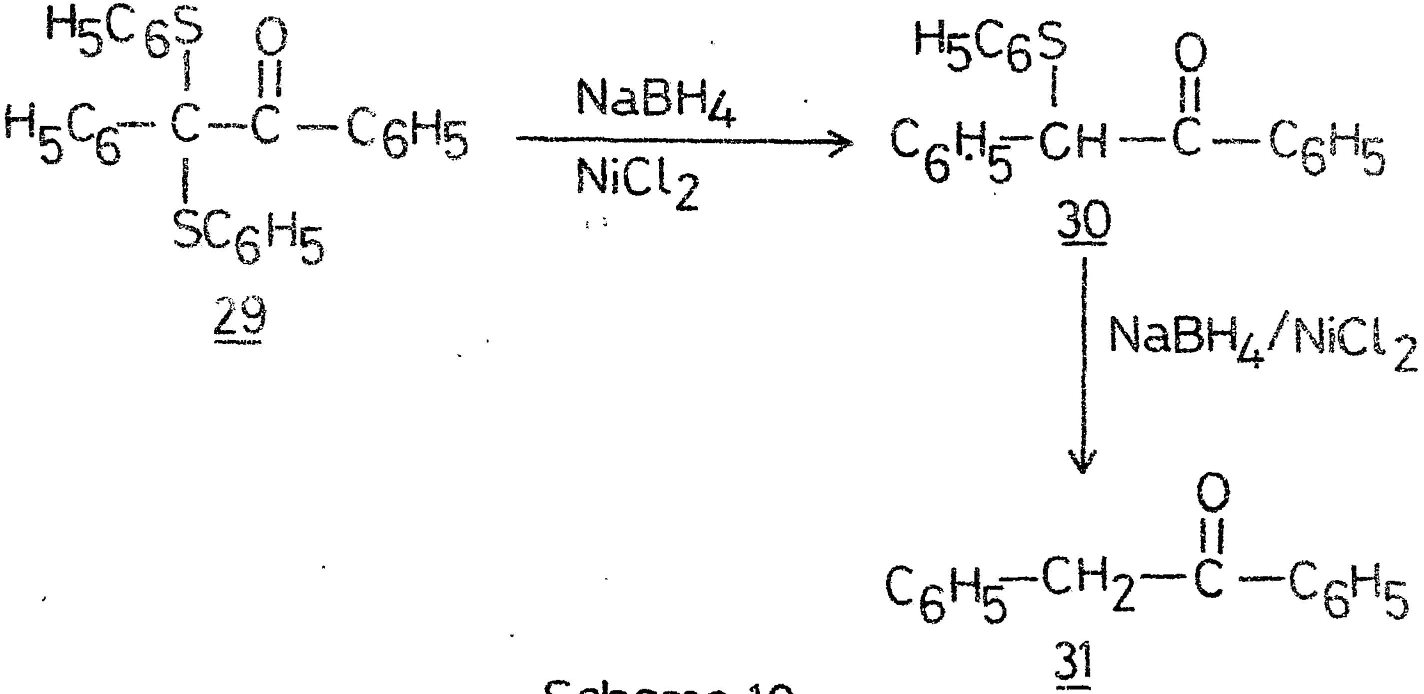
Scheme 8



Scheme 9

carbon-sulphur bonds. Its first use as desulphurising agent was reported in 1963[36] through the reduction of the mercaptan 29 to give 30 and 31 (Scheme 10). By varying the amount of nickel chloride it was possible to replace either one or both sulphur atoms in 29 by hydrogen to get exclusively 30 and 31 respectively. It has also been shown to be an effective reagent for desulphurisation of mercaptans,[37] sulphides[37] and sulphoxides[37] in yields comparable to those obtained by Raney nickel methods. It has been further shown that it is ineffective to cause desulphurisation of sulphones,[37] thus indicating a high degree of selectivity over Raney-nickel, which is known to cleave sulphones in high yields. In addition nickel boride[37] offers further advantages over Raney-nickel for efficient desulphurisation since, (1) it is more easily prepared than Raney-nickel, (2) it is completely non-pyrophoric and is less hazardous than Raney-nickel, (3) it can be generated in exact stoichiometric amounts by taking the correct weight of sodium borohydride and nickel chloride, thus ensuring control on the selectivity which is not otherwise the case when Raney-nickel is used in similar reactions.

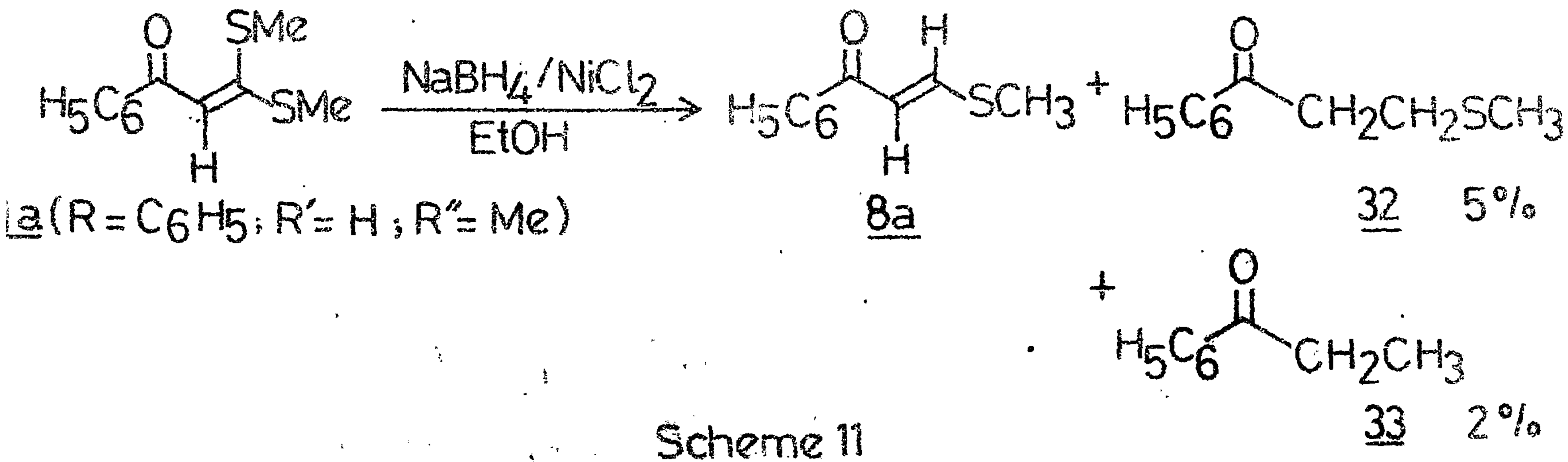
It is therefore apparent that the nickel boride is much more efficient, selective and safe as compared to Raney-nickel and should be a suitable choice as a reagent in undertaking selective demethylthiolation of ketoketendithioacetals where such selectivity can be used to the advantage.



Scheme 10

II.2. RESULTS AND DISCUSSIONS

In principle, a large variety of ketoketendithioacetals can be subjected to selective desulphurisation under one of the optimised conditions using a mixture of sodium borohydride and transition metal halides, preferably nickel (II) chloride. A few ketoketen S,S-acetals were selected to study the scope and generality of the method and they were prepared as described. They were fully characterized by spectroscopic and analytical methods for their structural authenticity. Since the sodium borohydride/nickel chloride combination was proved to be an efficient and selective desulphurisation agent, the same combination was studied under different conditions by varying the concentrations of nickel chloride, so that the conditions for maximum yields of the demethylthiolated products were achieved. It is apparent (Table 1) that a maximum yield of 8a (62%) was obtained when the nickel chloride and sodium borohydride were used in a 1:1 ratio, using ethanol as the solvent. Thus in one of the experiments when 1a($R=C_6H_5$, $R'=H$, $R'=Me$) was refluxed with a mixture of 1:1 of sodium borohydride and nickel chloride in ethanol for 24 hr, work up of the reaction mixture showed three spots (TLC) with one major product while the other two were in traces. The first fraction which was obtained in 3% yield was identified as corresponding to propiophenone (33). The second fraction which was obtained

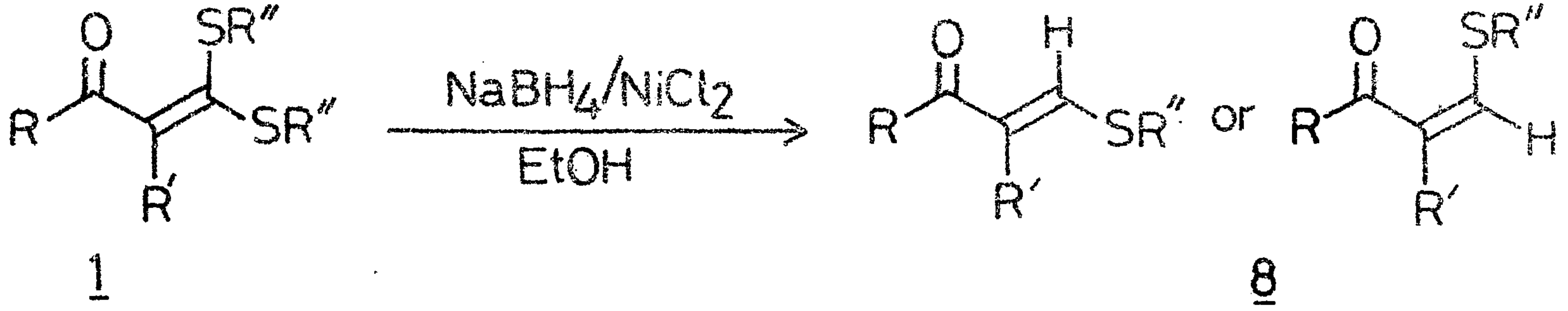


Scheme 11

Expt.No	$NaBH_4$(mole)	$NiCl_2$(mole)	1a(mole)	Yield %
1	0.15	0.025	0.75	20
2	0.1	0.04	0.03	42
3	0.1	0.06	0.03	51
4	0.1	0.08	0.03	62
5	0.1	0.1	0.03	62

Table 1

in 5% yield was identified as β-methylthiopropiophenone 32, the structure of which was confirmed by its analytical and spectral data. Both the compounds 32 and 33 were found to have identical values of analytical and spectral data with those reported in the literature (IR, NMR, Mass). The major fraction which was obtained in 62% yield was identified as *E*-3-methylthio-1-phenyl-2-propene-1-one (8a). It showed a molecular ion peaks at M^+ 178 and was analysed for $C_{10}H_{10}OS$. Its IR spectrum showed a strong band at 1643 cm^{-1} due to conjugated carbonyl group. Its structure was further confirmed by its ^1H-NMR spectrum ($CDCl_3$). The singlet at δ 2.32(3H) was assigned to the S-methyl protons and the doublet at δ 6.70 (1H, J=15 Hz) was assigned to the vinylic protons *cis*- to the methylthio group, while the other olefinic proton appeared buried with the aromatic protons at δ 7.4 (3H) and 7.7-7.9 (3H). Thus the geometry of 8a was assigned as *E*-isomer on the basis of its coupling constant (15 Hz). Similarly under identical reaction conditions the mercaptals 1b-e (Scheme 12), derived from the corresponding acetophenones gave the respective thiomethylene ketones 8b-e in 45-64% overall yields. A few higher homologs of the acetophenone dithioacelals (1f-h) also gave the corresponding thiomethylene ketones 8f-h in 56-66% overall yields. The physical and analytical data of these compounds were in conformity with their structures. The geometry of these compounds (8a-e) was found to be exclusively in favour of one



1, 8a, R = C_6H_5, R′ = H, R″ = CH_3

b, R = p-Me–C_6H_4, R′ = H, R″ = CH_3

c, R = p-Cl–C_6H_4, R′ = H, R″ = CH_3

d, R = p-EtO–C_6H_4, R′ = H, R″ = CH_3

e, R = p-MeO–C_6H_4, R′ = H, R″ = CH_3CH_2–

f, R = p-Me–C_6H_4, R′ = CH_3, R″ = CH_3

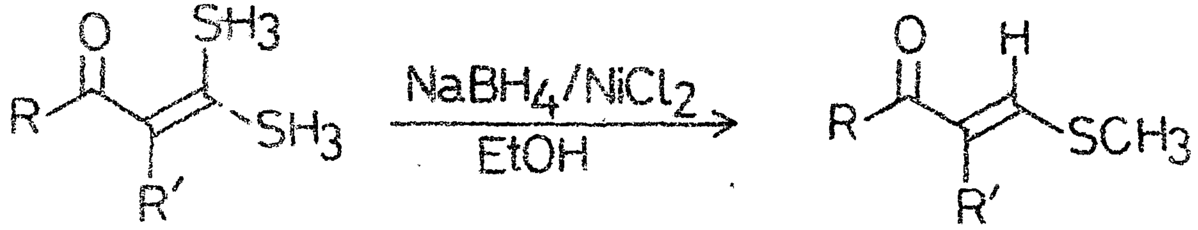
g, R = C_6H_5, R′ = C_2H_5, R″ = CH_3

h, R = C_6H_5, R′ = n-Pr, R″ = CH_3

Scheme 12

isomer and no mixture of stereo isomers was obtained in any of the experiments. Thus the reduction is not only regiospecific but also highly stereoselective (see table for geometry). Also the acetal 1i gave the corresponding thiomethylene ketone 8i (Scheme 13) exclusively as the E-isomer (IR, NMR, Mass) in 85% yield. The analogous compound 8a (Scheme 4) which is used in polyolefinic synthesis[7,13] was previously prepared by the Michael addition of t-butyl mercaptan with acetylacetylene involving difficult starting materials with comparatively low yields. Besides, the compound 8a was formed as a mixture of cis- and trans-isomer.[13] The vinylchloride method, although it gave exclusively the trans-isomer, the preparation of the acetylvinyl chloride itself is not so easy as for the preparation of 1i. The compound 8i being an important intermediate in olefinic synthesis, the present method for its preparation therefore, should be the method of choice. Besides the method is further extendable to the preparation of the thiomethylene ketone 8j obtained from the mercaptan 1j. It may be noted here that the preparation of 8j cannot be so easily achieved by extending the methods adapted by other workers.[7,13] The present method is therefore superior for it provides liberal structural flexibility for the synthesis of these important intermediates.

When the method was extended to the cyclic keten S,S-acetals 1k-1 derived from the respective tetralone and



1 i-j

8 i-j

1, 8 i, R = CH_3 ; R′ = H
j, R = CH_3 ; R′ = CH_3

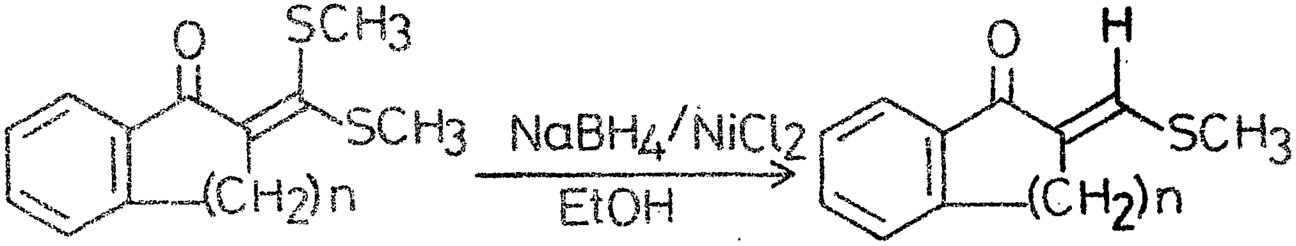
Scheme 13

benzsuberone, they also yielded the corresponding thiomethylene ketones 8k and 8l in 58% and 69% yields respectively (Scheme 14). Their analytical and spectral data are in conformity with the assigned structures E(Table). Also, under similar reaction conditions, 1m gave 8m with Z-geometry as confirmed from its analytical and spectral data (Table). Similarly the cyclopentanone and cyclohexanone acetals 1n and 1o gave the corresponding thiomethylene ketones 8n and 8o (Scheme 16) exclusively as their E-isomers in 66% and 75% yields respectively. Their analytical and spectral data are described in the Table.

The method is shown to be general and stereoselective. In each case the product is either E-or Z-isomer and a mixture of both was not observed in any of the experiments. The mechanism governing these highly stereoselective transformation is yet to be cleared although desulphurisation appears to be due to nickel boride formation rather than hydride attack. The geometry of all the compounds were assigned on the basis of their NMR coupling constants of the vinyl protons as described in the table.

II.3. CONCLUSION

In conclusion it may be summarised that (1) a method of preparative importance for methylthiomethylene ketones (8) has

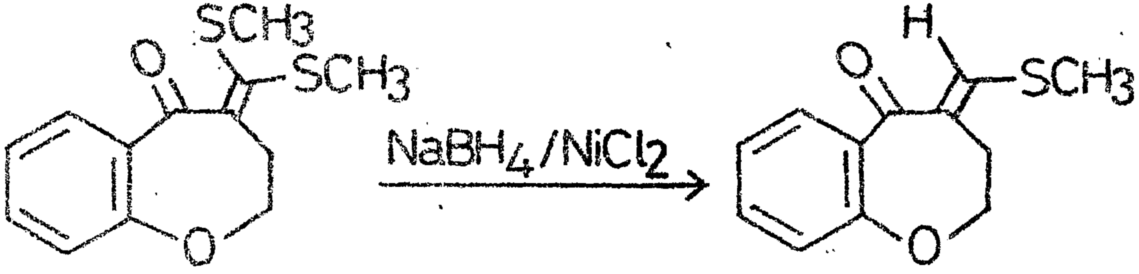


1k–l

8k–l

1, 8k, n = 2
l, n = 3

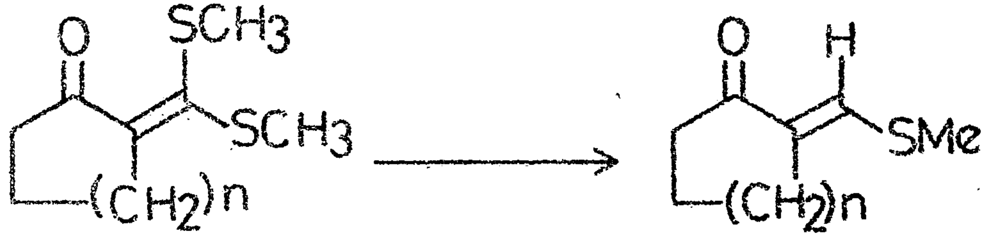
Scheme 14



1m

8m

Scheme 15



1n – 1o

8n , 8o

1, 8n, n = 1
o, n = 2

Scheme 16

been formulated from the easily available ketones via the α-ketoketen S,S-acetals (2) the method is shown to be flexible for the liberal structural variations, where other methods either fail or result in poor yields of the desired products (3) the reaction is stereoselective and (4) the method is suitable for the synthesis of both S-methyl and its higher homologs, whereas the existing methods use only high boiling mercaptans, since the methylmercaptan is a gas which is difficult to handle.

II.4. EXPERIMENTAL.

Melting points were determined on a Boetius (German) apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 297 spectrophotometer. The NMR spectra were recorded on a varian EM-390, 90 MHz spectrometer using TMS as internal standard and the chemical shifts are recorded as δ (ppm). Mass spectra were recorded on Hitachi RMU-6e mass spectrometer fitted with a direct inlet system.

The Starting Materials

The commercial samples of acetophenone, p-methylacetophenone, p-chloroacetophenone, p-methoxyacetophenone, p-ethoxyacetophenone, p-methylpropiophenone, butyrophenone, valerophenone, acetone, tetralone, cyclopentanone and cyclohexanone were purified before use.

Benzsuberone, b.p. 138-39° (12 mm)[42] and 3,4-dihydro-1-benzoxepin-5(2H)-one, b.p. 106°(2 mm)[43] were prepared according to the reported procedures.

The following previously reported keten S,S-acetal: 3,3-bis(methylthio)-1-phenyl-2-propen (1a), , m.p. 93°;[44] 3,3-bis (methylthio)-1-(p-methylphenyl)-2-propen-1-one(1b), m.p. 104-5°;[44] 3,3-bis(methylthio)-1-(p-chlorophenyl)-2-propen-1-one(1c), m.p. 109-10°;[44] 3,3-bis(methylthio)-1-(p-ethoxyphenyl)-2-propen-1-one(1d), m.p. 135-36°;[45] 3,3-bis(ethylthio)-1-(p-methoxyphenyl)-2-propen-1-one (1e) m.p. 65-66°;[45] 3,3-bis (methylthio)-1-(p-methylphenyl)-2-methyl-2-propen-1-one (1f) b.p. 185-90° (1 mm);[46] 3,3-bis(methylthio)-1-phenyl-2-ethyl-2-propen-1-one (1g) b.p. 192° (16 mm);[47] 3,3-bis(methylthio)-1-phenyl-2-(n-propyl)-2-propen-1-one (1h) b.p. 184° (10 mm);[47] 4,4-bis(methylthio)-3-buten-2-one (1i), m.p. 66-67°;[48] 4,4-bis (methylthio)-3-methyl-3-buten-2-one-1-one (1j) b.p. 68° (0.1 mm);[48] 2-[bis(methylthio) methylene]-1-tetralone (1k) m.p. 58°;[47] 2-[bis(methylthio) methylene]-1-benzsuberone (1l) m.p. 61-62;[49] 4-[bis(methylthio) methylene]-3,4-dihydro-1-benzoxepin-5-(2 H)one (1m) m.p. 78°;[49] 2-[bis(methylthio) methylene]-cyclopentanone, b.p. 118° (1 mm);[50] 2-[bis(methylthio) methylene]-cyclohexanone (1n) b.p. 123-24° (1 mm)[50] were prepared by the general method described below.

General method for the preparation of keten S,S-acetals using sodium t-butoxide:

A mixture of the ketone (0.2 mol) and carbon disulphide (0.2 mol) was added to a well stirred and suspension of sodium *t*-butoxide (0.4 mol) in dry benzene (170 ml) and the reaction mixture was allowed to stand at room temperature for 5-6 hr. Methyl iodide (0.4 mol) or ethyl iodide (0.4 mol) (**1e**) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand (5 hr) at room temperature with occasional shaking and then refluxed on a water bath for 0.5-1 hr. The mixture was poured on crushed ice and the bezene layer was separated. The aqueous portion was extracted with benzene and the combined extract was washed with water, dried (Na_2SO_4) and concentrated. The products thus obtained were purified by crystallisation or by column chromatography.

General method for the preparation of 2-methylthio-1-alkenyl ketones (Method A):

To a stirring suspension of nickel chloride hexahydrate (0.16 mol) in ethanol (150 ml), sodium borohydride (0.2 mol) was slowly added (15 min). Fresh addition was made only when effervescence due to evolution of hydrogen had stopped. The mixture was further stirred for 10 min and a solution of the keten S,S-acetal 1 (0.06 mol) in ethanol (50 ml) was added to the black suspension and the mixture was further stirred at room temperature for 10 min. It was then heated under reflux in an oil bath with stirring (9-36 hr, Table II), until the starting material has disappeared completely (TLC). The mixture was then filtered hot through a sintered funnel and the black residue was washed with boiling chloroform (3 x 200 ml). The combined filtrate was washed with water (2 x 300 ml), the organic layer dried with sodium sulphate and evaporated to give a dark brown viscous liquid which was then purified by column chromatography. Elution with hexane/benzene (9:1) for 8a-g, 8n-o or hexane/ethylacetate (99:1) for 8h-n yielded yellow viscous liquids or pale yellow crystalline solids. In a few cases (8a, 8f-j and 8o), the liquids were further purified by distillation under vacuum for microanalysis.

In some cases (8b, 8i, 8n-o), ethanol from the reaction mixture after refluxing was removed under reduced pressure and the slurry was directly charged into a chromatography column (Method B). Elution with hexane/ethylacetate (95:5) gave the corresponding 8b, 8i, 8m and 8o in higher yields (Table) (TLC single spot, N.M.R.

showed 99% purity), although the products were darker in colour.

Various experiments to get the optimum yields of 8a were also carried out according to the above general procedure by changing the proportions of sodium borohydride and nickel chloride (Table 1). The spectral and analytical data of various alkylthiomethylene ketones (8a-h) prepared by the above general procedure is given in Table 2 and 3 respectively. The data for other compounds (8i-8o) are given below:

E-4-methylthio-3-buten-2-one (8i): was prepared similarly by the above general method (refluxing time 11 hr). Work up of the reaction mixture yielded 8i as pale yellow oil, yield 3.5 g (85%) (TLC single pot); distillation under vacuum gave 65% of 8i b.p. 56°/1 mm. IR(Nujol): 1690 (C=O) cm^{-1}, M^+(Mass): 116; NMR (CCl_4); δ 2.15 (s, 3H, $-CH_3$); 2.33 (s, 3H, $-SCH_3$); 5.90 (d, 1H, J=15Hz), olefinic); 7.50 (d, 1H, J= 15 Hz, olefinic); (Found: C, 51.43; H. 6.45; Calc. for C_5H_8OS (116.2): C, 51.63, H. 6.88. The viscous liquid solidifies on cooling, m.p. 22°.

Z-4-methylthio-3-methyl-3-buten-2-one (8j) was similarly obtained as pale yellow needles (alcohol), (reflux time 9 hr); yield 3.7 g (67%), m.p. 21°, M^+(Mass): 204; IR(Nujol):

1685 (C=O) cm^{-1}; NMR (CCl$_4$): δ 2.13 (s, 3H, -C$\underline{H}_3$); 2.30 (s, 3H, -SC$\underline{H}_3$); 2.28 (s, 3H, -C$\underline{H}_3$); 6.15 (s, 1H, olefinic); (Found: C, 55.03; H, 7.48; Calc. for $C_6H_{10}OS$ (130) : C, 55.38, H, 7.69.

E-2-(Methylthiomethylene) tetralone (8k) was obtained as pale yellow solids (reflux time 9 hr), yield 2.3 g (58%), m.p. 68°; M$^+$(Mass): 204; IR(Nujol): 1660 (C=O) cm^{-1}; NMR (CCl$_4$): δ 2.48 (s, 3H, SC$\underline{H}_3$); 2.80 [A$_2$B$_2$, q, 4H, -(C$\underline{H}_2$)$_2$-]; 7.0 - 7.4 (m, 3H, arom); 7.51 (s, 1H, olefinic); 7.9 (m, 1H, arom); (Found: C, 70.72; H, 5.91, Calc. for $C_{12}H_{12}OS$ (204.3); C, 70.48; H, 5.87.

E-2(Methylthiomethylene) benzosuberone (8l) was isolated as pale yellow thick viscous liquid (reflux time 10 hr); yield 1.2 g (57%); M$^+$(Mass): 218; IR (neat): 1675 (C=O) cm^{-1}; NMR (CCl$_4$): δ 1.88 [A$_2$B$_2$, 2H -(C$\underline{H}_2$)-]; 2.25 [br t, 2H, -(C$\underline{H}_2$)-]; 2.40 (s, 3H, -SC$\underline{H}_3$); 2.71 [t, 2H, -(C$\underline{H}_2$)-]; 6.9 - 7.6 (m, 5H, arom + olefinic).

E-4(Methylthiomethylene)-3-4-dihydro-1-benzoxepin-5(H)one (8m) was isolated as a pale yellow thick viscous oil (reflux time 12 hr); yield 2.5 g (57%); M$^+$(Mass) 220; IR (neat): 1650 (C=O) cm^{-1}; NMR (CCl$_4$): δ 2.45 (s, 3H, -SC$\underline{H}_3$); 2.60 [t, 2H, -(CH$_2$)-]; 4.15 [t, 2H, -(C$\underline{H}_2$)-]; 6.7 - 7.1 (m, 2H, arom); 7.5 - 7.8 (m, 2H, arom); (Found;

C, 65.78; H, 5.35; Calc. for $C_{12}H_{12}O_2S$ (220.3); C, 65.36; H, 5.44.

E-2-(Methylthiomethylene) cyclopentanone (8n) was isolated as pale yellow soids (reflux time 15.5 hr); m.p. 47-8°; yield 2.8 g (66%); 4.3 g (75%) by method B ; M^+(Mass) 142; IR(Nujol); 1705 (C=O) cm^{-1}; NMR (CCl_4): δ 1.6-2.5 [m, 6H, $-(CH_2)_3-$]; 2.45 (s, 3H, $-SCH_3$); 7.10 (t, 1H, J=1.5 Hz, olefinic); (Found: C, 60.10; H, 7.54; Calc. for $C_7H_{10}OS$ (142.2): C, 59.07; H, 7.3.

E-2-(Mythylthiomethylene) cyclohexanone (8o) was isolated as a pale yellow oil (reflux time 10 hr), b.p. 65-97°/1 mm; yield 2.8 g (62%); [3.2 g (72%) by method B]; M^+(Mass) 156; IR (neat): 1712 (C=O) cm^{-1}; NMR (CCl_4); δ 1.5-2.0 [m, 4H, $-(CH_2)_2-$]; 2.0-2.6 [m, 4H, $-(CH_2)_2-$]; 2.45 (s, 3H, $-SCH_3$); 7.25 (br, t, 1H, olefinic) (Found: C, 61.71; H, 7.92; Calc. for $C_8H_{12}OS$ (156.2): C, 61.45; H, 7.68.

Table 2

Spectral data for products 8a-h

Product	IR(cm^{-1})[a]	^{1}H-NMR(δ/ppm)[b]	Configuration
8a	1643 (νCO)	2.32 (s, 3H, $-SC\underline{H}_3$); 6.70 (d, 1H, J=15 Hz, olefinic); 7.4 (m, 3H, arom); 7.7-7.9 (m, 3H arom + olefinic)	E
8b	1645 (νCO)	2.32 (s, 3H, $-SC\underline{H}_3$); 2.38 (s, 3H, $-C\underline{H}_3$); 6.91 (d, 1H, J=9 Hz, olefinic) 7.0 - 7.3 (m, 3H, arom); 7.50 - 7.85 (d, 2H, arom + olefinic)	Z
8c	1632 (νCO)	2.42 (s, 3H, $-SC\underline{H}_3$); 6.60 (d, 1H, J=15 Hz, olefinic); 7.32 (d, 2H, arom); 7.7 - 7.79 (m, 3H, arom + olefinic)	E
8d	1625 (νCO)	1.40 (t, 3H, $-C\underline{H}_3$); 2.37 (s, 3H, $-SC\underline{H}_3$); 4.07 (q, 2H, $-OC\underline{H}_2$); 6.85 (d, 2H, arom); 6.93 (d, 1H, J=9 Hz, olefinic); 7.85 (d, 2H, arom)	Z

Table 2 (contd.)

8e	1640 (νCO)	1.28 (t, 3H, $-C\underline{H}_3$); 2.68 (q, 2H, $-SC\underline{H}_2$); 3.75 (s, 3H, $-OC\underline{H}_3$); 6.71 (d, 2H, arom); 6.82 (d, 1H, J=9 Hz, olefinic); 7.12 (d, 1H, J=9 Hz, olefinic); 7.80 (d, 2H, arom)	Z
8f	1635 (νCO)	1.90 (s, 3H, $-SC\underline{H}_3$); 2.30 (s, 3H, $-C\underline{H}_3$); 2.35 (s, 3H, $-C\underline{H}_3$); 6.81 (s, 1H, olefinic) 7.0-7.6 (A_2B_2, m, 4H, arom)	Z
8g	1635 (νCO)	1.05 (t, 3H, $-CH_3$); 2.30 (s, 3H, $-SC\underline{H}_3$); 2.45 (q, 2H, $-C\underline{H}_2$); 6.80 (s, 1H, olefinic) 7.2-7.7 (m, 5H, arom)	Z
8h	1620 (νCO)	0.95 (t, 3H, $-C\underline{H}_3$); 1.4 (m, 2H, $-C\underline{H}_2$); 2.25 (s, 3H, $-SC\underline{H}_3$); 2.35 (t, 2H, $-C\underline{H}_2$); 6.82 (s, 1H, olefinic); 7.3-7.6 (m, 5H, arom)	Z

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[a] in nujol; [b] in CCl_4

Table 3

2-Methylthio-1-alkenyl Ketones (8a-h)

Products	Reflux time(hr)	Yield[a] (%)	m.p./b.p. °C/mm	Molecular formula	Mass (M^+)	Analysis (%)		
						Calc. Found	C	H
8a	30	62	oil:140-42/1	$C_{10}H_{10}OS$	178		67.41 67.70	5.62 5.92
8b	25	64(82)[b]	120-21	$C_{11}H_{12}OS$	192		68.75 69.97	6.25 6.50
8c	10	50	69-70	$C_{10}H_9$ ClOS	212.5		56.47 56.75	4.23 4.54
8d	12	75	127.5-28.5	$C_{12}H_{14}O_2S$	222		64.86 65.07	6.30 6.61
8e	12	42	thick liq.	$C_{12}H_{14}O_2S$	222		64.86 65.09	6.30 6.60
8f	8	56(51)[c]	oil:100-101/1	$C_{12}H_{14}OS$	206		69.90 70.21	6.79 7.02
8g	25	57(52)[c]	oil:129-130/a	$C_{12}H_{14}OS$	206		69.90 70.22	6.79 7.04
8h	28	66(55)[c]	oil:135/1	$C_{13}H_{16}OS$	220		70.90 71.21	7.29 7.35

[a] yields of pure isolated compounds by method A.

[b] yield obtained by method B.

[c] yields obtained after distillation.

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CHAPTER III

A NEW GENERAL HIGHLY STEREOSELECTIVE AND REGIOSPECIFIC METHOD FOR HOMOLOGATION OF KETONES TO α,β-UNSATURATED ESTERS VIA α-KETOKETEN S,S-ACETALS*

III. 1. INTRODUCTION

In the preceding chapter a convenient new general method for demethylthiolation of α-ketoketen S,S-acetals to the corresponding alkylthiomethylene ketones has been formulated by partial reductive desulphurisation using a mixture of sodium borohydride and nickel chloride. The method has been shown to be general and of preparative importance for the synthesis of useful synthons.

