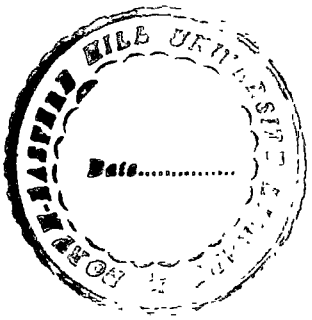
NOVEL METHODS FOR THE SYNTHESIS OF

(A) PYRIDAZINE DERIVATIVES AND RELATED N-HETEROCYCLES FROM SUBSTITUTED 1, 4-DIKETONES AND

(B) CYCLOPROPANE ACETIC ACID ETHYL ESTERS AND HEXA-3, 5-DIENOIC ACID METHYL ESTERS *VIA* LEAD (IV) ACETATE OXIDATIONS

By

RISHAN LANG NONGKHLAW



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I, **Mr Rishan Lang Nongkhlaw,** hereby declare that the subject matter of this thesis is the record of work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other university or institute. This is being submitted to the North Eastern Hill University for the degree of Doctor of Philosophy in Chemistry.

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Dedicated To

My Beloved Father

(Late) Makrom Pathaw

and Brother

(Late) Tyngshain Lang Nongkhlaw

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PREFACE

The thesis consists of six chapters which are divide into two parts: **Part A** deals with the synthesis of N-heterocycles. N-heterocycles formed the basic skeleton of many biologically important classes of natural products such as antibiotics, vitamins, marine products, animal toxins, and fungal metabolites. Porphyrin rings form the basic skeleton of life supporting systems such as Haemoglobin, Chlorophyll, Vitamin B_{12} etc. Heterocyclic units such as pyridazines, triazines and their analogues are of special interest in pharmacology, due to their important biological activities. The work here highlighted the novelty of synthetic studies of pyridazine derivatives and related N-heterocycles starting from simple starting compounds *via* the 1, 4-dicarbonyl compound in a one pot reaction without isolation of the intermediates.

The first chapter deals with the general introduction of N-heterocycles. In the second chapter the synthesis of 3, 5, 6-triaryl pyridazines from aryl methyl ketones and aromatic 1, 2-diketones is discussed. This method has been generalized by the use of heteroaromatic 1, 2-diketones.

The third chapter deals with the synthesis of trisubstituted 1, 2, 4-triazines starting from amides and 1, 2-diketones. The advantage of our methods is that in all the reported methods the reaction intermediates were isolated before proceeding to the next step.

Part B deals with the synthetic applications of lead tetra acetate. Lead tetra acetate, as a versatile oxidizing agent, has been used for selective and partial oxidation of various reactive groups, depending on the reaction condition and nature

of the substrate. It oxidizes organic molecules and itself gets reduced from lead (IV) to lead (II) either through ionic or radical mechanism.

The fourth chapter gives a general introduction on lead (IV) acetate oxidation. In In the fifth chapter the 1, 2-carbonyl transposition of cyclopropyl methyl ketones to give cyclopropane acetic acid ethyl esters effected by lead (IV) acetate in triethyl ortho formate and a catalytic amount of perchloric acid is discussed.

In continuation of the studies concerning the carbonyl transposition, the synthesis of substituted hexa-3, 5-dienoic acid methyl esters from conjugated dienones using lead (IV) acetate and boron trifluoride etherate-methanol combination is discussed in the last chapter.

Each chapter is framed into Introduction, Results and discussions and Experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The reference of the published work of the present investigation is cited in the respective chapter.

CHAPTER-I

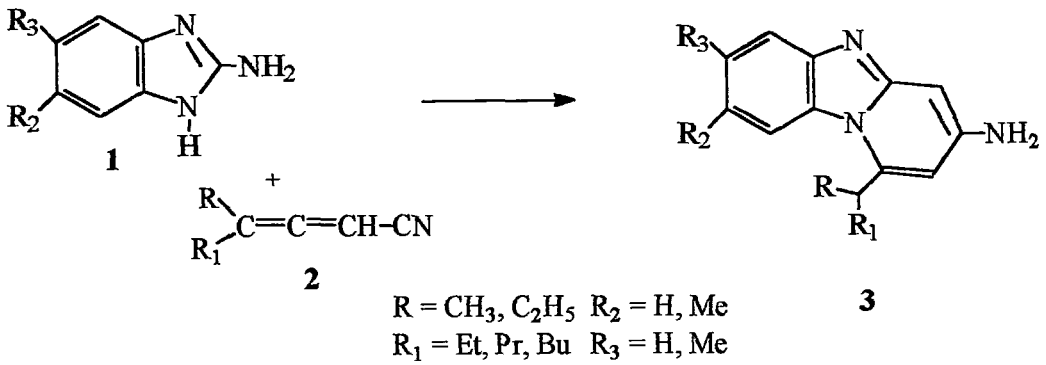
"GENERAL INTRODUCTION ON N-HETEROCYCLES"

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures and for the physiological and industrial significance of heterocyclic compounds.

The importance of N-heterocycles in natural product chemistry and pharmacology constantly drives the search for new methods for their construction. An important approach for the synthesis of these types of compounds involve application of annelation methods, that is construction of cyclic compounds from open chain precursors.

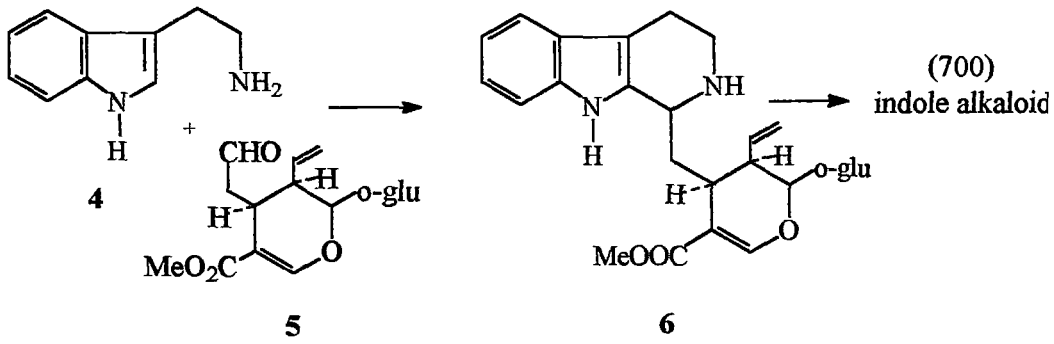
N-heterocycles formed the basic skeleton of many biologically important classes of natural products such as antibiotics, vitamins (vitamin B_{12} ie Cyanocobalamine), marine products, animal toxins, and fungal metabolites. Porphyrin rings form the basic skeleton of life supporting systems such as Hemoglobin, Chlorophyll, Vitamin B_{12} etc. Derivatives of dideoxynucleoside analogs[1, 2] were found to be potent anti-AIDS drugs. Substituted ellipticines were found to have anti-tumour activity.[3] 5-alkyl/aryl-2-(2, 4-dichlorophenyl)-1, 3, 4-oxa/thia-diazol-[3, 2-a]-s-triazine-7-thiones was found to have anti-bacterial activity. The building up of these heterocyclic compounds was found to be from small and simple starting compounds.

The reaction of allenic nitriles **2** with 2-amino benzimidazoles **1** give 2-amino pyrimido [1, 2-a]benzimidazoles **3** (Scheme-1) which are found to possess slight antibiotic and anti-arrythmic properties.[4]



Scheme-1

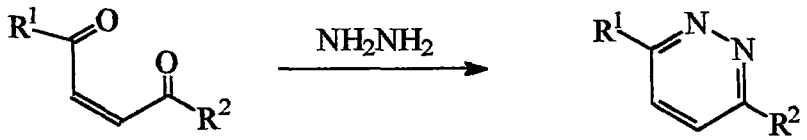
The condensation of tryptamine (or tryptophan) **4** with secologanin **5** gives rise to a nitrogenous glucoside **6** from which a great variety of indole alkaloids (700) are formed in living plants.



Scheme-2

Heterocyclic units such as pyridazines, pyrimidines and triazines and their analogues are of special interest in pharmacology, due to their important biological activities.[5, 6, 7] An important approach for the synthesis of these types of compounds involve cyclisations from open chain precursors. Dicarbonyl compounds were found to be important starting materials for the building up of these N-heterocycles.

Pyridazine derivatives **8** were easily obtained by the treatment of γ-keto acids or esters, 1, 4-diketones **7** etc with hydrazines.[8] (Scheme-3). Saturated and unsaturated 1, 4-diketones have been applied in several pyridazine syntheses. Reactions with hydrazine were usually performed in the presence of mineral acids.



7 R^1 = alkyl, aryl, R^2 = alkyl, aryl, OH, OR^1 **8**

Scheme-3

Another important class of heterocycles is the asymmetric triazines which have been widely reported in the literature and in a number of review papers. Interest in the biochemical properties of 1, 2, 4-triazines has remained constantly high because a number of 3, 5-disubstituted 1, 2, 4-triazines represent aza analogues of pyrimidine nucleo bases while a number of natural antibiotics are pyrimido-[5, 4-e]-1, 2, 4-triazines[9]. Common methods of preparation of 1, 2, 4-triazines also involve dicarbonyl compounds as the main component.

References:

1. D. M. Huryn, C. Sluboski, T. Barbara, Y. T. Steve, J. Luis, W. Manfred, *Tetrahedron Lett.*, **1989**, **30**: *46*, 6259.
2. M. Maillard, A. Faraj, F. Frappier, J. Florent, D. S. Grierson, C. Monneret, *Tetrahedron Lett.*, **1989**, 30: *15*, 1955.
3. A. J. Ratcliffe *et al*, *J. Chem. Soc. Perkin 1*, **1988**, 2933.
4. P. F. Asobo, H. Wahe, J. T. Mbafor, A. E. Nkengfack, Z. T. Fomum, E. F. Sopbue, D. Dopp, *J. Chem. Soc. Perkin 1*, **2001**, 457.
5. (a) M. S. South, T. L. Jakuboski, *Tetrahedron Lett.*, **1995**, *36*, 5703. (b) M. S. South, T. L. Jakuboski, M. D. Westmeyer, D. R. Dukesherer, *ibid.*, **1996**, *37*, 1351. (c) M. S. South, T. L. Jakuboski, M. D. Westmeyer, D. R. Dukesherer, *J. Org. Chem.*, **1996**, *61*, 8921.
6. (a) D. Samuels, D. J. Stouder, *J. Protozool.*, **1962**, *9*, 249. (b) H. E. Latuasan, W. Berends, *Biochem. Biophys. Acta.*, **1961**, *52*, 502. (c) C. Deboer, A. Deitz, J. S. Evans R. Michaels, *Antibiots. Annu.*, **1959-1960**, 220. (d) R. Brunner, G. Machek, *"Die Antibiotika,"* vol III, *"Die Kleine Antibiotika,"* Hans Carl, Nurnberg, Germany, **1970**, 270.
7. (a) H. R. Sullivan, W. M. Miller, D. G. Stark, P. G. Wood, *Xenobiotica*, **1981**, *9*, 548. (b) R. Carboni, R. V. Lindsay, *J. Am. Chem. Soc.*, **1959**, 81, 4342. (c) R. M. A. Rahman, M. Ghareib, *Ind. J. Chem.*, **1987**, 26(B), 496. (d) A. K. Mansour, M. M. Eid, R. A. Hassan, *J. Heterocycl. Chem.*, **1988**, *25*, 279. (e) R. M. A. Rahman, *Ind. J. Chem.*, **1988**, *27*(B), 548.
8. M. Tisler, B. Stanovnik, *Adv. Heterocycl. Chem.*, **1979**, *24*, 363.

CHAPTER-II

"NOVEL ONE POT SYNTHESIS OF 3, 4, 6-TRIARYLPYRIDAZINES"

INTRODUCTION:

Until recently pyridazine has not been found in nature and was therefore not considered a natural product. Pyridazines contain a potential hydrazine unit in the ring and as such not readily obtainable from biochemical transformations involving nitrogen. However this class of compounds has received much more attention from the theoretical stand point and since many derivatives were found to possess potential therapeutic or plant-growth inhibitory effect many new syntheses have been developed. It was believed that microorganisms do not generate hydrazine or the diamide necessary for building up the pyridazine skeleton. However Hassal and co-workers have now isolated from streptomyces jamaicensis antibacterial monomycins,[1] which are cyclohexadepsipeptides and contain structural unit hexahydropyridazine-3-carboxylic acid or its substituted derivatives.[2a, b, c]

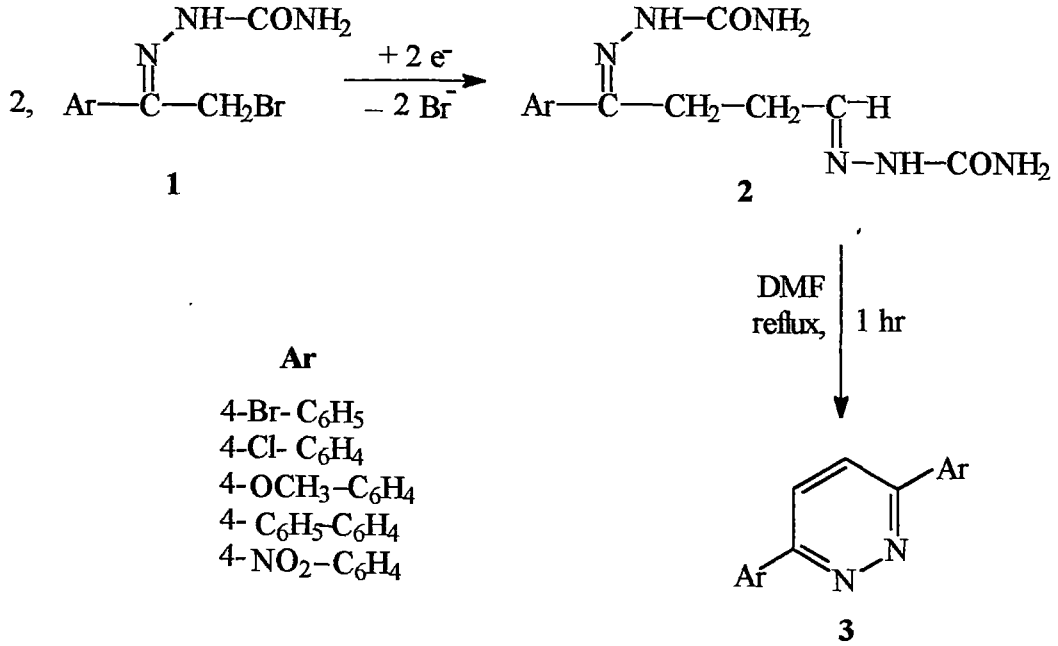
Due to their biological activity, the synthesis of pyridazine products has recently attracted increasing attention.[3] Pyridazines have also found wide applications as drugs[4] and agrochemicals.[5]

Our literature survey reveals that a number of methods have been developed for the synthesis of arylsubstituted pyridazines.[6] While 3, 6-diarylpyridazines can be easily obtained using various methods,[7] however, there are only a few reports available in the literature on the synthesis of triaryl pyridazines.

Aryl substituted pyridazines can be obtain by cyclisation from saturated or unsaturated 1, 4-diketones and hydrazines.[8, 9] A facile method has also been reported starting from simple and easily available materials than unsaturated or saturated 1, 4-diketones, since electrochemical reduction of phenacyl bromides semicarbazones **1** led to the 1, 4-diaryl-1, 4-butanedione disemicarbazones **2** in quantitative yields[10]

which upon refluxing for 1 hour in dimethyl formamide gave 3, 6-diarylpyridazines **3** (scheme-1) in high yields. The conversion of **2** to **3** led first to the corresponding 4, 5-dihydropyridazines which were not particularly stable and were dehydrogenated[8] under reflux conditions into the more stable pyridazines **3**.

The introduction of alkyl or aryl group into the pyridazine ring was not very successful even though some have reported[11] the nucleophilic substitution of the labile group in the ring. Alkylation or arylation of pyridazine was achieved by coupling between halopyridazines and organometals. Cross-coupled products were obtained by treatment of halopyridazines with Grignard reagents in presence of Nickel-Phosphine complexes[12] as catalysts.

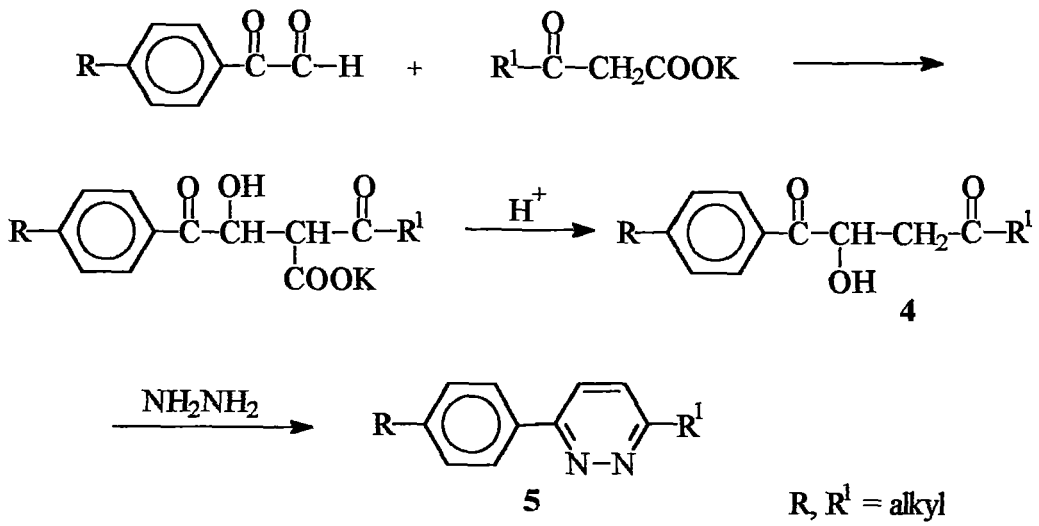


Scheme-1

It has been found that it was difficult to introduce a carbon chain into the pyridazine nucleus due to the electron deficiency of this heteroaromatic system,[13]

therefore C-C bond formation by direct electrophilic aromatic substitution is not a suitable synthetic methodology.

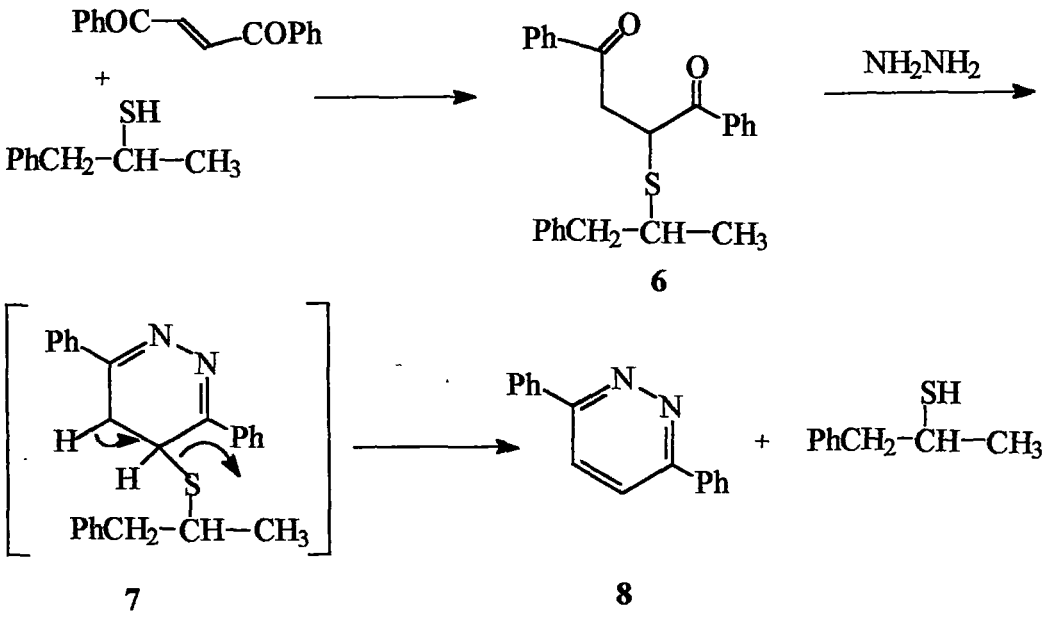
J. Liang[14] modified Levisalles' method[15] and synthesised 3-phenyl-6-methylpyridazine **5** in good yields with and easy purification step. He also claimed that when preparative HPLC was used to purify the final products, it was not necessary to purify most of the intermediates. This synthetic route is shown in scheme-2. The selenium dioxide oxidation reaction was easily conducted but purification of the keto aldehyde **4** was difficult. Vacuum distillation is effective for purification when R = H[16] but becomes increasingly difficult with larger R-groups. When R = hexyl or heptyl distillation often leads to decomposition.



Scheme-2

Ascaridole-initiated reaction of (+)1-phenylpropane-2-thiol with trans-1, 2-dibenzoylethylene gave a crystalline sulphide **6,** melting point 87.5°C, together with an oil probably containing a diastereoisomer.[17] The oil on reaction with hydazine,

formed a sulphur containing material which on purification yielded 3, 6-diphenylpyridazine. It was probable that the sulphide gave a dihydropyridazyl sulphide which upon elemination of the sulphide formed the diphenylpyridazine[18] **8** as shown in scheme-3.

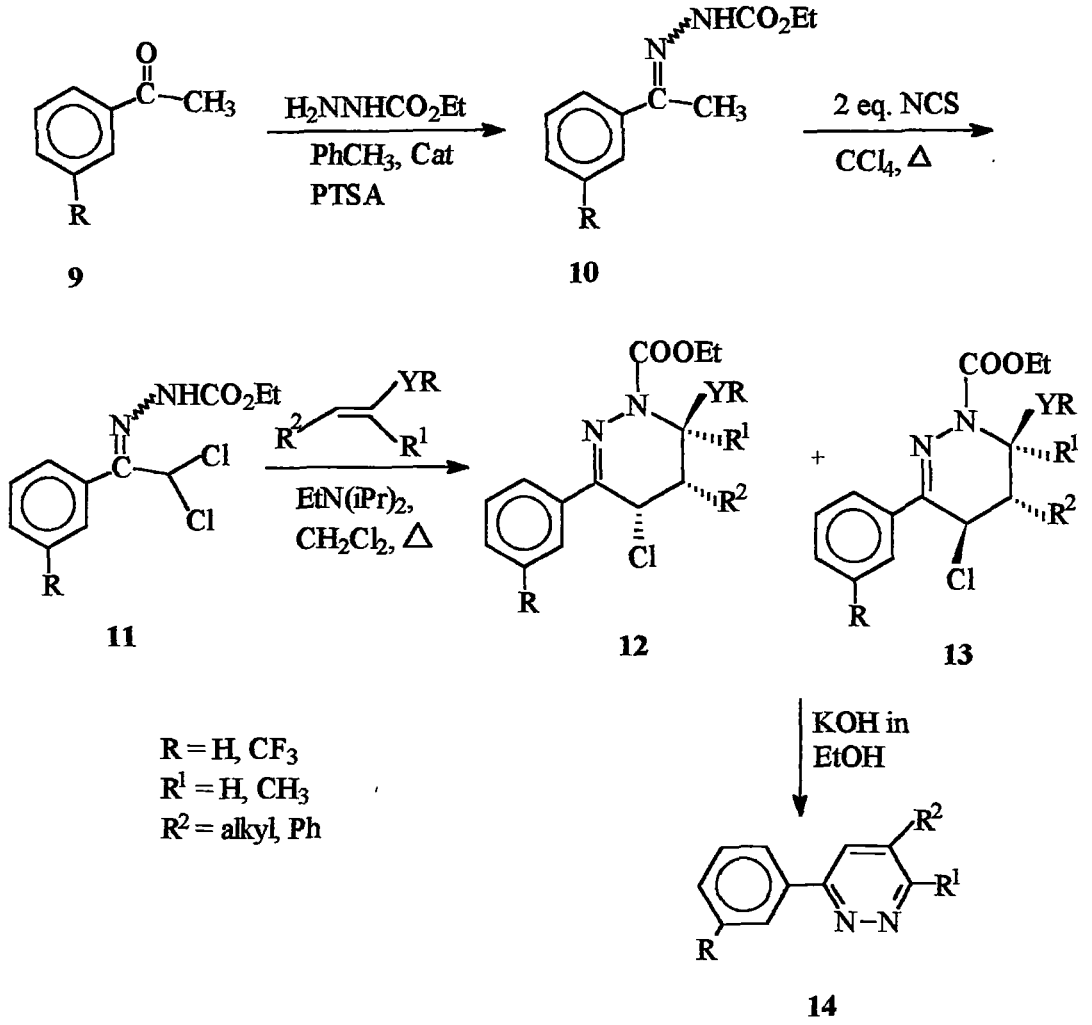


Scheme-3

In the same fashion treatment of 1, 2-dibenzoyl ethane[3] with hydrazine gave dihydropyridazine which upon heating in presence of oxygen get slowly oxidised to 3, 6- diphenylpyridazine.

Chloroazodiene cyclisations are best characterised as inverse electron demand (4+2) hetero Diels-Alder reactions that maintain a high degree of regio- and stereochemical control treatment of the dichlorohydrazones **11** obtain from the reaction of acetophenones **9** with ethyl carbazate followed by 2 equivalent of N-chlorosuccinamide[3b] with Hunig's base in methylene chloride. The 4-chloroazodiene

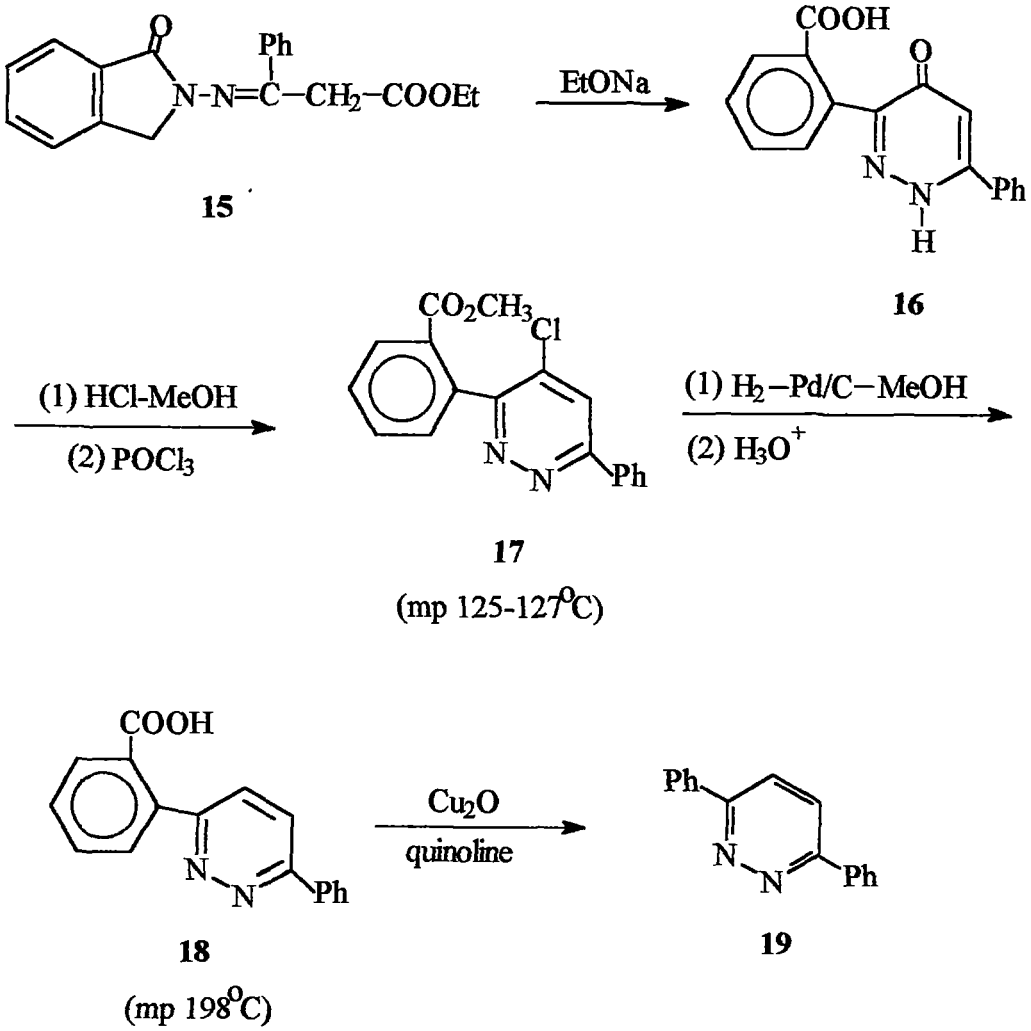
which is generated in-situ in presence of a variety of electron rich olefins reacts to give the tetrahydropyridazine adducts **12** and **13** (Scheme-4).



Scheme-4

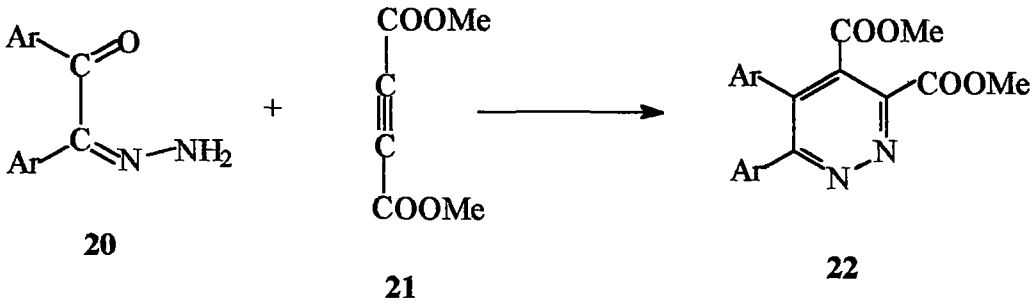
Subsequent aromatisation of the tetrahydropyridazines with a base gives the corresponding pyridazine **14** in high yields. Cyclisation reactions of dichloroazodiene not only occur in the correct oxidation state for aromatisation directly to pyridazines but also allows for the introduction of a chloro group into the molecule.

Base-promoted rearrangement of 2-amino-2, 3-dihydro-1H-isoindol-1-one **15** yields 3-aryl-4 (1H)-pyridazinones **16** as the main product[19] which is converted to 3, 6- diphenylpyridazine **19**.[20] Treatment of **15** with sodium ethoxide in ethanol at 60°C followed by acidification gives **16**. This transformation involves an intramolecular cyclisation of **15** to **16** (Scheme-5). Chlorination of **16** with phosphoryl chloride gave the chloro derivative **17** which upon hydrogenation and acidification followed by decarboxylation gives the 3, 6-diaryl pyridazine **19**.



Scheme-5

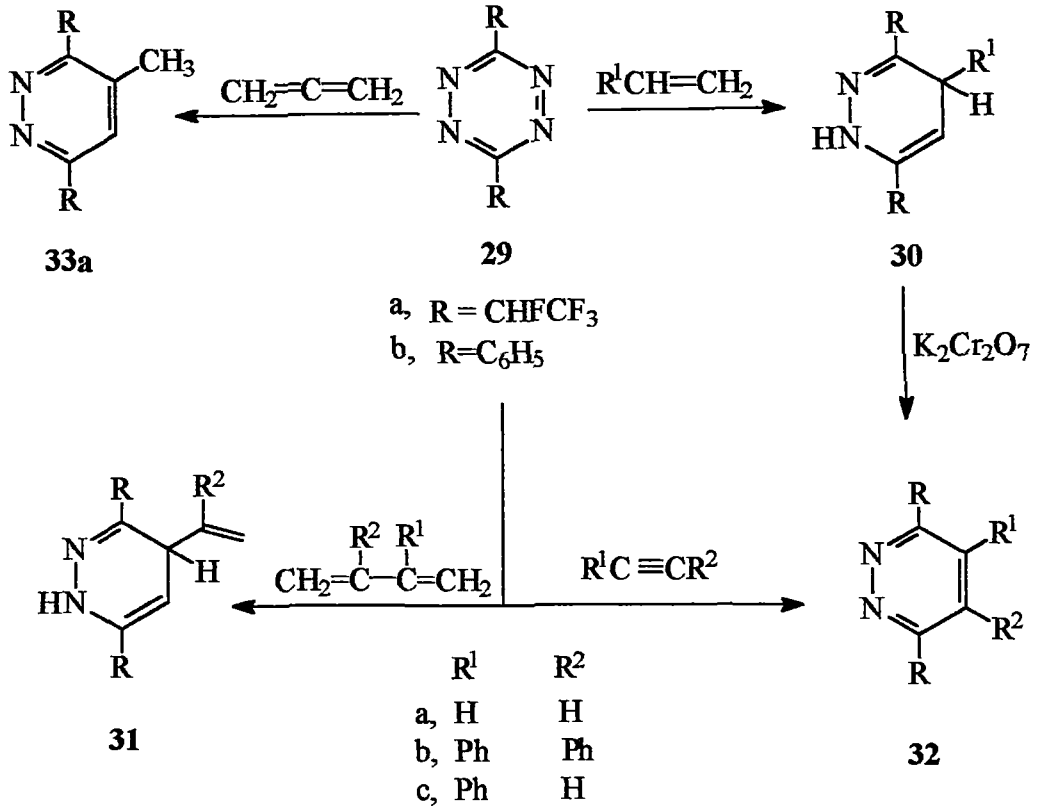
Pyridazines may also be obtained from 1, 2-diketones. The reaction between benzoin and hydrazine gave a complex mixture of various compounds of which among them was 3, 4, 5, 6-tetraphenyl pyridazine obtained in low yield.[21] Benzil monohydrazones and analogs when treated with vinyl triphenylphosphonium bromide give 2, 3-dihydropyridazines in moderate yield.[22] Benzil monohydrazone and related compounds react with dimethylacetylene dicarboxylate to give a mixture of the corresponding ketazine, bisketazine and pyridazine.[23] In absence of solvent pyridazine was the main product. The azine from benzil monohydrazones and ethylacetoacetate or benzoyl acetate is cyclised under basic conditions into the pyridazines[23b] (Scheme-6).



20 **21** **22**

Scheme-6

Our literature survey showed that there are few reports on the synthesis of triaryl substituted pyridazines. Acetophenone in the form of its azine or hydrazone has been a very good precursor for the synthesis of triaryl pyridazine. Acetophenone azine **23a**[24] was converted to its 1, 6-dilithio salt **24** by 2 equivalent of n-butylithium in ether-hexane,[25] The dilithio salt was cyclised with 2, 3-dibromo-2, 3-dimethylbutane to form dihydropyridazine **26** in 40% yield; presumably the



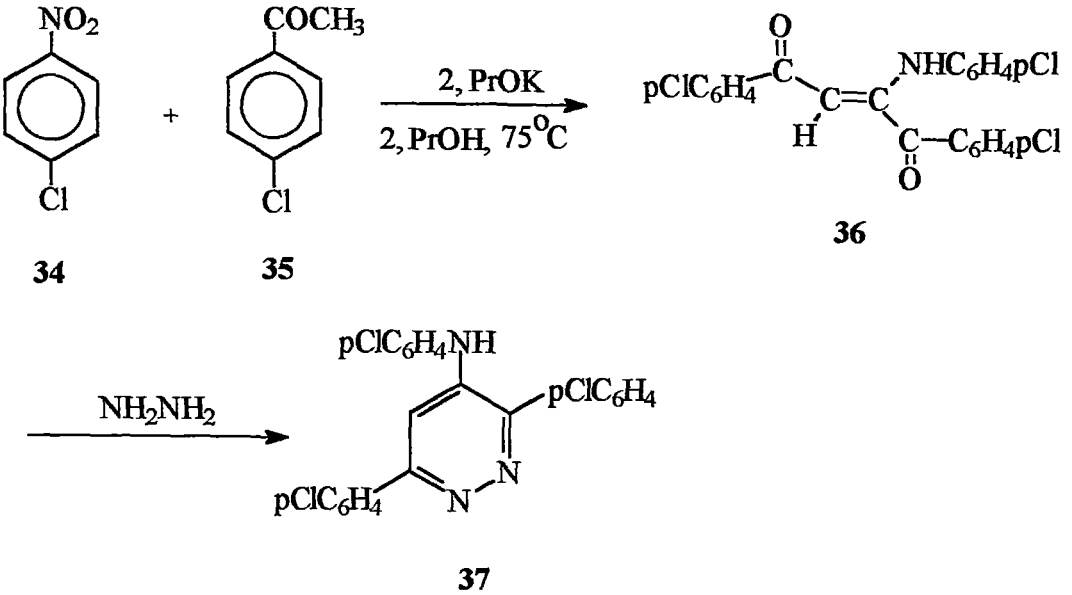
Scheme-8

Smith[28] has reported that the condensation of desylacetophenone with hydrazine gave 3, 4, 6-triphenyl-1, 2-dihydropyridazine as a yellow solid mp 186-188°C which on subsequent oxidation gave the colorless crystals of pyridazine, mp 173-175°C. [29,30] A simple one-step conversion of 3, 6-diphenyl tetrazine **29** to 3, 4, 6- triphenylpyridazine **32c** was achieved by the treatment with aldehydes or ketones in presence of base.[31] The reaction is often immediate and accompanied by the evolution of Nitrogen and the disappearance of the violet-red colour of the tetrazine. It was observed that aldehydes were more reactive than isomeric ketones.

Scorrano and coworkers[32] have developed a simple one pot synthesis of 1, 4-diaryl-2-(arylamino)but-2-ene-1, 4-diones **36** which reacts very easily with

hydrazine as expected.[33] To the refluxed mixture of nitrobenzene (0.5 mol) and acetophenone (0.2 mol) in 2-propanol (100 ml), 100 ml of 0.5 M 2-PrOK in 2-PrOH was added at the rate needed to maintain reflux without external heating. The resulting brown solution was refluxed till reaction was completed. (TLC) The cooled solution was poured into water and carefully acidified with 1 M hydrochloric acid. The brown solid was filtered, washed, and recrystallised. The bright yellow crystals was identified as 1, 4-diaryl-2-(arylamino)but-2-ene-1,4-diones.

Simple reaction of the but-2-ene-1, 4-diones **36** with hydrazine gave 3, 6-diaryl-4-p-chloro anilino pyridazine in 85% isolated yield. (Scheme-9) The fact that compound **37** was obtained starting from a diketobutene having a Z-configuration shows that isomerisation around the double bond occurs before cyclisation which is known to occur in α, β-unsaturated carbonyls.[34]



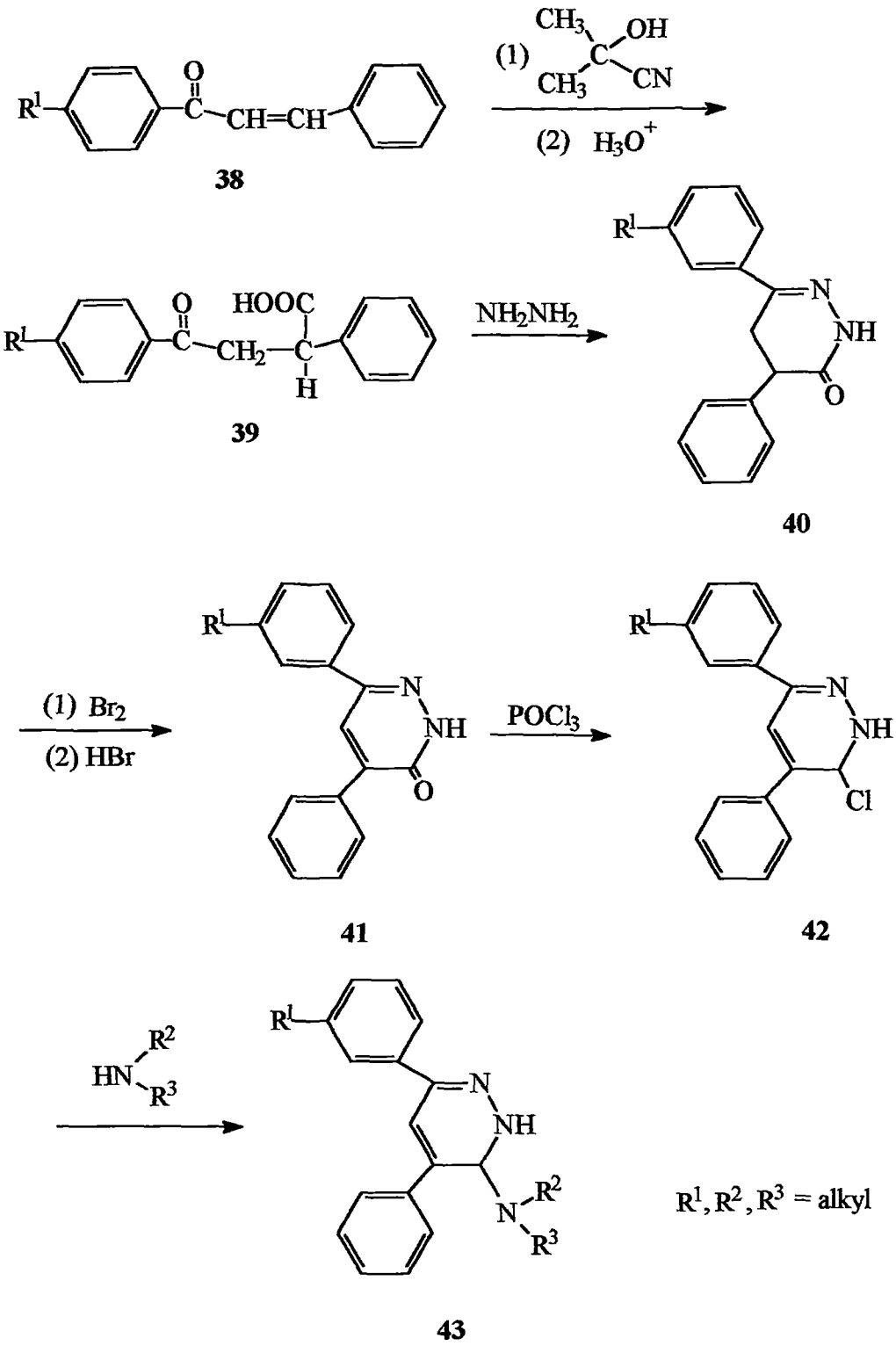
34 **35** **36**

37

Scheme-9

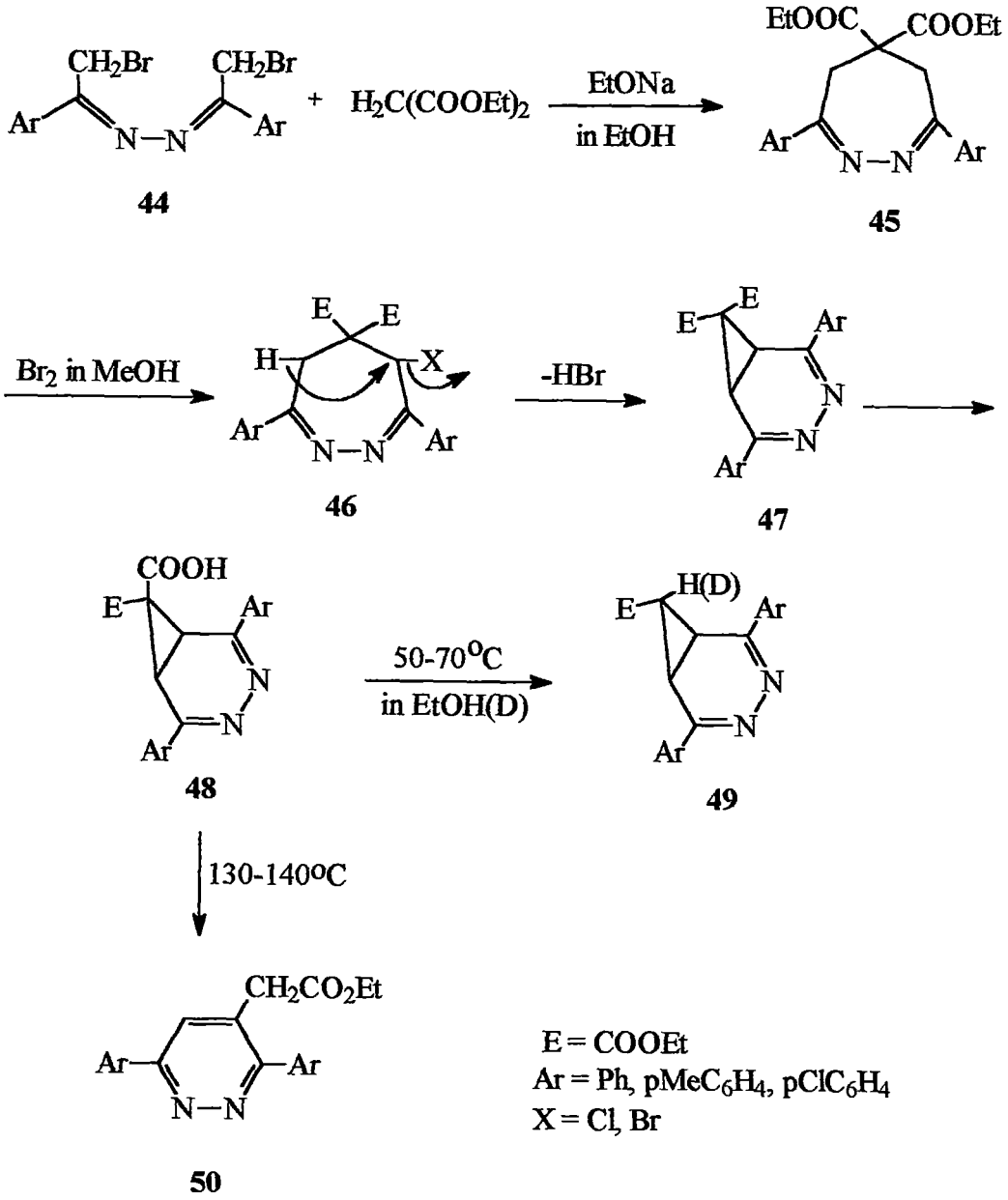
The synthesis of the trisubstituted pyridazines from chalcones has also been possible by the conversion into 1, 4-dicarbonyl system followed by cyclisation process.[35] Addition of hydrogen cyanide to substituted chalcones **38** was performed by an exchange with acetone cyanohydrin to give the γ-keto-nitriles which was hydrolysed to the corresponding 2, 4-diaryl-4-oxo-butanoic acids **39**. Condensation with hydrazine hydrate in refluxing n-butanol smoothly converted **39** to the expected 4, 6-diaryl-4, 5-dihydro-3(2H) pyridazinones **40**. Bromination and dehydrobromination in acetic acid gave 4, 6-diaryl-3-pyridazinones **41** which upon treatment with phosphorus oxychloride gave 3-chloro-4, 6-diaryl pyridazines **42** Reaction of **42** with amines afforded 3-amino-4, 6-diaryl pyridazines **43** (scheme-10).

