PART A:

SYNTHETIC STUDIES ON LEAD (IV) ACETATE OXIDATIONS: STUDIES ON 1,2-CARBONYL TRANSPOSITIONS AND RELATED REACTIONS

PART B:

DEVELOPMENT OF GENERAL METHODS FOR THE SYNTHESIS OF DIARYL METHANES AND STILBENES FROM AZINES

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

19/6/95

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1. Applications of Spectroscopy of Organic Compounds
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3. Medicinal Chemistry
4. Basic German Language

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CONTENTS

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Felix Mathew

FELIX MATHEW VATTAKUNNEL

PREFACE

Lead(IV) acetate is a versatile oxidising agent widely used in organic synthesis. The work that has been carried out in the laboratory revolves mainly around lead(IV) acetate oxidation of various ketones - saturated, unsaturated, cyclic and acylic.

The thesis is devided into 5 chapters. The first four Chapters discuss synthetic studied on lead(IV) acetate oxidations. First Chapter gives a general introduction on lead(IV)acetate oxidations. In the second Chapter, synthesis of methyl 4-phenyl-3-butenoate using lead(IV) acetate and boron trifluoride etherate-methanol combination has been discussed. In Chapter II the ring contraction of benzylidene cycloalkanone using lead(IV) acetate and triethyl orthoformate perchloric acid combination to afford the ring contracted cyclic esters is discussed. In continuation of the studies concerning the carbonyl transposition and ring contraction, the methodology discussed in Chapter III has been extended to unsaturated acylic ketones, saturated cyclic ketones and cyclopropyl methyl ketones. The details of the reaction and the products obtained are discussed in Chapter IV.

The synthetic utility of benzalazine for the preparation of diarylmethanes and stilbenes is the subject matter of the fifth and last Chapter.

Each Chapter is divided into Introduction, Results and Discussion and Experimental Section. The entire documentation in this thesis is supported by appropriate references at the end of each Chapter.

PART A

CHAPTER I

LEAD(IV) ACETATE OXIDATIONS

I. 1 GENERAL INTRODUCTION

Lead (IV) acetate (LTA) is a versatile oxidising agent widely used in organic synthesis. Its reaction with organic molecules generally involves 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 reactions of lead(IV) acetate with olefines,[1] oxidative decarboxylations 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 and intramolecular cyclization of alcohols with LTA[8,9] have also been discussed.

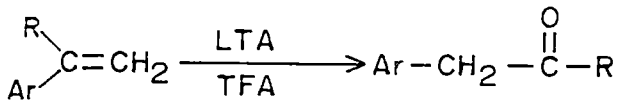
A general review by Criegee[10] on the behaviour of LTA towards O-H, C-H and single and multiple carbon-carbon bonds as well as some reactions involving organic compounds of sulphur, nitrogen and phosphorus have also been appeared. The initial work developed by Criegee laid the foundation for the development and growth of LTA as an important synthetic reagent.[11] The mechanistic aspects of LTA reactions have been included in the general reviews of oxidations.[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 led 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 posses `soft acid' character.[17] Lead(IV) is isoelectronic with mercury(II) and thallium(III). The redox potential of lead(IV) is lowest in the series[18] and consequently the relative oxidising ability of the three metal ions is in the order Hg(II), Tl(III) and 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 have not been obtained except as organic derivative of lead from the reaction of pregnenolene and diaacetatedifluoro lead(IV), $Pb(OAC)_2F_2$, which is particularly significant. 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 aryl acetaldehyde (2) and other ketones are obtained when 1 are oxidised with lead(IV) acetate in trifluoroacetic acid, which contains lead(IV) with four trifluoroacetate ligands[21] (Scheme 1). Similarly, several oxidations involving LTA in hydrofluoric acid and lead(IV) diacetate difluoride, which has been shown to be highly useful fluorinating agent, have been reported.[22,23]

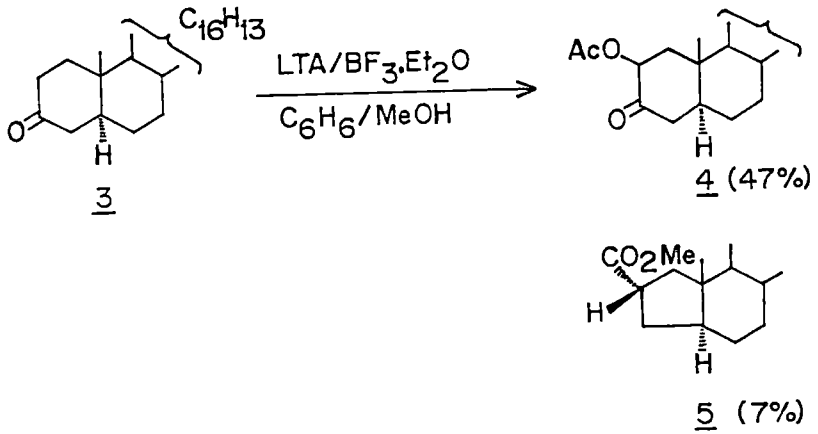
Ketones containing an α-methine moiety readly yield α-acetoxyketones on oxidation with lead(IV) acetate.[24] The enol form is considered to be the reactive species in these reactions. Boron trifluoride is shown to have a strong catalysing effect on the acetoxylation and this has been explained in terms of keto-enol tautomerism,though its effect could also arise from the 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 5α-cholestan-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). Subsequently Fujimoto and co-workers[26] accomplished ring contraction of α-santonin in preparative yield using



1 2

R = H, alkyl, aryl

Scheme—1



3

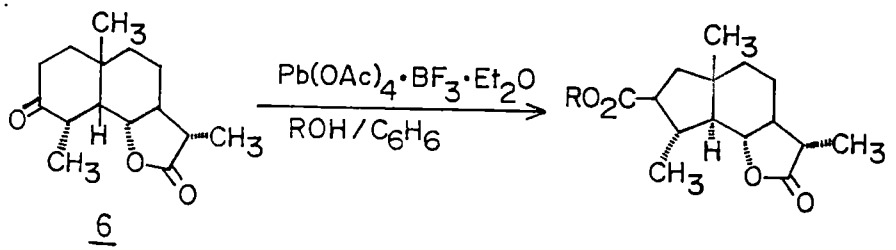
4 (47%)

5 (7%)

Scheme-2

lead(IV)acetate / boron trifluoride etherate in benzene methanol combination. Thus 6 on oxidation yielded 7 as major products (Scheme 3). These authors have postulated the formation of 7 via enol ether (9), which on oxyplumbation followed by subsequent rearrangement of the adduct 10 yields 7 (Scheme 4).

Willgerodt developed in 1887 a method for the preparation of phenyl acetic acid by reacting ammonium sulphide and the acetophenones under pressure at about 200°C, which later became known as the Willgerodt reaction.[27] Extention of this reaction was hampered by modest yields of the carboxylic acid. Several modifications were subsequently extended to improve upon the yields of the products. Since the conversion of the aryl ketones to the corresponding phenyl acetic acid 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 polymerization under these condition. 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 methyl aryl acetates at room temperature in modest to excellent yields. Their method involves the oxidation of the

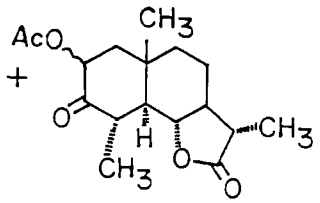


6

7 a, R=Me

b, R=Et

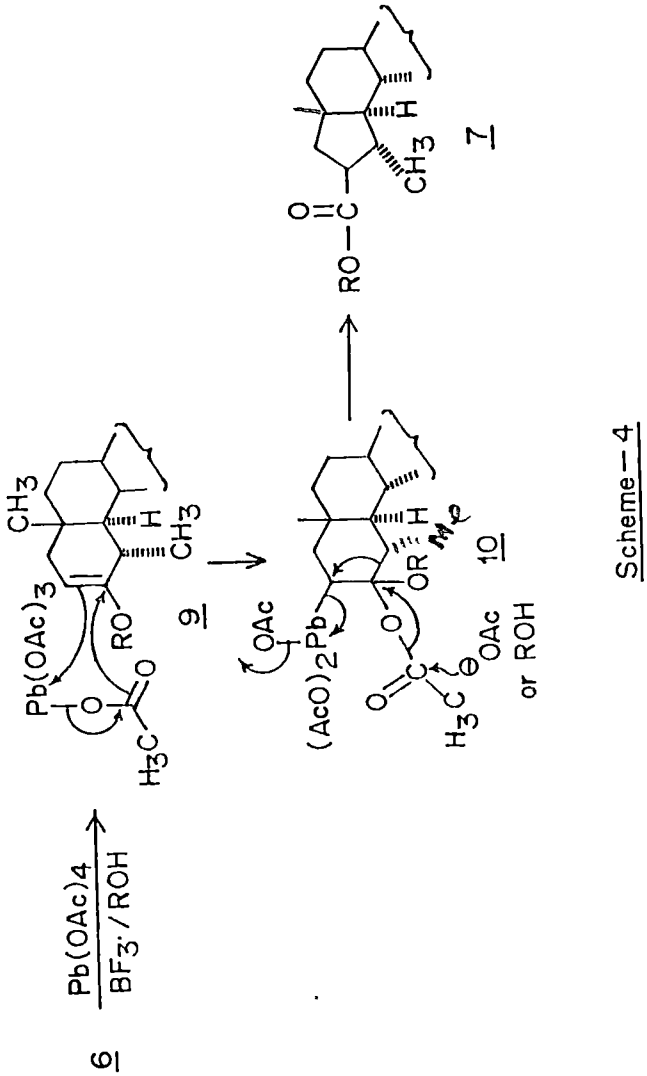
c, R=$CH_2C_6H_5$



8 a, α-OAc

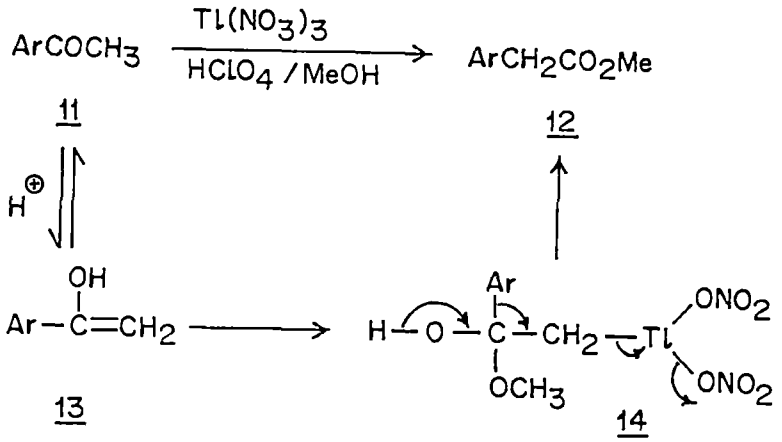
b, β-OAc

Scheme-3

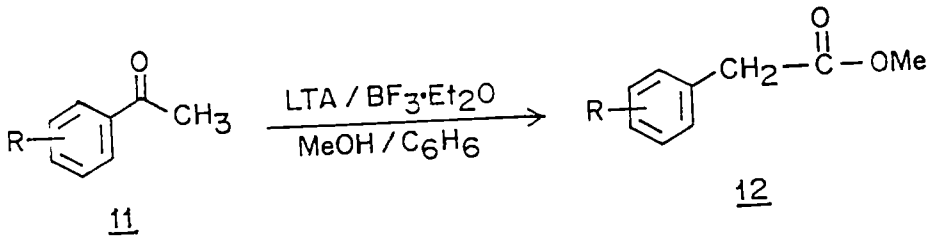

Pb(OAc)4
BF3·/ROH
6
Pb(OAc)3
RO
H3C
O
CH3
H
CH3
9
OAc
(AcO)2Pb
OR
H
10
O
H3C
OAc
or ROH
RO
7
Scheme—4

acetophenones (11) using thalium (III) nitrate (TTN) in the presence of perchloric acid and methanol, when they obtained the corresponding phenyl acetate (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 expensive but also extremely toxic requiring careful handling precautions to be strictly observed. Subsequently, Myrboh and co-workers have successfully reported similar conversion of the acetophenones to the corresponding phenylacetates by oxidation with lead(IV) acetate in presence of methanol and boron trifluoride etherate in dry benzene. Thus when methanol and boron trifluoride etherate added to a well stirred suspension of LTA in dry benzene containing acetophenone and stirred for 8 hours, work-up of the reaction mixture yielded the desired product in 86% overall yield (Scheme 6). The same methodology has been extended to desoxybenzoin (15), 2-acetyl naphthalene (17), and 2-acetylthiophene (19) to their corresponding esters (Scheme-7).

The plausible mechanism appears to involve the initial enolization of the ketones (11) assisted by boron trifluoride etherate followed by oxyplumbation to give 23, which by subsequent aryl group migration rearranges to 12 with the precipitation of lead(II)acetate (Scheme 8). The mechanism is analogus to the oxythallation of the acctophenones[30] in the

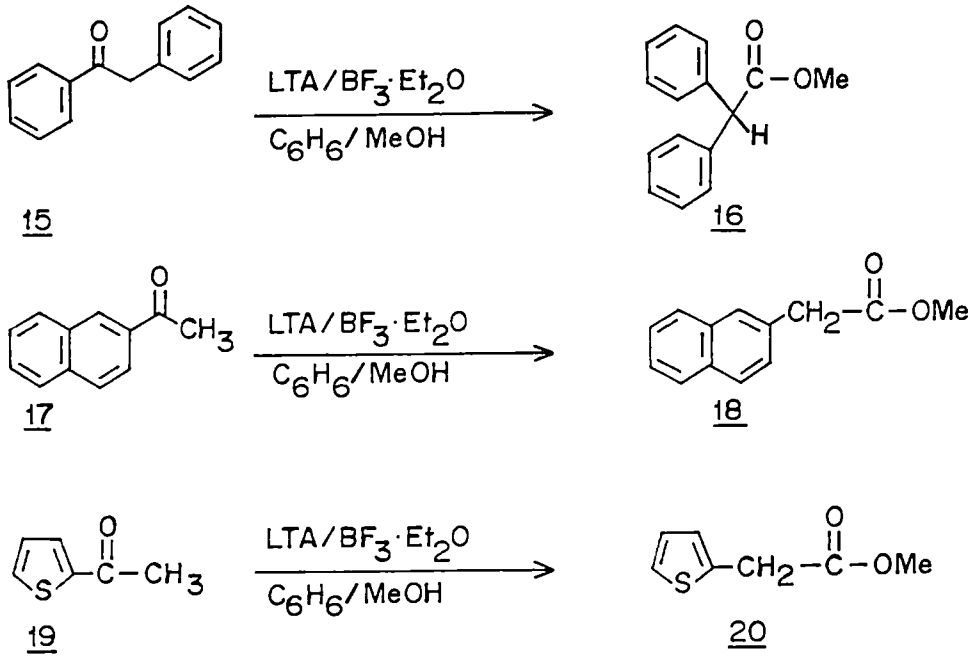

ArCOCH3
Tl(NO3)3
HClO4 / MeOH
ArCH2CO2Me
11
12
H⊕
OH
Ar–C=CH2
13
Ar
H–O–C–CH2–Tl
ONO2
ONO2
OCH3
14

Scheme — 5

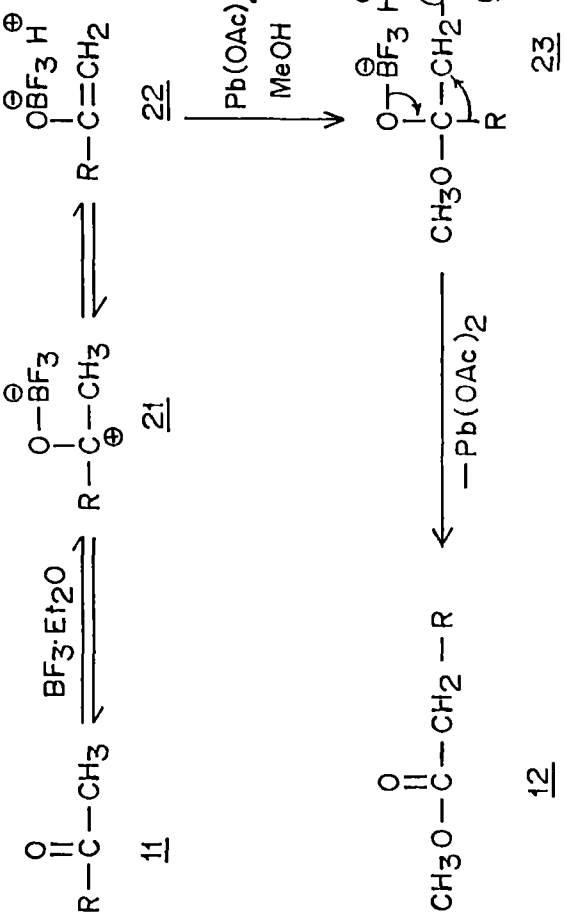


11 12

Scheme – 6


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

Scheme-7

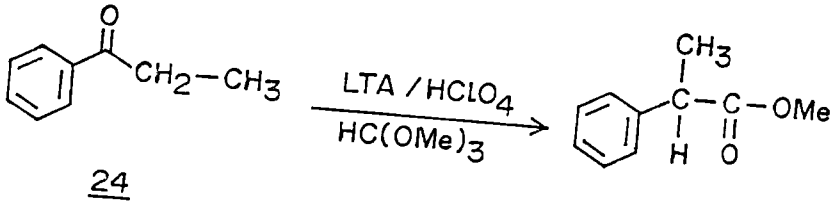


Scheme – 8

presence of perchloric acid and methanol as reproted by McKillop and co-workers (Scheme 5).

When the same reaction was extended to propiophenone (24) in order to prepare methyl α-methyl phenyl acetate (25), a majority of the starting material was recovered unchanged while GLC showed the presence of 25 as minor product (5%) along with several other products. Subsequently a Japanese group has reported the result on the facile preparation of alkyl 2-arylpropanoate[32] (Pharmaceutically important as antiinflamatory drugs) from aryl ethyl ketones 24 and lead(IV) acetate using catalytic amount of perchloric acid and trimethyl orthoformate or triethyl orthoformate as solvent in 78% yield (Scheme 9).

Later a paper by CeKovic and co-workers[33] appeard in which lead(IV) acetate 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 become redundant in the light of the observations, the method by Myrboh et al.[31] provided direct convertion 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 of the enamine derived form cycloalkanones analogous to the Favorski

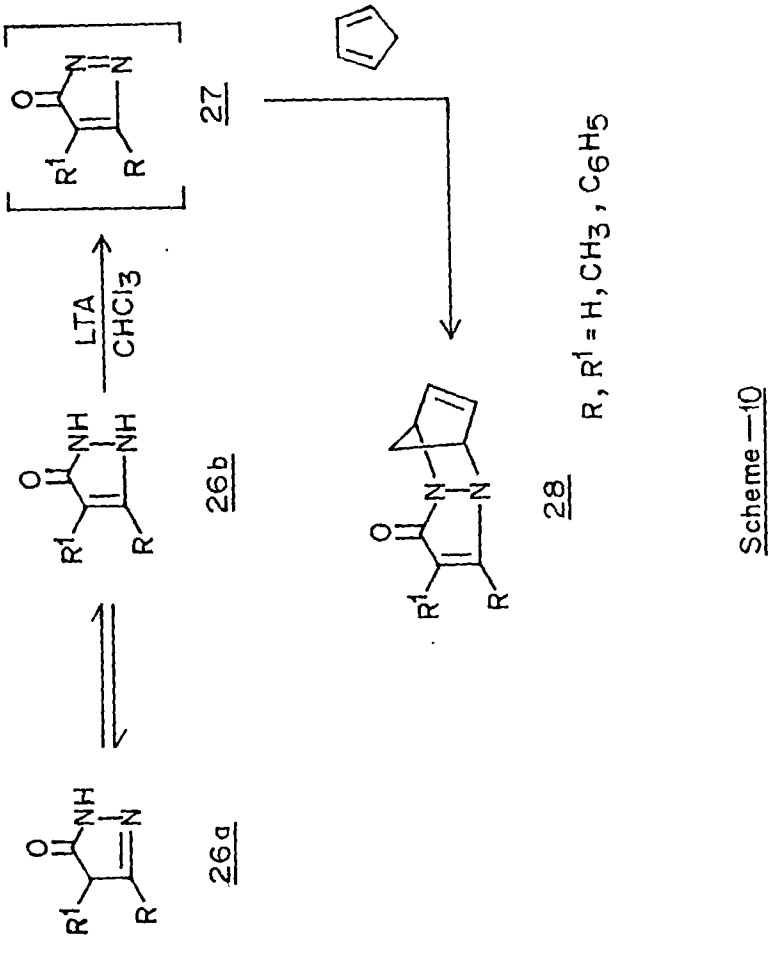


24 25

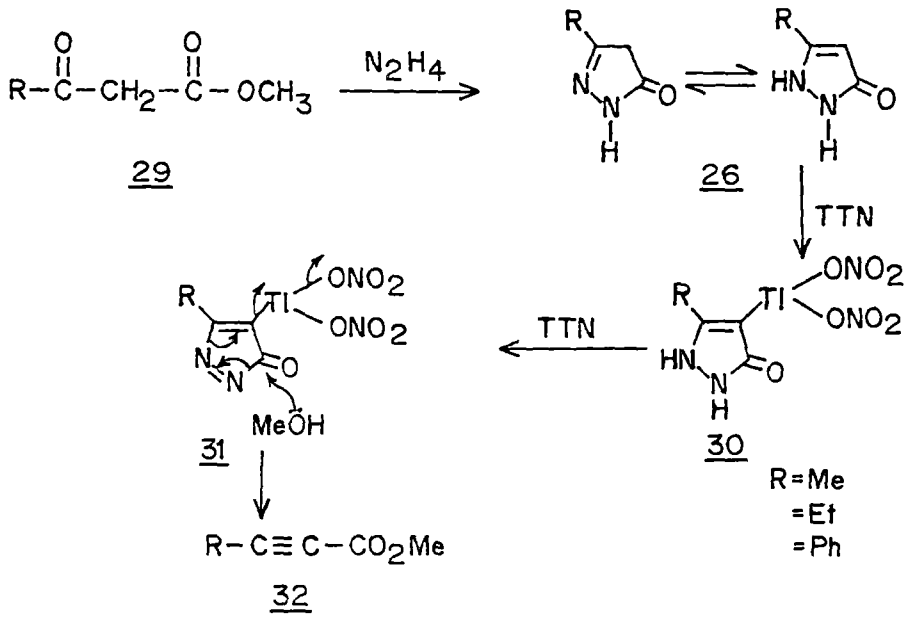
Scheme—9

type of rearrangement, while the reaction of enamines 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.

