THE SYNTHESIS OF 1,3 AND 1,5-DICARBONYL COMPOUNDS

By

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ABSTRACT

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The reaction of carbon dioxide with ketone and ketone equivalents in the presence of a weak base and magnesium halides was investigated. Three main lines of investigation were pursued:

1. Optimal conditions were found for the carboxylation of ketones. The best yields for this reaction were found to occur when ketones were added quantitatively to the weak base/magnesium halide mixture at room temperature in either THF or CH_3CN.

2. Esterification of the carboxylated intermediates was attempted. The reaction of mild esterifying agents such as boron triflouride etherate-methanol led to no reaction while the use of stronger electrophiles led to a reaction at the carbon a to the carboxylate. Esterification of the intermediate was accomplished by addition of hydrochloric acid and ethanol.

3. Ketone equivalents, such as enamines and imines were carboxylated under conditions similar to those for ketones.

Attempts to isolate the resulting ketoacids or their derivatives was unsuccessful.

The intermediates derived from the carboxylation of ketones underwent a Michael addition with methyl vinyl ketone to give the corresponding 1,5-dicarbonyl compounds. The reaction was found to be an efficient way to activate simple ketones so that they could undergo the Michael addition with very mild conditions. This prevented side reactions that happen with the basic conditions usually associated with lithium enolates. Intramolecular aldol of the 1,5-diketone (Robinson annulation) occurred when the mixture was refluxed. Unsymmetrical ketones led to regioisomers of the Michael adduct. Conjugate addition failed with weaker Michael acceptors such as acrylonitrile and ethylacrylate.

The trimethylsilyl enol ethers of a variety of ketones were acylated with acylphosphonates in the presence of zinc chloride. The best yields of the 1,3-diketones were obtained with the use of two equivalents of benzoylphosphonates. The use of acetylphosphonate gave poor yields due to the abstraction of the acidic protons of the acetylphosphonate-zinc chloride complex. Diethyl phosphite generated in the reaction reacted with the starting phosphonate to give an α-phosphophosphonate.

TO MY LOVING WIFE, LINDA, FOR ALL HER PATIENCE AND LOVE

AND TO MOM AND DAD, JEAN AND WENDELL, AND MEGGY,

I LOVE YOU ALL.

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INTRODUCTION

INTRODUCTION

Carbon-carbon bond forming reactions have always been the foundation of organic synthetic strategy. But with the continuing development of natural product synthesis the complexity of synthetic targets has led to the development of many specialized reactions. No longer is it sufficient for a chemist to create a molecule in a linear, step by step, fashion with no accounting for overall yield or stereochemistry. Synthetic strategy today takes into account the overall functionality and shape of a molecule so that seperate sections of of the molecule may be constructed individually and then locked together in a highly efficient manner. (A "convergent" synthesis as opposed to a "linear" synthesis.) In many cases today natural product chemists are building compounds that will be used for pharmaceuticals, toxilogical testing or in agriculture. The need for highly efficient, high yielding total synthesis is crucial. Accordingly, stringent demands have been placed on the individual carbon-carbon bond forming reactions that make up the overall synthetic strategy. Reactions must now be selective in many ways:

a) Chemoselective-bond formation at only one of many potential sites.

b) Regioselective-bond formation at only one of many possible sites relative to a given function.

c) Steroselective-bond formation giving primarily one of several possible orientations at the reaction site.

In addition to the above criteria, most reactions in organic synthetic strategy require very mild conditions in order not to destroy the multitude of functionality that is found in a complex molecule. Naturally, reactions should give high yields of easily isolatable products. A contribution to synthetic methodolgy should be evaluated by the criteria that are presented in the preceeding paragraphs.

The work that is presented in this thesis is derived from one of the most important carbon-carbon bond forming reactions: attack of an electrophile by an enolate or enolate equivalent. We have examined three main lines of research:

a) Carboxylation of enolates and enolate equivalents to produce β-ketoacids (Fig. 1).

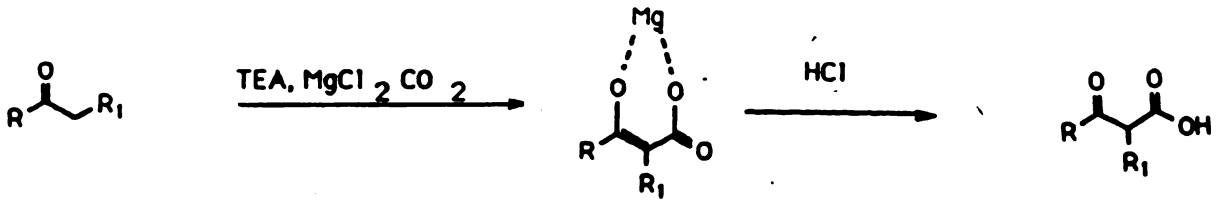


Fig. 1 Carboxylation of Ketones

b) Conjugate addition to magnesium chelated carboxylates to produce 1,5-diketones (Fig. 2).