5, 6-dihydro-1, 2-diazepines were also found to be important starting precursors for the synthesis of trisubstituted pyridazines.[36] Halogenation and dehalogenation resulted in ring contraction to pyridazines **50** which proceeded *via* the isolable[37] intermediate 3, 4-diazanorcaradienes **48** (Scheme-11). However halogenated intermediates have not been isolated. Treatment of 5, 5-bis(ethoxycarbonyl)-5, 6-dihydro-3, 7-diphenyl-4H-1, 2-diazepines **45** obtained from the reaction of α-bromoacetophenone azine **44**[36b] with diethylmalonate; with an equimolar amount of bromine in methanol at room temperature gave 7-bis(ethoxy carbonyl)-2, 5-diphenyl-3, 4-diazanorcaradiene **47**[37] mp 120-121°C in good yield. Hydrolysis of **47** with ethanolic potassium hydroxide solution afforded the half ester **48** which on heating in ethanol or ethanol-d_1 underwent decarboxylation to give 7-ethoxy carbonyl-2, 5-diphenyl-3, 4-diazanorcaradiene **49** or its 7-deuterio derivative **49** respectively.


R1
O
C
CH=CH
38
(1)
CH3
OH
C
CH3
CN
(2) H3O+
HOOC
CH2
H
39
NH2NH2
N
NH
O
40
(1) Br2
(2) HBr
41
POCl3
Cl
42
R2
HN
R3
N
NH
43
R1, R2, R3 = alkyl

Scheme-10

When **48** was heated at 130-140°C without solvent, ring opening occurred which yielded 4-ethoxycarbonylmethyl-3, 6-diphenylpyridazine **50**. Although the monohalide **46** has not been isolated it is clear that the diazanorcaradiene **47** was formed *via* the internal nucleophilic displacement of the monobromide **46** as shown in scheme-11. Dehalogenation was carried out by treating with sodium iodide in boiling methanol or with Zinc-dust in boiling ethanol.



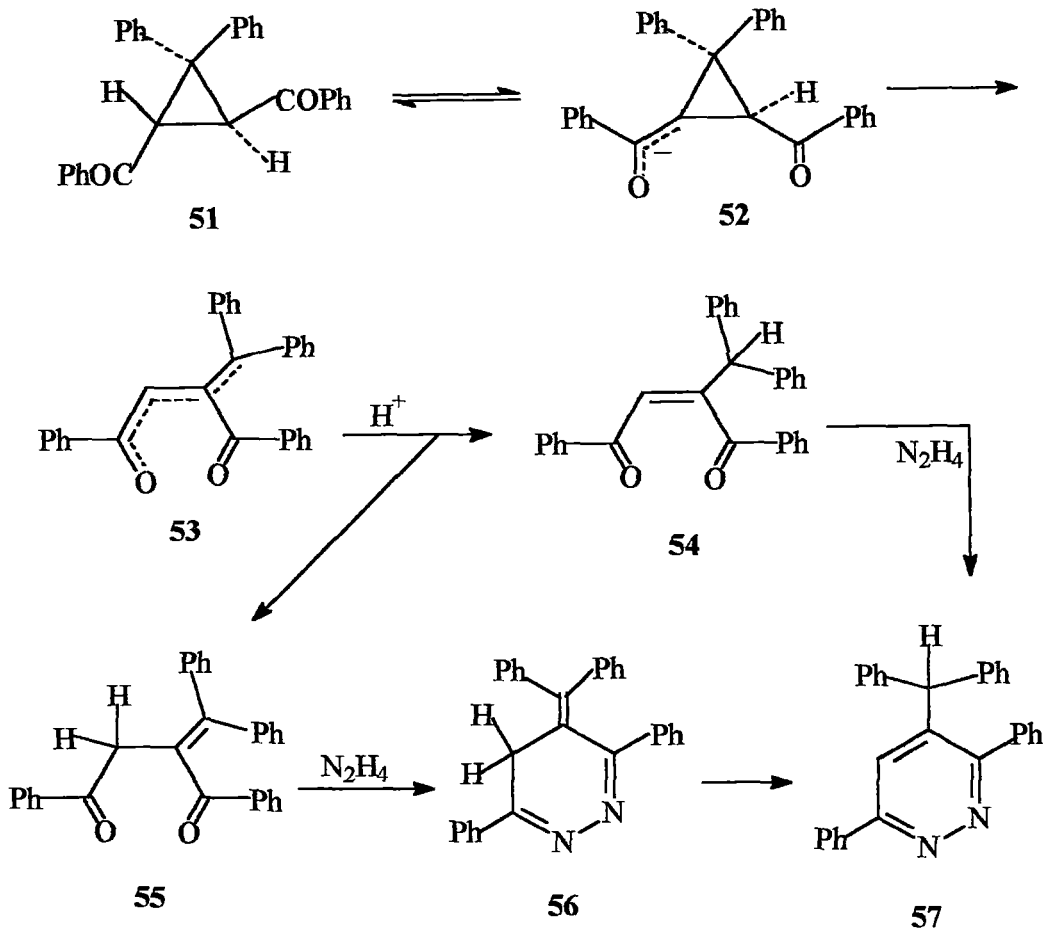
44 **45** **46** **47** **48** **49** **50**

Scheme-11

Base catalysed reaction of trans-1, 2-dibenzoyl-3, 3-diphenylcyclopropane with hydrazine afforded 3, 4, 6-trisubstituted pyridazine.[38] Refluxing a solution of trans-1, 2-dibenzoyl-3, 3-diphenyl cyclopropane[38b] (18.7 mmol), anhydrous 97% hydrazine (56.1 mmol) and sodium hydroxide in absolute ethanol for 72 hrs, followed by evaporation of the solvent gave a solid product which was recrystallised first from chloroform-hexane and then from 95% ethanol.

At room temperature a stirred solution of trans-1, 2- dibenzoyl-3, 3-diphenylcyclopropane **51**, hydrazine and sod hydroxide in ethanol gave no indication of the formation of the desired compound 2, 5, 7, 7-tetraphenyl-3, 4-diazabicyclo(4.1.0)hepta-2, 4-diene as revealed by the absence of the yellow color characteristic of the 2, 5-diphenyl diazanorcaradiene system. On refluxing, the reaction mixture developed an encouraging yellow color that disappeared completely after a total of 72 hrs. The colorless crystal isolated from the reaction mixture was identified as 3, 6-diphenyl-4-benzhydrylpyridazine **57** by its NMR spectrum.

The most straightforward rationalisation for the formation of **57** from **51** (scheme-12) involves the electrocyclic ring opening of the enolate ion **52** to give the oxapentadienly anion **53**. Protonation of **53** should afford either or both enediones **54** and **55** although **55** would be favoured on kinetic and thermodynamic ground. Treatment of either **54** or **55** with hydrazine gave **57**.

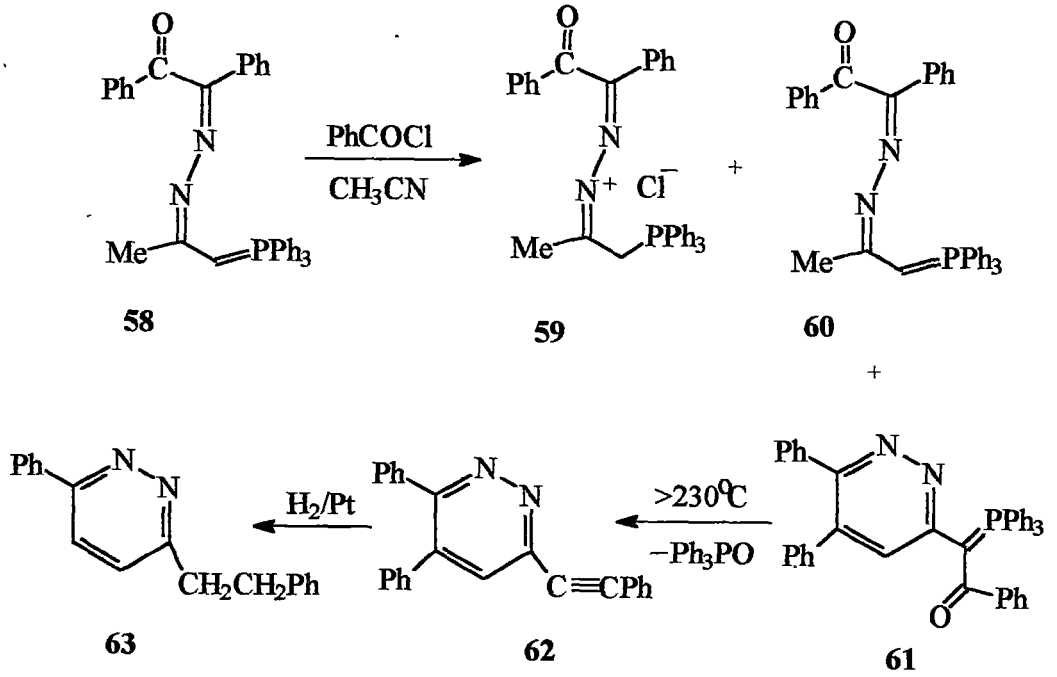


Scheme-12

Even though no separate attempt was made to isolate the diketones **54** or **55** from treatment of **51** with base, the presence of one or the other or both was inferred by analogy to the fluorenyl system[39] and by subsequent trapping with hydrazine to afford **57** either directly in the case of **54** or indirectly via the cyclic azine **56** as in the case of **55**. The transient yellow color observed during the progress of the reaction is consistent with the intermediacy of the enediones or the cyclic azine **56**. The reactivity of trans-1, 2-dibenzoyl-3-phenylcyclopropanes towards hydrazine in basic media was found to be lesser than that of 3, 3-diphenyl derivative **51**. This was explained on the basis of different steric and electronic requirements for base-

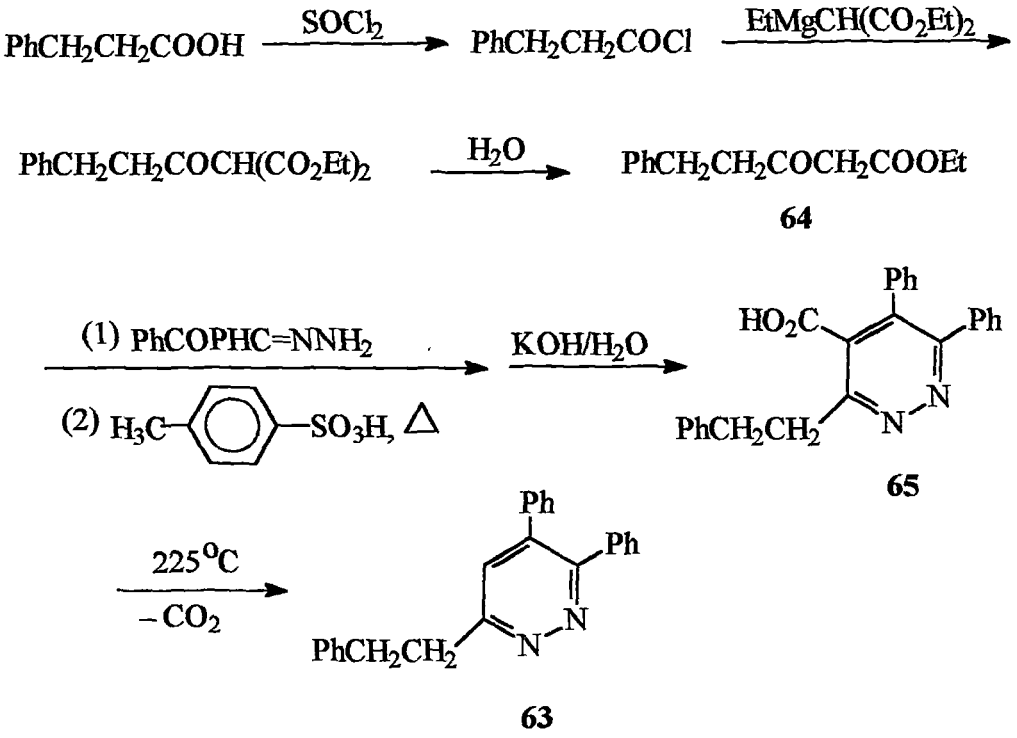
catalysed isomerisation *vs* ring opening. Thus the additional phenyl substituent at C-3 would be expected to greatly enhance the rate of ring opening of 3, 3-diphenyl derivative **51** relative to the 3-phenyl derivative through the extra conjugation provided in the transition state.

Benzoylation of triphenylphosphonium-2-(2-oxo-1, 2-diphenylethylidene) hydrazone) proplide **58** in acetonitrile[40] gave the expected stabilized benzoylated phosphorane **60**[43] (13% yield) and the matching salt **59**[41] (X = Cl; 91% yield) and 50% yield of triphenyl(1-benzoyl-1-(3, 4-diphenyl-6-pyridazinyl)methylene)phosphorane **61** Pyrolysis of compound **61** gave 3, 4-diphenyl-6-phenylethynylpyridazine **62** which upon hydrogenation over platinum oxide gave 3, 4-diphenyl-6-(2-phenylethyl) pyridazine **63** (Scheme-13).



Scheme-13

An authentic sample of **63** was prepared *via* ethyl-3-oxo-5-phenylpentanoate **64** which on reacting with benzil monohydrazone[42] gave 3, 4-diphenyl-6-(2-phenylethyl) pyridazine-5-carboxylic acid **65** which upon heating decarboxylates to give 3, 4-diphenyl-6-(2-phenylethyl) pyridazine **66** (Scheme-14).



Scheme-14

We wish to report here a simple and general procedure for the preparation of triaryl substituted pyridazines that relies on the condensation of aryl methyl ketones with 1, 2 diketones and subsequent cyclisation with hydrazine. A similar cyclisation has been reported by Japp[43] who carried out the reaction in two steps. Earlier it has been reported[44] that the reaction between the two bifunctional types of compounds diketones and hydrazine hydrate yielded polyazines.

Our literature survey showed that unsaturated 1, 4-diketones have been applied in several ways of pyridazine synthesis.[45] The reaction with hydrazine is usually performed in presence of mineral acids; otherwise N-amino pyrroles may be formed. Some saturated 1, 4-diketones are claimed to react with hydrazine to give pyridazines.[46] Levisalles[15] synthesised 3, 6-disubstituted pyridazine *via* the 1, 4-dicarbonyl system obtained from 1, 2-dicarbonyl system and 2-keto ester.

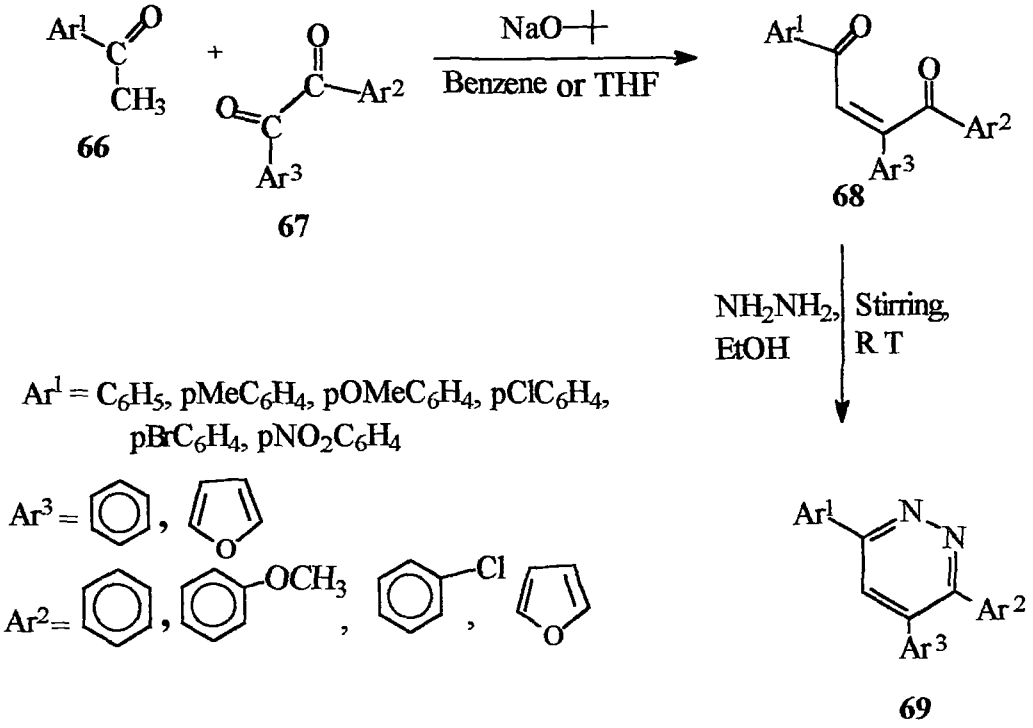
Several pyridazines were prepared unintentionally by the attempted Wolf-kishner reduction of ketoacids. It has been claimed that the ease of pyridazines formation during W-K-Huang Minlon reduction of aromatic 1, 4-ketoacids depends on the nature of the aryl group, the reaction being competitive with the normal reduction. The formation of pyridazinones is suppressed if esters are used instead of acids. In a somewhat lengthy procedure, hydrazones are prepared separated first and the cyclization step is performed separately.

Results and discussions:

From the above brief review it is evident that the 1, 4-diketones are versatile intermediates for many organic transformations and potential precursors for the construction of various N-heterocycles. In the present investigation we have developed a general synthetic method for the one-pot synthesis of pyridazine derivatives *via* the unsaturated 1, 4-diketones.

The one-pot synthesis of the title compound is achieved by the action of hydrazine on the but-2-ene-1, 4-dione system **68**, which is generated in *situ* by the condensation of aryl methyl ketones **66** with 1, 2-diketones **67** in presence of sodium tertiary butoxide (scheme-15). The but-2-ene-1, 4-dione system and its functionalised derivatives are potentially valuable. Their use[47] has however been limited because of their relatively difficult synthesis. The condensation takes place between the methyl group of the aryl methyl ketones with the carbonyl group of the 1, 2-diketones when 1:1 mol of the reactants are stirred at room temperature.

Isolation and purification of one of the reaction intermediate (before the addition of hydrazine) showed the presence of the but-2-ene-1, 4-dione system **68** whose data matches with those reported in literature.[43] The identity of **68a** [R = H, $Ar^1 = Ar^2 = Ph$] has also been checked by ^{13}C NMR analysis which shows a peak at δ 192.6 and 190.3 from tetramethylsilane as an internal standard in $CDCl_3$. The stereochemistry of the double bond is established as E which has a melting point 196.5°C and matches well with the reported one.[43]



Scheme-15

Room temperature stirring of but-2-ene-1, 4-dione system with hydrazine in ethanol (scheme-15) for 3-7 hours gave after work-up crude solid products in good yields (table-1) which were purified by repeated recrystallisation or column chromatography.

Table 1a: Preparation of 3, 4, 6-triarylpyridazines:

Entry	Products	Ar^1	Ar^2	Ar^3	Time/h	Yields (%)	M.Pt (°C)
1	**69a**	C_6H_5	C_6H_5	C_6H_5	3	56	170
2	**69b**	4-MeC_6H_4	C_6H_5	C_6H_5	4	78	110
3	**69c**	4-$OMeC_6H_4$	C_6H_5	C_6H_5	4	61	181
4	**69d**	4-ClC_6H_4	C_6H_5	C_6H_5	5	64	167
5	**69e**	4-BrC_6H_4	C_6H_5	C_6H_5	6	58	135
6	**69f**	4-$NO_2C_6H_4$	C_6H_5	C_6H_5	5	65	152
7	**69g**	C_6H_5	4-$OMeC_6H_4$	C_6H_5	3	60	118
8	**69h**	4-MeC_6H_4	4-$OMeC_6H_4$	C_6H_5	3	61	120
9	**69i**	4-$OMeC_6H_4$	4-$OMeC_6H_4$	C_6H_5	5	72	108
10	**69j**	4-ClC_6H_4	4-$OMeC_6H_4$	C_6H_5	5	57	135
11	**69k**	4-BrC_6H_4	4-$OMeC_6H_4$	C_6H_5	6	61	143
12	**69l**	4-$NO_2C_6H_4$	4-$OMeC_6H_4$	C_6H_5	5	58	162
13	**69m**	C_6H_5	4-ClC_6H_4	C_6H_5	6	59	155
14	**69n**	4-MeC_6H_4	4-ClC_6H_4	C_6H_5	7	63	141
15	**69o**	4-$OMeC_6H_4$	4-ClC_6H_4	C_6H_5	7	75	138
16	**69p**	4-ClC_6H_4	4-ClC_6H_4	C_6H_5	6	61	183
17	**69q**	4-BrC_6H_4	4-ClC_6H_4	C_6H_5	5	59	147
18	**69r**	4-$NO_2C_6H_4$	4-ClC_6H_4	C_6H_5	7	56	156
19	**69s**	Naphthyl	C_6H_5	C_6H_5	8	60	178
20	**69t**	Naphthyl	4-$OMeC_6H_4$	C_6H_5	7	62	161
21	**69u**	Naphthyl	4-ClC_6H_4	C_6H_5	6	58	173

Table 1b: Preparation of 3, 4-difuryl-6-arylpyridazines:

Entry	Products	Ar^1	Ar^2	Ar^3	Time/h	Yields[a] (%)	M.Pt (°C)
1	**69i**	C_6H_5	Furyl	Furyl	6	57	96
2	**69ii**	4-MeC_6H_4	Furyl	Furyl	7	64	120
3	**69iii**	4-$OMeC_6H_4$	Furyl	Furyl	7	70	183
4	**69iv**	4-ClC_6H_4	Furyl	Furyl	6	58	132
5	**69v**	4-BrC_6H_4	Furyl	Furyl	5	65	125
6	**69vi**	4-$NO_2C_6H_4$	Furyl	Furyl	7	57	102
7	**69vii**	Naphthyl	Furyl	Furyl	5	57	164

a. refer to pure products

The products have been characterized as 3, 4, 6-triaryl pyridazines on the basis of analytical data and spectral evidences. The elemental analysis of **69a** i.e $C_{22}H_{16}N_2$ gave the following results: C, 85.71%; H, 5.19%; N, 9.09% which matches very well with the calculated percentage. The compound melts at 171°C and matches well with the reported melting point. Detail spectroscopic and analytical data are given in the experimental section.

The formation of the products occured in two steps. The simple condensation between the aryl methyl ketones and the 1, 2-diketones led to the immediate formation of the but-2-ene-1, 4-dione systems which upon cyclisation with hydrazine gave the products. Previous reports[43] have shown that trans isomers of the but-2-ene-1, 4-dione system donot interact with the hydrazine easily. However in contrast to this it was observed that the cyclisation process is immediate as evidence from the colour change. The fact that the product is obtained from a diketone having the trans configuration shows that isomerisation around the double bond occurs before cyclisation probably under basic catalysis by hydrazine. This kind of isomerisation is known to occur in α, β-unsaturated carbonyls.[34]

Experimental:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 and BOMEM DA-8 FT-IR Spectrophotometer using KBr pellets and the frequencies are expressed in cm^{-1}. ^1H NMR (90 MHz) was recorded on Varian EM-390 spectrometer and high resolution ^1H and ^{13}C NMR (300 MHz) spectra were recorded on a Bruker ACF-300 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, m = multiplet. Mass spectra were obtained on a JEOL D-300 (EI) mass spectrometer. Masses are reported in units of mass upon charge (m/z), the molecular peaks are indicated by (M^+). Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution. Column chromatography was carried out using ACME's silica gel (60-120 mesh).

Chemicals, Reagents and solvents:

Dry benzene was obtained by keeping over Calcium Chloride followed by distillation and again storing over sodium wire. The commercial samples of aryl methyl ketones (substituted acetophenones), benzaldehydes and hydrazine hydrate, were purified by simple distillation. Substituted benzils and furil were prepared

using known methods.[50] Sodium tertiary butoxide was freshly prepared for each reaction.

General procedure for the preparation of 3, 4, 6-triaryl pyridazines 69:

To a stirring solution of sodium tertiary butoxide (20 mmol) in 30 ml of dry benzene or tetrahydrofuran at room temperature, aryl methyl ketone (10 ml) was added followed by the addition of a solution of 1, 2-diketones (10 mmol) in one lot. The jelly mass was formed immediately due to the formation of the but-2-ene-1, 4-dione system. The solid mass is dissolved by the addition of ethanol (10 ml) and then 1 ml of hydrazine is added. The reaction mixture is allowed to stir for three to eight hours so as to complete the reaction (monitored by TLC). The reaction mixture was then carefully poured into ice-cold water and extracted twice with benzene. The organic layer was separated and dried over anhydrous sodium sulphate. Removal of the solvent uder reduced pressure afforded a solid product that was further purified by fractional recrystallisation or column chromatography (over silica gel using hexane-ethyl acetate as the eluent).

3, 4, 6-triphenylpyridazine 69a:

Transparent white crystals; mp 170°C; Yield 56%; *^{1}H NMR*: δ 7.23-7.51 (m, 11H), 7.78 (s, 1H), 8.14-8.17 (m, 4H); *^{13}C NMR*: δ 127.1, 128.0, 128.6, 128.9, 129.0, 129.9, 135.9, 136.6, 137.0, 139.3, 157.6, 158.1; *IR* (KBr): ν_{max} 3019, 1614, 1521, 1490; *MS* (EI) m/z 308 (M^+), 231, 206, 154, 103, 102, 77; *Anal. Calcd for* $C_{22}H_{16}N_2$: C, 85.71; H, 5.19; N, 9.09; *Found*: C, 85.60; H, 5.30; N, 9.20.

3, 4-diphenyl-6-toloylpyridazine 69b:

Pale yellow crystals; mp 110°C; Yield 78%; *^{1}H NMR*: δ 2.42 (s, 3H), 7.25-7.49 (m, 12H), 7.80 (s, 1H), 8.07-8.09 (m, 2H); *^{13}C NMR*: δ 157.8, 157.3, 140.2, 139.3, 137.1, 136.7, 133.1, 129.9, 129.7, 129.0, 128.6, 128.4, 128.0, 126.6, 124.4, 21.4; *IR* (KBr): ν_{max} 3023, 2915, 1655, 1497; *MS* (EI) m/z 322 (M^+), 264, 249, 178, 132, 91, 77, 44; *Anal. Calcd. for* $C_{23}H_{18}N_2$: C, 85.71; H, 5.59; N, 8.69; *Found*: C, 85.75; H, 5.65; N, 8.74.

6-anisyl-3, 4-diphenylpyridazine 69c:

Pale yellow crystals, mp 181°C; Yield 61%; *^{1}H NMR*: δ 3.88 (s, 3H), 7.17-7.21 (m, 2H), 7.75 (s, 1H), 7.24-7.49 (m, 10H), 8.12-8.15 (m, 2H); *^{13}C NMR*: δ 55.3, 114.3, 124.0, 127.6, 128.0, 128.3, 128.4, 128.5, 128.7, 129.0, 129.9, 136.7, 137.2, 139.3, 157.1, 157.5, 161.2; *IR* (KBr): ν_{max} 3066, 2961, 1615, 1481, 1400, 1043; MS (EI) m/z 338 (M^+) 282, 178, 135, 91, 78, 51, 44; *Anal. Calcd. for* $C_{23}H_{18}N_2O$: C, 81.65; H, 5.32; N, 8.28; *Found*: C, 81.69; H, 5.30; N, 8.36.

3, 4-diphenyl-6-(p-chlorophenyl)pyridazine 69d:

Yellowish white crystals; mp 167°C; Yield 64%; *^{1}H NMR*: δ 7.31-7.50 (m, 12H); 7.80 (s, 1H), 8.14-8.18 (m, 2H); *^{13}C NMR*: δ 124.5; 128.1, 128.2, 128.7, 129.0, 129.2, 129.9, 134.5, 136.3, 136.5, 136.9, 139.5, 156.5, 158.3; *IR* (KBr): ν_{max} 3020, 1608, 1528, 1477; *MS* (EI) m/z 342 (M^+), 307, 231, 194, 188, 103, 76; *Anal. Calcd. For* $C_{22}H_{15}N_2Cl$: C, 77.08; H, 4.38; N, 8.17; *Found*: C, 77.15; H, 4.41; N, 8.13.

3, 4-diphenyl-6-(p-bromophenyl)pyridazine 69e:

Yellowish white crystalline solids; mp 135°C; Yield 58%; *^{1}H NMR*: δ 7.21-7.64 (m, 12H), 7.79 (s, 1H), 8.00-8.06 (m, 2H); *^{13}C NMR*: δ 126.3, 127.7, 128.4, 128.7,

128.9, 129.9, 130.1, 131.4, 132.1, 133.7, 134.9, 136.4, 136.8, 138.1, 156.6, 158.3; *IR* (KBr): ν_{max} 3045, 1649, 1494, 1437; *MS* (EI) m/z 387 (M^+), 310, 233, 182, 154, 103, 80, 77; *Anal. Calcd. For* $C_{22}H_{25}N_2Br$: C, 68.21; H, 3.87; N, 7.23; *Found*: C, 68.30; H, 3.84; N, 7.25.

3, 4-diphenyl-6-(p-nitrophenyl)pyridazine 69f:

Pale yellow crystalline solid; mp 152°C; Yield 65%; ^1H *NMR*: δ 7.29-7.52 (m, 10H), 7.93 (s, 1H), 8.21-8.39 (m, 4H); ^{13}C *NMR*: δ 124.2, 125.3, 127.9, 128.2, 128.9, 129.0, 129.4 130.0, 136.2, 136.6, 139.7, 142.0, 148.8, 155.5, 159.1; *IR* (KBr): ν_{max} 3067, 1602, 1522, 1446, 857, 701; *MS* (EI) m/z 353 (M^+), 307, 276, 231, 154, 122, 103, 77, 46; *Anal. Calcd. For* $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.24; N, 11.89; *Found* C, 74.50; H, 4.33; N, 11.71.

3-anisyl-4, 6-diphenylpyridazine 69g:

Yellow crystalline solid; mp 118°C; Yield 60%; ^1H *NMR*: δ 3.96 (s, 3H), 7.09-7.60 (m, 4H), 7.65-7.72 (m, 11H), ^{13}C *NMR*: δ 55.9 112.3, 114.1, 126.6, 127.0, 128.2,128.9, 129.1, 129.7, 130.0, 130.9, 131.1, 132.8, 135.6, 137.0, 144.0, 154.3; *IR* (KBr): ν_{max} 3076, 2961, 1641, 1483, 1033; *MS* (EI) m/z 338 (M^+), 282, 178, 135, 78, 51, 44; *Anal. Calcd. For* $C_{23}H_{18}N_2O$: C, 81.65; H, 5.32; N, 8.28; *Found*: C, 81.60; H, 5.37; N, 8.25.

3-anisyl-4-phenyl-6-toloylpyridazine 69h:

Yellowish white solid; mp 120°C; Yield 61%; ^1H *NMR*: δ 2.38 (s, 3H), 3.97 (s, 3H), 7.12-7.59 (m, 13H), 7.69(s, 1H); ^{13}C *NMR*: δ 21.3, 56.7, 112.6, 114.4, 126.6, 127.8, 128.3, 128.8,128.9, 129.0, 129.2, 129.5, 130.2, 131.8, 135.5, 136.3, 144.9, 155.2, 159.0, 160.4; *IR* (KBr): ν_{max} 3012, 2976, 1634, 1487, 1036; *MS* (EI) m/z 352 (M^+),

337, 321, 275, 245, 184, 117, 102, 77; *Anal. Calcd. For* $C_{24}H_{20}N_2O$: C, 81.81; H, 5.68; N, 7.95; *Found:* C, 81.90; H, 5.62; N, 7.97.

3, 6-dianisyl-4-phenylpyridazine 69i:

Pale yellow solid; mp 108°C; Yield 72%; *^{1}H NMR*: δ 3.85 (s, 3H), 3.95 (s, 3H), 6.86-6.95 (m, 5H), 7.26-7.60 (m, 4H), 7.80 (s, 1H), 7.86-7.95 (m, 4H); *^{13}C NMR*: δ 55.3, 55.7, 113.6, 126.8, 128.1, 128.3, 130.6, 132.1, 143.5, 145.6, 147.6, 157.8, 159.6, 160.8; *IR* (KBr): ν_{max} 3010, 2968, 1616, 1525, 1491, 1023; *MS* (EI) m/z 368 (M^+), 337, 306, 261, 239, 162, 76; *Anal. Calcd. for* $C_{24}H_{20}N_2O_2$: C, 78.26; H, 5.43; N, 7.60; *Found*: C, 78.26; H, 5.46; N, 7.65.

3-anisyl-6-(p-chlorophenyl)-4-phenylpyridazine 69j:

Pale yellow solid; mp 135°C; Yield 57%; *^{1}H NMR*: δ 3.99 (s, 3H); 7.12-7.36 (m, 5H), 7.84 (s, 1H), 7.46 -7.55 (m, 4H), 8.20-8.66 (m, 4H), *^{13}C NMR*: δ 56.8, 124.3, 126.6, 128.0, 128.4, 128.6, 129.0, 129.6, 129.9, 132.2, 136.7, 137.2, 139.3, 141.2, 155.1, 157.2, 158.6, *IR* (KBr): ν_{max} 3090, 1631, 1489, 1075, 1054; MS (EI) m/z 372 (M^+), 337, 306, 295, 261, 154, 134, 76; *Anal. Calcd. For* $C_{23}H_{17}N_2OCl$: C, 74.09; H, 4.56; N, 7.51; *Found*: C, 74.12; H, 4.60; N, 7.48.

3-anisyl-6-(p-bromophenyl)-4-phenylpyridazine 69k:

Pale brown solid; mp 143°C; Yield 61%; *^{1}H NMR*: δ 3.98 (s, 3H); 7.30-7.56 (m, 4H), 7.75 (s, 1H), 8.91-7.08 (m, 9H), *^{13}C NMR*: δ 55.7, 126.0, 126.5, 127.3, 128.1, 128.7, 129.1, 131.7, 132.6, 133.0, 134.9,136.4, 138.1, 140.3, 143.3, 157.3, 158.7; *IR* (KBr): ν_{max} 3088, 2977, 1639, 1496, 1038; *MS* (EI) m/z 417 (M^+), 386, 340, 310, 261, 184, 107, 77; *Anal. Calcd. For* $C_{23}H_{17}N_2BrO$: C, 66.18; H, 4.07; N, 6.71; *Found*: C, 68.28; H, 4.18; N, 6.60.

3-anisyl-6-(p-nitrophenyl)-4-phenylpyridazine 69l:

Yellowish brown solid: mp 162°C; Yield 58%; *^{1}H NMR*: δ 3.95 (s, 3H), 7.33-7.79 (m, 10H), 8.22-8.44 (m, 4H); *^{13}C NMR*: δ 55.8, 127.3, 129.2,129.9, 131.0, 133.1, 136.0, 136.3, 137.6, 139.9, 141.0, 143.0, 147.0, 149.1, 155.2, 158.3, 159.4, *IR* (KBr): ν_{max} 3091, 2966, 1637, 1489, 1038, 858; *MS* (EI) m/z 383 (M^+), 352, 337, 306, 276, 199, 148, 122, 77; *Anal. Calcd. For* $C_{23}H_{17}N_3O_3$: C, 72.06; H, 4.43; N, 10.96; *Found*: C, 72.00; H, 4.47; N, 10.95.

4, 6-diphenyl-3-(p-chlorophenyl)pyridazine 69m:

Pale brown crystals; mp 155°C; Yield 59%; *^{1}H NMR*: δ 7.34-7.70 (m, 10H), 7.80 (s, 1H), 7.84-8.15 (m, 4H); *^{13}C NMR*: δ 125.0, 127.4, 128.2, 128.7, 129.0, 129.4, 129.9, 131.3, 134.3, 136.2, 136.5, 137.0, 139.8, 141.3, 157.4, 158.1, 160.5; *IR* (KBr): ν_{max} 3035, 1617, 1530, 1461; *MS* (EI) m/z 342 (M^+), 265, 188, 111, 77(100); *Anal. Calcd. For* $C_{22}H_{15}N_2Cl$: C, 77.08; H, 4.37; N, 8.17; *Found*: C, 77.30; H, 4.27; N, 8.01.

3-(p-chlorophenyl)-4-phenyl-6-tolylpyridazine 69n:

Pale yellow crystals; mp 141°C; Yield 63%; *^{1}H NMR*: δ 2.40 (s, 3H), 7.20-7.68 (m, 9H), 7.78 (s, 1H), 7.81-8.10 (m, 4H), *^{13}C NMR*: δ 21.4, 126.1, 128.0, 128.4, 128.6, 129.0, 129.7, 130.4, 132.1, 143.8, 136.5, 137.1, 139.4, 140.3, 142.6, 156.8, 157.7; *IR* (KBr): ν_{max} 3030, 2920, 1637, 1471; *MS* (EI) m/z 356 (M^+), 279, 168, 137, 117, 91; *Anal. Calcd. For* $C_{23}H_{17}N_2Cl$: C, 77.41; H, 4.76; N, 7.85; *Found*: C, 77.57; H, 4.61; N, 7.70.

6-anisyl-3-(p-chlorophenyl)-4-phenylpyridazine 69o:

Pale yellow solid; mp 138°C; Yield 75%; *^{1}H NMR*: δ 3.85 (s, 3H). 7.58 (m, 9H), 7.25-7.55 (m, 5H); *^{13}C NMR*: δ 54.9, 125.7, 127.8, 126.0, 128.4, 128.9, 129.8, 130.0, 131.3, 133.7, 136.0, 137.6, 139.3, 140.7, 141.3, 157.1, 158.0; *IR* (KBr): ν_{max} 3064, 1648, 1471, 1038; *MS* (EI) m/z 372 (M^+), 295, 184, 137, 107, 77; *Anal. Calcd. For* $C_{23}H_{17}N_2ClO$: C, 74.09; H, 4.56; N, 7.51; *Found*: C, 74.25; H, 4.41; N, 7.76.

3, 6-bis(p-chlorophenyl)-4-phenylpyridazine 69p:

Brown solid; mp 183°C; Yield 61%; *^{1}H NMR*: δ 7.45-7.60 (m, 5H), 7.70-8.47 (m, 9H); *^{13}C NMR*: δ 127.6, 128.0, 128.5, 129.0, 130.8, 131.7, 133.8, 135.7, 136.8, 137.4, 139.6, 142.6, 144.8, 157.4, 158.9, 159.6; *IR* (KBr): ν_{max} 3080, 1629, 1476. *MS* (EI) m/z: 377 (M^+), 265, 154, 137, 77; *Anal. Calcd. For* $C_{22}H_{14}N_2Cl_2$: C, 70.02; H, 3.71; N, 7.42; *Found*: C, 70.34; H, 3.60; N, 7.33.

6-(p-bromophenyl)-3-(p-chlorophenyl)-4-phenylpyridazine 69q:

Yellow solid; mp 147°C; Yield 59%; *^{1}H NMR*: δ 7.30-7.60 (m, 5H), 7.67-8.31 (m, 9H); *^{13}C NMR*: δ 126.1, 128.0, 128.8, 129.3, 130.8, 131.7, 132.8, 135.7, 136.4, 139.6, 140.8, 142.1, 144.7, 145.3, 157.4, 158.8; *IR* (KBr): ν_{max} 3075, 1616, 1474; *Mass* (EI) m/z 420 (M^+), 309, 265, 181, 155; *Anal. Calcd. For* $C_{22}H_{14}N_2ClBr$: C, 62.63; H, 3.32; N, 6.65; *Found*: C, 62.62; H, 3.44; N, 6.84.

3-(p-chlorophenyl)- 6-(p-nitrophenyl)-4-phenylpyridazine 69r:

Dark brown solid; mp 156°C; Yield 56%; *^{1}H NMR*: δ 7.35-7.68 (m, 5H), 7.8-8.5 (m, 9H); *^{13}C NMR*: δ 127.9, 128.6, 128.8, 129.4, 130.9, 131.8, 132.7, 133.4, 136.4, 137.1, 141.3, 143.3, 145.7, 146.1, 158.4, 159.2; *IR* (KBr): ν_{max} 3027, 1618, 1587,

1496; MS (EI) m/z 387 (M^+), 341, 276, 265, 148, 137; *Anal. Calcd. For* $C_{22}H_{14}N_3ClO_2$: C, 68.12; H, 3.61; N, 10.83; *Found*: C, 67.98; H, 3.50; N, 10.94.

3, 4-diphenyl-6-naphthylpyridazine 69s:

Yellowish white solid; mp 178°C; Yield 60%; *^1H NMR*: δ 7.20-7.32 (m, 7H), 7.45-7.50 (m, 5H), 7.72 (s, 1H), 7.80-8.33 (m, 5H); *^{13}C NMR*: δ 124.1, 124.8, 126.5, 126.7, 127.0, 127.6, 128.0, 128.2, 128.6, 128.7, 129.0, 129.9, 133.2, 134.0, 136.6, 137.0, 139.3, 157.4, 158.8; *IR* (KBr): ν_{max} 3036, 1622, 1488, 1447; *MS* (EI) m/z 358(M^+), 231, 281, 204, 183, 103, 77; *Anal. Calcd. For* $C_{26}H_{18}N_2$: C, 87.15; H, 5.02; N, 7.82; *Found*: C, 87.07; H, 5.08; N, 7.71.

3-anisyl-6-naphthyl-4-phenylpyridazine 69t:

Yellowish solid; mp 161°C; Yield 62%; *^1H NMR*: δ 3.96 (s, 3H), 7.22-7.57 (m, 12H), 7.71 (s, 1H), 7.90-7.94 (m, 4H); *^{13}C NMR*: δ 55.1; 123.1, 124.8, 126.1, 126.4, 127.0, 127.8, 128.0, 128.2, 128.7, 129.2, 130.2, 131.4, 133.9, 134.2, 136.3, 137.4, 138.3, 156.1, 157.5, 158.0; *IR* (KBr): ν_{max} 3013, 2937, 1585, 1464, 1427, 1062; *MS* (EI) m/z 388 (M^+), 357, 311, 261, 203, 133, 108; *Anal. Calcd. For* $C_{27}H_{20}N_20$: C, 83.50; H, 5.15; N, 7.21; *Found*: C, 83.40; H, 5.21; N, 7.25.

3-(p-chlorophenyl)-4-phenyl-6-napthylpyridazine 69u:

Pale brown solid; mp 173°C; Yield 58%; *^1H NMR*: δ 7.30-7.61 (m, 12H), 7.80 (s, 1H), 7.85-8.30 (m, 4H); *^{13}C NMR*: δ 124.8, 125.3, 126.0, 127.6, 128.0, 128.3, 128.7, 129.4, 129.9, 130.3, 131.4, 132.1, 135.8, 136.5, 137.9, 139.1, 140.0, 141.3, 157.8, 158.7, *IR* (KBr): ν_{max} 3067, 1602, 1498, 1451; *MS* (EI) m/z: 368 (M^+), 257, 241, 153, 127, 111; *Anal. Calcd. For* $C_{24}H_{17}N_2Cl$: C, 78.15; H, 4.61; N, 7.59; *Found*: C, 79.03; H, 4.48; N, 7.66.

3, 4-difuryl-6-(p-chlorophenyl)pyridazine 69iv:

Light brown crystals; mp 132C°; Yield 58%; *^{1}H NMR*: δ 6.28-6.29 (d, 1H); 6.50-6.51 (t, 1H), 6.61-6.63 (d, 1H), 7.02 (s, 1H), 7.48-7.60 (m, 4H), 8.09-8.13 (m, 3H); *^{13}C NMR*: δ 157.6, 156.6, 147.5, 146.7, 144.7, 143.6, 136.5, 134.2, 129.3, 128.3, 128.2, 119.8,113.6, 112.6, 112.4, 112.5; *IR* (KBr): ν_{max} 3091, 1662, 1494, 1410, 1091. *MS* (EI) m/z 322´ (M^+), 287, 255, 211, 188, 144, 111, 93, 77, 67; *Anal. Calcd.* For $C_{18}H_{11}N_2O_2Cl$: C, 66.97; H, 3.41; N, 8.68; Found: C, 66.93; H, 3.45; N, 8.74.

3, 4-difuryl-4-(p-bromophenyl)pyridazine 69v:

Yellow brown crystals; mp 125°C; Yield 65%; *^{1}H NMR*: δ 6.27-6.28 (d, 1H), 6.50-6.52 (t, 1H), 6.62-6.64 (d, 1H), 7.03 (s, 1H), 7.49-7.61 (m, 4H), 8.11-8.14 (m, 3H); *^{13}C NMR*: δ 112.2. 112.5, 113.4, 119.6, 128.0, 128.3, 129.4, 134.3, 136.4, 143.5, 144.6, 147.8, 150.2, 151.5, 156.6,157.8; *IR* (KBr): ν_{max} 3065, 1648, 1477, 1064; *MS* (EI) m/z 367 (M^+), 300, 287, 233, 211, 182, 156, 144, 93, 77, 67; *Anal. Calcd. For* $C_{18}H_{11}N_2O_2Br$: C, 58.85; H, 2.99; N, 7.62; *Found*: C, 58.80; H, 2.96; N, 7.65.