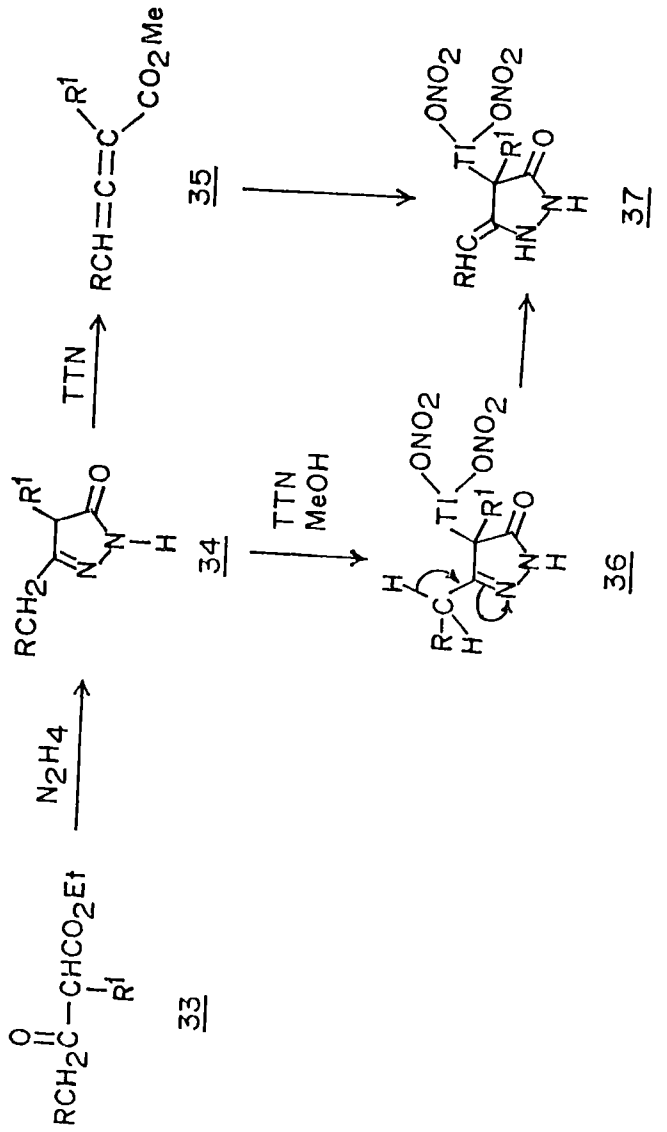
In continuation of lead(IV)acetate oxidation Myrboh et al.[34] reported the oxidation of 2-substituted and 2,3-disubstituted-5-pyrazolones with lead(IV)acetate in methanol which affords 2-alkynoic and 2,3-alkadienoic (allenic) esters respectively in moderate to high yields. Previously it was reported that 3,4-disubstituted-5-pyrozolones (26) underwent dehydrogenation with lead(IV) acetate in chloroform to give the unstable pyrazol-3-one (27) which has been trapped in the presence of dienes through the Diels-Alder reaction (Scheme 10).[35] Taylor and McKillop have reported [36] the conversion of 5-pyrazolones (26) which are readily prepared in quantitative yield from β-ketoesters (29), to the esters of β-alkynoic acids (32) by thallium(III)nitrate in methanol (Scheme 11). A mechanism involving initial thallation of enemine tautomer of 5-pyrazolone (26) followed by a sequence of reactions as depicted in Scheme 12, has been suggested for this transformation. The β-ketoesters (33) which are alkylated on the α-carbon atom are converted under similar conditions (by initial treatment with hydrazine followed by addition of Tl(III)nitrate) to the allenic esters (35) (Scheme 12).[37] Since the 4-position



Scheme—10



Scheme-11

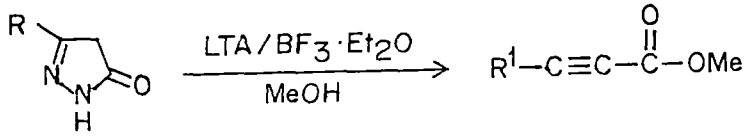


Scheme—12

in now blocked by an alkyl substituent, deprotonation occurs from the 3-substituent of the pyrazolone thus leading to the observed allenic esters (35).

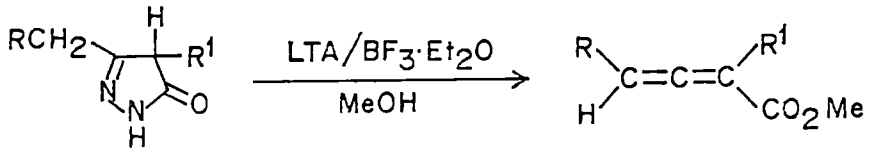
In the reported work by Myrboh et al.[34] the 5-oxo-3-phenyl pyrazole (26) was reacted with lead(IV) acetate in methanol, the corresponding methyl phenyl propyolate (32) was obtained in 40% yield (Scheme 13). When the reaction was extended to 3,4-disubstituted 5-oxo-4,5-dihydropyrazoles, the expected 2,3-alkanedienoic (allenic) esters (35) were formed in excellent yields (Scheme 14). Thus when 34 was treated with lead(IV) acetate in methanol the evolution of nitrogen was not observed. However, evolution of nitrogen sets in immediately when boron trifluoride etherate was added and afforded 35 in 60% yield.

The mechanism of the formation of 32 and 35 is shown in Scheme 15 and Scheme 16 respectively. The intermediate adduct (38) formed by electrophilic plumbation of enamine tautomer 26b undergoes subsequent oxidation with a second molecule of lead(IV) acetate to give the oxopyrazole (40). Solvolysis by methanol with concomitant elimination of nitrogen and lead(II) acetate yields the 2-alkynoic esters (32) directly. When the 4-position in 38 is blocked by an alkyl group, deprotonation occurs from 3-substituent of intermediate pyrazolone adduct (38) affording 39 (Scheme 16). The intermediate 39 on subsequent



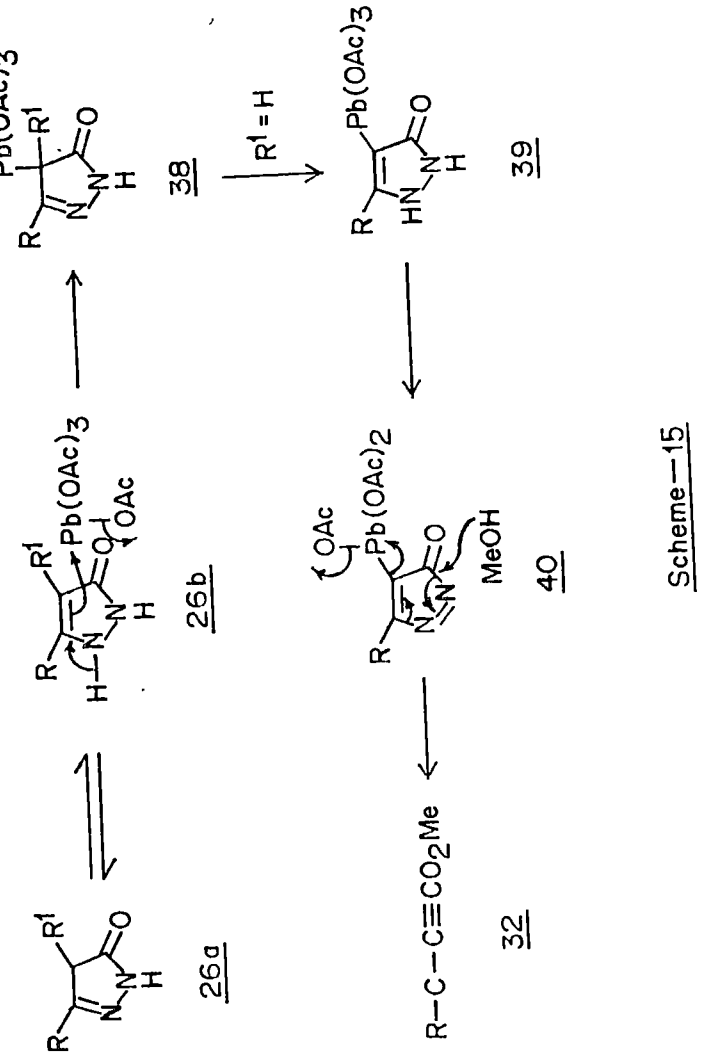
26 32

Scheme—13

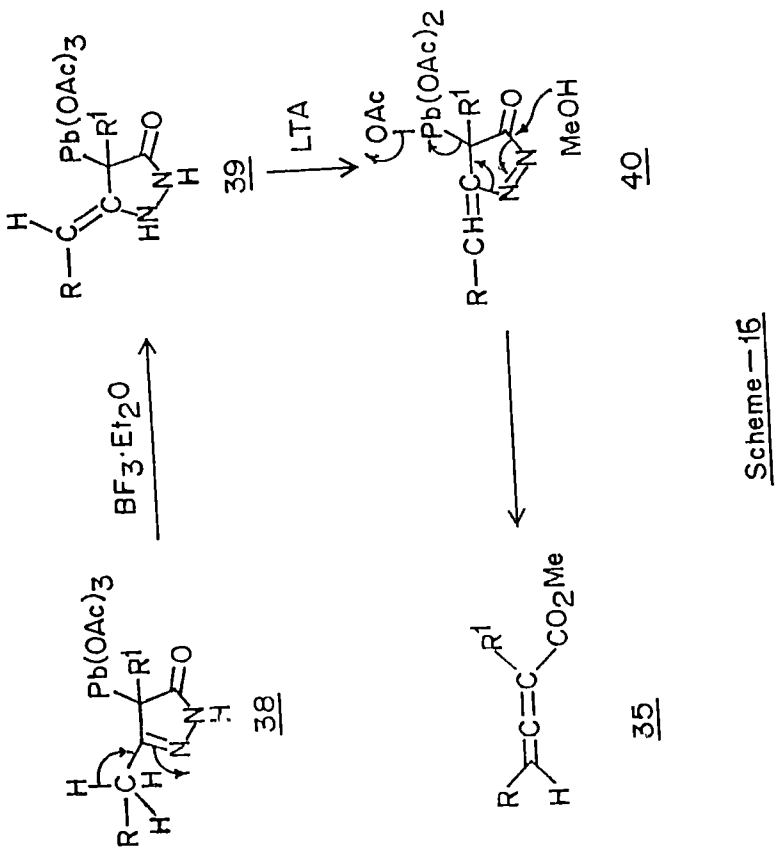


34 35

Scheme—14


Pb(OAc)3
R1
O
N
H
R
38
R1 = H
Pb(OAc)3
39
26b
OAc
Pb(OAc)2
MeOH
40
26a
R–C–C≡CO2Me
32

Scheme—15


Pb(OAc)3
R1
O
H
N
HN
H
R
C
H
38
BF3·Et2O
39
LTA
OAc
Pb(OAc)2
MeOH
40
CO2Me
35

Scheme—16

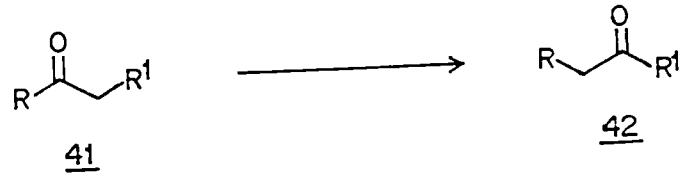
dehydrogenation followed by methanolysis yields the allenic esters (35). The role of boron trifluoride etherate in the formation of 35 apparently is to facilitate the deportonation-isomerization of intermediate 38 (Scheme 16).

The work that has been carried out in our laboratory revolves mainly around lead(IV) acetate oxidations of various ketones- saturated, unsaturated, cyclic and acylic. The carbonyl group in its various forms (aldehydes, ketones, carboxylic acids and its derivatives) is the most important functional unit in organic chemistry. It is generally considered as a functional group of choice in organic synthesis. The unparalleled importance of carbonyl compounds have prompted a continuous search for newer methods for their preparations. The versatility of the carbonyl functions in organic synthesis is based on its capability to undergo a wide variety of bond forming reactions both at the carbonyl carbon atom and at the sites influenced by its polarity.

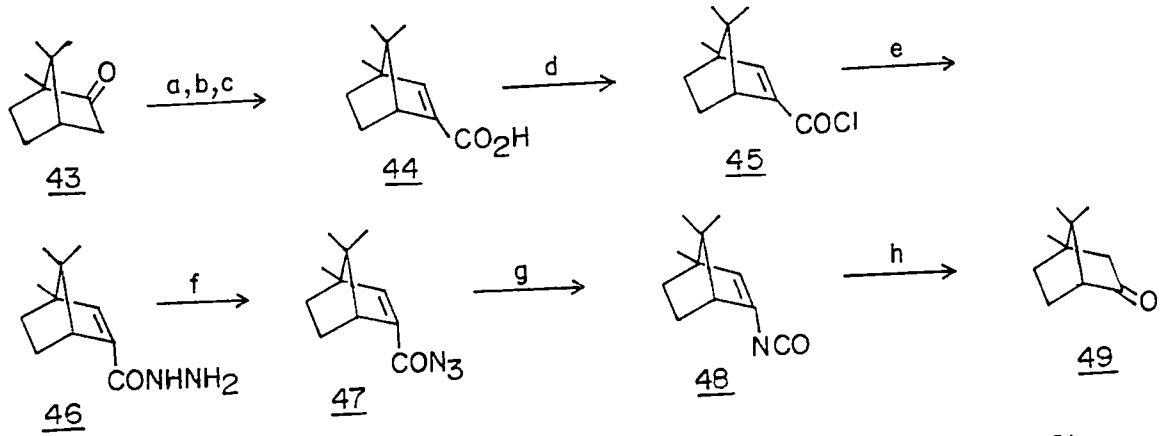
Since the begining of the 20th century, there has been a constant interest in finding suitable methods for the transposition of a carbonyl group from its original position to carbon atom α,β and to it. The most common transposition is the exchange of a carbonyl function with an adjacent methylene group referred to as 1,2-carbonyl transpositions. (Scheme 17).

A survey of the literature revealed that a successful attempt at 1,2-carbonyl transposition was simultaneously reported by Perkin[38] and Bredt[39] in 1911. The study refers to the transposition of (d) Camphor (**43**) to 1-epicamphor (**49**) (Scheme 18). The requisite starting material unsaturated carboxylic acid (**44**) was readily available [40] from (d) camphor in four steps.

Since then other methods were developed dealing with 1,2-carbonyl transposition in the terpene systems.[41,42] The importance of 1,2-carbonyl transposistion in the steroid field has been well documented and recognised. As early as 1944 Ruzika and co-workers developed a method for the conversion of chlolestan-3-one to cholestan-2-one.[43] But it was not until 1950's that a ketone transposition technique was applied to the cortisone problem. Here also the methodology found its success in transforming readly available 12-ketosteroids occurring in bile acids and sapogenins to the otherwise inaccessible 11-ketosteroids. Subsequently, numerous ketone transposition procedures have appeared in the literature as solution to problems especially in steroid chemistry and have employed a wide spectrum of organic reagents in the transposition step. A recent example lies in the work of Oka and Hara[44] who have very effectively utilized a 1,2-carbonyl transposition in their synthetic work leading to the synthesis of biologically active salamander alkaloids. The key step in this sequence was the



Scheme—17



a. $NaNH_2$,Et_2O, CO_2; b. Electrolytic Reduction ; c. $(CH_3CO)_2O/\Delta$; d. $SOCl_2$;

e. NH_2NH_2 ; f. HNO_2 ; g. Pyrolysis ; h. HCl .

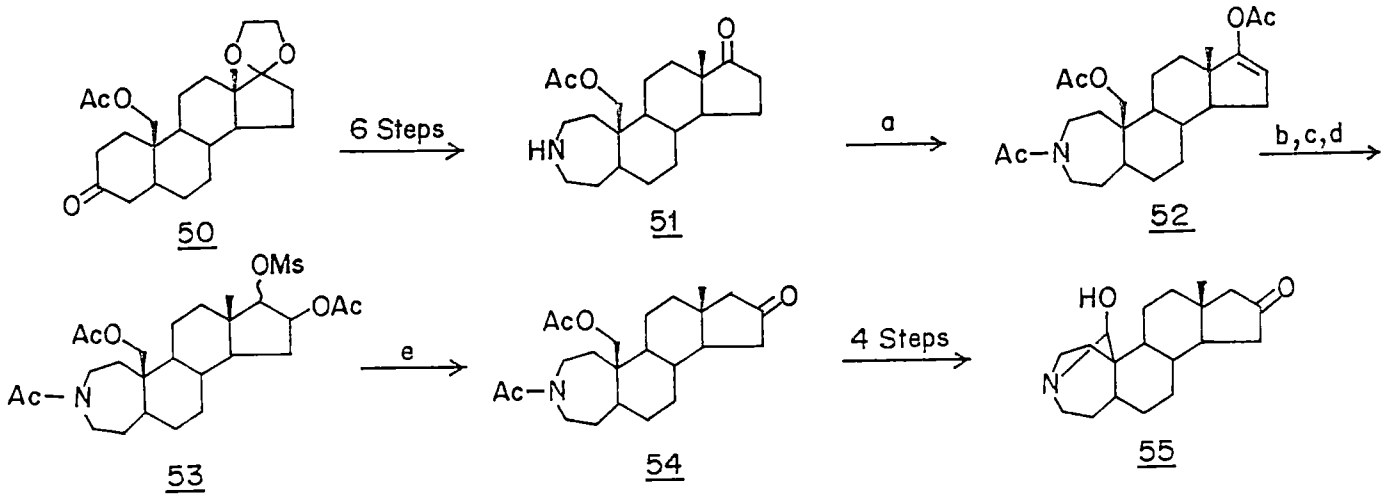
Scheme—18

conversion of α-acetoxy mesylate (53) to 54 on treatment with methanolic potassium hydroxide. The latter was then converted by these authors in four steps to cycloneosamandione (55) (Scheme 19).

Another method involving the use of lead(IV) acetate-borontrifluoride combination to achieve a 1,2-carbonyl transposition in a saturated system was reported by A. Leblache-Combier et al.[45] Thus lanost-8-en-3-one (56) on treatment with lead(IV) acetate-borontrifluoride gave the vicinal acetoxyketone (57) which isomerizes to (59) in the presence of basic alumina. Finally the product 60 was obtained as shown in Scheme 20.

A novel one-step transformation for 1,2-carbonyl transposition was reported by McKillop, Swann and Taylor,[30] wherein they have found that thallium(III) nitrate in acidic methanol rearranged acetophenones to methyl phenyl acetates (Scheme 5).

Recently Myrboh and co-workers have used lead(IV) acetate, boron trifluoride etherate and methanol combination in the synthesis of biologically important Indane-1-Carboxylates[46] (65). Here a 1,2-carbonyl transposition was obtained by a smooth ring contraction of the tetralones (61) to the Methyl Indane-1-Carboxylates (65) in moderate yields (Scheme 21).



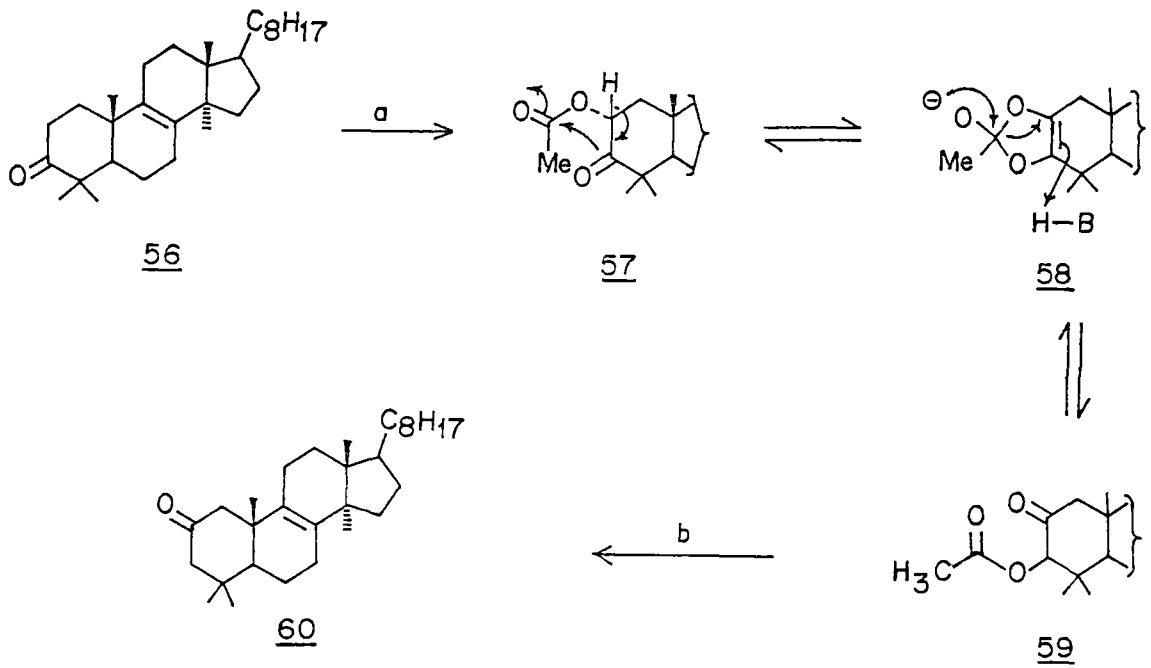
50 51 52

53 54 55

a. Isoprenyl acetate, $H^{\oplus}$; b. $Pb(OAc)_4$, CH_3CO_2H, trace $(CH_3CO)_2O$;

c. $NaBH_4$, CH_3OH; d. MsCl, C_5H_5N; e. KOH, CH_3OH.

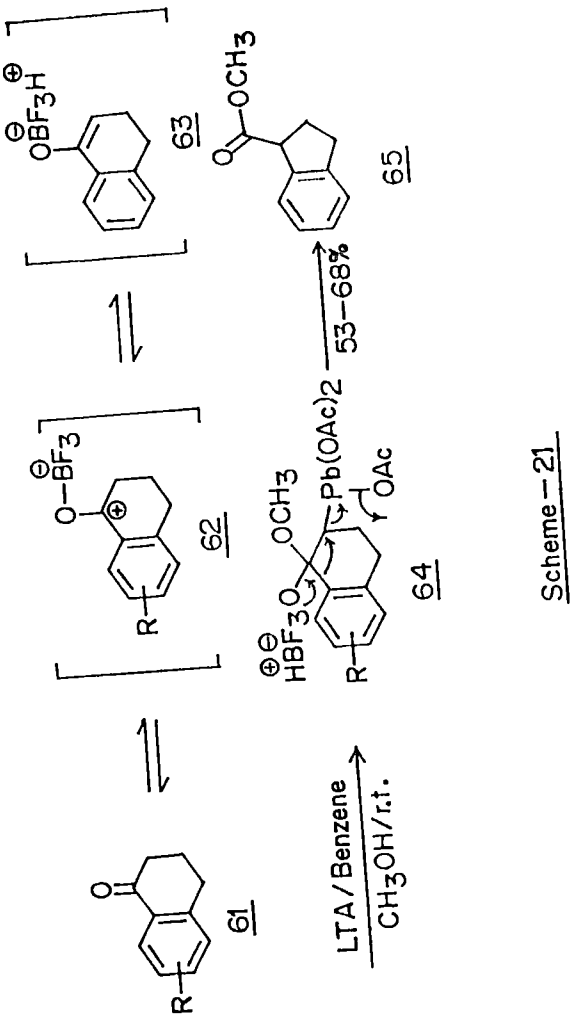
Scheme –19



56 57 58 59 60

a. $Pb(OAc)_4 - BF_3$ b. $Ca - NH_3$

Scheme—20



Scheme – 21

The examples available on the 1,2-carbonyl transposition using lead(IV) acetate and other isoelectronic oxidising agents have been done on saturated carbonyl compounds and no attempt has been made to affect similar conversion on the α,β-unsaturated ketones using lead(IV) acetate. This fact has prompted us to carry out investigations based on lead(IV) oxidation of unsaturated ketones and cyclopropyl ketones with a view to develop general methods for these type of carbonyl transposition. In Chapter II synthesis of Methyl-4-phenyl-3-butenoate using lead(IV) acetate and boron trifluoride etherate methanol combination has been discussed. The structural elucidation of the products were done on the basis of analytical data and spectral evidences are also discussed.