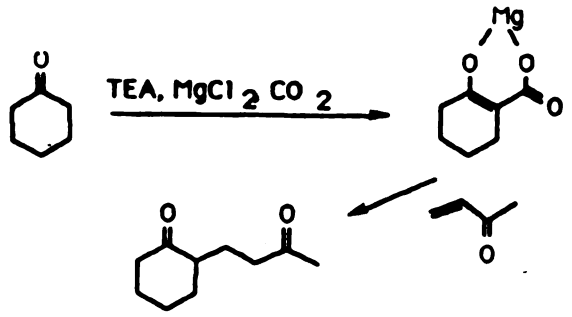


Fig. 2 Conjugate Addition to Ketone Enolates

c) Addition of acylphosphonates to silyl enol ethers to form β-diketones (Fig. 3).

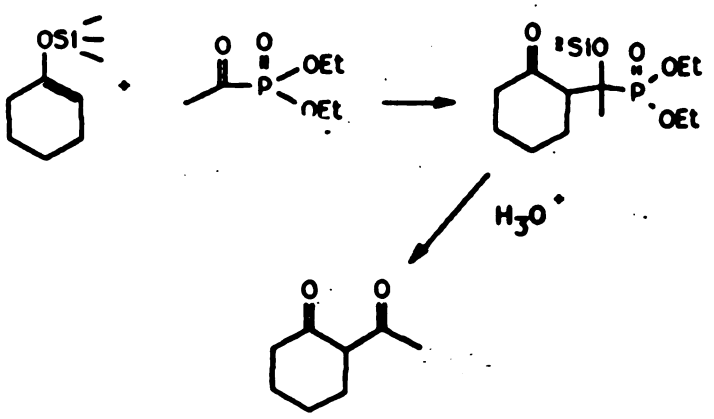


Fig 3. Acylation of Silyl Enol Ethers

The next few sections will show some examples of the importance that β-ketoacids, β-ketoesters, β-diketones and 1,5-diketones have as intermediates in synthetic strategy.

β-Ketoacids and β-Ketoesters

β-ketoacids and β-ketoesters have many properties that make their use in different synthetic strategies appealing.

A) Versatile transformations of functionality

B) Enhanced acidity of hydrogens on carbon

C) Regiospecificity of enolate formation

D) Chelation of dicarbonyls by metal cations

E) Facile cleavage of the acid/ester functionality

The next few examples will demonstrate these properties.

A) Versatile Transformation of Functionality. In many cases synthetic strategy dictates converting either the keto functionality or the ester/acid group to some other functionality. This can be seen in the following examples:

1. Despiridine.[1] As seen in Fig. 4, reduction of the ketone group to a hydroxyl group followed by methoxylation gives the product Despiridine[1].

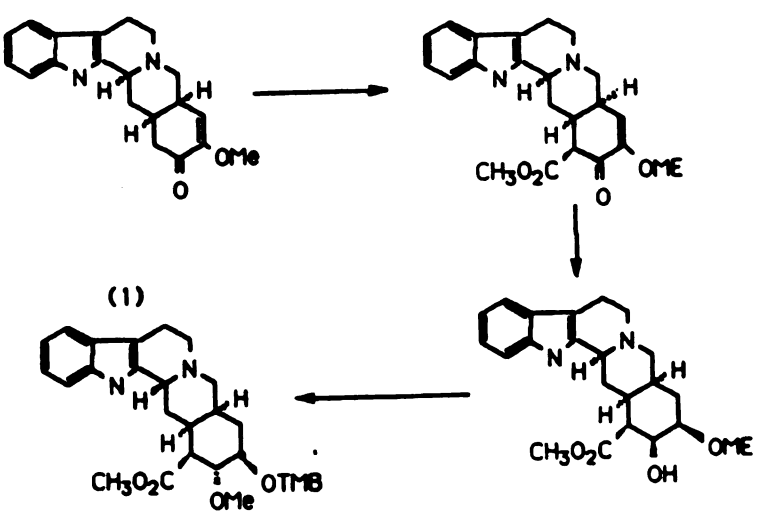


Fig. 4 Synthesis of Despiridine

2. Butterfly extract.[2] In the following example both the carbonyls of the β-ketoester[2] are transformed-the ketone becomes a vinyl methyl group while the ester function is reduced and brominated. The bromination permits the chain to be lengthened and the sequence to be repeated (Fig. 5).