3, 4-difuryl-6-(p-nitrophenyl)pyridazine 69vi:

Dark brown crystals; mp 102°C; Yield 57%; *^{1}H NMR*: δ 8.22-8.38 (m, 3H), 7.60-7.65 (m, 4H), 7.10 (s, 1H), 6.65-6.66 (d, 1H), 6.54-6.55 (t, 1H), 6.36-6.37 (d, 1H). *^{13}C NMR*: δ 112.2, 112.7, 112.9, 113.9, 124.2, 120.5, 127.9, 128.3, 141.8, 143.9, 144.9, 147.2, 148.8, 149.9, 158.0, 158.8, *IR* (KBr): ν_{max} 3041, 1594, 1490, 1053; *MS* (EI) m/z 333(M^+), 287, 266, 211, 199, 179, 148, 122, 93; *Anal. Calcd. For* $C_{18}H_{11}N_3O_4$: C, 64.86; H, 3.30; N, 12.61; *Found* C, 64.80; H, 3.35, N, 12.73.

3, 4-difuryl-6-naphthylpyridazine 69vii.

Brown solid; mp 164°C; Yield 57%; *^{1}H NMR*: δ 6.27-6.28 (d, 1H), 6.50-6.52 (t, 1H), 6.62-6.64 (d, 1H), 7.03 (s, 1H), 7.52-7.78 (m, 7H), 8.04-8.11 (m, 3H), ^{13}C NMR ($CDCl_3$): δ 112.1, 112.2, 112.5, 113.4, 119.6, 124.1, 124.8, 128.0, 128.5, 131.5, 132.2, 134.8, 138.1, 143.6, 144.6, 146.8, 147.5, 150.2, 156.7, 157.0; *IR* (KBr): ν_{max} 3033, 1643, 1471, 1064; *MS* (EI) m/z 340 (M^+), 273, 213, 206, 153, 146, 127, 92, 67; *Anal. Calcd. For* $C_{22}H_{14}N_2O_2$: C, 78.10; H, 4.14; N, 8.28; *Found*: C, 78.01; H, 4.19; N, 8.20.

References:

1. C. H. Hassal, R. B. Morton, Y. Ogihara and D. A. S. Phillips, *J. Chem. Soc.* C, **1971,** 526.
2. (a) K. Bevan, J. S. Davies, C. H. Hassal, R. B. Morton, D. A. S. Phillips, *J. Chem. Soc.* C, **1971,** 514. (b) C. H. Hassal, R. B. Morton, Y. Ogihara, W. A. Thomas, *J. Chem. Soc. Chem. Commun.*, **1969,** 1079. (c) C. H. Hassal, Y. Ogihara, W. A. Thomas, *J. Chem. Soc. C*, **1971**, 522.
3. (a) M. S. South, T. L. Jakuboski, *Tetrahedron Lett.*, **1995**, *36*, 5703. (b) M. S. South, T. L. Jakuboski, M. D. Westmeyer, D. R. Dukesherer, *ibid.*, **1996**, *37*, 1351. (c) M. S. South, T. L. Jakuboski, M. D. Westmeyer, D. R. Dukesherer, *J. Org. Chem.* **1996**, *61*, 8921. (d) W. J. Coates, Pyridazines and benzo derivatives in six membered rings with two or more heteroatoms and fused carbocyclic derivatives, Vol 6, Chapter 1, A. J. Boulton, in Comprehensive heterocyclic Chemistry II, A. R. Katritzky, Eds, Pergamon, **1996**.
4. (a) G. Heinisch; H. Frank, *Progress in Medicinal Chemistry* (G. P. Ellis; G. B. West, Eds) Elsevier, Amsterdam, **1990**, Part 1, Vol *27*, 1-49; b) *ibid* (G. P. Ellis, D. K. Luscombe), **1992** Part 2, Vol *29*, 141-183. (c) V. D. Piaz, M. P. Giovannoni, C. Castellana, J. M. Palacios, J. Belata, T. Domenech, V. Segarra, *J. Med. Chem.* **1997**, *40*, 1417.
5. (a) B. D. Schober, G. Megyeri, T. Kappe, *J. Heterocyclic. Chem.* **1989**, *26*, 169. (b) V. D. Piaz, M. P. Giovannoni, G. Giovanna, *Tetrahedron Lett.*, **1993**, *34*, 24, 3903.

6. M. Tisler, B. Stanovnik, *Advance in Heterocyclic Chemistry*; A. R. Katrizky, Ed; Academic Press, San Diego **1979**; *24*, 363.

7. (a) M. E. Komendantov, and R. R. Bekmukhametov, *Zh. Org. Khim.*, **1971**, *7*, 423. (b) M. E. Komendantov, R. R. Bekmukhametov, and V. G. Novinskii, *Zh. Org. Khim.*, **1976**, *12*, 801. (c) O. Tsuge, and K. Kamata. *Heterocycles*, **1975**, *3*, 547. (d) E. Ajello, *J. Heterocyclic. Chem.*, **1972**, *9*, 1427. (e) B. Koren, B. Stanovnik, and M. Tisle, *J. Heterocyclic. Chem.*, **1974**, *11*, 471. (f) J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, **1968**, 5979.

8. M. Tisler, B. Stanovnik, *Advance in Heterocyclic Chemistry*; A. R. Katrizky, A. J. Boulton, Academic Press, San Diego **1968**; *9*, 226.

9. H. M. F. Allah, R. Soliman, *J. Heterocyclic. Chem.*, **1987**, *24*, 1745.

10. F. Barba, M. D. Velasco, A. Guirado, N. Moreno, *Syn. Commun.*, **1985**, *15*, 10, 939.

11. A. Ohsawa, A. Igeta, H. Igeta, *Chem. Pharm. Bull. Jpn.*, **1978**, *26*, 2550.

12. (a) K. Tanao, K. Sumitani, M. Kymada, *J. Am. Chem. Soc.*, **1972**, *94*, 4374. ; (b) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fugioka, *Bull. Soc. Chem. Jpn.*, **1976**, *49*, 1958. (c) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.*, **1972**, 144.

13. V. D. Piaz, A. Capperucci, *Synlett*, **1998**, 762.

14. J. Liang, *J. Heterocycl. Chem.*, **1984**, 1297.

15. J. Levisalles, *Bull. Soc. Chim. Fr.*, **1957**, 997 and 1009

16. H. A. Riley, A. R. Gray, in "*Organic Synthesis*" Coll Vol II, A. H. Blatt, ed John Willey and Sons, Inc., New York, p 509-511.

17. C. L. Arcus, P. A. Hallgarten, *J. Chem. Soc.*, **1957**, *3*, 3407.

18. A. Padwa, H. Ku, *Tetrahedron Lett.*, **1980**, *21*, 1009.

19. E. Toja, A. O. Sale, G. Nathansohn, *Tetrahedron Lett.*, **1979**, *31*, 2921.

20. C. Paal, H. Schulze, *Chem. Ber.*, **1900**, *33*, 3795.

21. A. M. Comrie, *J. Chem. Soc. C.*, **1971**, 2807.

22. (a) E. E. Schweizer, C. M. Copay, *J. Org. Chem.*, **1972**, *37*, 1561. (b) E. E. Schweizer, C. S. Kim, C. S. Labaw, W. P. Murray, *Chem. Commun.*, **1973**, 7.

23. R. K. Gupta, M. V. George, *Ind. J. Chem.*, **1972**, *10*, 875.

24. Y. Tamaru, T. Harada, Z. Yoshida, *J. Org. Chem.*, **1978**, *43*, 17, 3370.

25. F. E. Henoch, K. Gerald Hampton, C. R. Hauser, *J. Am. Chem. Soc.*, **1969**, *91*, 3, 676.

26. See W. G. Kofron, C. R. Hauser, *J. Am. Chem. Soc.*, **1968**, *90*, 4126, also see K. Ziegler, B. Schnell, *Ann.*, **1924**, *227*, 437.

27. (a) R. A. Carboni, R. V. Lindsey, *J. Am. Chem. Soc.*, **1959**, *81*, 4342. (b) B. Burg, W. Dittmar, H. Reim, A. Steigel, J. Sauer, *Tetrahedron Lett.*, **1975**, 2897. (c) O. Meresz, P. A. Foster-Verner, *Chem. Commun.*, **1972**, 950. (d) F. H. Case, *J. Heterocycl. Chem.*, **1968**, *5*, 431. (e) L. Bircofer, R. Stilke, *J. Organomet. Chem.*, **1974**, *74*, C1.

28. A. Smith, *Ann.*, **1896**, *289*, 310.

29. S. Capauno, *Gazz. Chim. Ital.*, **1938**, *68*, 527.

30. S. S. Cohen, *J. Am. Chem. Soc.*, **1957**, *79*, 4400.

31. M. J. Haddadin, S. J. Firsan, B. S. Nader, *J. Org. Chem.*, **1979**, *44*, 629.

32. C. Parsdisi, P. Maurizio, U. Quintily and G. Scorrano, *J. Org. Chem.*, **1981**, *46*, 5156.

33. R. N. Castles, *"Pyridazynes"* Willey; NewYork, **1973**.

34. E. L. Elliel, " *Stereochem of Carbon Compounds*" Mc Graw Hill; New York, **1962**.

35. P. Coudert, J. Couquelet, *J. Heterocycl. Chem.*, **1988**, *25*, 799.

36. (a) O. Tsuge, K. Kamata, S. Yogi, *Bull. Soc. Chim. Jpn.*, 1977, *50*, 2153. (b) O. Tsuge, M. Tashiro, K. Kamata, H. Hokama, *Org. Prep. & Proceed. Int.*, **1971**, 3, 289.

37. (a) O. Tsuge, K. Kamata, *Heterocycles*, **1975**, *3*, 15. (b) G. G. Amiet, R. B. Johns, K. R. Markham, *J. Chem. Soc. Chem. Commun.*, **1965**, 128.

38. (a) R. M. White, M. A. Battiste, *J. Org. Chem.*, **1976**, *41*, 1245. (b) J. V. Alphen, *Recl. Trav. Chem. Pays-Bas.*, **1943**, *62*, 210.

39. (a) S. Ranganathan, C. S. Panda, H. Schecter, *J. Org. Chem.*, **1972**, *37*, 1071. (b) L. Horner and E. Lingnau, *Justus. Liebigs. Ann. Chem.*, **1955**, *21*, 591.

40. E. E. Schweizer and K. J. Lee, *J. Org. Chem.*, **1982**, *47*, 2768.

41. (a) S. Trippet, *Adv. Org. Chem.*, **1960**, *83*, 1. (b) H. J. Bestmann, *Chem. Ber.*, **1962**, *58*, 95.

42. S. Evans and E. E. Schweizer, *J. Org. Chem.*, **1977**, *42*, 2321.

43. F. R. Japp, J. Wood, *J. Chem. Soc.*, **1900**, *87*, 707.

44. B. G. Zimmerman and H. L. Lochte, *J. Am. Chem. Soc.*, **1938**, *60*, 2456.

45. (a) W. Ried, R. Lantzsch, *Justus Liebigs Ann. Chem.*, 1971, *97*, 750. (b) G. Rio, A. Lecas-Nawrocka, *Bull. Soc. Chim. Fr.*, **1971**, 1723. (c) G. Rio, A. Lecas-Nawrocka, *Bull. Soc. Chim. Fr.*, **1974**, 2824. (d) M. I. Shevchuck, A.

F. Tolochko, A. V. Dombrovskii, *Zh. Org. Khim.*, **1970**, *6*, 1108. (e) M. I. Shevchuck, A. F. Tolochko, A. V. Dombrovskii, *Zh. Org. Khim.*, **1971**, *7*, 1692. (f) J. C. Tisler, J. K. Doty, J. M. Robinson, *J. Org. Chem.*, **1969**, *34*, 3421.

46. (a) K. N. Zelenin, Y. Y. Dumpis, *Zh. Org. Khim.*, **1970**, *6*, 1349. (b) K. N. Zelenin, Y. Y. Dumpis, *Zh. Org. Khim.*, **1971**, *6*, 400. (c) F. Schon, L. Jung, P. Cordier, *C. R. Acad. Sci. Sr. C.*, **1968**, 267, 490.

47. A. Weissberger, "*The chemistry of heterocyclic compounds*"; Willey: New York, **1950**; Vol 1.

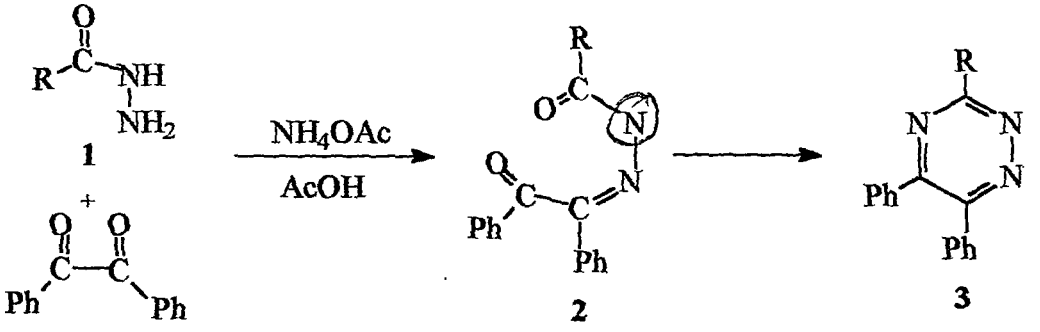
CHAPTER-III

"A NEW ONE POT SYNTHESIS OF 3, 5, 6-TRISUBSTITUTED 1, 2, 4-TRIAZINES"

Introduction:

1, 2, 4-triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivities. Some derivatives of 1, 2, 4-triazines were reported to have considerable biological activities.[1] The synthesis of 1, 2, 4-triazines and their derivatives are well documented and their methods of preparation are manifold and varied. A survey of the literature revealed that 1, 2-diketones (aromatic, aliphatic and aromatic-aliphatic) are the most common reagents used for the synthesis of 1, 2, 4-triazines and their derivatives.

Laakso and coworkers[2] as well as other groups[3] have reported the condensation of acylhydrazides **1** with benzil in acetic acid containing ammonium acetate to give 5, 6-diphenyl-1, 2, 4-triazines **3** with various aromatic and heterocyclic groups attached at position 3. The reaction was carried out by refluxing a mixture of α-diketone, acid hydrazide and ammonium acetate in acetic acid. The reaction proceeded *via* the monoacylhydrazone intermediate **2** which was then cyclised by ammonia to give **3** as shown in scheme-1.

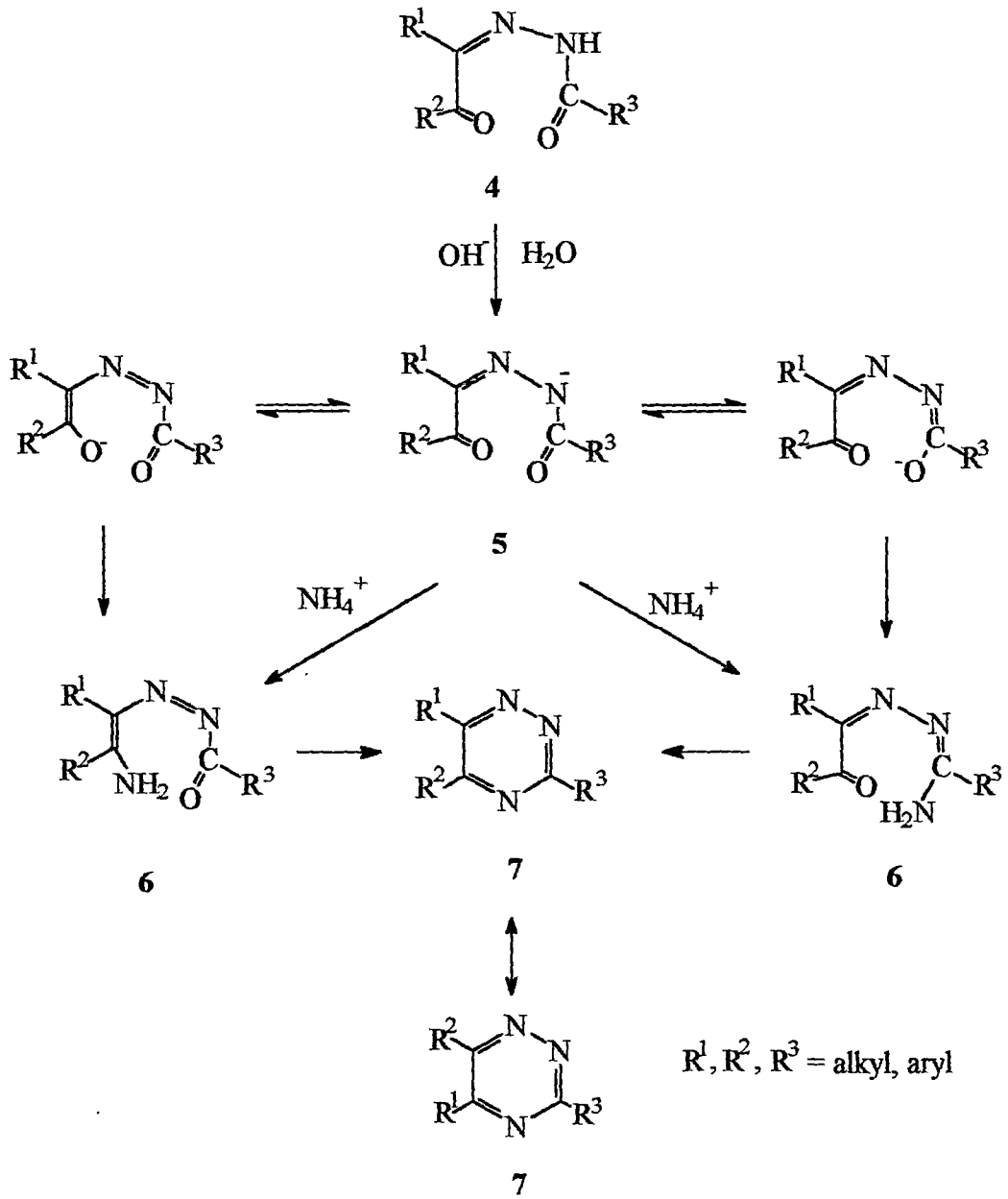


Scheme-1

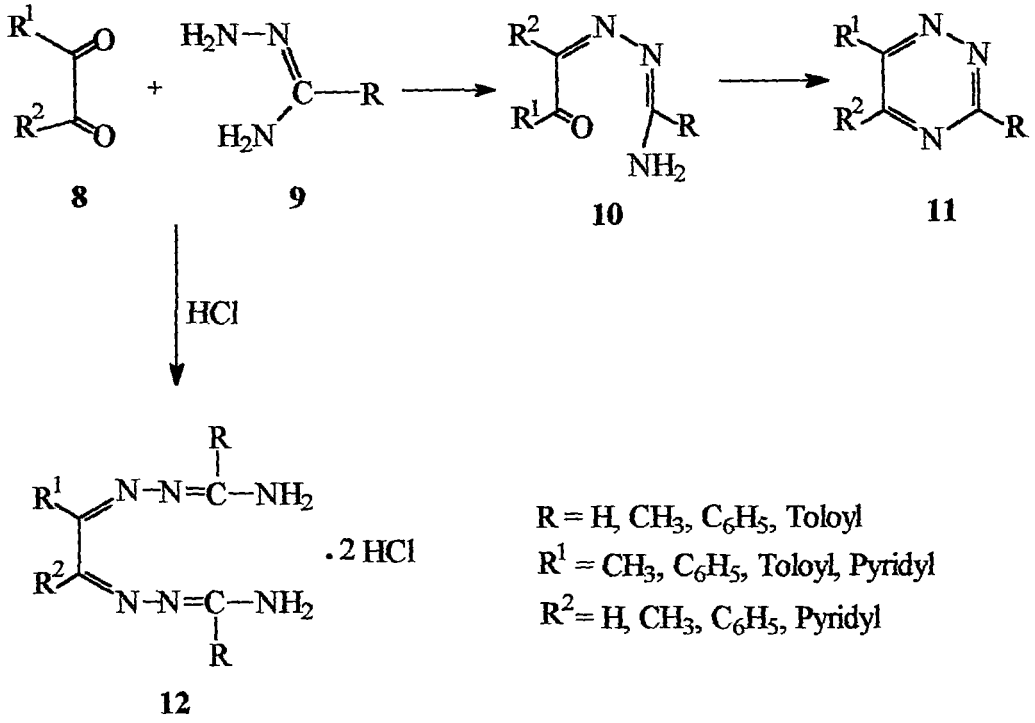
A similar method was also applied by Metze and his group[4] and also Hasselquist[5] using a variety of aliphatic and aromatic 1, 2-diketones and aliphatic, aromatic, and heterocyclic acid hydrazides but with preliminary isolation of the 1, 2-diketones monoacylhydrazones **4** followed by ring closure with alcoholic ammonia under pressure to give **7** as shown in Scheme-2. Metze also found that monohydrazones of aromatic (but not aliphatic) 1, 2-diketones react with formamide to give 5, 6-diaryl-1, 2, 4-triazines.[6]

The most convenient method involved the reaction of amidrazones with 1, 2-dicarbonyl compounds.[7] No limitation of this reaction was reported if the right reaction conditions were observed. The most suitable procedure for this reaction was the addition of the 1, 2-dicarbonyl compounds **8** to a solution of the free amidrazone **9** or of the amidrazone hydrochloride in the presence of 1 mole of the base and the reaction allowed to continue for about 12 hours. Ring closure of the intermediates was sometimes slow making their isolation possible in a few cases. This method has also been used for the synthesis of compounds containing more than one 1, 2, 4-triazine nucleus.

In the presence of free acid, compounds of the osazone type **12** were formed, which were very stable if R are aliphatic groups.[7p] The use of monosubstituted glyoxal as the 1, 2-dicarbonyl compound gave a mixture of two isomeric 1, 2, 4-triazines.

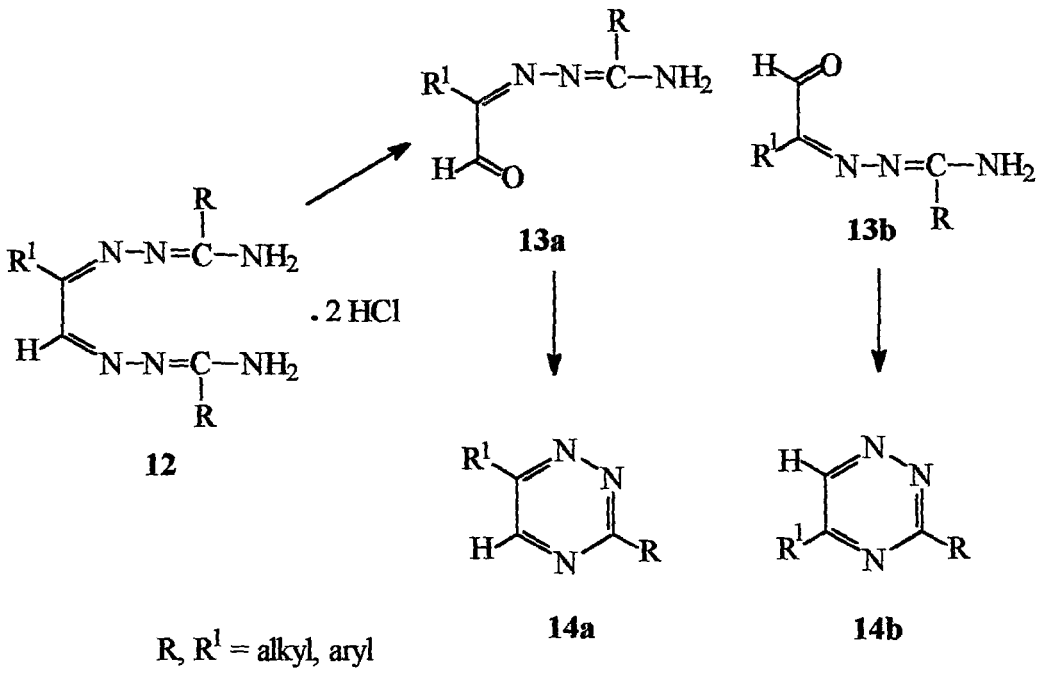


Scheme-2



Scheme-3

Mild hydrolysis of **12** with dilute acid[7p] or aqueous copper sulphate solution led to the formation of 1, 2, 4-triazines in high yield. If the starting 1, 2-dicarbonyl compound was a monosubstituted glyoxal the preferentially formed isomer was the 6-substituted 1, 2, 4-triazine. This was best explained by the preferential hydrolysis of **12** to **13b** and subsequent ring closure to **14b** as shown in Scheme-4.

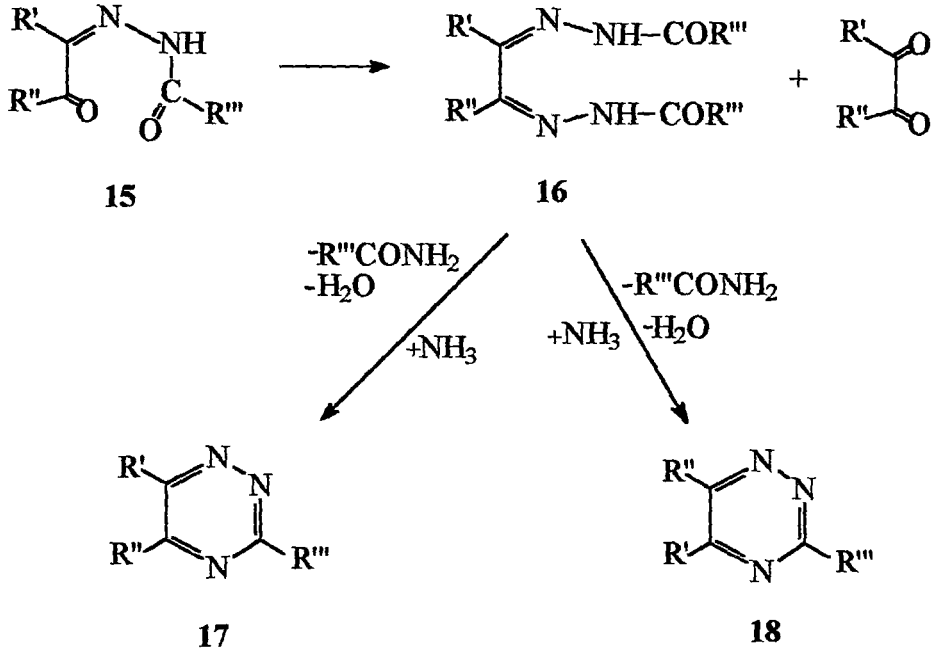


Scheme-4

Atkinson and cossey[8] applied this method to unsymmetrical aromatic and aromatic-aliphatic diketones. The rate of the ring closure appears to depend on the excess of ammonium acetate used, as longer times were required with ten fold excess used, contrary to the work of Laakso[2b] where usually a greater excess (and concentration) was employed. The general method gave rise to three anomalous reactions: first acetylation of the amino group occurred during the preparation of 3-p-aminophenyl-5, 6-diphenyl-1, 2, 4-triazine from p-aminobenzhydrazide but did not occur with the ortho isomer. The isolation of 2, 4, 5-triphenyl imidazole during the preparation of 3-methyl-5, 6-diphenyl-1, 2, 4-triazine was not unexpected in view of the work of Davidson, Weiss, and Jelling[9] who obtained imidazole from the reaction of benzil and ammonia in acetic acid. The third anomaly was the exchange

between the hydrazide and acetic acid, which gave 3-methyl-5, 6-diphenyl-1, 2, 4-triazine.

Metze[4e] also observed that with unsymmetrical 1, 2-dicarbonyl compounds, a mixture of positional isomers were formed. The two isomers 3, 6-diphenyl-5-methyl- and 3, 5-diphenyl-6-methyl-1, 2, 4-triazine were first isolated[10a] by manual separation of the crystals. The formation of the isomers was explained as due to the disproportionation of the monoacyl hydrazone **15** used to form the diketone and the bisacyl hydrazone **16.** Ring closure of this bisacyl hydrazone with ammonia[10b] gave the unexpected isomers **17** and **18** as shown in Scheme-5.



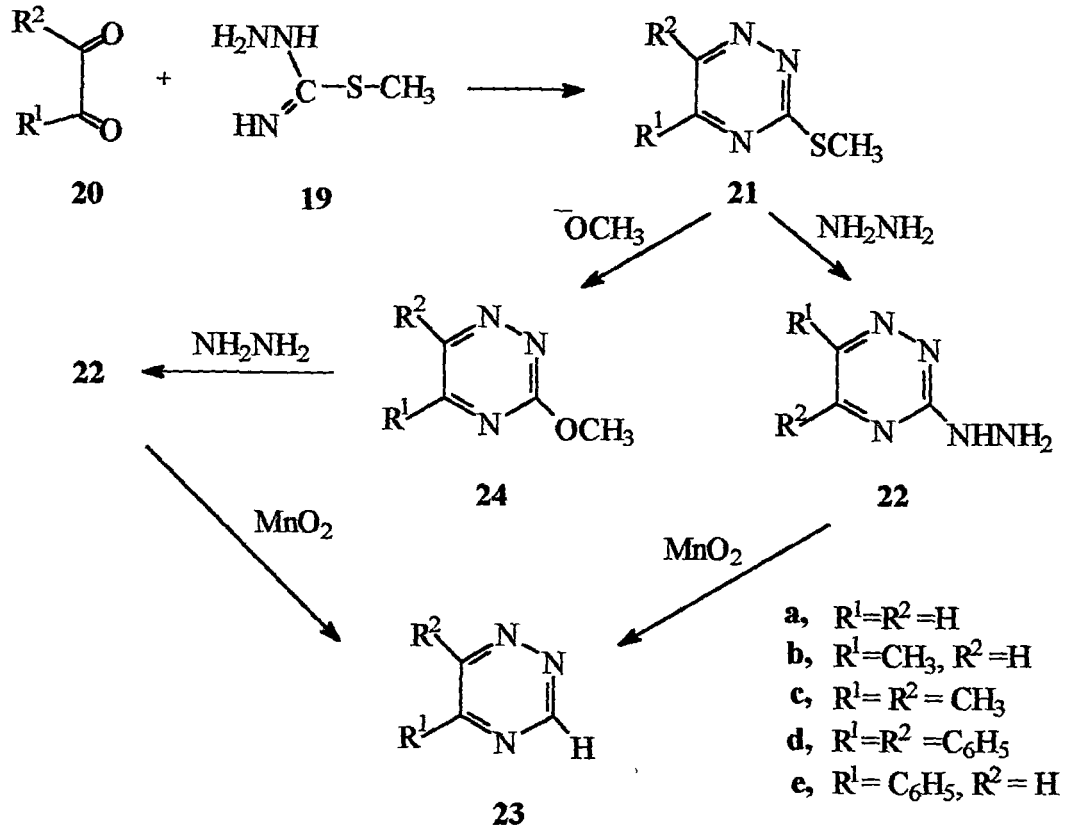
Scheme-5

In an attempt to prepare an α-diketone monoacylhydrazone isomeric with that formed by direct condensation, p-methoxybenhydrazide was condensed with a hydroxy iminopropiophenone to give hydroxy iminopropiophenone p-methoxybenzoyl hydrazone, hydrolysis of which caused clevage of the hydrazone in preference to that of the hydroxyimino group. When the condensation of the acyl hydrazide and α-hydroxy imino ketone and subsequent ring closure were carried out without the isolation of the intermediate acylhydrazone both isomeric triazines **17** and **18** were obtained. The isomeric triazines obtained from unsymmetrical 1, 2-diketones were identified by the unambiguous synthesis of one of them, by Sprio and Madonia's method[11] from an α-acyl amino ketone of unknown structure and hydrazine hydrochloride followed by hydrogenation of the dihydrotriazine so formed. These workers employed potassium dichromate in aqueous acetic acid for dehydrogenation of dihydro-3, 6-diphenyl-1, 2, 4- triazine in 38% yield.

Neunhoeffer and Hennig[12] synthesised 5, 6-disubstituted-1, 2, 4-triazine by the cyclisation of formamidrazones with aliphatic and aromatic 1, 2-diketones. Similar cyclisations has been reported by H. Paul[12b] in the synthesis of 3-benzyloxycarbonylamino methyl 5, 6-disubstituted-1, 2, 4-triazine, starting from benzyloxy carbonyl acetamidrazone. Subsequently Neunhoeffer and coworkers[13] found that the cyclisation of amidrazone with unsymmetrical 1, 2-diketone resulted in the formation of isomers as reported earlier.[7]

Cyclisation of the monohydrazones of the 1, 2-dicarbonyl compounds with amides or imidates[14] is another method for the preparation of 1, 2, 4-triazines. The first reaction product was the same intermediate as in the reaction of amidrazones with 1, 2-dicarbonyl compounds.

A convenient synthesis of 1, 2, 4-triazines from S-methyl thiosemicarbazide was reported by Paudler.[15] The condensation of S-methyl thiosemicarbazide **19** with glyoxal **20a** or other α, β-dicarbonyl compounds **20b-e** readily affords the 3-methylthio derivatives of 1, 2, 4-triazines **21**. These substances were readily converted to their 3-hydrazino derivatives **22** by treatment with hydrazine and were conveniently oxidized with active manganese dioxide to the appropriate 1, 2, 4-triazines **23**.

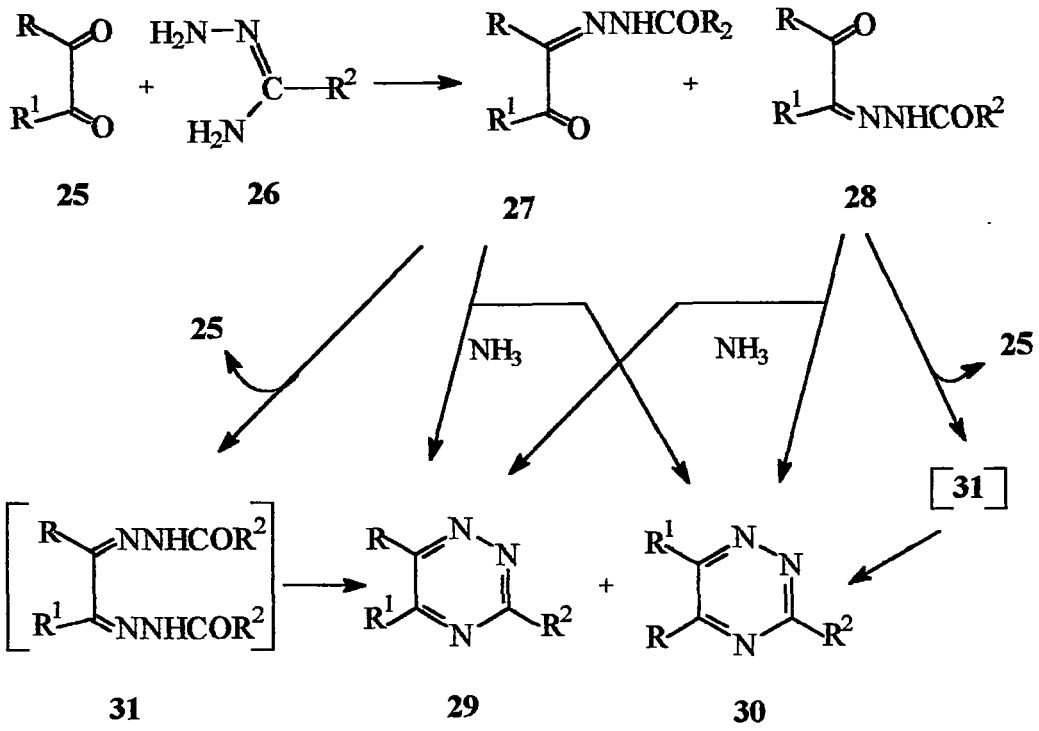


Scheme-6

However the transformation of the 3-hydrazino-1, 2, 4-triazines **22a**[16] from **21** resulted in low yield of the products. This was overcome by converting the 3-

methylthio-1, 2, 4-triazines **21a** first to its methoxy derivative **24a** which was then converted to the 3-hydrazino-1, 2, 4-triazines **22a** in high yield. **22** was readily oxidized to the parent compound **23a** by means of activated manganese dioxide. These transformations are delineated in scheme-6.

The synthesis of 5, 6-dialkyl-1, 2, 4-triazines was accomplished by the condensation of α-diketones **25** with acylhydrazines **26** and subsequent treatment of the resulting acyl hydrazones **27** or **28** with ammonia.[17] In the case of an unsymmetrical α-diketone however, the condensation resulted in the formation of two positional isomers of the acylhydrazones[4e] **27** and **28** unless the character of the two carbonyl groups is different. Furthermore when the pure acylhydrazone **27** and **28** were treated with ammonia the cyclisation still proceeded non-regioselectively to give two isomers of 5, 6-disubstituted-1, 2, 4-triazine **29** and **30** scheme-7. This fact was reasonably explained by assuming the formation of diacylhydrazones **31** due to intermolecular recomposition of the acylhydrazone **27** and **28** during the triazine cyclisation.[8] Tailor[18] also used this same method to synthesise 3-(o-hydroxyphenyl)-1, 2, 4-triazine which was used as the precursor for the synthesis of 3-[2'-(cyanomethoxy) phenyl]-5, 6-diphenyl-1, 2, 4-triazine and other heterocyclic systems.[19]



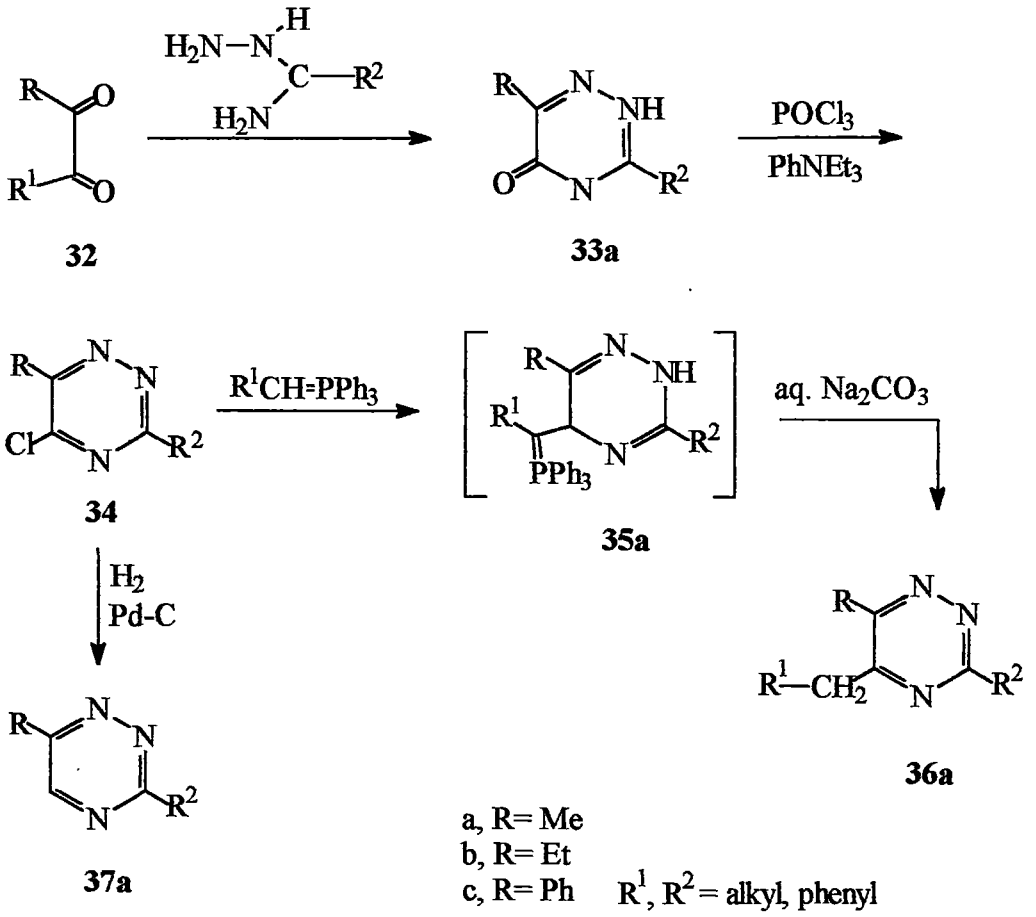
R, R^1, R^2, = alkyl, aryl,

Scheme-7

However the above route did not have wide applicability for the preparation of unsymmetrical 5, 6-disubstituted-1, 2, 4-triazines. Yakama[20] developed a new route which described the stepwise introduction of different alkyl groups at the 5- and 6- position of as-triazines using 5-triazinones as starting materials.

When 6-methyl-3-phenyl-1, 2, 4-triazin-5 (2H)-one **33a** obtained by the ring closure reaction of pure acyl hydrazone of the α-diketone in the presence of ammonia was treated with phosphoryl chloride in the presence of diethylaniline at room temperature for 30 minutes, 5-chloro-6-methyl-1, 2, 4-triazine **34a** was obtained in 83% yield. The condensation of **34a** with ethylidene triphenylphosphorane gave 5-ethyl-6-methyl-3-phenyl-1, 2, 4-triazine **35a** (Scheme-

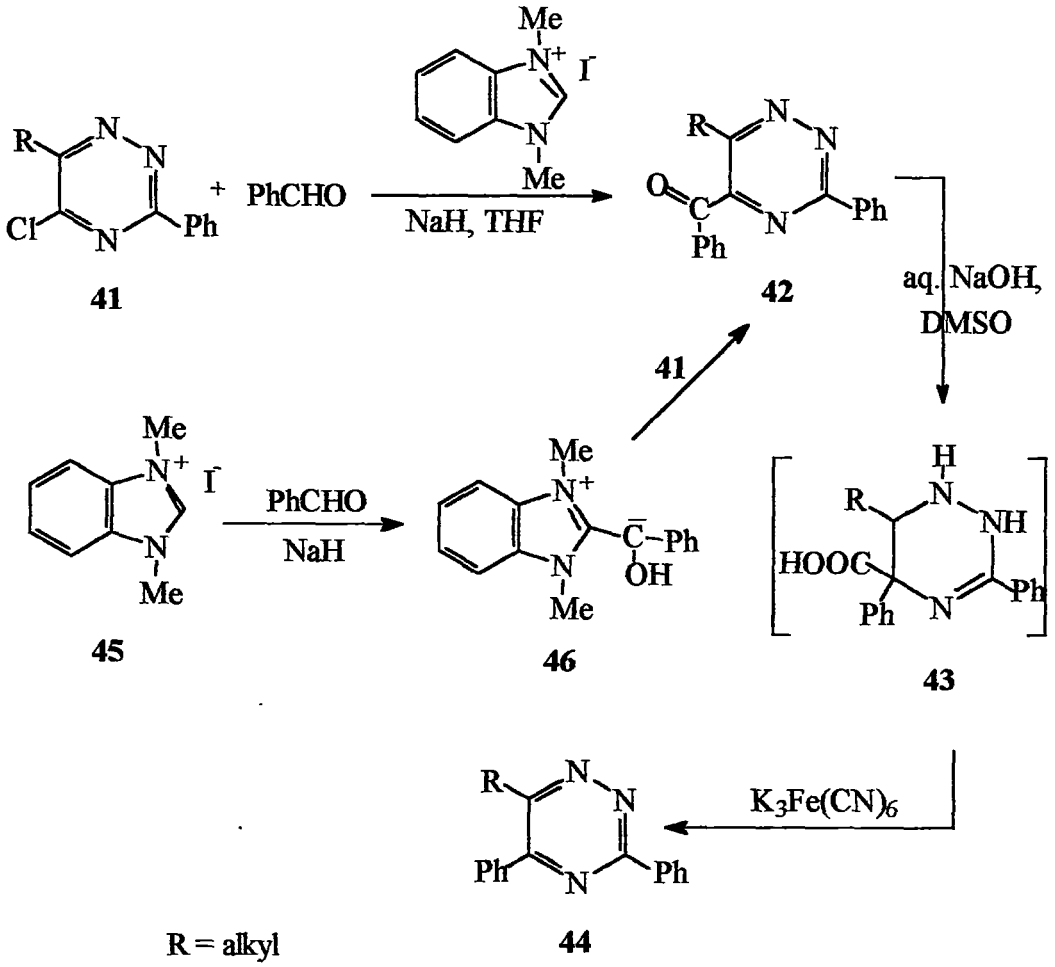
8). Hydrogenolysis of **34a** over palladium catalyst[21] in the presence of triethyl amine in benzene gave 3-phenyl-6-methyl-1, 2, 4-triazine **37a** mp 106-107°C[11] in 93% yields.



Scheme-8

Arylation[22] of 3-methyl-6-phenyl-1, 2, 4-triazine **38** was achieved by treating it with aryl magnesium bromide in ether when 5-aryl-3-methyl-6-phenyl-2, 4-dihydro-1, 2, 4-triazine **39** was obtained (scheme-9). The dihydro compound **39** was easily oxidized with potassium permanganate in acetone or with potassium ferricyanide under alkaline condition to give 6-aryl-3-methyl-5-phenyl-1, 2, 4-

(m, 2H), 8.42-8.68 (m, 2H)] was isolated in 62% yield. As shown in Scheme-10, an adduct of benzaldehyde with benzimidazolium, similar to the case of quinazolium derivatives probably acts as the main reagent for the formation of **42** from **41**. When **42a** was treated with sodium hydroxide in aqueous dimethyl sulphoxide, a benzilic acid type rearrangement occurred to give 6-methyl-3, 5-diphenyl-2, 5-dihydro-1, 2, 4-triazine-5-carboxylic acid **43** as an amorphous powder. The oxidation of crude **43** with potassium ferricyanide afforded 6-methyl-3, 5-diphenyl-1, 2, 4-triazine[24] **44**.