In Chapter III the ring contraction of benzylidene cycloalkanone using lead(IV) acetate and triethyl orthoformate perchloric acid combination to afford the ring contracted cyclic esters. The details concerning the ring contraction and analysis of the products are discussed there.

In continuation of our studies concerning the carbonyl transposition and ring contraction, we have extended the same methodology discussed in Chapter III to unsaturated acylic ketones, saturated cyclic ketones and cyclopropyl methyl ketones. The details of the reaction, and the confirmation of the products formed are discussed on the bases of analytical data and spectral evidence in Chapter IV.

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CHAPTER II

A FACILE ONE-STEP SYNTHESIS OF β,γ-UNSATURATED CARBOXYLICACID ESTERS VIA 1,2-CARBONYL TRANSPOSITION OF α,β-UNSATURATED KETONES

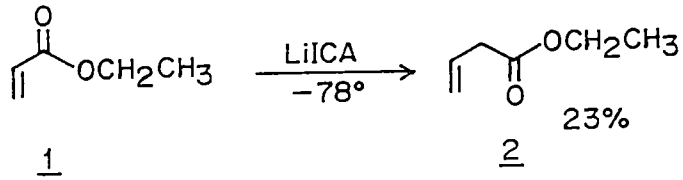
II. 1. INTRODUCTION

β, γ -unsaturated esters along with α,β-unsaturated esters play an important role in organic chemistry. The reactivity of these groups to both nucleophiles and electrophiles under a variety of reaction conditions has made them ideal precursors in many organic syntheses, and numerous natural products possess these structural subunits. The synthesis of α,β-unsaturated carboxylic acid esters are well documented and their methods of preparation are manifold and varied.[1] On the other hand the corresponding β, γ-unsaturated compounds are less readly accessible.[2] Therefore in our present work we have explored the

possibility of 1,2-carbonyl transposition of α,β-unsaturated ketones to afford β, γ-unsaturated carboxylates.

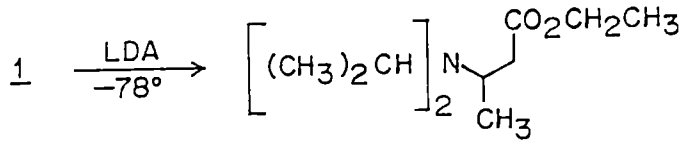
The pioneer work in the field of β, γ-unsaturated esters was carried out independently by Rathke[3] and Schlessinger.[4] Addition of ethyl crotonate (1) to a 1M solution of lithium N-isopropyl cyclohexylamide (LiICA) in tetrahydrofuran at temperature of -78°C followed by quenching with dilute hydrochloric acid produces a mixture of non-conjugated ester, ethyl 3-butenoate (2) in 23% yield.[3] Here the low yield of the β, γ-unsaturated ester was due to the rapid condensation of unsaturated enolate with the ethyl crotonate (Scheme 1).

In the deconjugative alkylation of the enolate anion derived from ethyl crotonate (1) the major experimental concern in generating crotonic enolate was the possibility that the base, lithium diisopropyl amide (LDA) employed for these reactions acted as a nucleophile and conjugatively added to the unsaturated ester at a rate competitive with proton abstraction[4] to afford 3. Therefore an essentially non-nucleophilic form of LDA was realized by the formation of 1:1 complex with hexamethylphosphoramide (HMPA). No Michael addition to ethyl crotonate was observed with this base mixture whereas it only act as a base towards ethyl crotonate (1) and permit the alkylation at the α-carbon atom to afford α-substituted β, γ-unsaturated ester (4) (Scheme 2).

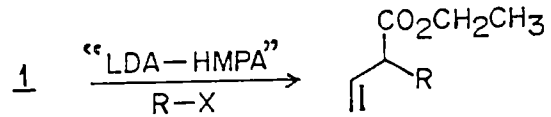


1 2

Scheme—1



1 3

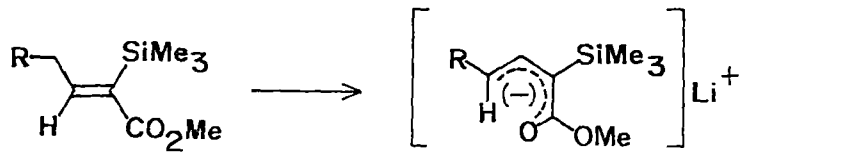


1 4

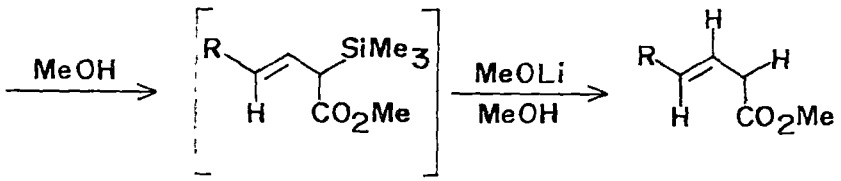
Scheme—2

Zweijel[5], et al. could achieve a stereo selective conversion of (Z)α-(trimethylsilyl) α,β-unsaturated ester (5) into α,β and β, γ-unsaturated esters. In their preliminary investigation to provide a convenient route for the preparation of useful and versatile allylsilyl and alkoxycarbonyl compound, they selected α-silyl β, γ-unsaturated ester (7) which afforded the corresponding desilylated (E) ester (8) instead. When the ester (5) was added to a solution of LDA or LHMDS (lithiumhexamethyldisilazide (1:1 equiv.) in tetrahydrofuran containing HMPA (3 equiv.) at -78°C, deprotonation took place leading to the dienolate (6). Protonation of 6 with methanol gave 7 which was however susceptible to nucleophilic attack on silicon by the lithium methoxide formed in the course of the reaction to furnish the desilylated esters(8)[6] in 98% isomeric purity (Scheme 3).

A widely applicable method developed by Salomon generates allylcarboxylic acids via. ene-reaction of alkenes with diethyl oxomalonate and successive oxidative bisdecarboxylation of the ene-adducts.[7,8] The drawback of the above method is the noncarboxylic acid biproducts which were isolated and charactarized from the oxidative bisdecarboxylation of tartronic acid, (9). Thus all of the starting material 9 not converted to carboxylic ester (10) is accounted for by the co-production of



5 6



7 8 a-c

R = a, nC_3H_7

b,c C_6H_{11}

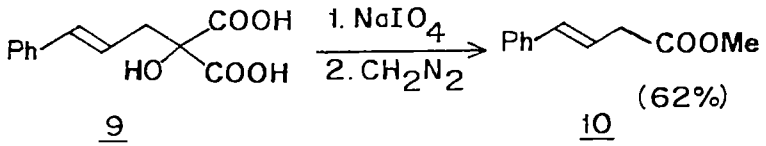
c, C_6H_5

Scheme-3

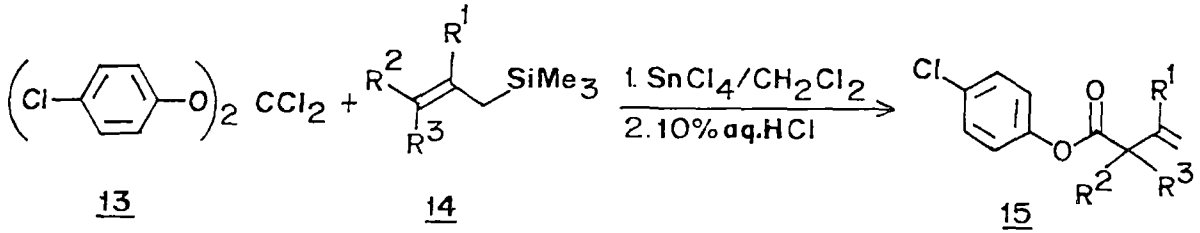
cinnamaldehyde (11) and benzaldehyde 12 in 13% and 22% yields respectively (Scheme 4). The oxidative bisdecarboxylation of allyltartronic acid is sometimes not effective with sodiumperiodate ($NaIO_4$). Thus tartronic acid derived from their respective ene-adduct gave only traces of (<5%) of allyl carboxylic acid under standard conditions.[7]

In another method for the preparation of β,γ-unsaturated esters, the allylsilanes are converted to the allylcarboxylic acid ester via aryloxycarbonylation with dichlorobis (4-chloro phenoxy) methane and tin(IV)chloride (1:1 equiv.) in dichloromethane at low temperature.[9] It was observed that the double bond of 17 can be attacked at both termini resulting in formation of compound 18 in addition to the normal product 15 (Scheme 5).

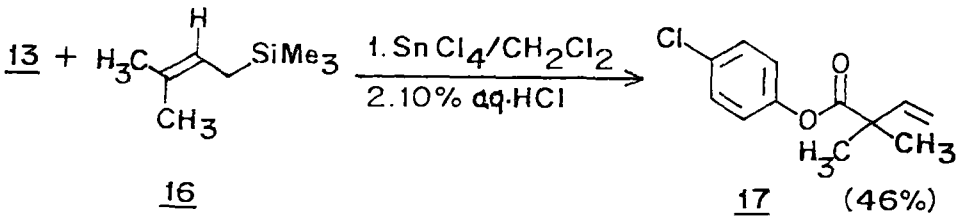
Our literature survey revealed that the only recent method for the preparation of β,γ-unsaturated esters involves carbonylation of allylic derivatives catalysed by palladium in its various oxidation states. In one of the methods, β, γ-unsaturated esters were obtained by the reaction of allyl alkyl carbonates[10] in the presence of palladium-phosphine complex as catalyst. In other words, the decarboxylation-carbonylation or exchange reaction of carbon dioxide with carbon monoxide. When the reaction of allylethyl carbonate (19) with carbon monoxide was carried out, the reaction proceeded


Ph
COOH
HO
COOH
1. NaIO4
2. CH2N2
Ph
COOMe
(62%)
9
10
+ Ph
CHO
(13%)
11
+ PhCHO
(22%)
12

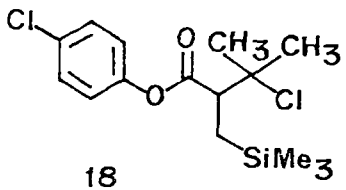
Scheme-4



13 14 15



16 17 (46%)



18 (18%)

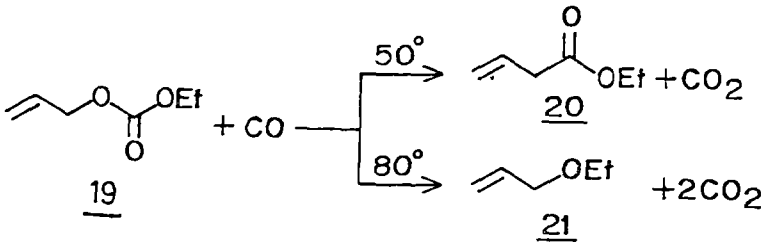
Scheme – 5

smoothly under mild condition to afford ethyl-3-butenoate (20) in good yield, along with allyl ethyl ether (21) as a biproduct. Here the reduced carbon monoxide pressure and the higher reaction temperature (above 50°C) enhances the yield of the biproduct 21 (Scheme 6).

In another palladium catalyst-assisted reaction[11] atmospheric pressure ethoxycarbonylation of allylic halides were realized under the influence of sodium ethoxide to afford β,γ-unsaturated esters. Here the reaction is catalysed by Na_2PdCl_4-bis(diphenylphosphino)ethane (dppe) (Scheme 7). The major disadvantage is that the ethoxycarbonylation of allylic halides such as allylbromide or methallyl chloride failed to give β,γ-unsaturated esters, since rapid isomerization occured under the basic conditions and the α,β-isomers were formed.

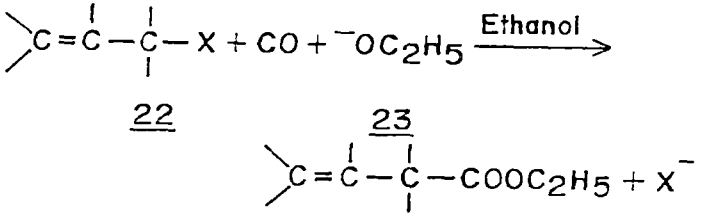
In a recent attempt for the preparation of β,γ-unsaturated esters, Murahashi and co-workers carried out alkoxycarbonylation on allylphosphates and allylacetates using palladium in its (0) oxidation state.

Thus the diethylcinnamyl phosphate (25) was carbonylated to afford (E)-Ethyl 4-Phenyl-3-Butenoate (26) stereoselectively which is thermodynamically stable. The corbonylations were carried out in the presence of 1 mol of $Pd_2(dba)_3$-$CHCl_3$ catalyst, 4 mol of PPh_3 and 1 equiv. of i-Pr_2NEt as a base in ethanol under



19 20 21

Scheme–6



22 23 24

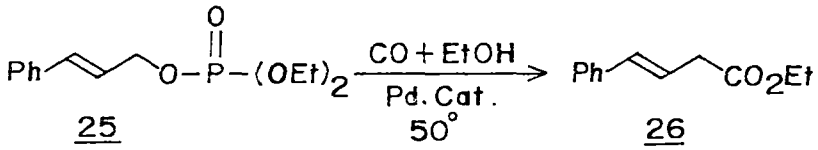
Scheme–7

CO pressure (30 atm.) at 50°C for 1 hour[12].

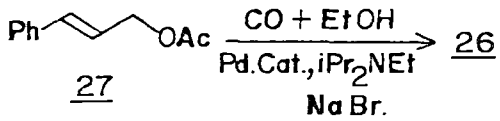
Further, **26** was prepared stereoselectively when the cinnamyl acetate was carbonylated upon treatment with CO (30 atm.) in ethanol in the presence of $Pd_2(dba)_3$-$CHCl_3$ (2 mol), PPh_3 (8 mol) catalyst, NaBr (20 mol) and i-Pr_2NEt (1.0 equiv.) at 50° (Scheme 8).

Nakanishi[13] has reported another route to the synthesis of β, γ-unsaturated ester via carbonylation of (η^3-Allyl) $Fe(CO)_2NO$ complexes. The title compound was prepared by one-pot conversion of allylhalides (**28**) with $[Bu_4N]^+Fe(CO)_3(NO)]^-$ followed by treatment with 1,2-bis(diphenylphosphino)ethane (dppe) gave β, γ-unsaturated acyl iron complexes (**30**) in good yields via regioselective carbonylation with retension of configuration of the allylic double bond. β, γ-unsaturated carboxylic acid esters were prepared upon treatment of the acyl iron complexes with alcohols in the presence of iodine (Scheme9).

Unsaturated organic molecules both aliphatic and aromatic containing the carbonyl functional group has been scantily subjected to lead(IV) acetate oxidation without altering the unsaturated nature of the compound to afford the corresponding unsaturated esters. On the other hand, the oxidation of the aromatic ketones **32**[14] and desoxybenzoin (**34**) using lead(IV) acetate/ boron trifluoride etherate and methanol system has been

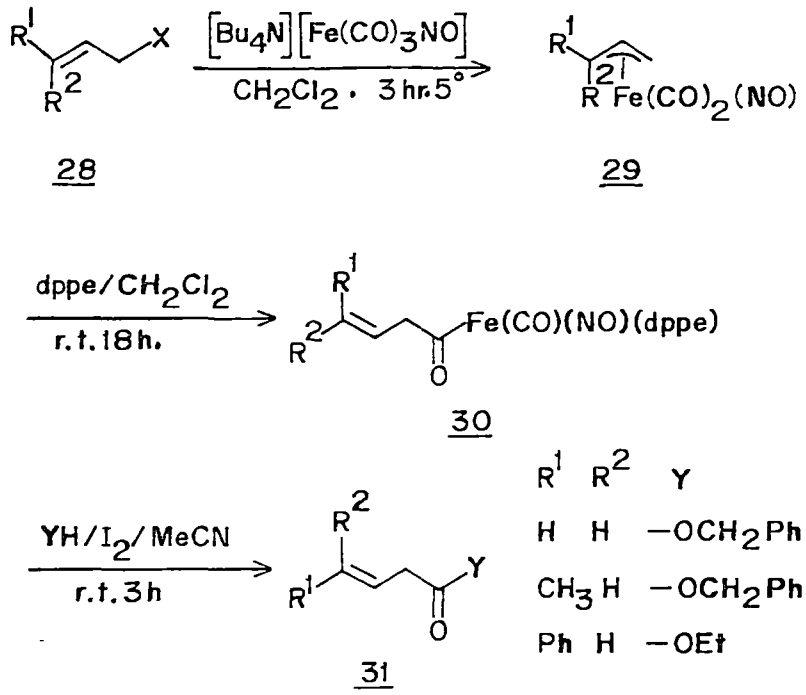


25 26



27

Scheme – 8


[Bu4N][Fe(CO)3NO]
CH2Cl2 · 3 hr. 5°
Fe(CO)2(NO)
28
29
dppe/CH2Cl2
r.t. 18 h.
Fe(CO)(NO)(dppe)
30
YH/I2/MeCN
r.t. 3 h
31
R1 R2 Y
H H —OCH2Ph
CH3 H —OCH2Ph
Ph H —OEt

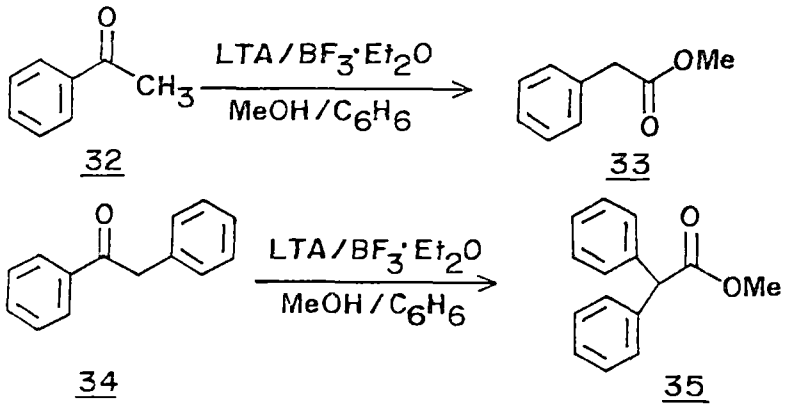
Scheme-9

carreid out successfully in their transformation to methyl aryl acetate (33) and 2,2-diphenylmethyl acetate (35) respectively (Scheme 10).

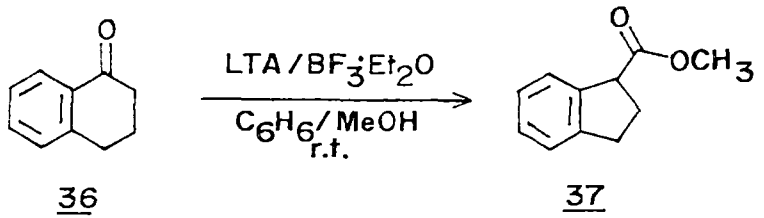
Earlier studies carried out in this laboratory[15] for the transformation of tetralones (36) to indane-1-carbonylic acids (37) (scheme 11) prompted us to extend the investigation to the oxidation of α,β-unsaturated ketones with a view to achieve a 1,2-carbonyl transposition in a single-step procedure involving oxyplumbation.

II.2. RESULTS AND DISCUSSIONS

The benzylidene acetones selected for the present lead(IV)acetate oxidation study were prepared according to the Vogel procedure. The procedure for the preparation of mesityl oxide is given in the experimental section. The β-ionone was available commercially and used for the reaction without further purification. The structures of all the α,β-unsaturated ketones were confirmed by comparison of their spectral and analytical data with those of the reported ones. The configuration of all the benzylidene acetones were confirmed from its IR and ^{1}H NMR spectra and were found to have (E) configuration.



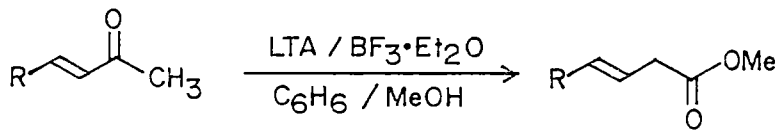
Scheme-10



Scheme-11

In an optimized reaction condition, to a suspension of lead(IV) acetate in dry benzene was prepared at 5°C, a solution of benzylidene acetone (in dry benzene) absolute methanol and borontrifluoride etherate complex were sequentially added and the reaction mixture was stirred for 12 hours. Work-up followed by silicagel column chromatography using hexane-ethylacetate as eluent afforded the product in 68% isolated yield.

The product has been characterized as (E)-metheyl 4-phenyl-3-butenoate, on the basis of elemental analysis and spectral evidence (Scheme 12). Thus **39a** was analysed for $C_{11}H_{12}O_2$ and the elemental analysis gave the following results, 75.01% carbon and 6.82% hydrogen which match very well with the calculated percentage for $C_{11}H_{12}O_2$. The IR spectrum of 39a exhibited characteristic absorption band at 1735 cm^{-1} for the ester carbonyl and 1655 cm^{-1} for the (C=C). From the ^1H NMR spectrum of the compound we could calculate the ratio (E:Z) of the isomer and was found to be (100:0). The δ_H ($CDCl_3$) displayed a doublet at 3.20 and has J value 7.0 Hz and was assigned to $-C=C-CH_2-CO-$ and a singlet at 3.66 was due to the presence of $-OCH_3$, the multiplet at 6.29 was for ($-CH=CH-CH_2$). The doublet at 6.40 (J = 16.0 Hz) was for (-CH=CH-) and multiplet at 7.30 for aromatic proton confirmed the (E) configuration of the compound **39a**.



38 39

a, R = C_6H_5
b, 4-CH_3 C_6H_4
c, 4-OCH_3 C_6H_4
d, 2-OCH_3 C_6H_4
e, 3-OCH_3 C_6H_4
f, 4-Cl C_6H_4
g, 2-Cl C_6H_4

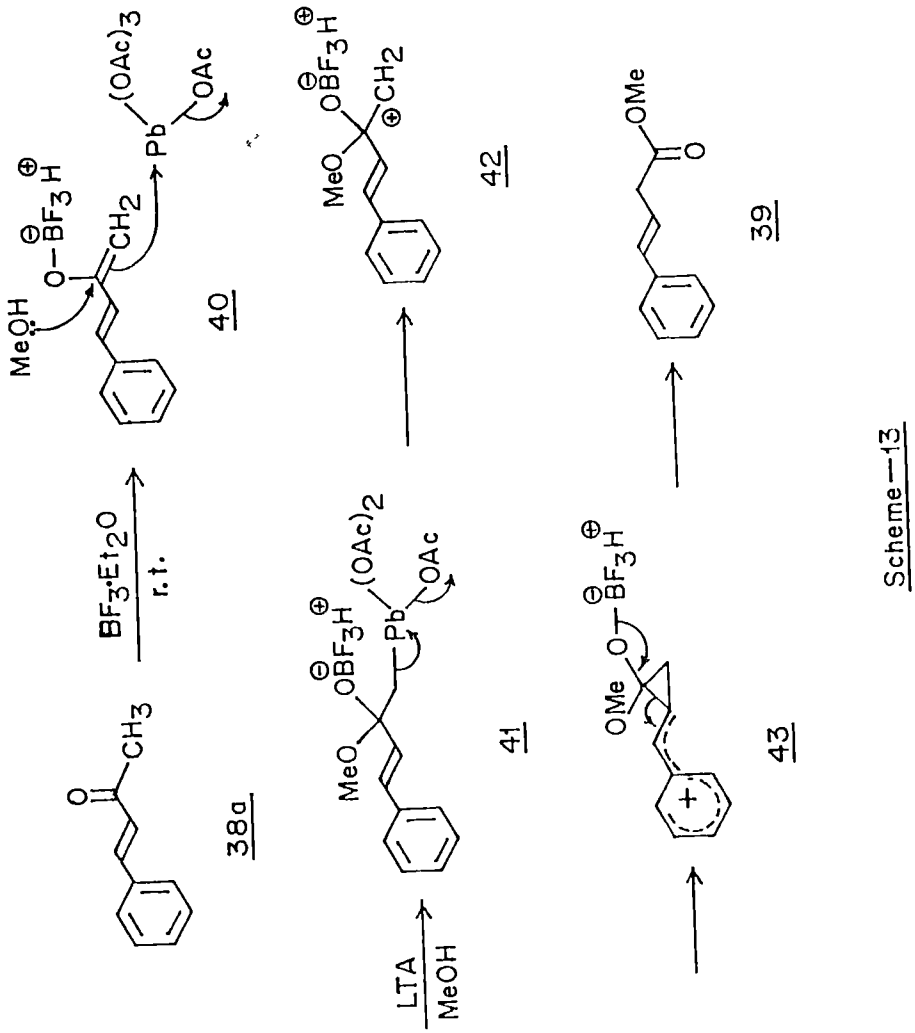
Scheme—12

The decoupled ^{13}C NMR of the compound **39a** shows the following peaks. 37.89 ($-CH_2-$), 51.59 ($-OCH_3$), 171.62 (C=O). The aromatic and olefinic carbons show peaks at 121.40, 126.04, 127.31,128.28, 133.19, 136.53. The analytical and spectra data for other substituted methyl-3-butenoates were in confirmity with assigned structure and are described in the experimental section.