In the present chapter it has been shown that the ketoketen S,S-acetals (1), which have been reported to undergo 1,2-reduction to the corresponding carbinols 2, can be converted into the corresponding α,β-unsaturated esters 3 in excellent yields (Scheme 1). The α,β-unsaturated esters of the general formula 3 and 5 (Scheme 2) are widely used intermediates in organic synthesis. The structural features of 3 and 5 are different as shown by the positions of R and R' and their methods of preparation from the ketone 4 should, therefore, be based on different synthetic strategies. The most general approach for the preparation of 5 from 4 is to subject the ketone 4 under one of the

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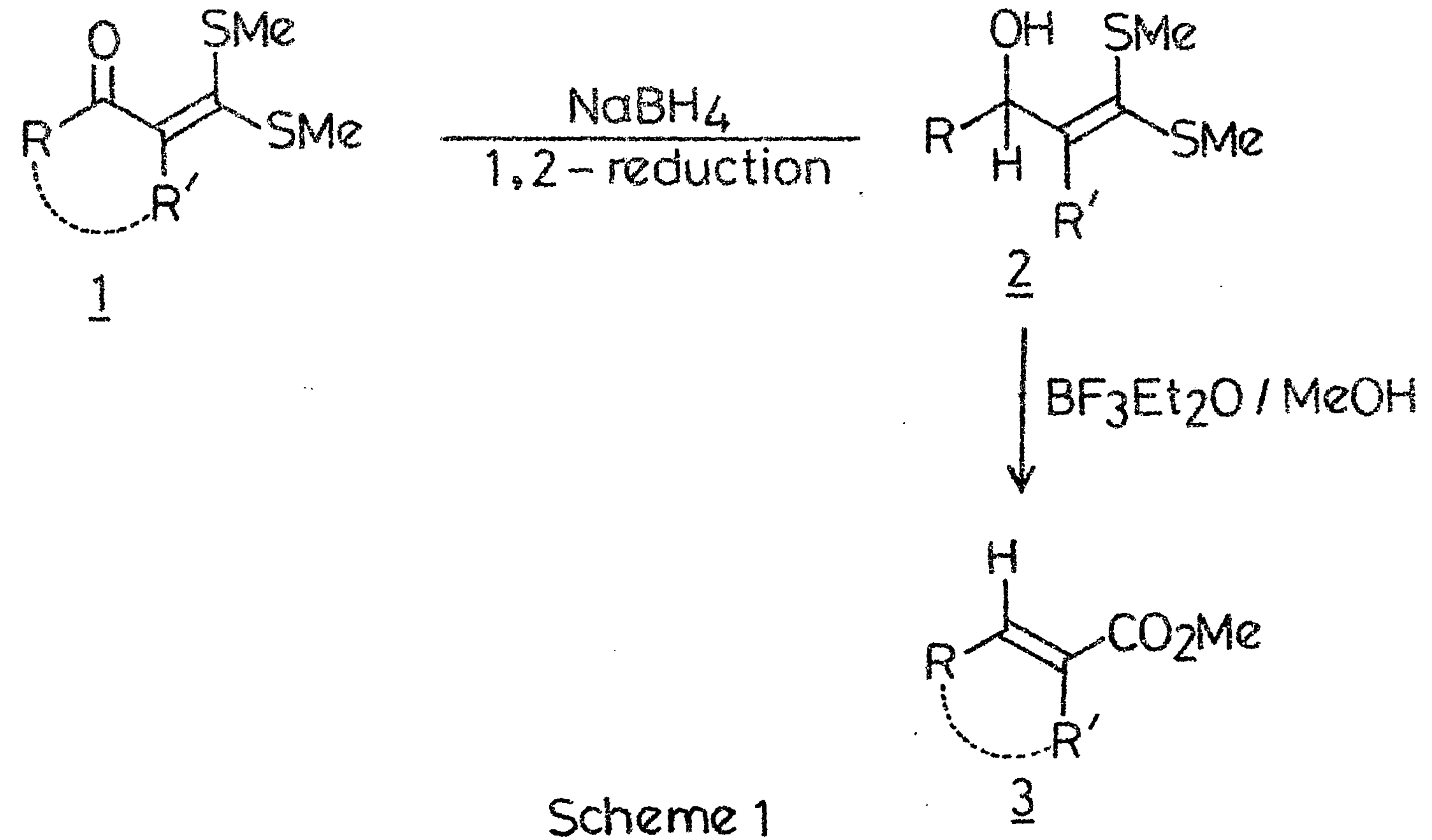
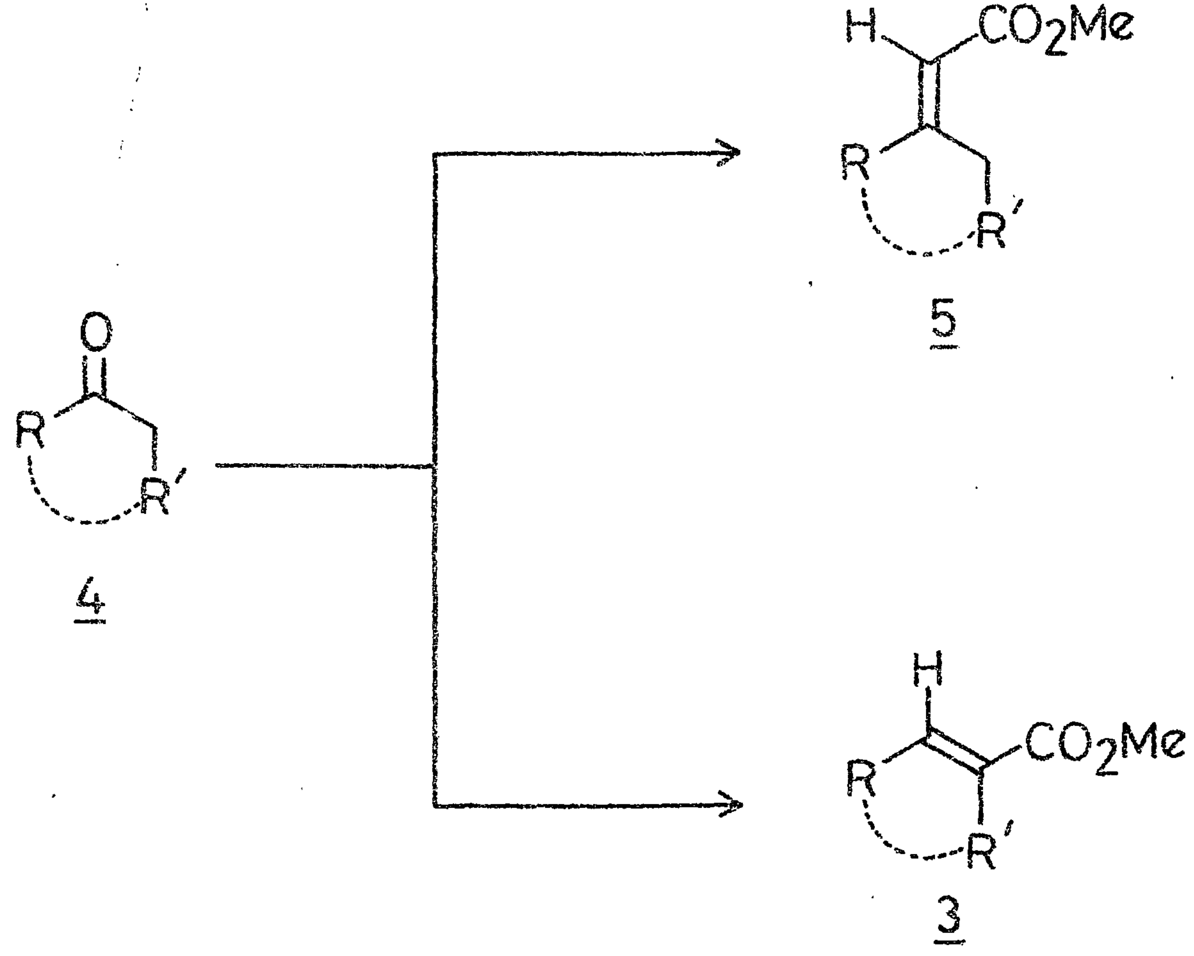
* B. Myrboh, H. Ila and H. Junjappa, accepted for publication in J. Org. Chem., 1983.


SMe
SMe
R
O
R′
1
NaBH4
1,2 – reduction
OH
SMe
SMe
R
H
R′
2
BF3Et2O / MeOH
H
CO2Me
R
R′
3

Scheme 1



Scheme 2

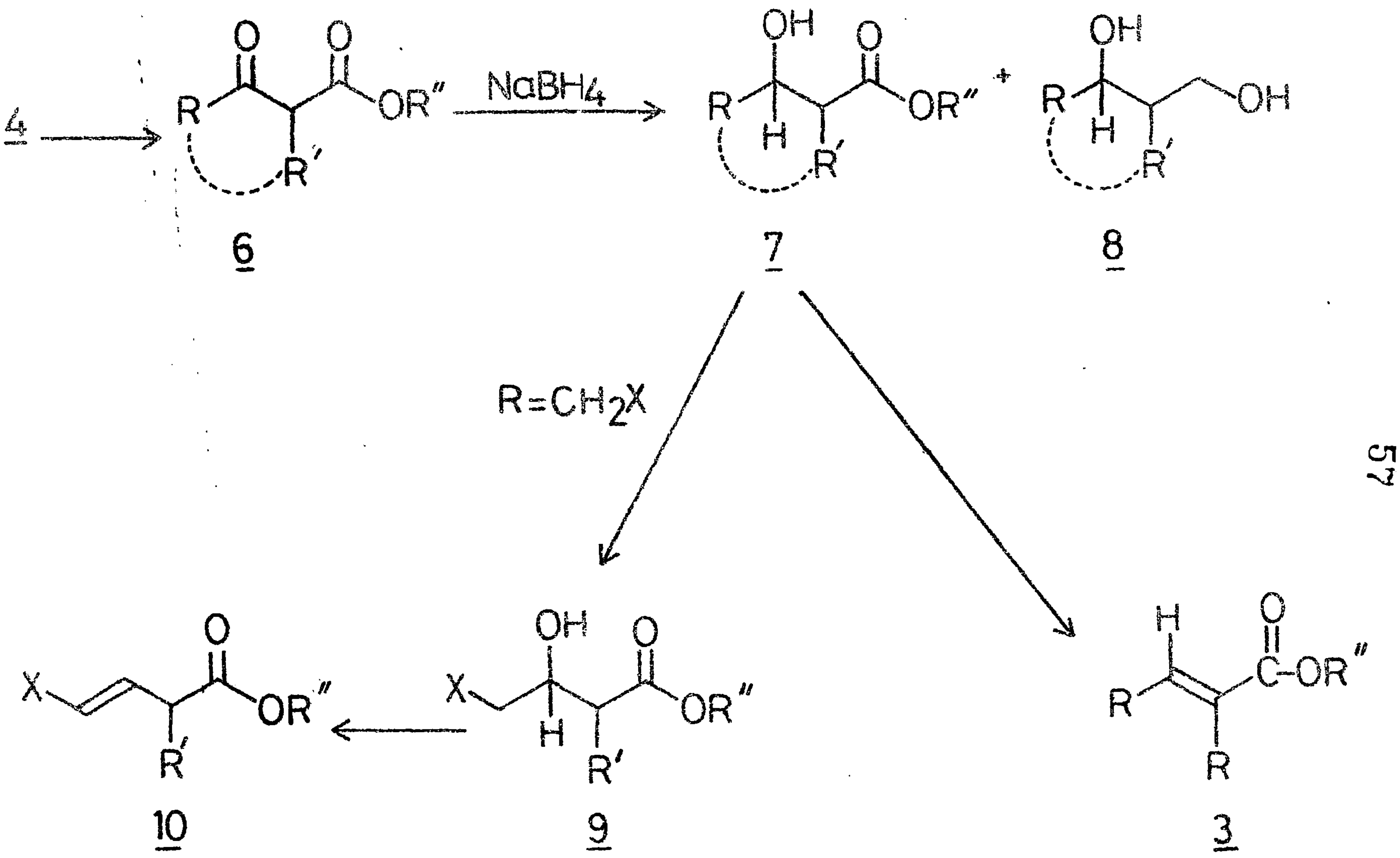
variants of aldol condensation,[1] which is considered to involve a two carbon homologation on carbonyl carbon. On the other hand, methods for the preparation of 3 from 4 are rarely described in the literature and can be considered as one carbon homologation of the ketone 4 at the α-carbon followed by reductive elimination of the carbonyl function. Other methods besides aldol condensation have also been used for the transformation of 4 to 5 which include (1) reaction of 4 with appropriate witting reagents;[2] (2) addition of lithium ethoxyacetylide to 4 followed by rearrangement involving 1,3-carbonyl transposition.[1] Methods which do not use the ketones as substrates, some of which are common for the preparation of both 3 and 5 include (a) carbonation of vinylmetallics[1,3a] (b) carbonylation/methoxycarbonylation of vinyl halides, acetylenes and organopalladium compounds[3b-3g] (c) conjugate addition of dialkylcopper lithium to unsaturated acetylenic esters and enolacetates[3h-3j] (d) dehydrohalogenation of saturated α-haloesters[1] (e) sulfenylation/selenylation and dehydrosulfenylation/selenylation of saturated esters.[3k-3n]

Surprisingly, there is only one method reported in the literature for the conversion of 4 to 3. Thus the β-ketoester 6 prepared from 4 was reduced with sodium *borohydride to give the alcohol 7 along with 8 (Scheme 3)* arising from 1,4-reduction. The alcohol 7 was subjected to dehydration to give 3.[4] The method apparently suffers from disadvantages due to lack of selectivity in the reduction step (6→7), since the ester group is concomitantly reduced with the formation of the undesirable 8 and giving rise to problems of separation of products arising from 8.[4a] Besides, the isomeric β, γ-unsaturated esters 10 are reported to be formed during dehydration of 7 derived from cyclic ketones.[4e] Therefore a preparative method for the conversion of 4 to 3 is desirable.

Consequently, it was decided to examine the keten S,S-acetals 1 derived from ketones of the general formula 4 as potential intermediates for the conversion of 4 to 3 via 2. The preparation of ketoketen S,S-acetals 1 from 4 have been been well established and they are obtained in one pot reaction in good to excellent yields.[5] They offer additional advantages over the β-ketoesters as starting materials for the synthesis of esters 3 in more than one way:

1. The dithioacetal group in 1 can be treated as a masked carboalkoxy group which is resistant to 1,4-reduction[6] under normal conditions of metal hydride reductions, yielding the carbinol dithioacetals 2 exclusively in excellent yields.

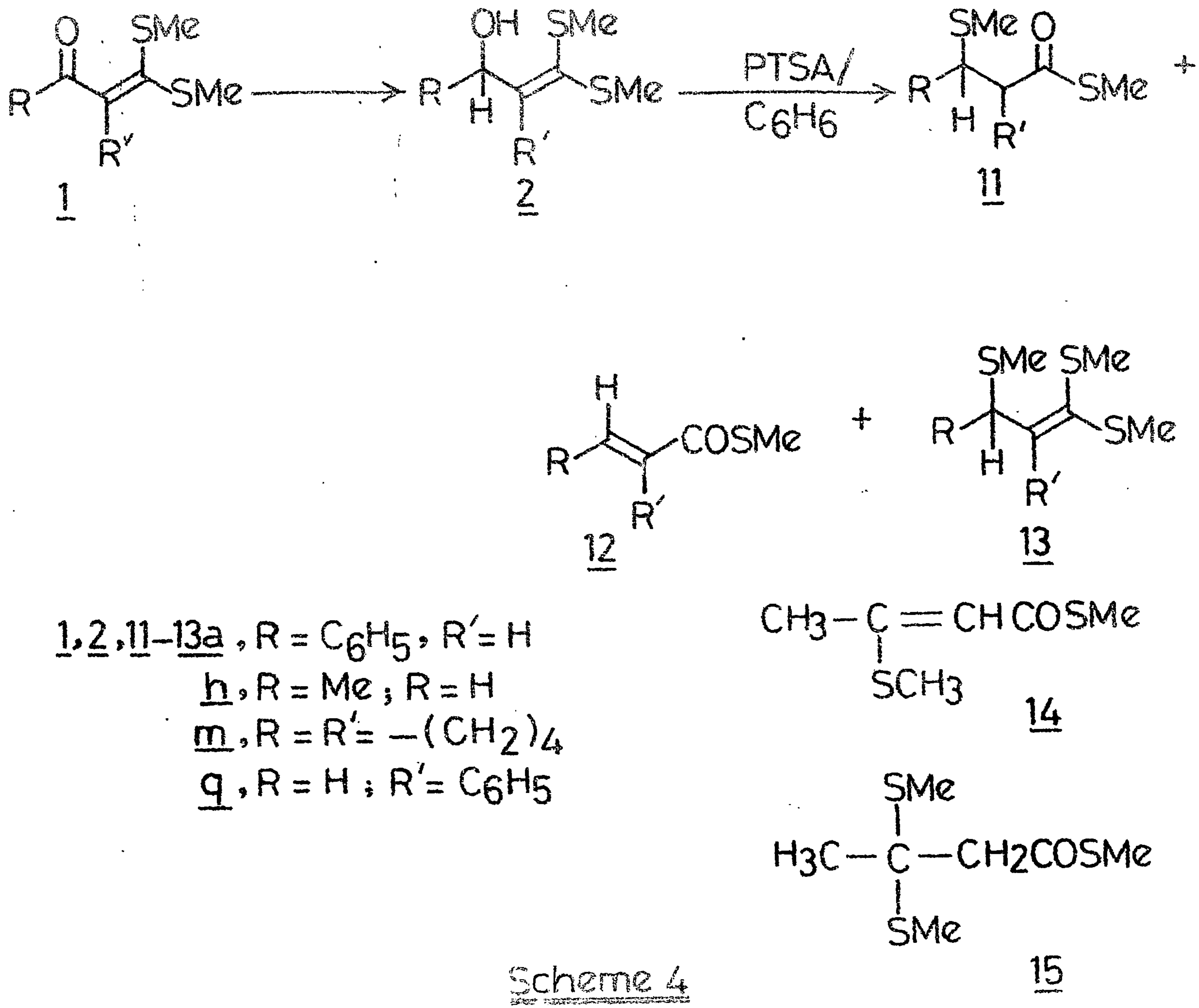
2. They provide larger structural flexibility through further modification of the bis(methylthio)methylene group



Scheme 3

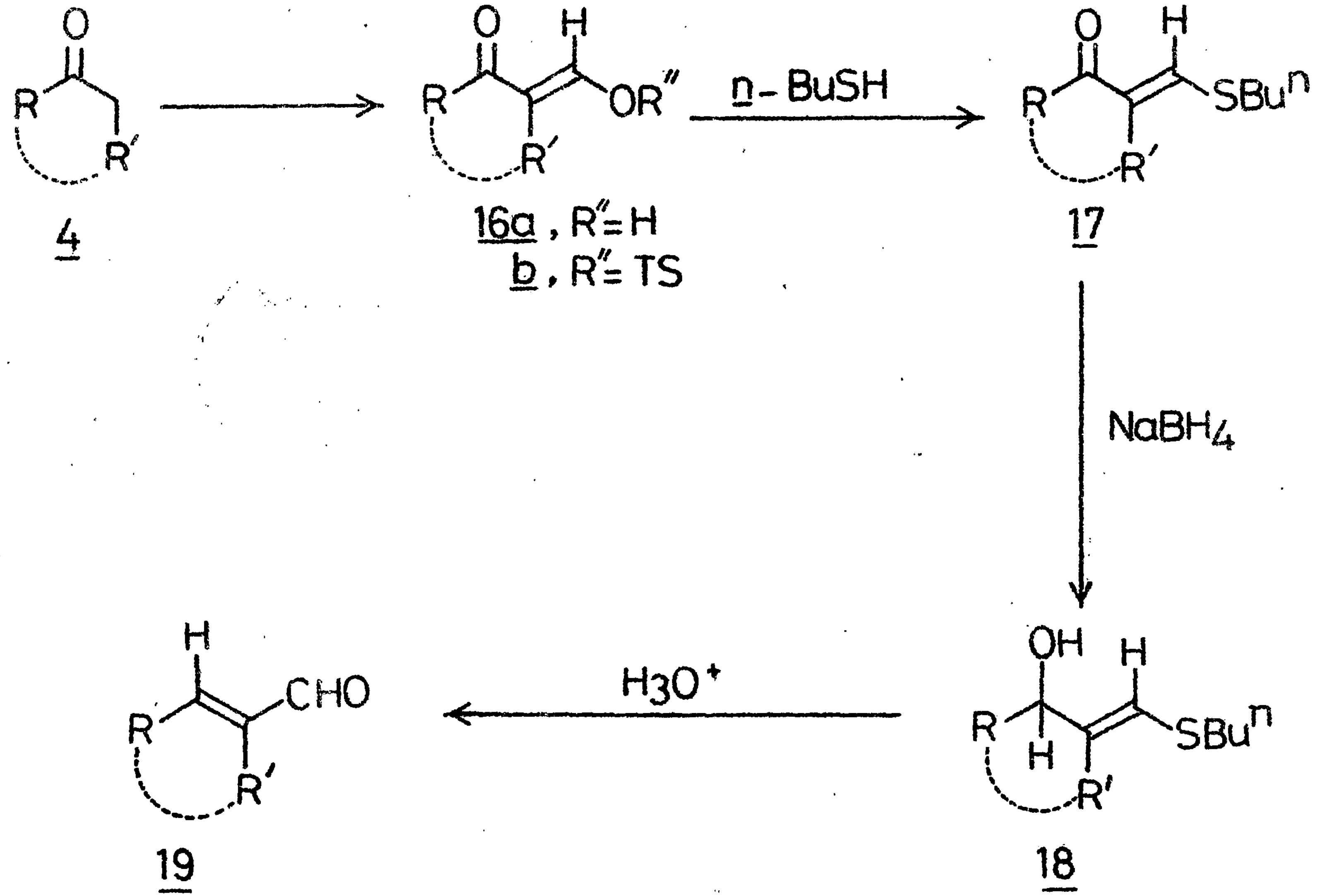
which are known to undergo partial demethylthiolation or substitution by either alkyl or aryl groups, thereby ensuring wider choice of substrates.[7]

From the literature survey,it was revealed that Thuillier and co-workers[8] have reported sodium borohydride reductions of several ketoketen S,S-acetals to the corresponding carbinols in excellent yields. These carbinols 2 on subsequent treatment with p-toluenesulphonic acid in refluxing benzene have been shown to yield a mixture of several products like 11, 12 and 13 in varying yields. Besides, products like 14 and 15 were also isolated from carbinol 2h (R=Me; R=H). Under these conditions the α, β-unsaturated esters were not formed and apparently these studies were not intended for the preparation of these esters. Interestingly the idea of using this approach for the synthesis of α, β-unsaturated aldehydes 19 (Scheme 5) has been elegantly accomplished by Ireland and Marshall.[9] However, they obtained the thiomethylene ketones 17 by reacting the hydroxymethylene ketones 16a or their tosylates 16b with n-butylmercaptan. The ketones 17 after 1,2-reduction with sodium borohydride followed by hydrolytic treatment gave the desired α, β-unsaturated aldehydes 19. The method is reported to be efficient and identical with the present ester synthesis.



1, 2, 11–13a, R = C_6H_5, R′ = H
h, R = Me ; R = H
m, R = R′ = $-(CH_2)_4$
q, R = H ; R′ = C_6H_5

Scheme 4



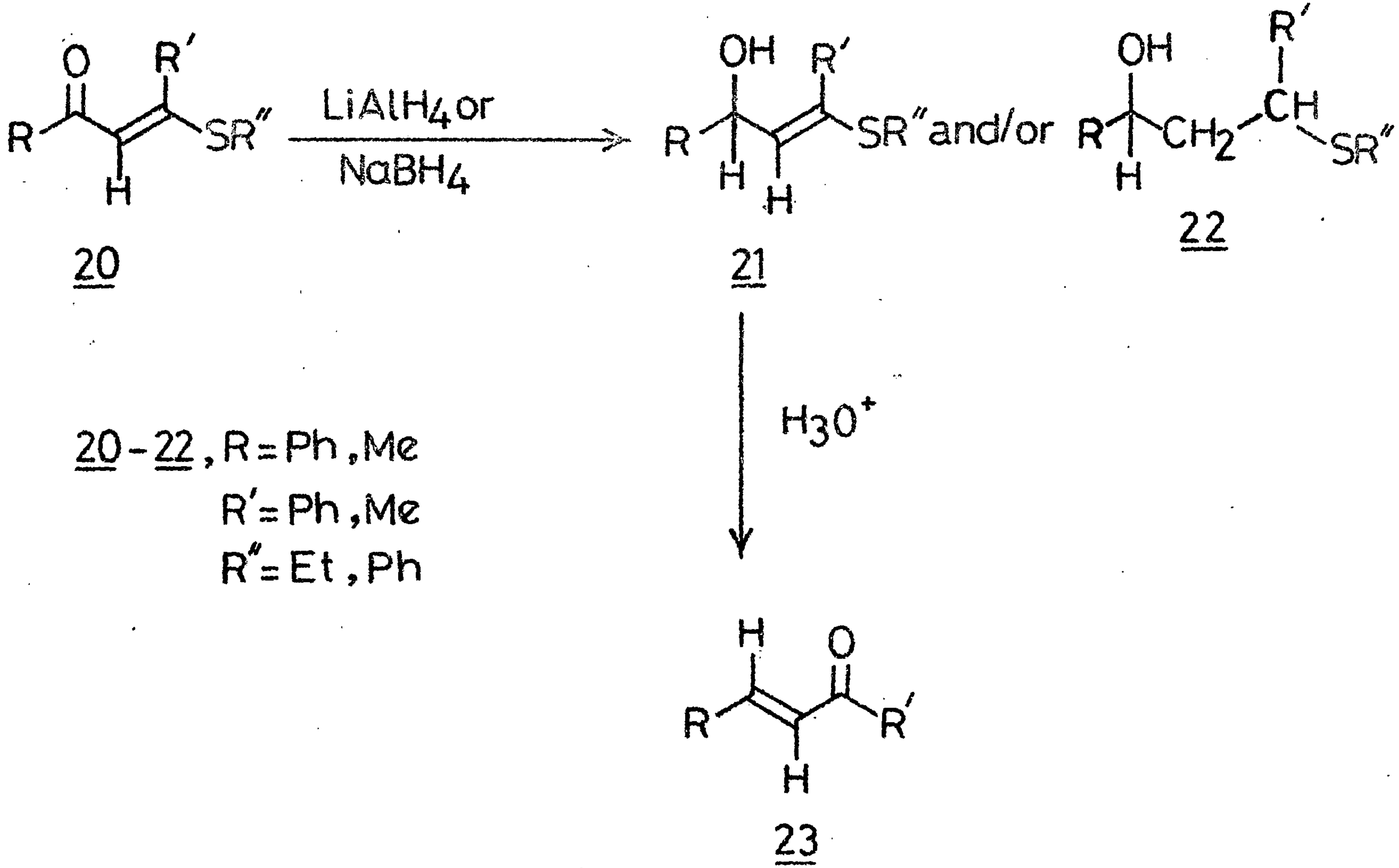
Scheme 5

Similarly, Omote and co-workers[10] have reported the reduction of thiomethylene ketones 20 to give the α,β-unsaturated ketones 23 via their carbinols 21. In some cases, however, the saturated β-hydroxysulfides (22) were obtained in high yields, which are apparently formed by concomitant 1,4-reduction of the ketone 20 (Scheme 6). The authors have not, however, described the preparation of 20.

It is therefore apparent from the literature that the isolated studies governing the synthesis of α,β-unsaturated aldehydes and ketones have been accomplished starting from alkyl/arylthio-methylene ketones. The only method using α-Ketoketen S,S-acetals as studied by Thuillier and co-workers[8] has not been investigated with a view to developing a general synthetic route for the preparation of α,β-unsaturated aldehydes, ketones and esters. In the present investigation, it was intended to develop a general method for the synthesis of α,β-unsaturated esters, S-methylesters, aldehydes and ketones starting from α-keto-keten S,S-acetals derived from easily available ketones.

III.2. RESULTS AND DISCUSSION

For the present studies, representative examples of linear, cyclic alipatic and aromatic ketones were selected. These ketones were conveniently converted to the corresponding



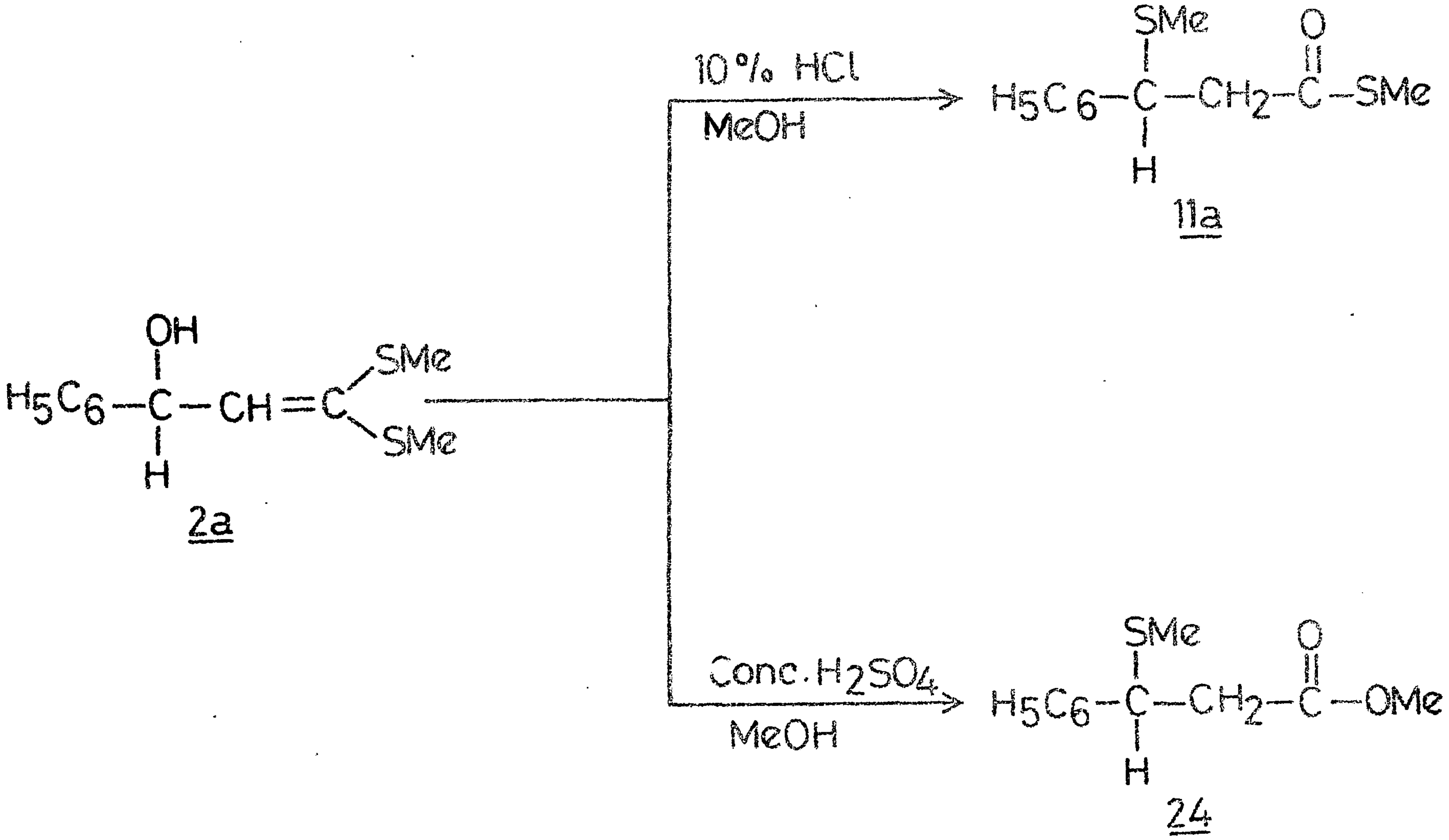
20-22, R = Ph, Me
R′ = Ph, Me
R″ = Et, Ph

Scheme 6

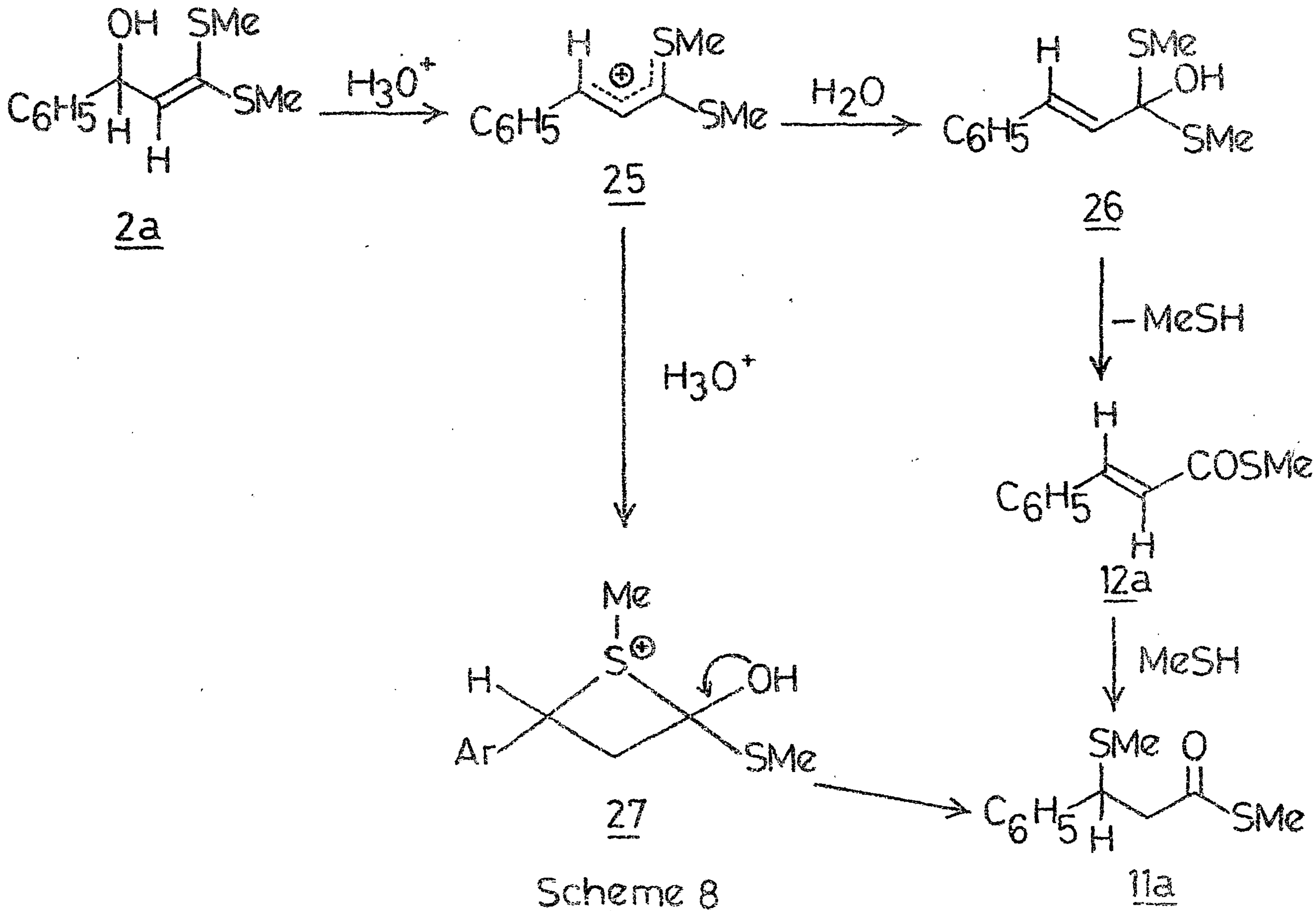
ketoketen S,S-acetals by the reported methods in excellent yields. The structures of all the known acetals 1 were confirmed by their spectroscopic and analytical data. Similarly, the acetals which were not reported in the literature were assigned their correct structures by their analytical and spectral data. These acetals were then subjected to sodium borohydride reduction in refluxing absolute ethanol and the progress of the reaction was monitored by TLC. The reductions were generally completed in 2-3 hr and the corresponding carbinols were obtained in more than 90% yields. No trace of compounds arising from 1,4-reduction were observed. These carbinols were not isolated in all the cases, while the known carbinols 2a, 2h & 2m were found to be in conformity as regards their structural assignments (IR, NMR). The other carbinols were directly subjected to hydrolytic or solvolytic reactions, when the corresponding α, β-unsaturated-O-methyl, and S-methyl esters were obtained.