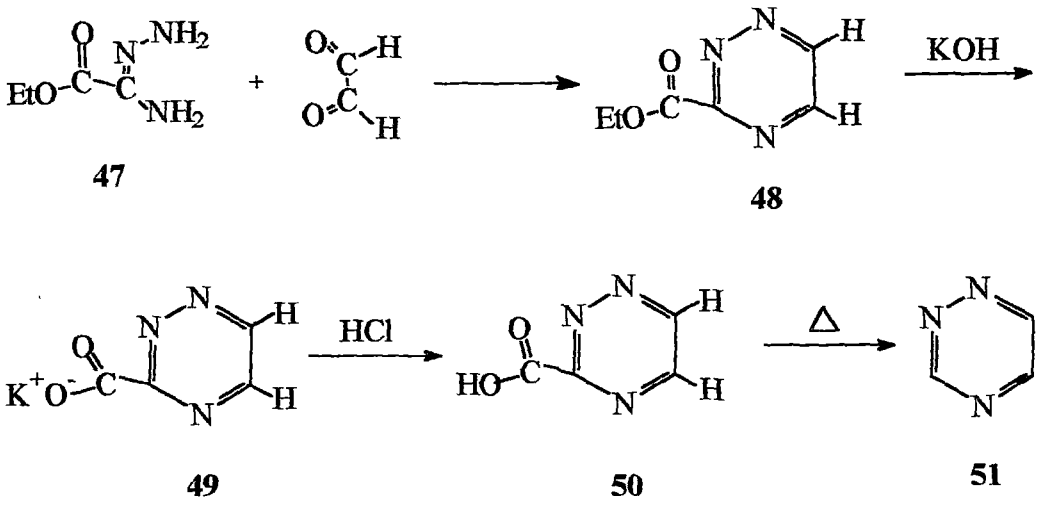


Scheme-10

After a number of unsuccessful attempts[25-27] to prepare the unsubstituted 1, 2, 4-triazine **51** the first synthesis of the 1, 2, 4-triazine series was reported by Paudler and Barton.[28] They synthesized this compound in 40% yield through the decarboxylation of 1, 2, 4-triazine-3-carboxylic acid **50**.

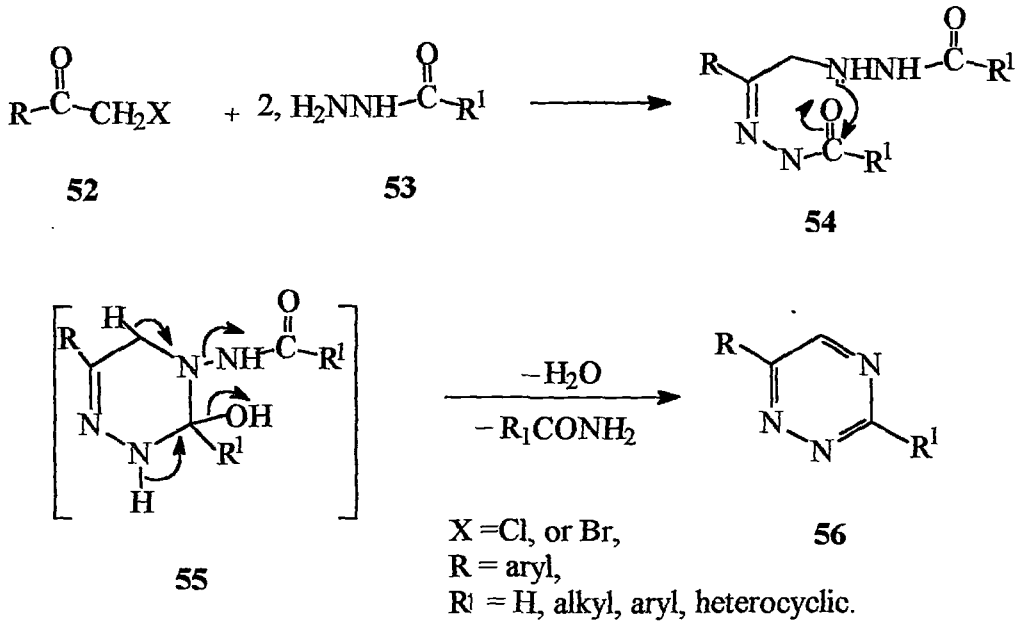
1, 2, 4-triazine-3-carboxylate **48** was obtained by the condensation of ethyl oxalamidrazonate **47** with glyoxal as shown in scheme-11. Previous attempts[26] failed to get the expected ester **48**. Treatment of **48** with alcoholic potassium hydroxide afforded the potassium salt of 1, 2, 4-triazine-3-carboxylic acid **49**. The free carboxylic acid **50** was obtained by treatment of the potassium salt with one equivalent of aqueous hydrochloric acid. This acid was readily decarboxylated at 110-120°C to yield a yellow oil which was identified as 1, 2, 4-triazine **51**. Later **51** was synthesized by direct synthesis[12a] from formamidrazone and glyoxal and by the oxidation of 3-hydrazino-1, 2, 4-triazine with manganese dioxide.[15] Substituent exchange was also established in 5-iodosubstituted-1, 2, 4-triazine[29] which was concluded to be better starting material than the chloride.

A different route for the synthesis of 3, 6-disubstituted-1, 2, 4-triazine **56** was reported by Saraswathi.[30] Heating a mixture of an acid hydrazide **53** and ω-haloacetophenone **52** (2:1) in ethanol or acetic acid in boiling water bath in the presence of equimolar quantities or a slight excess of sodium acetate, potassium acetate, or silver acetate for a few minutes resulted in the formation of **56**. A tentative mechanism by which these compounds were obtained is shown in scheme-12.



47 48 49 50 51

Scheme-11



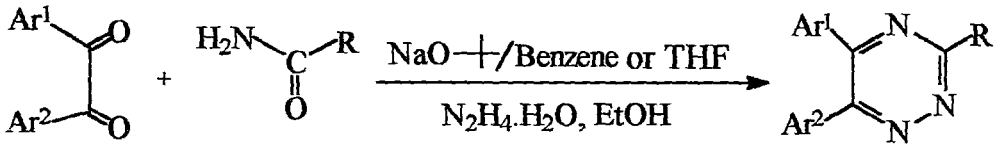
52 53 54 55 56

X =Cl, or Br,
R = aryl,
R^1 = H, alkyl, aryl, heterocyclic.

Scheme-12

Results and discussions:

Our work provides a simple and convenient route for the synthesis of 3, 5, 6-trisubstituted-1, 2, 4-triazines starting from common and easily available starting materials. The novelty of the procedure lies in the fact that the whole reaction sequence was carried out by stepwise addition of the reagents at the completion of each reaction step (as monitored by TLC) without isolating the intermediates as they were formed. Thus the one-pot synthesis of the title compound was achieved *via* the monoacyl hydrazone, which was generated in *situ* by the condensation of amides with 1, 2-diketones in presence of base. In general primary amides **58** like formamide, acetamide and benzamide when treated with aromatic 1, 2-diketones **57** like benzil, substituted benzils, and furil formed a jelly mass which is the monoacyl hydrazone (condensed product) which can then be cyclised to the stable substituted 1, 2, 4-triazine **59** (scheme-13) by treatment with hydrazine hydrate. In all these cases, solid products are obtained. Previous report[6] had shown similar cyclisation of 2-(acyl amino)-ketones or 2-[(thioacyl)amino]-ketones with hydrazine which yielded dihydro-1, 2, 4- triazines or its tautomers which were then oxidized to 1, 2, 4-triazines.



57 **58** **59**

R = H, CH_3,

Ar^1 = ,

Ar^2 = , , ,

Scheme-13

Table 2: Preparation of 3, 5, 6-trisubstituted-1, 2, 4-triazines.

Entry	Products	R^1	Ar^2	Ar^3	Time/h	Yields[a] (%)	M.Pt (°C)
1	**59a**[31]	H	C_6H_5	C_6H_5	3	56	112
2	**59b**[13]	CH_3	C_6H_5	C_6H_5	4	78	91
3	**59c**[32]	C_6H_5	C_6H_5	C_6H_5	4	61	144
4	**59d**	H	4-$OMeC_6H_4$	C_6H_5	5	64	167
5	**59e**	CH_3	4-$OMeC_6H_4$	C_6H_5	6	58	135
6	**59f**	C_6H_5	4-$OMeC_6H_4$	C_6H_5	5	65	152
7	**59g**	H	4-ClC_6H_4	C_6H_5	3	60	118
8	**59h**	CH_3	4-ClC_6H_4	C_6H_5	4	61	120
9	**59i**	C_6H_5	4-ClC_6H_4	C_6H_5	5	72	108
10	**59j**[12]	H	Furyl	Furyl	5	57	95
11	**59k**[13]	CH_3	Furyl	Furyl	6	61	143
12	**59l**	C_6H_5	Furyl	Furyl	5	58	162

[a] refer to pure products

Experimental:

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 and BOMEM DA-8 FT-IR Spectrophotometer using KBr pellets and the frequencies are expressed in cm^{-1}. ^1H NMR (90 MHz) was recorded on Varian EM-390 spectrometer and high resolution ^1H and ^{13}C NMR (300 MHz) spectra were recorded on a Bruker ACF-300 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, m = multiplet. Mass spectra were obtained on a JEOL D-300 (EI) mass spectrometer. Masses are reported in units of mass upon charge (m/z), the molecular peaks are indicated by (M^+). Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution. Column chromatography was carried out using ACME's silica gel (60-120 mesh).

Chemicals, Reagents and solvents:

Dry benzene was obtained by keeping over Calcium Chloride followed by distillation and again storing over Sodium wire. The commercial samples of formamide, benzaldehydes, hydrazine hydrate, were purified by simple distillation.

Substituted benzils and furil were prepared using known methods.[50] Sodium tertiary butoxide was freshly prepared for each reaction.

General procedure for the synthesis of 3, 5, 6-trisubstituted-1, 2, 4-triazines 59:

To a stirring solution of sodium tertiary butoxide (30 mmol) in benzene, or tetrahydrofuran (30 ml) at room temperature a solution of 10 mmol of amide (formamide, acetamide and benzamide) in benzene was added, followed by the addition of aromatic 1, 2-diketones (benzil, substituted benzils, and furil) (10 mmol) in one lot. This resulted in the formation of a solid jelly mass which made stirring ineffective. 5 ml of ethanol was added to dissolve the solid mass. Hydrazine was then added and the reaction mixture stirred at room temperature (3-8 hrs). After the reaction was completed (monitored by TLC) the product was extracted with benzene and dried over anhydrous sodium sulphate. Removal of the solvent by distillation under reduced pressure resulted in the formation of crystalline solids which were further purified by repeated recrystallisation from ethanol or by column chromatography.

5, 6-diphenyl-1, 2, 4-triazine 59a:

Pale yellow crystals; Yield 56%; Mp: 112°C; *^{1}H NMR*: δ 7.25-7.94 (m, 10H); 9.20 (s, 1H); *^{13}C NMR*: δ 125.0, 126.4, 127.2, 127.9, 129.4, 130.1, 131.2, 136.1, 140.0, 155.8, 160.0; *Mass*: 233 (M^+); *IR* (KBr): ν_{max} 3060, 1620, 1585, 1485, 1440, 1405; *Anal. Calcd.* for $C_{15}H_{11}N_3$: C, 77.25; H, 4.72; N, 18.02; *Found*: C, 77.41; H, 4.86; N, 17.87.

5, 6-diphenyl-3-methyl-1, 2, 4-triazine 59b:

Dirty white crystals; Yield 78%; Mp: 91°C; *^{1}H NMR*: δ 2.42 (s, 3H), 7.24-7.51 (m, 7H), 7.80-8.11 (m, 3H); *^{13}C NMR*: δ 21.4, 124.8, 126.9, 128.7, 128.9, 129.0, 129.2, 129.7, 130.1, 136.9, 156.4, 157.6, 158.9; Mass: 247 (M^+); *IR* (KBr): ν_{max} 3061, 2921, 1577, 1488, 1445, 1393; *Anal. Calcd.* for $C_{16}H_{13}N_3$: C, 77.73; H, 5.26; N, 17.00, *Found:* C, 77.84; H, 5.15; N, 16.83;

3, 5, 6-triphenyl-1, 2, 4-triazine 59c:

Pale yellow crystals; Yield 61%; Mp: 144°C; *^{1}H NMR*: δ 7.31-7.50 (m, 12H), 7.80 (s, 1H), 8.11-8.13 (m, 2H); *^{13}C NMR*: δ 124.5, 128.1, 128.3, 128.8, 129.0, 129.2, 129.9, 134.5, 136.2, 136.5, 136.9, 139.5, 156.5, 158.4, 162.1; *Mass*: 309(M^+); *IR* (KBr): ν_{max} 2978, 1672, 1477, 1414; *Anal. Calcd.* for $C_{21}H_{15}N_3$: C, 81.55; H, 4.85; N, 13.59; *Found*: C, 81.43; H 4.63; N, 13.50.

5-anisyl-6-phenyl-1, 2, 4-triazine 59d:

Brown solids; Yield 64%; Mp: 167°C; *^{1}H NMR*: δ 3.83 (s, 3H); 7.24-8.03 (m, 9H), 9.25 (s, 1H), *^{13}C NMR*: δ 50.8, 124.3, 126.9, 127.3, 128.7, 129.3, 131.2, 134.3, 135.8 153.4, 156.1, 161.8; *IR* (KBr): ν_{max} 3023, 2961, 1608, 1568, 1480; Mass: 263(M^+); *Anal. Calcd.* for $C_{16}H_{13}N_3O$: C, 73.00; H, 4.94; N, 15.96; *Found*: C, 72.90; H, 4.85; N, 16.00.

5-anisyl-3-methyl-6-phenyl-1, 2, 4-triazine 59e:

Pale brown solids; Yield 58%; Mp: 135°C; *^{1}H NMR*: δ 2.60 (s, 3H), 3.85 (s, 3H), 7.3-8.0 (m, 9H); *^{13}C NMR*: δ 28.0, 50.3, 125.3, 127.0, 127.9, 128.7, 129.4, 131.1, 131.3,136.1, 138.1, 154.3, 160.2; *IR* (KBr): ν_{max} 3041, 2930, 1625, 1560, 1482, 1431; *Mass*: 277(M^+); *Anal. Calcd.* for $C_{17}H_{15}N_3O$: C, 73.64; H, 5.41; N, 15.16; *Found*: C, 73.84; H, 5.33; N, 15.00.

6-anisyl-3, 5-diphenyl-1, 2, 4-triazine 59f:

Brown solids; Yield 65%; Mp: 152°C; *^{1}H NMR*: δ 3.84 (s, 3H); 7.31-7.80 (m, 12H), 8.10-8.25 (m, 2H), *^{13}C NMR*: δ 50.5, 125.7, 126.0, 126.4, 127.0, 127.8, 128.6,129.3, 129.7, 130.4, 131.0, 132.4, 135.7, 153.1, 156.4, 160.3; *IR* (KBr): ν_{max} 3061, 2941, 1618, 1570, 1480; *Mass*: 339 (M^+); *Anal. Calcd.* for $C_{22}H_{17}N_3O$, C, 77.87; H, 5.01; N, 12.38; *Found*: C, 77.70; H, 4.89; N, 12.10;

6-(p-chlorophenyl)-5-phenyl-1, 2, 4-triazine 59g:

Dark brown crystals; Yield 60%; Mp: 118°C; *^{1}H NMR*: δ 7.3-8.0 (m, 9H), 9.25 (s, 1H) ; *^{13}C NMR*: 125.6, 126.0, 127.5, 128.2, 129.7, 132.7, 134.0, 135.6, 154.3, 156.1,162.0; *IR* (KBr): ν_{max} 3040, 1610, 1568,1460,1405; Mass: 267 (M^+); *Anal. Calcd.* for $C_{15}H_{10}N_3Cl$: C 67.28, H 3.73, N 15.70; *Found*: C, 67.12; H, 3.84; N, 15.61.

3-methyl-6-(p-chlorophenyl)-5-phenyl-1, 2, 4-triazine 59h:

Dirty white solids; Yield 61%; Mp: 120°C; *^{1}H NMR*: δ 2.68 (s, 1H), 7.31-8.04 (m, 9H); *^{13}C NMR*: 29.8, 125.9, 127.0, 127.9, 128.6, 130.8, 131.8, 133.0, 134.7, 154.0, 155.6, 162.1; *IR* (KBr): ν_{max} 3050, 2940, 1622, 1591, 1505, 1450; Mass: 281 (M^+); *Anal. Calcd.* for $C_{16}H_{12}N_3Cl$: C, 68.20; H, 4.26; N, 14.92; *Found*: C, 68.45; H, 4.30; N, 14.81;

3, 5-diphenyl-(6-p-chlorophenyl)-1, 2, 4-triazine 59i:

Brown solids; Yield 72%; Mp: 108°C; *^{1}H NMR*: δ 7.29-7.96 (m, 12H), 8.07-8.22 (m, 2H); *^{13}C NMR*: δ 125.3, 126.5, 127.2, 127.6, 128.0, 128.6, 129.0, 129.7, 131.8, 132.1, 133.2, 134.1, 154.0, 155.4,161.9; *IR* (KBr): ν_{max} 3045, 1630, 1592, 1500,

1470; Mass: 343 (M^+);*Anal. Calcd.* for $C_{21}H_{14}N_3Cl$: C, 73.38; H, 4.07; N, 12.22; *Found*: C, 73.44; H, 4.20; N, 12.12.

5, 6-difuryl-1, 2, 4-triazine 59j:

Dark brown crystals; Yield 57%; Mp: 95°C; *^1H NMR*: δ 6.24-6.61 (m, 6H), 9.21 (s, 1H); ^{13}C NMR: δ 112.1, 113.3, 116.1, 120.0, 123.1, 124.3, 153.0, 154.1, 160.3; *IR* (KBr): ν_{max} 2978, 1624, 1477, 1415, 1074; *Mass*: 213(M^+), *Anal. Calcd.* for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.28; N, 19.71; *Found*: C, 62.08; H, 3.20; N, 19.50.

5, 6-difuryl-3-methyl-1, 2, 4-triazine 59k:

Pale brown solids; Yield 61%; Mp: 143°C; *^1H NMR*: δ 2.61 (s, 3H) 6.26-8 (m, 6H), *^{13}C NMR*: δ 27.9, 112.1, 112.6, 113.0, 114.3, 116.7, 120.6, 124.0, 125.3, 153.0, 154.1, 158.9; *IR* (KBr): ν_{max} 3002, 2924, 1620, 1495, 1415, 1033, *Mass*: 227(M^+), *Anal. Calcd.* for $C_{12}H_9N_3O_2$: C, 63.43, H, 3.96, N, 18.50, *Found*: C, 63.57; H, 3.84; N, 18.38.

5, 6-difuryl-3-phenyl-1, 2, 4-triazine 59l:

Yield 58%; Mp: 162°C; *^{1}HNMR*: δ 6.25-6.75 (m, 6H), 7.71-8.01 (m, 5H); *^{13}C NMR*: 112.0, 112.8, 113.6, 114.3, 115.0, 115.7, 117.1, 120.6, 129.0, 130.1, 132.6, 134.3, 153.6, 154.1, 161.2; *IR* (KBr): ν_{max} 3010, 1631, 1505, 1430, 1035; *Mass*: 289 (M^+); *Anal. Calcd.* for $C_{17}H_{11}N_3O_2$: C, 70.58, H, 3.80, N, 14.53; *Found*: C, 70.74; H, 3.71; N, 14.62.

REFERENCES:

1. (a) H. R. Sullivan, W. M. Miller, D. G. Stark, P. G. Wood, *Xenobiotica*, **1981**, *9*, 548. (b) R. Carboni, R. V. Lindsay, *J. Am. Chem. Soc.*, **1959**, 81, 4342. (c) R. M. A. Rahman, M. Ghareib, *Ind. J. Chem.*, **1987**, 26(B), 496. (d) A. K. Mansour, M. M. Eid, R. A. Hassan, *J. Heterocycl. Chem.*, **1988**, 25, 279. (e) R. M. A. Rahman, *Ind. J. Chem.*, **1988**, *27*(B), 548.
2. (a) P. V. Laakso, R. Robinson, "*Festchrift Karrer*," **1948**, Birkhauaer, Zurich, 38. (b) P. V. Laakso, R. Robinson, H. P. Vandrewala, *Tetrahedron*, **1957**, *1*, 103.
3. (a) CIBA Ltd., *Belg. Pat.*, 615, 619 (Sept. 27, **1962**); *Chem. Abstr.*, **1963**, *58*, 12583a. (b) A. G. Kalle, *Ger. Pat.* 1, 009, 846, (Feb, 16, **1961**); *Chem. Abstr.*, **1963**, *58*, 11382h.
4. (a) R. Metze, *Chem. Ber.*, **1958**, *91*, 1861. (b) R. Metze, G. Rolle, *Chem. Ber.*, **1958**, *91*, 422. (c) R. Metze, S. Meyer, *Chem. Ber.*, **1957**, *90*, 481. (d) R. Metze, *Chem. Ber.*, **1956**, *89*, 2056. (e) *Ibid.*, **1955**, *88*, 772. (f) R. Metze, *East Ger. Pat.* 13, 175, (May, 3, **1957**); *Chem. Abstr.*, **1959**, 53, 7216i. (g) R. Metze, and W. Kort, *Chem. Ber.*, **1957**, *91*, 417.
5. H. Hasselquist, *Ark. Kem.*, **1960**, *15*, 387
6. R. Metze, *Chem. Ber.*, **1954**, *87*, 1540.
7. (a) H. Neunhoeffer, H. W. Fruhauf, *Ann. Chem.*, **1972**, *102*, 760. (b) H. Neunhoeffer, F. Weischedel, *Ann. Chem.*, **1971**, *101*, 749. (c) H. G. O. Becker, G. Pauli, H-J. Timpe, H-D. Steinleitner, *Z. Chem.*, **1968**, *8*, *105*. (d) M. M. Bursey, T. A. Elwood, *J. Org. Chem.*, **1970**, *35*, 793. (e) F. H. Case, *J. Heterocycl. Chem.*, **1973**, *10*, 353 (g) *Ibid.*, **1971**, *8*, 1043, 173. (h) *Ibid.*,

1970, *7*, 1001. (i) *Ibid.*, **1968**, *5*, 413, 223. (j) F. H. Case, *J. Org. Chem.*, **1966**, *31*, 2398. (k) *Ibid.*, **1965**, *30*, 931. (l) F. H. Case, L. Kennon, *J. Heterocycl. Chem.*, **1967**, *4*, 483. (m) B. M. Culbertson, G. R. Parr, *J. Heterocycl. Chem.*, **1967**, *4*, 422 (n) J. F. Geldord, *Inorg. Chem.*, **1965**, *4*, 417. (o) E. Kiss, *Anal. Chim. Acta.*, **1974**, *72*, 127. (p) H. Neunhoeffer, L. Motitschke, H. Hennig, K. Ostheimer, *Ann. Chem.*, **1972**, *88*, 760).

8. C. M. Atkinson, H. D. Cossey; *J. Am. Chem. Soc.*, **1962**, 1805.
9. Davidson, Weiss, and Jelling, *J. Org. Chem.*, **1937**, 2, 319.
10. (a). R. Metze, G. Rolle, G. Scherowsky, *Chem. Ber.*, **1959**, *92*, 2478. (b) R. Metze, *Chem. Ber.*, **1958**, *91*, 1863.
11. V. Sprio, P. Madonia, *Gazz. Chim. Ital.*, **1957**, *87*, 992.
12. (a) H. Neunhoeffer, H. Hennig, *Chem. Ber.*, **1968**, *101*, 3952. (b) H. Paul, S. Chatterjee, G. Hilgetag, *Chem. Ber.*, **1968**, *101*, 3696.
13. H. Neunhoeffer, H. Hennig, H. W. Fruhauf, M. Mutterer, *Tetrahedron. Lett.*, **1969**, *37*, 3147.
14. Y. Kato, Y. Hirao, *Kyushu Kogyo Daigaku Kenkyu Hokoku*, **1965**, *15*, 57; *Chem Abstr.*, **1967**, *66*, 948439.
15. W. W. Paudler, T. K. Chen, *J. Heterocycl. Chem.*, **1970**, *7*, 767.
16. Rossi, Rend. Ist. Lombardi. Sci., Pt 1, *Classe Sci. Mat. Nat.*, **1955**, *88*, 185.
17. S. Konno, M. Sagi, M. Agata, Y. Aizawa, H. Yamanaka, *Heterocycles*, **1984**, *22*, 2241.
18. (a) E. C. Taylor, L. G. French, *J. Org. Chem.*, **1989**, *54*, 1245. (b) E. C. Taylor, J. E. Macor, J. L. Pont, *Tetrahedron;* **1987**, *43*, 5145.
19. J. Daunis, R. Jacquier, C. Pigiere, *Tetrahedron*, **1974**, *30*, 3171.

20. (a) S. Konno, M. Sagi, Y. Yuki, Y. Yamanaka, *Heterocycles,* **1985**, *23*, 2807. (b) S. Konno, S. Ohba, M. Sagi, Y. Yuki, Y. Yamanaka, *Chem. Pharm. Bull.*, **1987**, *23*, 1378.

21. The catalytic reduction of 34a in palladium charcoal did not give the desired product but gave the corresponding dihydro compound.

22. S. Konno, S. Ohba, M. Sagi, H. Yamanaka, *Heterocycles*, **1987**, *23*, 2807.

23. C. Grundmann, H. Schroeder, R. Ratz, *J. Org. Chem.*, **1958**, *23*, 1522.

24. The analogous result had been reported on the alkaline treatment of 4-benzoylquinazoline [T. Higashino, M. Takemoto, and E. Hayashi, *Chem. Pharm. Bull.*, **1985**, *33*, 1351.

25. C. Grundmann, R. Ratz, *Chem. Ber.*, **1968**, *91*, 1766.

26. R. Ratz, H. Schroeder, *J. Org. Chem.*, **1958**, *23*, 1931.

27. K. Koermendy, P. Sohar, J. Volford, *Ann. Univ. Sci.*, Budapest. R. E. Nominatae, *Sect. Chim.*, **1963**, *5*, 117; *Chem. Abstr.*, **1964**, *60*, 13243g.

28. W. W. Paudler, J. M. Barton, *J. Org. Chem.*, **1966**, *33*, 1720.

29. S. Konno, S. Fujimura, H. Yamanaka, *Heterocycles*, **1984**, *22*, 2245.

30. T. V. Saraswathi, V. R. Srinivasan, *Tetrahedron Lett.*, **1971**, *25*, 2315.

31. (a) P. Schmidt, J. Druey, *Helv. Chim. Acta.*, **1955**, *38*, 1560. (b) M. Gianturco, *Gazz. Chim. Ital.*, **1952**, *82*, 595. Also see references 2b, 6, 7p, 7b, 12a.

32. M. Mustafa, A. K. Mansour, H. A. A. Zaher, *J. Prakt. Chem.*, 1971, 313, 699. Also see references 2b, 8, 13, 7p, 4a.

33. *Vogel's Textbook of Practical Organic Chemistry; ELBS, Longman Group Ltd, England.*

CHAPTER-IV

"LEAD (IV) ACETATE OXIDATIONS"

GENERAL INTRODUCTION:

Lead tetra acetate, as a versatile oxidizing agent, has been used for selective and partial oxidation of various reactive groups, depending on the reaction conditions and nature of the substrate. It oxidizes organic molecules and itself gets reduced from lead (IV) to lead (II) either through ionic or radical mechanism. Synthetic applications of this reagent has increase in recent years. The manifold application of lead (IV) acetate during the last few decades have been naturally reflected in the publication of numerous papers and review articles.

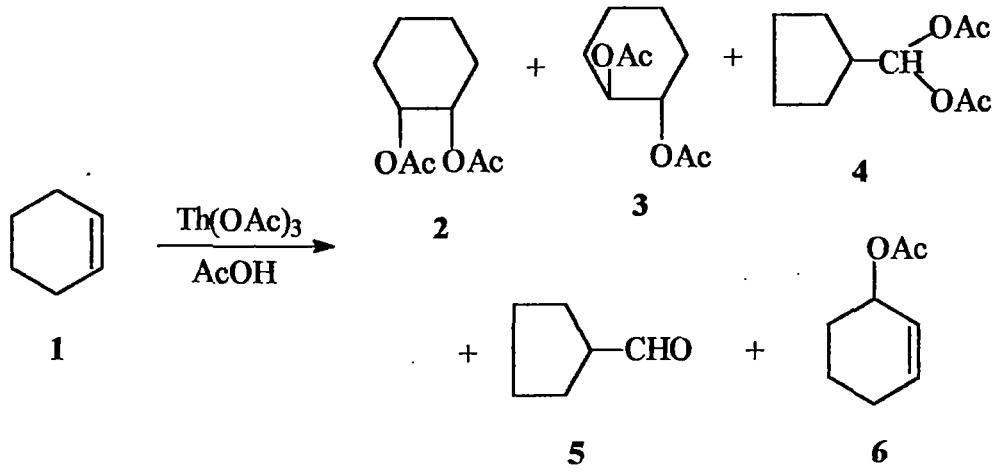
Some of these includes the reaction of lead (IV) acetate with olefins,[1] oxidative decarboxylation with lead (IV) acetate,[2] oxidation of alcohols by lead (IV) acetate,[3] the reaction of lead (IV) acetates with azomethines[4] and lead (IV) acetate oxidation of sugars with emphasis on glycol cleavage.[5] A number of useful general reviews on lead (IV) acetate have appeared. Fieser and Fieser[6] have discussed the uses of lead (IV) acetate in a broad range of of synthetic processes, while Aylward[7] has reviewed the general behaviour of lead (IV) acetate towards organic nitrogen compounds.

It is interesting to note that despite an array of diverse synthetic applications of lead (IV) acetate in organic synthesis, there were only a few synthetically useful processes based on oxyplumbation in contrast to oxymercuration[8] and oxythallation[9] studies which have led to the development of a series of reactions of immense synthetic utility in recent years.

Metallation and oxymetallation reaction have been observed with salts of a few metals only *viz* mercury (II), thallium (III), lead (IV), palladium (II), gold (III), and platinum (II) which are known to possess 'soft acid' character.[10] Lead (IV) is

isoelectronic with mercury (II) and thallium (III). The oxidation potential of lead (IV) is lowest in the series[11] and consequently the relative oxidizing 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 these three metals have shown that thallium (III) acetates occupies a place between lead (IV) acetate and mercury (II) acetate.[12] This has been elaborated by the oxidation of cyclohexene[13] with Thallium (III) acetate in acetic acid at room temperature for several days to yield cis/trans diacetates **2** and **3** (40-50%), ring contracted diacetate **4** and aldehyde **5** (50-60%) and allylic oxidation product **6** (2-3%) (Scheme-1).

In dry solvent the trans diacetate **3** is obtained in major yield (88%), whereas in moist solvent the cis diacetate **2** (81%) predominates.



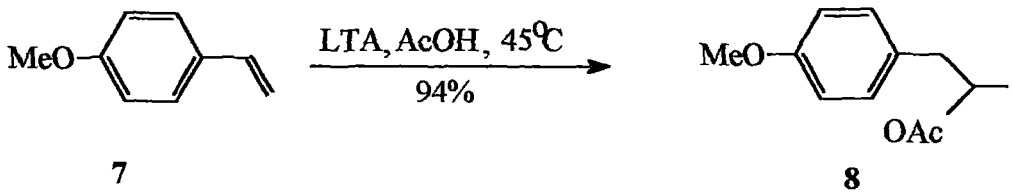
1 2 3 4 5 6

Scheme-1

Although oxyplumbation adducts have been postulated as intermediates in these reactions, direct evidence for the key organolead intermediate have not been obtained exept as organic derivative of lead from the reaction of pregnenolene and

diacetatedifluoro 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.

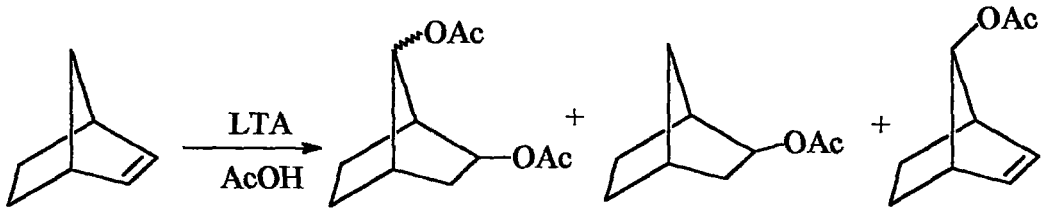
Lead (IV) acetate appears to have been first used as an oxidant by Dimroth, Friedamann, Kamerer.[14] One of the most widely applicable reactions of lead (IV) acetate is the introduction of the acetoxyl group in a molecule. The acetoxylation of saturated hydrocarbons by lead (IV) acetate in presence of short chain alcohol is considered to proceed *via* alkoxy radicals as transient intermediates, which abstract a hydrogen atom from cyclohexane.[15] In the oxidation of mono and disubstituted acyclic olefins with lead (IV) acetate, three competitive reactions occurs, namely, 1, 2-acetoxylation, allylic substitution and allylic migration leading to a complex mixture of products, without much synthetic value.[16] Styrene **7** affords 1, 1-diacetoxy derivatives **8** when the lead (IV) acetate reaction is performed in acetic acid, while in benzene solution products resulting from the addition of both the methyl and an acetoxy group to the alkenic double bond are formed[17] (Scheme-2).



7 **8**

Scheme-2

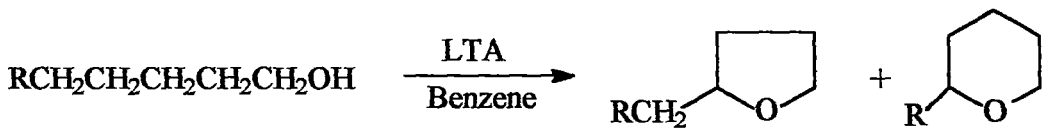
On oxidation with cyclic alkenes, the products formed depend on the ring size, solvent and reaction conditions. Thus the lead tetra acetate oxidation of cyclohexene,[18-21] cycloheptene and cyclooctene[22] gave 1, 2-diacetates, 3-acetoxy cycloalkenes as the major product. Norbornene **9** reacts with lead tetra acetate to give rearranged products in which 2, 7-acetoxy norbornene **10** predominates[23] (Scheme-3).



9 **10** **11** **12**

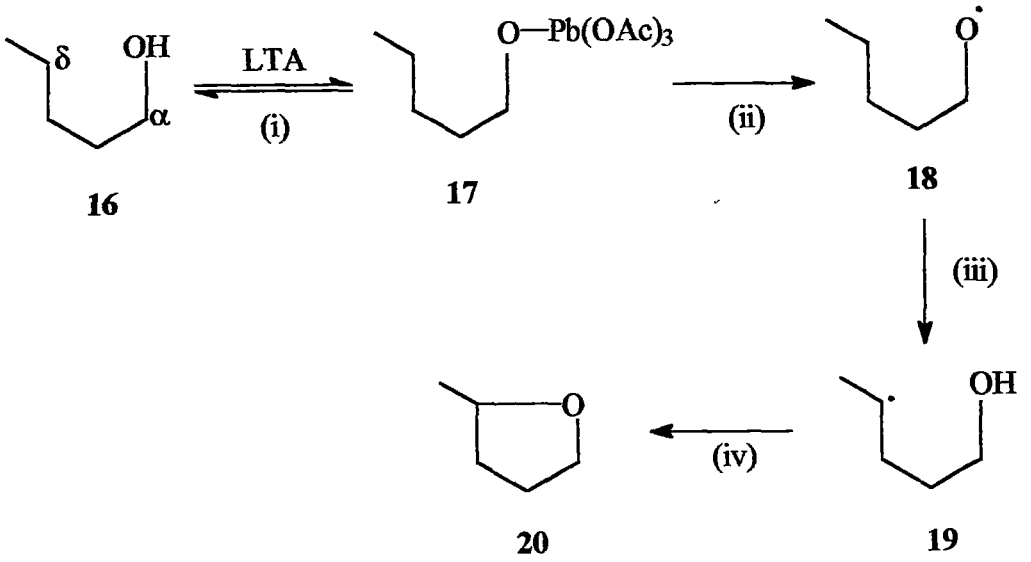
Scheme-3

Alcohols in presence of lead tetra acetate underwent cyclization to cyclic ethers. Treatment of saturated alcohols **13** with lead tetra acetate in hot benzene results in cyclization at the 4-C giving tetrahydrofuran **14** together with lesser yields of tetrahydropyrans[24, 25] **15** (Scheme-4).



13 **14** **15**

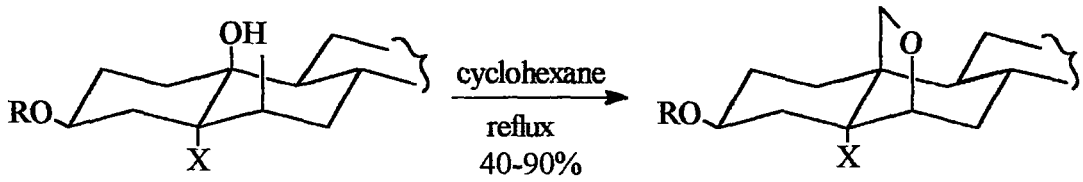
Scheme-4



16 17 18 19 20

Scheme-5

With short chain alcohols eg, 1-propanol where 4-C cyclization didnot occur, complicated reactions were observed in benzene giving large number of products.[26] The lead tetra acetate oxidation of alcohols to cyclic ethers has been successfully applied as a synthetic method for activation of the angular 18- and 19- methyl groups in steroidal alcohols containing a β-oriented hydroxy groups at C-2, C-4, C-6 and C-11[27, 28] (Scheme-6).

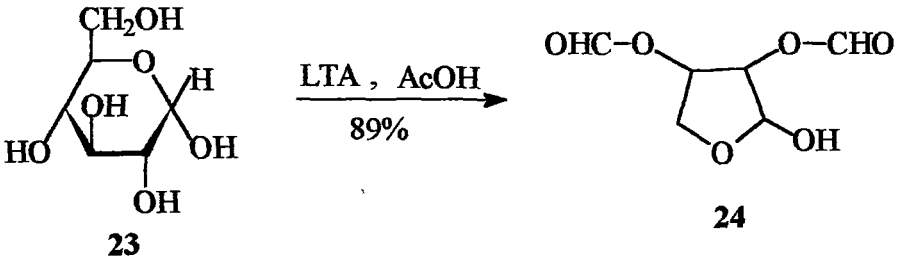


21 22

R= H, Cl, Br, OH X = halogens

Scheme-6

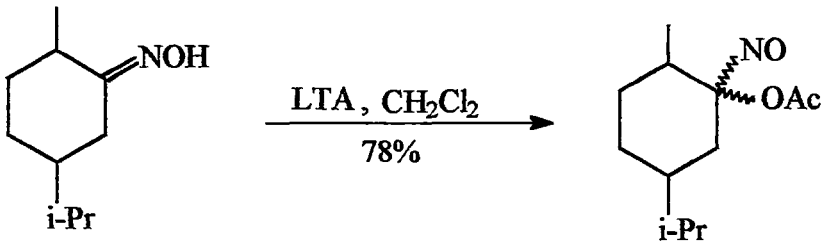
Lead (IV) acetate is also one of the most frequently used reagent for the cleavage of 1, 2-glycols and the preparation of carbonyl compounds.[29] The reactions are performed in either aprotic or in protic solvents.[30, 31] 1, 2-glycol cleavage by lead tetra acetate has been widely applied for the oxidation of carbohydrates and sugars.[32, 33] (Scheme-7).



23 **24**

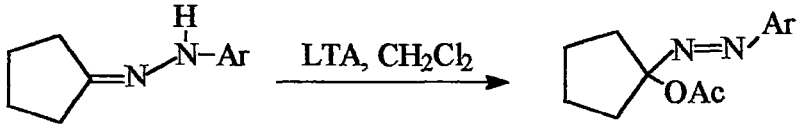
Scheme-7

The reaction of lead tetra acetate with nitrogen containing compounds have been studied extensively by R. N. Butler and coworkers.[32] Aliphatic ketoximes **25** upon treatment with Lead (IV) acetate in an inert solvent, undergoes acetoxylation at the α carbon producing 1-nitroso-1-acetoxy-alkanes[33] **26** (Scheme-8) whereas hydrazones **27** affords azoacetates **28** (Scheme-9) or, when the reactions are performed in alcoholic solvents, azo ethers.[34] Aryl hydrazines, N, N'-disubstituted hydrazines,[35] and N-amino compounds[36] are oxidised by Lead(IV) acetate to different products.



25 26

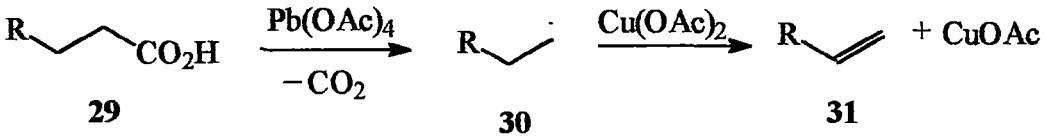
Scheme-8



27 28

Scheme-9

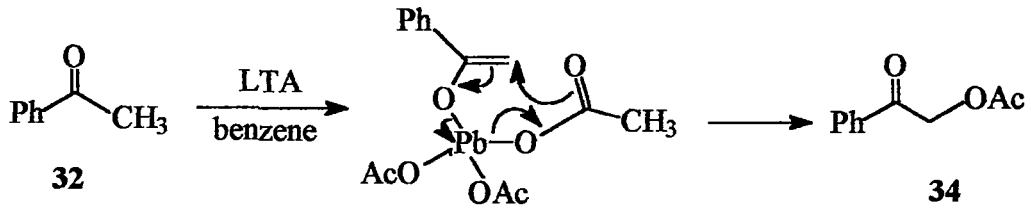
Lead tetra acetate has also been used as a decarboxylating agent. Buchi[37] effected oxidative decarboxylation of the monocarboxylic acid by refluxing it with lead (IV)acetate in benzene under nitrogen for 14 hours. The olefinic isomers were separated by gas chromatography and isolated in small amounts. However due to low yields and mixture of products this reaction proved to be of little synthetic value. So Bacha and coworkers modified this reaction by using catalytic amounts of Cu (II) acetate which greatly enhanced the rate of decarboxylation and yields of alkenes.[38] This effect of Cu (II) acetate is attributed to the rapid scavenging of the intermediately formed alkyl radicals by Cu (II) ions (Scheme-10).



29 **30** **31**

Scheme-10

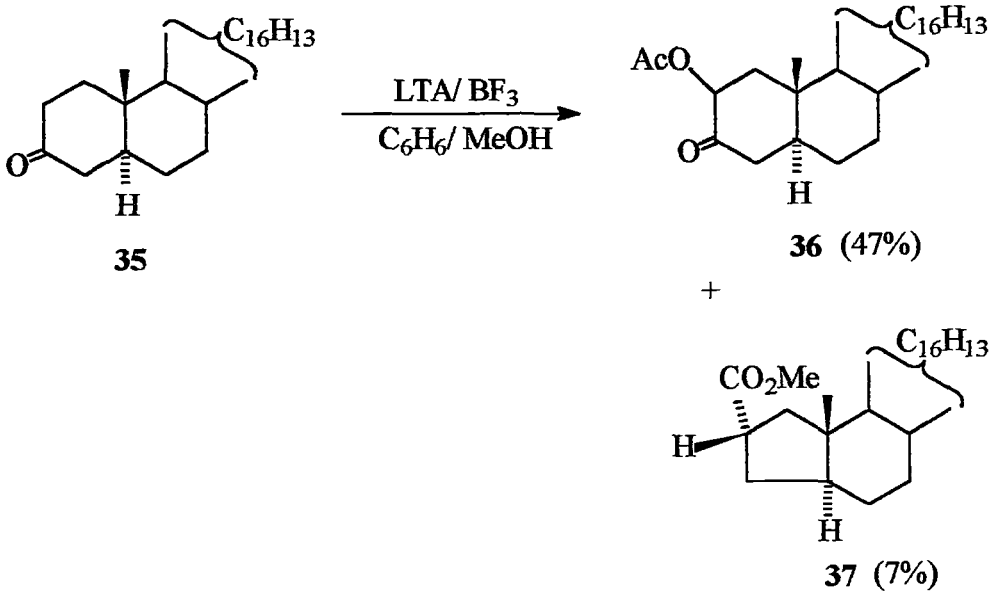
Enolisable ketones **32** readily yield α-acetoxy ketones **34** on oxidation with lead (IV) acetate[39] in hot acetic acid or benzene at reflux. The reaction proceeds *via* an organometallic intermediate **33** (Scheme-11).



32 **33** **34**

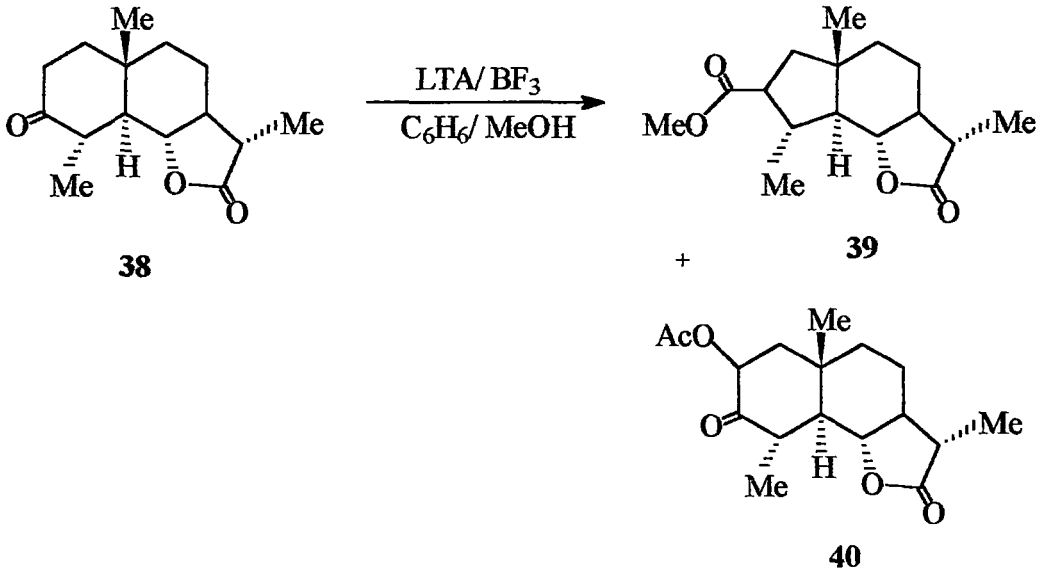
Scheme-11

Henbest and coworkers[40] have shown that BF_3 acts as a strong catalyst in acetoxylation and they observed that when 5 α-cholestan-3-one **35** was treated with lead (IV) acetate in benzene/methanol in presence of borontrifluoride-etherate yielded besides the actoxylation product **36**, a ring contracted product methyl A-norcholestane-2α-ccarboxylate **37** in low yield (Scheme-12).