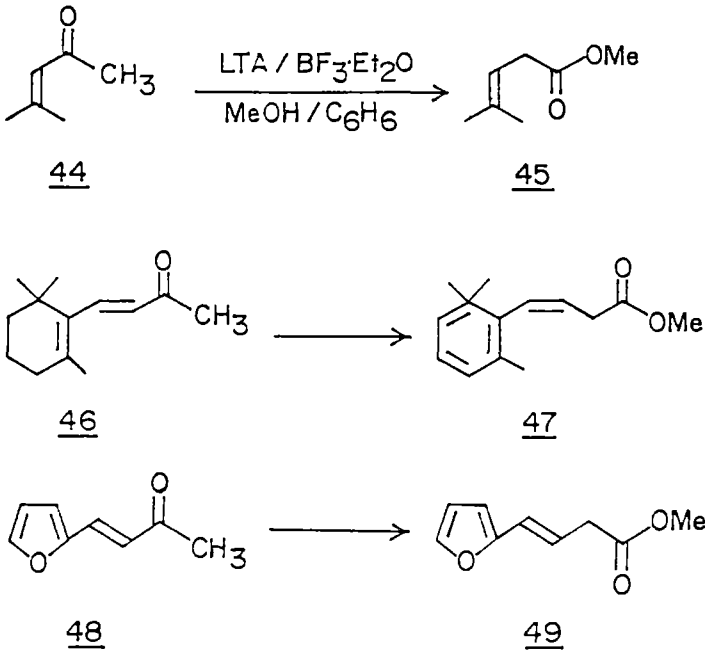
The plausible mechanism for the formation of the methyl-3-butenoate in this reaction is shown in Scheme 13. The mechanism appears to involve the initial enolization of the carbonyl function assisted by borontrifluoride etherate combination to give **40** followed by oxyplumbation to afford the intermediate **41**. The formation of carbocation (**42**) was stabilized by neighbouring π electron to give the cyclopropyl intermediate (**43**). Then upon the ring opening of **43** gave the product **39a** along with the formation of acetic acid and the regeneration of the catalyst, boron trifluoride, after the normal workup.

In a similar fashion, mesityl oxide (**44**), β-ionone (**46**) and 4-furyl-3-buten-2-one (**48**) gave the correspondig β,γ-unsaturated esters (Scheme 14).

The β,γ-unsaturated ester **39a** and **39b** were further hydrolysed by refluxing it with 2N. aq. NaOH (2 hours) followed by the addition of con. HCl gave the corresponding carboxylic



Scheme—13


O
CH3
LTA / BF3·Et2O
MeOH / C6H6
OMe
O
44
45
O
CH3
O
OMe
46
47
O
CH3
O
OMe
O
48
49

Scheme-14

acids **51** (a) and (b). The structure and configuration was assigned by elemental analysis and $^{1}H, ^{13}C$ NMR.

II.3.1 EXPERIMENTAL

Melting points were recorded on a Toshniwal capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 spectrometer in KBr unless otherwise specified. ^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz) and Bruker ACF 300 (300 MHz) in deutero chloroform with tetramethylsilane (TMS) as internal standard. Chemical shifts are expressed as δ ppm downfield for TMS. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet, m : multiplet and br: broad peak. ^{13}C NMR specra were recorded on a Bruker ACF 300 and are referenced to the central triplet peak of $CDCl_3$ at 77.00 ppm. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyser.

II.3.2 Starting Material

Aromatic aldehydes, acetone and β-ionone are commercially available. Acetone, benzaldehyde, p-tolualdehyde, 2-methoxy, 3-methoxy, 4-methoxy benzaldehydes and furfuraldehyde were distilled under vacuum prior to use. The solvent, benzene, was purified according to Vogel procedure and was dried using sodium wire. Super dry methanol also prepared according to the reported

procedure. Borontrifluoride etherate complex is commercially available. Lead(IV)acetate was prepared fresh for each reaction and carefully dried over potassium hydroxide to make it free from traces of acetic acid.

II.3.3. Preparation of Mesityl Oxide

To a 250 ml round-bottom flask fitted with a fractonating column attached to a condenser set for downward distillation, added 40 g (350 mmol) of diacetone alcohol, a pinch of iodine and a few fragments of porous porcelain. The flask was heated slowly with small free flame and collected the pure mesityl oxide fraction came out at the range between 120-126°C. This mesityl oxide without further purification was used for the reaction.

II.3.4 Synthesis of (E)-Methyl 4-Phenyl-3-butenoate (39a) General Procedure

A solution of the benzylidene acetone (2.92g, 20 mmol) in dry benzene (40 ml) was added in one lot to a suspension of lead(IV)acetate (11 g, 24 mmol) in dry benzene (50 ml) followed by the addition of absolute methanol(7ml) and borontrifluoride etherate complex (5 ml) sequentially. The reaction mixture kept in a cooled water bath was stirred for 2 hours and then at room temperature for 10 hours (monitored by TLC). A few drops of ethylene glycol was added to decompose any excess of

lead(IV)acetate present in the mixture. The precipitated lead diacetate was removed by filtration and the filtrate was washed with saturated sodium bicarbonate solution (25 ml) and saturated sodium chloride solution (25 ml) followed by water (3 x 50 ml), dried over anhydrous sodium sulphate. Distilled off benzene under low pressure to get the crude product. The product thus obtained was further purified by column chromatography on silica gel (60 x 120 mesh) using hexane as eluent.

II.3.5 Hydrolysis of Methyl 4-Phenyl-3-butenoate

A mixture of methyl 4-phenyl-3-butenoate (1.75 g, 10 mmol) and 2 N sodium hydroxide (10 ml) was heated under reflux until oily appearance of the ester no longer persists. The free acid was subsequently precipitated out from the mixture by the addition of conc. hydrochloric acid (3 ml). Filtered and washed with cold water (3 x 10 ml) and dried.

Methyl 4-Phenyl-3-butenoate (39a) Colourless viscous liquid, yield, 68 %. IR (neat) 1735 (C=O), 1655 (C=C), 1245 (CO) cm^{-1}. δ_H 3.12 (d, J = 5.70, 2H), 3.62 (s, $-OCH_3$), 6.29(m,=CH), 6.40(d, J = 16 Hz), 7.30 (m, ArH), δ_c 37.89 (C-2), 51.59 ($-OCH_3$), 121.40 (C-4), 133.19 (C-3), 126.04, 128.28, 127.31, 136.53 (Ar-C), 171.62 (CO). Anal. calcd. for $C_{11}H_{12}O_2$. C, 74.96; H, 6.87%; Found: C, 75.00; H, 7.00%.

Methyl 4 (4-methylphenyl)-3-butenoate (39b) Colourless viscous

liquid, yield, 70%, IR (neat) 1736 (C=O), 1655 (C=C), 1245(CO) cm^{-1}. δ_H 2.35 (s,$-CH_3$), 3.13 (d, J = 5.70, 2H), 3.61 (s, $-OCH_3$), 6.30 (m, =CH), 6.41 (d, J = 16.0 Hz), 7.30 (m, ArH). δ_c 21.32 ($-CH_3$), 37.93(C-2), 51.59 ($-OCH_3$), 121.50 (C-4), 133.31 (C-3), 126.31, 128.32, 135.86, 136.54 (Ar-C) 171.83 (CO). Anal. calcd. for $C_{12}H_{14}O_2$; C, 75.74; H, 7.4%. Found; C,75.38 ; H, 7.36%.

Methyl 4(4-methoxyphenyl)-3-butenoate (39c) Colourless viscous liquid, yield, 55%, IR(neat) 1738(C=O),1654(C=C), 1245 (CO) cm^{-1} δ_H 3.13 (d, J = 5.75, 2H), 3.59 (s, $-OCH_3$). 3.62 (s, $-OCH_3$), 6.30 (m, =CH), 6.41 (d, J = 16 Hz), 7.30 (m, ArH); Anal. calcd. for $C_{12}H_{14}O_3$; C, 69.86; H, 6.85%; Found: C, 70.02; H, 6.99%.

Methyl 4 (2-methoxyphenyl)-3-butenoate (39d). Colourless viscous liquid, yield, 57%, IR (neat) 1738, 1655, 1243 cm^{-1}, δ_H, 3.15 (d, J = 6 Hz, 2H), 3.60 (s, $-OCH_3$), 3.63 (s, $-OCH_3$), 6.30 (m, =CH), 6.43 (d, J = 16.1 Hz), 7.30 (m, ArH). Anal. calcd. for $C_{12}H_{14}O_3$: C, 69.86; H, 6.85%. Found : C, 69.56; H, 6.70%.

Methyl 4 (3-methoxyphenyl)-3-butenoate (39e). Pale yellow viscous liquid, yield 60%, IR (neat) 1740, 1653, 1248 cm^{-1}. δ_H 3.15 (d, J = 6.0 Hz, 2H), 3.60 (s, $-OCH_3$), 3.62 (s, $-OCH_3$), 6.37 (m, =CH), 6.43 (d, J = 16.4 Hz), 7.32 (m, ArH). Anal. calcd. for $C_{12}H_{14}O_3$: C, 69.86; H, 6.85%. Found: C, 69.51; H, 6.81%.

Methyl 4(4-chlorophenyl)-3-butenoate (39f). Colourless viscous

liquid, yield, 62%, IR (neat) 1738, 1655, 1245 cm^{-1}, δ_H 3.15 (d, J = 6.1 Hz, 2H), 3.60 (s, $-OCH_3$), 6.30 (m, CH), 6.44 (d, J = 16.5 Hz), 7.31 (m, ArH). Anal. calcd. for $C_{12}H_{11}ClO_2$: C, 62.68; H, 5.26%. Found: C, 62.51; H, 5.02%

Methyl 4(2-chlorophenyl)-3-butenoate (39g). Colourless viscous liquid, yield, 50%, IR(neat), 1739, 1650, 1241 cm^{-1}. δ_H, 3.18 (d, J = 6.0 Hz, 2H), 3.61 (s, $-OCH_3$), 6.31 (m, CH), 6.44 (d, J = 16.5 Hz), 7.35 (m, ArH). Anal. calcd. for $C_{12}H_{11}ClO_2$: C, 62.68, H, 5.26%. Found : C, 62.56; H, 5.31%.

Methyl(4-methyl)-3-Pentenoate (45) Colourless viscous liquid, yield, 69% IR(neat), 1738 cm^{-1}, δ_H 1.62 (s,$-CH_3$); 1.73 (s, $-CH_3$), 2.91 (d, J = 6 Hz, CH_2-), 3.58 (s, $-OCH_3$), 5.24 (brt, 1H). Anal. calcd. for $C_7H_{12}O_2$: C, 65.58; H, 9.44%. Found: C, 65.45; H, 9.41%.

Methyl 4(2,6,6-trimethyl)cyclohex-1-ene-3-butenoate (47). Colourless viscous liquid, yield, 68%, IR(neat), 1736 cm^{-1}, δ_H 0.80 (s, $-CH_3$), 0.90 (s,$-CH_3$), 1.40 (m,$-CH_2-CH_2-$), 1.58 (s, $-CH_3$), 2.18 (m, $-CH_2-$), 2.99 (d, J = 6Hz, $-CH_2-$), 3.66 (s,$-OCH_3$), 5.40 (brdd, 2H).Anal. calcd. for $C_{14}H_{22}O_2$: C, 75.62; H, 9.99. Found: C,75.53; H, 10.3%.

Methyl 4(2-furyl)-3-butenoate (49). Colourless viscous liquid,

yield, 50% , IR(neat), 1734, 1650, 1241 cm^{-1}, δ_H, 3.15 (d, J = 6.0 Hz, 2H), 3.61 (s, $-OCH_3$), 6.30 (m, CH), 6.44(d, J = 16.0 Hz), 7.40 (m, ArH). Anal. calcd. for $C_9H_{10}O_3$: C, 65.03; H, 6.07%. Found: C, 65.23; H, 6.12%.

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CHAPTER III

A FACILE AND NOVEL PREPARATION OF FUNCTIONALIZED 2(PHENYLMETHYLENE) CYCLOALKANES

III. 1. INTRODUCTION

In the previous Chapter we have described a facile method for the conversion of α,β-unsaturated ketones to β,γ-unsaturated carboxylates with lead(IV) acetate in the presence of boron trifluoride etherate-methanol combination in benzene. In the present Chapter we would like to report the oxidation of benzylidene cycloalkanones to afford 2(phenyl methylene) cycloalkane carboxylates.

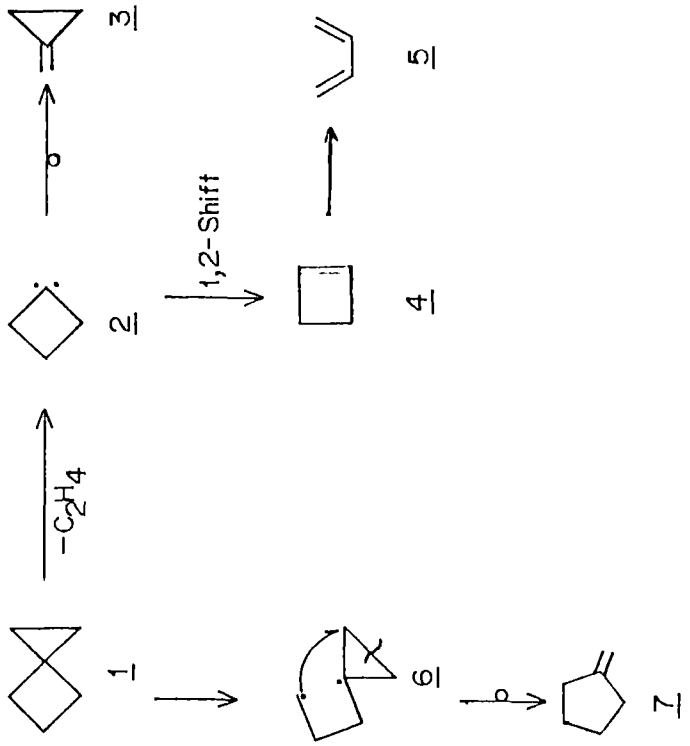
Methylene cycloalkanes are widely used as key compounds in the synthesis of various natural products and their analogous, e.g. prostaglandins,[1a] iridoids,[1b,c] antibiotics[2] and as models

in investigations of many addition reactions to C=C bond. The known methods for the preparation of methylenecyclanes may be divided into three major classes:

1. Elimination reactions mainly pyrolytic.[3a]
2. Wittig and related reactions.[3a-d]
3. Cyclization and oligomerization of some unsaturated compounds.[3a]

In the continuing research interest in chemistry of strained organic molecules[4-6] Josef Pola[7] reported the thermal decomposition of spirohexane in gas phase noticeably differs from the thermal decomposition of spiropentanes, in that it can be explained to occur exclusively via the expulsion of ethylene and intermediary formation of cyclic carbene. The reaction was carried out as truly homogeneous, laser photosensitized (SF_6) process in order to avoid possible heterogeneous reactions on hot reactor walls that were observed with the four and three-membered cyclic hydrocarbons.[8-10] The CW CO_2 laser induced decomposition of spirohexane (1) was carried out in the presence of energy conveying SF_6, since spirohexane is not a good absorber of the IR radiation at 10 μm. With the laser outputs as low as 4-6 W, the reaction yields 1,3-butadiene (5) and methylene cyclopropane (3). At higher laser outputs (8 W) some amounts of methylene cyclopentane (7) can be observed (Scheme 1).

Methylene cyclohexane (9) as the major (52%) product has



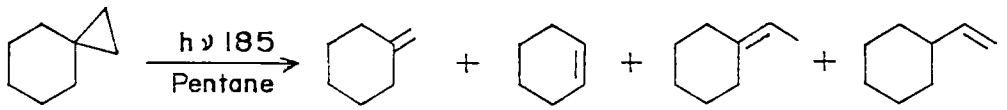
Scheme-1

been reported,[11] when photolysis on spiro [5,2] octane (8) was carried out in solution with 185 nm radiation. The compound 8 gave a mixture of products as minor along with the methylene cyclohexane (9) (Scheme 2).

A suitable example for the preparation of methylene cycloalkanes is the pyrolysis of the alicyclic esters.[12,13] The pyrolysis of primary acetate (13) gave only a single elimination product whereas the secondary and tertiary acetates gave a mixture of products (Scheme 3). The methylene cyclopentane and cyclohexane (14) were formed when its corresponding alicyclic primary esters (13) were subjected to pyrolysis at 530°C, whereas mixtures of products i.e. methylene cyclohexane (9) and 1-methyl cyclohexene (16) were formed when the secondary alicyclic esters were subjected to pyrolysis at 450°C.

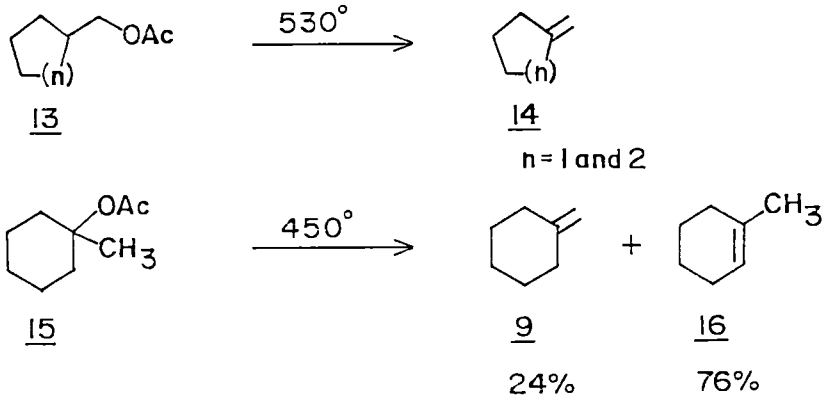
The second major example for the preparation of methylene cycloalkanes may be the Wittig and related reactions. The reaction of a tertiary phosphene with an alkyl halide results in phosphonium salt, followed by the formation of ylid (18) after the removal of acidic proton by a strong base from the salt. The subsequent reaction of these ylids with aldehydes or ketones offers very useful synthesis for olefins (14)[3(a-d)] (Scheme 4).

Methylene cyclopentanes with different functionalities at various positions are prepared by the cyclization of

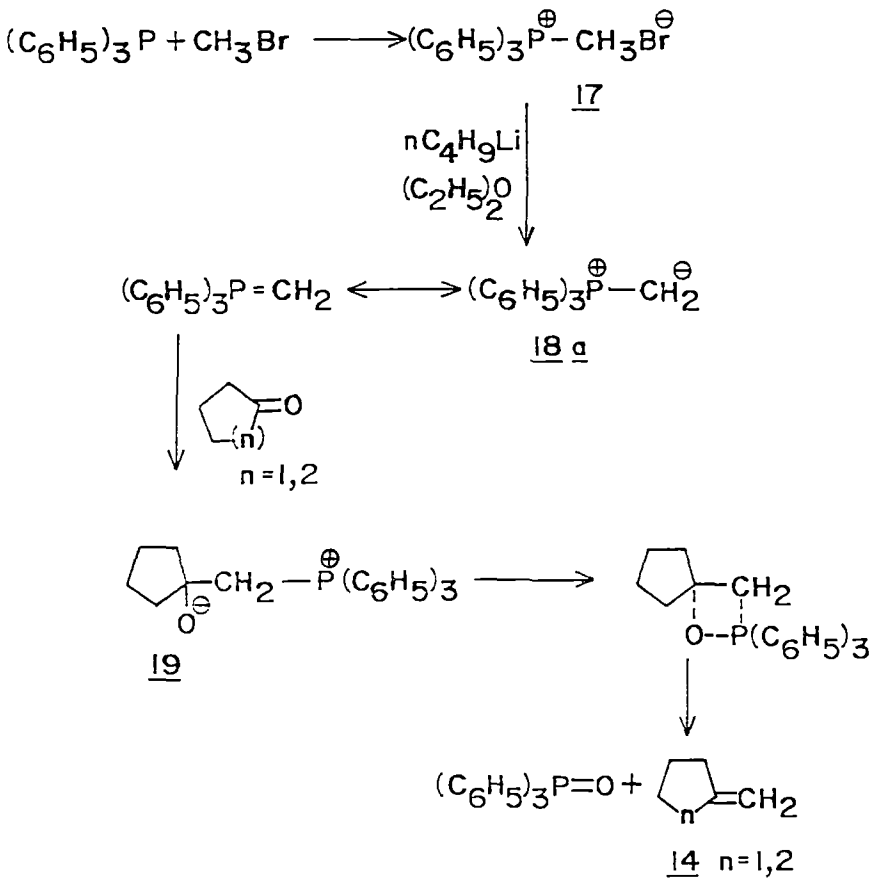


8 → 9 (52%) + 10 (7%) + 11 (14%) + 12 (13%)

Scheme-2



Scheme-3

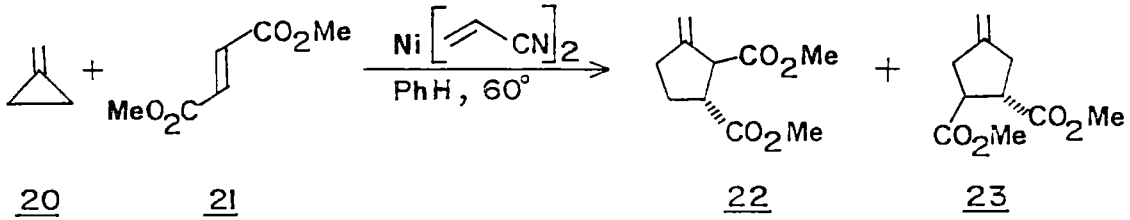

(C6H5)3P + CH3Br
(C6H5)3P⊕-CH3Br⊖
17
nC4H9Li
(C2H5)2O
(C6H5)3P=CH2
(C6H5)3P⊕-CH2⊖
18 a
O
(n)
n=1,2
CH2-P⊕(C6H5)3
O⊖
19
CH2
O--P(C6H5)3
(C6H5)3P=O +
CH2
n
14 n=1,2

Scheme-4

unsaturated compounds.[14] One of the best approaches is by cycloaddition and the most intriguing method involves the cycloaddition of trimethylene methane to olefins[15] which can almost be envisioned to be the Diels-Alder equivalent for five-membered rings. The use of transition-metal complexes of iron[16] and molybdenum[17] for cycloalkane synthesis gave unsatisfactory results. On the other hand, the co-oligomerization of alkylidene cyclopropanes has achieved greater success. For example, bis(acrylonitrile) nickel catalyses the cycloaddition of methylene cyclopropane (20) with electron deficient olefins (21)[18,19] (Scheme 5) to give differently substituted methylene cyclopentanes (22) and (23).