III.2.1. Preparation of α, β-Unsaturated-O-methyl esters

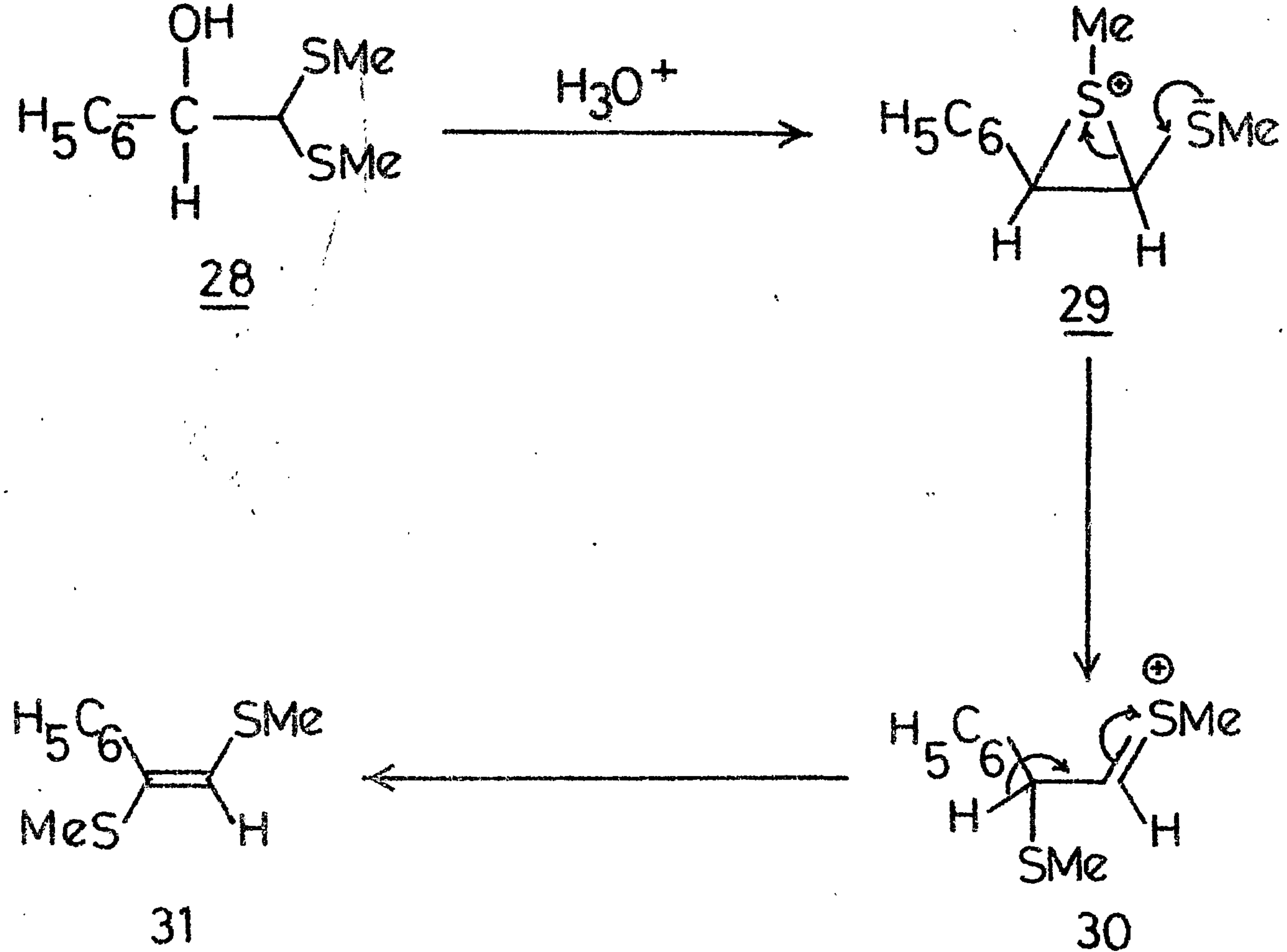
Several pilot experiments under acid catalysed hydrolytic conditions revealed that the carbinol acetals underwent rearrangement with the formation of a mixture of several products as observed by Thuillier and co-workers[8], and no sulphur free products were found to be formed in any of these experiments. The resistance of the S,S-acetals to undergo hydrolysis to the sulphur free compounds under these conditions is well documented.[11] Thus in one of the pilot experiments, when the carbinol 2a was stirred at room temperature with 10% hydrochloric acid in methanol, a mixture of several products (TLC) was formed, from which only the rearranged S-methyl-3-methylthio-3-phenyl propanthioate 11a (Scheme 7) was formed in 45% yield. The structure of this compound was proved to be identical with that reported by Thuillier (IR, NMR, Mass). However, when 2a was refluxed in 80% aqueous trifluoroacetic acid, the product 11a was obtained in improved yields (65%).[12] Similarly, 2a in refluxing methanol and concentrated sulfuric acid yielded only methyl 3-methylthio-3-phenylpropionate 24 (Scheme 7) isolate in 43% yield along with several unisolable products (TLC). The mechanism governing these transformations have been studied by Thuillier and co-workers, who suggested the formation of 11a by Michael addition of methyl-mercaptan to α, β-unsaturated thioester 12a (Scheme 8). However, an alternate mechanism involving the thiatenium ion intermediate 27 formed by R_2S-4 interaction of bivalent sulfur with developing cationic center can not be ruled out.[12] A similar 1,2-MeS shift via episulfonium ion intermediate 29 has been reported in the hydration of α-hydroxydithioacetals 28 to give the



Scheme 7


OH
SMe
C6H5
H
H
SMe
2a
H3O+
H
SMe
C6H5
SMe
25
H2O
H
SMe
OH
C6H5
SMe
26
H3O+
−MeSH
H
C6H5
COSMe
H
12a
MeSH
Me
S⊕
H
OH
Ar
SMe
27
SMe
O
C6H5
H
SMe
11a

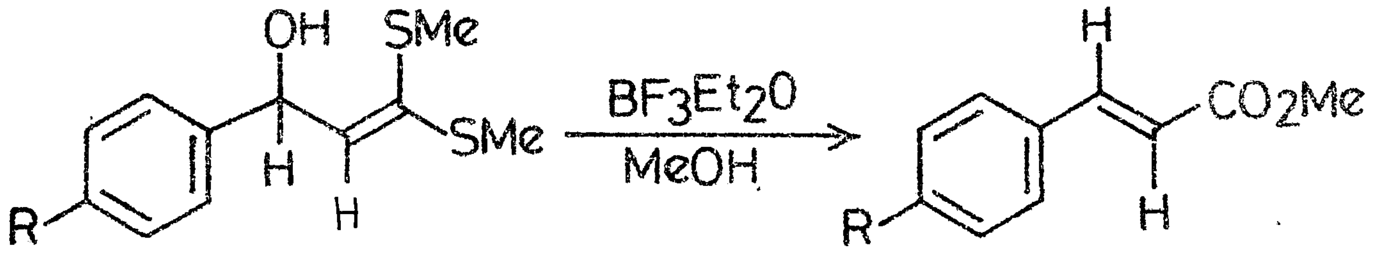
Scheme 8



Scheme 9

rearranged product 31 (Scheme 9).[13,14]

In view of the failure to get 3a under various solvolytic and hydrolytic conditions, further experiments were carried out with a view to achieving the desired solvolytic displacement to yield the α,β-unsaturated esters. Thus when 2a was refluxed with borontrifluoride etherate in methanol, the reaction was found to be proceeding towards only one compound identified as the corresponding cinnamate 3a ($R=C_6H_5$; R=H) in 70% yield. Thus the borontrifluoride/methanol combination yielded the desired unsaturated O-methyl esters in satisfactory preparative yields. The method was extended successfully to convert a wide variety of carbinol-acetals to the corresponding α,β-unsaturated O-methyl esters. No efforts were made to further improve the yields of these esters. The structure of 3a was identical with the reported cinnamate and found to be formed exclusively as its E-isomer. Similarly, 2b-d were solvolysed under the same conditions and the corresponding cinnamates 3b-d were formed in 68-75% overall yields.[15] (Scheme 10). All the cinnamates were found to be formed as E-isomers, their structural assignments were fully in conformity with their spectral data (Experimental). Thus a new general method has been developed to convert acetophenones to the corresponding E-cinnamates in excellent yields. The generality of the method was further extended to higher



2a - d

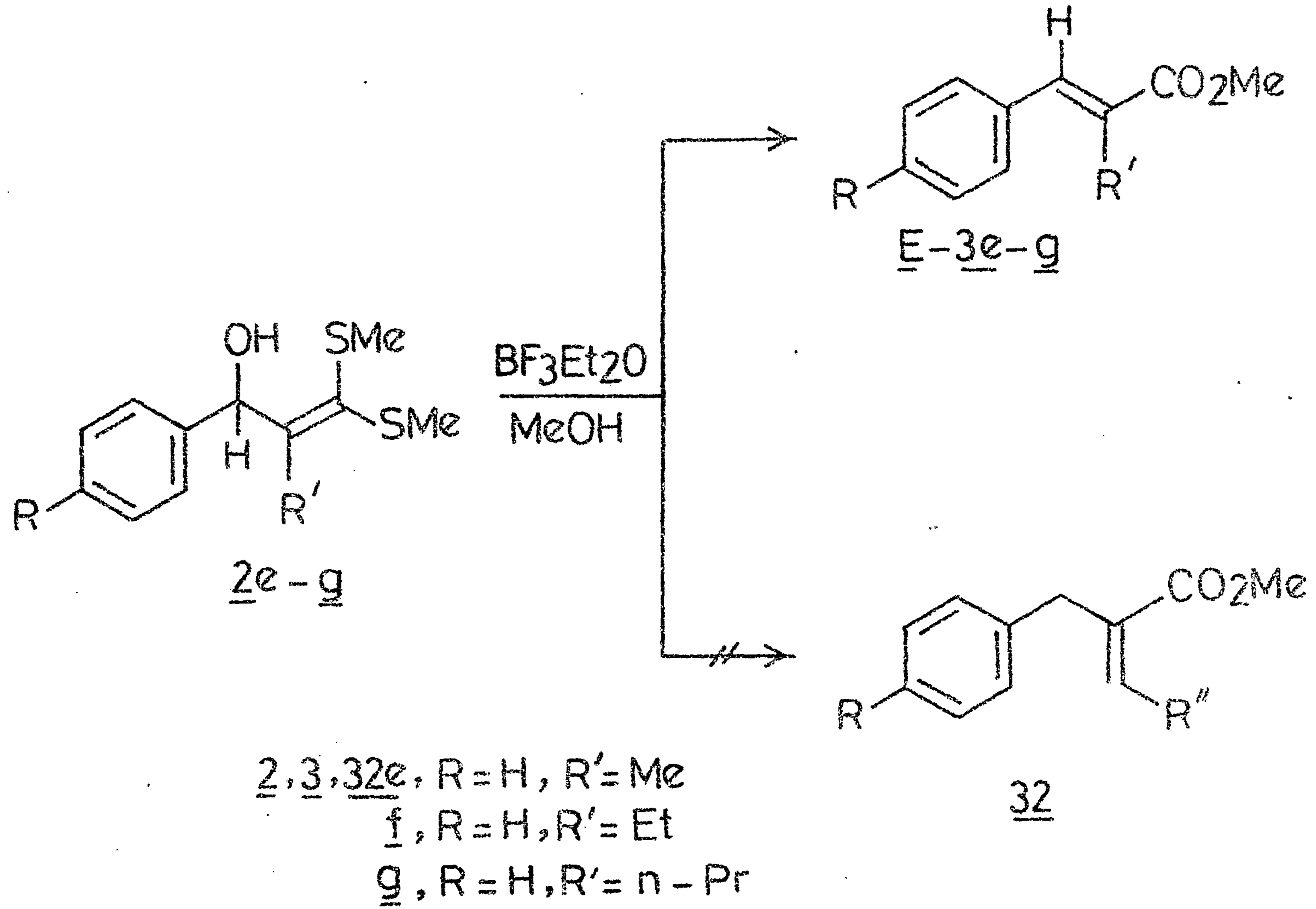
E-3a-d

2,3a, R = H
b, R = Me
c, R = Cl
d, R = OEt

Scheme 10

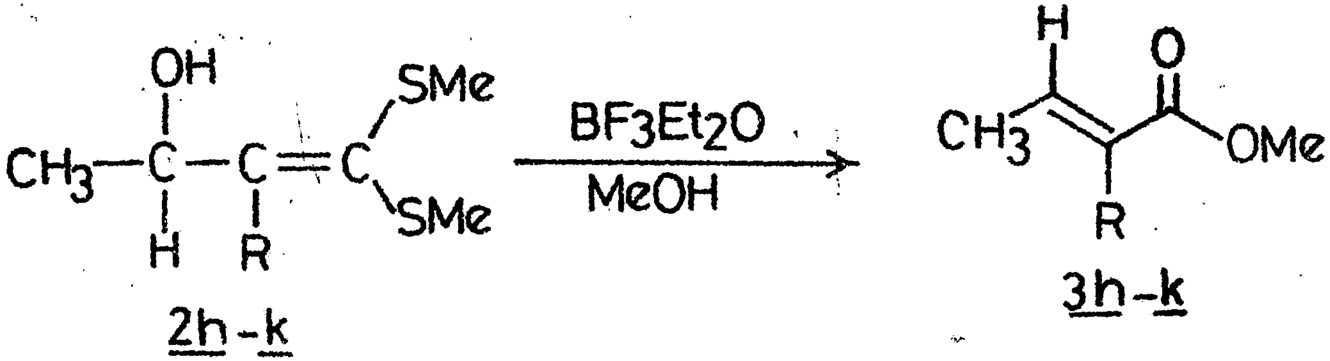
homologs of acetophenone. Thus when the carbinol 2e derived from propiophenone S,S-acetals was subjected to methanolysis in the presence of borontrifluoride etherate, the corresponding methyl α-methyl E-cinnamate (3e) (Scheme 11) was formed in 67% yield. The analytical and spectral data of 3e was in conformity with the reported values. Its NMR data showed to be formed exclusively as E-isomer. Similarly, the carbinoldithioacetals 2f and 2g gave the corresponding α-alkylcinnamates 3f and 3g in 75% yield. No trace of the Z-isomer, or the isomeric β,γ-unsaturated ester 32e-g (Scheme 11) were formed in any of these experiments.

The method was also extended to the carbinols derived from S,S-acetals of the aliphatic ketones. Thus the carbinol derived from the acetone mercaptal 1h underwent facile methanolysis in the presence of borontrifluoride etherate to give the corresponding E-methylcrotonate (3h) in 50% yield. Interestingly, the solvolysis yielded only one isomer, while no trace of its β,γ-unsaturated ester was detected.[4a] Further the mercaptals 2i-k (Scheme 12) derived from other aliphatic ketones also, under identical reaction conditions gave the corresponding E-methyl α-alkylcrotonates 3i-k in 54-80% overall yields.[16] Here again the reaction was stereoselective and regiospecific. The possible β,γ-unsaturated esters as well as the other geometrical



2, 3, 32e, R = H, R′ = Me
f, R = H, R′ = Et
g, R = H, R′ = n - Pr

Scheme 11



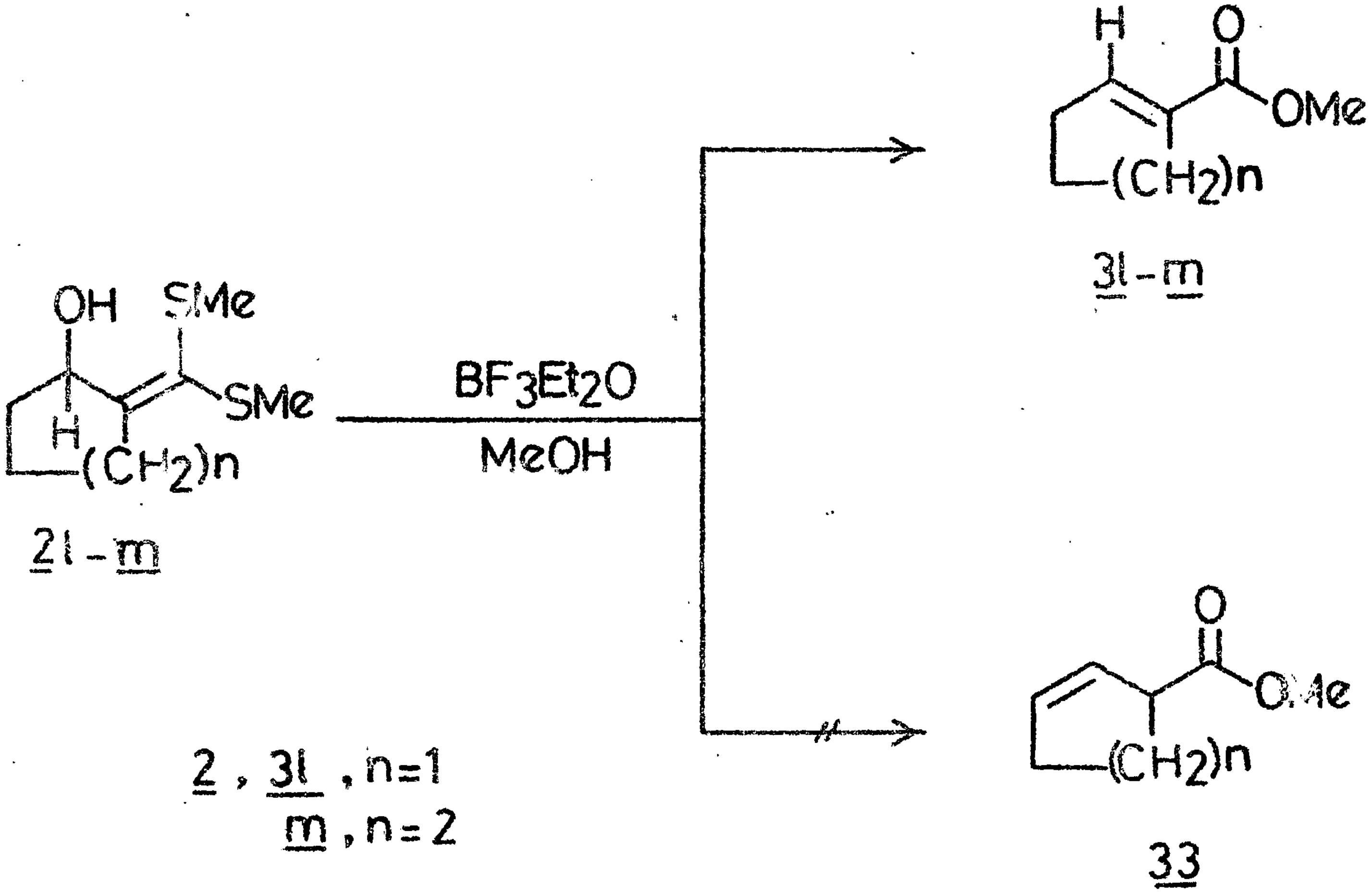
2, 3h, R = H
i, R = Me
j, R = n-Bu
k, R = n - pentyl

Scheme 12

isomers were not detected.[4a]

When the method was extended to the cyclic ketones the reaction was found to be equally efficient. Thus the mercaptal 1l derived from cyclopentanone after reduction with sodium borohydride underwent smooth methanolysis to give exclusively the α,β-unsaturated ester 3l (Scheme 13) in 70% yield. It is interesting to note that 3l is an intermediate in the synthesis of normepatillinic acid,[4b] which has previously been prepared through the dehalogenation, and decarbonylation[17] of 1-chloro-2-ketocyclohexane-1-carboxylate 35 (Scheme 14) and by the cyanohydrin method.[18] The present method provides an alternate shorter route for 3l. Similarly, the ene-ester 3m was prepared in 75% yield from the corresponding 2m (Scheme 13).

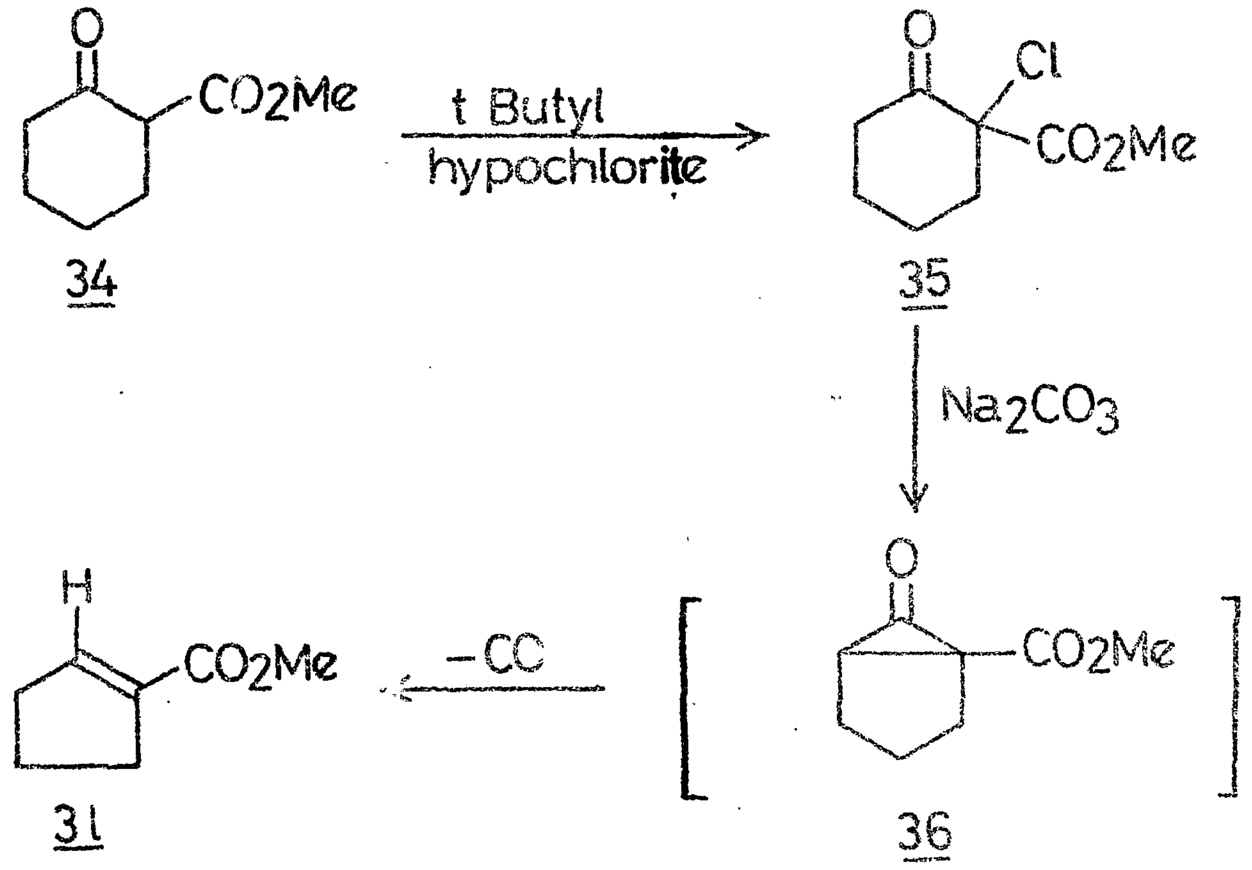
Under the same reaction conditions, the carbinol dithioacetals 2n-p derived from the corresponding tetralones and benzosuberone underwent smooth methanolysis to yield the corresponding ene-esters 3n-p in 67-73% overall yields (Scheme 15). The structures of thse compounds were determined from their IR, NMR and mass spectal data and were found to agree with their assigned structures. As an example of the synthetic application of the present method the preparations of α,β-unsaturated acid 41 and the aldehyde 43 from the same mercaptal 38 (Scheme 16) were conveniently accomplished. It



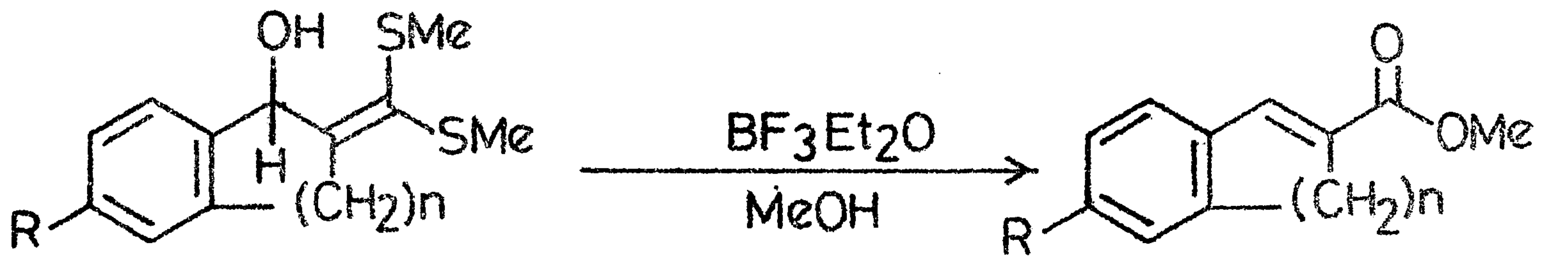
$\underline{2}$, $\underline{3l}$, n=1

$\underline{m}$, n=2

Scheme 13


CO2Me
t Butyl
hypochlorite
Cl
CO2Me
34
35
Na2CO3
H
CO2Me
−CO
CO2Me
31
36

Scheme 14



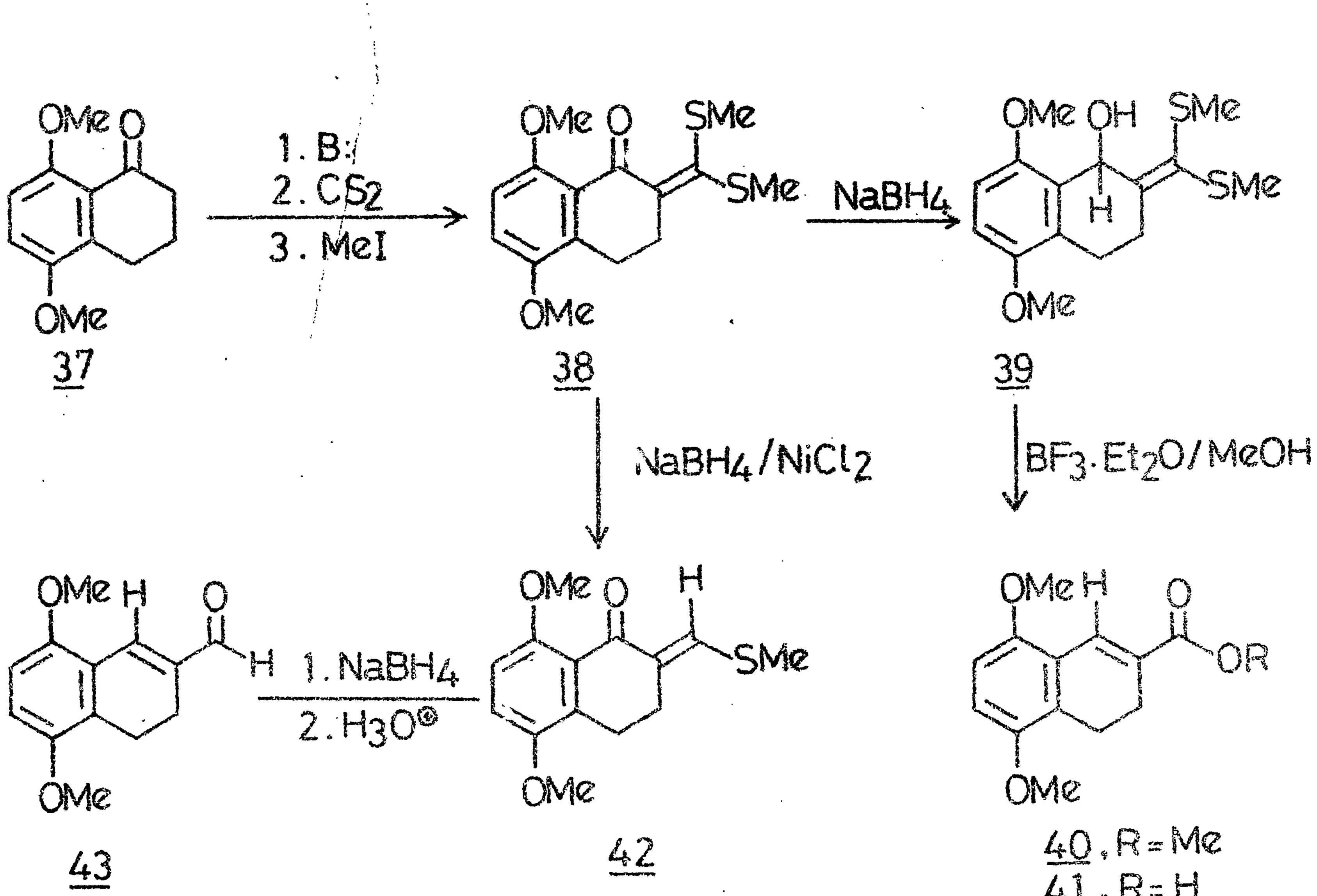
2

3n - p

2, 3n, R = H, n = 2
o, R = OMe, n = 2
p, R = H, n = 3

Scheme 15

is to be noted here that these are key intermediates in the anthracyclinones synthesis.[19] Thus the mercaptal 38 which was previously not reported was prepared from the corresponding tetralone 37 in one pot reaction in 70% yield. The structure of 38 was confirmed from its analytical and spectral data. The ketendithioacetal 38 underwent smooth 1,2-reduction with sodium borohydride in methanol to give 39 in quantitative yields (95%), The carbinol 39 underwent smooth methanolysis in the presence of borontrifluoride etherate/methanol to give the ene-ester 40 in 72% yield, which on hydrolysis afforded the desired acid in 95% yield. It may be noted that the formation of 43 was accomplished from the same 38 by first subjecting it to partial reductive demethylthiolation with a mixture of sodium borohydride and nickel chloride in ethanol as described in Chapter II, to yield the methylthiomethylene ketone 42 in 62% yield. After 1,2-reduction with sodium borohydride followed by acidic hydrolysis, 42 gave the desired aldehyde 43 in 60% yield. Thus the common intermediate 38 was suitably converted into both the ester 40 and the aldehyde 43 making the overall transformation a versatile preparative route. The intermediate 41 and 43 have been recently prepared from 37 through Vielsmeier reaction,[19c] while 41 has also been prepared by cyclocondensation of ethyl-4-(2,5-dimethoxyphenyl)-2-formylbutyrate.[19b]


OMe
OMe
37
1. B:
2. CS2
3. MeI
OMe
SMe
SMe
OMe
38
NaBH4
OMe
OH
SMe
SMe
H
OMe
39
NaBH4/NiCl2
BF3·Et2O/MeOH
OMe
H
OMe
43
1. NaBH4
2. H3O⊕
OMe
H
SMe
OMe
42
OMe
H
OR
OMe
40, R = Me
41, R = H

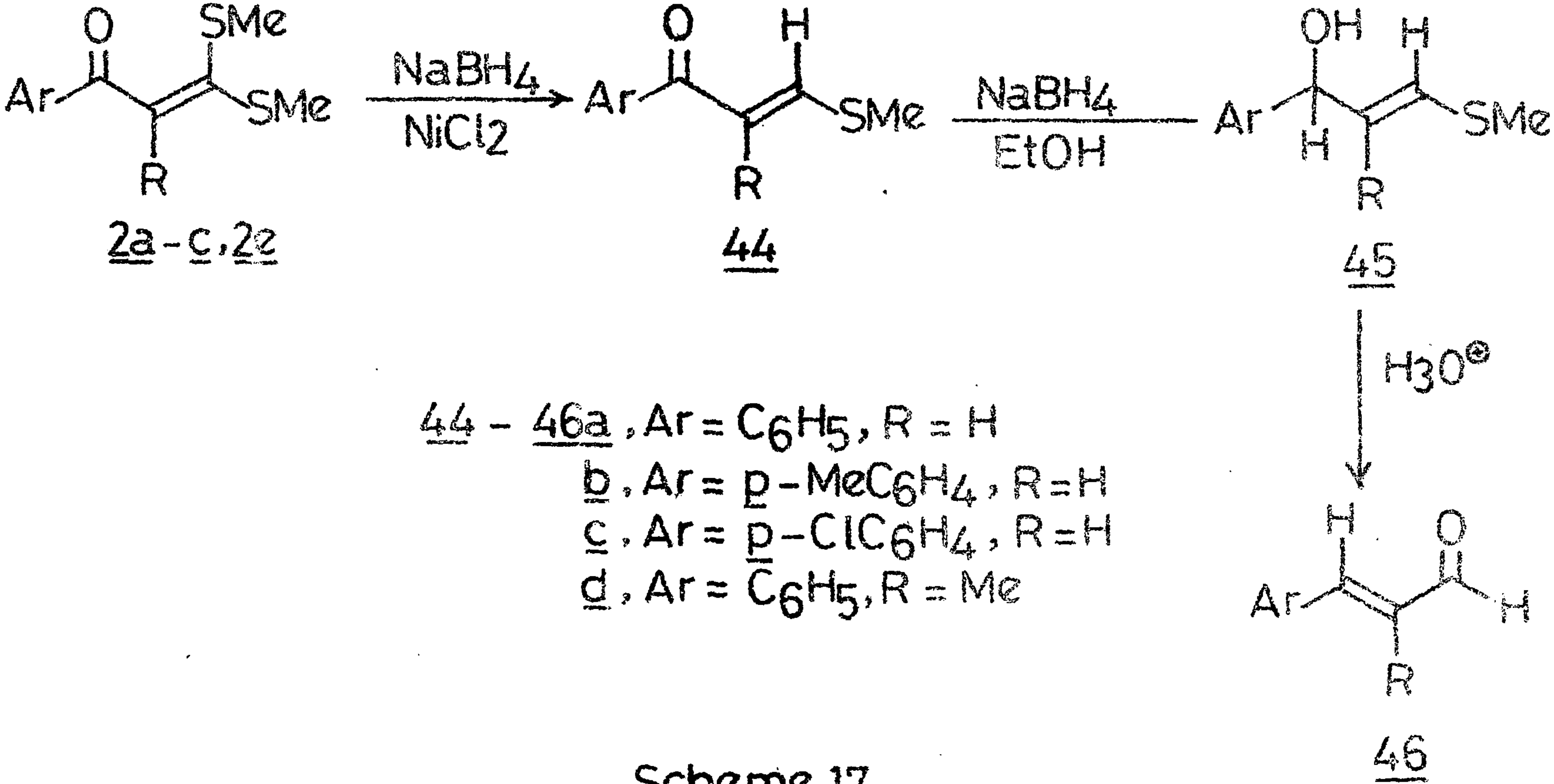
Scheme 16

III.2.2. Preparation of α,β-Unsaturated Aldehydes

The formation of 43 from 42 described in scheme 16 is identical with that reported by Ireland and co-workers[9] who have utilized this method for the preparation of several alicyclic α,β-unsaturated aldehydes (Scheme 5). With a variety of methylthiomethylene ketones 44 readily available from 1 by the method described in chapter II, it was further decided to test the generality of the method for the conversion of methylthiomethylene ketones 44a-d derived from acetophenone and its higher homologues to the corresponding cinnamaldehydes (Scheme 17). Thus 2a was converted to 44a as described in the second chapter and subsequently reduced to the carbinol 45a which on acid hydrolyses yielded the E-cinnamaldehyde 46a in 60% yield. Similarly, 44b-d were converted to the corresponding E-cinnamaldehydes in 55-65% overall yields. Thus the keten S,S-acetals 1 are shown to be common intermediates for the synthesis of α,β-unsaturated esters and aldehydes.