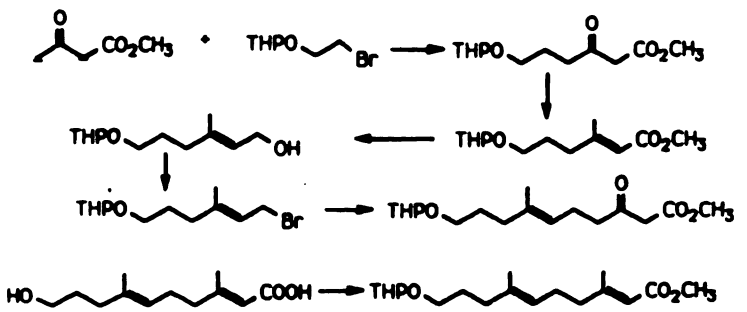


Fig. 5 Synthesis of Butterfly Extract

B) Enhanced Acidity. Since β-ketoacids and β-ketoesters are able to delocalize a negative charge over two heteroatoms the protons located between the two carbonyls are much more acidic that those adjacent to monocarbonyl compounds. (pka of dicarbonyl compounds = 10-15 while the pka of monocarbonyl compounds = to 20-26, Fig. 6). This means the enolates of β-ketoesters and β-ketoacids can be formed with weaker bases. The following examples demonstrate the mild conditions involved.

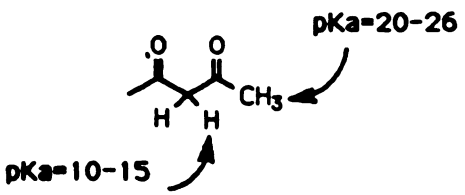


Fig. 6 Acidity of Protons on B-Dicarbonyls

1. Conjugate addition to acetonedicarboxylate. In this example a magnesium enolate is generated by the use of $MgCl_2$ and triethylamine. The resulting enolate then undergoes a Michael Reaction with methyl vinyl ketone (Fig. 7).[3]

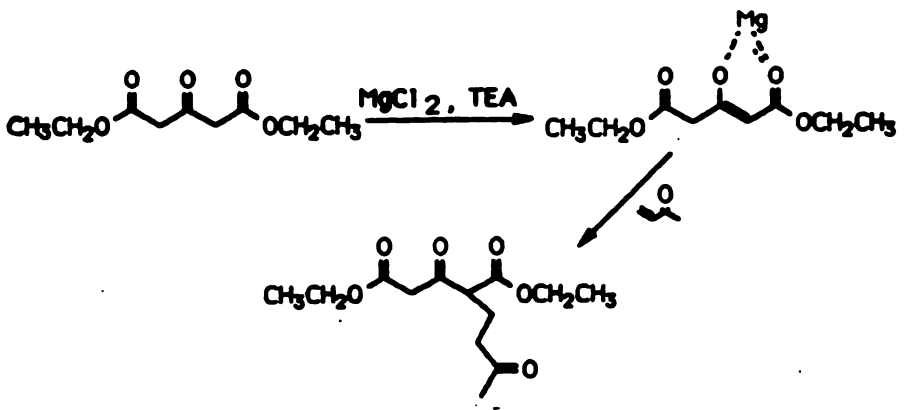


Fig. 7 Conjugate Addition to Dicarbonyl Compounds

2. Aldol condensation. In this example an aldol condensation takes place between a β-ketoester and an aldehyde in the presence of zinc metal (Fig. 8).[4].

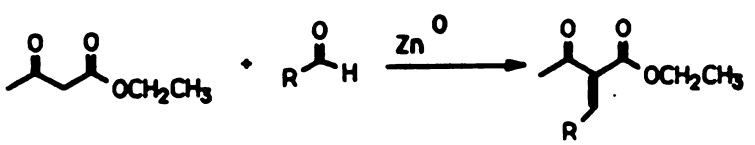


Fig. 8 Aldol Condensations of Dicarbonyls

3. Synthesis of Malonomicin(K16). In this example the authors complete a cyclization of the key intermediate by the use of triethylamine. The use of stronger bases led to decomposition of the material (Fig. 9).[5]

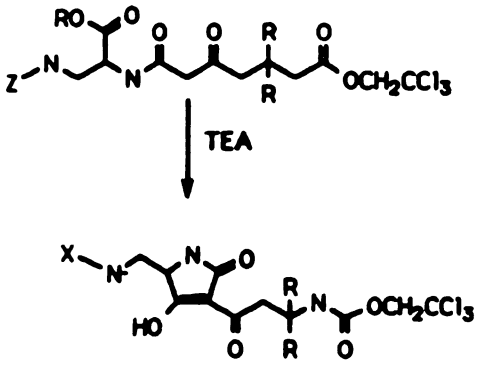


Fig. 9 Synthesis of Malonomicin

The idea of using metal ions and weak bases to produce enolate anions in dicarbonyl compounds is a recurrent theme in this thesis. By way of example the following two cases demonstrate the possibilities of metal cation activation in similar systems.