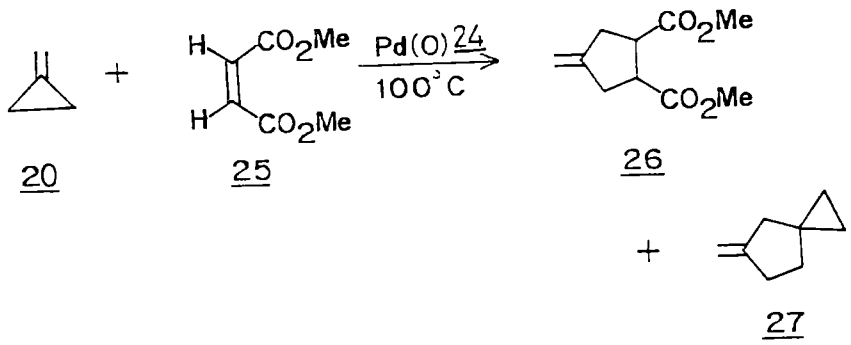
[2σ +2π] cycloadditions of methylene cyclopropane to alkenes catalysed by palladium (0) has been first reported by Binger and Schuchardt.[20] Exclusive [2σ + 2π] cycloaddition of 20 with alkene (25) was achieved on palladium (0) catalyst in contrast to nickel (0) catalysed reaction where the three-membered ring is opened between C-2 and C-3. At 100-115°C, methylene cyclopentane derivatives (26) are obtained -upto 300 ml of 25 being converted per 1 mol palladium (0) catalyst. Here the codimerization always has to compete with cyclodimerization of 20 which affords 5-methylene spiro [2.4] heptane (27) (Scheme 6).

In another cyclization method for the preparation of



20 21 22 23

Scheme-5

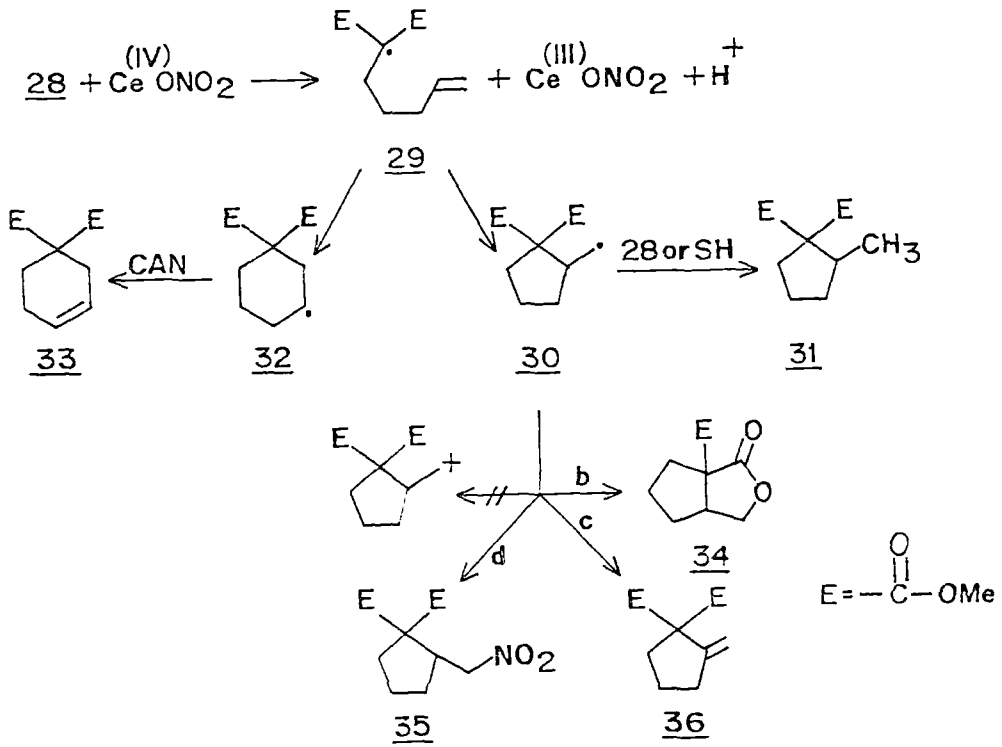


20 25 26 27

Scheme-6

methylene cyclopentanes, Ruzziconi reported the results concerning cyclization of dimethyl 4-pentenylmalonate (28) induced by cerium(IV) ammonium nitrate (CAN) in methanol and acetic acid in the absence and presence of copper salts.[21] First, the electrophile radical (29) which is formed by the reaction of dicarbonyl compound with CAN undergoes either 5-exo or 6-endo ring closure to the cyclized radicals (30) and (32). For the former radical, several reaction paths are then available. a) abstraction of a hydrogen atom, presumably from 28 or from the solvent to give the methylcyclopentane (31) (path a in Scheme 7). b) oxidation by CAN to give the lactone (34) or the methylene cyclopentane (36) (paths b and c respectively). The products of 5-exocyclization are obtained in 64% combined yield, whereas the yield of cyclohexene (33) from 6-endo cyclization is 6%. Here 5-exo/6-endo reactivity ratio is quite close to those found in the corresponding reactions of 28 induced by $Mn(OAc)_3$/ $Cu(OAc)_2$ in acetic acid[22] and in the cyclization reactions of 4- pentenyliodomalonate promoted by hexabutylditin.[23] When copper salts are added, the lactone (34) and alkene (36) are the main reaction products. This indicates that the 5-exo/6-endo reactivity ratios are significantly influenced by the presence and the nature of copper salts.

A novel isomerization of hexynyl iodide to (iodomethylene) cyclopentane was reported by Curren and co-workers,[24,25] wherein


28 + Ce(IV)ONO2
+ Ce(III)ONO2 + H+
29
CAN
28 or SH
33
32
30
31
b
c
d
34
35
36
E = —C(=O)—OMe

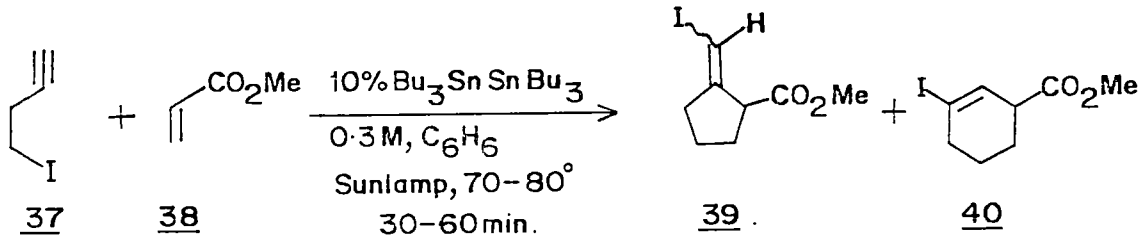
Scheme – 7

the (iodomethylene) cyclopentane was prepared by atom-transfer cyclization. The preparation has been achieved by sequencing a free radical addition and cyclization reaction which is uniquely controlled by iodine atom transfer.

Sunlamp irradiation for 30 min. of a solution of butynyl iodide (37)(0.3M) and methylacrylate (38)(0.3M) in benzene (-80°C) containing 10 mol % hexabutylditin produced a mixture of (iodomethylene) cyclopentane (39) and cyclohexenyl iodide (40). The ratio of 39/40 was 15:1 and (iodomethylene) cyclopentane (39) was a 3:1 mixture of stereoisomers with predominant E-isomer[25] (Scheme 8).

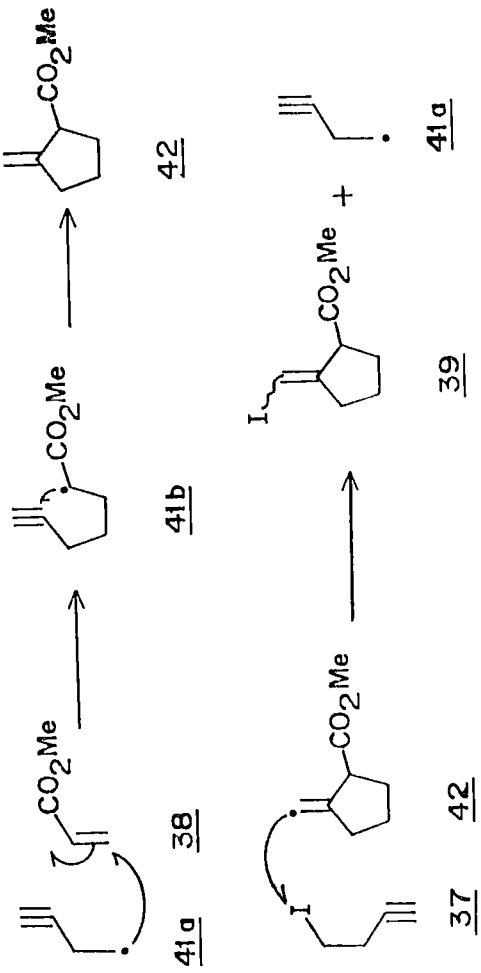
The proposed propagation sequence for this reaction attained is shown in Scheme 9. The best option available to the initial radical **41a** is through a well precedented [26] intermolecular addition to the electron deficient acrylate (38) to produce stabilized radical (**41b**). In turn **41b** prefers cyclization and partitions via the 5-exo mode and the 6-endo mode (not shown). While intermolecular addition of **42** to the acrylate must be a reasonably facile alternative. In a chain-transferstep, near diffusion controlled iodine atom abstraction from **37** produces (E/Z)-**39** and the radical **41**.[27,28]

A new route to carbocycles has been reported[29] which involves the formation of a β-acetylenic radical (**46**) in the persence of a Michael aceptor. The β-acetylenic radical (**46**)



37 38 39 40

Scheme–8



41a 38 41b 42

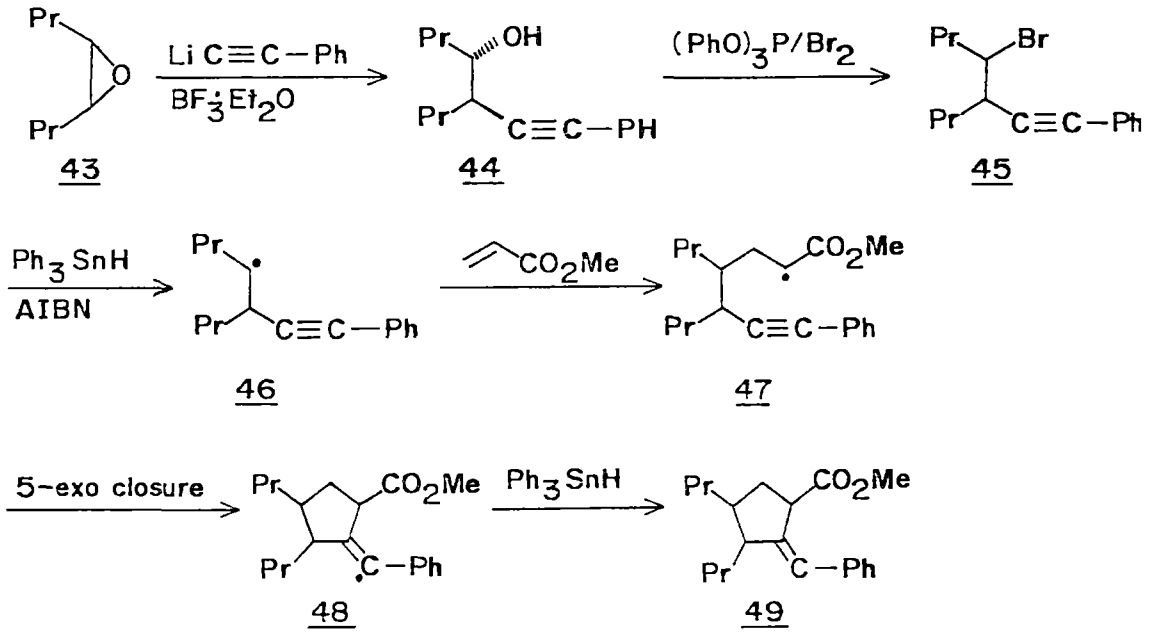
37 42 39 41a

Scheme-9

generated in three steps from epoxides, reacts with electron deficient olefins to produce five membered carbocycles by a process of conjugate addition and 5-exodiagonal closure.

Treatment of the epoxide (43) with lithium phenyl acetylide according to known procedure[30] afforded the hydroxy acetylene (44) in 96% yield. The oxygen function in this compound is not a suitable precursor to the desired radical (46) (Scheme 10). When alcohol (44) was first converted into bromide (45)(50%), then the desired radical (46) was formed when it was treated with triphenyl tin hydride in the presence of AIBN (Azobis isobutyronitrile). Then it underwent a conjugate addition to methyl acrylate to give the radical (47) followed by 5-exoclosure to afford the product 49, 2(Phenyl methylene) cyclopentane carboxylate, in 38% yield as a mixture of isomers.

In the search for new and effective ways to these compounds, Bubnov[31] developed a new general approach to methylenecyclanes (7) and (9) and 2-substituted methylene cyclanes (53) and (54), using cycloalkenyl methyl boranes of the type 50. 1-(Dipropyl)borylmethyl cycloalkenes (50a) and (50b) possess the high specific reactivity and are cleaved by alcohols to form Pr_2BOR and methylene cyclopentane (7) and methylene cyclohexane (9) respectively. Similarly addition of simple β, -unsaturated boron derivatives (50a)[32,33] and (50b) to


Pr
O
Pr
43
Li C≡C−Ph
BF3·Et2O
Pr
OH
Pr
C≡C−PH
44
(PhO)3P/Br2
Pr
Br
Pr
C≡C−Ph
45
Ph3SnH
AIBN
Pr
Pr
C≡C−Ph
46
CO2Me
Pr
CO2Me
Pr
C≡C−Ph
47
5-exo closure
Pr
CO2Me
Pr
C−Ph
48
Ph3SnH
Pr
CO2Me
Pr
C−Ph
49

Scheme—10

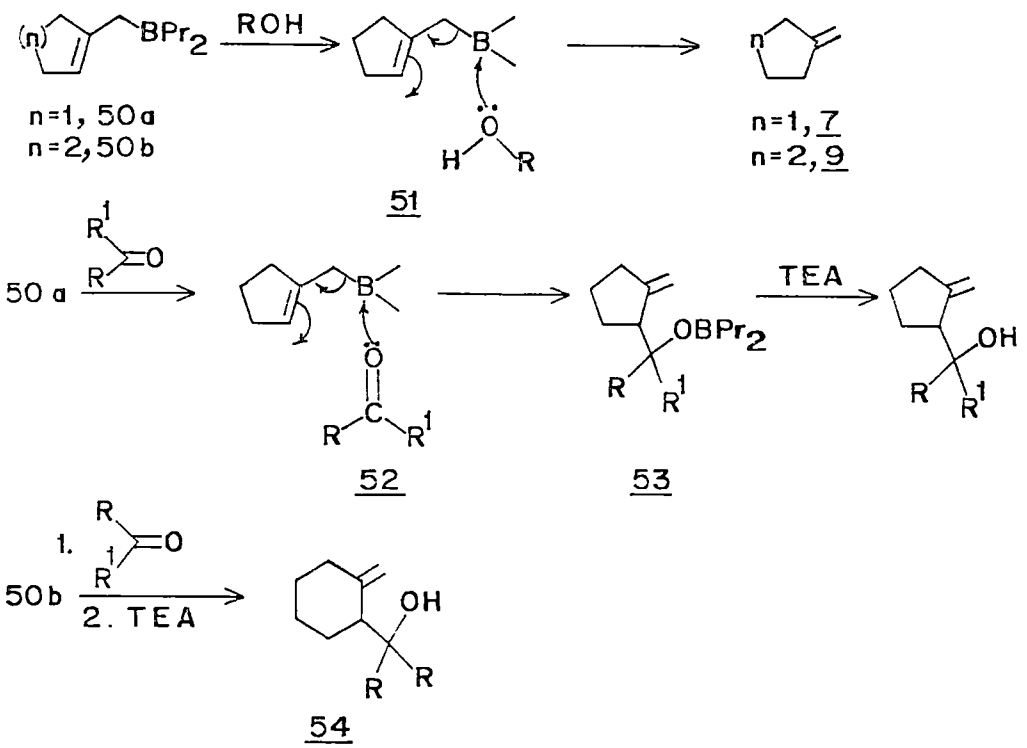
aromatic and aliphatic aldehydes and ketones at -30 to 0°C led to ester 53. Deesterification of which with higher alcohols furnished corresponding carbinols (53) and (54).

In majority of cases, the methods described above are not general and requires costly starting materials, while the reaction conditions are not always simple. It was therefore felt that a new route be developed for the synthesis of these novel carbocycles.

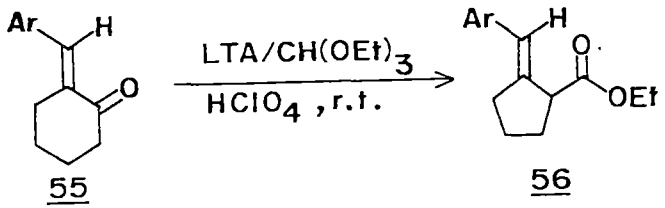
In this Chapter, one-step synthesis of 2(phenylmethylene) cycloalkane carboxylates from benzylidene cycloalkanones using lead(IV) acetate in triethyl orthoformate with catalytic amount of perchloric acid is discussed.

III. 2 RESULTS AND DISCUSSION

When a solution of benzylidene cyclohexanone (55a) was added to a stirring suspension of lead(IV) acetate and perchloric acid in triethyl orthoformate at room temperature, work-up of the reaction mixture after 24 hours gave the ring contracted product (56a) in 56% isolated yield (Scheme 12). The structure of 56a was confirmed by its IR, NMR and ^{13}C spectral data. Similarly the ketones (55b) and (56c) were converted to the corresponding esters (56b) and (56c) respectively in 54 -65% overall yields. When the method was extended to 7-membered and 8-membered rings, it was found to be equally successful. Thus


BPr2
ROH
n=1, 50a
n=2, 50b
51
n=1, 7
n=2, 9
50 a
52
OBPr2
53
TEA
OH
1.
2. TEA
50b
54

Scheme–11



55 56

a, Ar = C_6H_5

b, Ar = 4-ClC_6H_4

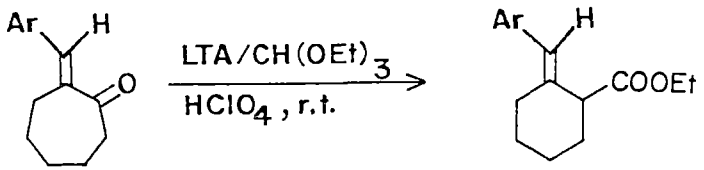
c, Ar = 2-ClC_6H_4

Scheme-12

when **57a** was subjected to similar reaction conditions, it underwent a smooth ring contraction to the ester (**58a**) in 61`% isolated yield (Scheme 13). Similarly the ketones (**57b**) - (**57f**) were converted to their respective ring contracted esters (**58b**) - (**58f**) in 55 - 65 % isolated yields.

Although the lead(IV) acetate borontrifluoride etherate-methanol system was quite successful in the previous cases, it was not suitable at all as the yields of the products were very low. For example when **55a** was subjected to lead(IV) acetate/boron trifluoride etherate methanol system at 25°C for 24 hours, only 7% yield of **56a** was obtained, leaving 65% of the starting ketone unreacted.

Although the role of the orthoformate is not yet clear, its low dielectric constant, favouring SN^2 type reactions (ring contraction), seems to be important as has been reported in a similar reaction using thallium (III) nitrate,[34] rather than its high acetylization ability. This may be corroborated from the fact that propiophenone dimethyl acetal reacted at a slightly lower rate than propiophenone itself in triethyl orthoformate solution, and almost no oxidation of propiophenone dimethylacetal occured when methanol was used as solvent[35]



57a 58a

57 a, Ar = C_6H_5, n = 1 d, Ar = C_6H_5, n = 2

b, Ar = 4-Cl C_6H_4, n = 1 e, Ar = 4-Cl C_6H_4, n = 2

c, Ar = 2-Cl C_6H_4, n = 1 f, Ar = 2-Cl C_6H_4, n = 2

Scheme-13

III.3 EXPERIMENTAL

The benzaldehyde used for the preparation of benzylidene cycloalkanone was distilled prior to use. Other aldehydes were used without further purification. Cyclohexanone, cycloheptanone and cyclooctanone were readly available and were used without further purification.

III.3. 1 General Procedure

(a) Preparation of Benzylidene Cycloheptanone (57a)

Cycloheptanone (10 g) and benzaldehyde (6g) were added to a solution of potassium hydroxide (2g) in 35 ml water. The reaction mixture was refluxed for 4 hours and allowed to cool. Extracted with ether and acidified with dil. H_2SO_4, washed with water (2 x 50 ml) and dried (Na_2SO_4). The ether was distilled off and the residue is distilled under vacuum to get the pure compound (150°C/ 15 mm Hg). It was further purified by recrystallising from pentane.

(b) Preparation of Ethyl 2(phenyl methylene)cyclopentanonate

To a stirring suspension of lead(IV) acetate (9g, 20 mmol) in 30 ml triethyl orthoformate, a solution of 55a (3.72 g, 20 mmol) in 20 ml triethyl orthoformate was added followed by 3 ml of perchloric acid. The reaction mixture was stirred for 24

hours at r.t. The triethyl orthoformate was distilled off under reduced pressure from the mixture and the residue was treated with chloroform (100 ml). The precipitate formed were filtered off and the filtrate was washed with water (2 x 100 ml),dried removed the solvent. The crude product was further purified by column chromatography using hexane as eluent.

Benzylidene cyclohexanone (55a). Yellow crystalline solid, m.p. 64-65 °C, yield 52%, IR(neat), 1700, 1625 cm^{-1} δ_H ($CDCl_3$) 1.80 (m, 4H), 2.51 (brt, 2H), 2.82 (brt, 2H), 7.48 (m, 6H). Anal. calcd. C, 83.83; H, 7.57%. Found: C, 83.53; H, 7.77%.

4-Chlorobenzylidene cyclohexanone (55b). Yellow crystalline solid, m.p. 74-75 °C, yield 50% ,IR(neat), 1705, 1629 cm^{-1}, δ_H ($CDCl_3$) 1.81 (m, 4H), 2.53 (brt, 2H), 2.84 (brt, 2H), 7.52 (m, 5H). Anal. calcd. C, 70.74; H, 5.93%. Found: C, 70.98; H, 5.99%.