III.2.3. Preparation of S-Methyl α,β-Unsaturated Thioesters

It was considered appropriate to study whether 2 could be converted under partial hydrolytic conditions to the corresponding S-methyl α,β-unsaturated thioesters 12 (Scheme 18). Thus when 2a was treated with borontrifluoride etherate



44 - 46a, Ar = C_6H_5, R = H
b, Ar = p-MeC_6H_4, R = H
c, Ar = p-ClC_6H_4, R = H
d, Ar = C_6H_5, R = Me

Scheme 17

and water, the corresponding S-methyl cinnammate 12a was obtained in 55% yield. The corresponding thiocinnamates 12b-d were similarly obtained in 60-75% overall yields (Scheme 18). All the thiocinnammates showed E-geometry in conformity with the previous observations.* The cyclic carbinol dithioacetals 2l, 2m and 2n similarly gave the corresponding S-methylenethioesters 12e-g in 55-70% overall yields (Scheme 19). The earlier reports for the synthesis of S-alkylthioesters employ condensation of lithiotrimethylsilylthioacetate[20] or α-halogenated theioester (under Reformatsky conditions)[21] with aldehydes and ketones. Apparently the present method offers and efficient route to the S-methyl-α, β-unsaturated esters in good yields from the easily available ketones.

III.2.4. Mechanism

The mechanism governing the formation of highly stereoselective and regiospecific α, β -unsaturated esters appears to be interesting although not very unusual. The fact that the carbinols 2 failed to yield the desired esters either in the presence of mineral acids or under the reaction conditions of Thuillier's experiments, indicates that the

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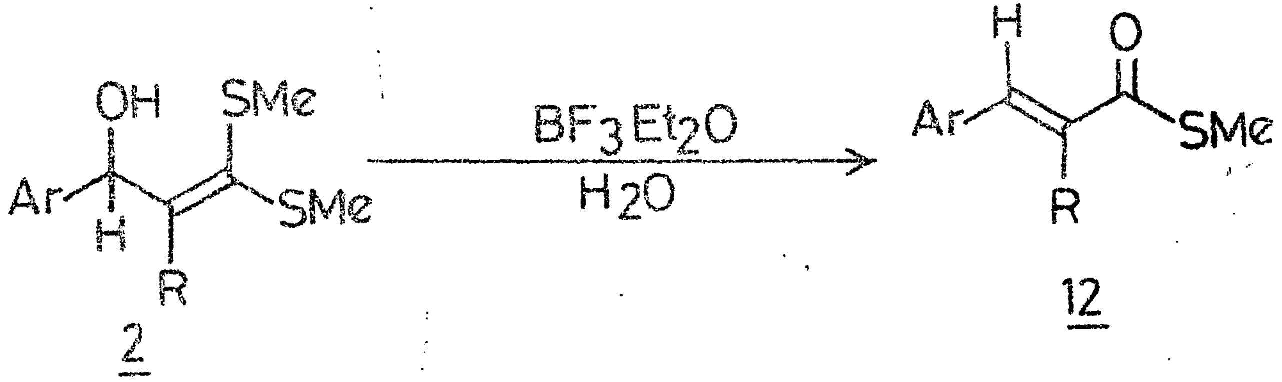
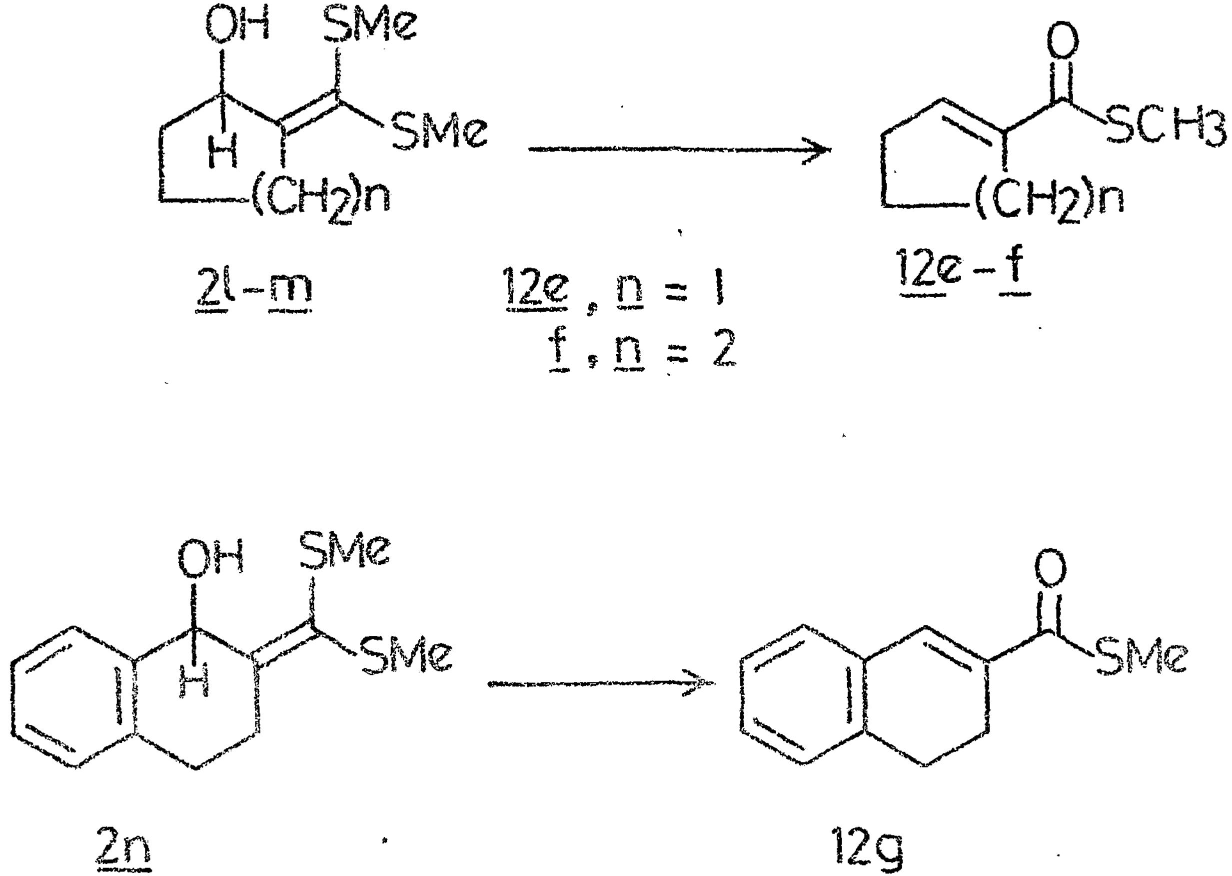
* Interestingly, while 12a-b and 12d are E-isomers, 12c was found to be exclusively Z-isomer. The reason for this stereoselectivity is, however, not clear and requires further study.



2 12

2 , 12a , Ar = C_6H_5 , R = H
b , Ar = p-MeC_6H_4 , R = H
c , Ar = p-Cl-C_6H_4 , R = H
d , Ar = p-EtO-C_6H_4 , R = H

Scheme 18

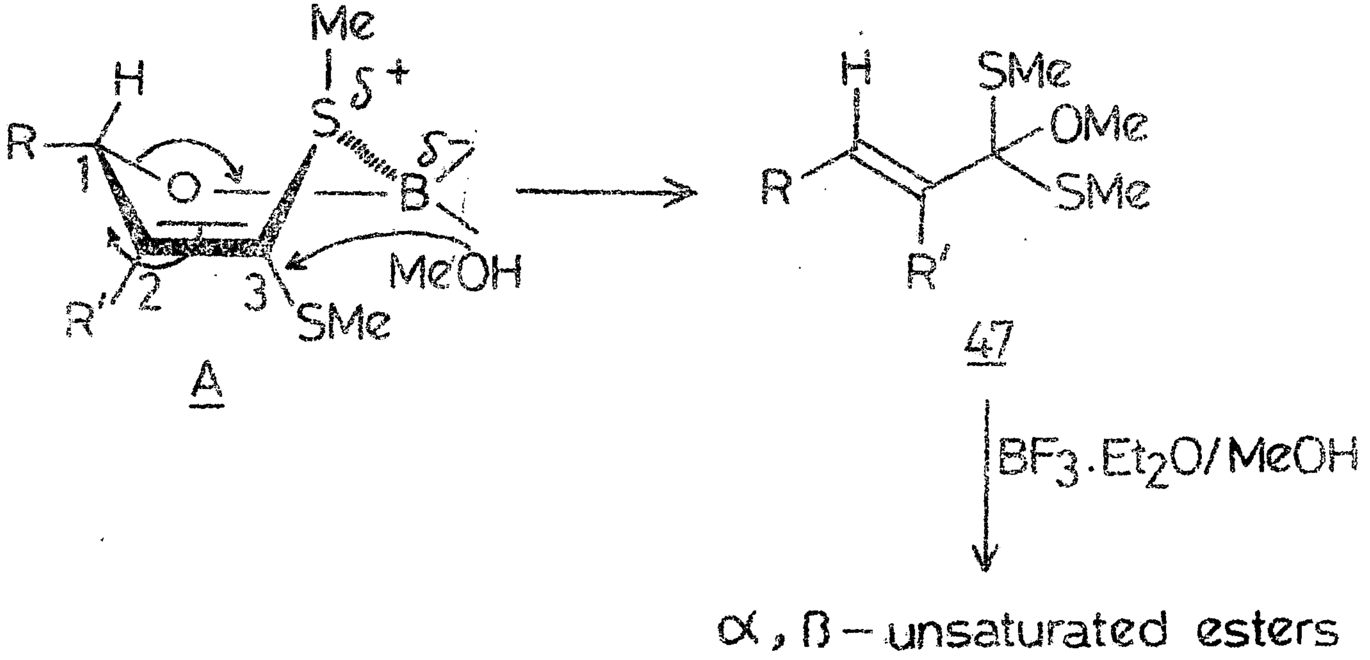

OH
SMe
SMe
H
(CH2)n
2l-m
12e, n = 1
f, n = 2
O
SCH3
(CH2)n
12e-f
OH
SMe
SMe
H
2n
O
SMe
12g

Scheme 19

carbonium ion appears to have been formed in the initial step directing the course of reaction to each of the several products described. However, when the carbinol acetals 2 were treated with borontrifluoride etherate in methanol, it appears that the formation of the carbonium ion is not involved. Instead, a six membered boat-like transition state A as proposed by Katzenllenbogen[4a] is formed (Scheme 20), wherein the bulkier substituent R at C_1 preferentially occupies the exo position in A yielding only the corresponding E-isomer, while the substituent R' at C_2 occupies sterically neutral position. The ketendithioacetal group appears to function, through the participation of divalent sulphur, more efficiently than the corresponding ester group in directing the stereoelectronic feature leading to a highly stereoselective cyclic elimination via A with concomitant addition of methanol to form the orthoester 47, which on solvolysis affords the corresponding E-isomer of the α,β-unsaturated esters 3.

III.3. SUMMARY AND CONCLUSION

In conclusion, a new general method for the conversion of easily available ketones to the corresponding stereoselective and regiospecific α,β-unsaturated esters/S-methylesters and aldehydes has been formulated through the easily available ketoketen S,S-acetals. The method provides


Me
δ+
S
δ−
B
R
H
1
O
2
3
R″
SMe
MeOH
A
H
R
R′
SMe
OMe
SMe
47
BF3.Et2O/MeOH
α, β – unsaturated esters

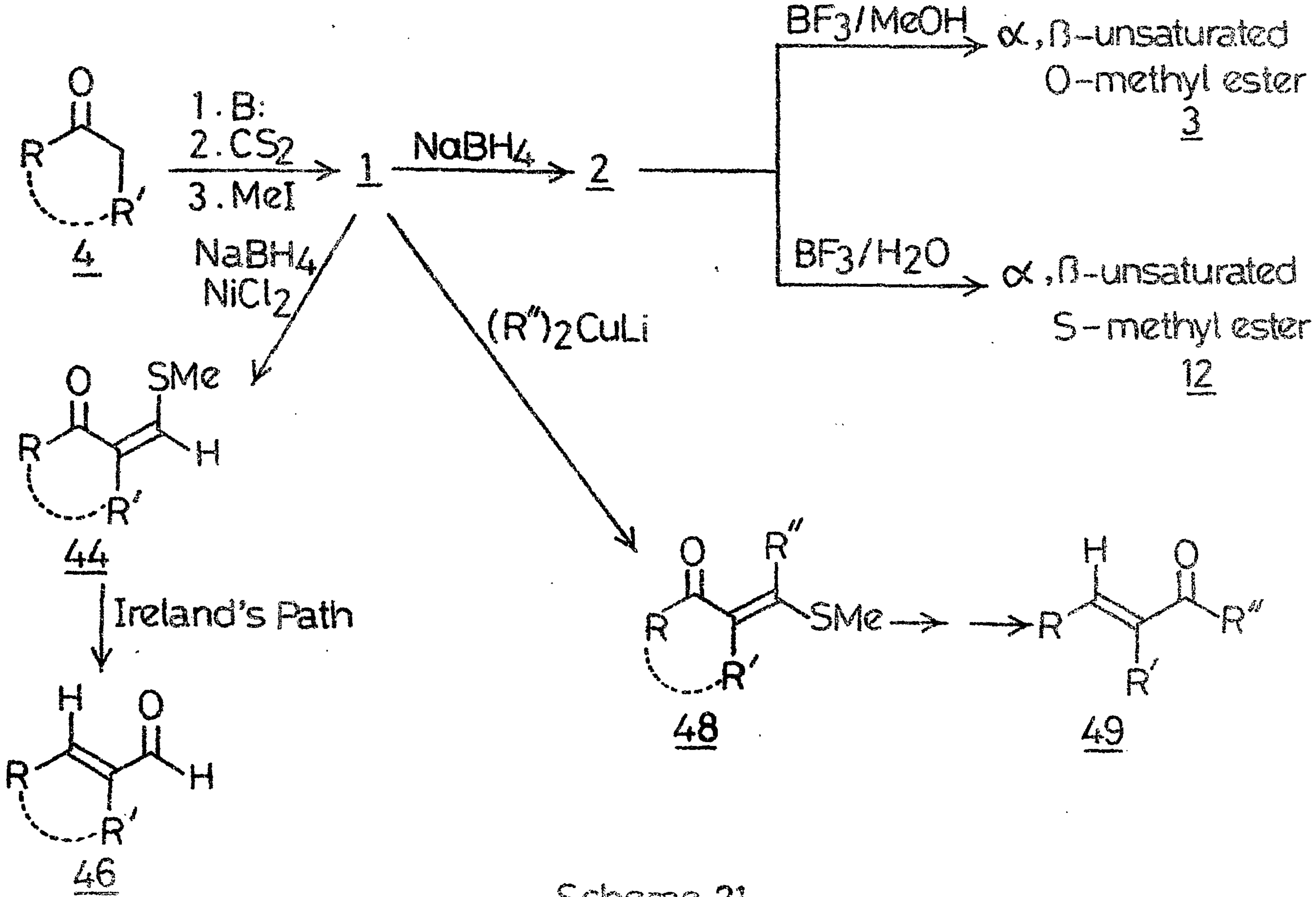
Scheme 20

a direct ester synthesis, which is advantageous in many instances, since they are more often preferred to their free acids in many synthetic applications. The only known method for the transformation $\underline{4} \rightarrow \underline{3}$ involves reduction of β-ketoester and subsequent dehydration of the resulting β-hydroxyester. However, the dehydration of hydroxyesters with various reagents are known to yield the α,β-unsaturated esters contaminated with several side products.[49] In the present method, the carbinol thioacetal, $\underline{2}$ can under suitable solvolytic conditions be converted into the corresponding α,β-unsaturated esters without any unwanted contaminants.

2. The overall transformation can be viewed as homologation of ketones at α-position through intermolecular 1,3-carbonyl transposition $(4 \rightarrow 1 \longrightarrow 2 \longrightarrow 3)$ (Scheme 21).[22]

3. The ketoketendithioacetals are shown to be excellent precursors as masked carboalkoxy groups with better selectivity during the reduction as well as solvalysis than the corresponding carboalkoxy group.

4. The ketoketendithioacetals derived from a variety of ketones can be common intermediates for the preparation of the corresponding α,β-unsaturated esters, thioesters and aldehydes and the corresponding ketones[11e] as shown in Scheme 21, thus making them versatile intermediates useful for the


4
1. B:
2. CS$_2$
3. MeI
1
NaBH$_4$
2
BF$_3$/MeOH
α,β-unsaturated
O-methyl ester
3
BF$_3$/H$_2$O
α,β-unsaturated
S-methyl ester
12
NaBH$_4$
NiCl$_2$
(R″)$_2$CuLi
44
Ireland's Path
46
48
49
R
R′
R″
O
H
SMe

Scheme 21

preparation of synthetically important series of α,β-unsaturated aldehydes, ketones and esters.

III.4. EXPERIMENTAL

General Methods: Melting points were determined on Boetius (German) apparatus and are uncorrected. Infrared Spectra were recorded on Perkin-Elmer Model 297 instrument. ^{1}H-NMR spectra were taken on a varian EM-390, 90 MHz spectrometer using Me_4Si as internal reference and the mass spectra were recorded on Hitachi RMU-6e mass spectrometer.

Starting materials: All the acetophenones, acetone, ethylmethyl ketone, cyclopetanone, cyclohexanone, α-tetralone and 6-methoxy-α-tratralone were available commercially and were purified before use, while propiophenone, b.p. 125-130° (21 mm);[23,24] butyrophenone b.p. 125-130 (21 mm);[21] valerophenone b.p. 135-140° (25 mm);[21] valerophenone b.p. 135-140° (25 mm);[21] methyl-n-butylketone b.p. 126-128°;[25] 5,8-dimethoxytetralone m.p. 58-62°[26] and benzosuberone 90-93°/1mm[27] were prepared according to the reported procedures.

All the known keten S,S-acetals 1a-m, were prepared by the known method as described in chapter II, while the known mercaptals 1n-p and the unknown 39 were prepared by the method described below:

To a suspension of the ketone (0.1 mol), 80% sodium hydride (6g) carbon disulphide (0.15 mol) and methyl iodide (0.25 mol) taken in 160 ml of dry benzene, dimethylacetamide (20 ml) was added in portions. After stirring the reaction mixture for 1-5 hr, it was poured over ice cold water (350 ml) and the organic layer separated. The aqueous extract is further washed with benzene and the combined extracts washed twice with water, dried over Na_2SO_4 and concentrated. The products thus obtained were purified by column chromatography on silica gel using hexane-benzene (4:1) as eluent. The physical and spectral properties of the unknown keten S,S-acetal are given below:

2,2-Bis(Methylthio)methylene-5,8-dimethoxy-1-tetralone (38) was obtained in 70% yields; yellow crystals (hexane/benzene), m.p. 56°C IR(KBr): 1670 (C=O); 1620 (C=C) cm^{-1}; NMR ($CDCl_3$): δ 2.33 (s, 6H, two $-SCH_3$): 2.55-3.10 [m, 4H, $-(CH_2)_2-$]; 3.73 (s, 6H, two $-OCH_3$); 6.70 (d, 2H, arom). Analysis (Found: C, 58.10; H, 5.78; Calc. for $C_{15}H_{18}O_3S_2$: C, 58.06, H, 5.80).

All the known methylthioalkenyl ketones 44a-d and the unknown 42 were prepared by the reduction of the corresponding ketoketen S,S-acetals with sodium borohydride and nickelchloride as reported in Chapter II.

2-Methylthiomethylene-5,8-dimethoxy tetralone (42) was obtained as a yellowish solid in 70% yield, m.p. 61°C; IR (Nujol): 1667 (C=O); 1618 (C=C) cm^{-1}; NMR (CCl_4); δ 2.47 (s, 3H, SCH_3); 2.81 [A_2B_2, 4H, $-(CH_2)_2-$]; 3.75 (s, 6H, two-OCH_3); 6.75 (m, 2H, arom); 7.86 (s, 1H, vinylic). Analysis (Found: C, 63.95; H, 6.32; Calc. for $C_{14}H_{16}O_3S$: C, 63.63; H, 6.32%).

Reduction of α-ketoketen S,S-acetals (1) to the carbinols (2): General procedure:

3,3-Bis(methylthio)-1-phenyl-2-propen-1-ol (2a)

To a well stirred suspension of keten S,S-acetal 19 (6.72 g, 0.03 mol) in absolute ethanol (70 ml), excess sodium borohydride (3.8 g, 0.1 mol) was added and the mixture was refluxed with stirring for 1 hr. The reaction mixture was then cooled and poured into water (150 ml) and extracted with chloroform (2 x 35 ml). The chloroform extract was washed twice with saturated salt solution (100 ml) and dried over Na_2SO_4. Evaporation of the solvent under vacuum yielded the carbinol 2a (6.8 g, 100%) as an undistillable thick viscous liquid, IR (neat): 3100-3600 (ν_{OH}) cm^{-1}; NMR (CCl_4); δ 2.08 (s, 3H, $-SCH_3$); 2.21 (s, 3H, $-SCH_3$); 4.07 (s, 1H, -OH); 5.80 (brS, 2H, olefinic and CHOH) 7.0-7.5 (m, 5H, arom).

The keten S,S-acetals **1b**-**d**, **1n**-**p** and **38** were reduced by the same procedure and the carbinols **2b**-**d**, **2n**-**p** and **39** were all obtained as unstable thick viscous liquids in nearly quantitative yields, which were directly used for the preparation of α,β-unsaturated esters without further purification and characterization.

The keten S,S-acetals **1e**-**m** which were liquids and soluble in methanol were reduced by a slightly different method. To a stirring solution of the keten S,S-acetal **1e** (7.14 g, 0.03 mol) in absolute methanol (70 ml), excess sodium borohydride (5.7 g, 0.15 mol) was added in small lots. Fresh addition was made only when evolution of hydrogen has subsided. The mixture was further stirred for 0.5 hr at room temperature after complete addition of the sodium borohydride and worked up as described above.

The infra-red spectra of all the carbinols **2a**-**p** and **39** showed strong band between 3100-3600 cm^{-1} due to O-H stretching.

Solvolysis of 2a in 10% methanolic HCl: A solution of **2a** (4g, 0.015 mol) in methanol (75 ml) and 10% HCl (15 ml) was stirred at room temperature for 24 hr. It was then poured into water (150 ml), extracted with chloroform (2 x 35 ml), washed with saturated sodium bicarbonate and finally with water. It was then dried over Na_2SO_4 and concentrated to give a dark brown liquid, which when passed through a column of silica gel and eluted with hexane gaves S-methyl-3-methylthio-3-phenyl propanethioate **11a**, 1.75 g (45%) as a colorless viscous liquid (TLC single spot). IR (neat): 1675 (C=O) cm^{-1}; NMR (CCl_4): δ 1.27 (d, 3H, $-CH_3$); 2.07 (s, 3H, $-SCH_3$); 2.28 (s, 3H, $-SCH_3$); 2.4 - 3.4 (m, 3H, CH- and $-CH_2$); Analysis (Found: C, 43.63; H, 7.60; Calc. for $C_6H_{12}OS_2$ (164): C, 43.90; H, 7.31.

Solvolysis of 2a in refluxing methanol and conc. H_2SO_4: Methyl-3-methylthio-3-phenylpropionate **28**: A solution of **2a** (3.89 g, 0.015 mol) in absolute methanol (35 ml) and conc. H_2SO_4 (3 ml) was refluxed for 14 hr. work-up of the reaction mixture as described in the above experiment yielded a dark viscous residue which was column chromatographed over silica gel. Elution with hexane yielded **24** as a colorless viscous liquid, 1.55 g (43%) (TLC single spot); IR (neat): 1740 (C=O) cm^{-1}; NMR (CCl_4): δ 1.8 (s, 3H, SCH_3); 2.75 (d, 2H, $-CH_2-$); 3.5 (s, 3H, $-OCH_3$); 4.07 (t, 1H, $-CH$); 7.2 (brS, 5H, arom); Mass: M^+ 210; Analysis: (Found, C, 62.58; H, 6.85; Calc. for $C_{11}H_{14}SO_2$ (210): C, 62.85; H, 6.66..

Solvolysis of **2a** in aqueous trifluoroacetic acid: To 4 g (0.015 ml) of **2a**, 10 ml of trifluoroacetic acid was added and the mixture was stirred for 5 min. The reaction mixture was diluted with 3 ml of water and the stirring was continued for another 5 min. The mixture was then refluxed in an oil bath for 8 hr and worked-up as described above. Purification by column chromatography yielded 11a, (superimposable IR and NMR) 2.3 g (65%).

Preparation of O-Methyl α,β-unsaturated esters (3).

General procedure:

Preparation of Methyl Cinnamate (3a)

To the crude carbinol 2a (6.80 g, 0.03 mol) obtained by reduction of 6.72 g (0.03 mol) of 1a, 17 ml of borontrifluoride etherate was added and the reaction mixture was stirred at room temperature for 5 min. It was then diluted with 70 ml of absolute methanol and the solution was refluxed for 8-24 hr (Table III). The cooled reaction mixture was poured over water (200 ml) and extracted with chloroform (2 x 50 ml). The combined chloroform extract was washed successively with saturated sodium hydrogen carbonate solution (200 ml) and saturated salt solution (100 ml) and dried over Na_2SO_4. Evaporation of solvent gave the crude cinnamate (3a) which was further purified by passing through a short column of silica gel and eluted with hexane. The IR and NMR spectra of 3a were identical with the reported values. The esters 3a-g, 3n-p and 4o were purified by passing through a silica gel column, using hexane as eluent, while the esters 3h-m were purified by distillation under reduced pressure. All the known esters were characterised by comparison of their b.p./m.p. and IR/NMR spectral data (Table I and III) with those of reported data and with authentic samples. The spectral and analytical data of the unknown esters and of those esters whose spectral data are not reported in the literature are given in Tables I and III.

Hydrolysis of 4o : The ester 4o (2.5 g, 0.01 mol) was refluxed with 10% NaOH (10 ml) in 50 ml ethanol for 5 hr. The ethanol was removed under reduced pressure and the reaction mixture diluted with 50 ml water. The water extract was washed once with ether (30 ml) and acidified with conc. HCl (1.5 ml). The white solids obtained were filtered off and washed 2-3 times with water and dried in vacuum. The acid 43 is obtained as a white solid, yield 2.2 g (96%), m.p. >230°C (lit. > 220°C).[19a] The IR and NMR spectra of 43 were identical with those of reported.[19a]

Preparation of S-methyl α,β-unsaturated thiocarboxylate (12)

General procedure:

Preparation of S-methyl thiocinnamate 12a:

The carbinol 2a (6.80 g, 0.03 mol) obtained by reduction of 6.72 g (0.03 mol) of 1a was dissolved in 100 ml of dry ether and 25 ml of borontrifluoride etherate was added and stirred at room temperature for 5 min. The reaction mixture was then diluted with 20 ml of water and after refluxing for 12 - 16 hr (Table IV) it was poured into 150 ml of water and extracted with benzene (2 x 75 ml). The benzene layer was washed with saturated bicarbonate solution (250 ml) and finally with water, dried over sodium sulphate and evaporated to give a dark coloured residue, which on column chromatography over silica gel using hexane as eluent gave 12a (2.94 g, 55%) as a low melting solid, m.p. 48°C (lit. 49-9°).[21] IR (Nujol): 1660 (C=0) cm^{-1}; NMR (CCl_4); δ 2.35 (s, 3H, $-SC\underline{H}_3$); 6.6 (d, J=15 Hz, 1H, olefinic); 7.1 - 7.65 (m, 6H, arom+olefinic). Analysis (Found: C, 67.72; H, 5.93; Calc. for $C_{10}H_{10}OS$: C, 67.41, H, 5.61%).

The S-methylesters 12b-g were prepared by the above general method and their spectral and analytical data are given in Tables II and IV.

Preparation of substituted connamaldehydes 46a-d and 43

Preparation of 43:

To a stirring suspension of 42 (6.6 g, 0.025 mol) in 100 ml of absolute ethanol, 3.09 (0.78 mol) of sodium borohydride was added and the reaction mixture was refluxed for 2 hr. Work up of the reaction mixture as described in the general procedure for the reduction of keten S,S-acetal

1a yielded the crude carbinol (6.60 g, 99%) as thick viscous liquid; IR (neat): 3100-3600 (O-H) cm^{-1}. The carbinol was then dissolved in 150 ml of ethanol and 22 ml of 10% HCl and the solution was stirred at room temperature for 48 hr. It was then poured over water (150 ml), extracted with benzene (3 x 50 ml), washed with sodium bicarbonate solution (2 x 100 ml) and water (2 x 100 ml), dried (N_2SO_4) and evaporated to yield the crude aldehyde 43 which was further purified by passing through silica gel column. Elution with hexane gave 3.24 g (60%) of 43, m.p. 91.5 - 92.8 (lit. 91-92°C).[19d] Its IR and NMR spectra were identical with the reported values.