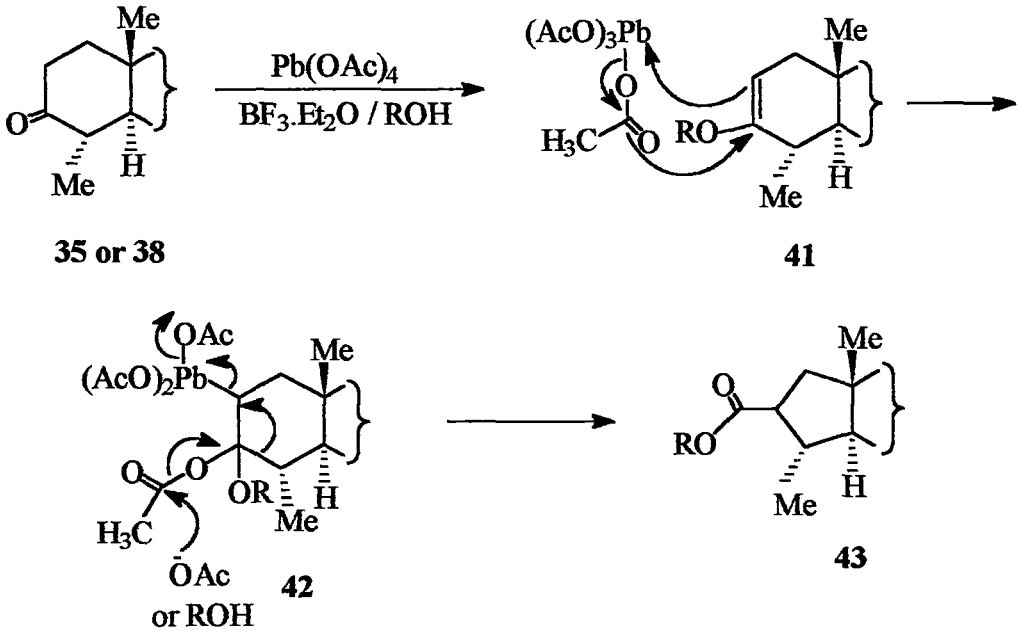
Scheme-12

Using the same reagent combination, α-santonin **38** was reported[41] to give 40% of the ring contracted product **39**, besides 20% of the acetoxylated product **40**.



Scheme-13

These authors have postulated the formation of **43** *via* the enol ether **41** which on oxyplumbation followed by subsequent rearrangement of the adduct **42** yielded **43** (Scheme-14).

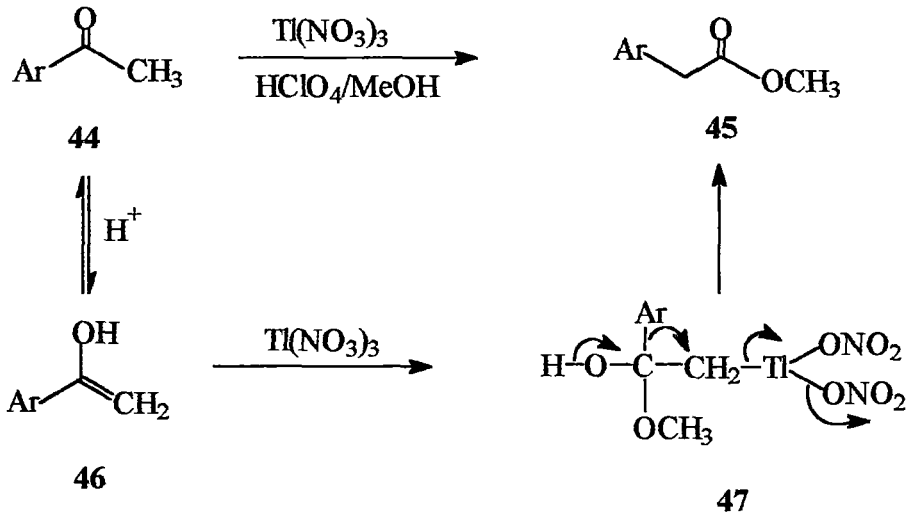


Scheme-14

In 1887, Willgerodt developed a method for the preparation of phenyl acetic acid by reacting ammonium sulphide and acetophenones under pressure at about 200°C, which later became known as the Willgerodt reaction.[42] Extension of this reaction was hampered by modest yields of the carboxylic acid. Several modifications were subsequently extended to improve the yields of the products. Since the conversion of aryl ketones to the corresponding phenyl acetic acid was of synthetic use, substantial modification of this reaction was first introduced by Kindler[43, 44] in 1923, wherein the use of pressure was avoided and by introducing anhydrous aliphatic amines at a maximum temperature of 180°C, the yield was

improved. This method was continued to be used although it could not be extended to acetophenones which undergo polymerisation under these conditions.

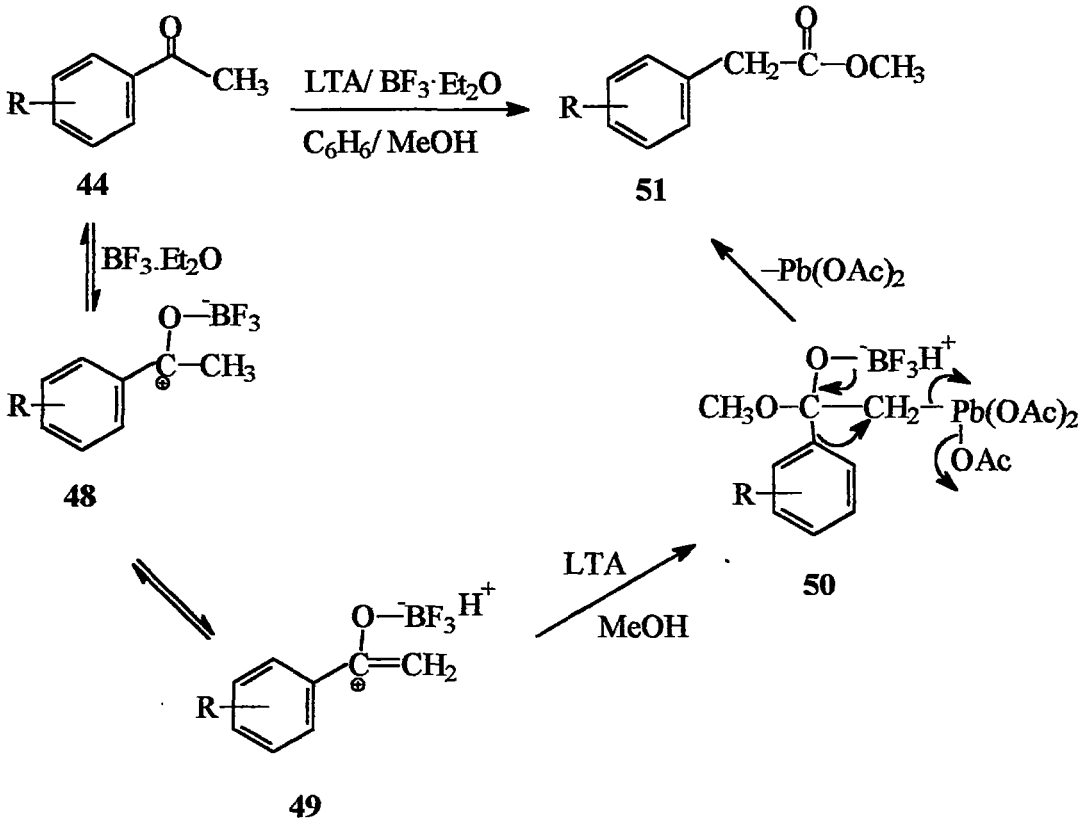
Taylor and Mc Killop[45] in 1971 developed a method for the conversion of acetophenones **44** to the corresponding methyl aryl acetates **45** at room temperature. The oxidation was carried out using Thallium (III) nitrate in presence of perchloric acid and methanol. A mechanism involving oxythallation adduct **47** *via* enol **46** has been suggested for this rearrangement (Scheme-15).



Scheme-15

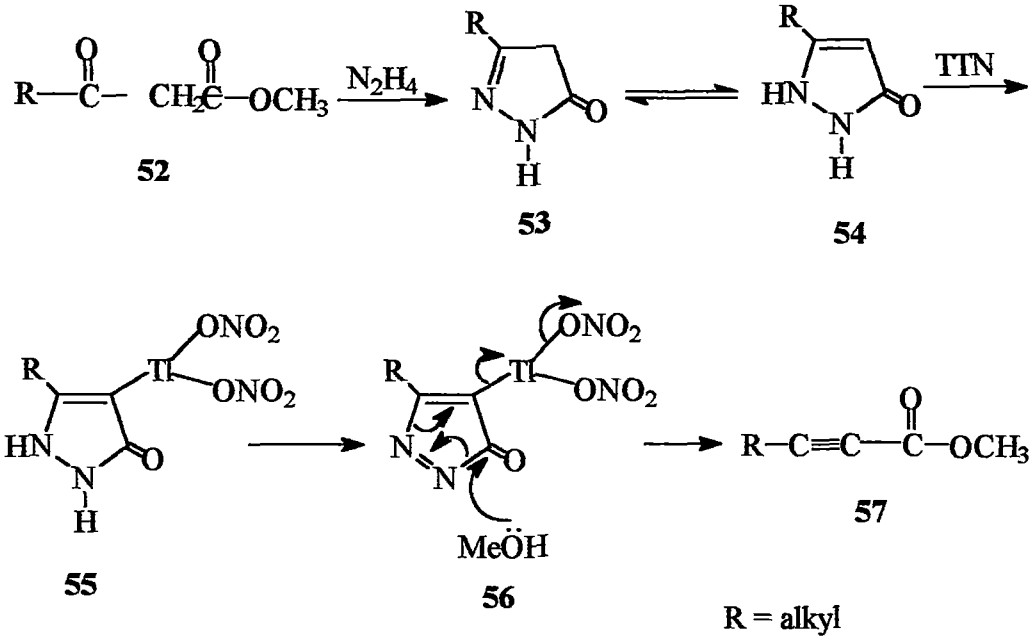
A similar conversion was reported by Myrboh and coworkers[46] where oxidation was carried out by lead tetra acetate in presence of methanol and borontrifluoride-etherate in dry benzene with the yield being excellent. The mechanism suggested involves the initial enolisation of the ketones **44** assisted by borontrifluoride-etherate followed by oxyplumbation to give **50** and subsequent

migration of the aryl group with the removal of lead (II) acetate gives the product **51** (Scheme-16).



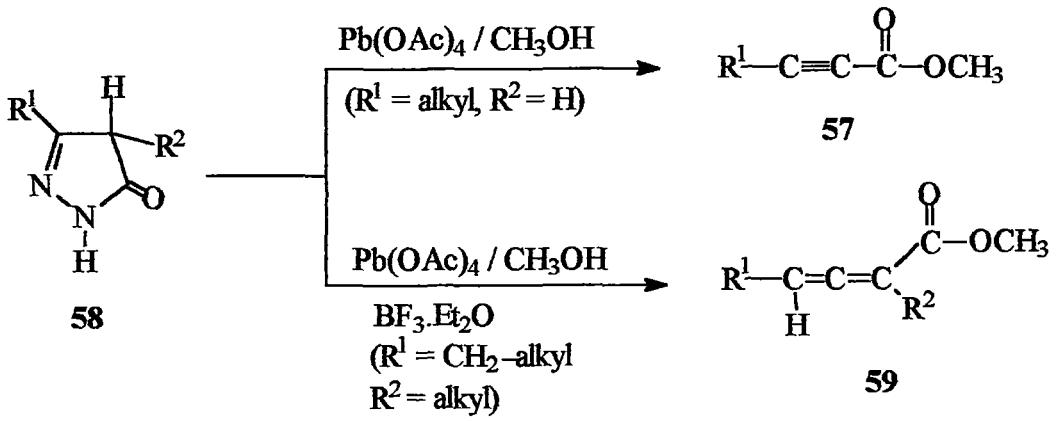
Scheme-16

Previously Taylor and Mc Killop[47] have reported the conversion of 5-pyrazolones **53**, which were readily prepared from β-keto esters **52** to the esters of β-alkynoic acid by thallium (III) nitrate in methanol (Scheme-17). A mechanism involving initial thallation of enemine tautomer of 5-pyrazolone followed by a sequence of reactions as depicted in scheme-15 has been suggested for the transformation.



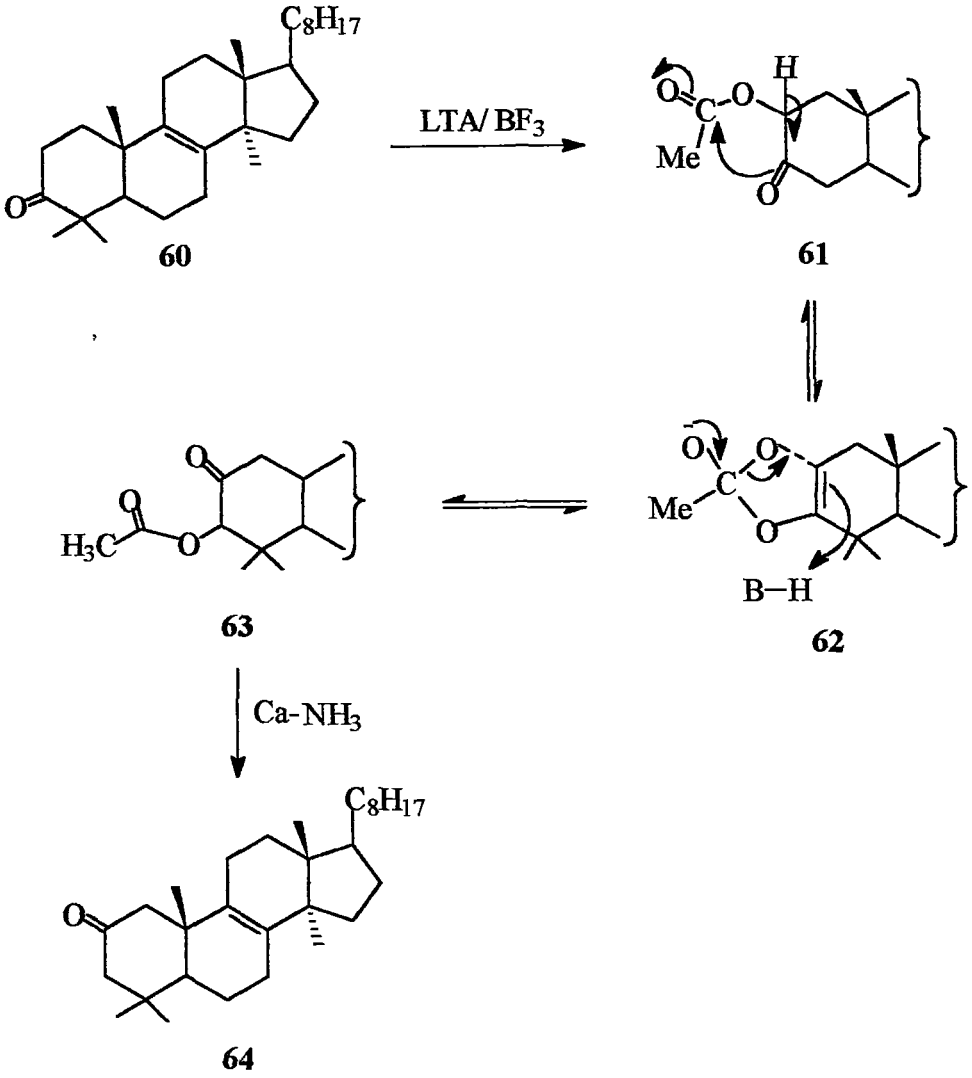
Scheme-17

Myrboh and coworkers[46] further reported the oxidation of 2, 3-disubstituted-5-pyrazolones **58** with lead (IV) acetate in methanol which afforded 2-alkynoic **57** and 2,3-alkadienoic (allenic) **59** esters respectively in moderate to high yields. It was found[47] that when the 5-oxo-3-phenyl pyrazole was treated with lead (IV) acetate in methanol, the corresponding methyl phenyl propyolate was obtained in 40% yield. (Scheme-18). When the reaction was extended to 3, 4-disubstituted 5-oxo-4, 5-dihydropyrazoles, the expected 2, 3-alkenedienoic (allenic) esters **59** were formed in excellent yields.



Scheme-18

A survey of the literature revealed that a successful attempt at 1, 2-carbonyl transposition was simultaneously reported by Perkin[48] and Bredt[49] in 1911. Since then other methods were developed dealing with 1,2-carbonyl transposition in the terpene systems[50,51] and steroids systems. In 1944, Ruzika and Coworkers[52] developed a method of conversion of cholestan-3-one **60** to chlostan-2-one **64**. Subsequently, numerous ketones transposition have appeared in literature as solutions to problems especially in steroid chemistry and have employed a wide spectrum of organic reagents in the transposition step. A. Leblache Combier and coworkers[53] have reported that lanos-8-en-3-one **60** on treatment with lead (IV) acetate-borontriflouride gave the vicinal acetoxy kotone **61** which undergo isomerisation to **63** which then gave the desired product **64** (Scheme-19).

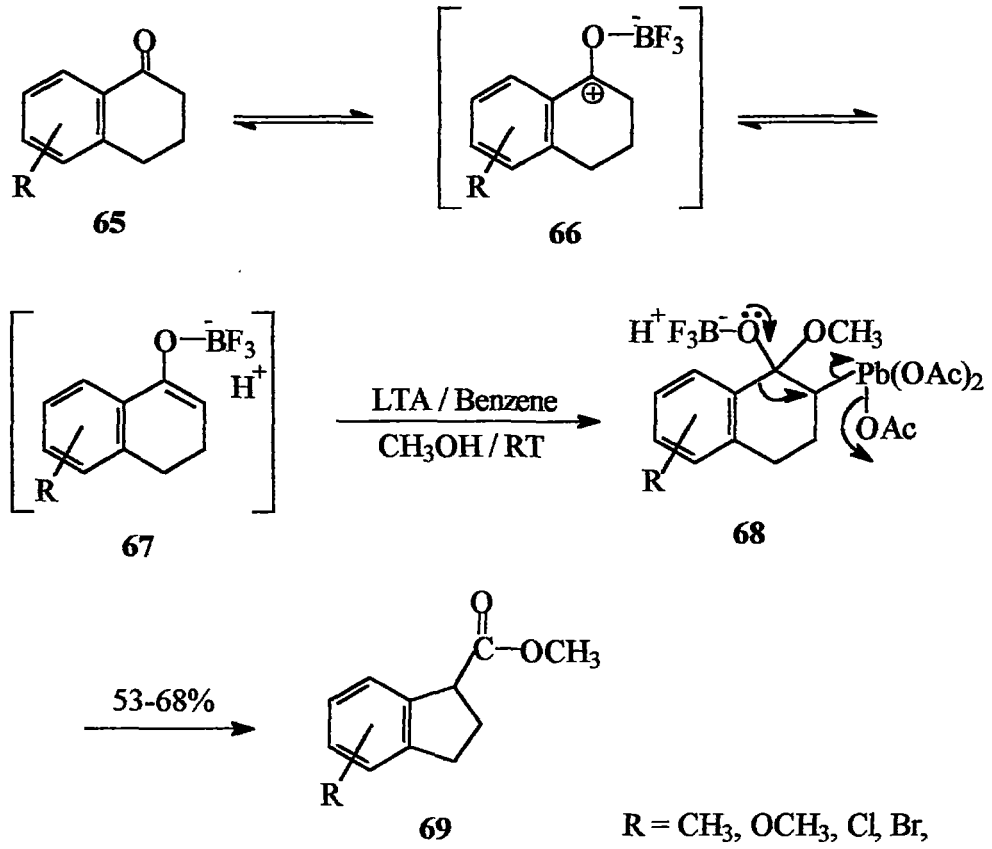


Scheme-19

A novel one step transformation for 1, 2-carbonyl transposition was reported by Mc Killop and Taylor[54] wherein they have found that Thallium (III) nitrate in acidic methanol rearranged acetophenones to methyl phenyl acetate.

In 1987, Myrboh and coworkers[55] have used Lead (IV) acetate, boron trifluoride etherate and methanol combination in the synthesis of biologically important indane-1-carboxylates. Here a 1, 2-carbonyl transposition was obtained by

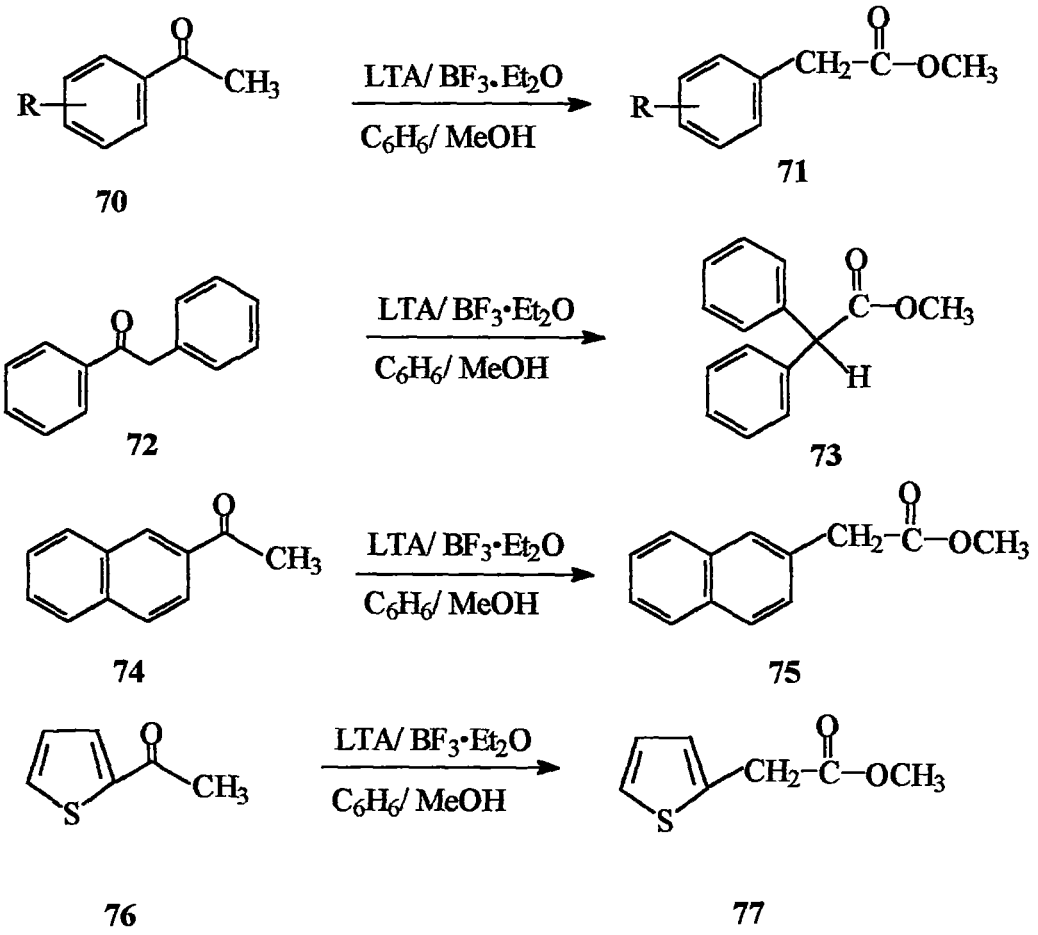
a smooth ring contraction of tetralones **65** to the methyl indane-1-carboxylates **69** in moderate yield (Scheme-20).



Scheme-20

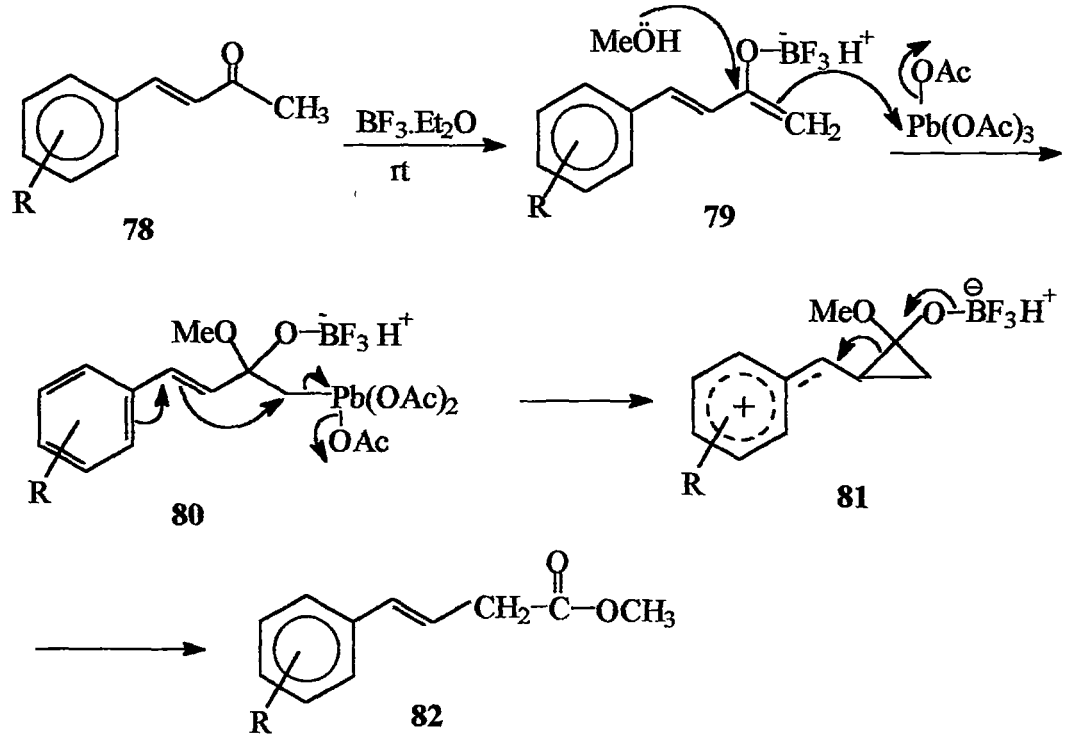
Rathke[56] and Schlessinger[57] had independently carried out the detail work in the field of β,γ-unsaturated esters. Nakanishi[58] has reported a route to the synthesis of β,γ-unsaturated esters *via* carboxylation of $(\eta^3$-Allyl)$Fe(CO)_2NO$ complexes. Unsaturated organic molecules both aliphatic 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 substituted acetophenones[59] **70** and deoxybenzoin **72** using Lead (IV) acetate/ borontrifluoride etherate and methanol system has been carried out successfully in the transformation to methyl aryl acetate **71** and 2, 2-diphenyl methyl acetate **73** respectively. The same methodology has been extended to acetyl naphthalene **74** and 2-acetyl thiophene **75** to their corresponding esters (Scheme-19)



Scheme-21

The synthesis of β, γ-unsaturated carboxylic esters **82** *via* 1, 2-transposition of α, β-unsaturated ketones was reported by F. Mathew and Myrboh.[60] The mechanism seems to involve the initial enolisation of the carbonyl function assisted by boron trifluoride etherate combination followed by oxyplumbation to afford **80**. The formation of the carbocation was stbilised by neighbouring π-electron to give the cyclopropyl intermediate **81** that upon ring opening yielded the product **82** (Scheme-22). The β,γ- unsaturated esters were further hydrolysed with 2 N aqueous NaOH to give the corresponding carboxylic acid.



Scheme-22

References:

1. R. M. Moriorty, in *"Selective Organic Transformations"* (editted by B. S. Thyagaragin) John Willey and sons, Inc., Newyork **1972**, *2*, 183.
2. R. A. Sheldon, and J. K. Kochi, *Organic reactions*, **1972**, *19*, 279.
3. M. Mihialovich, R. E. Partch, in *"Selective Organic Transformations"* (editted by B. S Thyagaragin) John Willey and sons, Inc., Newyork **1972**, *2*, 97-181.
4. R. N. Buttler, F. L. Scott, T. A. F. Mahony, *Chem. Rev.*, **1973**, *73*, 93.
5. A. S. Perlin, *Adv in Carbohydrate Chem.*, **1959**, *14*, 9.
6. L. F. Fieser and M. Fieser, *Reagents for organic synthesis*," **1962**, *1*, 536, **1969**, *2*, 234, **1972**, *3*, 168.
7. J. B. Aylward, *Quart. Rev.*, **1971**, *25*, 407.
8. (a) W. Kitching, Organometal. *Chem. Rev.*, 1968, 3, 61. (b) H. O. House, in *"Modern Synthetic Reactions"*, W. A. Benjamin Inc., 2nd edition, **1972**, 387.
9. A. Mckillop, E. C. Taylor in '*Adv. Organometal. Chem.*,' Vol II, edited by F. G. A. Stone, and R. West, Academic Press, **1973**, 147.
10. R. G. Pearson, *Surv. Progr. Chem.*, **1969**, *5*, 1.
11. W. Latimer, "oxidation potentials" 2nd edition, Prentice Hall, Englewood Cliffs, New Jersy, **1961**.
12. H. Kabbe, *Justus. Liebigs. Ann.*, **1962**, *256*, 204.
13. C. B. Anderson, S. Winstein, *J. Org. Chem.*, **1963**, *28*, 605.
14. O. Dimroth, O. Friedmann, H. Kammerer, *Ber.*, **1920**, *53*, 481.
15. Walling, and J. Kjellgren, *J. Org. Chem.*, **1969**, *34*, 1488.

16. (a) E, Detilluex, J. Jadol, *Bull. Soc. R. Sci. Liege.*, **1955**, *24*, 366. (b) A. Lithbridge, R. O. C. Norman, and C. B. Thomas, *J. Chem. Soc. Perkin Trans. 1*, **1974**, 1929, **1975**, 231.

17. K. B. Wiberg, D. Nielsen, *J. Org. Chem.*, **1964**, *29*, 3353.

18. R. Criegee, *Angew Chem.*, **1958**, *70*, 173.

19. C. B. Anderson, S. Winstein, *J. Org. Chem.*, **1963**, *28*. 605.

20. R. Criegee, *Angew Chem.*, 1940, *53*, 321.

21. H. J. Kabbe, *Ann. Chem.*, **1962**, *204*,656.

22. A. C. Cope, M. Gordon, S. Moon, C. H. Park, *J. Am. Chem. Soc.*, **1965**, *87*, 3119.

23. (a) J. Kagan, *Helv. Chemi. Acta.*, **1972**, *55*, 2356. (b) K. Alder, F. H. Flockand, H. Wirtz, *Chem. Ber.*, **1958**, *91*,609, *52*, 13652g.

24. V. M. Micovic, R. I. Mamuzic, D. Jeremic, M. Lj. Mihailovic, *Tetrahedron Lett.*, **1963**, 2091.

25. D. Hauser, K. Schaffner, O. Jeger, *Helv. Chim. Acta.*, **1964**, *47*, 1883, 62, 3997b.

26. M. Lj. Michailovic, Z. Cekovic, Z. Maksimovic, D. Jeremic, Lj. Lorenc, R. I. Mamuzic, *Tetrahedron*, **1965**, 21, 1395.

27. K. Heusler, J. Kalvoda, *Ann. Chem.*, **1964**, *3*, 525.

28. K. Heusler, J. Kalvoda, In *"Steroid Synthesis"*; J. Fried, J. A. Edwards, Eds Reinhold; New York, **1972**; Vol II pp 237-287.

29. (a) C. A. Bunton, in *"Oxidation in Organic Chemistry"*, K. Wilberg, ed; Acedamic; New York, **1965**; part A pp 398-405. (b) A. S. Prelin, *Adv. Carbohydr. Chem.*, **1959**, *9*, 14.

30. (a) R. Criegee, E. Hoger, G. Huber, P. Kruck, F. Marktscheffel, H. Schellenberger, *Liebigs. Annalen,* **1956**, *81*, 599. (b). R. Criegee, E. Buchner, W. Walther; *Chem. Ber.*, **1940**, *73*, 571.

31. (a). F. J. Wolf, J. Weijlard, *Org. Synth. Chem.*, **1963**, 4, 124. (b) C. T. Bishop, *Methods in Carbohydr. Chem.*, **1972**, *6*, 350. (c). P. S. O. Colla, *Methods in Carbohydr. Chem.*, **1965**, *5*, 382.

32. R. N. Butler, F. L. Scott, T. A. F. O'Mahony, *Chem. Rev.*, **1973**, *73*, 93.

33. (a) H. Kropf, R. Lambek, *Liebigs Annalen*, **1966**, *18*, 700. (b) D. Shafiullah, H. Ali, *Synthesis*, **1979**, 124. (c) S. Kaufmann, L. Tokes, J. W. Murphy, P. Crabbe, *J. Org. Chem.*, **1969**, *34*, 1618.

34. (a) D. C. Iffland, L. Salisbury, W. R. Schafer, *J. Am. Chem. Soc.*, **1961**, *83*, 747. (b) M. J. Harrison, R. O. C. Norman, W. A. F. Gladstone, *J. Chem. Soc. (c)*, **1976**, 735.

35. (a) J. B. Aylward, *J. Chem. Soc.(c)*, **1969**, 1663. (b) R. W. Hoffman, *Chem. Ber.*, **1964**, *97*, 2772. (c) R. J. Clement, *J. Org. Chem.*, **1960**, *25*, 1724. (d) A. P. Schaap, G. R. Faler, *J. Org. Chem.*, **1973**, *38*, 3061.

36. H. Pearson, C. Fayat, F. Tonnard, A. Foucand, *Bull. Soc. Chim. Fr.*, **1974**, 635.

37. G. Buchi, R. E. Erikson, N. Wakabayashi, *J. Am. Chem. Soc.*, **1961**, *84*, 927.

38. J. D. Bacha, J. K. Kochi, *Tetrahedron*, **1968**, *24*, 2215.

39. K. Ichikawa, Y. Tamaguchi, *J. Chem. Soc. Jpn.*, **1952**, *73*, 415; 47: 10474d.

40. H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.(c).*, **1967**, 756.

41. H. Miura, Y. Fijumato, T. Talsuno, *Synthesis*, **1979**, 898.

42. C. Willgerodt, *Ber. Deut. Chem. Ges.*, **1887**, *20*, 2467.

43. K. Kindler, *Ann. Chem. Liebigs.*, **1923**, 431, 187.

44. K. Kindler, *Arch. Pharm.*, **1927**, *265*, 389; *German Patent*, 405675, **1923**; P. Friedlander, *'Fortschritte der Teerfarbenfabrikation and Verdwanter Industriesweige,'* vol 14, p 372; Springer, Berlin, 1921-1925; K. Kindler, and W. Psechke, *Arch. Pharm.*, 1932, 270, 340, 347.; 1934, 272, 236; K. Kindler, and T. Li, *Ber. Deut. chem. Ges.*, 1941, 74, 321.

45. A. Mc. Killop, B. P. Swann, E. C. Taylor, *J. Am. Chem. Soc.*, **1971**, 93, 4919.

46. B. Myrboh, H. Ila, H. Junjappa, *Synthesis*, **1982**, 1100.

47. E. C. Taylor, R. L. Robey, A. McKillop, *J. Org. Chem.*, **1972**, *37*, 2797.

48. L. R. Lankshear, Jr. W.H. Perkin, *J. Chem. Soc.*, **1911**, 27, 161.

49. J. Bredt, Von W. Hilbing, *Chem. Zeit.* **1911**, 35, 765. see also *Chemisches Zentralblatt*, **1911**, 2954.

50. J. Bredt, Jr. W. H. Perkin, *J. Chem. Soc.*, **1913**, *29*, 2182.

51. G. Gompa, A. Klami, A. M. Kuvaja, *Ann.*, **1941**, 547, 185.

52. L. Ruzicka, D. A. Plattner, M. Fulirer, *Helv. Chim. Acta.*, **1944**, *27*, 524.

53. A. Lablache-Combier, B. Lacoume, J. Levislks, *Bull. Soc. Chim. Fr.*, **1966**, 897.

54. A. Mc. Killop, B. P. Swann, E. C. Taylor, *J. Am. Chem. Soc.*, **1973**, 95, 3340.

55. F. M. Nongrum, B. Myrboh, *Synthesis*, **1987**, 845.

56. M. W. Rathke, D. Sullivan, *Tetrahedron Lett.*, **1972**, 4249.

57. J. L. Herrmann, G. R. Kieczykowski, R. H. Schlessinger, *Tetrahedron Lett.*, **1973**, 2433.

58. S. I. Nakanishi, T. Yamamoto, N. Furukawa, Y. Otsuji, *Synthesis*, **1994**, 609.

59. B. Myrboh, H. Ila, H. Junjappa, *Synthesis*, **1981**, 126.

60. F. Mathew, B. Myrboh, *Tetrahedron. Lett.*, **1990**, 31, 3757.

Chapter-V

"Novel synthesis of substituted cyclopropane acetic acid ethyl esters from cyclopropyl alkyl ketones"

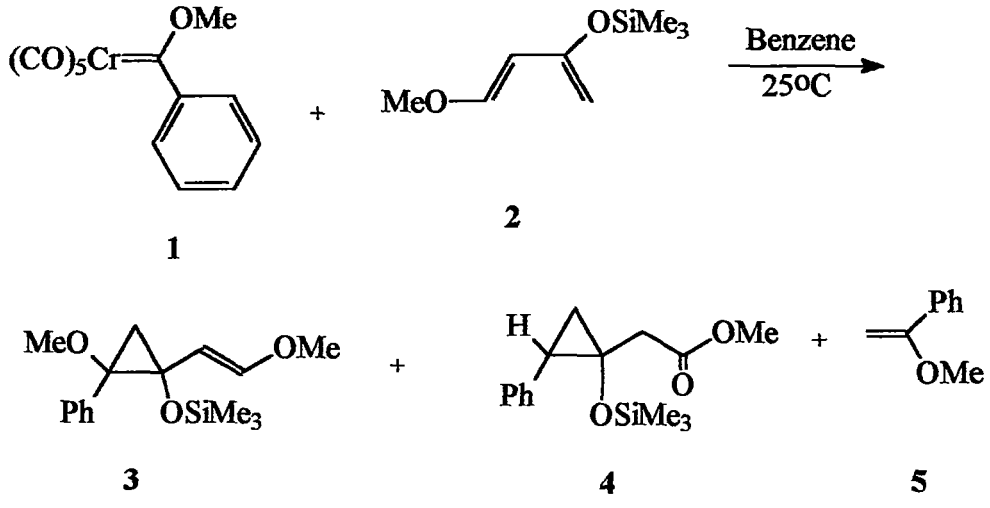
Introduction:

Organic structures containing small rings have received and are still receiving increasing attention over the years. The cyclopropane moiety can be found in a number of natural and unnatural substances, and some of these have received particular attention due to their biological properties.[1, 2] Hence this group continues to attract a lot of attention in synthetic organic chemistry as well as in medicinal and agricultural chemistry.[2a] Several methods for the preparation of cyclopropane and its derivatives have been developed, most of which however, suffer from lack of generality. The unique electronic properties of the cyclopropyl group[3] in conjunction with its inherent ring strain[4] make it a valuable entity in composite functionalities[5] which are indispensable for efficient organic synthesis.[6] Despite the many existing strategies for the efficient construction of cyclopropanes[7] search for improved methodologies towards functionalised cyclopropanes are still going on. Investigations are progressing[8] for the development of new, efficient methods for the selective synthesis of substituted cyclopropanes.

Our literature survey revealed that a number of research papers describing the synthesis, synthetic utility and reactions of cyclopropane system is tremendous. The well established techniques for the preparation of cyclopropanes from alkene involves using classical carbenoid reagents, free carbenes[9] or diazo reagents.[10] Reaction of mononuclear electrophilic transition metal carbonyl complexes with olefins[11] produce cyclopropanes. The pattern of reactivity observed in such reactions and the range of carbonyl moieties which may be transferred *via* an intermediate organometallic species demonstrate that this class of reaction is often complementary to the well established techniques. The reaction of transition metal

carbonyl complexes with olefins produced the substituted acetic acid ester with Danishefsky's diene in benzene.[12] However in almost all these transformations, cyclopropanation is always the last step in the synthesis of cyclopropyl derivatives. The cyclopropane was the result of the regioselective transfer of the carbonyl ligand to the more electron rich double bond of the diene.[13, 14]

Also produced in this reaction was α-methoxy styrene **5** (36%) which is the metathesis product resulting from the fragmentation of a metallocyclobutane intermediate and the interesting cyclopropane **4** is formally related to the expected products by an internal oxidative/reductive disproportionation which is unprecedented in cyclopropanation products from the reaction of transition metal carbonyl complexes (Scheme-1).



Scheme-1

Cyclopropanation reactions using ethyl diazoacetate has been reported widely, which can be achieved by heating with alkenes either with[15, 16, 17] or

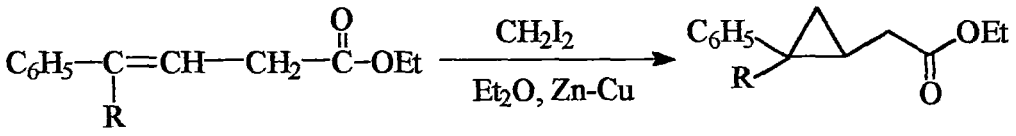
without[18] a catalyst. Various forms of copper have served most effectively as the catalyst.[15,16, 17, 19] Palladium (II) acetate has been found to be an efficient catalyst for carbene generation from diazomethane, [20,21,22] and for the ethyldiazoacetate cyclopropanation reaction. The advantage of Pd (II) acetate was that no dimerisation products were observed like in other catalysts. Also its compatibility in the presence of electron withdrawing substituents such as alkoxy carbonyl and acetyl groups. The best yields (65-85%) were obtained with monosubstituted alkenes the best examples of which are styrene, acrylic esters and methyl vinyl ketones.

Simmon and Smith[23] have shown the synthesis of cyclopropyl derivatives by reacting olefins with methylene iodide in Zn-Cu couple. It is also found that copper chelates[24, 25] catalysed the decomposition of ethyl diazoacetate in styrene to give an optically active mixture of cis and trans isomers of ethyl 2-phenylcyclopropane carboxylate.

This asymmetric cyclopropanation is generally applicable to monosubstituted and to 1, 1- disubstituted alkenes but not to 1, 2-disubstituted alkenes. Also the trans selectivity increases with increase in the bulk of the ester group. The ester derived from 2, 6- di-t-butyl-4-methyl phenol forms essentially only the trans-cyclopropyl ester in 99% enatiomeric excess.

Our literature survey revealed that there is no general reported methods available for the synthesis of the titled compounds. Ethyl trans 2-phenylclopropyl acetate was prepared by the cycloaddition of the ethyl-4- phenyl-3-pentenoate.[26] Zn-cu couple was suspended in dry ether. A crystal of iodine was added and the mixture stirred for 0.5 hour. A mixture of ethyl-4-phenyl-3-pentenoate **6** and CH_2I_2 was added to the solution of Zu-Cu in either and refluxing for 30 hours afforded the

compound 7 (Scheme-2). Alkali hydrolysis of trans-2-alkylcyclopropylacetate 7 gave the corresponding acid in about 70% yield.



6 7

Scheme-2

H. E. Zimmerman and C. J. Samuel[27] isolated methyl-1-methylcyclopropane acetate **9** in the synthesis of 1-(2, 2-Diphenylvinyl)-1-methyl cyclopropane. Refluxing Zn-Cu couple[28] in anhydrous ether with methylene iodide and methyl-3-methyl-3-butenoate **8** for 22 hours, gave a mixture which upon distillation gave the methyl methylcyclopropaneacetate, 4 a colourless liquid, as the distillate (Scheme-3).