2-Chlorobenzylidene cyclohexanone (55c). Yellow crystalline solid, m.p. 70-71 °C, yield 48%, IR(neat), 1702, 1625 cm^{-1}, δ_H ($CDCl_3$) 1.79 (m, 4H), 2.56 (brt, 2H), 2.86 (brt, 2H), 7.60 (m,5H). Anal. calcd. C, 70.74; H, 5.93 %. Found: C, 70.53; H, 5.84%.

Benzylidene cycloheptanone (57a). Pale yellow crystalline solid, m.p. 70-71°C, yield 45%, IR(neat), 1700, 1625 cm^{-1}, δ_H ($CDCl_3$ 1.71 (m, 6H), 2.66 (m, 4H), 7.38 (m,6H). Anal. calcd. C, 83.95; H, 8.05% . Found: C, 83.53; H, 8.23%.

4-Chlorobenzylidene cycloheptanone (57b). Yellow crystalline solid, m.p. 79-80°C, yield 45%, IR(neat), 1705, 1628 cm^{-1}, δ_H ($CDCl_3$) 1.73 (m, 6H), 2.65 (m, 4H), 7.42 (m, 5H). Anal. calcd. C, 71.63; H, 6.44%. Found: C, 71.89; H, 6.53%.

2-Chlorobenzylidene cycloheptanone (57c). Yellow crystalline solid, m.p. 74-75°C. yield 45%, IR(neat), 1703, 1625 cm^{-1}, δ_H ($CDCl_3$) 1.75 (m, 6H), 2.68 (m, 4H), 7.45 (m, 5H). Anal. calcd. C, 71.63; H, 6.44 %. Found: C, 71.92; H, 6.59%.

Benzylidene cyclooctanone (57d). Colourless crystalline solid, m.p. 76-77°C, IR(neat), 1705, 1623 cm^{-1} δ_H ($CDCl_3$) 1.51 (m, 8H), 1.69 (m, 4H), 7.36 (m, 6H). Anal. calcd. C, 84.06; H, 8.46%. Found: C,83.92; H, 8.53%.

4-Chlorobenzylidene cycloctanone (57e). Crystalline solid, m.p. 87-89°C. yield 45% IR(neat), 1705, 1623 cm^{-1}, δ_H ($CDCl_3$), 1.56 (m, 8H), 1.70 (m, 4H), 7.36 (m, 5H). Anal. calcd. C, 72.42; H, 6.89 %, Found: C, 72.12; H, 6.63%.

2-Chlorobenzylidene cyclooctanone (57f). Crystalline solid, m.p. 80-82°C, IR(neat), 1700, 1623 cm^{-1}, δ_H ($CDCl_3$), 1.53 (m, 8H), 1.72 (m, 4H), 7.38 (m, 5H). Anal. calcd. C, 72.42; H, 6.89%. Found: C, 72.32; H, 6.53%.

Ethyl 2(phenyl methylene)cyclopentane carboxylate (56a). Colourless viscous liquid, yield 58%, IR(neat), 1735, 1625 cm^{-1}, δ_H ($CDCl_3$), 1.28 (q, 3H, CH_3), 2.00 (m, 4H, $-CH_2-CH_2-$) 2.63 (brt, 2H, $-CH_2-$), 3.50 (brt. 1H, -CH-), 3.70 (q, 2H, $-OCH_2-$), 6.52(=CH, 1H), 7.30 (m, 5ArH), δ_C ($CDCl_3$) 14.28, 25.93, 29.44, 31.53, 51.13, 60.62, 123.66, 127.16, 128.18, 128.33, 138.03, 143.93, 174.36. Anal. calcd. C, 78.22; H, 7.87%. Found: C, 78.34; H, 7.93.

Ethyl 2(4-chlorophenylmethylene)cyclopentane carboxylate (56b). Colourless viscous liquid, yield, 56%, IR(neat), 1736, 1625 cm^{-1}, δ_H ($CDCl_3$), 1.29 (q, 3H, CH_3), 2.00 (m, 4H, $-CH_2-CH_2-$), 2.65 (brt, 2H, $-CH_2-$), 3.50 (brt, 1H, -CH-), 3.70 (q, 2H, $-OCH_2-$), 6.54 (=CH, 1H), 7.30(m, 4ArH), δ_C ($CDCl_3$), 14.26, 25.93, 29.48, 31.52, 51.21, 60.61, 123.60, 128.20, 130.31, 132.04, 136.03, 140.81, 173.65. Anal. calcd. C, 68.04; H, 6.47%. Found: C, 68.23; H, 6.59%.

Ethyl 2(2-chlorophenylmethylene)cyclopentane carboxylate (56c) Colourless viscous liquid, yield, 59%, IR(neat), 1738, 1625 cm^{-1}, δ_H ($CDCl_3$) 1.30 (q, 3H, CH_3), 2.01 (m, 4H, $-CH_2-CH_2-$), 2.65 (brt, 2H, $-CH_2-$), 3.51 (brt, 1H, -CH-), 3.72 (q, 2H, $-OCH_2-$), 6.54 (=CH, 1H), 7.30 (m, 4ArH), δ_C ($CDCl_3$) 14.26, 25.95, 29.46, 31.53, 51.25, 60.65, 123.65, 127.14, 127.21, 127.85, 129.17, 135.93, 136.03, 140.81, 173.65 Anal. calcd. C, 68.04; H, 6.47%.

Found: C, 68.21; H, 6.53%.

Ethyl 2(phenylmethylene)cyclohexane carboxylate (58a) Colourless viscous liquid, yield, 55%, IR(neat), 1736, 1628 cm^{-1} δ_H ($CDCl_3$), 1.29 (q, 3H, CH_3), 1.63 (m, 6H, $-CH_2-CH_2-CH_2$), 2.41(m,2H,$-CH_2-$), 3.24(brt, 1H, -CH-), 4.21(q, 2H, $-OCH_2-$), 6.21 (1H, =CH), 7.21 (m, 5ArH), δ_C ($CDCl_3$) 14.32, 23.60, 27.31, 27.86, 30.49, 50.98, 60.45, 123.62, 127.15, 128.18, 128.34, 138.03, 144.01, 174.36. Anal. calcd. C, 78.65; H, 8.25%.Found: C, 78.69; H, 8.31%.

Ethyl 2(4-chlorophenylmethylene)cyclohexane carboxylate (58b). Colourless viscous liquid, yield, 55%, IR(neat), 1735, 1625 cm^{-1}, δ_H ($CDCl_3$), 1.28 (t, 3H, CH_3), 1.61(m, 6H, $-CH_2-CH_2-CH_2$), 2.40 (m, 2H, $-CH_2-$), 3.23 (brt, 1H, -CH-), 4.20 (q, 2H, $-OCH_2-$), 6.20 (1H, =CH), 7.11-7.27 (m, 4ArH), δ_C ($CDCl_3$), 14.30, 23.59, 27.29, 27.84, 30.46, 50.97, 60.47, 123.60, 128.20, 130.31, 132.04, 136.03, 140.61, 173.65.

Ethyl 2(2-chlorophenylmethylene)cyclohexane carboxylate (58c). Colourless viscous liquid, yield, 53%, IR(neat), 1736, 1624 cm^{-1}, δ_H ($CDCl_3$) 1.30 (t, 3H, CH_3), 1.63 (m, 6H, $-CH_2-CH_2-CH_2$), 2.42 (m, 2H, $-CH_2-$), 3.23 (brt, 1H, -CH-), 4.21 (q, 2H, $-OCH_2-$), 6.20 (1H, =CH), 7.10-7.28 (m, 4ArH) δ_C ($CDCl_3$), 14.30, 23.61, 27.31, 27.85, 30.45, 50.98, 60.49, 123.63, 127.15, 127.23, 127.91, 129.18, 135.93, 136.05, 140.83, 173.89. Anal. calcd. C, 68.93; H, 6.86 %. Found: C, 68.69; H, 6.93%.

Ethyl 2(phenylmethylene)cycloheptane carboxylate (58d). Colourless viscous liquid, yield, 61%. IR(neat), 1736, 1625 cm^{-1}. δ_H ($CDCL_3$) 1.25 (t, 3H, CH_3), 1.42 (m, 4H, $-CH_2-CH_2$), 1.84(m, 6H, $-CH_2-CH_2-CH_2$), 2.41 (m, 2H, $-CH_2-$), 3.34 (brt, 1H, -CH-), 4.15 (q, 2H, $-OCH_2-$), 6.39 (1H, =CH), 7.26-7.29 (m, 5ArH), δ_C ($CDCl_3$) 14.23, 26.48, 28.67, 29.20, 29.94, 30.43, 53.59, 60.42, 126.36, 128.15, 128.59, 128.86, 137.72, 141.95, 174.74. Anal. calcd. C, 79.02; H, 8.58%. Found: C,78.98, H, 8.64%.

Ethyl 2(4-chlorophenylmethylene)cycloheptane carboxylate (58e). Colourless viscous liquid, yield, 60%, IR(neat), 1734, 1628 cm^{-1}, δ_H ($CDCl_3$) 1.26 (t, 3H, CH_3), 1.40 (m, 4H, $-CH_2-CH_2-$), 1.85 (m, 6H, $-CH_2-CH_2-CH_2-$), 2.42 (m, 2H, $-CH_2-$), 3.34 (brt, 1H, -CH-), 4.16 (q, 2H, $-OCH_2-$), 6.40(1H, =CH), 7.28-7.31 (m, 4 ArH), δ_C ($CDCl_3$), 14.23, 26.50, 28.70, 29.22, 29.96, 30.48, 53.62, 60.49, 126.60, 128.20, 130.31, 132.05, 136.08, 140.2, 174.56. Anal. calcd. C, 69.73; H, 7.23%. Found: C, 69.63; H, 7.32%.

Ethyl 2(2-chlorophenylmethylene)cycloheptane carboxylate (58f). Colourless viscous liquid, yield, 56%, IR(neat), 1736, 1625 cm^{-1}, δ_H ($CDCl_3$) 1.28 (t, 3H, CH_3), 1.40 (m, 4H, $-CH_2-CH_2-$), 1.89(m, 6H, $-CH_2-CH_2-CH_2-$), 2.46 (m, 2H, $-CH_2-$), 3.38 (brt, 1H, -CH-), 4.16 (q, 2H, $-OCH_2$), 6.42 (1H, =CH), 7.30-7.32 (m, 4ArH), δ_C ($CDCl_3$) 14.26, 26.49, 28.62, 29.26, 29.96, 30.44, 53.68, 60.48, 125.32, 127.18, 127.23, 127.98, 129.15, 136.00, 136.08, 140.88, 174.81. Anal.calcd. C, 69.73; H,7.23%. Found: C, 69.53;H, 7.11%

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CHAPTER IV

SYNTHESIS OF 2-METHYL-4-PHENYL-3-BUTENOATES, CYCLOALKANE CARBOXYLATES AND ETHYL (CYCLOPROPYL) ACETATES

IV. 1. 2-METHYL-4-PHENYL-3-BUTENONATES

IV.1.1 INTRODUCTION

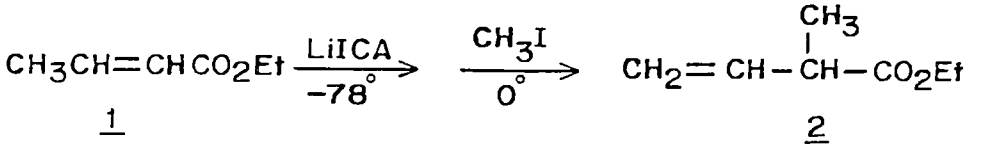
The β, ϒ-unsaturated carboxylic acids, esters and their α, -substituted counterparts have been widely studied in terms of their reactivities and synthetic utility. The pioneer work in this field has been done by Rathke and Sullivan[1], where the deconjugative alkylation of the enolate anion derived from the α-β, unsaturated ester has been investigated. Alkylation of the enolate solution derived from the α,β-unsaturated esters with methyl iodide or benzyl bromide furnished the corresponding alkylated non-conjugated esters. Apparently in alkylation the

α-carbon of unsaturated ester enolates is the center of greatest reactivity (Scheme 1).

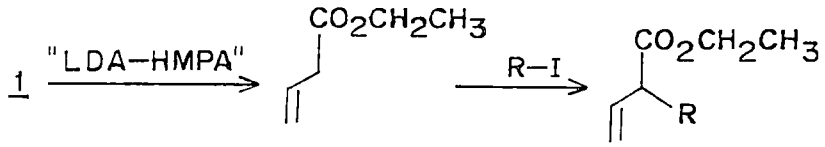
Schlessinger and co-workers[2] later reported an essentially non-nucleophilic form of lithium diisopropylamide (LDA) which act as a base towards ethyl crotonate and permits high yield of mono and dialkylation at the α-carbon atom of the ester. This modification of LDA is an apparent 1:1 complex of the nitrogeneous base with hexamethylphosphoramide (HMPA). Alkylation of ethyl crotonate is conveniently carried out by preparing one equivalent of the LDA-HMPA complex at -78°C, adding one equivalent of the ester followed, after 10 minutes, by 1.1 to 1.3 equivalents of the desired alkylating agent (Scheme 2).

Another example for the synthesis of α-methylated β, γ-unsaturated carboxylate is the direct methylation of the unsaturated species with methyl iodide using the lithium diisopropylamide-hexamethyl phosphortriamide (LDA-HMPT) system in THF.[3] Here methylation of styrylacetic acid (5) with methyl iodide leads to only 50% of 2-methyl-4-phenyl but-3-enoic acid and 22% of 2,2-dimethyl-4-phenyl but-3-enoic acid (Scheme III).

A novel method for the preparation of 2-methyl-3-butenoic acid was proposed by a Japanese group.[4] A π-allyltitanium complex with a chiral cyclopentadienyl ligand reacts with carbon dioxide under mild conditions to form a carbon-carbon bond, thus



Scheme-1



R = CH_3

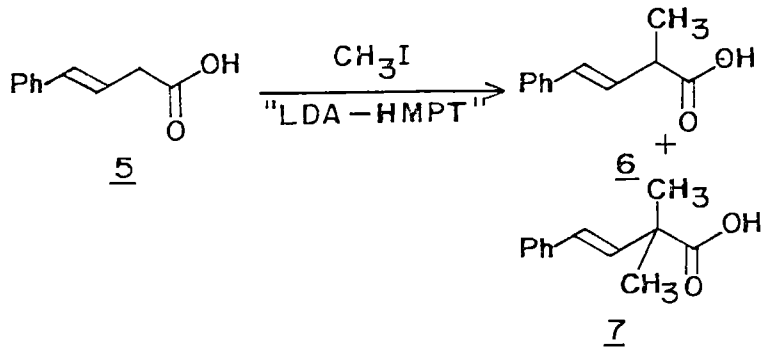
= CH_3CH_2

= $(CH_3)_2CH$

Scheme-2

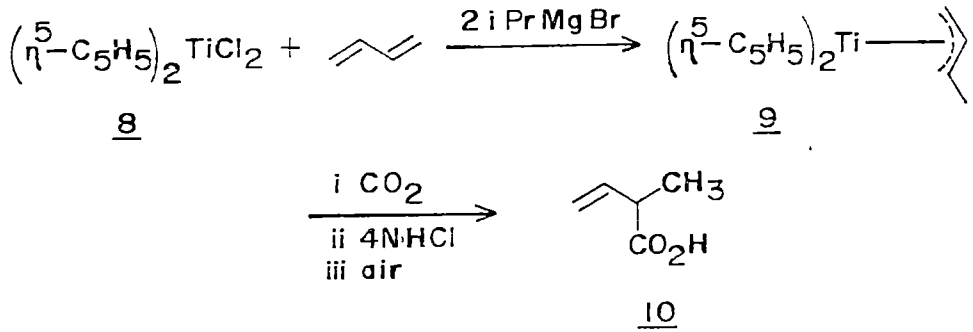
providing the first demonstration of asymmetric carbon dioxide fixation. The π-allyl titanium complex (η^5-$C_5H_5)_2Ti(\ \eta^3$-C_4H_7) (9) preformed or formed *in situ* by the reaction of (η^5-$C_5H_5)_2TiCl_2$ (8) and butadiene in the presence of isopropyl magnesium bromide, (Scheme 4), reacted with carbondioxide at ordinary pressure at room temperature in ether to afford 2-methyl-3-butenoic acid (10) and 8 in 85 and 87% yields respectively, by hydrolysis of the reaction mixture with 4N.HCl, followed by oxidation with air.

Addition of 2-alkenyl halides to precondensed active magnesium in THF gave clean solution of 2-alkenylmagnesium halides which on carbonation furnished β, γ-unsaturated carboxylic acids (13) in high yields.[5] In its representative procedure magnesium was evaporated at 0.01 Torr over a period of 1.5 hour from a resistance heated alumina crucible and condensed into a surrounding layer of THF within a rotating reaction flask cooled to -110°C. Slow addition of the 2-alkenyl chloride (11) in THF to the rotating black Mg-slurry under argon at -70°C furnished the Grignard solution into which dry CO_2 was condensed at -118°C for 5 minutes. The reaction mixture was kept at -70°C for 0.5 hour, then allowed to warm upto 0°C and quenched with aqueous NH_4Cl. Additin of ether, extraction with 10% aqueous NaOH and reextraction from the acidified aqueous phase gave the corresponding carboxylic acid (13) in high yield (Scheme 5).



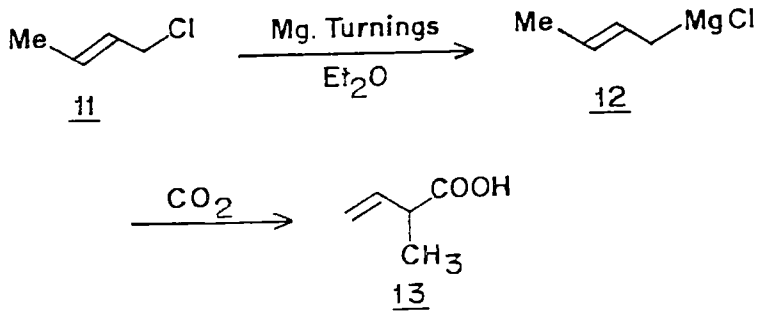
5 6 7

Scheme-3



8 9 10

Scheme–4



11 12 13

Scheme-5

However all the previously reported methods for the synthesis of this class of compounds involves costly chemicals and difficult reaction conditions for the preparation of α-methyl β, γ-unsaturated carboxylates. Literature survey revealed that all the reported synthesis of α-methylated β, γ-unsaturated carboxylates were by the methylation of charge-stabilized carbanions derived from compounds containing a reactive methylene group which leads in most cases to a mixture of mono- and dialkylated products. For monoalkylation specific methods depending on the nature of the carbanion were developed.[1,2,6-11] In our present study, we have achieved a novel one-pot synthesis of α-methyl β, γ-unsaturated carboxylates which does not require alkylation step.

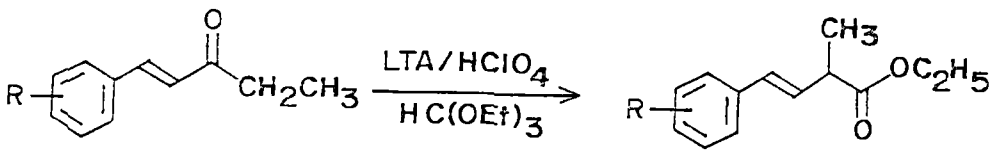
IV. 1. 2. RESULTS AND DISCUSSION

The selected α,β-unsaturated ketones used for the present lead(IV)acetate oxidation study were prepared according to the reported procedure and is given in the experimental section. The structures of all the α,β-unsaturated ketones were confirmed by comparison of their spectral and analytical data with those of the reported ones. The configuration of all the 1-aryl pent-1-en-3-one were confirmed from its IR and ^{1}H NMR spectra and were found to have (E) configuration.

The lead(IV) acetate prepared fresh for each reaction was

recrystallized and dried before use. The triethyl orthoformate was redistilled before the reaction.

In an optimized reaction condition, a suspension of lead(IV) acetate (4.5 g, 10 mmol) in triethylorthoformate (30 ml) was prepared at 5°C. A solution of the unsaturated ketone (14) in triethylorthoformate (20 ml) and perchloric acid (2 ml) were sequentially added to the above suspension of lead(IV) acetate and the reaction mixture was stirred for 16 hours. The solvent (triethyl orthoformate) was distilled under reduced pressure from the mixture and the residue was treated with chloroform (50 ml). The precipitate formed are filtered off and the filtrate was washed with water (2 x 50 ml) and dried (Na_2SO_4). The solvent was removed to afford the crude product which was further purified by column chromatography using hexane-ethyl acetate as eluent. The product was characterized as (E)-Ethyl 2-methyl-4-phenyl-3-butenoate (Scheme 6). The IR spectrum (neat) of the compound **15a** exhibited characteristic absorption bands at 1730 (ester C=O) 1655 (C=C). The compound **15a** has the δ_H values at 1.27 (t, 3H), 1.34 (d, J = 6 hz, 3H) for 6 methyl protons and at 3.25 gave a multiplet for the methine protons and **15a** analysed for $C_{13}H_{16}O_2$ and the elemental analysis gave the following results, 76.45% carbon and 7.94 % hydrogen which match very well with the calculated percentage of carbon and hydrogen.



14

a, R = H

b, = 2Cl

c, = 4Cl

15

Scheme-6

IV. 2 CYCLOALKANE CARBOXYLATE

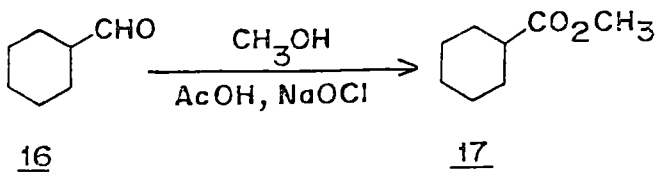
IV.2.1 INTORUDUCTION

The general methods for the synthesis of cycloalkane carboxylic acids/esters are a) conversion of the primary alcohols to the corresponding carboxylic acids. These conversion can be achieved using a wide variety of reagents currently available. For example chromic acid in sulfuric acid,[12,13] nickel peroxide in an aqueous alkaline solution[14], argentic oxide,[15] a mixture of potassium metaperiodate and ruthenium dioxide,[16] electrochemical (using a nickel hydroxide electrode),[17] potassium ruthenate in the presence of persulfate ion,[18] sodium permanganate monohydrate,[19] hydrated copper permanganate,[20] potassium permanganate in the presence of phase-transfer catalyst[21] and sodium bromate-hydrobromic acid system in the presence of tert. butanol.[22] b) Conversion of aldehydes to esters. In this process an aldehyde is dissolved in methanol and 1-2 equivalents of acetic acid, presumably resulting in equilibrium concentrations of the methyl hemiacetal. The additions of 1-2 equivalents of the aqueous NaOCl solution usually resulted in the rapid conversion of the aldehyde to the corresponding methyl ester in good yield[23] (Scheme 7). c) Ring cleavage reaction of oxazoline.[24] d) Favorski type rearrangement in the lead(IV)acetate oxidation of enamines promoted by boron

trifluoride.[25] Here the oxidative conversion of enamine (18) of cyclic ketones into esters of contracted cycloalkanoic acids (19) and enamines of aryl methyl ketones (20) into esters of arylacetic acids (21) achieved by using lead(IV) acetate - borontrifluoride etherate reagent and alcohol (Scheme 8).