The following cinnamaldehydes were also prepared according to the above general procedure. The IR and NMR spectra of 46a-d were identical with those of the authentic samples. Cinnamaldehyde (46a) b.p. 130°/20 mm;[35a] *p*-methylcinnamaldehyde (46b), m.p. 42°;[35b] *p*-chlorocinnamaldehyde (46c), 62-63°C;[35c] 2-methylcinnamaldehyde (46d), b.p. 131°/16 mm.[35d]

Table 1

Spectral data of products (3f-g), (3j-k), (3o-p) and (4o)

Product	IR^a(ν_{max}) cm^{-1}	NMR (CCl_4) δ
E 3f	1715 (C=O) 1640 (C=C)	1.15 (t, 3H, $C\underline{H}_3CH_2$); 2.45 (q, 2$\underline{H}$, $CH_3C\underline{H}_2$-); 3.72 (s, 3H, -$OC\underline{H}_3$); 7.28 (s, 5H, arom); 7.52 (s, 1H, olefinic).
E 3g	1720 (C=O) 1635 (C=C)	0.92 [t, 3H, $C\underline{H}_3$ $(CH_2)_2$]; 1.1-1.6 (m, 2H, $CH_3C\underline{H}_2CH_2$); 2.40 (t, 2H, $CH_3CH_2C\underline{H}_2$); 3.72 (s, 3H, -$OC\underline{H}_3$); 7.25 (brs, 5H, arom); 7.52 (s, 1H, olefinic).
E 3j	1730 (C=O) 1600 (C=C)	0.91 [brt, 3H, $C\underline{H}_3(CH_2)_2CH_2$]; 1.20-1.55 [brm, 4H, $CH_3(C\underline{H}_2)_2CH_2$]; 1.79 (d, 3H, J=6Hz, $C\underline{H}_3CH$=); 2.18-2.40 [brt, 2H, $CH_3(CH_2)_2C\underline{H}_2$]; 3.61 (s, 3H, -$OC\underline{H}_3$); 6.71 (q, J=6Hz, 1H, olefinic).
E 3k	1731 (C=O) 1600 (C=C)	0.9 [brt, 3H, $C\underline{H}_3(CH_2)_3CH_2$]; 1.15-1.55 [brm, 6H, $CH_3(C\underline{H}_2)_3CH_2$]; 1.8 (d, 3H, $C\underline{H}_3CH$=); 2.28 [brt, 2H, $CH_3(CH_2)_3C\underline{H}_2$]; 3.65 (s, 3H, -$OC\underline{H}_3$); 6.70 (q, J=6Hz, olefinic).
E 3o	1715 (C=O)^b 1640 (C=C)	2.42-2.90 [m, 4H, -$(CH_2)_2$-]; 3.71 (s, 3H, -$OC\underline{H}_3$); 3.76 (s, 3H, -$OC\underline{H}_3$); 6.56-7.15 (m, 3H, arom); 7.35 (s, 1H, olefinic).

Table I (contd.)

3p	1715 (C=O) 1640 (C=C)	0.80 (m, 2H, $-C\underline{H}_2$); 1.80-2.15 (t, 2H, $-C\underline{H}_2$); 2.55 (t, 2H, $-C\underline{H}_2$); 3.70 (s, 3H, $-OC\underline{H}_3$); 7.20 (m, 4H, arom); 7.55 (s, 1H, olefinic).
4o	1716 (C=O)^b	2.25-2.80 (m, 4H, $-(C\underline{H}_2)_2-$; 3.70 (s, 3H, $-OC\underline{H}_3$); 3.73 (s, 3H, $-OC\underline{H}_3$); 3.77 (s, 3H, $OC\underline{H}_3$); 6.72 (d, 2H, arom); 7.78 (s, 1H, olefinic).

[a] neat

[b] nujol

Table II

Spectral data of S-Methyl α, β -Unsaturated Thioesters (12b-g)

Product	IR (ν_{max}) cm^{-1}	NMR (CCl_4) (δ)
12b	1665 (C=O)[a]	2.32 (s, 3H, $-SC\underline{H}_3$); 6.55 (d, J = 16Hz, 1H, olefinic); 7.1-7.65 (m, 5H, aromatic+olefinic).
12c	1660 (C=O)[b]	1.35 (t, 3H, $C\underline{H}_3CH_2O$); 2.28 (s, 3H, $-SC\underline{H}_3$); 3.93 (q, 2H, $CH_3C\underline{H}_2O$); 5.05 (d, J = 9Hz, 1H, olefinic); 5.93 (d, J = 9Hz, 1H, olefinic); 6.55-7.31 (dd, A_2B_2, 4H, aromatic).
12d	1655 (C=O)[c]	2.15 (s, 3H, $-SC\underline{H}_3$); 2.20 (s, 3H, $-C\underline{H}_3$); 2.22 (s, 3H, $-C\underline{H}_3$); 7.01-7.32 (q, A_2B_2, 4H, arom); 7.51 (brs, 1H, olefinic).
12e	1660 (C=O)[b]	1.70-2.72 [m, 6H, $-(CH_2)_3-$]; 2.28 (s, 3H, $-SC\underline{H}_3$); 6.85 (brs, 1H, olefinic).
12f	1662 (C=O)[b]	1.61-1.84 [m, 4H, $-(C\underline{H}_2)_2-$]; 2.05-2.41 [m, 4H, $-(C\underline{H}_2)_2-$]; 6.85 (brs, 1H, olefinic).
12g	1658 (C=O)[b]	2.30 (s, 3H, $-SC\underline{H}_3$); 2.40-2.92 [m, 4H, [$-(C\underline{H}_2)_2-$]; 6.85-7.15 (m, 4H, arom); 7.36 (s, 1H, olefinic).

[a] neat.

[b] nujol

[c] KBr

Table III

Analytical Data for α,β-Unsaturated O-Methyl Esters (3a-p)

Product^{a,b}	Reflux time (hr)	Isolated yields (%)	m.p/b.p	lit. m.p/b.p	Molecular formula	Analysis(%)	
						Calc. found C	H
3a	24	70	37	36.5^{28a}	$C_{10}H_{10}O_2$ (162.19)	73.95 74.41	6.16 6.45
3b	18	68	73-74	$72-73^{29}$	$C_{10}H_9ClO_2$ (188.68)	63.83 64.22	4.78 4.99
3c	15	75	57-58	$55-56^{29}$	$C_{11}H_{12}O_2$ (176.21)	75.00 75.45	6.82 7.20
3d	24	72	68-69	$68-69^{30}$	$C_{12}H_{14}O_3$ (206.24)	69.90 70.33	6.79 7.20
3e	24	67	38-39	$38-39^{15e,g^c}$	$C_{11}H_{12}O_2$ (176.21)	75.00 75.46	6.82 7.25
3f	24	75	Yellow viscous liquid	Acid known^{15f} m.p. 103-104°	$C_{12}H_{14}O_2$ (190.24)	75.79 76.20	7.37 7.75
3g	20	75^d	Yellow viscous liquid	Acid known^{15f} m.p. 93°	$C_{13}H_{16}O_2$ (204.27)	76.47 76.88	7.84 8.25

Table III (contd.)

3h	16	50[d]	121 (b.p.)	121°[28b, 31c]	$C_5H_8O_2$ (93.12)	64.51 64.93	8.60 8.95
3i	16	54[d]	140 (b.p.)	139.4[28b, 31c]	$C_6H_{10}O_2$ (114.14)	63.15 63.47	8.77 9.20
3j	18	75[d]	91-93°/25 mm	Et-ester[16c] known	$C_9H_{16}O_2$ (156.22)	69.23 69.66	10.25 10.67
3k	24	80[d]	98-100/25 mm	-	$C_{10}H_{18}O_2$ (170.25)	70.58 70.96	10.59 10.98
3l	15	70[d]	87-88°/15 mm	57°/10 mm[17c, 32]	$C_7H_{10}O_2$ (126.15)	66.66 66.97	7.93 8.35
3m	15	75[d]	87-88°/15 mm	100°/30 mm[32c, 33]	$C_8H_{12}O_2$ (140.18)	68.57 68.96	8.57 8.98
3n	15	73	68	Ref.[34c]	$C_{12}H_{12}O_2$ (188.27)	76.59 76.97	6.38 6.77
3o	16	67	50-51°	51-50[4c]	$C_{13}H_{14}O_3$ (218.25)	71.56 71.98	6.42 6.83
3p	16	70	Yellow viscous liquid	-	$C_{13}H_{14}O_2$ (202.25)	77.23 77.50	6.93 7.43

(a) All the known esters were also characterized by comparison of b.p/m.p. and IR/NMR spectral data with those reported in the literature. (b) HNMR spectra of all products indicated 98% purity. (c) Literature references for IR and NMR spectra. (d) glc showed 95% purity : condition : Column : 10% DC-200 (2 m x 1/8 in.).

Table IV

S-Methyl α,β-Unsaturated Thiocarboxylate, 12b-g

Product	Reaction time	Isolated yield(%)	m.p./b.p.	Molecular formula	Mass (M^{+})
12b	16	60	95-96 (m.p.)	$C_{10}H_{8}ClOS$	211
12c	14	75	Viscous liquid	$C_{12}H_{3}O_{2}S$	221
12d	15	75	150-152 (b.p.)	$C_{11}H_{11}OS$	191
12e	15	55	71-73 (b.p.)	$C_{7}H_{10}OS$	142
12f	16	70	51/10 mm	$C_{8}H_{12}OS$	153
12g	18	65	160 (b.p.)	$C_{12}H_{12}OS$	204

Analytical data for carbon and hydrogen were found satisfactory.

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CHAPTER IV

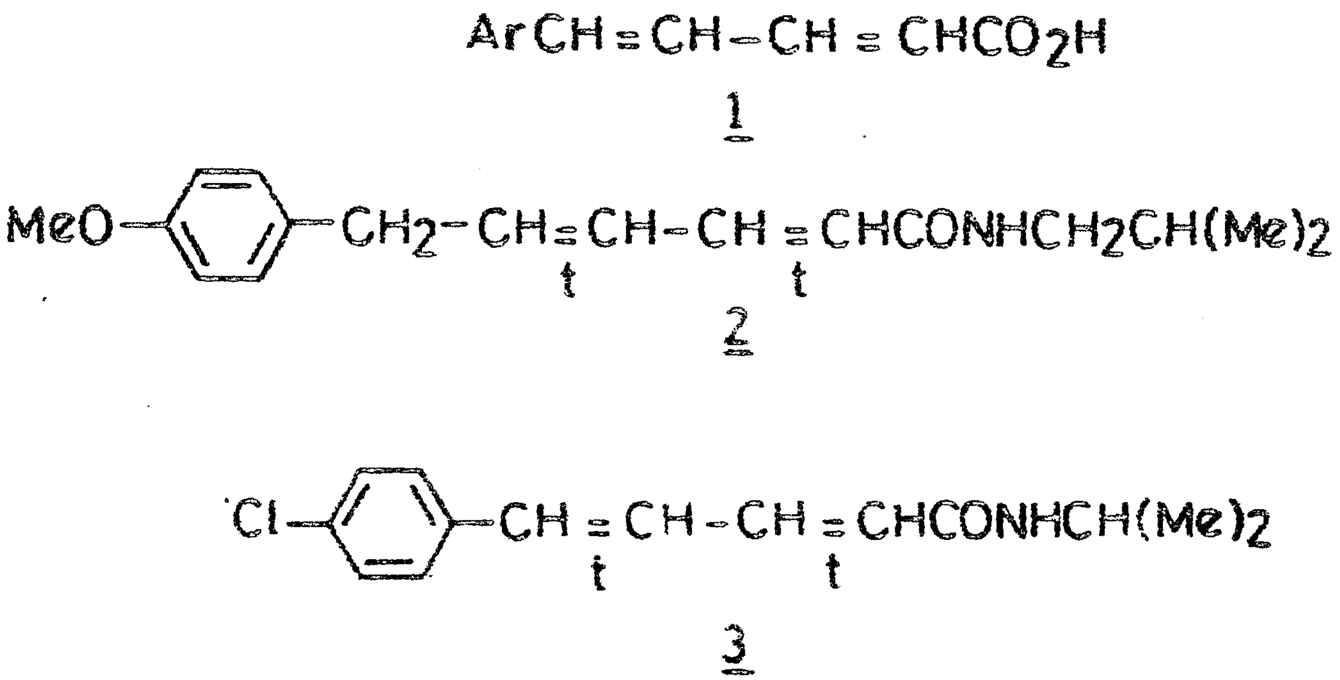
A NOVEL GENERAL METHOD FOR 5-ARYL -2,4-PENTADIENOATES

IV.1. INTRODUCTION

In the preceding chapter a new general method for the conversion of easily available ketones to the corresponding α,β-unsaturated esters has been devised. These esters have been shown to be formed with high stereo- and regioselectivity. The scope of the method has been demonstrated by choosing substrates of wide structural variations. The further applicability of this method was contemplated with a view to extending it to the synthesis of diene- and polyene esters. In the present chapter a few selected experiments have been presented, wherein the method was extended for the synthesis of methyl 5-aryl-2,4-pentadienoates, which are known to exhibit marked biological activity. For example, a number of 5-aryl-2,4-pentadienoic acids <u>1</u> and their esters are known to exhibit activity similar to that of abscisic acid,[1-4] which is known to enable plants to cope up with water deprivation arising from draught conditions. Inspite of the fact that these synthetic acids and their esters exhibit lower activity than abscisic acid itself, their easy accessibility synthetically should prove useful in the studies regarding adaptability of plants under draught conditions. Similarly pipervatine (2), a naturally occurring amide, having structural features similar to 1 has been shown to possess marked physiological activity like nerve depressant, heart poison local anesthetics and powerful silagogue 5. The 5-(p-chlorophenyl)-N-isopropyl-2,4-pentadieneamide 3 (Scheme 1) exhibit potential antimalarial activities more potent than quinine itself.[6] Some of the 5-aryl-2,4-pentadienoic acids are also shown to have marked antibacterial and antifungal activities.[7] In view of the marked and diverse physiological activities exhibited by these dienoic acids and esters, it was of interest to extend our method of ene-ester synthesis for the preparation of these 1,3-dienoic esters 5 (Scheme 5).

IV.2. RESULTS AND DISCUSSIONS

Our literature survey at this stage revealed that the methods described for the synthesis of these acids are not always satisfactory due to one reason or the other. One of the methods for such compounds (1) involves the condensation of substituted cinnamaldehyde with malonic acid followed by decarboxylation of the intermediate product.[8-12] The difficulties encountered in the synthesis of both substituted cinnamaldehydes and the malonic acids make the method less attractive besides overall poor yields

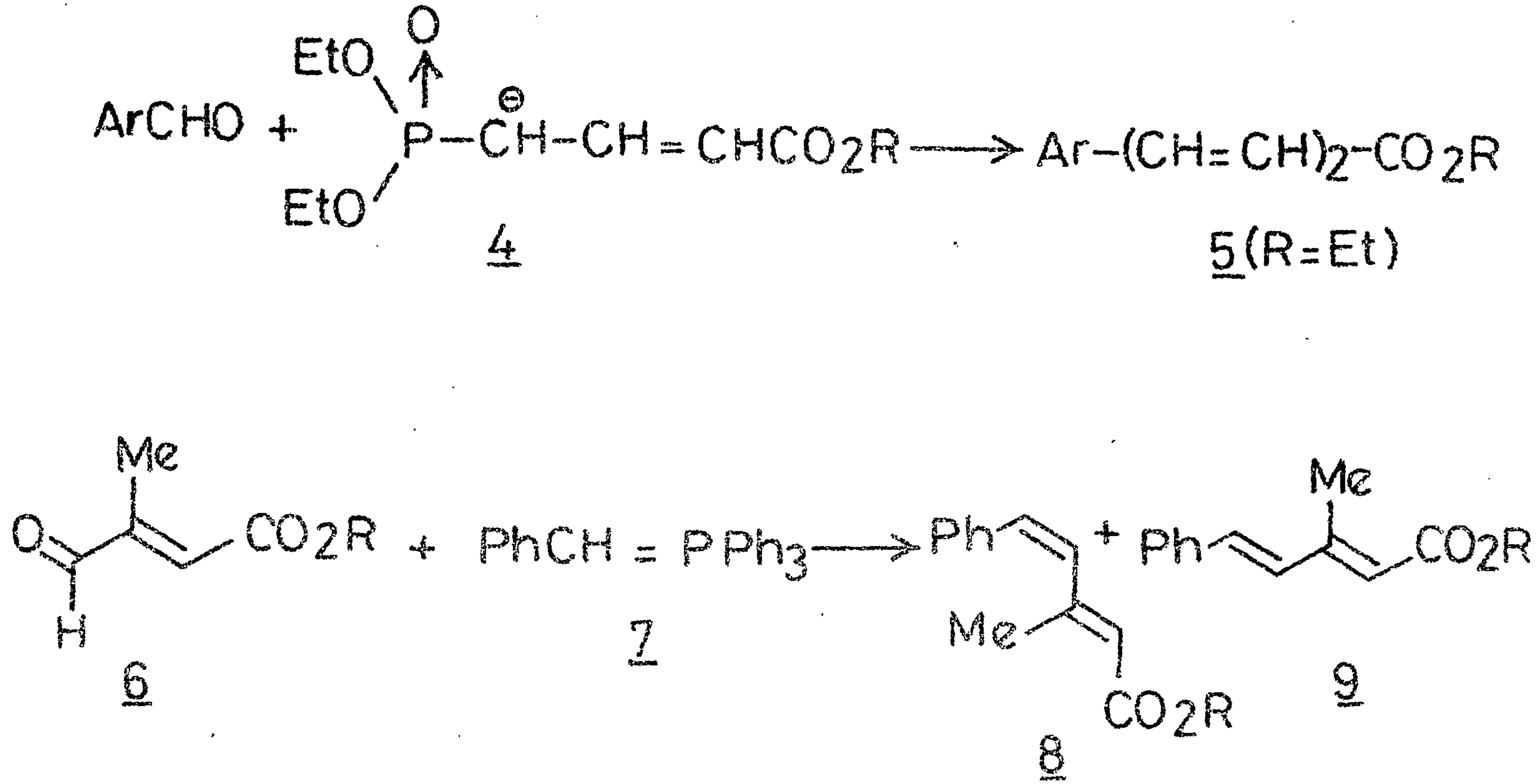

ArCH=CH–CH=CHCO2H
1
MeO
CH2–CH=CH–CH=CHCONHCH2CH(Me)2
t
t
2
Cl
CH=CH–CH=CHCONHCH(Me)2
t
t
3

Scheme 1

of the desired products. The Reformatsky reaction has also been used for the preparation of these compounds. Thus p-chlorobenzaldehyde and ethyl-γ-iodocrotonate gave the corresponding pentadienoic acid through its ethyl ester.[13] Under similar conditions, 3,4,5-trimethoxybenzaldehyde and methyl-γ-bromocrotonate afforded the corresponding methyl ester[14] in low yields. This method was not further explored due to the reported abnormal reaction on the carbon atom in the Reformatsky reaction.[15]

Bohlmann[15] extended the method developed by Wittig and Hagg[16] to successfully convert a series of aromatic aldehydes to the corresponding 5-phenyl-2,4-pentadienoic acid methyl esters by treatment with appropriate triphenyl phosphonium salts of methyl-γ-bromocrotonate and sodium methoxide. Subsequent modification of this reaction involved use of cinnamaldehyde for the synthesis of 5-aryl-2,4-pentadienoic acid esters.[19-23] Elslager[6] has synthesized a series of the ethyl esters 5 of 1 by reacting substituted benzaldehydes with 4-diethylphosphonocrotonate anions 4 (Scheme 2) which are known to give improved yields over the corresponding phosphoranes.[25]

Recently Reddy and Krishna Rao[25] have reported the synthesis of 5-aryl-2,4-pentadienoic acids (1) by using Vilsmeier reaction with styryl alcohol 10 to give the


ArCHO
EtO
EtO
O
P
CH–CH = CHCO2R
4
Ar–(CH= CH)2-CO2R
5(R=Et)
Me
O
H
CO2R
6
PhCH = PPh3
7
Ph
Me
CO2R
8
Ph
Me
CO2R
9

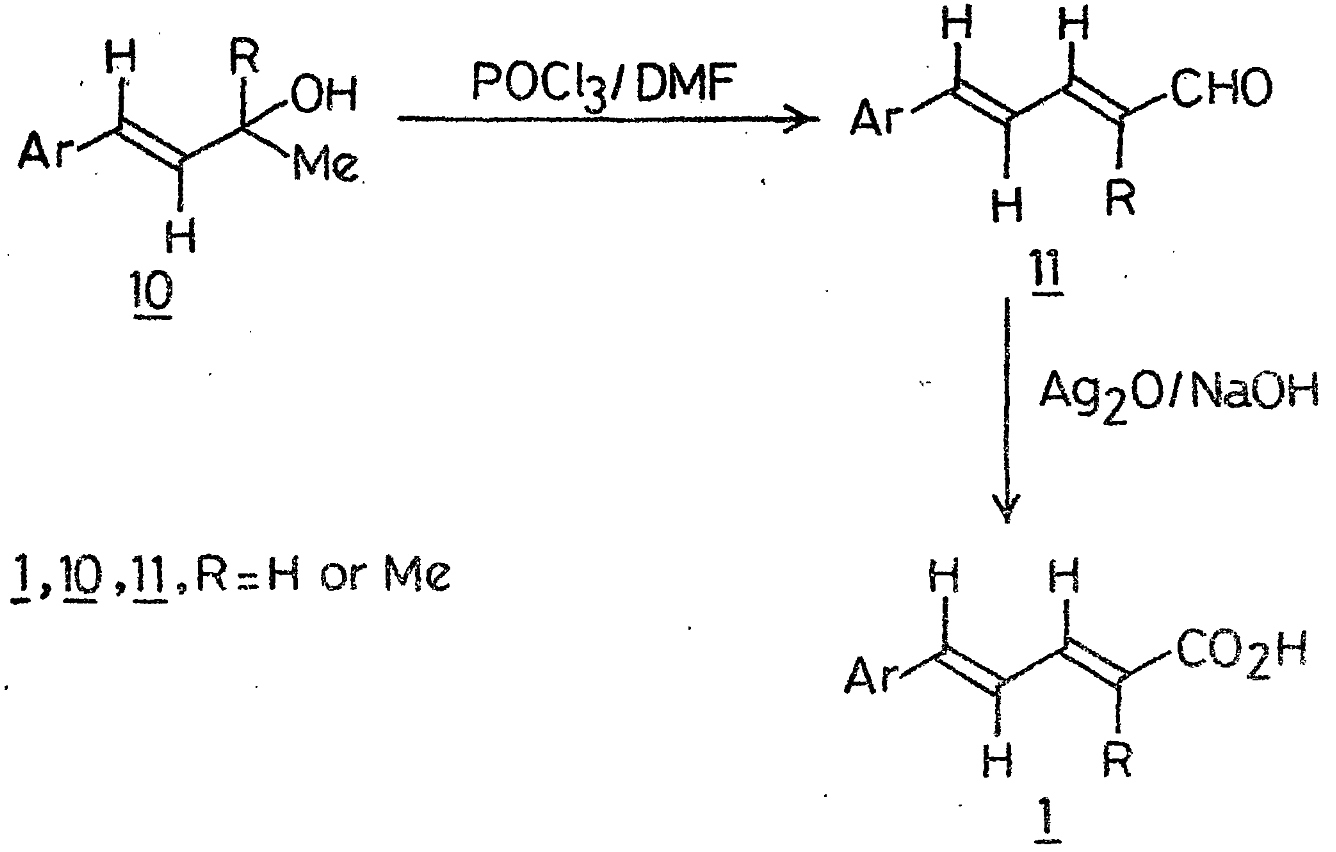
Scheme 2

corresponding aldehyde 11 which were subsequently oxidized to the desired acids 1 (Scheme 3).

Another novel approach has been described by Ghera and co-workers[26] involving alkylative elimination and ring opening of cyclopropylcarbinyl anions 13, derived from cyclopropane sulphonates 12 (Scheme 4). There are other less important methods for the synthesis of 1 or 5 which are not of general synthetic utility, have also been described in the literature.

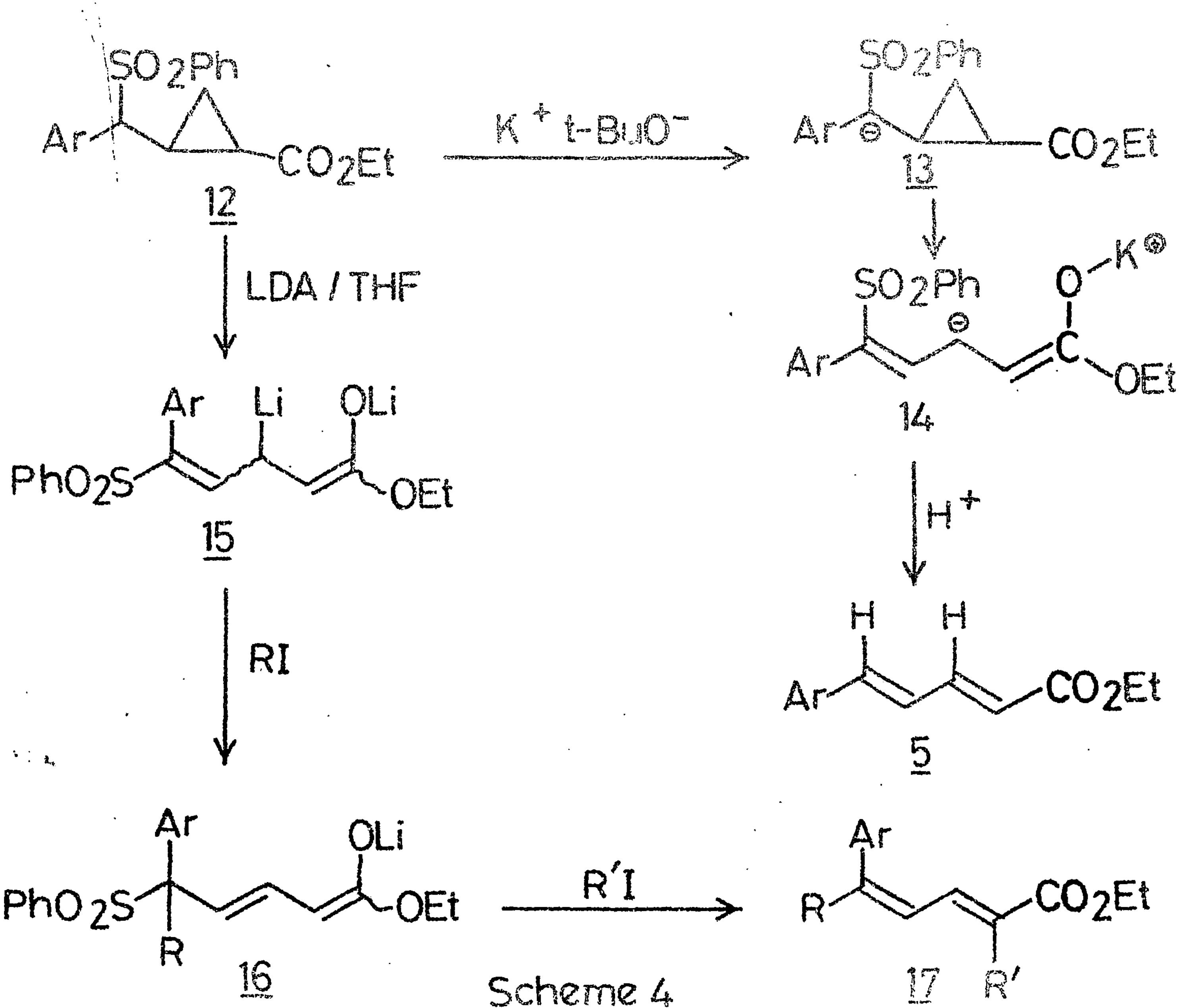
In the present investigation it was considered of interest to use the condensation product 19 (Scheme 5) which are easily obtained from the corresponding benzaldehyde and the keten S,S-acetal 18 derived from acetone (18a) or ethyl methyl ketone (18b), in excellent yields. These condensation products 19 underwent smooth 1,2-reduction exclusively with sodium borohydride to give the corresponding carbinols in quantitative yields. These carbinols underwent smooth solvolytic rearrangement to give the corresponding dieneesters 5 in excellent yields.

A similar approach was reported by Nakagawa and co-workers[27-28] for the synthesis of polyene aldehydes using condensation product of benzaldehyde and thiomethylene ketones 21 (Scheme 6). However, their method of preparation of the



1, 10, 11, R = H or Me

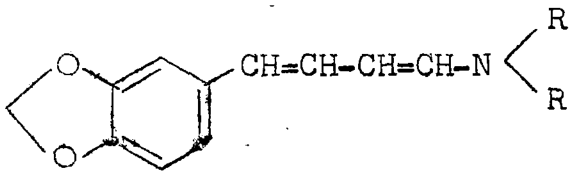
Scheme 3


SO2Ph
Ar
CO2Et
12
K+ t-BuO−
13
14
LDA / THF
Li
OLi
OEt
PhO2S
15
H+
H
5
RI
R
16
R′I
R′
17
K⊕

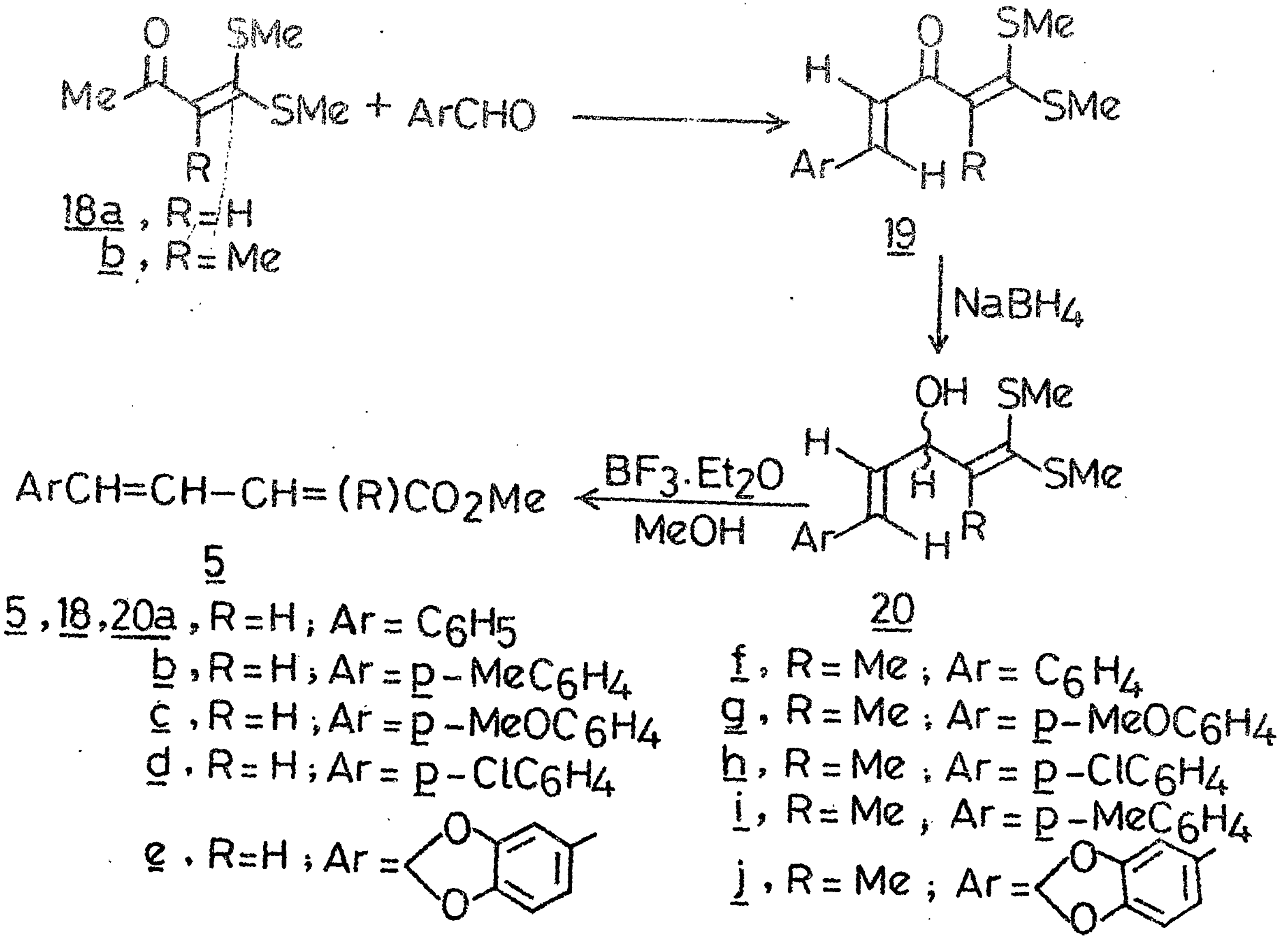
Scheme 4

thiomethylene ketones 18 involved the use of n-butylemercaptan and acetylacetylene, where the latter is not so easily available as starting material. On the other hand the ketoketendithioacetals 19 derived from acetone or ethylmethylketone can be prepared in large quantities with easy starting materials and should therefore, be an attractive method for the synthesis of dienes and polyene esters.