8 9

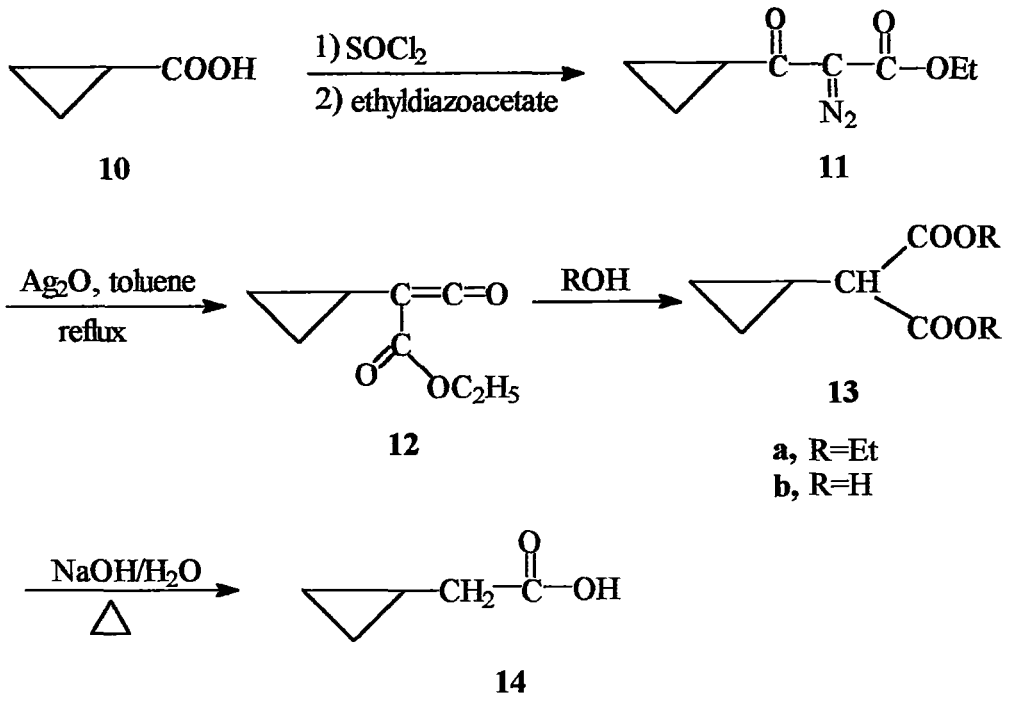
Scheme-3

Cyclopropane carboxylic acid has been converted into cyclopropyl acetic acid by a sequence of reactions[29] involving no attack upon the carbon atom joined directly to the ring. The acid **10** was converted into the acid halide where upon action of ethyl diazoacetate was converted into the acyl diazoester[30] **11**. The

diazoester **11** when refluxed in toluene in the presence of silver oxide rearranged into the ketene **12** with concomitant lost of nitrogen and was further converted to ethyl cyclopropyl malonate **13** by the action of ethanol. Alkaline hydrolysis of **13a** gave the malonic acid **13b** which underwent decarboxylation on heating to give cyclopropyl acetic acid **14** (scheme-4).

D. B. Bigley and coworkers in the study of the decarboxylation of cyclopropylacetic acid[31] have prepared acid by the following sequence. The hydroxy ester from a Reformatsky reaction between isobutyraldehyde and ethyl bromoacetate was dehydrated to the α, β- unsaturated ester with $POCl_3$ in pyridine. This was hydrolysed and isomerised (80% β, γ, 20% α, β) by 48 hours refux with 40% KOH in aqueous ethanol; the β, γ-unsaturated acid was preferentially esterified by the method of Ecott and Linstead[32] and the resultant ester was then cyclopropanated and hydrolysed.

Using excess of the Simmon-Smith regent[23] it was possible to convert methyl 1, 4-dihydrobenzoate[33] to a pair of epimeric cyclopropyl acetic acid derivatives, cis and trans[34] evidenced by vapor phase chromatography in the relative proportions of 80% cis and 20%trans. If pure isomers of cis or trans or the reaction mixture above was refluxed with a catatylic amount of sodium methoxide in dry methanol an identical equilibrium mixture containing 30% cis and 69% trans was obtained. Three bis adducts could have been formed in the cyclopropanation reaction, two meso compounds cis- and trans- and a dl pair.



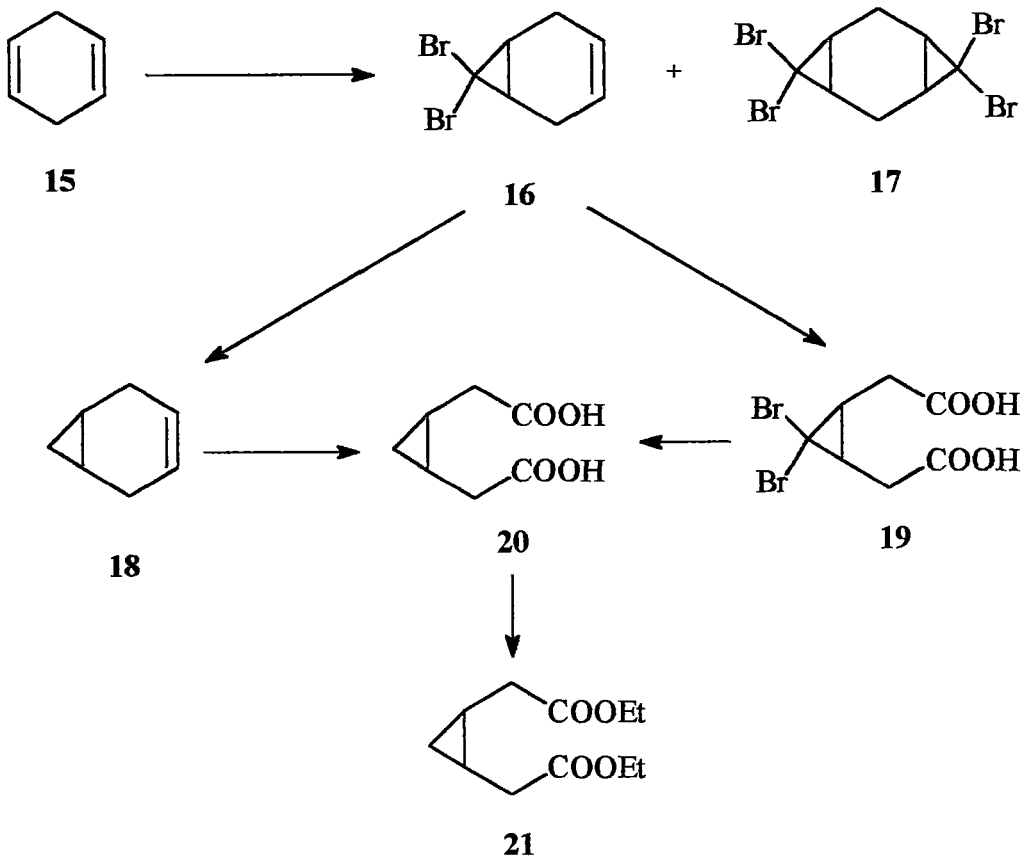
10 **11** **12** **13**

a, R=Et
b, R=H

14

Scheme-4

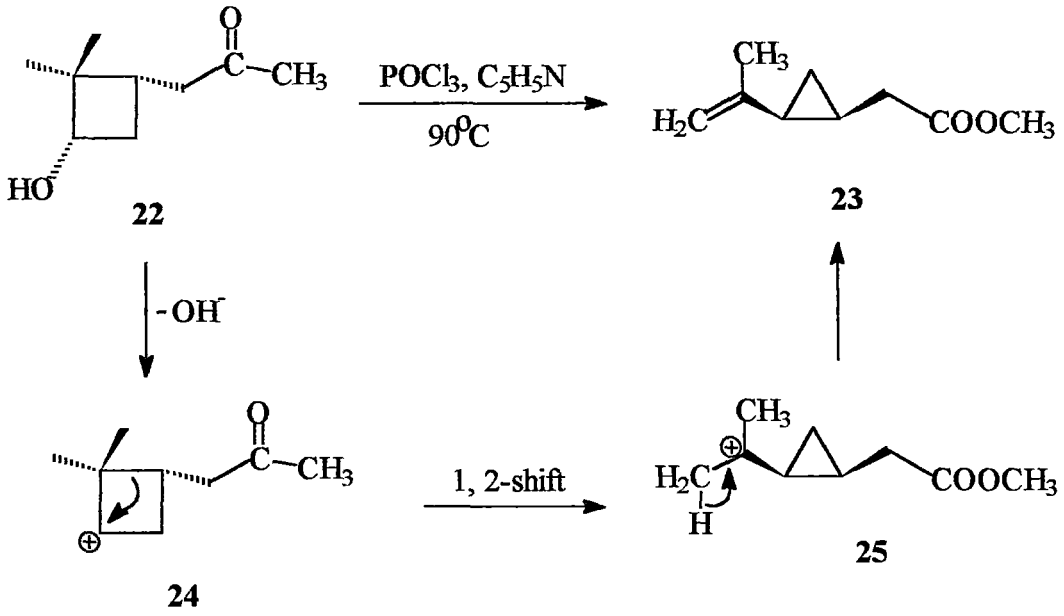
When the above stereochemical result is compared with that obtained by carrying out the Simmon-Smith reaction on 1, 4-dihydrobenzene, which results in the predominately trans configuration of cyclopropyl ring[35] it is seen that the carbomethoxyl group has exerted a profound directing influence on the reaction. Treatment of 1, 4-cyclohexadiene **15** with 7, 7-dibromocarbene[36] gave a satisfactory yield of dibromocarene[37] **16** together with a small amount of tetrabromide **17**. Debromination of the dibromonorcarene **16** proceeds in high yield with a large excess of sodium in moist methanol. Conversion of the norcarene **18** to cyclopropane cis 1, 2-diacetic acid was carried out by ozonolysis in a 2:1 acetic acid-acetic anhydride mixture. The yield of acid (63%) was definitely better than in glacial acetic acid alone and far superior to that in ethyl acetate.



Scheme-5

Dehydration of cyclobutanol(+) **22** with phosphorus oxycholoride in pyridine gave cyclopropyl acetate(-) (1S, 2S) **23** in 96% yield.[38] The cyclopropane produced represented the thermodynamically less stable cis isomer, thus pointing to kinetic rather than thermodynamic control. A concerted ionisation rearrangement in which the 1, 2 bond cleavage and the backside attack at the carbon of the 4 membered rings bearing the leaving group was facilitated by a favoured 1, 3-diequatorial conformation[39, 40] was suggested to explain this result. The mechanism seems to involve an initial ionisation of **22** to the cyclobutyl cation **24** and subsequent bond shift to the stabilized tertiary homoconjugated cyclopropyl carbinyl cation **25**

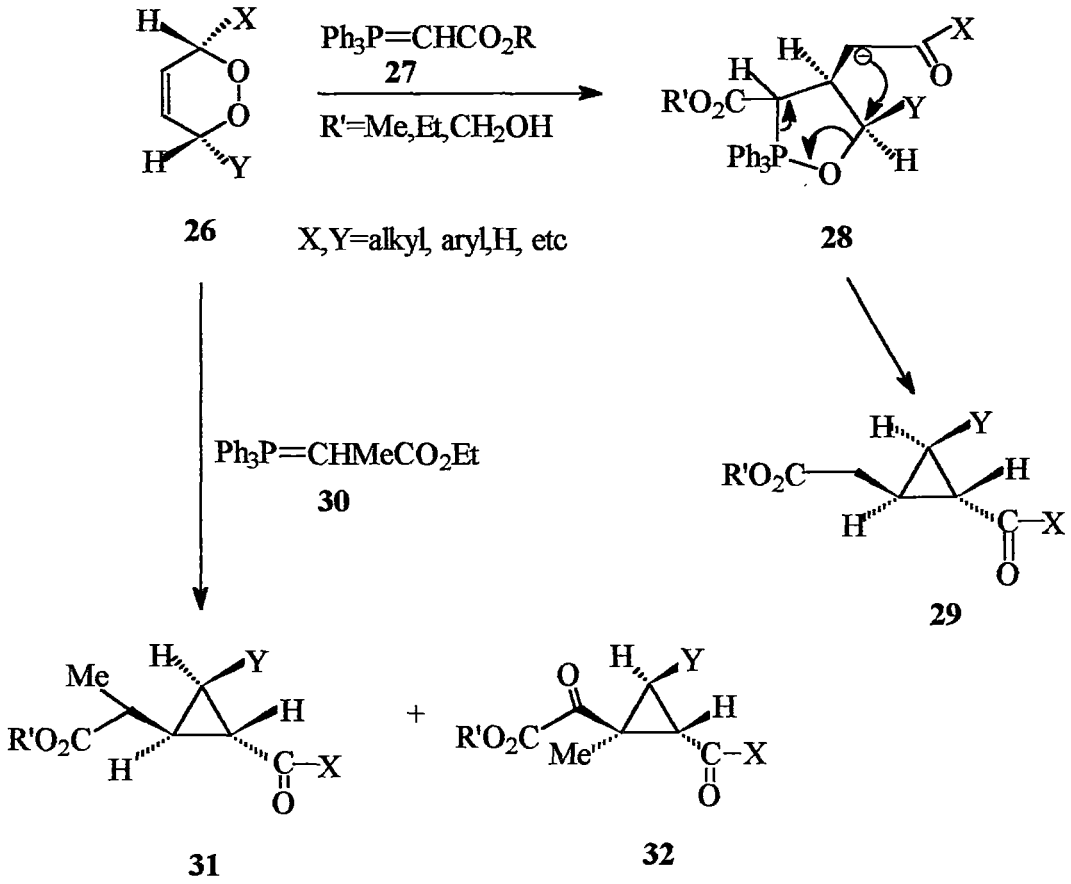
(Scheme-6). The lost of a proton from **25** resulted in the formation of **23** in high yield. Alternatively, attack of the hydride nocleophile at different sites gave different products.



Scheme-6

Recently D. K. Taylor and coworkers[41, 42] have shown that the reaction of 1, 2-dioxines **26** with stabilized phosphorus ylides containing an ester moiety **27** afforded diastereomerically pure cyclopropanes **29** in excellent yields, through the collapse of the intermediate 1, 2 λ^5-oxaphospholanes **28** (scheme-7). It was also shown that the use of bulkier disubstituted ylide **30** allows for the incorporation of another stereogenic center within the side chain of the cyclopropane **31**. However another cyclopropane **32** was isolated (7%) which did not appear to originate from the mechanism discussed above and it was speculated that the steric bulk of the ylide might be the reason behind the formation of **32**. Analysing the effect of steric bulk

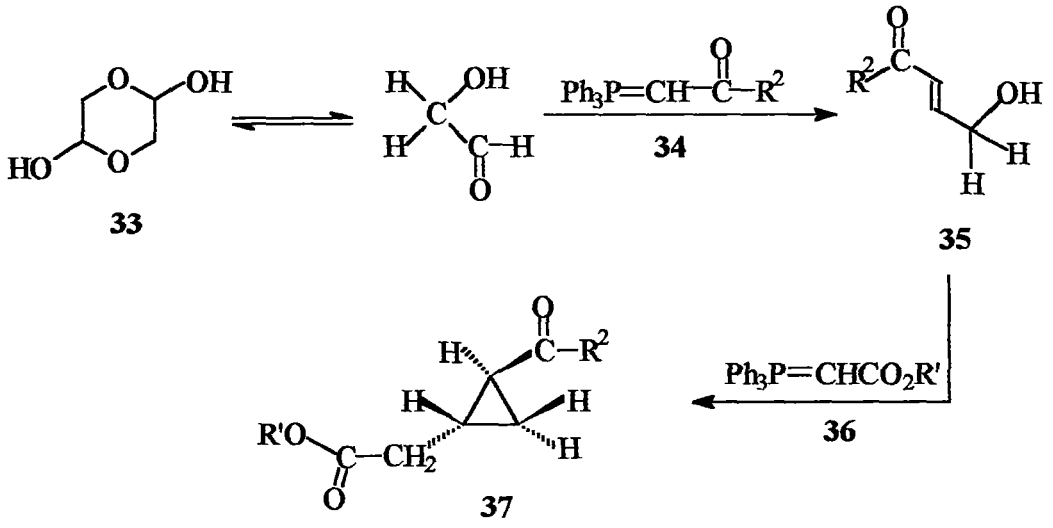
on cyclopropanation outcome with diphenyl methyl (DPM) grouping, it was found that reaction of 1, 2-dioxine **26** (Y=Ph) with ylide **27** (R^1= Ph_2CH) resulted in the formation of distereomerically pure cyclopropane **29**. Hence the DPM grouping failed to alter the cyclopropanation outcome.



Scheme-7

Reaction of the glycolaldehyde dimer **33** with keto ylides **34** resulted in the smooth generation of the trans-γ-hydroxy enones **35** of 90% purity.[42] Direct addition of the ester stabilized ylides **36** to the reaction mixture resulted in the formation of the desired cyclopropanes **37** (Scheme-8). Under thermal conditions the formation of

the desired cyclopropanes was extremely slow due to the cis-trans γ-hydroxy enone equilibrium favouring the thermodynamically more stable trans isomers. Further more the isolated yields were poor due to base induced Kornblum De La Mare competing rearrangement of the resultant hemiacetals in solution and the formation of unidentified decomposition products.



Scheme-8

Our method of preparation of cyclopropane acetic acid ethyl esters involves lead tetra acetate oxidation. We have previously illustrated the successful use of lead (IV) acetate in combination with Lewis acids to effect a 1,2-carbonyl transposition in acetophenones[43] and acyclic α, β-unsaturated ketones[44] and a ring contraction in cyclic α, β-unsaturated ketones and related systems.[45a, b, c]

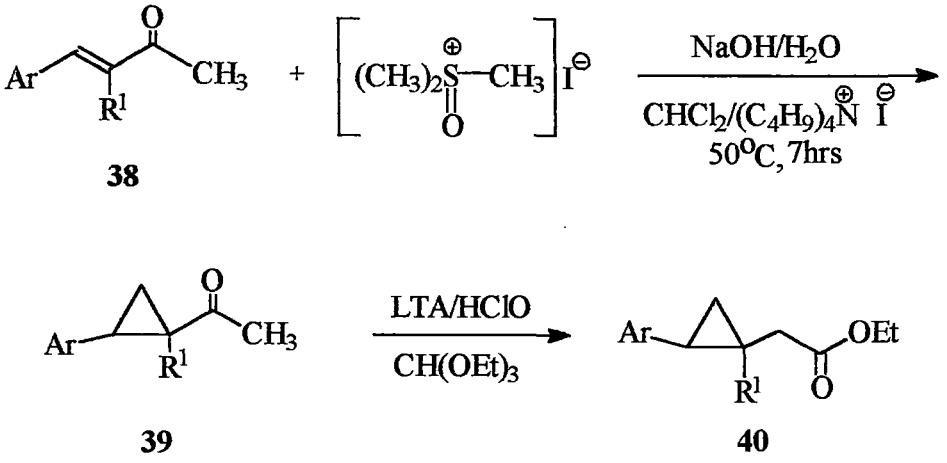
As a final test to the effectiveness of this reagent combination, we inserted a cyclopropyl group between the carbonyl and the aryl substituent to see whether the

cyclopropyl ring in the cyclopropyl alkyl ketone will also facilitate a 1,2-carbonyl shift.

In this chapter we report the synthesis of substituted cyclopropaneacetic acid ethyl esters *via* a lead (IV) acetate-perchloric acid assisted 1, 2-carbonyl transposition of the corresponding cyclopropyl alkyl ketones in triethyl orthoformate.

Results and discussions:

For our investigation we have chosen ketones **39** prepared by cyclopropanation of benzylidene acetones with trimethyloxosulphoxonium iodide in 50% aqueous sodium hydroxide in dichloromethane with tetrabutylammonium iodide as the phase tranfer catalyst.[46] Treatment of substituted cyclopropyl methyl ketones **39** with lead (IV) acetate in triethyl ortho formate and catalytic amount of perchloric acid lead to the formation of substituted cyclopropaneacetic acid ethyl esters **40** (Scheme-9).



$R^1 = H, CH_3$

$Ar = C_6H_5,\ 2\text{-}ClC_6H_5,\ 4\text{-}ClC_6H_5,\ 4\text{-}CH_3C_6H_5$

Scheme-9

Previously it was found that the use of boron trifluoride-etherate as the Lewis acid in tandem with lead (IV) acetate in benzene-methanol system gave excellent results of the expected products.[43, 44] In the present investigation these reaction conditions failed and most of the starting material was recovered. Presumably boron

trifluoride etherate is not strong enough to enolize the ketone for the subsequent attack by lead (IV) acetate. However, when boron trifluoride-etherate was replaced by perchloric acid and the reaction carried out in triethyl orthoformate the reaction proceeded at room temperature to give the products **40** in moderate to good yields.

The products obtained were characterized by analytical and spectral data. The cyclopropyl alkyl ketones were subjected to lead tetra acetate oxidation in triethyl ortho formate and a catalytic amount of perchloric acid. Interestingly the cyclopropane ring did 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 cyclopropyl methyl ketone **39** in triethyl ortho formate was added to a stirring suspension of lead (IV) acetate in triethyl ortho formate followed by the addition of perchloric acid. Normal work up after 15 hours of stirring at room temperature afforded the ethyl cyclopropyl acetate in moderate to good yields. ^{1}H NMR clearly showed the presence of the cyclopropyl ring in the oxidation product.

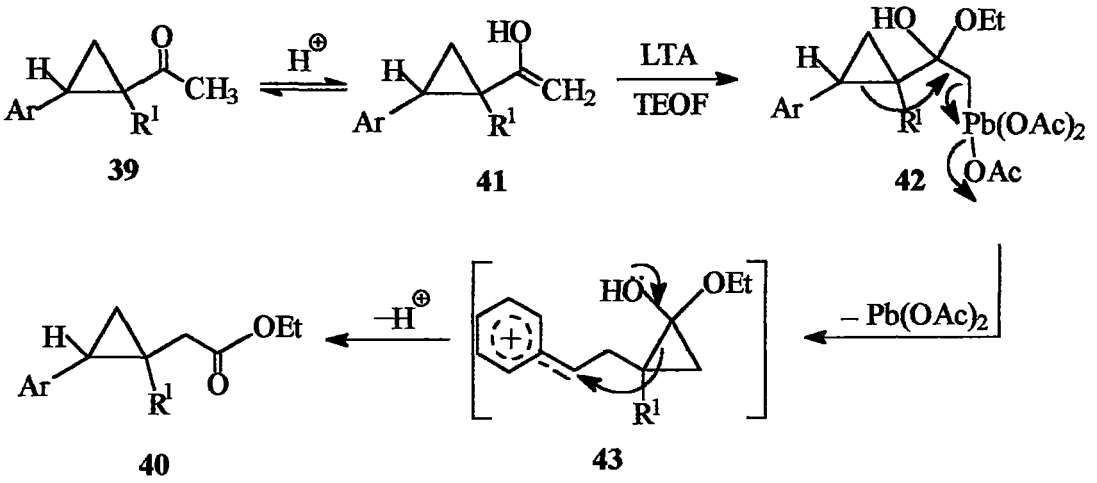
Table-3: Prepartion of Ethyl 2-arylcyclopropyl acetate:

Entry	Products	Ar	R^1	Time/h	Yields (%)[a]
1	**40a**	C_6H_5	H	28	37
2	**40b**	2-ClC_6H_4	H	31	54
3	**40c**	4-ClC_6H_4	H	30	56
4	**40d**	C_6H_5	CH_3	30	58
5	**40e**	2-ClC_6H_4	CH_3	32	50
6	**40f**	4-ClC_6H_4	CH_3	31	54
7	**40g**	4-MeC_6H_4	H	27	60
8	**40h**	4-$OMeC_6H_4$	H	28	47
9	**40i**	4-$OMeC_6H_4$	CH_3	30	42
10	**40j**	3,4-$(MeO)_2C_6H_3$	H	31	39

a: Refer to isolated yields.

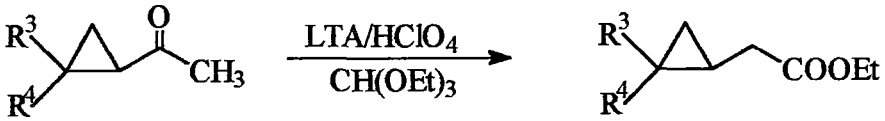
The probable mechanism for the transformation is shown in scheme-10. Evidently the elimination of lead (II) acetate from the intermediate **42** is made possible by neighboring group participation of the adjacent cyclopropane ring, thereby generating a carbocation **43** which is stabilized by the aromatic ring and which subsequently rearranges to the more stable product **40**. The product **40a** was further hydrolysed to the corresponding acid by refluxing with 2 N NaOH for 3

hours. The recrystallised acid (mp 45-46°C) gave IR and ^{1}H NMR spectral data comparable to those reported in the literature.[5]



Scheme-10

In order to ascertain whether the presence of the aromatic ring is a prerequisite for the successful rearrangement, this procedure was extended to other cyclopropyl ketones that do not have an aromatic ring as one of the substituents. We found that the unsubstituted cyclopropyl methyl ketone **44a** yielded only trace quantities of the expected products (from TLC analysis). However 2, 2-dimethyl cyclopropaneacetic acid ethyl ester **45b** was obtained in comparable yields (Scheme-11). These results agree with the observation that aryl or alkyl substituents at the 2-positions of the cyclopropyl ketone stabilize the carbocation presume to be involved thereby enhancing the yields of the rearranged products.



	R^3	R^4		Yield (%)
44a	H	H	**45a**	<5
44b	CH_3	CH_3	**45b**	59
44c	C_2H_5	H	**45c**	47

Scheme-6

Experimental:

Infrared spectra were recorded on a NICOLET 410, Perkin-Elmer 983 and BOMEM DA-8 FT-IR Spectrophotometer and the frequencies are expressed in cm-1. ^{1}H NMR (90 MHz) was recorded on Varian EM-390 spectrometer and high resolution ^{1}H and ^{13}C NMR (300 MHz) spectra were recorded on a Bruker ACF-300 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. J values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution. Column chromatography was carried out using ACME's silica gel (60-120 mesh).

Chemicals, Reagents and Solvents:

The ketones and benzaldehyde used for the preparation of benzylidene alkanone were distilled before use. The commercial samples of 2-chloro and 4-chloro benzaldehydes are used without further purification. Lead (IV) acetate[46] m.p. 175°C was freshly prepared for each reaction and carefully dried in a vacumn desicator over KOH pellets. Triethyl ortho formate (Aldrich) was directly used without further purification.

General procedure for the preparation of 1-aryl-pent-1-en-3-one:

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

General procedure for the preparation of 1-alkyl-2-arylcyclopropyl alkyl ketone 38:

A suspension of benzylidene acetone (10 mmol), trimethylsulphoxonium iodide (13 mmol) and tetrabutyl ammonium iodide (15 mmol) in an aqueous solution of 50% NaOH (30 ml) was stirred at 50^0C for 7 hours. The organic layer was separated and concentrated, the residue was diluted with ethyl acetate to precipitate out the tetrabutyl ammonium iodide. The filtrate was evaporated to give the crude product which was purified by column chromatography on silica gel using hexane-ethylacetate as eluent.

General procedure for the preparation of Ethyl 2-aryl cyclopropyl acetate 39:

To a stirring suspension of lead (IV) acetate (10 mmol) in triethyl ortho formate (15 ml), a solution of 2-arylcyclopropyl alkyl ketone (10 mmol) in triethyl ortho formate (10 ml) was added in one lot followed by 70% perchloric acid (2 ml). The reaction mixture was further stirred for 14-28 hours at room temperature. The

solvent was distilled off under vacuo and the residue treated with chloroform. The precipitate formed was removed by filtration and the filtrate washed with water (2x50 ml) and dried (anhydrous Na_2SO_4). Removal of the solvent yielded the crude product, ethyl-2-arylcyclopropyl acetate which was further purified by column chromatography on silica gel using hexane-ethyl acetate as eluent.

Ethyl 2-phenylcyclopropylacetate 40a:

Colorless viscous liquid; *IR* (neat): ν_{max} 1735 cm^{-1}; *^1H NMR*: δ 0.23-0.94 (m, 4H, cyclopr-*H*), 1.21 (t, 3H, CH_2CH_3), 2.31 (m, 2H, CH_2COOEt), 4.01 (q, 2H, OCH_2), 6.89-7.16 (m, 3H, Ar-*H*), 7.22-7.27 (m, 2H, Ar-*H*); *^{13}C NMR*: δ 14.1, 16.2, 17.4, 21.4, 32.0, 60.3, 127.3, 129.4, 133.5, 136.6, 172.5; *Anal. Calcd. for* $C_{13}H_{16}O_2$: C, 76.47; H, 7.84; *Found*: C, 76.63; H, 7.94.

Ethyl 2-(2-chlorophenyl)cyclopropylacetate 40b:

Colorless viscous liquid; *IR* (neat): ν_{max} 1736 cm^{-1}; *^1H NMR*: δ 0.30-0.90 (m, 4H, cyclopr-*H*), 1.24 (t, 3H, CH_2CH_3), 2.32 (m, 2H, CH_2COOEt), 4.03 (q, 2H, OCH_2), 6.91-7.51 (m, 4H, Ar-*H*); *^{13}C NMR*: δ 14.4, 16.8, 17.2, 21.4, 33.1, 60.8, 128.1, 129.2, 134.3, 138.3, 140.4, 172.3; *Anal. Calcd.* for $C_{13}H_{15}O_2Cl$: C, 65.40; H, 6.29; *Found*: C, 65.53; H, 6.37.

Ethyl 2-(4-Chlorophenyl)cyclopropylacetate 40c:

Colorless viscous liquid; *IR* (neat): ν_{max} 1738 cm^{-1}; *^1H NMR*: δ 0.28-1.11 (m, 4H, cyclopr-*H*), 1.21 (t, 3H, CH_2CH_3), 2.29 (m, 2H, CH_2COOEt), 4.08 (q, 2H, OCH_2), 6.94-7.21 (m, 2H, Ar-*H*), 7.24-7.81 (m, 2H, Aromatic); *^{13}C NMR*: δ 14.6, 15.0, 17.1,

21.2, 32.3, 60.2, 129.8, 130.1, 137.1,139.6, 173.4; *Anal. Calcd.* for $C_{13}H_{15}O_2Cl$; C, 65.40; H, 6.29; *Found*: C, 65.47; H, 6.33.

Ethyl 2-phenyl-1-methylcyclopropylacetate 40d:

Colorless viscous liquid; *IR* (neat): ν_{max} 1737 cm^{-1}; ^1H *NMR*: δ 0.24-0.96 (m, 3H, cyclopr-*H*), 1.21 (t, 3H, CH_2CH_3), 1.43 (d, 3H, CH_3), 2.28 (s, 2H, CH_2COOEt), 4.10 (q, 2H, OCH_2), 6.89-7.10 (m, 3H, Ar-*H*), 7.15-7.54 (m, 2H, Ar-*H*); ^{13}C *NMR*: δ 14.5, 17.1, 19.0, 22.1, 26.3, 32.1, 61.3, 129.4, 131.1, 133.6, 134.7, 172.3; *Anal. Calcd. for* $C_{14}H_{18}O_2$; C, 77.06; H, 8.25; *Found* C, 77.20; H, 8.33.

Ethyl 1-methyl-2-(2-chlorophenyl)cyclopropylacetate 40e:

Colorless viscous liquid; *IR* (neat): ν_{max} 1739 cm^{-1}; ^1H *NMR*: δ 0.25-1.2 (m, 3H, cyclopr-*H*), 1.23(t, 3H, CH_2CH_3), 1.40(d, 3H, CH_3), 2.31 (s, 2H, CH_2COOEt), 4.09 (q, 2H, OCH_2), 6.87-7.53 (m, 4H, Ar-*H*); ^{13}C *NMR* (300 MHz, $CDCl_3$): δ 14.8, 17.1, 19.4, 21.7, 26.3, 31.4, 61.8, 129.4, 131.2, 133.2, 136.7, 173.8; *Anal. Calcd. for* $C_{14}H_{17}O_2Cl$: C, 66.53; H, 6.73; *Found*: C, 66.59; H, 6.88.

Ethyl 1-methyl-2-(4-chlorophenyl)cyclopropylacetate 40f:

Pale yellow viscous liquid; *IR* (neat): ν_{max} 1740 cm^{-1}; ^1H *NMR*: δ 0.28-1.2(m, 3H, cyclopr-*H*), 1.24 (t, 3H, CH_2CH_3), 1.44 (d, 3H, CH_3), 2.30 (s, 2H, CH_2COOEt), 4.10 (q, 2H, OCH_2), 6.91-7.66 (m, 4H, Ar-*H*); ^{13}C *NMR*: δ 14.6, 17.5, 19.3, 22.0, 25.8, 30.9, 62.0, 129.3, 133.4, 136.7, 139.6, 173.7.; *Anal. Calcd. for* $C_{14}H_{17}O_2Cl$: C, 66.53; H, 6.73; *Found*: C, 66.71; H, 6.81.

Ethyl 2-(4-methylphenyl)cyclopropylacetate 40g:

Colorless viscous liquid; *IR* (neat): ν_{max} 1736 cm^{-1}; ^1H *NMR*: δ 0.28-1.10 (m, 4H, cyclopr-*H*), 1.20 (t, 3H, CH_2CH_3), 1.91 (s, 3H, Ar-CH_3), 2.25 (m, 2H, CH_2COOEt),

4.08 (q, 2H, OC*H*$_2$), 6.88-7.01 (m, 2H, Ar-*H*), 7.09-7.51 (m, 2H, Aromatic); ^{13}C *NMR*: δ 14.1, 18.7, 19.6, 19.8, 24.3, 26.8, 31.4, 60.4, 127.2, 129.4, 131.8, 135.3, 173.3; *Anal. Calcd.* for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25; *Found*: C, 77.24; H, 8.46.

Ethyl 2-(4-methoxyphenyl)cyclopropylacetate 40h:

Colorless viscous liquid; *IR* (neat): ν_{max} 1737 cm^{-1}; ^{1}H *NMR*: δ 0.27- 1.15 (m, 4H, cyclopr-*H*), 1.22 (t, 3H, CH$_2$C*H*$_3$), 2.28 (m, 2H, C*H*$_2$COOEt), 3.76(s, 3H, Ar-OC*H*$_3$), 4.05 (q, 2H, OC*H*$_2$); 6.89-7.88 (m, 4H, Ar-*H*) ^{13}C *NMR*: δ 14.3, 15.6, 16.3, 19.3, 31.8, 52.4, 61.1, 128.6, 130.3, 136.6, 139.0, 174.3; *Anal. Calcd.* for $C_{14}H_{18}0_3$: C, 71.79; H, 7.69; *Found*: C, 71.90; H, 7.60.

Ethyl 1-methyl-2-(4-methoxyphenyl)cyclopropylacetate 40i:

Brownish viscous liquid; *IR* (neat): ν_{max} 1739 cm^{-1}; ^{1}H *NMR*: δ 0.30- 1.11 (m, 3H, cyclopr-*H*), 1.21 (t, 3H, CH$_2$C*H*$_3$), 1.41 (s, 3H, C*H*$_3$), 2.30 (s, 2H, C*H*$_2$COOEt), 3.75 (s, 3H, Ar-OC*H*$_3$), 4.09 (q, 2H, OC*H*$_2$), 6.98-7.74 (m, 4H, Ar-*H*); ^{13}C *NMR*: δ 14.0, 15.1, 17.2, 20.6, 24.2, 32.6, 55.4, 60.7, 127.8, 129.9, 131.2, 134.0, 136.9, 140.0, 174.8; *Anal. Calcd.* for $C_{15}H_{20}0_3$: C, 72.58; H, 8.06; *Found*: C, 72.68; H, 8.13.

Ethyl 2-(2,4-dimethoxyphenyl)cyclopropylacetate 40j:

Yellow viscous liquid; *IR* (neat): ν_{max} 1738 cm^{-1}; ^{1}H *NMR*: δ 0.28-1.13 (m, 4H, cyclopr-*H*), 1.22 (t, 3H, CH$_2$C*H*$_3$), 2.29 (s, 2H, C*H*$_2$COOEt), 3.74(s, 3H, Ar-OC*H*$_3$), 3.76(s, 3H, Ar-OC*H*$_3$), 4.10 (q, 2H, OC*H*$_2$), 6.98-7.56 (m, 3H, Ar-*H*); ^{13}C *NMR*: δ 14.0, 15.6, 17.8, 21.0, 31.8, 55.5, 55.8, 61.0, 128.4, 129.4, 130.6, 133.2, 136.2, 140.7, 174.0; *Anal. Calcd.* for $C_{15}H_{20}0_4$: C, 68.18; H, 7.57; *Found*: C, 68.30; H, 7.67.

Ethyl cyclopropylacetate 45a:

Colorless viscous liquid; *IR* (neat): ν_{max} 1736 cm^{-1}; ^{1}H *NMR*: δ 0.23-0.98 (m, 5H, cyclopr-*H*), 1.24 (t, 3H, CH_2CH_3), 2.30 (m, 2H, CH_2COOEt), 4.11 (q, 2H, OCH_2); ^{13}C *NMR*: δ 15.0, 16.3, 17.2, 21.4, 30.8, 62.1, 172.3; *Anal. Calcd.* for $C_7H_{12}O_2$: C, 65.62; H, 9.37; *Found*: C, 65.77; H, 9.46.

Ethyl 2,2-dimethylcyclopropylacetate 45b:

Colorless viscous liquid; *IR* (neat): ν_{max} 1740 cm^{-1}; ^{1}H *NMR*: δ 0.23-0.88 (m, 3H, cyclopr-*H*), 1.11-1.21 (m, 6H, CH_3), 1.25 (t, 3H, CH_2CH_3), 2.29 (m, 3H, CH_2COOEt), 4.20 (q, 2H, OCH_2); ^{13}C *NMR*: δ 14.9, 15.6, 17.8, 18.6, 20.7, 21.0, 31.5, 61.8, 171.5; *Anal. Calcd.* for $C_9H_{16}O_2$: C, 69.23; H, 10.25; *Found*: C, 69.40; H, 10.10.

Ethyl 2-ethylcyclopropylacetate 45c:

Colorless viscous liquid; *IR* (neat): 1739 cm^{-1}; ^{1}H *NMR*: δ 0.26-0.97 (m, 4H, cyclopr-*H*), 1.23 (t, 3H, CH_2CH_3), 1.17 (t, 3H, CH_3), 1.30 (m, 2H, CH_2CH_3), 2.28 (m, 2H, CH_2COOEt), 4.13 (q, 2H, OCH_2); ^{13}C *NMR*: δ 14.1, 13.2, 16.8, 19.4, 21.8, 24.6, 30.0, 61.2, 172.1; *Anal. Calcd.* for $C_9H_{16}O_2$: C, 69.23; H, 10.25; *Found*: C, 69.44; H, 10.36.

References:

1. J. Salaun, M. S. Baird, *Curr. Med. Chem.*, **1995**, *2*, 511.
2. H. N. C. Wong, M-Y. Hon, C-W. Tse, Y-C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.*, **1989**, *89*, 165.
3. (a) A. de Meijere, *Angew. Chem.*, **1979**, *91*, 867; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809; (b) D. Seebach, *Angew. Chem.*, **1979**, *91*, 259; *Angew. Chem., Int. Ed. Engl.*, **1979**, *18*, 239. (c) T. Hudlicky, J. W. Reed, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds. Pergamon Press: New York, **1991**; Vol. *5*, 899. (d) T. A. Hase, *Umpoled Synthons, A Survey of Sources And Uses in Synthesis*; Wiley: New York, **1987**.
4. K. B. Wiberg, in *Carbocyclic Three- and Four-Membered Ring Compounds*; A. de Meijere, Ed.; Houben-Weyl Vol. E 17, Thieme, Stuttgart, **1996**; p 1 ff and references cited therein.
5. B. M. Trost, in *Strain and its implications in Organic Chemistry-Organic Stress and Reactivity;* A. de Meijere, S. Blechert, Eds, NATO ASI Series C Vol. *273*, Kluwer Academic Publishers: Dordrecht, **1989**; p 1 ff.
6. (a) *Small Ring Compounds in Organic Synthesis*, I-V; A. de Meijere, Ed.; *Topics in Current Chemistry*; Springer: Berlin, Heidelberg, **1986**, **1987**, **1988**, **1990**, **1996**; Vols. *133*, *135*, *144*, *155*, *178*. (b) H. U. Reissing, in *The Chemistry of the Cyclopropyl Group*; Z. Rappoport, Ed.; Wiley. Chichester, New York, **1987**; p 375 ff. (c) J. Salaun, *Chem. Rev.*, **1983**, *83*, 619. (d) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.*, **1989**, *89*, 165. (e) A. de Meijere, L. Wessjohann, *Synlett*, **1990**,

20. (f) A. de Meijere, in *New Aspects of Organic Chemistry II*, Z. I. Yoshida, Y. Oshoro, Eds; Kodansha: Tokyo, **1992**; p 181 ff.

7. For some reviews see. (a) M. P. Doyle, *Chem. Rev.*, **1986**, *86*, 919, (b) G Top, *Cur Chem.*, **1987**, *137*, 75. (c) M. P. Doyle, *Recl. Trav. Chim.*, **1991**, *110*, 305.
8. M. Lautens, P. H. M. Delanghe, *J. Org. Chem.*, **1995**, *60*, 2474.
9. W. Von, E. Doering, and A. K. Hoffman, *J. Am. Chem. Soc.*, **1954**, *76*, 6162.
10. R. Huisgen, *Angew. Chem.*, **1995**, *67*, 439,
11. M. Brookhart, W. B. Studbaker, *Chem. Rev.*, **1987**, *87*, 411.
12. E. O. Fischer, B. Hecken, K. H. Dotz, J. Muller, H. Werner, *J. Organomet. Chem.*, **1969**, *16*, 29-32.
13. J. Barluenga, P. L. Bernard, J. M. Concellon, *J. Org. Chem.*, **1997**, *62*, 6870.
14. E. O. Fischer, K. H. Dotz, *Chem. Ber.*, **1972**, *105*, 3966.
15. P. S. Skell, P. M. Etter, *Proc. Chem. Soc.*, **1961**, 443.
16. R. R. Sauers, P. E. Sonnet, *Tetrahedron*, **1964**, *20*, 1029.
17. R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.*, **1973**, *95*, 3300.
18. P. W. Erhardt, R. J. Gorczynski, W. G. Anderson, *J. Med. Chem.*, **1979**, *22*, 907.
19. V. Dave, E. W. Warnhoff, *Org. React.*, **1970**, 18, 217.
20. J. Kottowitz, H. Vorbruggen, *Synthesis*, **1975**, 636.
21. M. Suda, *Synthesis*, **1981**, 714.
22. U. Mende, B. Raduchel, M. Skuballa, H. Vorbruggen, *Tetrahedron Lett.*, **1975**, 629.
23. H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.*, **1958**, *1*, 4256.

24. H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron,* **1968**, *24*, 3655.

25. R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.*, **1990**, *42*, 6005.

26. T. Shano, and I. Nishiguchi, *Tetrahedron,* **1974**, *30*, 2173.

27. H. E. Zimmerman, C. J Samuel, *J. Am. Chem. Soc.*, **1975**, *97*, 4025.

28. E. Legoff, *J. Org. Chem.*, **1964**, *29*, 2048.

29. L. I. Smith, S. Mekenzie, *J. Org. Chem.*, **1950**, *15*, 74.

30. H. Staudinger, S. Becker, B*er.*, **1916**, *49*, 1978.

31. (a) D. E. Bigley, C. I. Fetter, M. J. Clarke, *J. Chem. Soc. Perkin II.*, **1980**, 553. (b) D. E. Bigley, J. C. Thurman, *Tetrahedron Lett.*, **1965**, 4687.

32. A. A. Goldgerg, and R. P. Linstead, *J. Chem. Soc.*, **1931**, 2343. (26) E. N, Ecott and R. P. Linstead, *J. Chem. Soc.*, **1929**, 2160.

33. M. E. Kuchne and B. F. Lambert, *Org. Synth.*, **1963**, 43, 22.

34. (a) T. Hanafusa, L. Birladeanu, S. Winstein *J. Am. Chem. Soc.*, **1965**, *87*, 3510. (b) J. J. Sims *J. Am. Chem. Soc.*, **1965**, *87*, 3511.

35. W. D. Kumbler, R. Boikess, P. Bruck, and S. Winstein *J. Am. Chem. Soc.*, **1964**, *86*, 3126.

36. W. E. Doering, A. K. Hoffmann, *J. Am. Chem. Soc.*, **1954**, *76*, 6162.

37. A. K. Hoffmann, S. F. Orochena, S. M. Sax, C. A. Jeffrey, *J. Am. Chem. Soc.*, **1959**, *81*, 992.

38. M. Karpf, C. Djerassi, *J. Am. Chem. Soc.*, **1981**, *103*, 302.

39. K. B. Wiberg, B. A. Hess, J. A. Ashe, in *Carbonium ions*; P. V. R. Eds; New York, **1972**, Vol III, Chapter 26.

40. J. M. Conia, J. Salaun, *Acc. Chem. Res.*, **1972**, *5*, 33.

41. T. D. Avery, B. W. Creatrex, D. K. Taylor, *J. Chem. Soc. Perkin. Trans I,* **2000**, 1319.

42. F. N. Palmer, D. K. Taylor, *J. Chem. Soc. Perkin. Trans I,* **2000**, 1323.

43. B. Myrboh, H. Ila, and H. Junjappa, *Synthesis,* **1981**, *2*, 126.

44. F. Mathew, B. Myrboh, *Tetrahedron Lett.*, **1990**, *31*(26), 3757.

45. (a) F. M. Nongrum, B. Myrboh, *Synthesis,* **1987**, *9*, 845. (b) F. Mathew, B. Myrboh, *Synthetic Commun.*, **1996**, *26*, 1097. (c) F. Mathew, B. Myrboh, *Molecules,* **1996**, *1*, 79.

46. *Vogel's Text Book of Practical Organic Chemistry, ELBS/Longman Group Ltd.*

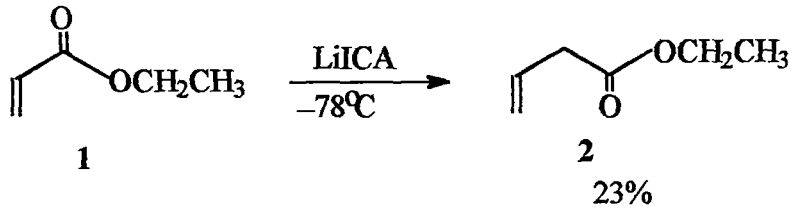
CHAPTER-VI

"Synthesis of Substituted Hexa-3, 5-dienoic Acid Methyl Esters from Conjugated Dienones"

INTRODUCTION:

Conjugated and non-conjugated dienoic acid esters play an important role in synthetic as well as theoretical 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 containing these structural subunits. The synthesis and chemistry of α, β- and α, β, γ, δ-unsaturated carboxylic acid esters[1, 2, 3] are well documented and their methods of preparations are manifold and varied. On the other hand, the corresponding β, γ- and β, γ, δ, η-unsaturated compounds[4, 5, 6] are less readily accessible.