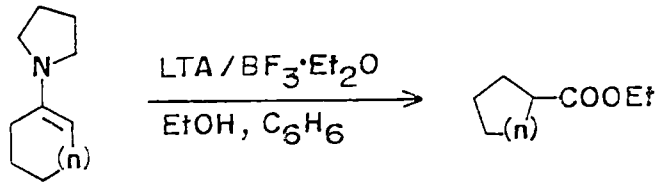
Favorski type rearrangement in the oxidative transformations of ketones were also observed in the lead(IV) acetate oxidation of ketones and their derivatives[26,27] and thalium(III) nitrate oxidation of ketones.[28] In the Favorski type rearrangement Cekovic and co-workers[25] used enamines derived from cycloalkanones to the corresponding esters of contractd cycloalkanoic acids. However, the additional step involving the formation of moisture sensitive enamines becomes redundant in the light of our observation. While our method provides a direct conversion of cycloalkanones to the correspondig esters of ring contracted cycloalkane carboxylic acids.

In this method we have used the readily available triethyl orthoformate, perchloric acid and lead(IV) acetate. It was found that, it is an excellent method to achieve the cycloalkanoic acid ester in a one-pot synthesis (Scheme 9).



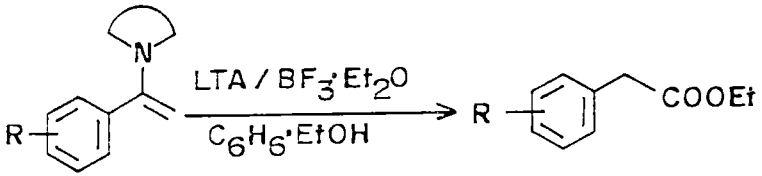
16 17

Scheme-7



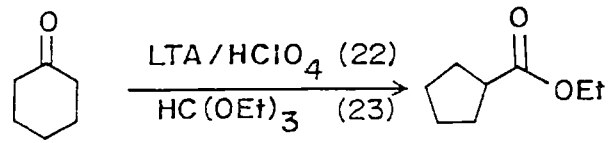
18 19

n = 1, 2.

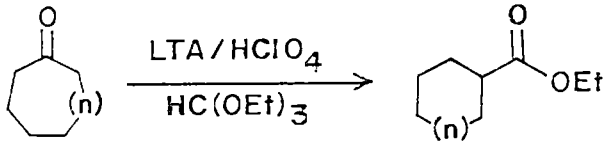


20 21

Scheme-8



24 25



n = 1,2

26 27

Scheme - 9

IV. 2. 2. RESULTS AND DISCUSSION

Here a new approach to Favorski type rearrangement has been presented. For this study the cyclic ketones used were cyclohexanone, cycloheptanone and cyclooctanone.

In an optimized reaction condition a suspension of lead(IV) acetate (9 g, 20 mmol) in triethylorthoformate (50 ml) was prepared at 5°C. A solution of the cyclohexanone (20 mmol) in 20 ml triethyl orthoformate and perchloric acid (4 ml) were sequentially added to the above suspension of lead(IV) acetate and the reaction mixture was stirred for 20 hours at room temperature. The triethyl orthoformate was distilled off under reduced pressure, extracted with chloroform (50 ml), washed, dried and purified by column chromatography. The product was characterized as ethyl cyclopentane carboxylate. When we tried to carry out the ring contraction using LTA, boron trifluoride-etherate and methanol combination in dry benzene the yield was very poor, (< 5%), ever after it was stirred for 48 hours at room temperature.

IV. 3 ETHYL(2-PHENYL CYCLOPROPYL) ACETATE

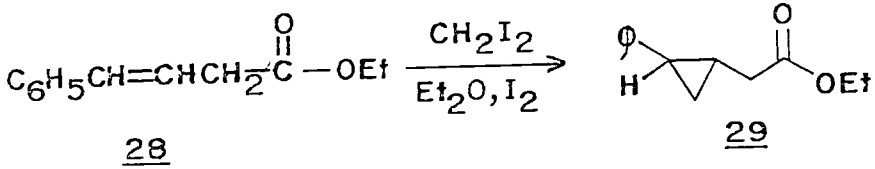
IV. 3. 1 INTRODUCTION

Our literature survey revealed that the number of research papers, which describe the synthesis, synthetic utility and reactions of cyclopropane system is tremendous. The well established techniques for the preparation of cyclopropanes from alkene involve using classical carbenoid reagents, free carbenes or diazo reagents. The complementary method[30] to the synthesis of cyclopropane is the reaction of mononuclear electrophilic transition metal carbonyl complexes with olefins to produce cyclopropanes. The patterns of reactivity observed in such reactions and the range of carbonyl moieties which may be transferred via an intermediate organometallc species demonstrate that this class of reaction is often complementary to the well established techniques. However in almost all these transformations the cyclopropanation is always the last step in the synthesis of cyclopropyl derivatives. Again our literature survey has revealed that there is no general reported method available for the synthesis of the titled compounds. Some of the reported methods for this class of compounds are a) the Simon-Smith cycloaddition to the ethyl 4-phenyl-3-pentenoate.[31] Zn-Cu couple was suspended in anhydrous ether. A crystal of iodine was added and the mixture is stirred for 0.5 hour. A mixture of ethyl

4-phenyl-3-pentenoate (28) and CH_2I_2 was added to a solution of Zn-Cu couple in ether and refluxing for 30 hours afforded the compounds 29 (Scheme 10). b) The 2-methyl cyclopropyl acetic acid (31) was prepared in 75% yield by the palladium(II)acetate-catalysed reaction of vinylacetic acid (30) with an excess of diazomethane (Scheme 11). c) Transition metal carbonyl complexes and the olefin have been employed to produce the substituted cyclopropyl acetic acid ester (35)[32] with Damishefsky's diene (33) in benzene. The cyclopropane is the result of the regioselective transfer of the carbonyl ligand to the more electron rich double bond of the diene.[33,34] Also produced in this reaction is α-methoxy styrene (36) (36%) which is the metathesis product resulting from the fragmentation of a metallocyclobutane intermediate and the interesting cyclopropane (35) is formally related to the expected products 34 by an internal oxidative/reductive disproportionation which is unprecedented in cyclopropanation products from the reaction of transition metal carbonyl complexes (Scheme 12).

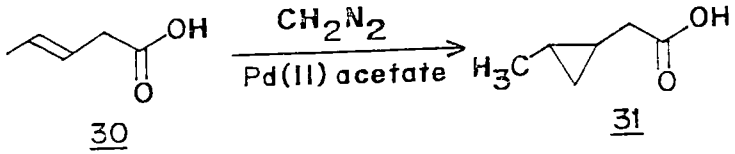
IV. 3. 2 RESULTS AND DISCUSSION

The selected benzylidene acetones used for the cyclopropanation were prepared according to the Vogel procedure. The cyclopropanation was carried out with trimethyl oxosulphoxonium iodide in 50% aqueous sodium hydroxide and



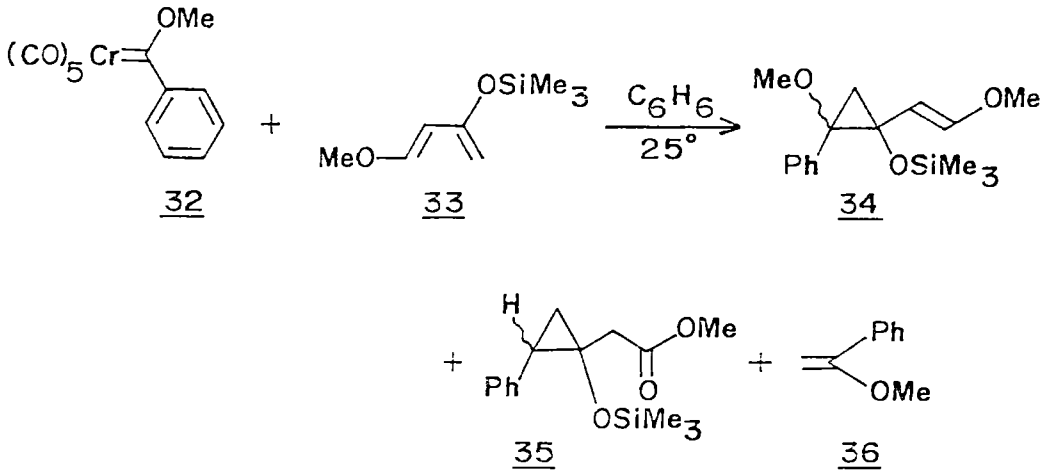
28 29

Scheme-10



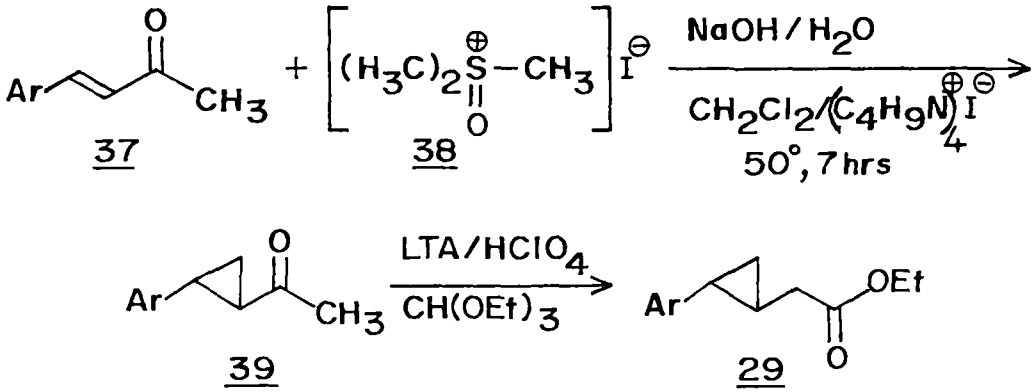
30 31

Scheme-11


(CO)5Cr
OMe
32
MeO
OSiMe3
33
C6H6
25°
MeO
OMe
Ph
OSiMe3
34
H
Ph
OMe
O
OSiMe3
35
Ph
OMe
36

Scheme-12

dichloromethane with tetrabutylammonium iodide as the phase transfer catalyst. The products obtained were characterized by analytical and spectral data. The products were then subjected to lead(IV) acetate oxidation in triethyl orthoformate and catalytic amount of perchloric acid. Interestingly the cyclopropane ring does not get opened up even in the presence of 70% perchloric acid and lead(IV) acetate. Evidently, cyclopropane does not exhibit "push-pull" effect and therefore stable enough to withstand the perchloric acid. The reaction has been carried out as follows. The cyclopropyl methyl ketone (39) in triethyl orthoformate was added to a stirring suspension of lead(IV) acetate in triethylorthoformate followed by the addition of perchloric acid. Normal work-up after 15 hrs of stirring at r.t. afforded the ethyl cyclopropyl acetate 55% yield. ^{1} H. NMR clearly shows the presence of cyclopropyl ring in the oxidation product. The four protons present in the cyclopropane ring gave δ_H values as follows : the four multiplets were seen for each protons at 0.86, 0.99, 1.37 and 1.75. The triplet at 1.25 and the quartet at 4.13 are due to the presence of $-CH_3$ and $-OCH_2$ respectively. A quatret at 4.13 and the aromatic protons appearing between 7.14-7.27 confirms the compound as ethyl(2-phenylcyclopropyl)acetate (Scheme 13).



	Ar
a	C_6H_5
b	$2-ClC_6H_4$
c	$4-ClC_6H_4$

Scheme-13

IV. 4 EXPERIMENTAL

The ketone and benzaldehyde used for the preparation of benzylidene propanone were distilled prior to their use. 2-chloro and 4-chloro benzaldehydes commercially available are used without further purification. Lead(IV) acetate, m.p. 175°C[29] was prepared fresh for each reaction and carefully dried in a vacuum desiccator over potassium hydroxide. The triethyl orthoformate was distilled and used for each reaction.

IV.4.1(a) Preparation of 1-Aryl Pent-1-en-3-one:General Procedure

To a cooled solution of freshly distilled benzaldehyde (4.2g) and ethytl methyl ketone (8.0 g) in a 150 ml R.B. flask equipped with a mechanical stirrer, 2 ml of 10% sodium hydroxide solution was added dropwise. The mixture was stirred at room temperature for 4 hours and was rendered acidic to litmus by the addition of dilute hydrochloric acid, extracted with diethyl ether (20 ml), washed with water (2x50ml), dried (Na_2SO_4). Removed the solvent and distilled the residue under vacuum yielded the product.

IV.4.1(b) Preparation of Ethyl 2-Methyl-4-Phenyl-3-Butenoate (15) General Procedure:

To a stirring suspension of lead (IV) acetate 9 g (20 mmol) in 30 ml of triethyl orthoformate kept in a cold water bath

benzylidene propanone 3.2 g (20 mmol) in 20 ml of triethyl orthoformate was added followed by 3 ml of perchloric acid. The reaction mixture was allowed to stirr for 20 hours at room temperature. The triethyl orthoformate was distilled off under reduced pressure from the mixture and the residue was treated with chloroform (50 ml). The precipitate formed were filtered off and the filtrate was washed with water (2 x 100 ml), dried (sodium sulphate) and the solvent was distilled off. The crude product was purified by column chromatography. The yield was found to be 65%.

Ethyl 2-methyl-4-phenyl-3-butenoate (15a). Colourless viscous liquid, yield, 65%, IR(neat), 1730 , 1655, 1245 cm^{-1} δ_H ($CDCl_3$) 1.27, (t, CH_3), 1.34 (d, J = 6 Hz, CH_3), 3.25 (m, 1H), 4.12 (q, $-OCH_2$), 6.21 (1H, =CH), 6. 36 (d , J = 18 Hz, 1H), 7. 23 (m, 5ArH), δ_C ($CDCl_3$), 14.17,17.42, 43,.12, 60.59, 121.23, 127.95, 128.41, 128.73, 129.80, 131.02, 175.65. Anal. calcd. C, 74.43; H, 7.89%. Found: C, 74.38; H, 7.75%.

Ethyl 2-methyl 4(4-chlorophenyl)3-butenoate (15b) Colourless viscous liquid, yield, 60%, IR(neat), 1731, 1650, 1245 cm^{-1}, δ_H $CDCl_3$ 1.29 (t, J = 7Hz, CH_3), 1.36 (d, J = 6 Hz, CH_3), 3.25 (m, 1H), 4.14 (q, $-OCH_2-$), 6.21 (1H, =CH), 6.38 (d, J = 18 Hz, 1H), 7.23 (m, 4ArH), δ_C ($CDCl_3$), 14.18, 17.42, 43.18, 60.61, 122.71, 127.91, 128.43, 12875, 129.84, 131.03, 176.02. Anal. calcd.: C, 65.39; H, 5.91%. Found: C, 65.23; H, 5.81%.

Ethyl 2-methyl 4(2-chlorophenyl) 3-butenoate (15c). Colourless viscous liquid, yield 61%, IR(neat), 1734, 1650, 1245 cm^{-1}, δ_H ($CDCl_3$), 1.31 (t, CH_3), 1.38 (d, J = 6Hz, CH_3), 3.29 (m, 1H), 4.14 (q, $-OCH_2-$), 6.24(1H, =CH), 6.41 (d, J = 18Hz, 1H), 7.23 (m, 4ArH), δ_C ($CDCl_3$), 14.20, 17.44, 43.18, 60.63, 121.71, 126.71, 127.14, 127.21, 127.85, 129. 17, 135.52, 137.41, 175.83. Anal. calcd. C, 65.39; H, 5.91%. Found: C, 65.23; H, 5.82%.

IV. 4.2 Preparation of Ethyl cycloalkane carboxylates : General Procedure

To a stirring suspension of lead(IV) acetate 9g (20 mmol) in triethyl orthoformate (25 ml) a solution of cyclooctanone 2.52 (20 mmol) in 10 ml triethyl orthoformate was added followed by 3 ml of perchloric acid. The reaction mixture was stirred for 20 hours. The mixture was filtered and solvent was distilled off under vacuo. and extracted with chloroform, washed with water (2x10ml) and distilled off the solvent. The crude product was further purified by column chromatography. The overall yield was found to be 70%. The cyclic esters (23) and (25) were also prepared by the above general method.

Ethyl cyclopentane carboxylate (23). Colourless liquid, yield, 70%, IR(neat), 1738 cm^{-1}, δ_H ($CDCl_3$) ,1.25 (t, 3H, $-CH_3$), 1.53-1.90 (m, 8H, $-CH_2-$), 2.27 (m, 1H, -CH), 4.09 (q, $-OCH_2-$), δ_C

($CDCl_3$), 14.30, 25.48, 28.89, 43.13, 59.77, 176.10. Anal. calcd. C, 67.57; H, 9.92%. Found: C, 67.45; H, 9.83%

Ethyl cyclohexane carboxylate (25). Colourless liquid, yield, 68%, IR(neat), 1735 cm^{-1}, δ_H ($CDCl_3$), 1.24 (t, 3H, $-CH_3$), 1.52-1.92 (m, 10H, $-CH_2-$), 2.27 (m, 1H), 4.09 (q, $-OCH_2-$), δ_C ($CDCl_3$), 14.22, 25.41, 28.75, 28.93, 43.08, 59.77, 175.62. Anal. calcd. C, 69.19; H, 10.32%. Found: C, 69.28; H, 10.41%.

Ethyl cycloheptane carboxylate (27) Colourless viscous liquid, yield, 65% , IR(neat), 1738 cm^{-1}, δ_H ($CDCl_3$), 1.24 (t, 3H, $-CH_3$), 1.51-1.70 (m, 12H, $-CH_2-$), 2.38 (m, 1H), 4.11 (q, 2H, $-OCH_2-$), δ_C ($CDCl_3$), 14.24, 26.35, 26.53, 28.28, 28.47, 30.50, 30.81, 45.00, 60.40, 176.91. Anal. calcd. C, 70.54; H, 10.65%. Found: C, 70.48; H, 10.53%.

IV.4.3(a) Preparation of 2-Phenyl Cyclopropyl Methyl ketone (39)

General Procedure

A suspension of benzylidene acetone (10 mmol), trimethyl sulphoxonium iodide (13 mmol), tetrabutyl ammonium iodide (15 mmol) in an aqueous solution of 50% NaOH (30 ml) and dichloromethane (30 ml) was stirred at 50 °C for 7 hrs. The organic layer was separated and concentrated, the residue was diluted with ethyl acetate to preceipitate out the tetrabutyl ammonium iodide. The filtrate was evaporated to give the crude

product which was purified by column chromatography using hexane-ethylacetate as eluent.

IV.4.3(b) Preparation of Ethyl(2-Phenyl Cyclopropyl)acetate (29a)

To a stirring suspension of lead (IV) acetate 4.5 g (10 mmol) in triethyl orthoformate (10 ml) a solution of **39a** 1.75 g (10 mmol) in 10 ml of triethyl orthoformate was added followed by 2 ml perchloric acid. The reaction mixture was stirred for 15 hours at room temperature. The solvent was distilled under reduced pressure from the reaction mixture and the residue was treated with chloroform (50 ml). The precipitate formed was filtered off and the filtrate was washed with water (2 x 50 ml) and evaporated in vacuo. The crude product was further purified by column chromatography using hexane as eluent.

2-Phenyl cyclopropyl methyl ketone (39a) Colourless viscous liquid, yield, 60%, IR(neat), 1720 cm^{-1}, δ_H ($CDCl_3$), 1.29 (m, 1H), 1.61 (m, 1H), 2.15 (m, 1H), 2.21 (s, $-CH_3$), 2.48 (m, 1H), 7.16 (m, 5 ArH), δ_C ($CDCl_3$), 18.93, 28.79, 30.58, 32.69, 125.95, 126.42, 128.40, 140.22, 206.26. Anal. calcd. C, 82.98; H, 7.60%. Found: C, 82.63; H, 7.52%.

2 (2-chloro)phenylcyclopropyl methyl ketone (39b) Colourless viscous liquid, yield, 56%. IR(neat), 1622 cm^{-1}, δ_H $CDCl_3$, 1.38 (m, 1H), 1.64 (m, 1H), 2.03 (m, 1H), 2.32 (s, $-CH_3$), 2.65 (m,

1H), δ_C ($CDCl_3$) 16.61, 27.07, 30.59, 30.95, 126.71, 127.14, 127.85, 129.17, 135.52, 137.41, 206.26. Anal. calcd. C, 67.87; H, 5.69%. Found: C, C, 67.38; H, 5.56%.

2(4-chloro)phenylcyclopropylmethyl ketone 39c. Colourless viscous liquid, yield, 58%, IR(neat), 1620 cm^{-1}, δ_H ($CDCl_3$), 1.36 (m, 1H), 1.62 (m, 1H), 2.00 (m, 1H), 2.29 (s, $-CH_3$), 2.61 (m, 1H), δ_C ($CDCl_3$) 17.01, 27.12, 31.01, 31.46, 126.5, 127.18, 135.58, 137.48, 206.28. Anal. calcd. C, 67.87; H, 5.69%. Found: C, 67.36; H, 5.38%.

Ethyl (2-phenyl cyclopropyl) acetate (29a). Colourless viscous liquid, yield, 55%, IR(neat), 1736 cm^{-1}, δ_H ($CDCl_3$), 0.86 (m, 1H), 0.98 (m, 1H), 1.25 (t, $-CH_3$), 1.37 (m, 1H), 1.75 (m. 1H), 2.40 (q, 2H), 4.11 (q, 2H), 6.89 - 7.27 (m, 5ArH), δ_C ($CDCl_3$), 14.30, 27.56, 30.83, 31.01, 43.15, 60.52, 125.93, 126.45, 128.39, 140.21, 175.31.Anal. calcd. C, 76.43; H, 7.89%. Found: C, 76.56; H, 7.69.

Ethyl (2 (2-chloro)phenylcyclopropyl)acetate 29b. Colourless viscous liquid, yield, 52%, IR(neat), 1738 cm^{-1}, δ_H ($CDCl_3$ 0.89 (m, 1H), 1.00 (m, 1H), 1.25 (s, $-CH_3$), 1.38 (m, 1H), 1.76 (m, 1H), 4.42 (q, 2H), 4.13 (q, 2H), 6.90-7.25 (m, 4ArH), δ_C ($CDCl_3$), 14.31, 27.56, 30.81, 31.02, 43.14, 60.53, 126.43, 127.18, 127.83, 129.18, 135.53, 137.43, 175.36. Anal. calcd. C, 65.40; H, 6.33%. Found: C, 65.31; H, 6.12%.

Ethyl (2(4-chloro)phenyl cyclopropyl) acetate (29c) Colourless viscous liquid, yield, 50%, IR(neat), 1740 cm^{-1}, δ_H ($CDCl_3$), 0.86 (m, 1H), 0.96 (m, 1H) , 1.28 (t, $-CH_3$), 1.36 (m, 1H), 1.809 (m, 1H), 2.45 (q, 2H), 4.23 (q,2H), 6.93 - 7.25 (m, 4ArH), δ_C ($CDCl_3$), 14.36, 27.58, 30.84, 31.02, 43.16, 60.52, 126.78, 127.16, 135.60, 137.49, 175.30.