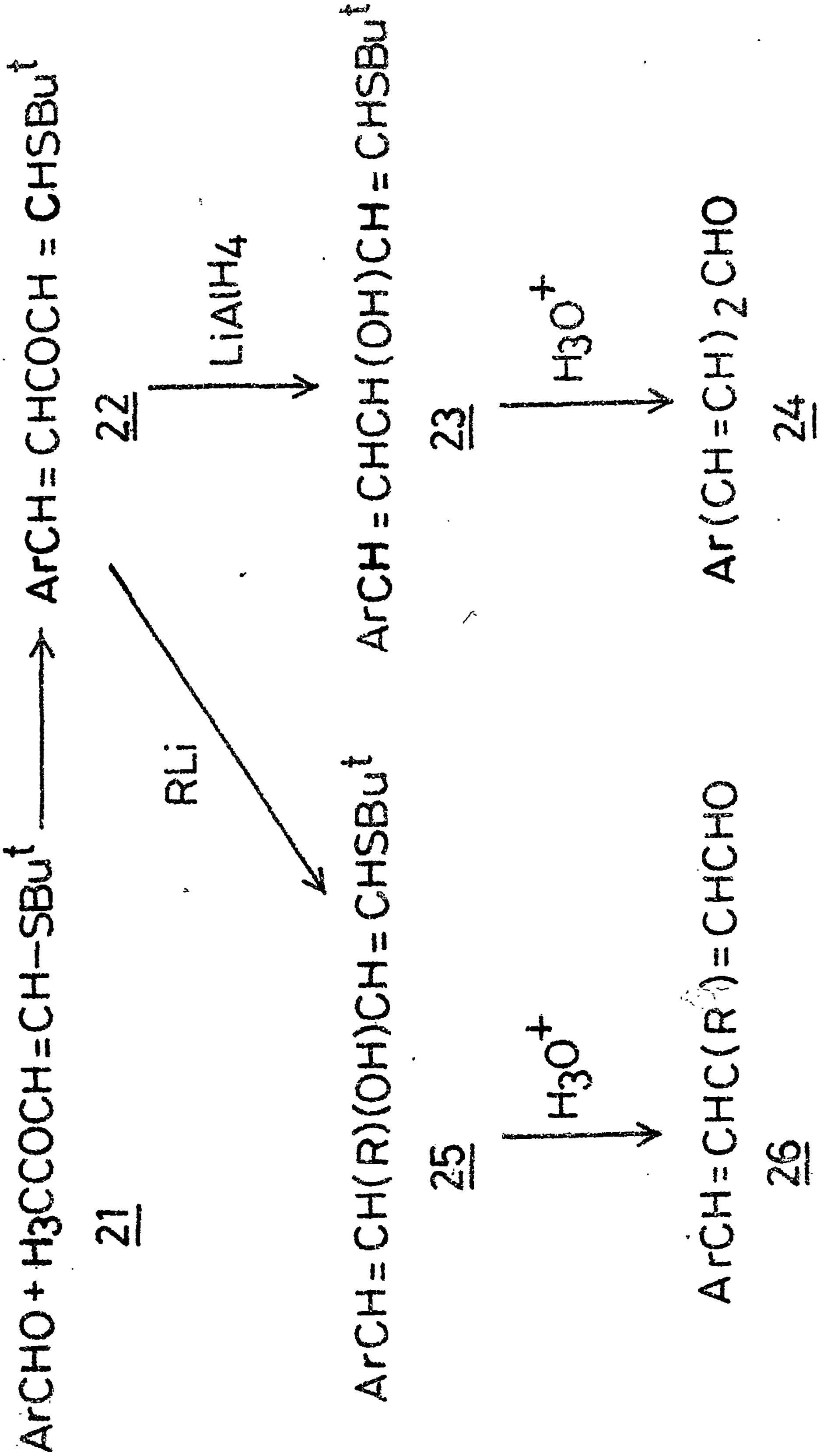
When the condensation product 19a obtained from acetone mercaptal 18a and benzaldehyde was reduced with sodium borohydride in refluxing methanol, the corresponding carbinol acetal 20a was obtained in quantitative yield. The carbinol acetal 20a on solvolytic rearrangement with boron trifluoride etherate in methanol gave diene ester 5a in 75% yield. The structure of 5a was confirmed by its spectral and analytical data (Table II). The other arylidene derivatives 19h-j similarly yielded the corresponding esters 5b-j in 55-77% overall yields. It is pertinent to note that methyl piperate (5e) has been isolated from some species of Piper[29] and is the starting material for the synthesis of piperine (27) and related pepper alkaloids Trichostachine (28) and Piperlongumine (29).[30]



27, R,R' = $-(CH_2)_5-$; 28, R,R' = $-(CH_2)_4-$; 29, R, R' = Me_2CH-CH_2.


Me
O
SMe
SMe
R
ArCHO
18a, R = H
b, R = Me
H
O
SMe
SMe
Ar
H
R
19
NaBH4
OH
SMe
H
H
SMe
Ar
H
R
20
BF3.Et2O
MeOH
ArCH=CH–CH=(R)CO2Me
5
5, 18, 20a, R = H ; Ar = C6H5
b, R = H ; Ar = p-MeC6H4
c, R = H ; Ar = p-MeOC6H4
d, R = H ; Ar = p-ClC6H4
e, R = H ; Ar =
f, R = Me ; Ar = C6H4
g, R = Me ; Ar = p-MeOC6H4
h, R = Me ; Ar = p-ClC6H4
i, R = Me ; Ar = p-MeC6H4
j, R = Me ; Ar =
O
O

Scheme 5


ArCHO + H3CCOCH=CH–SBu^t
21
ArCH=CHCOCH=CHSBu^t
22
LiAlH4
RLi
ArCH=CHCH(OH)CH=CHSBu^t
23
ArCH=CH(R)(OH)CH=CHSBu^t
25
H3O+
Ar(CH=CH)2CHO
24
ArCH=CHC(R)=CHCHO
26

Scheme 6

IV.3. STEREOCHEMICAL ASSIGNMENTS

The melting points of the esters **5a**-**e** were found to be identical with the earlier reported values for these esters which were arbitrarily assigned α-trans γ-trans (2-*E*, 4-*E*) configurations.[15,31,32] However, our studies of NMR spectra of the esters **5a**-**e** (Table II) showed them to possess α-trans-γ-cis (2-*E*,4-*Z*) configuration. The infra-red spectra of **5a**-**d** exhibited medium to strong intensity band between 995-1015 cm^{-1} (Table II) and were inconclusive in deciding the configuration. The hydrolysis of the ester **5a** yielded an acid m.p. 163-164°, which was earlier assigned α-trans-γ-trans configuration[6,25,33,34] but later shown to possess α-trans-γ-cis configuration on the basis of NMR spectra.[35]

The physical and the spectral data for the 2-methyl ester **5f** were found to be in agreement with the reported values for the α-trans-α-trans isomer.[37,38] Thus **5f** melted at 84° (reported 86°) and on hydrolyses yielded an acid m.p. 162-163° which is identical with that reported for α-trans-α-trans isomer. The olefinic protons in the NMR spectrum of **5f** were merged with aromatic protons, which appeared as broad multiplet between δ 6.8-7.4. The NMR data is in agreement with the reported values for α-trans-γ-*trans* isomer. The ester **5g**-**h** also showed similar pattern for olefinic and aromatic protons signals (Table II).

Thus it is apparent from the above data that the unsubstituted esters 5a-d are formed in α-trans, γ-cis configuration while the 2-methyl esters 5e-g are obtained in α-trans-γ-trans configuration. The reason for this stereoselectivity is not clear.

EXPERIMENTAL

The keten S,S-acetals 18a and 18b were prepared from the acetone and ethylmethyl ketone respectively according to the procedure described in chapter II.

Preparation of 5-aryl 1,1-bis(methylthio)-1,4-pentadiene-3-ones (19):

General procedure:[39]

Preparation of 19a :

Sodium (1.4g, 0.06 mol) was dissolved with cooling in 50 ml of 95% ethanol. Keten-S,S-acetal (4.8g, 0.03 mol) in 35 ml of 95% ethanol and benzaldehyde (3.2g, 0.03 mol) were then added to the sodium ethoxide solution and the mixture was stirred at room temperature for 4 hr. The precipitate was filtered, washed with water and dried and was used as such in the subsequent reaction.

All the petadienone (19b-j), were prepared by the above general method and their physical and spectral data are given in Table I.

Reduction of the 19 to the carbinols 20:

General procedure:

5-phenyl 1,1-bis(methylthio)-2,4-pentadiene-3-ol (20a):

To a well stirred suspension of 19a (5.2g, 0.02 mol) in absolute ethanol (70 ml), excess sodium borohydride (2.5g, 0.07 mol) was added and the mixture was refluxed for 2 hr. The cooled reaction mixture was poured into water (150 ml) and extracted with chloroform (2 x 35 ml). The chloroform extract was washed twice with saturated salt solution (100 ml), dried (Na_2SO_4) and evaporated under vacuum to give the carbinol 20a (5g, 100%) as an undistillable thick liquid, IR(neat); 3100-3600 (ν_{OH}) cm^{-1}.

The pentadienones 19b-j were reduced by similar procedure and the resulting carbinols 20b-j obtained as unstable thick viscous liquids in nearby quantitative yields were used as such without further purification.

Preparation of 5-aryl-2,4-pentadienoates (5).

General procedure:

Preparation of Methyl 5-phenyl 2,4-pentadienoate 5a.

To the crude carbinol 20a (5g, 0.02 mol) obtained as above, 15 ml of borontrifluoride etherate was added and the reaction mixture was stirred at room temperature for 5 min. It was then diluted with 50 ml absolute methanol and the solution was refluxed for 12-24 hr. (Table II). The cooled reaction mixture was poured into water (200 ml), extracted with chloroform (2 x 50 ml), the chloroform extract washed successively with bicarbonate solution (200 ml), dried (Na_2SO_4) and evaporated to give the crude diene ester 5a, which was further purified by passing through a short column of salica gel and eluted with hexane.

All the diene esters 5b-j were prepared by the above general procedure and purified by passing through silica gel column using hexane as eluent. Their physical and spectral data are given in Table II.

Hydrolysis of the diene esters 5a and 5f : General Procedure :

To a solution of diene ester 5a (3g, 0.01 mol) in 15 ml of methanol, 1.4g (0.05mol) of sodium hydroxide was added and the solution was refluxed for 3 hr. The precipitate obtained was filtered, washed with ether and dried in vacuum. It was then dissolved in 35 ml water and acidified with 0.5 ml conc. HCl, filtered, washed with water and dried. Yield 2.0g (80%), m.p, 163-164°C (lit. 165°).[33]

The ester 5e was hydrolysed similarly to yield the corresponding acid; yield, 25g (78%); m.p. 163-164 (lit. 164-65°).[24]

Table I

Spectral data for <u>25a-j</u>

Product	Ar	R	Yield (%)	m.p.	IR ν max (KBr.)	NMR δ ($CDCl_3$)
19a	C_6H_5	H	71	87-88°	1640 (C=O) 1601 (C=O)	2.37 (s, 3H, $-SC\underline{H}_3$); 2.45 (s, 3H, $-SC\underline{H}_3$); (s, 1H, olefinic, H_a); 6.61 (d, 1H, J=15 Hz, H_b); 7.1-7.55 (m, 6H, arom+olefinic Hc).
19b	$\underline{p}$-Me-C_6H_4	H	70	130-131°	1650 (C=O) 1595 (C=C)	2.30 (s, 3H, $-C\underline{H}_3$); 2.45 (s, 6H, 6.2 (s, 1H, olefinic H_a); 6.72 (d, 1H, J=15 Hz, olefinic H_b); 7.05-7.78 (m, 5H, arom+olefinic H_c).
19c	$\underline{p}$-MeO-C_6H_4	H	67	116-117°	1650 (C=O) 1590 (C=C)	2.48 (s, 6H, two-$SC\underline{H}_3$); 3.80 6.18 (s, 1H, olefinic H_a); 6.67 (d, 1H, J=15 Hz, olefinic H_b); 6.80-7.70 (m, 5H, arom+olefinic H_c).
19d	$\underline{p}$-Cl-C_6H_4	H	73	102-103°	1650 (C=O) 1592 (C=C)	———

Table I (cont'd.)

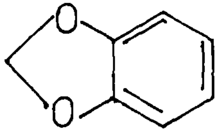
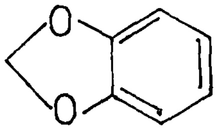
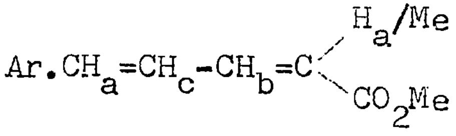
19e		H	68	157-159°	1630 (C=0) 1600 (C=C)	—
19f	C_6H_5	Me	65	82-83°	1650 (C=0) 1600 (C=C)	2.20 (s, 3H, $-C\underline{H}_3$); 2.30 (s, 3H, 2.42 (s, 3H, $-SC\underline{H}_3$); 6.75 (d, 1H, J=15 Hz, olefinic H_b); 7.22-7.60 (m, 6H, arom+olefinic H_c).
19g	p-MeO-C_6H_4	Me	72	132-133°	1650 (C=0) 1590 (C=C)	
19h	p-Cl-C_6H_4	Me	65	102-103°	1610 (C=0)	2.10 (s, 3H, $-C\underline{H}_3$); 2.21 (s, 3H, $-SC\underline{H}_3$); 2.32 (s, 3H, $-SC\underline{H}_3$); 6.80 (d, 1H, J=15 Hz, olefinic H_b); 7.22-7.55 (m, 5H, arom+olefinic H_c).
19i	p-Me-C_6H_4	Me	70	82-84°	1650 (C=0) 1595 (C=C)	—
19j		Me	71	65-66°	1648 (C=0) 1595 (C=C)	—

Table II

Spectral Data for Dieneesters 5a-j, Ar.CH$_a$=CH$_c$-CH$_b$=C(H$_a$/Me)(CO$_2$Me)



$$Ar.CH_a{=}CH_c{-}CH_b{=}C\begin{smallmatrix}H_a/Me\\ CO_2Me\end{smallmatrix}$$

Product	Ar.	Reflux time	H/M_e	Yield (%)	m.p.	IR ν max (KBr)	δ NMR ($CDCl_3$)	M^+ (Mass)
5a	C_6H_5	18	H	75	68-70° (70°)^{31}	1720 (C=O) 1630 (C=C) 995 1000(s)	3.48 (s, 3H, OCH_3); 5.85 (d, J=15 Hz, Ha); 6.8 (brd, 2H, J=6Hz, H_b and H_c) 7.2-7.6 (m, 6H, arom+H_d).	188
5b	p-MeC_6H_4	12	H	72	98-99° (100°)^{31}	1718 (C=O) 1628 (C=C) 810 (m),840 (m) 1015(s)	2.3 (s, 3H, -CH_3); 3.7 (s,3H, -OCH_3); 5.88 (d, J=15 Hz, H_a); 6.75 (brd, J=6 Hz, 2H, H_c,H_b); 6.96-7.58 (m, 5H, arom + H_d).	202
5c	p-MeOC_6H_4	14	H	69	125-26° (127°)^{31}	1720 (CO) 1630 (C=C)	3.71 (s, 3H, OCH_3) 3.78 (s,3H, OCH_3); 5.88 (d, J=15 Hz, H_a); 6.65-6.95 (m, 4H, 2 arom+ 2 olefinic) 7.22-7.56 (m, 3H, 2 arom + 1 olefinic).	218

Table II (cont'd.)

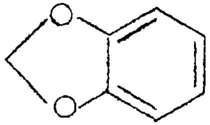
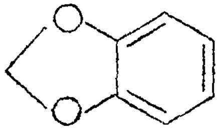
5d	p-ClC_6H_4	15	H	71	129–30° (32°)[31]	1712 (CO) 1630 (C=C) 1015, 850(s) 818 (m) 740	3.72 (s, 3H, $OC\underline{H}_3$); 5.95 (d, J=15 Hz, H_a, 6.8 (brd, J=6 Hz, 2H, H_b, H_c); 7.2–7.6 (m, 5H, arom+1 olefinic).	222.5
5e		10	H	55	150–151° (146°)[40]	1715 (C=O) 1620 (C=C) 1000 (S); 865 (m) 810 (m)	3.6(s, 3H, $-OC\underline{H}_3$); 5.70–6.15 (m, 3H, $-O-C\underline{H}_2-O-$ + H_a); 6.6–7.65(m, 6H, arom + olefinic).	232
5f	C_6H_5	14	Me	78	84–85° (86–87°)[24]	1720 (CO) 1628 (C=C) 998 (m) 975 (s) 870, 830 (w) 765(m)	2.01 (brS, 3H, $C\underline{H}_3$); 3.72 (s, 3H, $OC\underline{H}_3$); 6.8–7.1 (m, 3H, olefinic); 7.1–7.4 (m, 5H, aromatic)	202
5g	p-$MeOC_6H_4$	11	Me	67	67°	1715 (CO) 1600 (C=C) 970, 940(s) 1028 (s); 820 (s) 755(m)	2.0 (brs, 3H, CH_3); 3.72 (s, 3H, $OC\underline{H}_3$); 3.79 (s, 3H, $OC\underline{H}_3$); 6.7–7.45 (m, 7H, aromatic+olefinic)	232

Table II (cont'd.)

5h	p-ClC_6H_4	13	Me	78	101-102°	1708 (CO) 1630 (C=C) 971, 980(m) 818 (m), 750 (m)	2.02 (brS, 3H, CH_3); 3.75 (s, 3H, $OC\underline{H}_3$); 6.7-7.1 (m, 3H, olefinic); 7.1-7.45 (m, 4H, arom).	236.5
5i	p-MeC_6H_4	16	Me	71	Viscous	1710 (C=O) 1620 (C=C) 970 (m)[a] 800 (m)	2.30(s, 3H, $-C\underline{H}_3$); 2.38(s, 3H, $-C\underline{H}_3$); 3.72(s, 3H, $-OC\underline{H}_3$); 6.31-7.91(m, 7H, arom + olefinic).	216
5j		11	Me	76	110-13°	1700 (C=O) 1610 (C=C) 980 (m) 925 (m) 800 (m)	2.01 (s, 3H, $-C\underline{H}_3$); 3.75(s, 3H, $-OC\underline{H}_3$); 5.91(s, 2H, $-O-C\underline{H}_2-O-$); 6.1-7.4(m, 6H, arom + olefinic).	246

[a] neat

Table III

Product	Molecular Formula	Analysis(%) Calc. Found	C	H
5a	$C_{12}H_{12}O_2$ (188)		76.59 76.88	6.38 6.57
5b	$C_{13}H_{14}O_2$ (202)		77.23 77.54	6.93 7.15
5c	$C_{13}H_{14}O_3$ (218)		71.56 71.85	6.42 6.71
5d	$C_{12}H_{11}ClO_2$ (222.5)		64.72 64.97	4.94 5.25
5e	$C_{13}H_{14}O_4$ (232)		67.24 67.53	5.17 5.48
5f	$C_{13}H_{14}O_2$ (202)		77.23 77.52	6.93 7.21
5g	$C_{14}H_{16}O_2$ (216)		77.78 78.03	7.41 7.72
5h	$C_{14}H_{16}O_3$ (232)		72.41 72.72	6.90 7.23
5i	$C_{13}H_{14}ClO_2$ (237.5)		65.68 65.97	5.89 6.17
5j	$C_{14}H_{14}O_2$ (214)		78.50 78.85	6.54 6.87

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CHAPTER V

SYNTHETIC STUDIES ON LEAD (IV) ACETATE OXIDATIONS : ONE STEP SYNTHESIS OF METHYL ARYLACETATES FROM ACETOPHENONES USING LEAD (IV) ACETATE*

V.1. INTRODUCTION

Lead tetraacetate (LTA) is a versatile oxidising agent widely used in organic synthesis. Its reaction with organic molecules generally involve the reduction of lead (IV) to lead (II) either through ionic or radical mechanisms. Synthetic applications of this reagent as it is now commercially available, has since been increased in recent years. These results have been published in a number of reviews highlighting its synthetic applications. For instance, they include the reaction of lead (IV) acetate with olefins,[1] oxidative decarboxylation with lead (IV) acetate,[2] oxidation of alcohols by LTA,[3] reaction of LTA with azomethines[4] and the LTA oxidation of sugars with emphasis on glycol cleavage.[5] Also a number of useful general reviews on LTA have appeared. Fieser and Fieser[6] have discussed the uses of LTA for a broad range of synthetic processes, while Aylward[7] has reviewed the general behaviour of LTA towards organic nitrogen compounds. The reactions of LTA with steroids[8] and intramolecular cyclization of alcohols with LTA[8,9] have also been discussed.

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* B. Myrboh, H. Ila, H. Junjappa, Synthesis, 126 (1981).

A general review by Criegee[10] on the behaviour of LTA towards OH, C-H and single and multiple carbon-carbon bonds as well as some reactions involving organic compounds of sulfur, nitrogen and phosphorus has also appeared. The initial work developed by Criegee laid the foundations for the development and growth of LTA as an important synthetic reagent.[11] The mechanistic aspects of LTA reactions have been included in the general reviews of oxidation.[12,13]

It is interesting to note that despite an array of diverse synthetic applications of lead (IV) acetate in organic synthesis, there are only a few synthetically useful processes based on oxyplumbation in contrast to oxymercuration[14,15] and oxythallation[16] studies, which have lead to the development of a series of reactions of immense synthetic utility in recent years.

Metallation and oxymetallation reactions have been observed with the salts of only a few metals, namely mercury (II), thallium (III), lead (IV), palladium (II), gold (III) and platinum (II) which are known to possess "soft acid" character.[17] Lead (IV) is isoelectronic with mercury (II) and thallium (III). The redox potential of Pb (IV) is lowest in the series[18] and consequently the relative oxidizing ability of the three metal ions is in the order Hg (II) < Tl (III) < Pb (IV). A comparative study of oxymetallation of olefins with the acetates of the three metals have shown that while stable oxymercuration adducts[14] are formed with Hg (II) acetate, oxythallation adducts have been isolated only occasionally[11,19] while the treatment of olefins with lead (IV) acetate gives complex mixture of products,[10] which often renders these reactions of little synthetic value. Although oxyplumbation adducts have been postulated as intermediates in these reactions, direct evidence for the key organolead intermediate has not been obtained.* Attempts have been made in recent years to direct these oxidations towards products formed through electrophilic oxyplumbation by employing more electrophilic lead (IV) salts. Thus, although styrene gives very low yield of phenylacetaldehyde (a product of oxyplumbation reaction) by oxidation with Pb (IV) acetate under vigorous condition, however excellent yields of arylacetaldehyde (2) and other ketones are obtained when (1) are oxidized with lead (IV) acetate in trifluoroacetic acid, which contains lead (IV) with four trifluoroacetate ligands [21] (Scheme 1). Similarly, several oxidations

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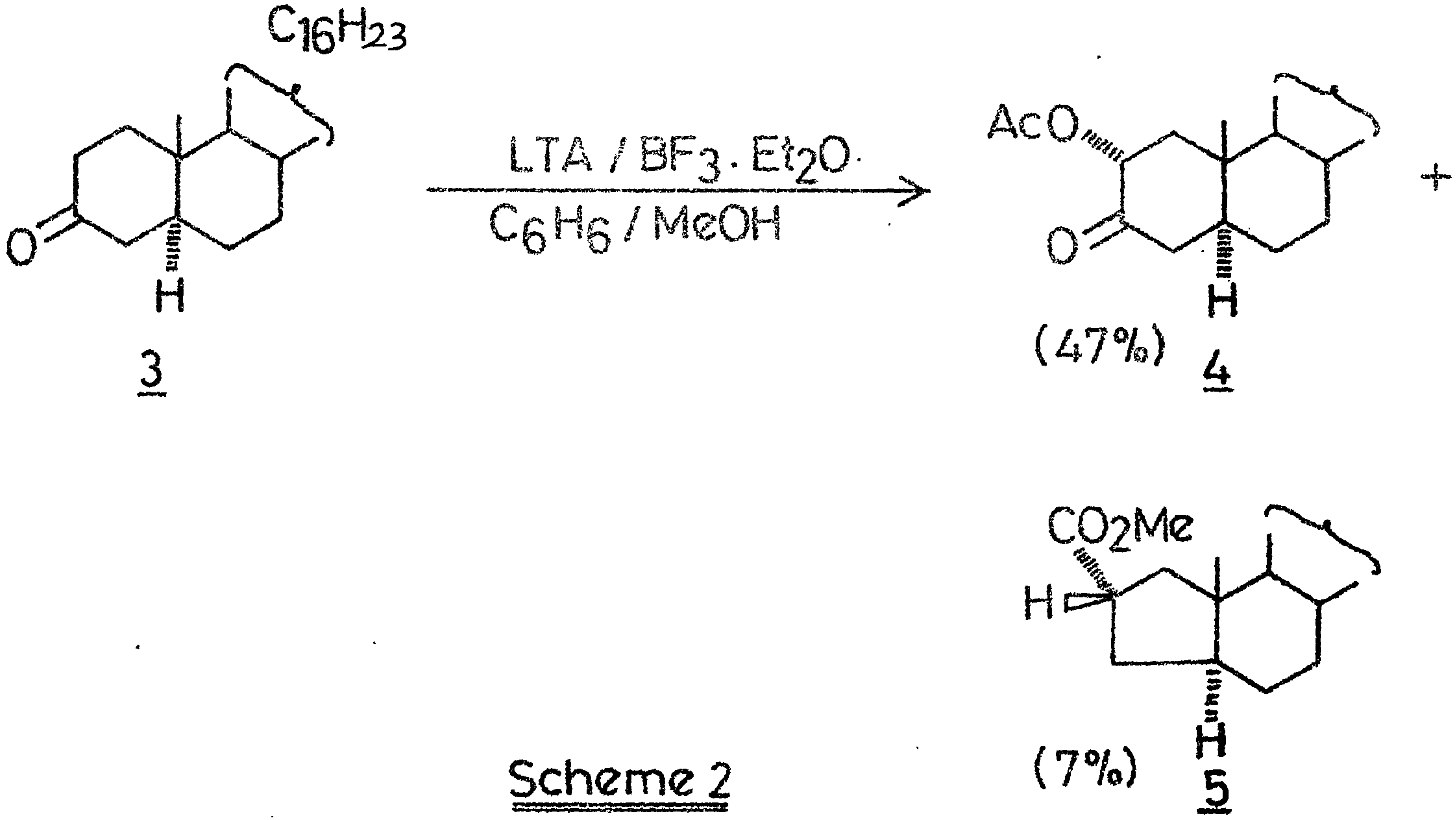
*Recently an organic derivative of lead from the reaction of pregnenolene and diacetate-difluorolead (IV), $Pb(OAc)_2F_2$ has been isolated[20] which is particularly significant.

R = H, alkyl, aryl

Scheme 1

involving LTA in hydrofluoric acid and lead (IV) diacetate difluoride, which has been shown to be highly useful fluorination agent, have been reported.[22,23]

Ketones containing an α-methine moiety readily yield α-acetoxyketones on oxidation with lead (IV) acetate.[24] The enol form is considered to be the reactive species in these reactions. Boron trifluoride is shown to have a strong catalysing effect on the acetoxylation and this has been explained in terms of accelration of keto-enol tautomerism, though its effect could also arise from interaction with the reagent. Although α-acetoxylation is the predominant pathway in the oxidation of ketones with lead (IV) acetate, products resulting through oxidative rearrangement have also been reported in some cases. Thus Henbest and co-workers[25] observed that 5-α-cholestane-3-one (**3**) on treatment with lead (IV) acetate in benzene/methanol in the presence of boron trifluoride etherate yielded, besides the normal acetoxylation product **4** (47%), a ring contracted product, methyl **A**-norcholestane-2α-carboxylate (**5**) in low yields (7%) (Scheme 2). Recently Fujimoto and co-workers[26] accomplished ring contraction of α-santonin in preparative yield using lead tetraacetate/boron trifluoride etherate in benzene/methanol. Thus (**6**) on oxidation yielded (**7**) as major product (57%), while the corresponding α-acetoxy compounds **8a** and **8b** were formed as minor products (Scheme 3). These



Scheme 2

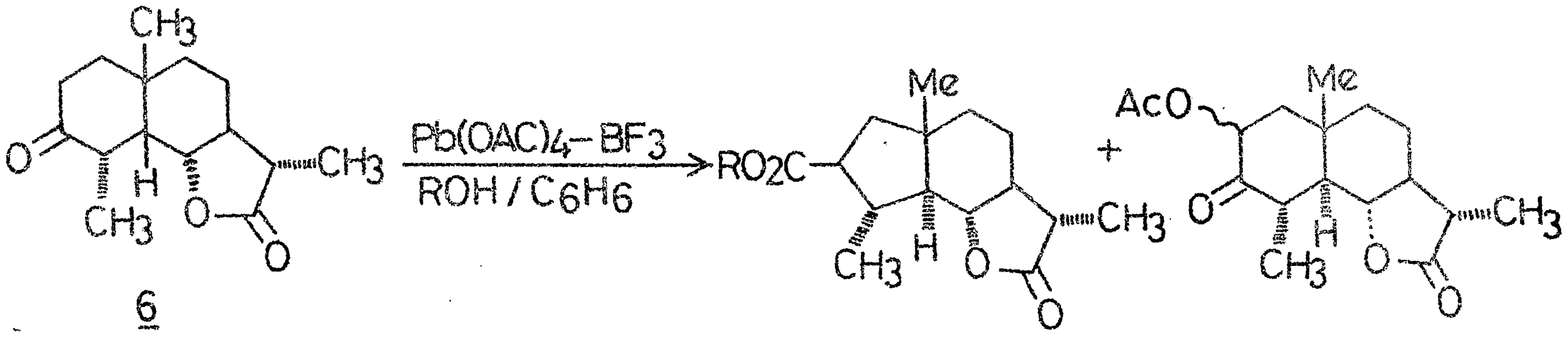
authors have postulated formation of <u>7</u> via enol ether <u>9</u> , which on oxyplumbation followed by subsequent rearrangement of the adduct <u>10</u> yields <u>7</u> (Scheme 4).

Thus, from the above studies it is apparent that it is possible to achieve significant measure of product control in lead (IV) oxidations, by carefully manipulating proper reagents and reaction conditions and through knowledge of competing pathways. Apparently the oxyplumbation studies have been sporadic and require systematic investigation. Consequently, two systems were chosen for the present investigation which are of practical importance: (1) conversion of the arylmethyl ketones to the arylmethyl acetates and (2) conversion of 3-monosubstituted and 3,4-disubstituted-5-pyrazolones to the corresponding 2-alkynoic esters and 2,3-alkanedienoic esters respectively (Chapter VI).

V.2. One Step Synthesis of Methyl Arylacetates from Acetophenones using Lead (IV) acetate.