The pioneer work in the field of β, γ-unsaturated esters was carried out independently by Rathke[7] and Schlessinger.[8] Addition of ethyl crotonate **1** to a 1 M solution of lithium N-isopropylcyclohexyl amide (LiICA)[9] in tetrahydrofuran at a temperature of -78°C, followed by quenching with dilute hydrochloric acid produced a mixture of the nonconjugated esters, ethyl-3-butenoate **2** in 23% yield[7] (scheme-1). Here the low yield of the β, γ-unsaturated esters was due to the rapid condensation of unsaturated enolate with the ethyl crotonate. The yield of the non-conjugated esters was improved by the addition of hexamethyl phosphoramide (HMPA).

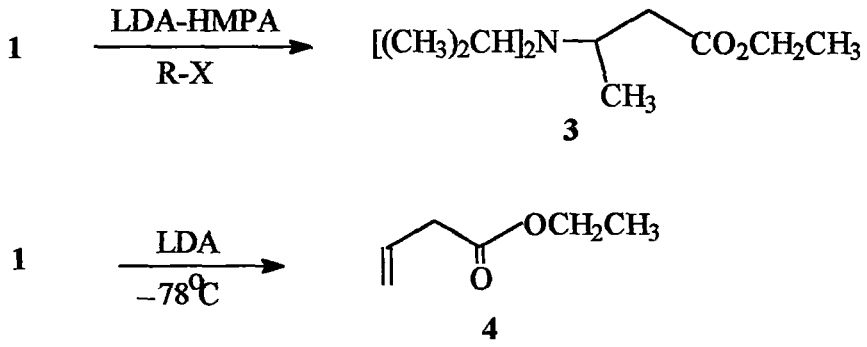


1 2

23%

Scheme-1

In the deconjugative alkylation of the enolate anion derived from ethyl crotonate **1** the major experimental concern in generating crotonic enolates was the possibility that the base lithium diisopropylamide (LDA) employed for these reactions acted as a nucleophile and conjugatively added to the unsaturated esters at a rate competitive with proton abstraction to afford **3**. Therefore an essentially non-nucleophilic form of lithium diisopropyl amide was realised by the formation of 1:1 complex with hexamethylphosphoramide. No Michael addition to ethyl crotonate was observed with this base mixture whereas it only acted as a base and permit the alkylation of ethyl crotonate at the α-carbon atom to afford β, γ-unsaturated esters[8] **4** (Scheme-2).

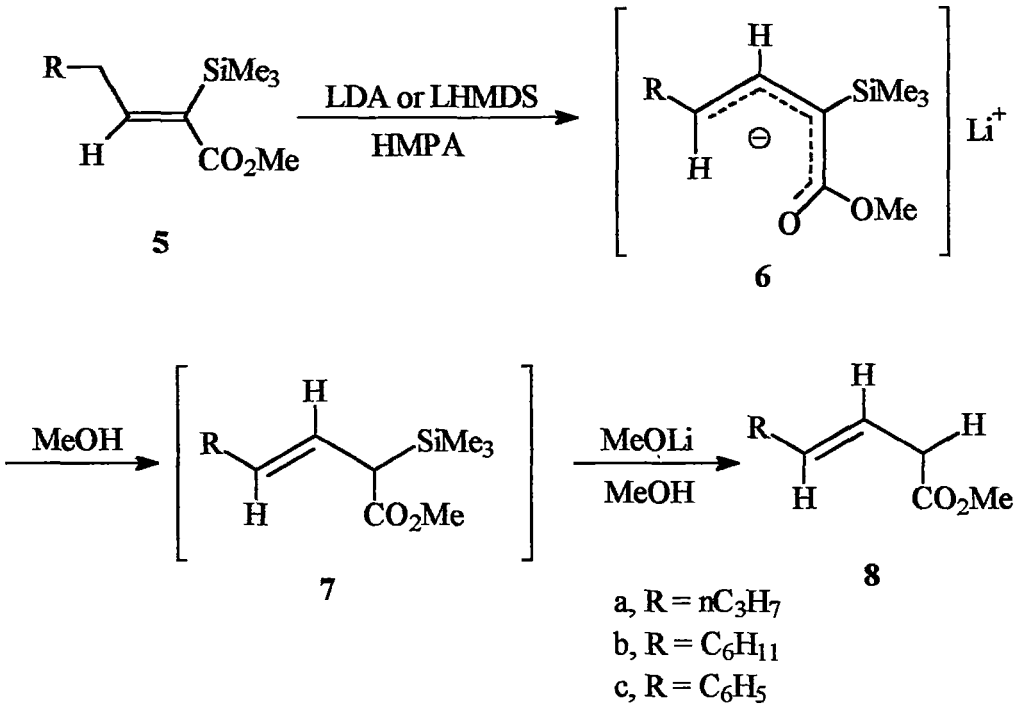


Scheme-2

Alkylation of β, γ-unsaturated acids and esters has been carried out by Cerfontain.[10] Alkylation was achieved by using the Lithium diisopropylamide-hexamethylphosphortriamide (LDA-HMPT) system which acts as a strong base and chelates the formed anions.[11] Occasionally γ-alkylation was encountered as a side reaction when both mono- and dianions were used as nucleophiles. In the methylation of 2-indenylacetic acid the ratio of γ to α-alkylation increases with increasing temperature.[12] In presence of added Cu (I) salts the degree of γ-alkylation was greatly enhanced.[13, 14]

A stereoselective conversion of (Z) α-(trimethylsilyl) α, β-unsaturated esters into α, β- and β, γ-unsaturated esters has been reported by G. Zweifel.[15] In their preliminary investigation to provide a convenient route for the preparation of useful and versatile allylsilyl and alkoxy carbonyl compounds, they selected (Z)α-(trimethylsilyl) α, β-unsaturated esters[16] **5** which afforded the β, γ-unsaturated silyl esters **7** and finally yielded the desilylated β, γ-unsaturated esters **8** as shown in scheme-3.

When the ester **5** was added to a solution of lithium diisopropylamide (LDA) or lithiumhexamethyldisilazide (LHMDS) (1:1 equivalent) in tetrahydrofuran containing hexamethyl phosphoramide (3 equivalent) at –78°C, deprotonation took place leading to the dienolate **6**. Protonation of **6** with methanol gave **7** which was however succeptible to nucleophilic attack on silicon by the lithium methoxide formed in the course of the reaction to furnish the desilylated esters[17] **8** in 98% isomeric purity (Scheme-3).



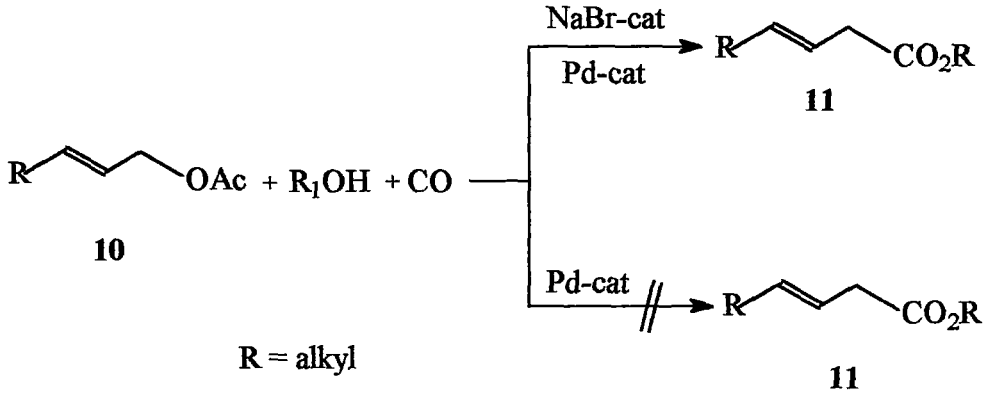
Scheme-3

Palladium (0) catalysed alkoxy-carbonylation of allylic compounds[18] was also one of the attractive methods for the synthesis of β, γ-unsaturated esters which are versatile building blocks. It has been found that allylic halides undergo carbonylation with ease by using Nickel,[19] Cobalt,[20] and Palladium complex catalysts[21, 22] whereas carbonylation of synthetically more important allylic alcohol derivatives such as allyl acetates[21b, 23-25] and ethers[26] was difficult and usually requires several reaction conditions. It was found that alkoxycarbonylation of allyl phosphates proceded highly selectively under mild reaction conditions.

However many attempts at carbonylation of allylic acetate failed. This is due to the fact that π-allyl palladium acetates which were readily formed by oxidative addition of Pd (0) species to allyl acetate undergone back reaction to the starting

allyl acetates[27] rather than insertion of carbon monoxide to give β, γ-unsaturated esters upon treatment with carbon monoxide.

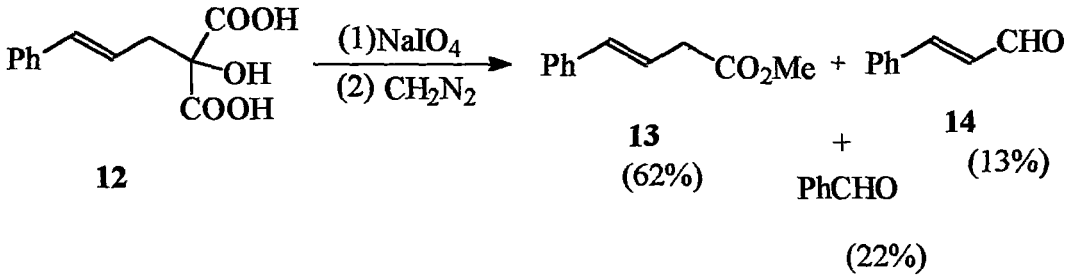
In contrast to the highly selectively alkoxy carbonylation of allyl phosphates **9** and allyl halides *via* π-allyl palladium halide complexes,[22] allylic acetates failed to give the expected β, γ-unsaturated esters **10**. In order to overcome this difficulty, Pd (0)-catalysed carbonylation of cinammyl acetate was carried out in the presence of stiochiometric amount of $Na[Co(CO)_4]$ in methanol under carbon monoxide atmosphere to give methyl-4-phenyl-3-butenoate.[22] Also by using bromide ion as cocatalyst, the carbonylation of allyl acetates proceeded smoothly under mild reaction conditions (Scheme-4).



Scheme-4

Salomon developed a widely applicable method in which allyl carboxylic acid was generated *via* ene-reaction of alkenes with diethyl oxomalonate and successive oxidative bisdecarboxylation of the ene adducts.[28, 29] The drawback of the above method was the noncarboxylic acid by-products which were isolated and characterised from the oxidative bisdecarboxylation of tartronic acid **12**. Thus all of

the starting material not converted to carboxylic ester was accounted for, by the co-production of cinnamaldehyde and benzaldehyde in 13% and 22% yields respectively (scheme-5). The oxidative bisdecarboxylation of allyl tartronic acid was sometimes not effective with sodium periodate ($NaIO_4$). Thus tartronic acid derived from their respective ene-adduct gave only traces (<5%) of allylic carboxylic acid under standard conditions.[28]

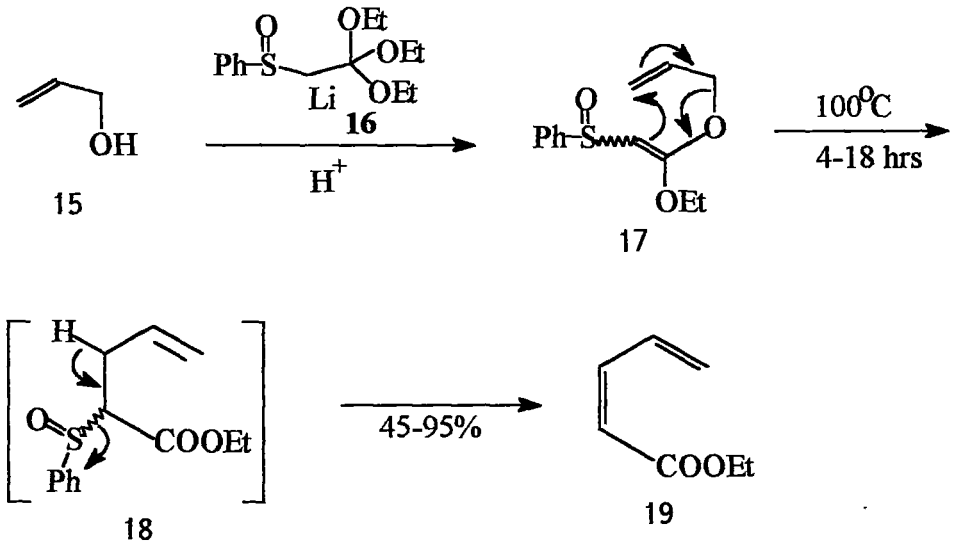


Scheme-5

Regioselective conversions of allylic alcohols into two carbon extended conjugated dienoate esters was achieved by the use of sulfinyl ortho ester.[30] Earlier a high yield synthetic method for the conversion of cyclohexenyl allylic alcohol into the corresponding two carbon-extended conjugated dienoate ester[31] has been reported. Although the standard protocol of ortho ester Claisen rearrangement to form a γ, δ-unsaturated ester[32] proceeded fast, subsequent introduction of the requisite α, β-unsaturation under various conditions proceed slowly.[33]

Treatment of unsubstituted allyl alcohol with 2 equivalent of sulfinyl ester **16** and a catalytic amount of 2, 4, 6-trimethyl benzoic acid in methylene chloride in a sealed tube at 100°C for 6 hours yielded ethyl pentadienoate **19** isolated by column chromatography as a 1:4 mixture of Z and E geometric isomers in 75% yields. The

reaction proceeded through an initial [3, 3] sigmatropic rearrangement (scheme-6) to **18** which then undergone spontaneous thermal β-elimination to the dienoate ester. β-substituted, γ-substituted and β, γ-disubstituted primary allylic alcohols reacted similarly to form 2 carbon-extended conjugated dienoates in 51-90% yield. Unsubstituted secondary allylic alcohols reacted smoothly with sulfinyl orthoester to form linear alkadienoates in 67-79% yields. Sometimes under these reaction conditions, nonconjugated trienoate was formed to the exclusion of its fully conjugated isomer. As expected from the established stereochemical outcome of the Claisen orthoester [3, 3] sigmatropic rearrangement process, the α, β-double bond geometry was almost completely E_e.[32, 34]



Scheme-6

Our literature survey showed that there are numerous methods for the synthesis of α, β, γ, δ-unsaturated carboxylic acids and their esters but very few methods have been reported for the synthesis of β, γ, δ, η-analogs. The 3, 5-

hexadienoic acid esters were found to be important synthons in organic syntheses. The unsaturated ester has also been found to be one of the key intermediates used for the synthesis of the southern half of vitamin B_{12}.[35] It has also been used as an intermediate in the synthesis of the alkaloid lycorine,[36] and strobilurin A.[37] Methyl sorbate (0.5 mol) was added to the cold solution (-78°C) of Lithium diisopropyl amide under nitrogen over 2 hours. Stirring was continued for an additional hour, and the mixture was siphoned into a rapidly stirred solution of acetic acid (1.5 mol) in 1.8 litter of water. The dried extract after column chromatography gave the pure β, γ, δ, η-unsaturated esters as the residue.[35]

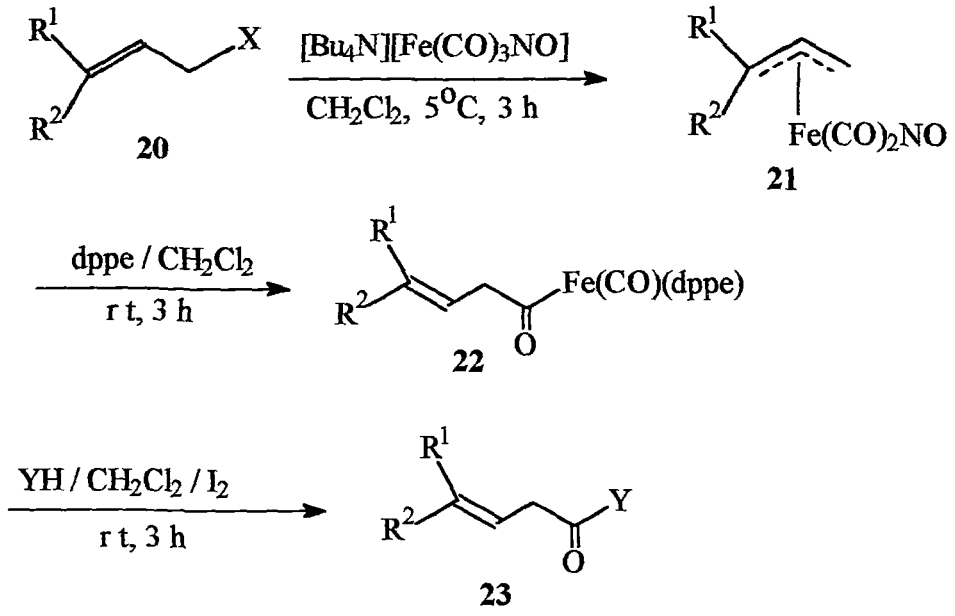
A palladium catalysed synthesis of 2, 4-dienoic acid methyl esters from vinylic halides and olefinic compounds was investigated by R. F. Heck.[38] The reaction was believed to occur in 3 steps.[39] The catalyst was first reduced by the olefinic compound to a Pd(0) phosphine complex which then reacted with the vinylic halide by oxidative addition. The vinylic Palladium complex formed next added on to the olefins and the aduct then eliminate a hydrido palladium group forming the conjugated diene. The hydrido complex then lost hydrogen halide to the tertiary amine present reforming the Pd (0) phosphine complex.

The reactivity of the disubstituted olefinic compounds in the vinylic halide reaction was considerably lower than that of the related monosubtstituted olefinic compounds. Thus methyl (E)-3-bromo-2-methylpropenoate reacted with methyl acrylate about eight times faster than it did with methyl acrylate.

Treatment of (E)-1-iodo-1-hexene with methyl acrylate at 100°C in presence of 1 mol percentage of $Pd(OAc)_2[P(C_6H_5)_3]_2$ or its equivalent, produced methyl-(E, E)-2, 4-nonadienoate in 45% yield and the E, Z isomer in 8% yield in 38 hours by

which time the vinylic iodide had all reacted. The Z iodide under the same conditions reacted in about 15 hours, forming 51% of the (E, E) ester and 30% of the E, Z isomer (Scheme-7). Lowering the reaction temperature to 70°C in the last reaction improved the selectivity of some; producing 39% E, E and 44% E, Z ester, but 150 hour was required to complete the reaction. Substantial improvement in the selectivity occurred when more (2 mol %) of triphenyl phosphine per mole of vinylic halides was used per mol percent of Palladium in the bromide reaction.

Nakanishi[39] has reported a convenient 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 the one-pot conversion of allyl halides **20** with $[(Bu_4N)^+Fe(CO)_3(NO)]^-$ followed by treatment with 1, 2-bis(diphenyl phosphino) ethane (dppe); which gave β, γ-unsaturated acyl iron complexes **22** in good yields, *via* regioselective carbonylation with retention of configuration of the allylic double bond. β, γ-unsaturated carboxylic acid esters **23** were obtained by the treatment of the acyl iron complexes with alcohols in the presence of iodine in methylene chloride (Scheme-7).



R^1	R^2	Y
H	H	OCH_2Ph
CH_3	H	OCH_2Ph
Ph	H	OEt

Scheme-7

Starting from vinylic halides the 3, 5-hexadienoic acid methyl esters were synthesised by R. F. Heck and coworkers.[20] Successive treatment of 2-methyl-5-phenyl-2, 4-pentadienoic acid ethyl ester with lithium alluminium hydride, PBr_3 in pyridine-diethyl ether at 5°C and with $LiC(SMe)_3$ yielded 3-methyl-6-phenyl-3, 5-hexadienoic acid methyl ester as almost colorless oil, IR (film): 1740cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.93 (s, 3H), 3.70 (s, 3H), 6.08 (d, 1H, J 10 Hz), 6.47 (d, 1H, J 15 Hz), 6.96 (dd, 1H, J 15 and 10 Hz); ^{13}C NMR ($CDCl_3$): δ 17.2, 45.1, 51.8, ppm.

It has also been reported[40] that 3, 5-hexadienoate acted as a useful diene in the aqueous Diels-Alder reaction. Sodium 6-methoxy (E, E)-3, 5-hexadienoate was generated in *situ* from 6-methoxy (E, E)-3, 5-hexadienoic acid which was prepared

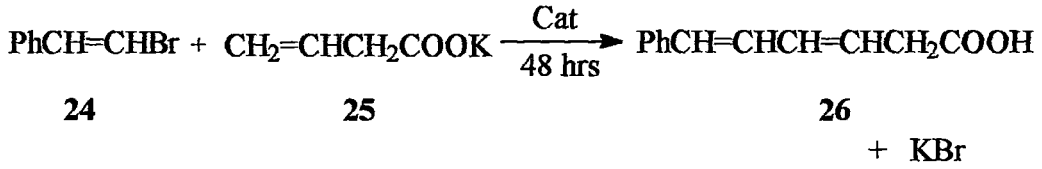
from 4-methoxy-(Z)-2-buten-1-ol.[41] Oxidation [$(CoCl)_2$, DMSO, i-Pr_2NEt, CH_2Cl_2] of the 2-buten-1-ol and subsequent condensation with the sodium salt of triethylphosphono acetate in tetrahydrofuran afforded ethyl 6-methoxy-2 (E), 4 (Z)-hexadienoate which upon treatment with potassium hydroxide in aqueous methanol provided in 95% yield the corresponding acid. The acid was then quantitatively deconjugated (2.2 equiv. LDA, THF, -78°C) to hexa-3, 5-hexadienoic acid.[42] Deconjugation of the 6-methoxy (E, E)-2, 4-hexadienoic acid, readily available from 4-methoxy-(E)-2-buten-1-ol, yielded mainly the undesired 6-methoxy 3E, 5Z-hexadienoic acid. 3, 5-hexadienoate was also obtained by the addition of 0.95 equivalent of solid sodium bicarbonate to a suspension of (E)-3, 5-hexadienoic acid[43] in water.

Ethyl (E) 4-methyl-3, 5-hexadienoate plays an important part in the construction of the ABC ring system of quassin[44] through an intermolecular Diels-Alder strategy. The diene was prepared in 61% overall yield by the condensation of commercially available tiglic aldelhyde with the sodium salt of triethyl phosphonoacetate in benzene followed by deconjugation of the resultant α, β, γ, δ-unsaturated ester which was confirmed by ^1H NMR to possess the trans olefinic geometry.

A transition metal-catalysed syntheses of organic acids by regioselective double bond insertion was reported by G. P. Chiusoli.[45] The Rhodium or Nickel catalysed reactions of vinyl halides with alkali salts of 3-butenoic acids leads to the regioselective formation of dienoic acids containing 3, 5-conjugated double bonds.

The reaction between β-bromostyrene and the potassium salt of 3-butenoic acids gave 6-phenyl-3, 5-hexadienoic acids. Two stereoisomers 3E, 5E and 3Z, 5E were

formed in approximately equal amounts from E β-bromostyrene (30 mmol) and potassium 3-butenoate (30 mmol) and $RhCl(PPh_3)_3$ (0.01mmol) in 27 ml of ethanol at 85°C (scheme-8).

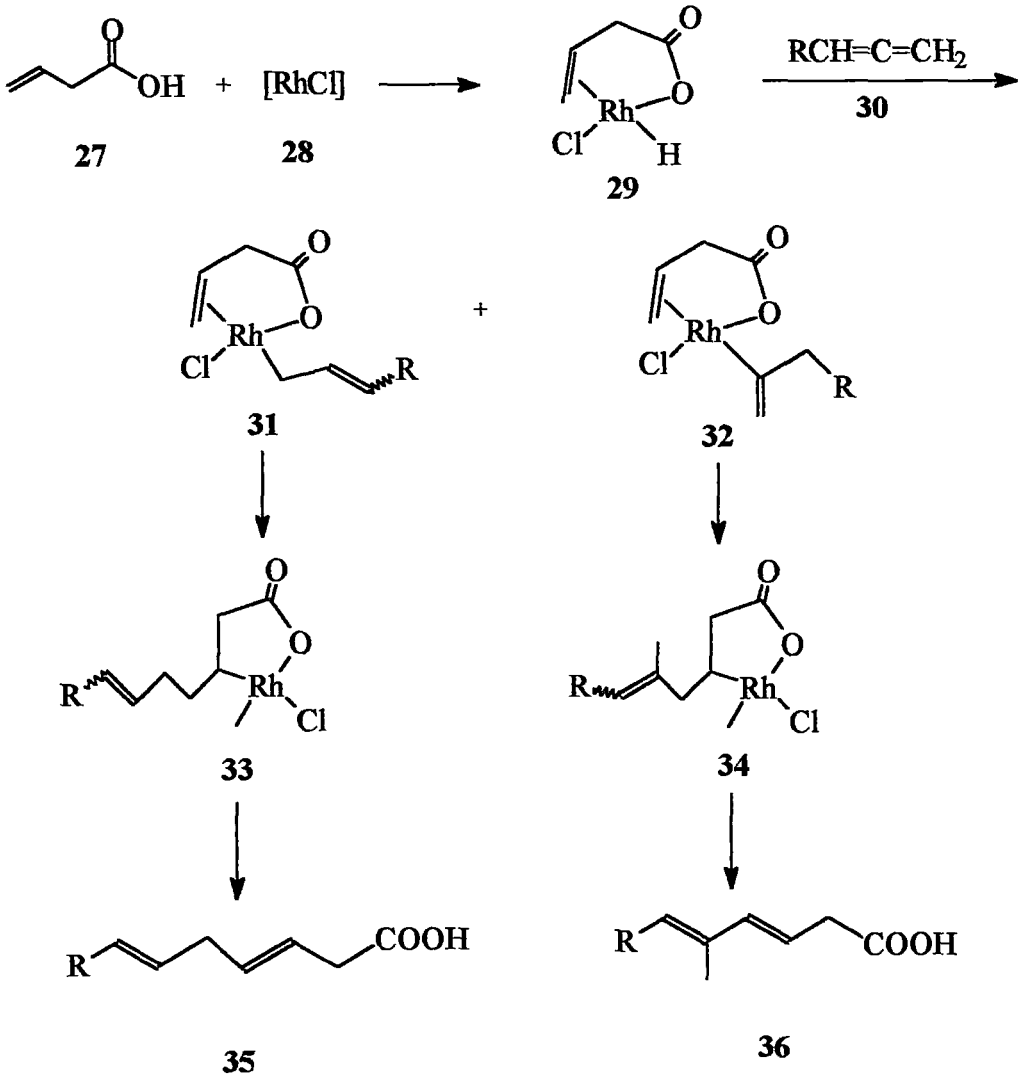


24 **25** **26**

Scheme-8

Allene also was found to react with 3-butenoic acid at 85°C in the presence of a catalytic amount of Rhodium (I) complexes with phosphorus ligands to yield mixtures of esters of 3, 6- and 3, 5-dienoic acids.[45b] The reaction involves formation of η^3-allylic complexes. Higher dienes mainly give substituted allyls, which afforded predominantly branched dienoic acids. When an allene to catalyst [$RhCl(PPh_3)_3$] molar ratio of 800/1 and a butenoic acid to catalyst ratio of 850 were used, 3, 5- and 3, 6-dienoic acids were formed in a 3:1 molar ratio. Monosubstituted allenes also reacted with 3-butenoic acids to give 3, 5- and 3, 6-dienoic acids but the latter were predominant. The use of different ligands in the Rhodium complexes provides control of the selectivity of the reaction towards 3, 6- and 3, 5-dienoic acids. For example the ratio between 3, 6- and 3, 5-dienoic acids vary from 80/20 in the case of triphenyl phosphine to 6/94 in the case of triisopropyl phosphite. Scheme-9 depicts the proposed course of reaction and involved oxidative addition of butenoic acid to the rhodium (I) complex and formation of an allyl or vinyl-rhodium bond by reaction with allenes followed by insertion and hydrogen-elimination. Since allyl

rhodium complexes were preferred with triphenyl phosphine as ligand, linear dienoic acids were obtained in higher proportion than with the corresponding 1, 3-dienes. The stereochemistry of the trisubstituted 5-double bond was probably E in all cases.

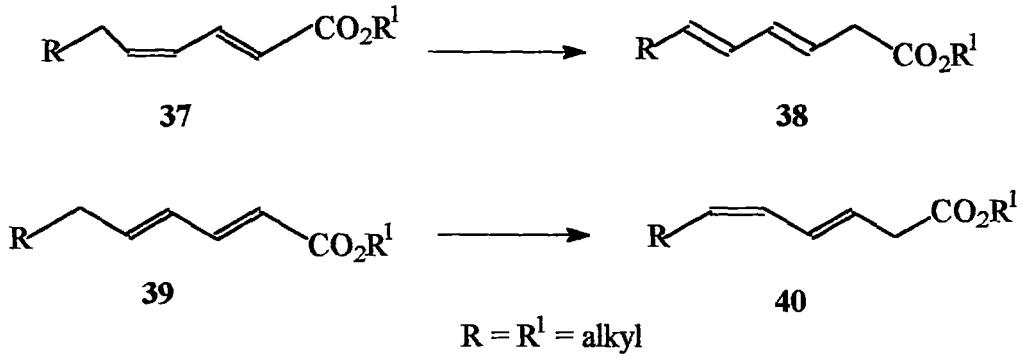


Scheme-9

Rhodium catalysed reactions of 1, 3-dienes with 3-alkenoic acids led to a class of 3, 6-dienoic acids[46] not readily accessible by other ways. Steric effects

profoundly influence the course of the reaction, in respect of both the catalytic efficiency and the selectivity. A high proportion (93%) of linear products was obtained from the reaction of butadiene with 3-butenoic acids in the presence of a cationic rhodium complex. Complete regioselectivity at the diene-unsaturated acid coupling site was observed for butadiene and 3-pentenoic acids, and the same product was obtained for 4-pentenoic acids. However reactions of butadiene homologues with 3-butenoic acid homologues gave poor results. Cyclopentadiene gave only the Diels Alder adduct with 3-butenoic acid.

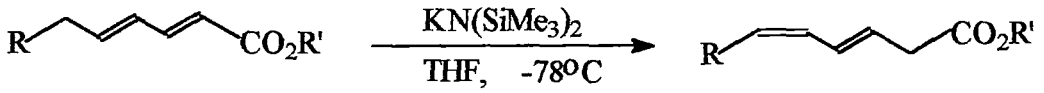
Deconjugative protonations of 2(E), 4(Z)- and 2(E), 4(E)-alkadienoates gave respectively 3E, 5E and 3E, 5Z isomers.[32] Photodeconjugation of α, β-unsaturated to γ, δ-unsaturated esters was reported in the photoisomerisation of butenoic[47-50] and dienoic esters.[51, 52]



Scheme-10

Deconjugative protonation and isomerisation of (E, E)-2, 4-dienoate to (E, Z)-3, 5-dienoate has been reported[53] in the synthesis of megatomoic acid. To a stirred solution of dienoate **41** (0.55 mmol) in tetrahydrofuran (4 ml) was added the

solution of $KN(SiMe_3)_2$ (0.8 mmol) at –78°C. The resulting pale yellow solution was stirred for two hours and then quenched with saturated aqueous ammonium chloride solution at –78°C. The product was extracted with ether, washed with brine, dried and concentrated in vacou to give an oil which on chromatographic purification afforded the 3, 5-dienoate **42** (Scheme-11).



41
(E, E)

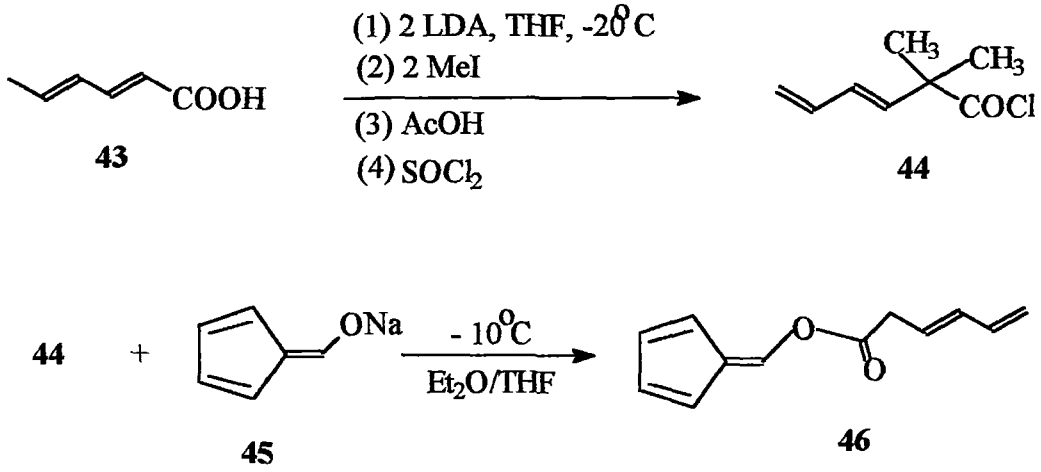
42
(E, Z)

Scheme-11

K. N. Houk and coworkers[54] reported the synthesis of 2, 2-dimethyl-3, 5-hexadienoate from sorbic acid. Sorbic acid was first converted to acid chloride by methylation with Lithium disopropyl amide and methyl iodide, followed by reaction with thionyl chloride as shown in scheme-12. Reaction of the acid chloride **44** with sodium formyl cyclopentadienide produced the light yellow ester 3,5-dienoic acid esters **46**.

The reactions of vinyl bromides **47** with dimethyl fumarate **48** was found to give 3, 5-dienoic acid methyl esters **49** which was unexpected.[55] 1-bromo-2-methyl-1-propene yielded 59% of (E)-methyl-3-carbomethoxy-5-methyl-3, 5-hexadienoate as the only isolable product while in the same reaction (Z)-1-bromo-1-hexene gave 80% (E, E)-methyl 3-carbomethoxy)-3, 5-nonadienoate (Scheme-13). In both examples a simple elimination of the hydrido palladium bromide group would have given 2, 4-dienoate esters rather than the 3, 5-dienoate isomers. A possible

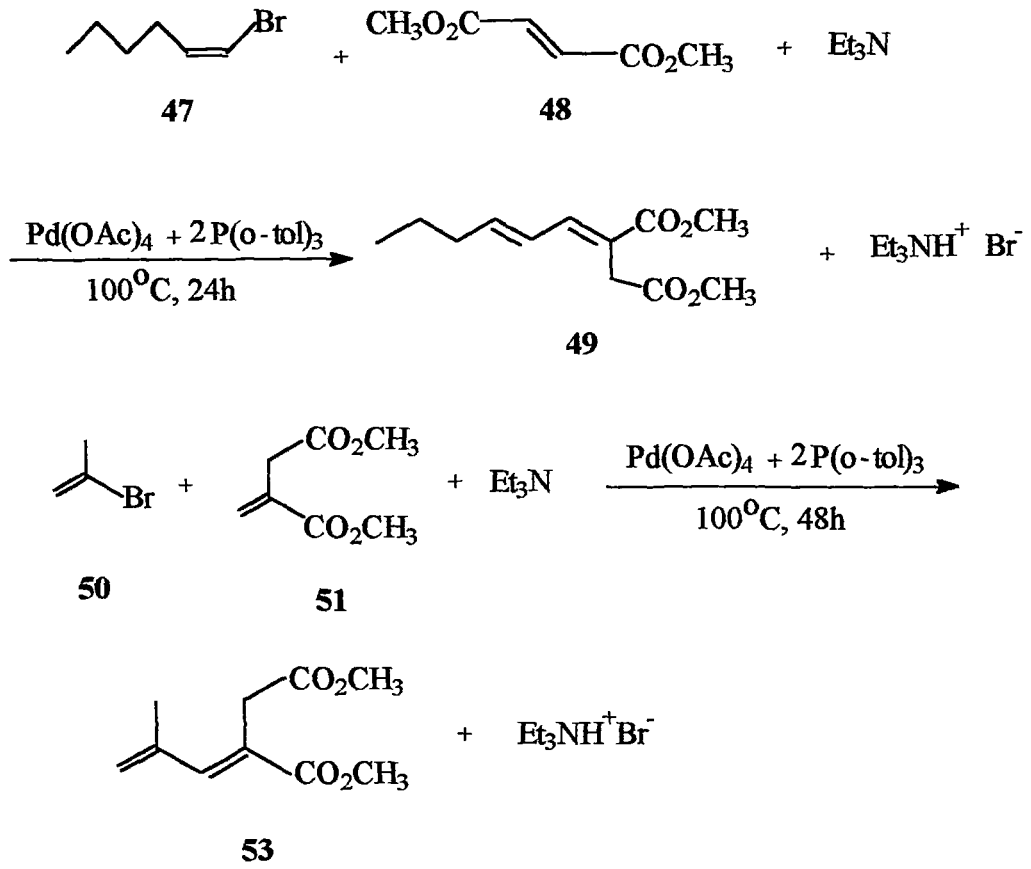
explanation was that both reactions proceeded by way of 3, 4, 5-π-allylic palladium complexes and that the terminal carbomethoxyl group was coordinated to the palladium in the π-complex. The elimination then probably would only be favourable for the formation of the 3, 5-isomer.



Scheme-12

It was also found that treatment of 2-bromopropene **50** with dimethyl itaconate **51** gave the same product **52** (50%) as that obtained from 1-bromo-2-methyl-1-propene and dimethyl fumarate (Scheme-13). Methyl methacrylate reacted fairly readily with all types of vinylic halides, but mixtures were generally formed. Increase in the phosphine concentration and the palladium concentration were helpful in the 1-bromo-1-hexene reactions, but because the reaction rate was lower than with related methyl acrylate reaction a high yield of a single isomer could not be obtained.

Unsaturated organic molecules both aliphatic and aromatic containing the carbonyl functional group has been scantily subjected to Lead (IV) acetate oxidation without altering the double bond to afford the corresponding unsaturated esters.



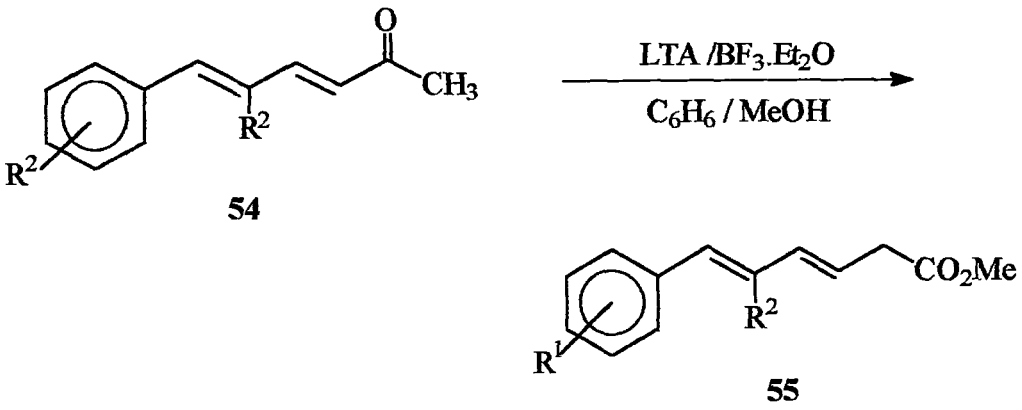
Scheme-13

Earlier studies carried out in our laboratory have shown the successful use of Lead (IV) acetate in combination with Lewis acids to effect a 1, 2-carbonyl transposition in acetophenones[56] and acyclic α, β-unsaturated ketones[57] and a ring contraction in cyclic α, β-unsaturated ketones and related systems.[58a-c] As part of our continuing work to test the effectiveness of this reagent combination, we inserted one more double bond between the carbonyl and the benzylidene system to see whether the presence of the doubly conjugated moiety in the ketone **54** would also facilitate a 1, 2-carbonyl shift.

RESULTS AND DISCUSSIONS:

The conjugated dienones used for the present lead (IV) acetate oxidation were prepared in two steps by successive condensation of aromatic aldehydes with aliphatic aldehydes and then with aliphatic ketones in the procedure which is detailed in the experimental section. At each step the products were purified by column chromatography before proceeding to the next step. The structures of all the unsaturated ketones were confirmed by spectral and analytical data. The stereochemistry of the double bond was assigned on the basis of the coupling constant and were found to have 3E, 5E configuration.

In a typical procedure, to a stirred suspension of lead (IV) acetate in benzene purged with nitrogen at -30°C a solution of the dienone **54** was added in one lot followed by methanol and boron trifluoride-etherate complex (scheme-14). The reaction mixture was stirred at room temperature for 17-24 hours. Work-up followed by column chromatography using hexane-ethylacetate as the eluent afforded the products **55** in varying yields (Table-4).



54 **55**

R^1 = H, p–CH_3, p–Cl, p–OCH_3, p–NO_2, 3,4-$(OMe)_2$ R^2 = H, CH_3, CH_2CH_3

Scheme-14

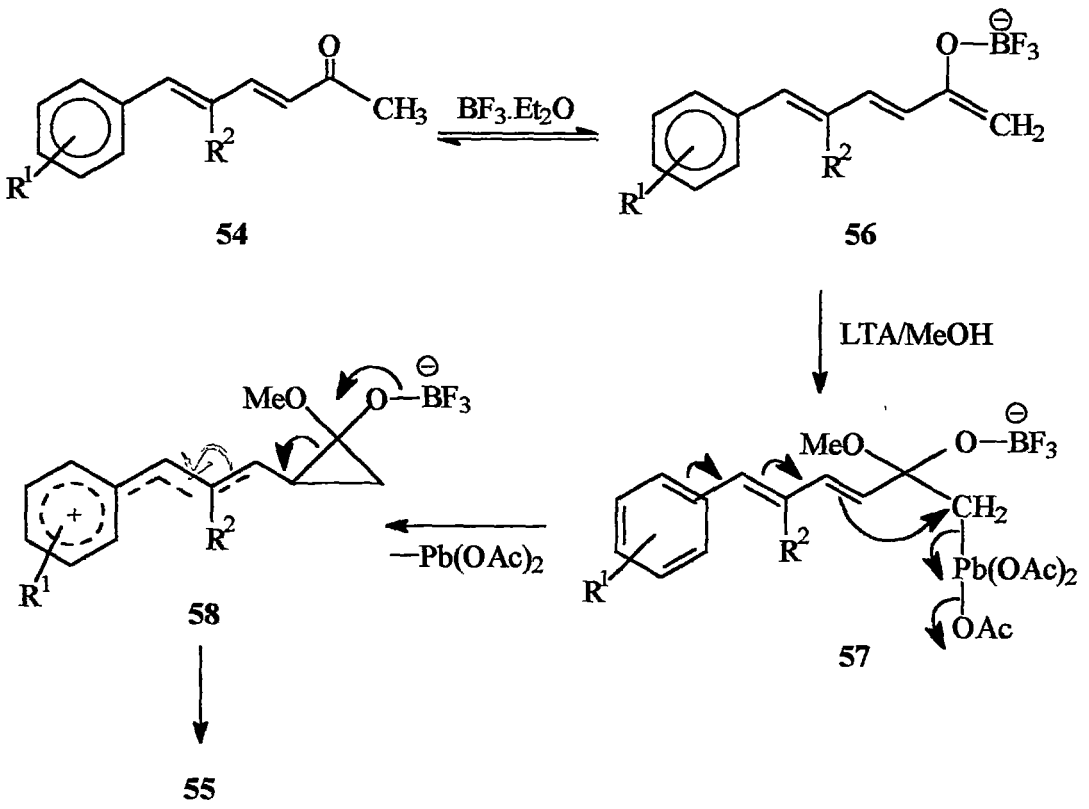
The stereochemistry of the product (scheme-14) is retained or changed depending on the nature of the substituent at C-5. As R^2 becomes increasingly bulkier the concentration of the E isomer (3E) becomes greater and only a trace amount of the Z isomer (3Z) is obtained.[59] The stereochemistry of the double bond at C-3 was assigned on the basis of the coupling constant and also on the basis of the CH_2COOMe signal, which is generally at lower field in the Z than in the corresponding E compounds.[10] For example, methyl (E, E)-6-(4-methylphenyl) hexa-3, 5-dienote gives a doublet at δ 3.20 (J 7.2 Hz) due to CH_2CO, whereas the Z, E isomers give a doublet at δ 3.18 (J= 7.2 Hz).

Table-4: Preparation of substituted hexa-3, 5-dienoic acid methyl esters:

Entry	Products	R^1	R^2	Time/h	Yield/% Cis[a]	Yield/% trans[a]
1	**55a**	H	H	24	10	40
2	**55b**[44b]	H	CH_3	17	7	40
3	**55c**	H	CH_2CH_3	24	0	35
4	**55d**	p-CH_3	H	24	10	38
5	**55e**	p-CH_3	CH_3	12	7	40
6	**55f**	p-CH_3	CH_2CH_3	24	0	47
7	**55g**	p-Cl	CH_3	24	0	45
8	**55h**	p-Cl	CH_2CH_3	24	0	40
9	**55i**	p-OCH_3	CH_3	20	8	35
10	**55j**	p-OCH_3	CH_2CH_3	24	0	42
11	**55k**	3,4-di-OCH_3	CH_3	24	0	38
12	**55l**	3,4-di-OCH_3	CH_2CH_3	24	0	35
13	**55m**	p-NO_2	CH_3	24	0	0

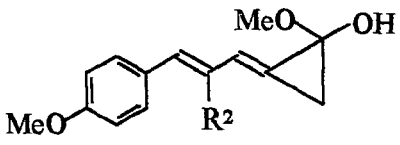
[a] Based on H – H coupling constants.

The plausible mechanism for the formation of hexa-3, 5-dienoate is shown in scheme-15. The mechanism for this transformation appears to involve an initial Lewis acid catalysed enolisation of the ketone **54** to give the enolate **56** which then undergoes oxyplumbation reaction in presence of lead (IV) acetate and methanol to give the organometallic intermediate **57** (not isolated). The elimination of lead (II) acetate evidently assisted by neighboring group participation of the adjacent π electrons resulted in the generation of the carbocation stabilized by the conjugated π system which in presence of methanol rearranges to the more stable product **55**.