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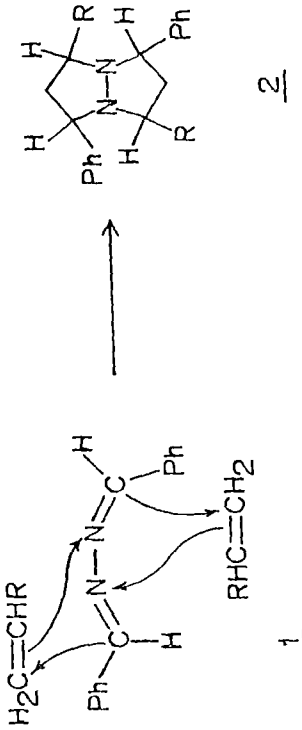
PART B — CHAPTER V

DEVELOPMENT OF GENERAL METHODS FOR THE SYNTHESIS OF DIARYL METHANES AND STILBENES FROM AZINES

V. I INTRODUCTION

Azines have been known since 1917[1] to undergo consecutive [3+2] cycloaddition reactions with 1,3-dipolarophiles to give bicyclic products having fused five-membered rings (Scheme 1), a transformation commonly known as the criss-cross reaction.[2] The azines are electron rich molecules and typically require electron deficient alkenes as partners. The reaction often requires elevated temperatures and prolonged reaction times. In contrast, azines with electron-withdrawing CF_3 substituents react with a



Scheme—1

variety of substrates, including electron-rich olefines.[3,4] Recently the first example of organometallic analogous of this criss-cross cycloaddition involving benzalazine and vinylidene or carbyne complexes has been reported (Scheme 2).

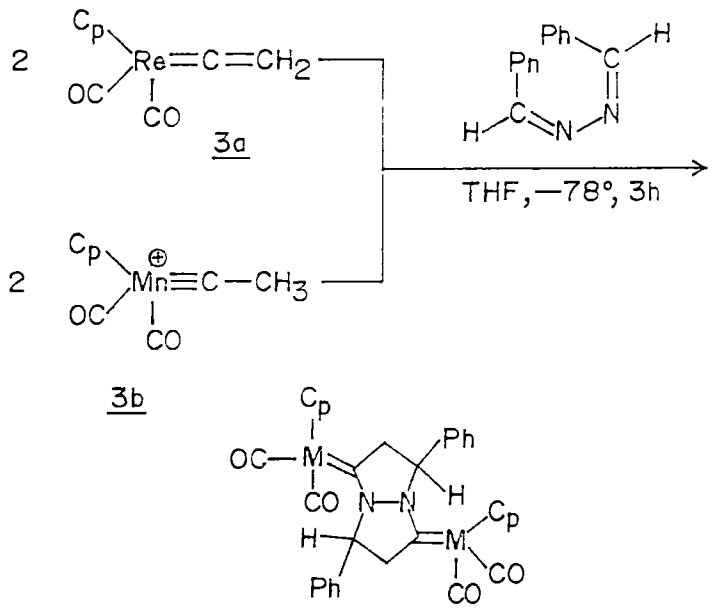
However, because they are easily hydrolysed back to the original aldehydes, the synthetic utility of the azines has not been explored to any extent. Infact the hydrolytic susceptibility of the benzalazine has been made use of in the preparation of methyl hydrazine by its reaction with dimethyl sulphate in the preparation of methyl hydrazine (6) (Schene 3).

In the present study, it was decided to explore the synthetic application of the azines with a view to develop some general method for the preparation of diphenylmethanes and stilbenes.

V.2 Synthesis of Diaryl Methanes by Friedel-Craft Condensation of Benzalazines with Aromatic Hydrocarbons

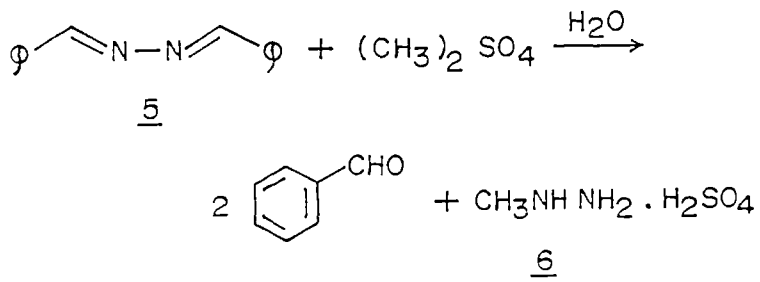
V. 2. 1. Introduction

The synthesis of diphenyl methanes is widely reported in the literature. The usual method of synthesis for these compounds include : (i) Condensation between one mole of formaldehyde and two moles of benzene in presence of conc. sulphuric acid[6]; (ii) Reduction of aromatic ketones by Wolff-Kishner[7a] or Clemmensen reduction method[7b]; (iii) Catalytic condensation of Grignard



4 a,(41%)
b,(53%)

Scheme—2



5

6

Scheme—3

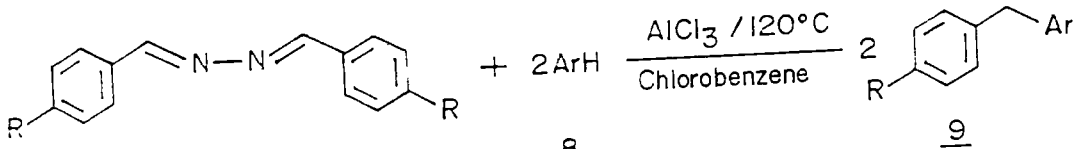
reagent with hydrocarbons[8] besides other methods where diphenyl methanes are obtained as side products.[9-11]

We have therefore developed a route based on the Friedel-Craft condensation between the benzalazines and aromatic hydrocarbons to give diphenyl methanes having differently substituted aryl groups (Scheme 4)

V.2.2 RESULTS AND DISCUSSIONS

When aluminium chloride was added to a solution of benzalazine (7) (R = H) in dry benzene and the mixture refluxed for 8 hours, work-up of the reaction mixture gave diphenyl methane (9) (R = H, Ar = C_6H_5) in 67% isolated yield. Similarly the reaction between 7 (R = 4-Me) and 8 (Ar = tolyl) was carried out using dry toluene as solvent. The products obtained were found to be identical with genuine samples of diphenyl methane and di-p-tolyl methane respectively, as determined by their mixed melting points and superimposable IR. The method was extended to the preparation of diaryl methanes 9C - 9K from the corresponding azine and aromatic hydrocarbon under similar reaction condition except that chlorobenzene was now used as the reaction medium, in yields ranging from 60 -71%.

Although no attempt has been made to study the mechanism of the reaction, the high yield of the products might indicate that each mole of benzalazine could have produced two moles of the



7 8 9

R	Ar
a, H	phenyl
b, H	tolyl
c, H	2,5—dimethyl phenyl
d, H	3,5—dimethyl phenyl
e, H	naphthyl
f, H	biphenyl
g, H	isopropyl
h, H	t-butyl phenyl
i, H	allyl phenyl
j, 4—CH_3	phenyl
k, 4—CH_3	tolyl

Scheme —4

diarylmethane as shown in the mechanism (Scheme 5). However, it is too early to say with any certainty that the actual course of the mechanism. Work is still going on in this area.

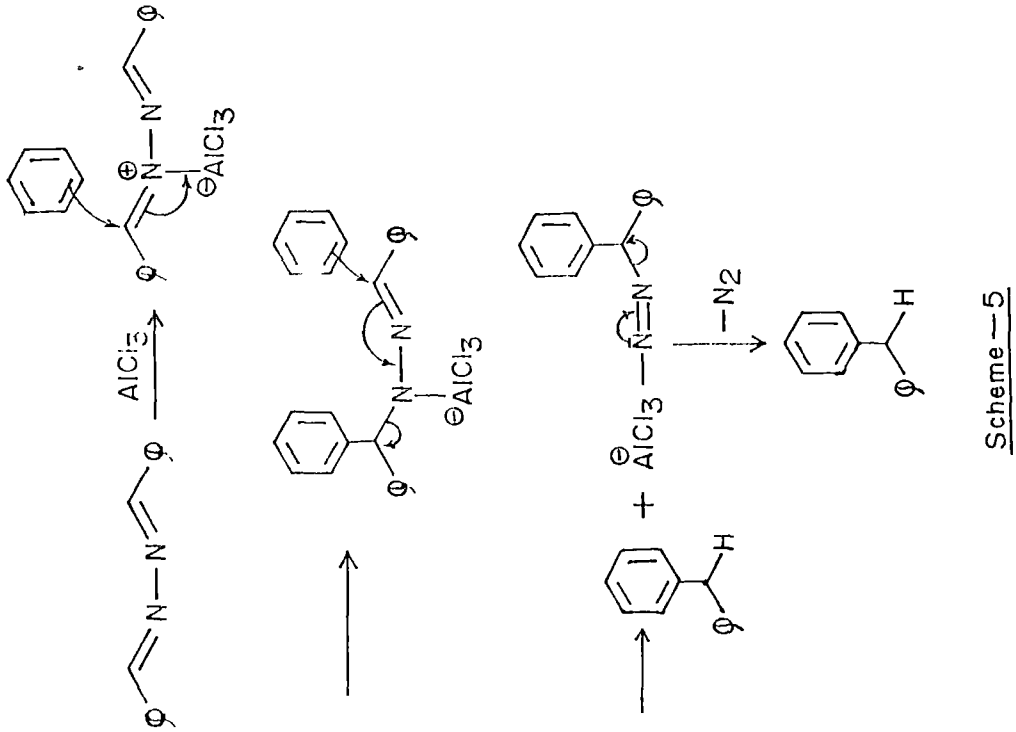
V.3. Synthesis of Stilbenes by Condensation of Benzalazines and Aromatic Hydrocarbons in Presence of Sodium in DMF

V. 3. 1 Introduction

The introduction of a carbon carbon double bond into a molecule may be effected by the following procedures.

1. 1,2-elimination processes (β-elimination) applied to alcohols, allyl halides, quaternary ammonium salts and acetate or xanthate esters.
2. The partial catalytic hydrogenation of alkynes.
3. The reaction between an alkylidene phosphorane and a carbonyl compound.
4. Wurtz-type coupling reaction involving allylic halides and
5. Rearrangement of alkynes.

The Wittig reaction is a well-established method for the preparation of carbon-carbon double bonds.[12] In 1954, Georg Wittig reported a method of synthesizing alkenes from carbonyl compounds, which amounts to the replacement of the carbonyl oxygen, =O, by the group =CRR′. The heart of the synthesis is the nucleophilic attack on the carbonyl carbon by an ylide to form a betaine which often spontaneously undergoes elimination to

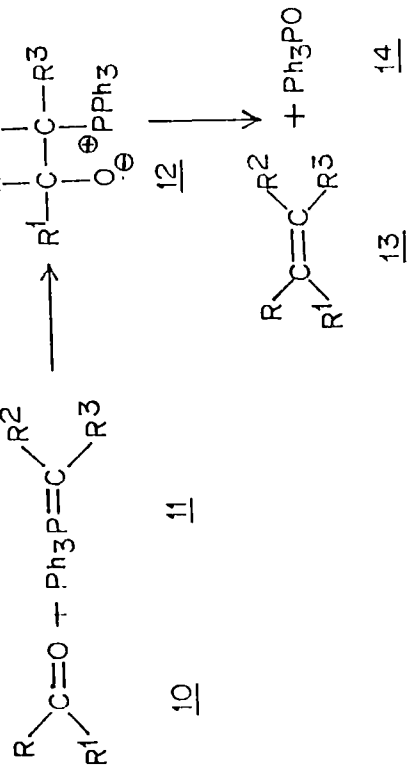


Scheme—5

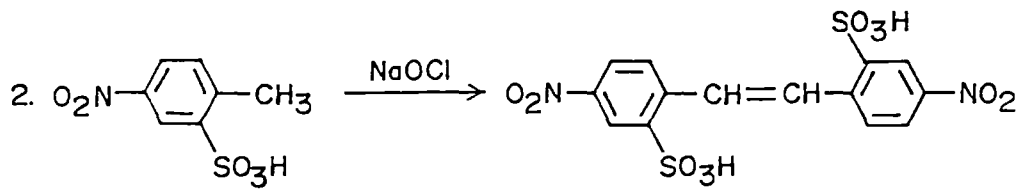
yield the product (Scheme 6). The reaction is carried out under mild conditions and the position of the C-C double bond is not in doubt. However the usual requirements of expensive phosphines and organic halides and one equivalent of strong base coupled with the two step preparation of the ylide and lack of environmentally safe disposal of the phosphone product all add up to make the Wittig reaction not ammenable to large scale preparation.

Recently a review by Konrad B. Becker[12] has described in detail the various synthetic methods leading to stilbenes and stilbene derivatives with substituted aromatic rings. Synthetically more important are the dimerization reactions : Oxidative or eliminative dimerization of a suitable methyl arene often constitutes the method of choice for the preparation of a symmetric stilbene as highlighted in Scheme 7. Oxidizing agents such as lead dioxide, phosphorus trichloride or sulfur have been used. Recent reports describe the use of oxygen and/or superheated steam at high temperatures (400-700°C) over mixtures of metal oxides (e.g. lead, cadmium, bismuth, tin oxides)[14] on different supports to affect partial dehydrogenation of toluene to stilbene.

Benzyl chloride (17) yield, stilbene when treated with a strong base.[15] This type of reaction is common with halides which do not bear hydrogen atoms β- to the halogen atom, and the



Scheme—6



15 16

Scheme—7

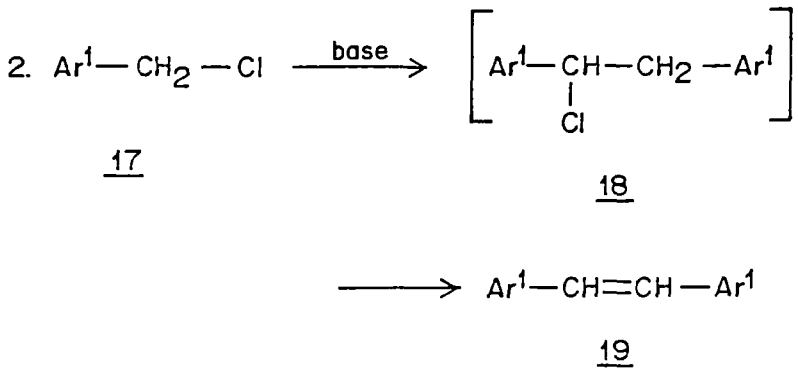
α-position of which is activated by conjugation, eg. with aryl methyl halides (17) allylic halides, and phenacyl bromide.[16] The carbanion formed is alkylated by additional arylmethyl chloride (18). Simple 1,2-elimination of hydrogen chloride finally gives the stilbene (Scheme 8).

The Siegrist reaction, that is the reaction of aromatic schiff bases (20), with methyl substituted aromatic compounds (21) in the presence of potassium tert-butoxide or powdered potassium hydroxide in dimethyl formamide to yield stilbenes (22) is an attractive alternative (Scheme 9). Although there are a series of publications and patents[17-19] in which Siegrist has utilised the anil synthesis for the preparation of over one thousand substituted stilbenes, this reaction is still relatively unknown.

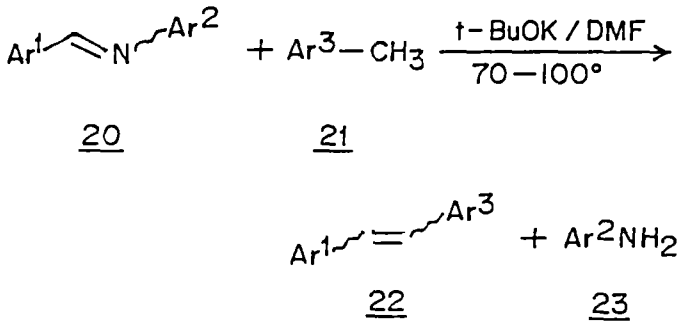
More recently Hay and co-workers[20] have extended the anil synthesis to the synthesis of a number of dienes and tetraenes. During our studies on the synthetic utility of the azines, we investigated the possibility of using these class of coumpounds for the synthesis of stilbenes by reactions parallel to the anil synthesis.

V.3.2. RESULTS AND DISCUSSION

When sodium is reacted with DMF, these anionic species



Scheme — 8



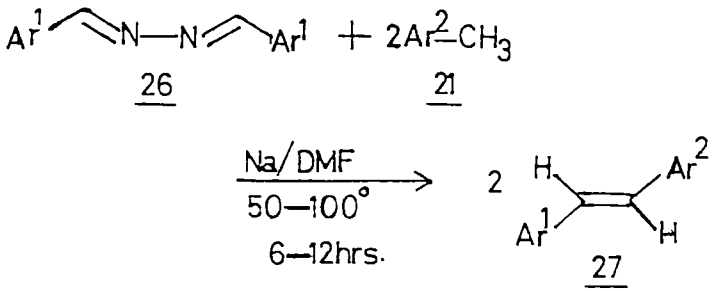
Scheme —9

result with a preponderance of sodium dimethylamide above 100°C.[21] The sodium dimethyl aminoformamide and sodium N,N-dimethyl-2-(dimethylamino)-2-oxidoethanamide[21] can essentially be regenerated by sodium dimethyl amide when in the presence of more dimethyl formamide, by analogy with the behaviour of sodium hydride[22] and other alkali amide derivatives.[23,24] This medium, abbreviated as Na/DMF, has the advantage of being effective in preparing trans-stilbene (27) from excess toluene and 26 (Scheme 10).

At this stage the mechanism by which (27) formed has not been worked out. However, it probably involves the initial abstraction of a methyl hydrogen. This carbnion then adds on to the azine. A second hydrogen abstraction gives the product in 50-57% overall yields. Although the azine is completely consumed, its fate in the reaction is yet to be established.

V. 5.4 EXPERIMENTAL

The recorded boiling points and melting points are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM 390 (90 MHz) and Infra Red (IR) spectra were recorded on Perkin-Elmer 297 spectrophotometer. C, H, N analyses were done on Heraeus Elemental Analytser CHN-O-Rapid.



Scheme –10

The azines were prepared from distilled benzaldehyde and hydrazine sulphate according to Vogel procedure.

V. 4.1. General Method for the Preparation of Diaryl Methane

Benzalazine (7) (0.02 mole) was taken in 250 ml round bottom flask containing chlorobenzene (35 ml) and aromatic hydrocarbon (8) (0.06 mole). Aluminium chloride (0.03 mole) was then added and the mixture refluxed for 8-12 hours. After the reaction was completed (monitored by TLC), the mixture was cooled and poured onto ice; extracted with ether, dried (Na_2SO_4) and the solvent distilled off to give a viscous residue which was purified by silica gel column chromatography (ethyl acetate-hexane eluent) to give pure diarylmethanes.

Diphenyl methane (9a) Colourless viscous liquid, yield, 67%, IR(neat), 2920, 2850 cm^{-1}, δ_H, 4.05 (s,2H), 7.20 (m, 10H); Anal. calcd. C, 92.80; H, 7.20%. Found: C, 92.76; H, 7.21%.

Phenyl(4-tolyl)methane (9b):Colourless viscous liquid, yield 60%, IR (neat) 2925, 2848 cm^{-1} ; δ_H ,2.30 (s, 3H), 3.85 (s, 2H); 6.92 - 7.15 (m, 9H). Anal. calcd. : C, 92.24; H, 7.76%. Found : C, 92.15; H, 7.80%.

Phenyl (2,5-xylyl) methane (9c). Colourless viscous liquid, yield 56%, IR (neat) 2923, 2845; δ_H 2.16 (s, 3H), 2.3 (s, 3H), 3.9 (s, 2H), 6.80 (m, 5H), 7.00 - 7.21 (m, 3H). Anal. calcd.:C, 91.77, H, 8.23%; Found : C, 91.79; H, 8.25%.

Phenyl(3,5-xylyl)methane (9d). Yield, 55%, IR (neat), 2923, 2840; ^{1}H NMR 2.20 (s, 6H), 3.83 (s, 2H); 6.7-6.97 (m, 3H); 6.97 - 7.25 (m, 5H). Anal. calcd. C, 91.77; H, 8.23%. Found: C, 91.71; H, 8.29%.

Phenylnaphthyl methane (9e). Yellow viscous liquid, yield, 50%, IR (neat), 2938, 2850 CM^{-1} δ_H 3.96 (s, 2H), 7.18 (m, 5H), 7.34 (m, 3H), 7.52 (s, 1H), 7.66 (m,3H), Anal. calcd. : C, 93.39; H, 6. 61%. Found: C, 93.30; H, 6.69%.

Biphenyl phenyl methane (9f). Yellow viscous liquid, yield 56%, IR (neat) 2938, 2840 cm^{-1} δ_H 3.96 (s,2H), 7.18 (m, 5H), 7.34 (m, 5H), 7.47(m, 4H). Anal. calcd. C, 93.39, H, 6.61%. Found: C, 93.30, H, 6.69%.

Phenyl (4-isopropylphenyl) methane (9g). Colourless viscous liquid, yield, 53 %, IR(neat), 2959, 2860; δ_H 1.20 (d, J = 7Hz, 6H), 2.73 (m, 1H); 4.05 (s, 2H), 7.23 (m, 9H). Anal. calcd.: C, 91.36; H, 8.64%. Found: C, 91.38; H, 8.54%.

Phenyl (4-tert.butylphenyl) methane (9h). Colourless viscous liquid, yield 52 %, IR(neat), 2925, 2850cm^{-1} δ_H 1.35 (s,9H), 4.02 (s, 2H); 7.23 (m, 9H). Anal. calcd. C, 91.00; H, 9.00%. Found: C, 91.04; H, 9.05%.

Phenyl(4-styryl) methane (9i). Colourless viscous liquid, yield, 50 %, IR(neat), 2950, 2875 cm^{-1}, δ_H 4.03 (s, 2H), 7.30 (m, 12H)

Anal. calcd. :C, 92.72; H, 7.28% Found: C, 92.79; H, 7.32%.

Di (4-tolyl) methane (3j). Colourless viscous liquid, yield 55%, IR(neat), 2930, 2840 cm^{-1} δ_H 2.33 (s, 6H), 3.89 (s, 2H); Anal.calcd. C, 91.77; H, 8.23%, Found: C, 91.23; H, 8.29%.

V.4.2a Preparation of Na/DMF : General Procedure

To DMF (40 ml) is added methallic sodium (1.0 g, 0.043 mol) in seven portions at 105-110°C under a slow stream of N_2 and with stirring. Additional portions of Na are introduced after the initial vigorous reaction abates. The addition of Na takes 15 min. The mixture is brought to the desired temperature.

V.4.2b Preparation of Stilbene from Benzal azine (28)

To the Na/DMF mixture prepared as above is added a solution of toluene and the benzalazine in DMF, at a reaction temperature of 105-110°C. The mixture is allowed to stirr for 8 hours. The mixture is cooled and extracted with ether, washed with water (2 x 50 ml), dried and concentrated. The crude product is further purified by column chromatography using hexane as eluent.

Stilbene (27a). Crystalline solid, m.p. 124-126°C. yield, 52%, IR, 1647 cm^{-1}, δ_H ($CDCl_3$) 7.20 - 7.60 (m, 12H). Anal. calcd. C, 93.29; H, 6.71%. Found: C, 93.35, 6.80%.

4-Chloro stilbene (27 b). Crystalline solid, m.p. 129-131°C, IR 1650 cm^{-1}, δ_H ($CDCl_3$) 7.00 - 7.90 (m, 11H). Anal. calcd. C, 77.59; H, 5.08%. Found: C, 77.69, H, 5.17%.

2-Chloro stilbene (27c) Crystalline Solid, m.p. 39-41, yield 60%, IR 1650 cm^{-1}, δ_H ($CDCl_3$) 7.10 - 8.00 (m, 11 H), Anal. calcd. C, 77.59, H, 5.08%, Found: C, 77.51; H, 5.09%.

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