V.2.1 INTRODUCTION

Willgerodt developed in 1887, a method for the preparation of phenylacetic acids by reacting ammonium sulphide and the acetophenones under pressure at about 200°C, which later became known as the Willgerodt reaction.[27]

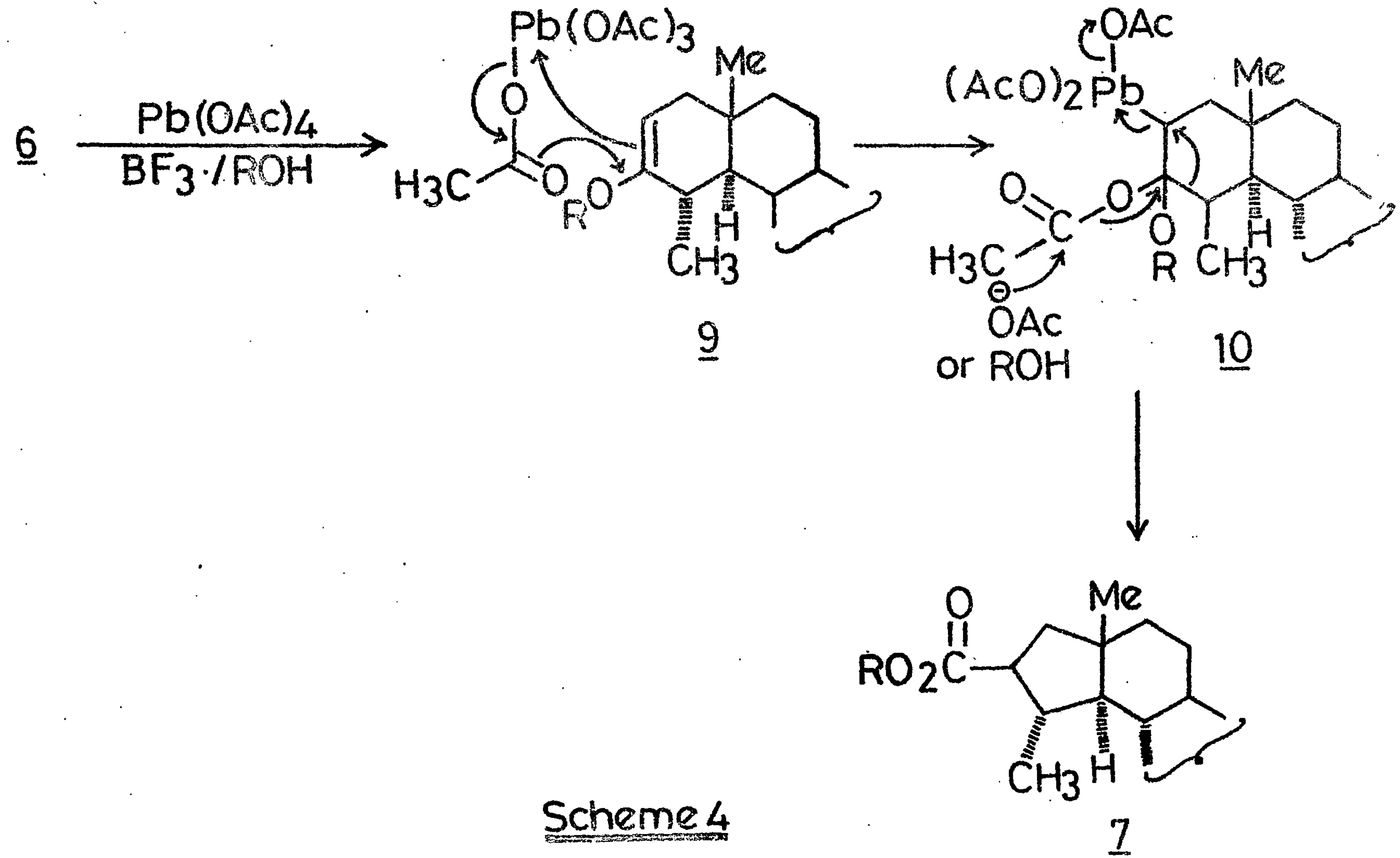


6

7a, R = Me
b, R = Et
c, R = $C_6H_5CH_2$

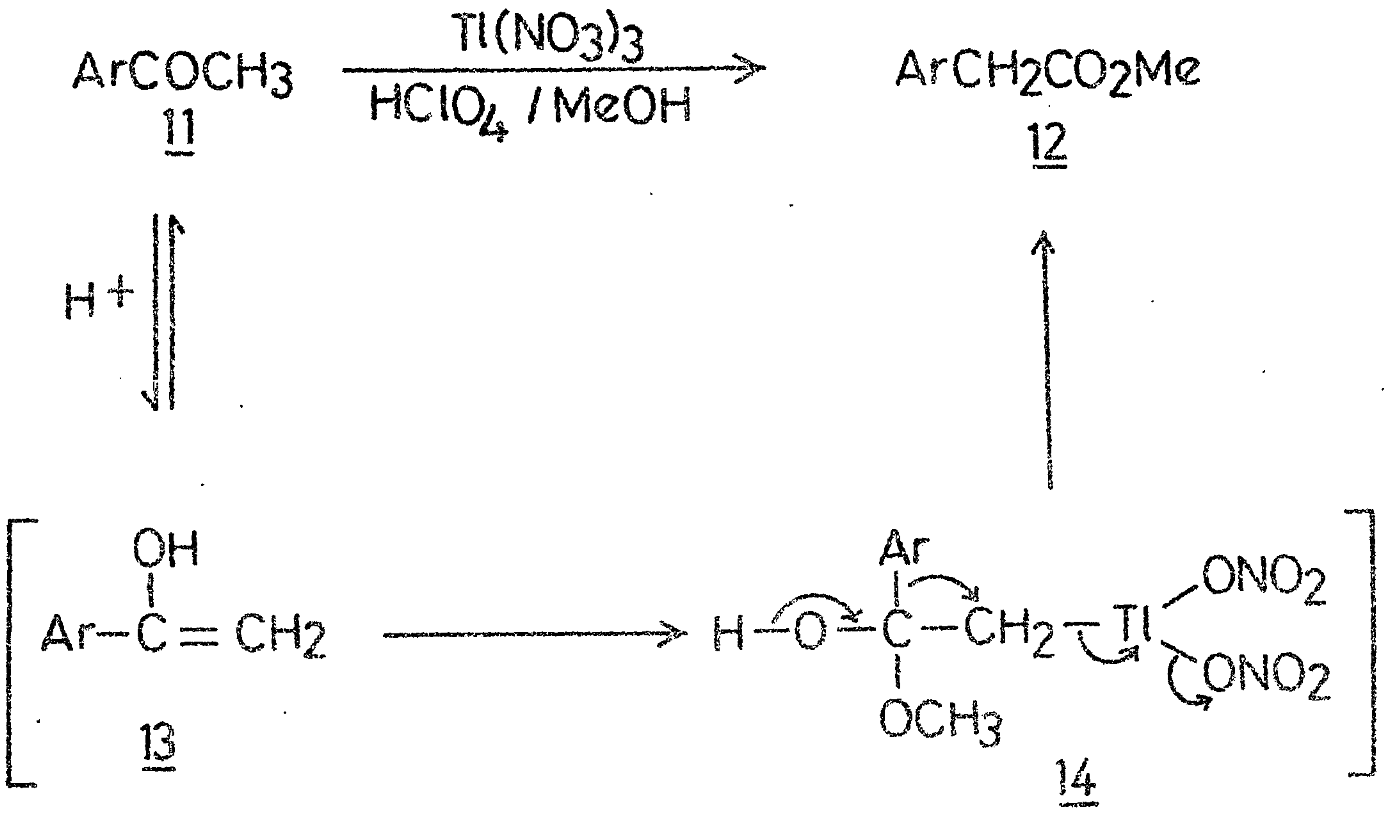
8a, α – OAc
b, β – OAc

Scheme 3


6
Pb(OAc)4
BF3·/ROH
Pb(OAc)3
H3C
O
O
RO
Me
H
CH3
9
(AcO)2Pb
OAc
O
C
O
H3C
OAc
or ROH
O
R
Me
H
CH3
10
RO2C
O
Me
CH3
H
7

Scheme 4

Extension of this reaction was hampered by modest yields of the carboxylic acids. Several modifications were subsequently extended to improve upon the yields of the products. Since the conversion of the aryl alkyl ketones to the corresponding phenylacetic acids was of synthetic use, substantial modification of this reaction was first introduced by Kindler[28,29] in 1923, wherein the use of pressure was avoided and by introducing anhydrous aliphatic amines at a maximum temperature of 180°C, he was able to considerably improve the yield. This method was continued to be used although it could not be extended to the acetophenones which undergo polimerisation under those conditions. However an excellent modification of this reaction was introduced by Taylor and McKillop[30] in 1971, when they were able to convert acetophenones to the corresponding methylarylacetates at room temperature in modest to excellent yields. Their method involves the oxidation of the acetophenone 11 using thallium (III) nitrate (TTN) in presence of perchloric acid and methanol, when they obtained the corresponding phenylacetate 12 in excellent yield (Scheme 5). A mechanism involving oxythallation adduct 14 via enol 13 has been suggested for this rearrangement (Scheme 5). Thallium and its compounds are not only expansive, but also extremely toxic requiring handling precautions to be strictly observed. As discussed earlier lead (IV) acetate has been used for α-acetoxylation and Favorskii-type ring contraction (Scheme 4),

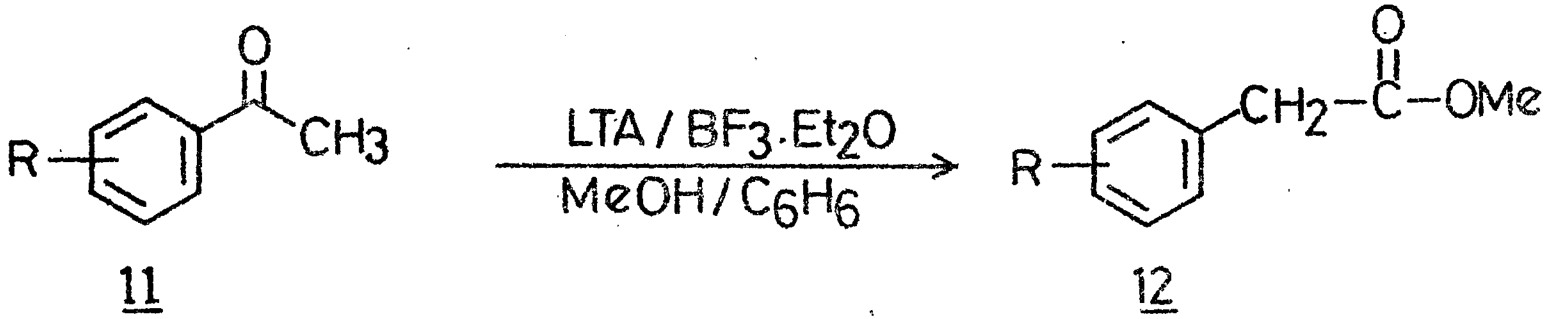

ArCOCH3
11
Tl(NO3)3
HClO4 / MeOH
ArCH2CO2Me
12
H+
OH
Ar—C=CH2
13
Ar
H—O—C—CH2—Tl
OCH3
ONO2
ONO2
14

Scheme 5

while its application in the rearrangement of acetophenones to the corresponding phenylacetates has received no attention at all. It was therefore decided to undertake the study of these transformations involving oxyplumbation.

V.2.2 RESULTS AND DISCUSSIONS

When a solution of acetophenone (11a) in methanol and borontrifluoride etherate was added to a stirring suspension of lead (IV) acetate in dry benzene at room temperature, work-up of the reaction mixture after 5 hr gave methyl phenylacetate (12a) in 86% yield (Scheme 6). The purity of the phenylacetate was determined by GLC and the structure by IR spectral data, which was found to be exactly superimposable with that of authentic sample. The ester was also hydrolysed to the free acid, which was also found to be identical with the authentic sample (superimposable IR and mixed m.p.). Similarly the acetophenones 11b-h were converted to the corresponding phenylacetates 12b-h in 54-95% overall yields. It may be noted here that only p-nitroacetophenone gave lower yields (54%) of the corresponding phenylacetate 12h, while all the other substituted acetophenones gave above 80% yield of 12. The structure of all these esters was confirmed by their superimposable IR spectra as well as by the mixed melting points of the corresponding free acids. It is interesting to note that desoxybenzoin 15, under identical reaction conditions underwent

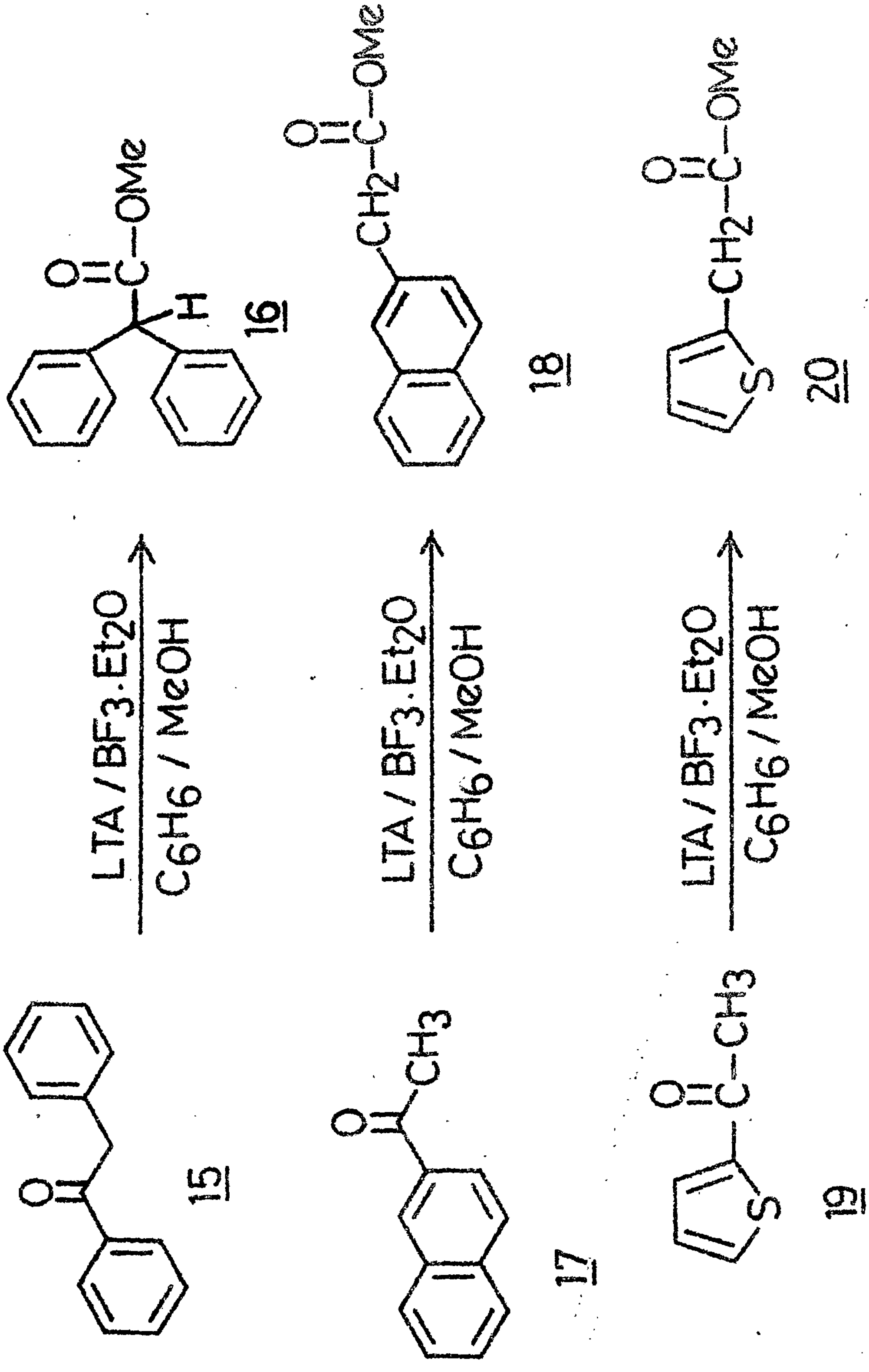


<u>11</u>, <u>12a</u>, R = H
<u>b</u>, R = <u>p</u>-Me
<u>c</u>, R = <u>p</u>-MeO
<u>d</u>, R = <u>m</u>-MeO
<u>e</u>, R = <u>p</u>-Cl
<u>f</u>, R = <u>p</u>-Br
<u>g</u>, R = 2, 4-dichloro
<u>h</u>, R = <u>p</u>-NO_2

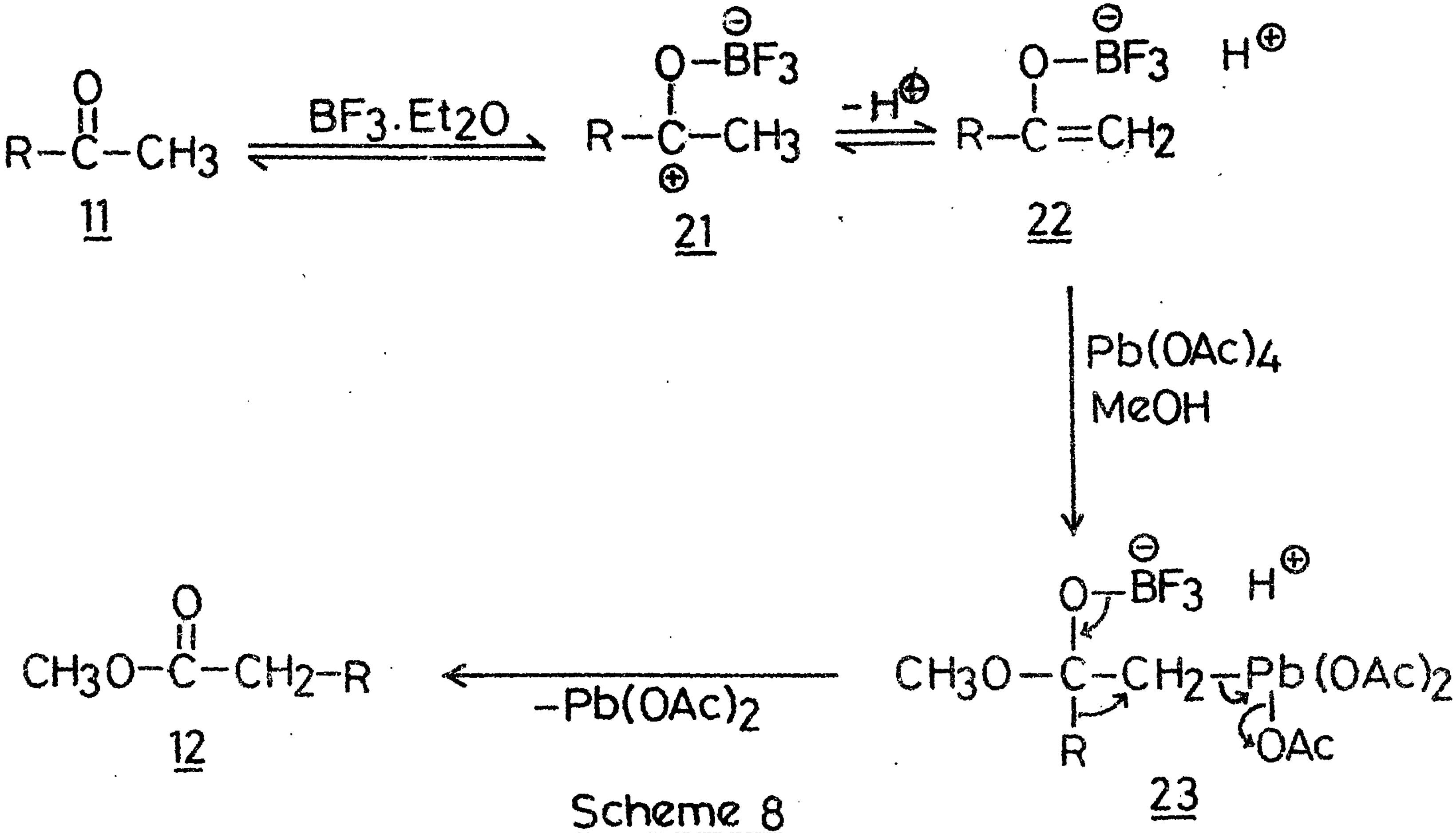
Scheme 6

similar transformation to give the 2,2-diphenyl substituted methylacetate 16 in 85% yield (Scheme 7). The structure of 16 was again determined by its superimposable IR as well as the mixed melting of its free acid. Similarly 2-acetylnaphthalene 17 gave the corresponding rearranged acetate 18 in excellent yield (88%) (Scheme 7). The IR spectral data and the mixed melting point of the free acid confirmed its structure. The method was further found to be applicable to heterocyclic methyl ketones such as 2-acetylthiophene 19, which gave under similar reaction conditions the corresponding methyl-2-thienylacetate 20 in overall 83% yield (Scheme 7). However, acetone gave a mixture of several products in which methylpropanoate could not be detected. Apparently, the method is general for the coversion of aromatic methyl ketone to the corresponding methylarylacetates in high yields involving simple reaction conditions and procedures.

The plausible mechanism appears to involve initial enolization of the ketones11 assisted by boron trifluoride etherate followed by oxyplumbation to give 23 which by subsequent aryl group migration, rearranges to 12 with precipitation of lead (II) acetate (Scheme 8). The mechanism is analogous to the oxythallation of the acetophenones[30] in the presence of perchloric acid and methanol as reported by McKillop and co-workers (Scheme 5).


15
LTA / BF3.Et2O
C6H6 / MeOH
16
17
LTA / BF3.Et2O
C6H6 / MeOH
18
19
LTA / BF3.Et2O
C6H6 / MeOH
20

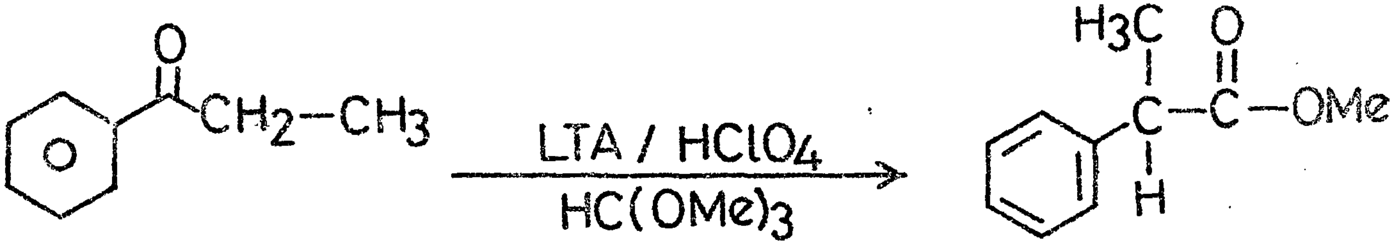
Scheme 7



Scheme 8

When the same reaction was extended to propiophenone 24 in order to prepare methyl α-methylphenylacetate 25, a majority of the starting material was recovered unchanged while GLC showed presence of 25 as minor product (5%) along with several other products. However, a Japanese group[31] has achieved this transformation (after publication of our work) by reacting 24 with lead (IV) acetate in presence of perchloric acid and trimethylorthoformate, when the corresponding 25 was obtained in 78% yield (Scheme 9). Thus lead (IV) acetate is the reagent of choice for the conversion of alkylaryl ketones to methylarylacetates in preference to thallium (III) nitrate, since lead (IV) acetate is much less toxic and cheap.

When this work was sent for publication a paper by CeKovic and co-workers[32] appeared in which LTA was used under similar conditions to convert the enamines derived from acetophenones to the corresponding phenylacetates in comparable yields. However, the additional step involving the formation of moisture sensitive enamines becomes redundant in the light or our observations when our method provides direct conversion of the acetophenones to the corresponding phenylacetates. It may be noted that the enamine derived from *p*-nitroacetophenone failed to undergo the rearrangement. However their method has been shown to be of practical importance for ring contraction,



24

25

Scheme 9

of the enamines derived from cycloalkanones analogous to the Favorskii-type of rearrangement (Scheme 10), while the reaction of cyclohexanone and tetralone with lead (IV) acetate and boron trifluoride etherate yielded mixture of several products, from which the desired carboxylates could not be isolated.

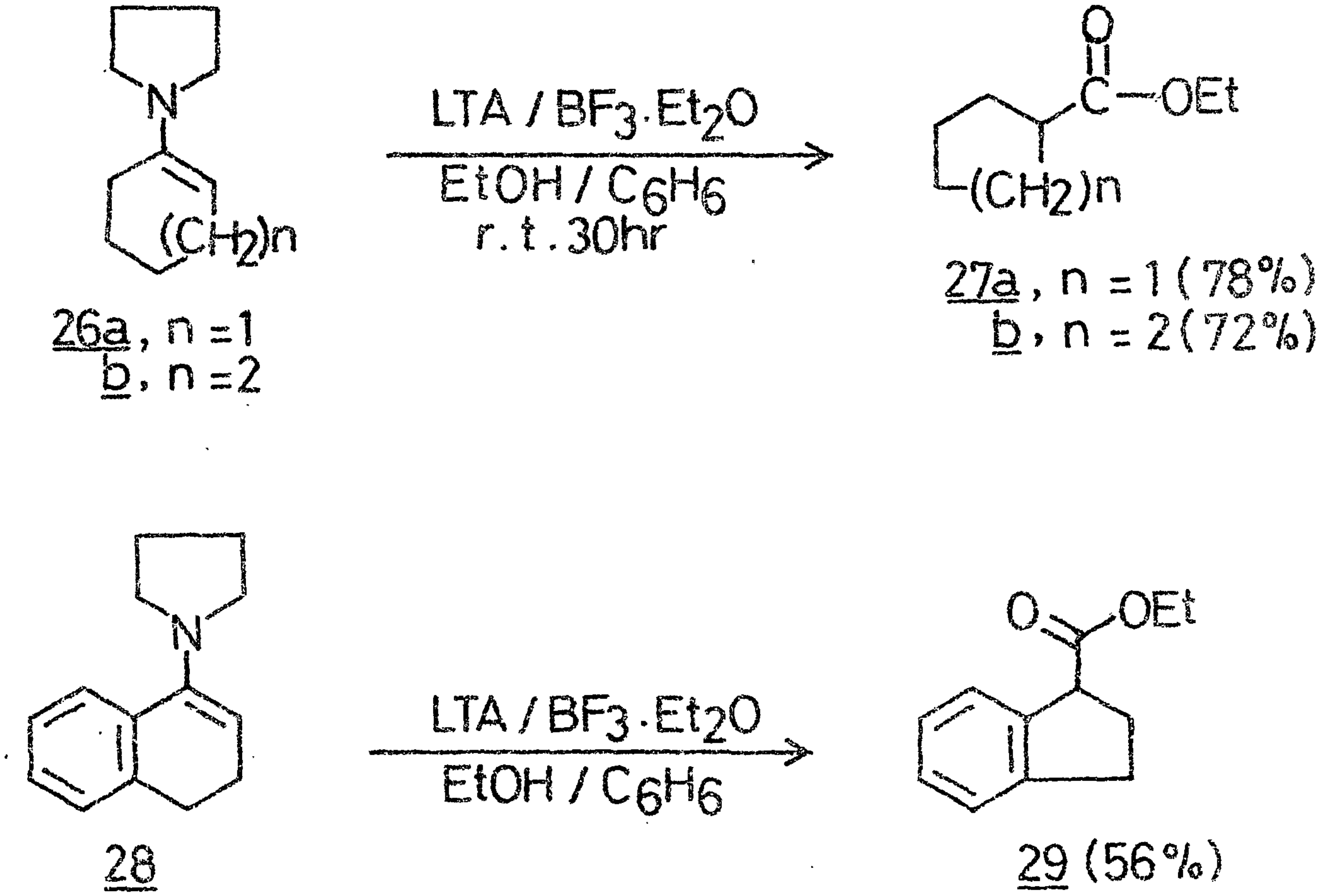
V.3.1 EXPERIMENTAL

Melting points were determined on a 'Boetius' (German) apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 297 spectrophotometer.

The commercial samples of acetophenone, p-methylacetophenone, p-chloroacetophenone, 2,4-dichloroacetophenone, 2-acetylnaphthalene, 2-acetylthiphene were purified before use.

The p-methoxyacetophenone, b.p.100° (1 mm),[33] p-bromoacetophenone, b.p. 137-40° (2 mm);[34] p-nitroacetophenone, m.p. 80-81°;[35] desoxybenzoin, m.p. 60°[36] were prepared by the reported methods.

Lead tetraacetate, m.p. 175°,[37] was prepared fresh for each reaction and carefully dired in a vacuum dessicator over potassium hydroxide.


LTA / $BF_3 \cdot Et_2O$
EtOH / C_6H_6
r.t. 30hr
(CH$_2$)n
OEt
26a, n = 1
b, n = 2
27a, n = 1 (78%)
b, n = 2 (72%)
LTA / $BF_3 \cdot Et_2O$
EtOH / C_6H_6
28
29 (56%)

Scheme 10

V.3.2 General Method for the Preparation of Methyl Arylacetate.

To a well stirred suspension of lead tetraacetate (17.17g, 0.04 mol) in dry benzene (100 ml), the ketone (0.38) in 25 ml of benzene was added in one lot followed by the addition of absolute methanol (10 ml) and boron trifluoride etherate (22g, 0.15 mol, 20 ml) sequentially. The reaction mixture was further stirred at room temperature for 3-14 hr (Table I), diluted with cold water (500 ml) and extracted with benzene (600 ml). The benzene extract was washed sequentially with saturated sodium bicarbonate solution (150 ml) and saturated sodium chloride solution (200 ml), dried over sodium sulphate and the solvent distilled off. The products thus obtained were further purified by distillation or by column chromatography (12h). The esters 12a-h, 16, 18 and 20 were all prepared by the above general method.

Attempted oxidation of Propiophenone

Propiophenone was oxidized under the identical conditions reported above. Work-up of the reaction yielded a residue which on GLC analysis (condition: 10% SE-30 on 60/80 mesh chromosorb W, 6 ft x 1/8 in column, 200°C) showed 68% of propiophenone, 5% of α-methyl phenylacetate and several other products.

Hydrolysis of Methyl Arylacetates

A mixture of methyl arylacetate (0.016 mol) and 2 N sodium hydroxide solution (10 ml) is heated under reflux for 2 hr. The free acid is subsequently precipitated by addition of concentrated hydrochloric acid (3 ml) (Table 2). The p-nitrophenylacetate is obtained by refluxing the ester **12h** (0.025 mol) in 4% sulphuric acid (20 ml) for 2 hr.

Table 1

Analytical Data of Methyl Arylacetates, (12a-h),(16),(18),(20)

Product	Reaction time(hr)	Yield (%)[a]	b.p.(°C)/torr or m.p. (°C)	Lit. b.p. (°C)/torr or m.p. (°C)	Molecular formula	Analysis Calc: Found C	H
12a	5	86[b]	94-96/5	96-98/6[30]	$C_9H_{10}O$ (150.8)	72.00 72.41	6.66 6.97
12b	5	85	76-78/0.3	73-74/0.2[38]	$C_{10}H_{12}O_2$ (164.2)	73.17 76.23	7.32 7.60
12c	3	90	120-122/5	122-125/6[30]	$C_{10}H_{12}O_3$ (180.2)	66.66 66.97	6.66 6.89
12d	10	95[c]	96-97/0.3	132-136/9[30]	$C_{10}H_{12}O_3$ (180.2)	66.66 66.95	6.66 6.91
12e	8	87[b]	95-97/0.4	102-103/1.2-1.3[39]	$C_9H_9ClO_2$ (184.62)	58.70 58.51	4.89 4.47
12f	12	92[b]	100-102/0.4	138-140/13[40]	C_9H_9BrO (229.07)	47.16 47.57	3.93 4.35
12g	9.5	92	101-104/0.21	100-102/0.21[41]	$C_9H_8Cl_2O_2$ (219.06)	49.31 49.80	3.65 3.97
12h	14	67	52-53	54[42]	$C_9H_9NO_4$ (195.17)	55.38 55.83	4.61 4.39

Table 1 (cont'd.)

16	21	74	61-62	60[43]	$C_{15}H_{14}O_2$ (226.28)	79.64 79.98	6.19 6.43
18	4	88	130-132/0.2	136/0.3[44]	$C_{13}H_{12}O_2$ (200)	78.32 78.61	6.26 6.00
20	11	83	100-104/14	100-104/14[45]	$C_7H_8O_2S$ (156.20)	53.84 54.21	5.13 5.42

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[a] Yield of pure isolated products.

[b] Purity >95% as checked by GLC analysis. (Conditions: 10% SE-30 on 60/80 mesh Chromosorb W, 6 ft x 1/8 in column; Column temperature after injection : 200°C.

[c] Purity >98% as checked by GLC analysis. (Conditions: as above).

Table 2

Physical Data for Aryl Acetic Acids

$R-CH_2-CO_2H$

R	Yield (%)	m.p. (°C)	Lit. m.p. (°C)
A C_6H_5	92	76-76.5	76-76.5[46a]
B p-MeC_6H_4	92	93	94[46b]
C p-$MeOC_6H_4$	93	86-86.5	85-87[46c]
D m-$MeOC_6H_4$	96	69-69.5	68[47]
E p-ClC_6H_4	92	105-106	105-106[46d]
F p-BrC_6H_4	93	112-113	114[46e]
G 2,4-diClC_6H_3	91	131-132	132-133[48]
H p-$NO_2C_6H_4$	96	149-150	151-152[42]
I 2-napthyl	82	143	143.1-143.4[46f]
J 2-thienyl	94	63-64	63-64[45]
K $(C_6H_5)_2CHCO_2H$	92	145-146	146[49]

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CHAPTER VI

LEAD (IV) ACETATE OXIDATIONS OF 3-SUBSTITUTED AND 3,4-DISUBSTITUTED 2-PYRAZOLINE-5-ONES : A FACILE SYNTHESIS OF 2-ALKYNOIC AND 2,3-ALKANEDIENOIC (ALLENIC) ESTERS*

In the previous chapter, we have described a facile method for the conversion of acetophenones to methyl arylacetates with lead tetraacetate in the presence of boron trifluoride etherate in methanol and benzene. In the present chapter, we report the oxidations of 2-substituted and 2,3-disubstituted-5-pyrazolones with lead (IV) acetate in methanol which affords 2-alkynoic and 2,3 alkadienoic (allenic) esters respectively in moderate to high yields.

VI.1. INTRODUCTION

Previously it was reported that 3,4-disubstituted-5-pyrazolones (1) underwent dehydrogenation with lead (IV) acetate in chloroform to give the unstable pyrazol-3-one (2) which have been trapped in the presence of dienes through the Diels-Alder reaction (Scheme 1).[1] Taylor and McKillop have recently reported[2] the conversion of 5-pyrazolones (1), which are readily prepared in quantitative yield from β-ketoesters (4), to the esters of β-alkynoic acids (7) by thallium (III) nitrate in methanol (Scheme 2). A mechanism involving initial thallation of enamine tautomer of 5-pyrazolone (7) followed by

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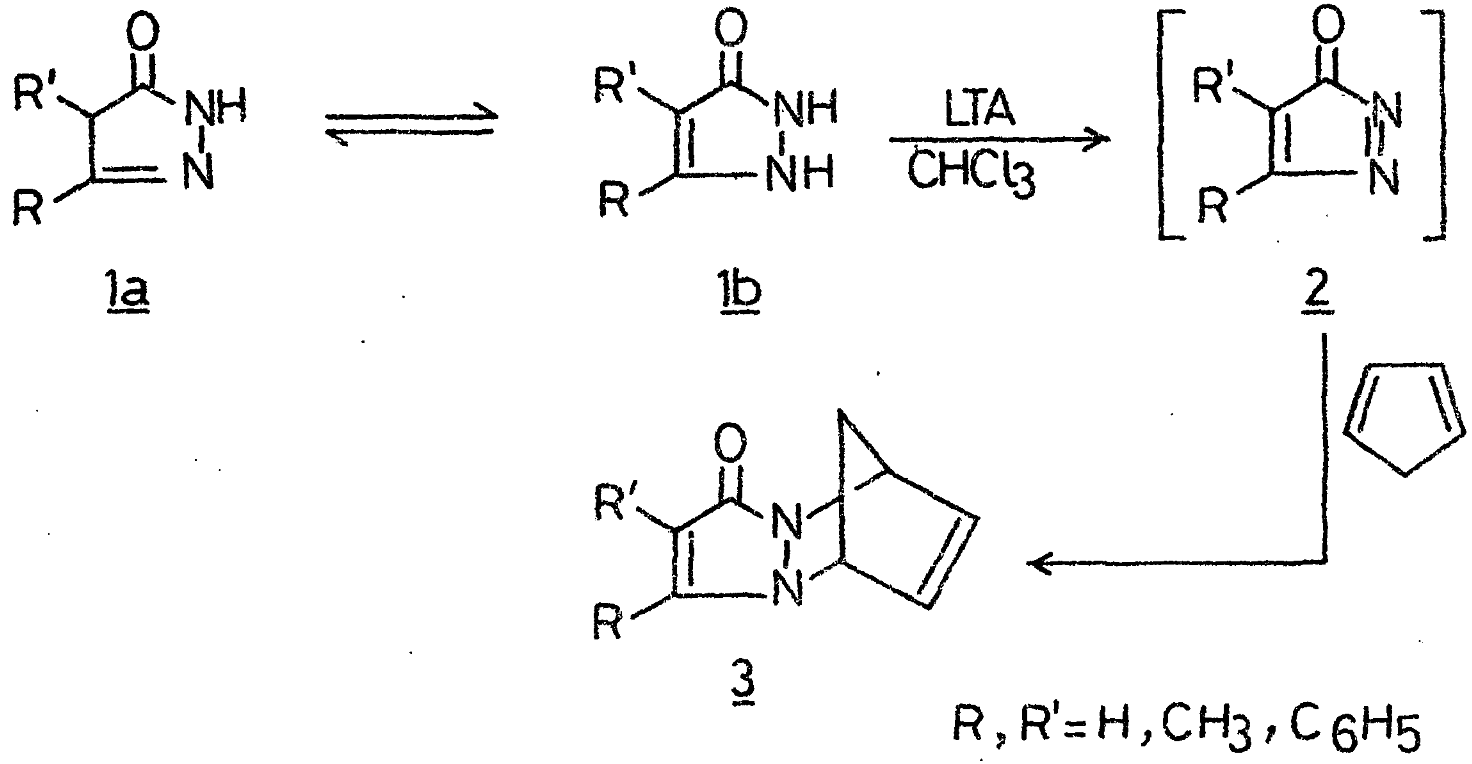
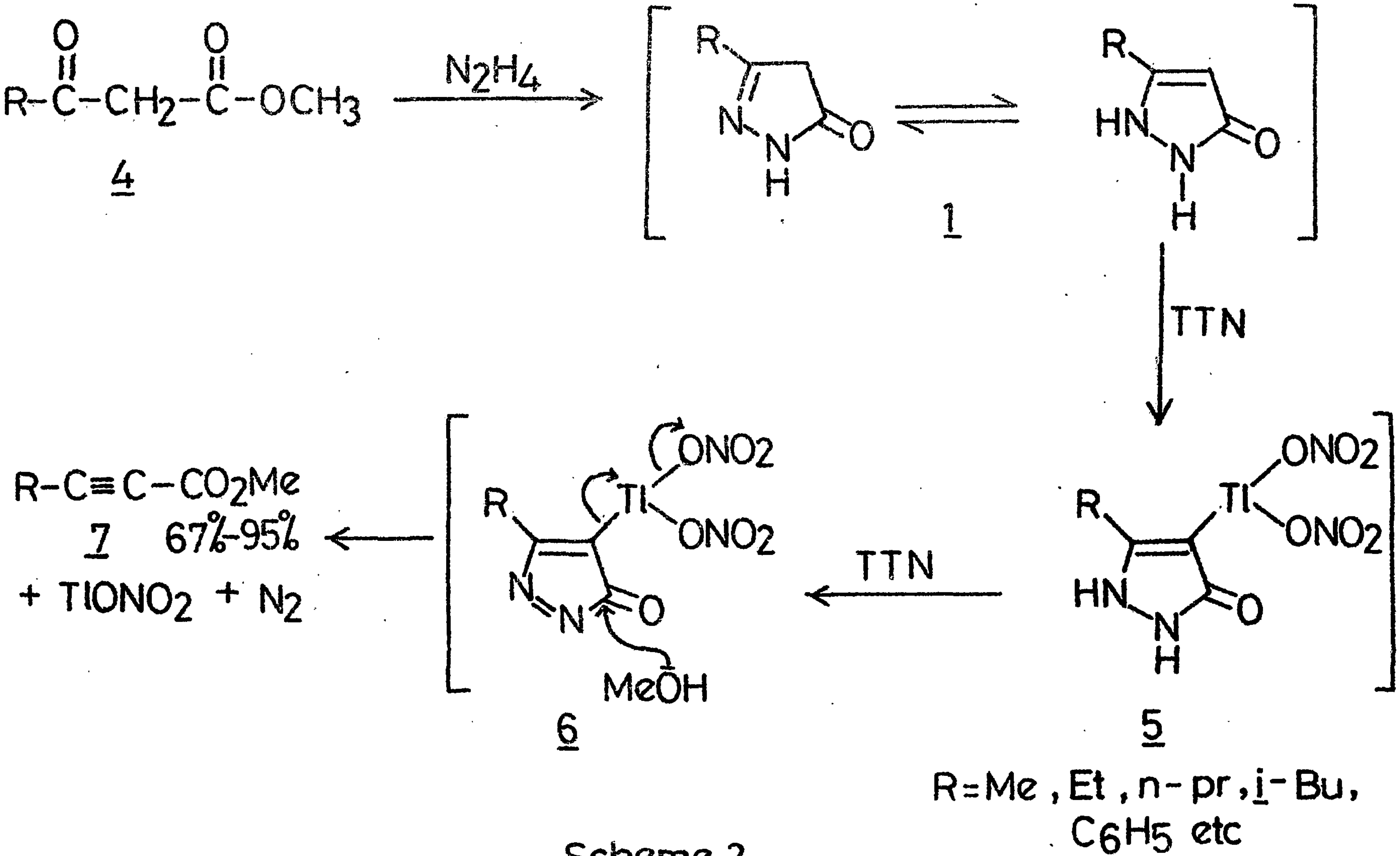
* B. Myrboh, H. Ila and H. Junjappa, Synthesis, 1100 (1982).