Scheme-15

^{1}H NMR analysis of two reaction mixtures where R^1 = OMe and R^2 = Me, CH_2Me showed the presence of methylene protons as multiplets at *ca* δ 1.87 and 1.71, while ^{13}C NMR showed a resonance at *ca* δ 12.3, (scheme-16) suggesting the presence of the cyclopropyl intermediate **58**, which evidently rearranges to the more stable product **55** during work-up.



56

R^2= $-CH_3$, $-CH_2CH_3$

Scheme-16

Thus the starting ketone **54** which showed *trans* geometry, reacts with lead (IV) acetate in presence of boron trifluoride etherate and methanol in benzene at –30°C to give the product **55** in which the stereochemistry is retained or changed depending on the nature of the substituent R^2.

EXPERIMENTAL:

Infrared spectra were recorded on a Perkin-Elmer 983, NICOLET 410, or BOMEM DA-8 FT-IR Spectrophotometer and the frequencies are expressed in cm^{-1}. ^1H NMR (90 MHz) was recorded on Varian EM-390 spectrometer and high resolution ^1H and ^{13}C NMR (300 MHz) spectra were recorded on a Bruker ACF-300 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm from internal tetramethylsilane and are given on the δ scale. J values are given in Hz. The following abbreviations are used to describe peak patterns when appropriate: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were obtained on a JEOL D-300 (EI) mass spectrometer. Masses are reported in units of mass upon charge (m/z), the molecular and base peaks are indicated by (M^+) and (%) respectively. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

All reactions were monitored by thin layer chromatography on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution. Column chromatography was carried out using ACME's silica gel (60-120 mesh) as the solid phase and hexane-ethyl acetate as the eluent.

Chemicals, Reagents and Solvents:

Dry benzene was obtained by keeping over calcium chloride followed by distillation and again storing over sodium wire. The commercial samples of benzaldehyde, substituted benzaldehydes, aliphatic aldehydes and aliphatic ketones were purified

by simple distillation. Methanol was dried by refluxing with calcium oxide followed by distillation. Freshly prepared lead tetraacetate[60] was used in all reactions.

General procedure for the preparation of 5-alkyl-6-arylhexa-3, 5-dien-2-one 54:

Step 1: Preparation of 3-arylpropenaldehyde:

To a cooled (0°C), stirred solution of freshly distilled aromatic aldehyde (50 mmol) and aliphatic aldehyde (50 mmol), 2 ml of 10% sodium hydroxide solution were added drop-wise. The mixture was brought to room temperature and further stirred for another 4 hours. The solution was then rendered acidic to litmus by the addition of dilute hydrochloric acid and extracted with diethyl ether. The organic layer was separated, dried and evaporated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel using hexane as the eluent, to give the 3-arylpropenaldehyde in yields ranging from 50-67%. The product obtained was then used in the next step.

Step 2: Preparation of 5-alkyl-6-arylhexa-3, 5-dien-2-one 54:

To a cooled (0°C), stirred solution of 3-arylpropenaldehyde (30 mmol), obtained as above, dry acetone (30 mmol) was added followed by dropwise addition of 10% sodium hydroxide solution (1.5 ml). The mixture was further stirred at room temperature for another 4 hours, rendered acidic to litmus by the addition of dilute hydrochloric acid and extracted with diethyl ether. The organic layer was separated, dried and evaporated under reduced pressure to give a brown oil. Column chromatography on silica gel using hexane as the eluent yielded the dienone in varying yields (Table-4).

General procedure for the preparation of methyl-5-alkyl-6-arylhexa-3, 5-dienoate 55:

In a typical procedure, a stirred suspension of lead (IV) acetate (10.5 mmol) in benzene (30 ml) was purged with nitrogen and cooled to –30°C. A solution of the dienone (**54**) (10 mmol) was then added in one lot followed by methanol (5 ml) and boron trifluoride (3 ml). The reaction mixture was allowed to warm to room temperature and stirring was continued under nitrogen for 17-24 hours. The precipitated lead (II) acetate was filtered off and the filtrate successively washed with saturated $NaHCO_3$ solution, water and brine, dried over anhydrous sodium sulphate and the solvent removed *in vacuo*. The crude product was purified by column chromatography using silica gel as the solid phase and hexane as eluent to give the pure products **55** in varying yields (Table-4).

6-Phenylhexa-3, 5-dien-2-one 54a:

IR (neat): ν_{max} 1674 cm^{-1}; *^1H NMR*: δ 2.24 (s, 3H, $COCH_3$), 5.96 (d, 1H, J 15.2, H-3), 6.28 (dd, 1H, J 15.2, 10.1, H-5), 6.31 (d, 1H, J 15.2, H-6), 6.42 (dd, 1H, J 15.2, 10.1, H-4), 7.25-7.48 (m, 4H, Ar-H); *^{13}C NMR* δ 31.2, 130.1, 132.4, 134.3, 137.4, 137.8, 139.5, 139.7, 143.2, 193.3; MS (EI) *m/z* (%): 172 (M^+, 23), 129 (74), 77 (65), 43 (100); *Anal. Calcd. for* $C_{12}H_{12}O$ (172): C, 83.72; H, 6.97; *Found*: C, 83.80; H, 6.95%.

Methyl (E, E)-6-phenylhexa-3, 5-dienoate 55a:

IR (neat): ν_{max} 1738 cm^{-1}; *^1H NMR*: δ 3.20 (d, 2H, J 7.2, CH_2CO), 3.68 (s, 3H, OCH_3), 5.88 (m, 1H, H-3), 6.29 (dd, 1H, J 15.2, 10.1, H-4), 6.36 (dd, 1H, J

15.2,10.1, H-5), 6.42 (d, 1H, J 15.2, H-6), 7.21-7.53 (m, 5H, Ar-H); *^{13}C NMR*: δ 42.1, 51.3, 129.4, 131.0, 133.6, 136.0, 137.1, 138.1, 144.2, 172.7; MS (EI) m/z (%): 202 (M^+, 56), 171 (46), 143 (100), 77 (70), 59 (80); *Anal. Calcd. for* $C_{13}H_{14}O_2$ (202): C, 77.22; H, 6.93; *Found*: C, 77.30; H, 6.98%.

Methyl (Z, E)-6-phenylhexa-3, 5-dienoate 55a:

IR (neat): ν_{max} 1741 cm^{-1}; *^{1}H NMR*: δ 3.19 (d, 2H, J 7.2, CH_2CO), 3.69 (s, 3H, OCH_3), 5.90 (m, 1H, H-3), 6.31 (dd, 1H, J 11.5, 10.1, H-4), 6.35 (dd, 1H, J 15.2, 10.1, H-5), 6.40 (d, 1H, J 15.2, H-6), 7.21-7.51 (m, 5H, Ar-H); *^{13}C NMR*: δ 40.2, 51.9, 131.2, 131.8, 134.0, 134.8, 136.1, 138.9, 143.4; MS (EI) *m/z* (%): 202 (M^+, 31), 171 (26), 143 (100), 77 (68), 59 (74); *Anal. Calcd. for* $C_{13}H_{14}O_2$ (202): C, 77.22; H, 6.93; *Found*: C, 77.32; H, 6.95%.

5-Methyl-6-phenylhexa-3, 5-dien-2-one 54b:

IR (neat): ν_{max} 1675 cm^{-1}; *^{1}H NMR*: δ 1.94 (s, 3H, CH_3), 2.22 (s, 3H, $COCH_3$), 5.92 (d, 1H, J 15.2, H-3), 6.30 (s, 1H, H-6), 6.39 (d, 1H, J 15.2, H-4), 7.28-7.40 (m, 5H, Ar-H); *^{13}C NMR*: δ 20.8, 29.8, 129.8, 130.1, 133.6, 136.8, 138.4, 138.7, 140.3, 142.8, 193.1; MS (EI) *m/z* (%): 186 (M^+, 62), 143 (36), 77 (68), 43 (100); *Anal. Calcd. for* $C_{13}H_{14}O$ (186): C, 83.87; H, 7.52; *Found*: C, 83.91; H, 7.56%.

Methyl (E, E)-5-methyl-6-phenylhexa-3, 5-dienoate 55b:

IR (neat): ν_{max} 1736 cm^{-1}; *^{1}H NMR*: δ 1.95 (s, 3H, CH_3), 3.19 (d, 2H, J 7.2, CH_2CO), 3.70 (s, 3H,OCH_3), 5.86 (m, 1H, H-3), 6.30 (d, 1H, J 15.2, H-4), 6.45 (s, 1H, H-6), 7.18-7.42 (m, 5H, Ar-H); *^{13}C NMR*: δ 21.6, 37.4, 51.8, 129.4, 130.2, 134.3, 135.6, 138.7, 139.6, 142.1, 172.5; MS (EI) *m/z* (%): 216 (M^+, 47), 157 (100),

77 (71), 59 (67); *Anal Calcd. for* $C_{14}H_{16}O_2$ (216): C, 77.77; H, 7.40; *Found*: C, 77.85; H, 7.51%.

Methyl (Z, E)-5-methyl-6-phenylhexa-3, 5-dienoate 55b:

IR (neat): ν_{max} 1738 cm^{-1}; *^{1}H NMR*: δ 1.95 (s, 3H, CH_3), 3.18 (d, 2H, J 7.2, CH_2CO), 3.68 (s, 3H, OCH_3), 5.82 (m, 1H, H-3), 6.30 (d, 1H, J 11.5, H-4), 6.42 (s, 1H, H-6), 7.14-7.41 (m, 5H, Ar-H); *^{13}C NMR*: δ 21.3, 40.8, 51.6, 126.8, 129.9, 130.1, 133.0, 134.5, 136.9, 138.5, 140.1, 171.7; MS (EI) *m/z* (%): 216 (M^+, 32), 157 (100), 77 (74), 59 (81); *Anal. Calcd. for* $C_{14}H_{16}O_2$ (216): C, 77.77; H, 7.40; *Found*: C, 77.81; H, 7.46%.

5-Methyl-6-phenylhexa-3, 5-dien-2-one 54c:

IR (neat): ν_{max} 1674 cm^{-1}; *^{1}H NMR*: δ 1.03 (t, 3H, J 7.3, CH_2CH_3), 2.20 (q, 2H, J 7.3, CH_2CH_3), 2.24 (s, 3H, $COCH_3$), 5.90 (d, 1H, J 15.2, H-3), 6.33 (s, 1H, H-6), 6.44 (d, 1H, J 15.2, H-4), 7.21-7.43 (m, 5H, Ar-H); *^{13}C NMR*: δ 16.7, 29.0, 31.5, 129.4, 131.7, 133.8, 136.2, 136.8, 137.4, 139.7, 145.3, 193.7; MS (EI) *m/z* (%): 200 (M^+, 61), 157 (41), 77 (56), 43 (100); *Anal. Calcd. for* $C_{14}H_{16}O$ (200): C, 84.00; H, 8.0; *Found*: C, 84.10; H, 8.02%.

Methyl (E, E)-5-ethyl-6-phenylhexa-3, 5-dienoate 55c:

IR (neat): ν_{max} 1737 cm^{-1}; *^{1}H NMR*: δ 1.02 (t, 3H, J 7.3, CH_3CH_2), 2.21 (q, 2H, J 7.3, CH_2CH_3), 3.10 (d, 2H, J 7.2, CH_2CO), 3.68 (s, 3H, OCH_3), 5.62 (m, 1H, H-3), 5.98 (d, 1H, J 15.2, H-4), 6.23 (s, 1H, H-6), 7.09-7.38 (m, 4H, Ar-H); *^{13}C NMR*: δ 15.8, 29.9, 34.1, 51.7, 126.5, 129.1, 131.2, 134.6, 136.6, 139.6, 144.1, 173.1; MS (EI) *m/z* (%): 230 (M^+, 67), 171 (100), 77 (71), 59 (72); *Anal. Calcd. for* $C_{15}H_{18}O_2$ (230): C, 78.26; H, 7.82; *Found*: C, 78.31; H, 7.91%.

6-(4-Methylphenyl)hexa-3, 5-dien-2-one 54d:

IR (neat): ν_{max} 1677 cm^{-1}; *^{1}H NMR*: δ 2.05 (s, 3H, Ar-C*H*$_3$), 2.28 (s, 3H, COC*H*$_3$), 5.96 (d, 1H, J 15.2, H-3), 6.30 (dd, 1H, J 15.2, 10.1, H-5), 6.36 (d, 1H, J 15.2, H-6), 6.49 (dd, 1H, J 15.2, 10.1, H-4), 7.18-7.51 (m, 4H, Ar-H); *^{13}C NMR*: δ 25.4, 33.5, 127.8, 130.8, 134.6, 135.3, 136.9, 137.4, 144.5, 149.3, 194.1; MS (EI) *m/z* (%): 186 (M^+, 55), 123 (45), 91 (100), 43 (70); *Anal. Calcd. for* $C_{13}H_{14}O$ (186): C, 83.87; H, 7.52; *Found*: C, 83.84; H, 7.54%.

Methyl (E, E)-6-(4-methylphenyl)hexa-3, 5-dienoate 55d:

IR (neat): ν_{max} 1739 cm^{-1}; *^{1}H NMR*: δ 2.08 (s, 3H, Ar-C*H*$_3$), 3.20 (d, 2H, J 7.2, C*H*$_2$CO), 3.69 (s, 3H, OC*H*$_3$), 5.88 (m, 1H, H-3), 6.30 (dd, 1H, J 15.2, 10.1, H-5), 6.35 (dd, 1H, J 15.2, 10.1, H-4), 6.45 (d, 1H, J 15.2, H-6), 7.11-7.45 (m, 4H, Ar-H); *^{13}C NMR*: δ 26.8, 44.2, 51.4, 126.4, 129.3, 130.6, 136.4, 136.6, 137.4, 138.2, 147.2, 173.9; MS (EI) *m/z* (%): 216 (M^+, 47), 157 (81), 91 (100), 59 (67); *Anal. Calcd. for* $C_{14}H_{16}O_2$ (216): C, 77.77; H, 7.40; *Found*: C, 77.85; H, 7.50%.

Methyl (Z, E)-6-(4-methylphenyl)hexa-3, 5-dienoate 55d:

IR (neat): ν_{max} 1740 cm^{-1}; *^{1}H NMR*: δ 2.05 (s, 3H, Ar-C*H*$_3$), 3.18 (d, 2H, J 7.2, C*H*$_2$CO), 3.70 (s, 3H, OC*H*$_3$), 5.90 (m, 1H, H-3), 6.30 (dd, 1H, J 15.2, 10.1, H-5), 6.35 (dd, 1H, J 11.5, 10.1. H-4), 6.46 (d, 1H, J 15.2, H-6), 7.15-7.43 (m, 4H, Ar-H); *^{13}C NMR*: δ 25.8, 43.2, 52.1, 128.9, 129.3, 131.6, 135.9, 136.1, 136.9, 137.4, 147.8, 173.4; MS (EI) *m/z* (%): 216 (M^+, 31), 157 (57), 91 (100), 59 (69); *Anal. Calcd. for* $C_{14}H_{16}O_2$ (216): C, 77.77; H, 7.40; *Found*: C, 77.80; H, 7.45%.

5-Methyl-6-(4-methylphenyl)hexa-3, 5-dien-2-one 54e:

IR (neat): ν_{max} 1673 cm^{-1}; *^{1}H NMR*: δ 1.93 (s, 3H, C*H*$_3$), 2.00 (s, 3H, Ar-C*H*$_3$), 2.23 (s, 3H, COC*H*$_3$), 5.93 (d, 1H, J 15.2, H-3), 6.34 (s, 1H, H-6), 6.46 (d, 1H, J 15.2, H-4), 7.20-7.45 (m, 4H, Ar-H); *^{13}C NMR*: δ 22.0, 24.8, 30.7, 128.4, 131.8, 133.4, 135.6, 136.3, 138.3, 143.2, 147.4, 192.8; MS (EI) *m/z* (%): 200 (M^+, 58), 157 (47), 91 (100), 43 (74); *Anal. Calcd. for* $C_{14}H_{16}O$ (200): C, 84.0; H, 8.0; *Found*: C, 84.07; H, 8.06%

Methyl (E, E)-5-methyl-6-(4-methylphenyl)hexa-3, 5-dienoate 55e:

IR (neat): ν_{max} 1738 cm^{-1}; *^{1}H NMR*: δ 1.92 (s, 3H, C*H*$_3$), 1.98 (s, 3H, Ar-C*H*$_3$), 3.23 (d, 2H, J 7.2, C*H*$_2$CO), 3.68 (s, 3H, OC*H*$_3$), 5.84 (m, 1H, H-3), 6.25 (d, 1H, J 15.2, H-4), 6.48 (s, 1H, H-6), 7.21-7.50 (m, 4H, Ar-H); *^{13}C NMR*: δ 20.8, 25.0 45.2, 51.1, 129.1, 131.4, 135.2, 136.3, 138.2, 138.5, 148.4, 170.8; MS (EI) *m/z* (%): 230 (M^+, 61), 171 (71), 91 (100), 59 (60); *Anal. Calcd for* $C_{15}H_{18}O_2$ (230): C, 78.26; H, 7.82; *Found*: C, 78.31; H, 7.86%.

Methyl (Z, E)-5-methyl-6-(4-methylphenyl)hexa-3, 5-dienoate 55e:

IR (neat): ν_{max} 1739cm^{-1}; *^{1}H NMR*: δ 1.95 (s, 3H, C*H*$_3$), 2.00 (s, 3H, ArC*H*$_3$), 3.21 (m, 2H, J 7.2, C*H*$_2$CO), 3.71 (s, 3H, OC*H*$_3$), 5.87 (m, 1H, H-3), 6.28 (d, 1H, J 11.5, H-4), 6.48 (s, 1H, H-6), 7.10-7.44 (m, 4H, Ar-H); *^{13}C NMR*: δ 21.7, 26.3, 44.3, 52.6, 128.7, 132.6, 135.4, 136.4, 137.3, 137.7, 138.1, 148.1, 171.0; MS (EI) *m/z* (%): 230 (M^+, 55), 171 (39), 91 (100), 59 (75); *Anal. Calcd for* $C_{15}H_{18}O_2$ (230): C, 78.26; H, 7.82; *Found*: C, 78.36; H, 7.90%.

5-Ethyl-6-(4-methylphenyl)hexa-3, 5-dien-2-one 54f:

IR (neat): ν_{max} 1674cm^{-1}; *^{1}H NMR*: δ1.05 (s, 3H, J 7.3, CH_2CH_3), 1.94 (s, 3H, $ArCH_3$), 2.20 (q, 2H, J 7.3, CH_2CH_3), 2.22 (s, 3H, $COCH_3$), 5.91 (d, 1H, J 15.2, H-3), 6.35 (s, 1H, H-6), 6.45 (d, 1H, J 15.2, H-4), 7.23-7.43 (m, 4H, Ar-H); *^{13}C NMR*: δ 18.3, 22.8, 28.7, 29.3, 130.0, 134.7, 135.6, 136.2, 137.8, 138.8, 144.2, 146.7, 191.9; MS (EI) *m/z* (%): 214 (M^+, 42), 171 (51), 91 (100), 43 (70); *Anal. Calcd. for* $C_{15}H_{18}O$ (214): C, 84.11; H, 8.41; *Found*: C, 84.07; H, 8.07%.

Methyl (E, E)-5-ethyl-6-(4-methylphenyl)hexa-3, 5-dienoate 55f:

IR (neat): 1735cm^{-1}; *^{1}H NMR*: δ 1.05 (t, 3H, J 7.3, CH_2CH_3), 1.90 (s, 3H, $ArCH_3$), 2.22 (s, 2H, J 7.3, CH_2CH_3), 2.24 (d, 2H, J 7.2, CH_2CO), 3.70 (s, 3H, OCH_3), 5.85 (m, 1H, H-3), 6.28 (d, 1H, J 15.2, H-4), 6.46 (s, 1H, H-6), 7.18-7.48 (m, 4H, Ar-H); *^{13}C NMR*: δ 16.7, 21.1, 30.4, 46.3, 51.9, 128.3, 130.3, 134.1, 136.5, 138.1, 144.1, 148.6; MS (EI) *m/z* (%): 244 (M^+, 51), 213 (27), 185 (88), 91 (100), 59 (65); *Anal. Calcd. for* $C_{16}H_{20}O_2$ (244): C, 78.68; H, 7.82; *Found*: C, 78.74; H, 7.95%.

5-Methyl-6-(4-chlorophenyl)hexa-3, 5-dien-2-one 54g:

IR (neat): ν_{max} 1676 cm^{-1}; *^{1}H NMR*: δ 1.95 (s, 3H, CH_3), 2.28 (s, 3H, $COCH_3$), 5.95 (d, 1H, J 15.2, H-3), 6.38 (s, 1H, H-6), 6.52 (d, 1H, J 15.2, H-4), 7.25-7.58 (m, 4H, Ar-H); *^{13}C NMR*: δ 24.6, 34.0, 129.3, 132.7, 133.7, 135.4, 136.8 141.3, 144.3, 146.7, 193.4; MS (EI) *m/z* (%): 220 (M^+, 48), 177 (39), 111 (91), 43 (100); *Anal. Calcd. for* $C_{13}H_{13}ClO$ (220.5): C, 70.74; H, 5.89; *Found*: C, 70.85; H, 5.94%.

Methyl (E, E)-5-methyl-6-(4-chlorophenyl)hexa-3, 5-dienoate 55g:

IR (neat): ν_{max} 1739 cm^{-1}; *^{1}H NMR*: δ 1.93 (s, 3H, CH_3), 3.21 (d, 2H, J 7.2, CH_2CO), 3.71 (s, 3H, OCH_3), 5.94 (m, 1H, H-3), 6.30 (d, 1H, J 15.2, H-4), 6.48 (s, 1H, H-6),

7.18-7.56 (m, 4H, Ar-H); *^{13}C NMR*: δ 22.7, 40.2, 52.1, 128.4, 132.1, 134.9, 136.3, 137.0, 138.5, 146.3; MS (EI) *m/z* (%): 250 (M^+, 70), 219 (21), 191 (100), 111 (84), 59 (67); *Anal. Calcd. for* $C_{14}H_{15}O_2Cl$ (250.5): C, 67.06; H, 5.98; *Found*: C, 67.11; H, 6.03%.

5-Ethyl-6-(4-chlorophenyl)hexa-3, 5-dien-2-one 54h:

IR (neat): ν_{max} 1675 cm^{-1}; *^{1}H NMR*: δ1.06 (t, 3H, J 7.3, CH_2CH_3), 2.25 (q, 2H, J 7.3, CH_2CH_3), 2.27 (s, 3H, $COCH_3$), 5.94 (d, 1H, J 15.2, H-3), 6.33 (s, 1H, H-6), 6.48 (d, 1H, J 15.2, H-4), 7.24-7.55 (m, 4H, Ar-H); *^{13}C NMR*: δ 18.8, 31.4, 33.1, 130.3, 132.6, 133.7, 135.8, 136.4, 138.4, 139.8, 148.3, 193.8; MS (EI) *m/z* (%): 234 (M^+, 61), 191 (41), 111 (81), 43 (100); *Anal. Calcd. for* $C_{14}H_{15}ClO$ (234.5): C, 71.64; H, 6.39; *Found*: C, 71.69; H, 6.48%.

Methyl (E, E)-5-ethyl-6-(4-chlorophenyl)hexa-3, 5-dienoate 55h:

IR (neat): ν_{max} 1738 cm^{-1}; *^{1}H NMR*: δ 1.08 (t, 3H, J 7.3, CH_2CH_3), 2.25 (q, 2H, J 7.3, CH_2CH_3), 3.24 (d, 2H, J 7.2, CH_2CO), 3.70 (s, 3H, OCH_3), 5.91 (m, 1H, H-3), 6.32 (d, 1H, H-4), 6.48 (s, 1H, H-6), 7.20-7.54 (m, 4H, Ar-H); *^{13}C NMR*: δ 17.0, 31.8, 44.3, 52.0, 130.2, 133.4, 134.0, 134.7, 136.8, 138.7, 139.4, 149.2, 174.3; MS (EI) *m/z* (%): 248 (M^+, 55), 217 (23), 189 (100), 111 (79), 59 (61); *Anal. Calcd. for* $C_{15}H_{17}O_2Cl$ (248.5): C, 68.05; H, 6.42; *Found*: C, 68.13; H, 6.51%.

5-Methyl-6-(4-methoxyphenyl)hexa-3, 5-dien-2-one 54i:

IR (neat): ν_{max} 1675 cm^{-1}; *^{1}H NMR*: δ 1.98 (s, 3H, CH_3), 2.24 (s, 3H, $COCH_3$), 3.75 (s, 3H, OCH_3), 5.92 (d, 1H, J 15.2, H-3), 6.33 (s, 1H, H-6), 6.49 (d, 1H, J 15.2, H-4), 7.23-7.49 (m, 4H, Ar-H); *^{13}C NMR*: δ 24.6, 31.5, 55.2, 129.1, 131.4, 133.3, 137.4, 140.0, 146.7, 150.2, 158.3, 192.8; MS (EI) *m/z* (%): 216 (M^+, 48), 173 (32), 107

(100), 43 (92); *Anal. Calcd. for* $C_{14}H_{16}O_2$ (216): C, 77.77; H, 7.40; *Found*: C, 77.82; H, 7.47%.

Methyl (E, E)-5-methyl-6-(4-methoxyphenyl)hexa-3, 5-dienoate 55i:

IR (neat): ν_{max} 1739 cm^{-1}; *^{1}H NMR*: δ 1.95 (s, 3H, CH_3), 3.20 (d, 2H, J 7.2, CH_2CO), 3.68 (s, 3H, $COOCH_3$), 3.74 (s, 3H, $ArOCH_3$), 5.90 (m, 1H, H-3), 6.25 (d, 1H, J 15.2, H-4), 6.47 (s, 1H, H-6), 7.15-7.49 (m, 4H, Ar-H); *^{13}C NMR*: δ 22.3, 35.9, 51.6, 54.3, 129.7, 132.0, 135.4, 136.4, 138.9, 143.2, 146.5, 159.1, 173.5; MS (EI) *m/z* (%): 246 (M^+, 50), 187 (100), 107 (94), 59 (78); *Anal. Calcd. for* $C_{15}H_{18}O_3$ (246): C, 73.17; H, 7.31; *Found*: C, 73.26; H, 7.45%.

Methyl (Z, E)-5-methyl-6-(4-methoxyphenyl)hexa-3, 5-dienoate 55i:

IR (neat): ν_{max} 1741 cm^{-1}; *^{1}H NMR*: δ 1.98 (s, 3H, CH_3), 3.18 (d, 2H, J 7.2, CH_2CO), 3.75 (s, 3H, $ArOCH_3$), 5.95 (m, 1H, H-3), 6.27 (d, 1H, J 11.5, H-4), 6.48 (s, 1H, H-6), 7.15-7.51 (m, 4H, Ar-H); ^{13}C NMR: δ 23.4, 34.2, 51.9, 54.5, 129.2, 133.2, 134.2, 138.4, 140.2, 144.1, 144.6, 158.4, 173.8; MS (EI) *m/z* (%): 246 (M^+, 46), 215 (17), 187 (100), 107 (94), 59 (78); *Anal. Calcd. for* $C_{15}H_{18}O_2$ (246): C, 73.17; H, 7.31; *Found*: C, 73.22; H, 7.39%.

5-Ethyl-6-(4-methoxyphenyl)hexa-3, 5-dien-2-one 54j:

IR (neat): ν_{max} 1674 cm^{-1}; *^{1}H NMR*: δ 1.07 (t, 3H, J 7.3, CH_2CH_3), 2.22 (q, 2H, J 7.3, CH_2CH_3), 2.25 (s, 3H, $COCH_3$), 3.74 (s, 3H, $ArOCH_3$), 5.93 (d, 1H, J 15.2, H-3), 6.35 (s, 1H, H-6), 6.45 (d, 1H, J 15.2, H-4), 7.20-7.48 (m, 4H, Ar-H); *^{13}C NMR*: δ 18.9, 30.6, 32.0, 54.6, 132.3, 133.6, 135.4, 136.4, 141.7, 142.7, 146.8, 156.7, 192.6; MS (EI) *m/z* (%): 230 (M^+, 61), 187 (34), 107 (100), 43 (76); *Anal. Calcd. for* $C_{15}H_{18}O_2$ (230): C, 78.26; H, 7.82; *Found*: C, 78.31; H, 7.89%.

Methyl (E, E)-5-ethyl-6-(4-methoxyphenyl)hexa-3, 5-dienoate 55j:

IR (neat): ν_{max} 1738 cm^{-1}; ^1H NMR: δ 1.09 (t, 3H, J 7.3, CH_2CH_3), 2.21 (q, 3H, J 7.2, CH_2CH_3), 3.23 (d, 2H, J 7.3, CH_2CO), 3.69 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $ArOCH_3$), 5.93 (m, 1H, H-3), 6.33 (d, 1H, J 15.2, H-4), 6.46 (s, 1H, H-6), 7.13-7.50 (m, 4H, Ar-H); *^{13}C NMR*: δ 18.0, 28.8, 40.8, 51.6, 55.6, 132.2, 133.3, 136.4, 138.4, 139.6, 143.5, 148.4, 155.3, 173.0; MS (EI) *m/z* (%): 260 (M^+, 64), 201 (100), 107 (83), 59 (87). *Anal. Calcd. for* $C_{16}H_{20}O_3$ (260): C, 73.84; H, 7.69; *Found*: C, 73.94; H, 7.81%.

5-Methyl-6-(3, 4-dimethoxyphenyl)hexa-3, 5-dien-2-one 54k:

IR (neat): ν_{max} 1675 cm^{-1}; *^1H NMR*: δ 1.97 (s, 3H, CH_3), 2.26 (s, 3H, $COCH_3$), 3.74 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, $ArOCH_3$), 5.93 (d, 1H, J 15.2, H-3), 6.38 (s, 1H, H-6), 6.48 (d, 1H, J 15.2, C-4), 7.24-7.53 (m, 3H, Ar-H); ^{13}C NMR: δ 26.3, 33.4, 54.8, 55.4, 131.5, 132.5, 136.4, 138.4, 139.8, 142.7, 149.1, 158.6, 159.4, 194.0; MS (EI) *m/z* (%): 246 (M^+, 41), 203 (45), 137 (72), 43 (100); *Anal. Calcd. for* $C_{15}H_{18}O_3$ (246): C, 73.17; H, 7.31; *Found*: C, 73.24; H, 7.38%.

Methyl (E, E)-5-methyl-6-(3, 4-dimethoxyphenyl)hexa-3, 5-dienoate 55k:

IR (neat): ν_{max} 1740 cm^{-1}; *^1H NMR*: 1.96 (s, 3H, CH_3), 3.18 (d, 2H, J 7.2, CH_2CO), 3.70 (s, 3H, $COOCH_3$), 3.76 (s, 3H, $ArOCH_3$), 3.77 (s, 3H, $ArOCH_3$), 5.91 (m, 1H, H-3), 6.30 (d, 1H, J 15.2, H-6), 6.48 (s, 1H, H-4), 7.22-7.58 (m, 3H, Ar-H); *^{13}C NMR*: δ 23.7, 34.7, 52.4, 54.3, 55.1, 132.7, 134.3, 136.4, 138.6, 139.7, 142.3, 144.1, 149.0, 158.4, 159.6, 173.8; MS (EI) *m/z* (%): 276 (M^+, 47), 245 (35), 217 (100), 59 (64); *Anal. Calcd. for* $C_{16}H_{20}O_4$ (276): C, 69.56; H, 7.24; *Found*: C, 69.63; H, 7.36%.

5-Ethyl-6-(3, 4-dimethoxyphenyl)hexa-3, 5-dien-2-one 54l:

IR (neat): ν_{max} 1676 cm^{-1}; *^{1}H NMR*: δ 1.06 (t, 3H, J 7.3, CH_2CH_3), 2.20 (q, 2H, J 7.3, CH_2CH_3), 2.25 (s, 3H, $COCH_3$), 3.75 (s, 3H, $ArOCH_3$), 3.76 (s, 3H, $ArOCH_3$), 5.91 (d, 1H, J 15.2, H-3), 6.30 (s, 1H, H-6), 6.50 (d, 1H, J 15.2, H-4), 7.23-7.51 (m, 3H, Ar-H); *^{13}C NMR*: δ 17.8, 29.4, 32.1, 55.3, 55.9, 133.3, 134.4, 135.8, 136.8, 139.8, 142.3, 143.2, 151.0, 157.8, 159.0, 194.8; MS (EI) *m/z* (%): 260 (M^+, 41), 217 (20), 137 (72), 43 (100); *Anal. Calcd. for* $C_{16}H_{20}O_3$ (260): C, 73.84; H, 7.69; *Found*: C, 73.90; H, 7.74%.

Methyl (E, E)-5-ethyl-6-(3, 4-dimethoxyphenyl)hexa-3, 5-dienoate 55l:

IR (neat): ν_{max} 1739 cm^{-1}; *^{1}H NMR*: δ 1.05 (t, 3H, J 7.3, CH_2CH_3), 2.21 (q, 2H, J 7.3CH_2CH_3), 3.21 (d, 2H, J 7.2, CH_2CO), 3.70 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $ArOCH_3$), 3.76 (s, 3H, $ArOCH_3$), 5.91 (m, 1H, H-3), 6.31 (d, 1H, J 15.2, H-4), 6.51 (s, 1H, H-6), 7.15-7.54 (m, 3H, Ar-H); *^{13}C NMR*: δ 21.6, 29.3, 38.6, 51.8, 54.7, 55.6, 132.6, 136.7, 136.9, 137.4, 139.1, 139.3, 143.5, 147.7, 158.9, 159.4, 174.6; MS (EI) *m/z* (%): 290 (M^+, 31), 259 (31), 231 (100), 137 (72), 59 (61); *Anal. Calcd. for* $C_{17}H_{22}O_4$ (290): C, 70.34; H, 7.58; *Found*: C, 70.50; H, 7.69%.

References:

1. E. W. Colvin, D. H. R. Barton, W. D. Ollis, in *Comprehensive Organic Chemistry*, Pergamon: Oxford, **1979**; *2*, 617.
2. (a) G. H. Posner, R. D. Crouch, C. M. Kinter, *J. Org. Chem.*, **1991**, *56*, 6981. (b) M. Matsumoto, K. Kuroda, *Tetrahedron Lett.*, **1982**, *23*, 1285.
3. (a) M. Kotzian, C. G. Kreiter, S. Ozkar, *J. Organomet. Chem.*, **1982**, *229*, 29. (b) S. G. Davies, G. D. Smyth, A. M. Chippindale, *J. Chem. Soc. Perkin. Transaction 1*, **1999**, 3089.
4. E. W. Colvin, in "*Comprehensive Organic Chemistry*," D. H. R. Barton, W. D. Ollis, Pergamon: Oxford **1979**; *2*, 620.
5. H. Mayr, A. Cambanis, E. Bauml, *Synthesis*, **1988**, 962.
6. A. S. Kende, B. H. Toder, *J. Org. Chem.*, **1982**, *47*, 163.
7. M. W. Rathke, D. Sullivan, *Tetrahedron Lett.*, **1972**, *42*, 4249.
8. J. L. Horrmann, G. R. Kieczykowski, R. H. Schlessinger, *Tetrahedron Lett.*, **1973**, 2433.
9. M. W. Rathke, A. Lindert, *J. Am. Chem. Soc.*, **1971**, *93*, 2318.
10. R. H. Vander Veen, H. Cerfontain, *J. Org. Chem.*, **1985**, *50*, 342.
11. (a) P. E. Pfeffer, L. S. Silvert, E. Kinsel, *Tetrahedron Lett.*, **1973**, 1163. (b) P. E. Pfeffer, L. S. Silvert, E. Kinsel, *J. Org. Chem.*, **1971**, *36*, 3290.
12. E. S. Stratford, N. D. Aggerwal, *J. Org. Chem.*, **1979**, *44*, 1570.
13. (a) J. Katzenellenbogen, A. L. Crumrine, *J. Am. Chem. Soc.*, **1974**, *96*, 5662. (b) P. M. Savu, J. Katzenellenbogen, *J. Org. Chem.*, **1981**, *46*, 239.
14. M. Majewski, G. P. Mpango, M. T. Thomas, A. Snieckus, *J. Org. Chem.*, **1981**, *46*, 2029.

15. M. R. Najafi, M. L. Wang, G. Zweifel, *J. Org. Chem.*, **1991**, *56*, 2468.

16. (a) R. L. Dansheimer, H. Sard, *J. Org. Chem.*, **1980**, *45*, 4810. (b) M. P. Cooke, *J. Org. Chem.*, **1987**, *52*, 5729.

17. Oxygen nucleophiles such as alkoxides are known to attack α-silyl esters at silcon rather than at the α-hydrogen atoms to give the desilyleted enolate ions, on the other hand nitrogen bases such as LDA usually attack the α-hydrogen atoms to give silcon substituted enolates; I. Fleming, in *Comprehensive. Org. Chem.*, D. H. R. Barton, W. D. Ollis, Eds; pergamon Oxford, **1979**, *3*, 657.

18. S. I. Murahashi, Y. Imada, Y. Taniguchi, S. Higashiura, *J. Org. Chem.*, **1993**, *58*, 1538.

19. (a) G. P. Chiusoli, L. Cassar, *Angew Chem.*, Int. Ed. Engl. **1967**, *6*, 124. (b) M. Foa, L. Cassar, F. Guerrieri, *Synthesis*, **1973**, 509, (c) M. Foa, L. Cassar, *Gazz. Chim. Ital.*, **1979**, *109*, 619. (d) F. Joo, H. Alper, *Organometallics*, **1985**, *4*, 1775.

20. R. F. Heck, D. S. Bresslow, *J. Am. Chem. Soc.*, **1963**, *85*, 2779.

21. Synthesis of β, γ-unsaturated carboxylic acids, derivatives: (a) W. T. Dent, R. Long, G. H. Whitfield, *J. Chem. Soc.*, **1964**, 1588. (T. Tsyji, J. Kiji, S. Imamura, M. Morikawa, *J. Am. Chem. Soc.*, **1964**, *86*, 4350. (c) D. Medema, R. V. Helden, C. F. Kohll, *Inorg. Chim. Acta.*, **1969**, *3*, 255. (d) J. F. Kniffton, *J. Organomet. Chem.*, **1980**, *188*, 223. (e) J. Kiji, T. Okano, H. Konishi, W. Nishiumi, *Chem. Lett.*, **1989**, 1873.

22. (a) Synthesis of allyl ketones and aldehydes: J. H. Merrifield, J. P. Godschalk, J. K. Stille, *Organometallics*, **1984**, *3*, 1108. (b) B. P. Baillargeon, J. K. Stille, *J. Am. Chem. Soc.*, **1986**, *108*, 452.

23. L. S. Hegedus, R. Tamura, *Organometallics*, **1982**, *1*, 888.

24. (a) H. Matsuzaka, Y. Hiroe, M. Iwasaki, Y, Ishii, Y. Koyasu, M. Hidai, *J. Org. Chem.*, **1988**, *53*, 3832. (b) M. Iwasaki, J-P. Li, H. Matsuzaka, Y, Ishii, M. Hidai, *J. Org. Chem.*, **1991**, *56*, 1922.

25. J. Kiji, T. Okano, I. Ono, H. Konishi, *J. Mol. Catal.*, **1987**, *39*, 355.

26. D. Neibacker, J. Poirier, J. Tkatchenko, *J. Org. Chem.*, **1989**, *54*, 2459.

27. (a) D. Milstein, *Organometallics*, **1982**, *1*, 888. (b) D. Milstein, *Acc. Chem. Res.*, 1988, *21*, 428.

28. M. F. Solomon, S. N. Pardo, R. G. Solomon, *J. Am. Chem. Soc.*, **1984**, *106*, 3797.

29. M. F. Solomon, S. N. Pardo, R. G. Solomon, *J. Org. Chem.*, **1984**, *46*, 2446.

30. J. I. Kim, B. A. Patel, R. F. Heck, *J. Org. Chem.*, **1984**, *46*, 2446.

31. G. H. Posner, C. M. Kinter, *J. Org. Chem.*, **1990**, *55*, 3967.

32. (a) S. J. Rhoads, N. R. Raolins, *Org. Reactions.*, **1975**, *22*, 1 (b) F. E. Ziegler., *Acc. Chem. Res.*, **1977**, *10*, 227. (c) P. A. Barlett, *Tetrahedron*, **1980**, 36, 1. (d) F. E. Ziegler, *Chem. Rev.*, **1988**, *88*, 1243. (e) S. Blechert, *Synthesis*, **1989**, *71*. (f) W. S. Johnson, L. Barlett, T. J. Brocksom, T. Li, D. Faulkner, *J. Am. Chem. Soc.*, **1970**, *82*, 741.

33. R. E. Ireland, *J. Am. Chem. Soc.*, **1972**, *94*, 5897.

34. For structurally related Claisen rearrangements of silyl ketene acetals, *see* R. E. Ireland, P. Wipf, J. D. Amstrong, *J. Org. Chem.*, **1991**, *56*, 650 and references cited therein.

35. R. V. Stevens, R. E. Cherpeck, B. L. Harrison, R. Lapalme, *J. Am. Chem. Soc.*, **1976**, *98:20*, 6317.

36. K. Tossell, *Tetrahedron Lett.*, **1974**, *8*, 623.

37. K. Beautenent, J. M. Clough, *Tetrahedron Lett.*, **1974**, 8, 475.

38. (a) H. A. Dieck, R. F. Heck, *J. Org. Chem.*, **1984**, 46, 2446. (b) H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc.*, **1974**, *96*, 1133.

39. S. Nakanishi, T. Y. Yamamoto, N. Furukawa, Y. Otsuji, *Synthesis,* **1994**, 609.

40. P. A. Grieco, K. Yoshida, Z. He, *Tetrahedron Lett.*, **1984**, 5715.

41. H. O. Kalinowski, G. Grass, D. Seebach, *Chem. Ber.*, **1981**, *114*, 477.

42. (a) M. P. Zimmerman, *Synth. Commun.*, **1977**, *7*, 189. (b) A. S. Kende, B. H. Todder, *J. Org. Chem.*, **1982**, *47*, 168.

43. R. K. Boeckmann, D. M. Demko, *J. Org. Chem.*, **1982**, *47*, 1789.

44. (a) P. A. Grieco, K. Yoshida, Z. He, *Tetrahedron Lett.*, **1974**, *8*, 623. (b) P. A. Grieco, K. Yoshida, P. Garner, *J. Org. Chem.*, **1983**, *48*, 3137. (c) P. A. Grieco, G. Vidari, S. Ferrino, *J. Am. Chem. Soc.*, **1984**, *106*, 3539.

45. (a) G. P. Chiusoli, G. Salerno. L. Pallini, *J. Organomet. Chem.*, **1981**, *219 (1)*, C_{16}-C_{20}. (b) G. Salerno, G. P. Chiusoli, M. Costa, C. Gallo, *J. Organomet. Chem.*, **1986**, *317(3)*, 373.

46. (a) G. P. Chiusoli, G. Salerno. F. Dallatomasina, *J. Chem. Soc. Chem. Commun.*, **1977**, 793. (b) G. P. Chiusoli, G. Salerno. F. Dallatomasina, *J. Organomet. Chem.*, **1986**, *314*, 231.

47. (a) R. R. Rando, W. E. Doering, *J. Org. Chem.*, **1968**, *33*, 1671. (b) P. J. Kropp, H. J. Krauss, *J. Org. Chem.*, **1967**, *32*, 3222.

48. J. A. Barltrop, J. Wills, *Tetrahedron Lett.*, **1968**, 4987.

49. P. Borrell, J. D. Holmes, *J. Photochem.*, **1972/1973**, *1*, 433.

50. (a) I. A. Skinner, A. C. Weedon, *Tetrahedron Lett.*, **1983**, 4299. (b) A. C. Weedon, *Can. J. Chem.*, **1984**, *62*, 1933. (c) R. M. Duhaime, D. A. Lombardo, I. A. Skinner, A. C. Weedon, *J. Org. Chem.*, **1985**, *50*, 873.

51. (a) K. J. Crowley, *J. Am. Chem. Soc.*, **1963**, *85*, 1210; (b) K. J. Crowley, *J. Photochem. Photobiol.*, **1968**, *7*, 775.

52. (a) T. V. Singh, G. P. Pandey, K. N. Mehrotra, *Ind. J. Chem.*, **1979**, *18B*, *8*; (b) B. S. Green, M. Lahav, G. M. Schmidt, *J. Chem. Soc. B.*, **1971**, 1552.

53. Y. Ikeda, J. Ukai, H. Yamamoto, *Tetrahedron*, **1987**, *43*, 743.

54. Y. N. Gupta, R. T. Patterson, A. Z. Bismanand, K. N. Houk, *Tetrahedron Lett.*, **1986**, *27*, 295.

55. J. I. Kim, B. A. Patel, R. F. Heck, *J. Org. Chem.*, **1981**, *46*, 1067.

56. B. Myrboh, H. Ila, H. Junjappa, *Synthesis*, **1981**, 126.

57. F. Mathew, B. Myrboh, *Tetrahedron Lett.*, **1990**, *31*, 3757.

58. (a) F. M. Nongrum, B. Myrboh, *Synthesis*, 1987, 845. (b) F. Mathew, B. Myrboh, *Synth Commun.*, **1996**, *26*, 1097. (c) F. Mathew, B. Myrboh, *Molecules*, **1996**, *1*, 79.

59. R. L. Nongkhlaw, R. Nongrum, B. Myrboh, *J. Chem. Soc. Perkin. Trans 1.*, **2001**, 1300.

60. *Vogel's Textbook of Practical Organic Chemistry; ELBS, Longman Group Ltd, England.*

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