R, R' = H, CH_3, C_6H_5

Scheme 1


N2H4
4
1
TTN
5
TTN
6
MeOH
ONO2
ONO2
Tl
R-C≡C-CO2Me
7 67%-95%
+ TlONO2 + N2
R=Me, Et, n-pr, i-Bu, C6H5 etc

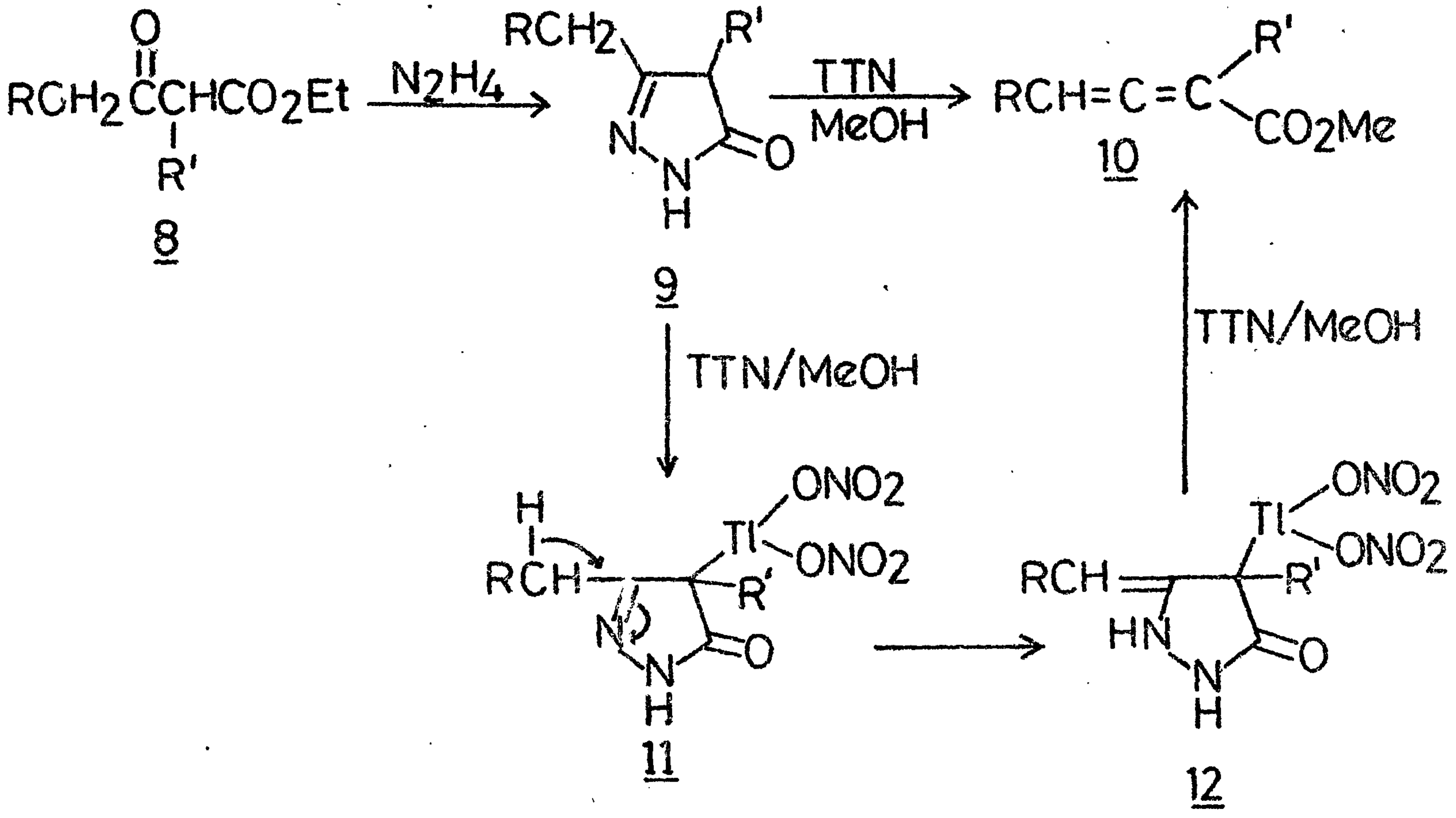
Scheme 2

a sequence of reactions as depicted in Scheme 2, has been suggested for this transformation. The β-keto esters (8) which are alkylated on the α-carbon atom are converted under the similar conditions (by initial treatment with hydrazine followed by addition of Tl (III) nitrate) to the allenic esters 10 (Scheme 3).[3] Since the 4-position is now blocked by an alkyl substituent, deprotonation occurs from the 3-substituent of the pyrazolone thus leading to the observed allenic esters 10.

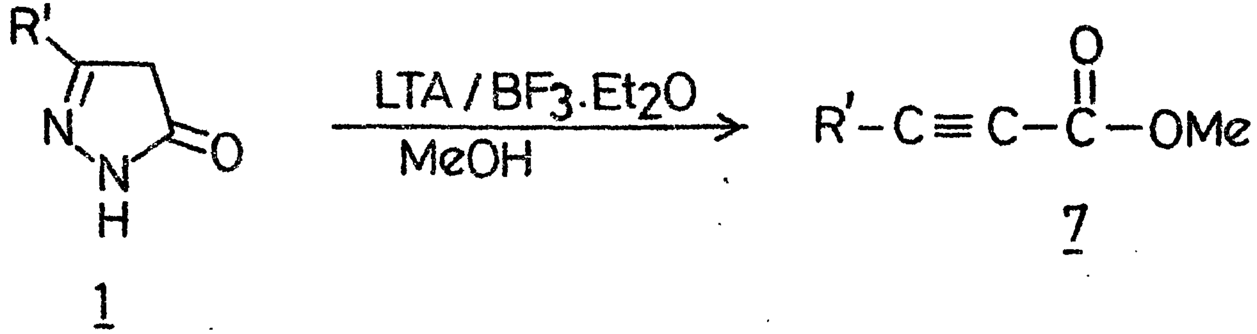
It was therefore contemplated that under the oxyplumbation conditions similar to those employed in the conversion of acetophenones to methyl phenylacetates, these pyrazolones 1 and 9 should yield the corresponding alkynoic 7 and allenic esters 10 respectively.

VI. 2. RESULTS AND DISCUSSIONS

When 5-oxo-3-phenylpyrazole (1a) was reacted with lead tetraacetate in methanol, the corresponding methyl phenylpropiolate (7a) was obtained in 40% yield (Scheme 4). The structure of 7a was confirmed by comparison of its spectral and analytical data with that of authentic sample. Similarly the pyrazolones 1b-f (Scheme 4) were converted to the corresponding acetylenic esters 7b-h in 35-50% yield. The analytical and spectral data of these compounds are described in the



Scheme 3



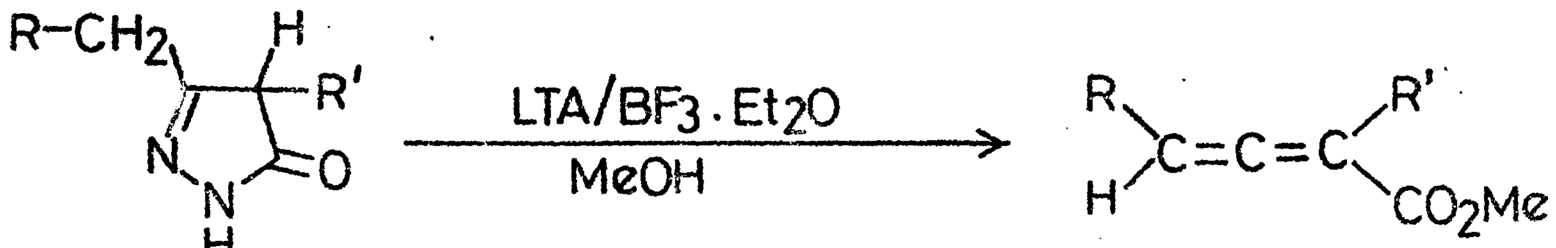
1, 7a, R′= C_6H_5
b, R′= p-CH_3-C_6H_4
c, R′= p-Cl-C_6H_4
d, R′= CH_3
e, R′= n-C_4H_9
f, R′= n-C_5H_{11}

Scheme 4

experimental section (Table 1). Further efforts to improve the yields of 7 by carrying out the reactions in the presence of boron trifluoride etherate were not successful. Similarly 7a was obtained in lower yields (30%) when 1a was generated insitu by treatment of β-keto ester 4a ($R = C_6H_5$) with hydrazine.

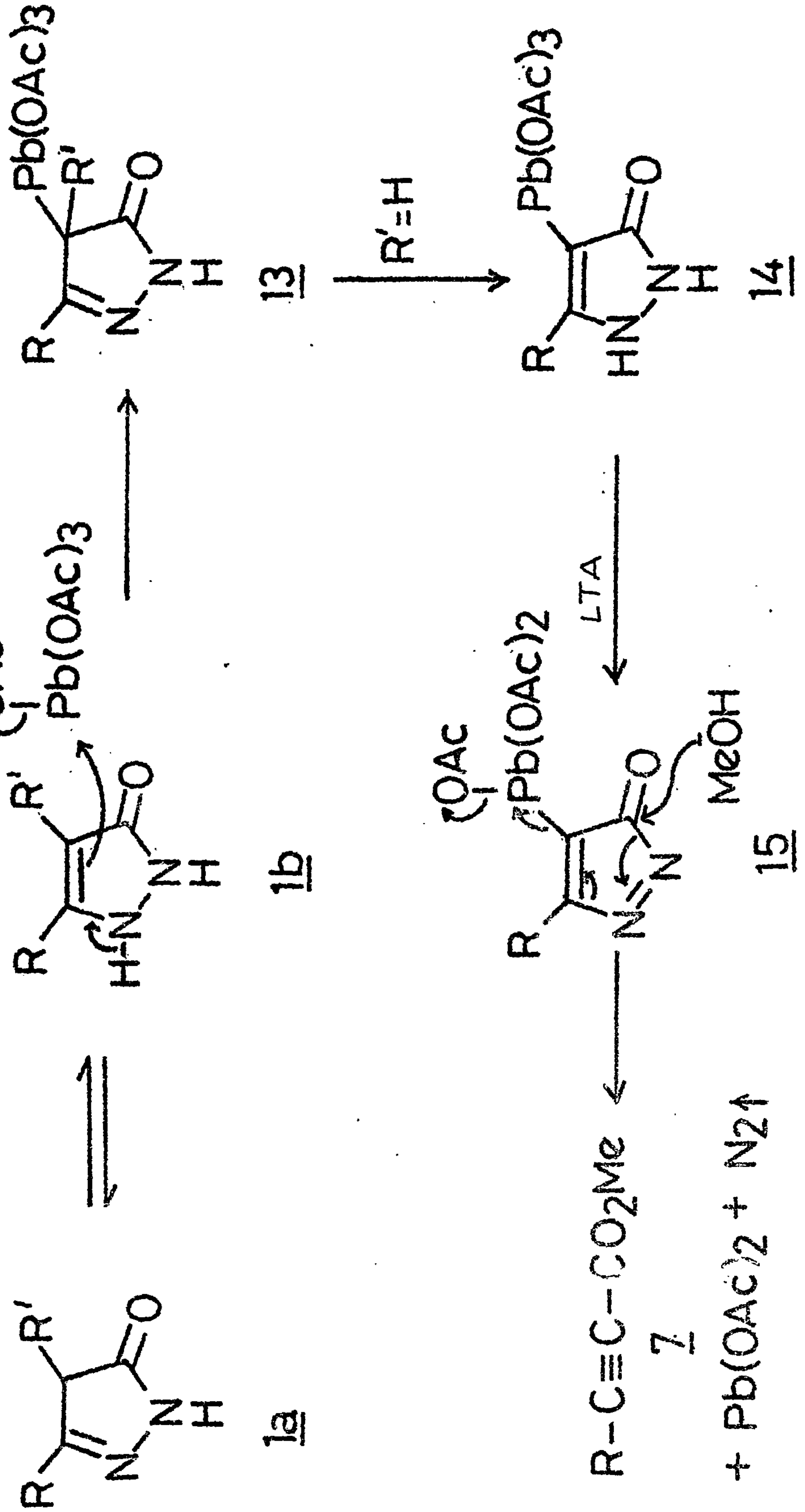
When the reaction was extended to 3,4-disubstituted-5-oxo-4,5-dihydropyrazoles, the expected 2,3-alkanedienoic (allenic) esters 10 were formed in excellent yields. Thus when 9a was treated with lead (IV) acetate in methanol, evolution of nitrogen was not observed. However, evolution of nitrogen sets in immediately when boron trifluoride etherate was added and work-up afforded 10a in 60% yield. Similarly the pyrazolones 9b-i were converted to the corresponding 2,3-alkadienoic esters 10b-i in 70-76% yields. The structures of 9b-i were confirmed with the help of spectral and analytical data (Table 2).

The mechanism of the formation of 7 and 10 is shown in Scheme 6 and 7 respectively. The intermediate adduct 13 formed by electrophilic plumbation of enamine tautomer 1b undergoes subsequent oxidation with a second molecule of lead (IV) acetate to give the oxopyrazole 15. Solvolysis by methanol with concomitant elimination of nitrogen and lead (II) acetate yields the 2-alkynoic esters 7 directly. When the 4-position in 13 is blocked by an alkyl group, deprotonation occurs from



9, 10a, R = H ; R′ = CH_3
b, R = H ; R′ = C_2H_5
c, R = H ; R′ = n−C_3H_7
d, R = H ; R′ = n−C_4H_9
e, R = H ; R′ = n−C_5H_{11}
f, R = H ; R′ = n−C_6H_{13}
g, R = H ; R′ = n−$C_{10}H_{21}$
h, R = CH_3 ; R′ = CH_3
i, R = C_2H_5 ; R′ = C_2H_5

Scheme 5


1a
1b
13
14
15
7
R'=H
LTA
Pb(OAc)3
OAc
Pb(OAc)2
MeOH
R–C≡C–CO2Me
+ Pb(OAc)2 + N2↑

Scheme 6

3-substituent of intermediate pyrazolone adduct 13 affording 14 (Scheme 7). The intermediate 14 on subsequent dehydrogenation followed by methanolysis yields the allenic esters 10. The role of boron trifluoride etherate in the formation of 10 apparently is to facilitate in deprotonation-isomerization of intermediate 13 (Scheme 7).

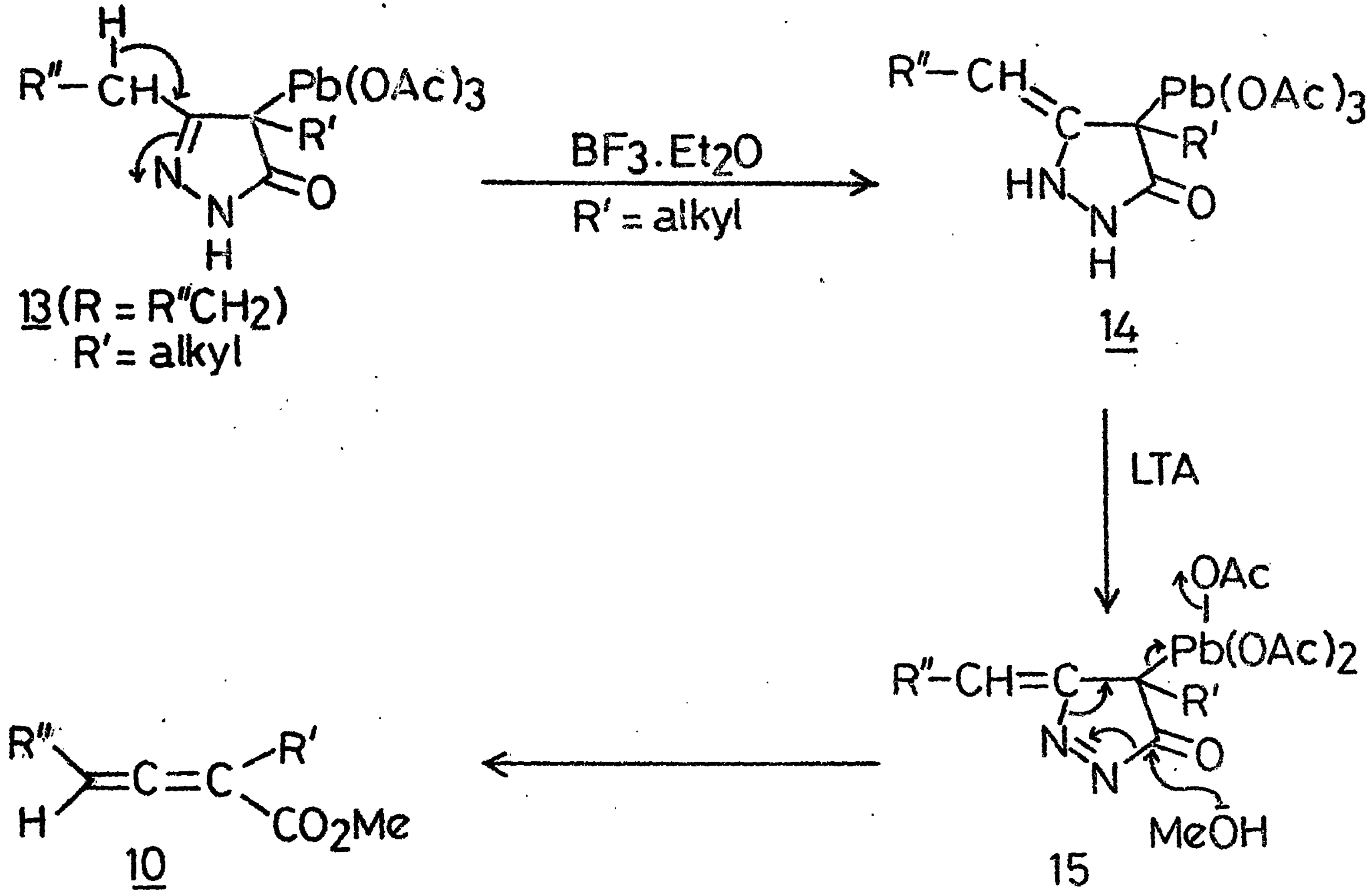
It is apparent that for the synthesis of 2-alkynoic esters 7, the yields are lower than those obtained by Tl (III) nitrate oxidation of 1. However the yields of 2,3-alkadienoic esters (10a-i) are either comparable or superior to those obtained by Tl (III) oxidation. In view of the easy accessibility of lead (IV) acetate and the simplicity of the method including its less hazardous nature, the conversion of the pyrazolones to the synthetically useful 2-alkynoic and 2,3-alkadienoic esters by lead (IV) acetate should be considered the method of choice.

VI.3. EXPERIMENTAL

Preparation of 3-substituted 5-oxo-4,5-dihydropyrazoles (1):

General Procedure : 5-oxo-3-phenylpyrazole (1a):

To a solution of ethyl benzoylacetate (9.6g, 0.05 mol) in 5 ml of 55% ethanol, hydrazine hydrate (2.75g, 0.05 mol) in 5 ml of 95% ethanol was added slowly with stirring at room temperature. Stirring was continued for one hour after the


R″–CH
H
Pb(OAc)3
R′
N
N
H
O
13 (R = R″CH2)
R′ = alkyl
BF3.Et2O
R′ = alkyl
R″–CH
C
Pb(OAc)3
R′
HN
N
H
O
14
LTA
OAc
Pb(OAc)2
R″–CH=C
R′
N
N
O
MeOH
15
R″
H
C=C
R′
CO2Me
10

Scheme 7

addition was completed. Cooling in an ice bath caused precipitation of 7g (90%) of the pyrazolone, m.p. 245°C (lit. m.p. 244-245°C)[4] which was used without further purification.

The following pyrazolones 1b-f were prepared by the above general method and their melting points were compared with those reported in the literature.

3-methyl-2-pyrazoline-5-one (1d); yield : 6g (75%); m.p. 215-216°C (lit. 215°);[45] n-butyl-2-pyrazoline-5-one (1e), yield : 7.5g (85%); m.p. 210° (lit. m.p. 210°);[5] n-pentyl-2-pyrazoline-5-one (1f), yield : 9g (83%); m.p. 197-198° (lit. m.p. 198°);[5] 3,4-dimethyl-2-pyrazoline-5-one (9a), yield, 10g (73%); m.p. 272° (lit. m.p. 272°);[5] 3-methyl-4-ethyl-2-pyrazoline-5-one (9b), yield, 11.6g (79%), m.p. 228-230° (lit. m.p. 229°);[5] 3-methyl-4-(n-propyl)-2-pyrazoline-5-one (9c), yield, 12g (69%); m.p. 210-211° (lit. m.p. 211°)[5]; 3-methyl-4-(n-butyl)-2-pyrazoline-5-one (9d), yield, 15g (85%); m.p. 196-197° (lit. m.p. 197°)[5]; 3-methyl-4-(n-pentyl)-2-pyrazoline-5-one (9e), yield, 10g (77%); m.p. 197-198° (lit. m.p. 198°);[5] 3-ethyl-4-methyl-2-pyrazoline-5-one (9h), yield, 9g (72%); m.p. 230-232° (lit. m.p. 232°)[5].

Preparation of Methyl 2-alkynoates (7) : General Procedure : Methyl 2-phenylpropiolate(7a):

To a well stirred and ice-cooled suspension of lead (IV) acetate (18g, 0.04 mol) in absolute methanol (70 ml), 10 ml of boron trifluoride etherate was added and the pyrazolone 1a (3,2g, 0.02 mol) was added portionwise when an immediate evolution of nitrogen was observed. Fresh addition was made only when the nitrogen evolution had ceased. The reaction mixture was then stirred for a further 15 min, poured into water (100 ml) and extracted with chloroform (3 x 50 ml). The chloroform extract was dried with sodium sulphate and concentrated to give the crude ester 7a as a dark brown liquid which was purified by passing through Florisil. Elution with hexane yielded the pure ester 7a which was further purified by distillation under reduced pressure. Yield, 1.3g (40%): b.p. 95-96°C/1 mm (lit. b.p. 128°C/4)[6]; IR (neat) : 1720 (ν C=O); 2222 (ν C≡C) cm^{-1}. NMR (CCl_4) : δ 3.64 (s, 3H,-$OC\underline{H}_3$); 7.42 (s, 5H, arom).

Methyl 2-(p-methylphenyl) propiolate(7b); yield, 1.7g (45%); m.p. 68°C (lit. m.p. 68-70°C);[6] IR (nujol) : 1720 (ν C=O), 2224 (νC≡C) Cm^{-1}; NMR (CCl_4) : δ 2.31 (s, 3H, -$C\underline{H}_3$); 3.77 (s, 3H, -$OC\underline{H}_3$); 7.30 (q, A_2B_2, 4H, arom).

Methyl 2-(p-chlorophenyl)propiolate (7c); yield, 2g (50%); m.p.

90-91°C, (lit. m.p. 90-94°C);[6] IR (nujol) : 1720 (νC=O); 2225 (νC=C) Cm^{-1}; NMR (CCl$_4$) : δ 3.76 (s, 3H, -OC$\underline{H}_3$); 7.25-760 (1, A$_2$B$_2$, 4H, arom).

Methyl 2-methylpropiolate (7d); yield, 1.4g (35%); b.p 85-88°C/ 90 mm, (lit. b.p. 80-82°/85 mm)[7]; IR (neat); 1720 (νC=O); 2240 (νC=C) Cm^{-1}; NMR (CCl$_4$) : δ 2.25 (s, 3H, -C$\underline{H}_3$); 3.62 (s, 3H, -OC$\underline{H}_3$).

Methyl 2-n-butylpropiolate (7e); yield, 1g (35%); b.p. 45-46°C (lit. b.p. 72-74°/10 mm)[8]; IR (neat); 1720 (νC=O); 2240 (νC=C) Cm^{-1}1 NMR (CCl$_4$): δ 0.95 (t, 3H, -C$\underline{H}_3$); 1.4-18 [m, 4H, -(C$\underline{H}_2$)$_2$-]; 2.32 (t, 2H, -C$\underline{H}_2$); 3.65 (s, 3H, -OC$\underline{H}_3$).

Methyl 2-n-pentylpropiolate (7f); yield, 1g (38%); b.p. 50-51°C/ 3 mm (lit. b.p. 94-96°C/100mm);[8] IR (neat) : 1720 (ν C=O); 2240 (νC=C) Cm^{-1}; NMR (CCl$_4$): δ 0.90 (br.t., 3H, -C$\underline{H}_3$); 1.15-1.72 [br.m., 6H, -(CH$_2$)$_3$-]; 2.30 (t, 2H, -C$\underline{H}_2$); 3.65 (s, 3H, -OC$\underline{H}_3$).

VI.3.3. Preparation of Methyl 2,3-Alkadienoate 10 : General Procedure : Methyl (2-Methyl)-2,3-propadienoate (10a);

To a well stirred and ice-cold slurry of lead(IV) acetate (45g, 0.1mol) and boron trifluoride etherate (15 ml) in absolute methanol (100 ml), the 3,4-dissubstituted pyrazolone 9a (5.6g, 0.05mol) was added in portions. After evolution of nitrogen ceased, the mixture was stirred for a further 15 min, poured into water (250 ml), and extracted with chloroform (3 x 150 ml). The chloroform extract was dried over Na_2SO_4 and concentrated to give the crude ester 10a, which was then passed through a column of Florisil, using hexane as eluent. The product obtained was purified by distillation under pressure. The yields, melting points and spectral data of the products 10a-i are given in the Table.

Table I

Spectral Data of Methyl 2,3-Alkadienoates 10a-i

Product	Yield[a] (%)	b.p./torr (°C)	IR (neat) ν (cm^{-1})	^{1}H-NMR (CCl$_4$/TMS)[b] δ (ppm)
10a[c]	60	50-52/10	1720 (CO) 1960, 1940 (allenic)	2.10 (l, 3H, J = 3Hz, -CH$_3$); 3.60 (s, 3H, -OCH$_3$); 5.00 (q, 2H, J = 3Hz, allenic)
10b[c]	70	60-62/11	1720 (CO) 1960, 1940 (allenic)	1.05 (t, 3H, -CH$_2$ -CH$_3$); 2.1 (m, 2H, CH$_2$ - CH$_3$); 3.60 (s, 3H, -OCH$_3$); 5.05 (t, 2H, J = 3Hz, allenic).
10c	70	68-70/10	1720 (CO) 1960, 1940 (allenic)	0.95 (t, 3H, -CH$_2$ -CH$_3$); 1.45 (sext, 2H, -CH$_2$ -CH$_3$); 2.2 (m, 2H, -CH$_2$ -CH$_2$ -CH$_3$); 3.65 (s, 3H, -OCH$_3$); 5.00 (t, 2H, J = 3Hz, allenic)
10d	70	77-80/10	1722 (CO) 1965, 1940 (allenic)	0.90 [brt, 3H, CH$_3$ -(CH$_2$)$_3$]; 1.32 [m, 3H, CH$_3$ -(CH$_2$)$_2$-CH$_2$]; 2.15 [m, 2H, -CH$_2$ -(CH$_2$)$_2$ -CH$_3$] 3.65 (s, 3H, -OCH$_3$); 4.98 (t, 2H, J = 3Hz, allenic)
10e	76	57-58/1	1710 (CO) 1960, 1940 (allenic)	0.90 [brt, 3H, -(CH$_2$)$_2$ -CH$_3$]; 1.10-1.55 [br.s. 6H, -CH$_2$ -(CH$_2$) -CH$_3$]; 2.2 [m, 2H, -CH$_2$ -(CH$_2$)$_3$ -CH$_3$]; 3.64 (s, 3H, -OCH$_3$); 4.98 (t, 2H, J = 3Hz, allenic)

Table I (cont'd.)

10f	74	70-72/1	1710 (CO) 1963, 1940 (allenic)	0.85 [br.t, 3H, $-(CH_2)_5-C\underline{H}_3$); 1.10-1.60 (br.s, 8H, $-CH_2-(C\underline{H}_2)_4-CH_3$]; 2.15 (m, 2H, $-C\underline{H}_2-(CH_2)_4-CH_3$]; 3.65 (s, 3H, $-OC\underline{H}_3$); 4.95 (t, 2H, J = 3Hz, allenic)
10g	75	125-127/1	1720 (CO) 1968, 1940 (allenic)	0.90 [br.t, 3H, $-(CH_2)_6-C\underline{H}_3$]; 1.25 (br.s, 16H, $-CH_2-(C\underline{H}_2)_8-CH_3$]; 2.15 [br.m, 2H, $-CH_2-(CH_2)_8-CH_3$]; 3.62 (s, 3H, $-OC\underline{H}_3$); 4.95 (t, 2H, J = 3Hz, allenic)
10h	72	67-69/10	1720 (CO) 1956 (allenic)	1.70 (d, 3H, J = 6.5Hz, $=CH-C\underline{H}_3$); 1.85 [d, 3H, J = 3Hz, $=C(C\underline{H}_3)$]; 3.65 (s, 3H, $-OC\underline{H}_3$); 5.3 (m, 1H, allenic)
10i	74	48-50/1	1720 (CO) 1958 (allenic)	1.00 (t, $-CH_2-C\underline{H}_3$); 1.08 (t, 3H, $-C\underline{H}_3$); 1.95-2.25 (m, 4H, $2C\underline{H}_2-CH_3$); 3.65 (s, 3H, $-OC\underline{H}_3$); 5.55 (sept, 1H, J = 6Hz and 3Hz, allenic).

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[a] yield of pure isolated product; purity 97% as checked by G.L.C. analysis (Carbowax 20M on Chromosorb W-HP).

[b] For ^{1}H-NMR spectra of related allenic compounds, see Ref. 9

[c] Reported in Ref.[3] without physical and spectral data.

Table II

Product	Molecular Formula	Analysis (%) Calc. Found	C	H
10c	$C_8H_{12}O_2$ (140.2)		68.47 68.76	8.56 8.77
10d	$C_9H_{14}O_2$ (154.2)		70.03 70.35	9.08 9.42
10e	$C_{10}H_{16}O_2$ (168.2)		71.34 71.65	9.51 9.82
10f	$C_{11}H_{18}O_2$ (182.3)		72.41 72.71	9.87 9.98
10g	$C_{15}H_{26}O_2$ (238.4)		75.50 75.81	10.90 11.22
10h	$C_7H_{10}O_2$ (126.15)		66.59 66.88	7.93 8.24
10i	$C_9H_{14}O_2$ (154.2)		70.04 70.35	9.08 9.42

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