1. Carboxylation of ketones with $MgCl_2$ and DBU. This example shows that ketones can be enolized under weak base conditions and "trapped" by CO_2 (Fig. 10).[6]

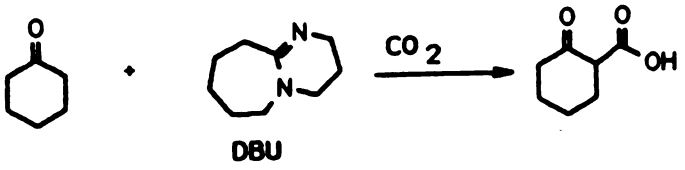


Fig. 10 Carboxylations with DBU

2. Wittig reaction of triethyl phosphonoacetate in the presence of a metal ion and triethylamine.

Phosphonoacetates usually require n-butyllithium or sodium hydride to form the enolate. But as can be seen a weaker base such as triethylamine in the presence of the correct cation can produce the same result (Fig. 11).[7]

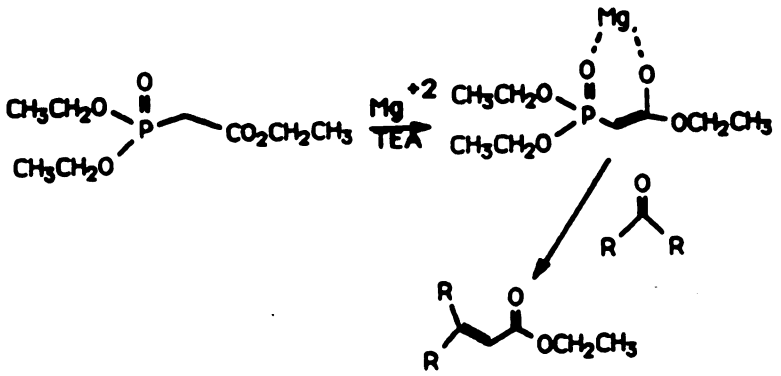


Fig. 11 Wittig Reactions with Phosphonoacetates

C) Regiospecificity of Enolate Formation. Because of the increase in acidity of the protons between the two carbonyl groups the regioselectivity of enolate formation can be rigorously controlled. This is demonstrated in the next few examples.

1. Synthesis of Pyrethrolone. In this synthesis the authors condense pyruvaldehyde with β-ketoester.[1] With two equivalents of base (the first equivalent abstracts the acid proton) the enolate is formed regiospecifically on the carbon next to the acid functionality (Fig. 12).[8]

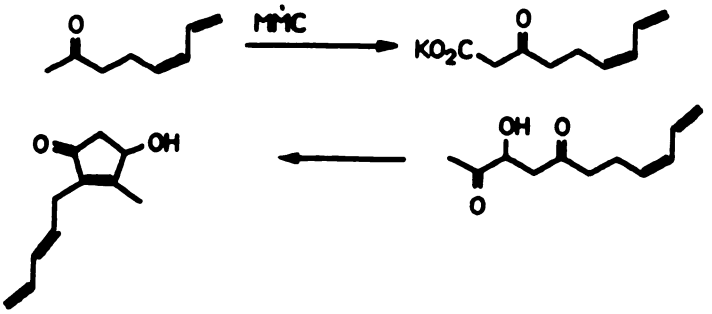


Fig. 12 Synthesis of Pryethrolone

2. Synthesis of Latia luciferin. In this example attack occurs at the most reactive site of a β-ketoacid dianion, the carbon γ to the ester functionality. (Fig. 13).[9]

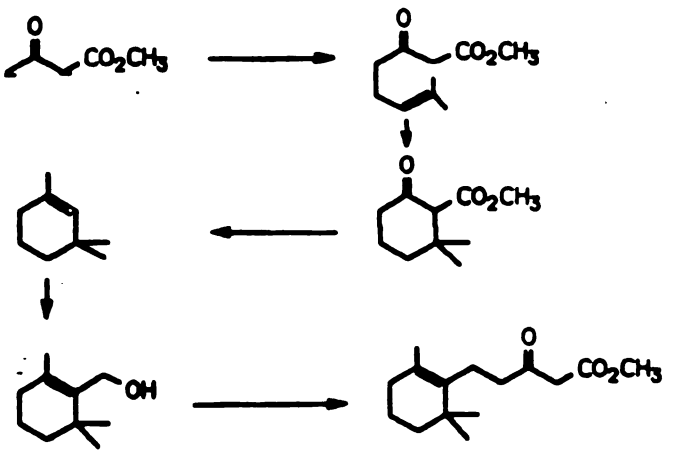


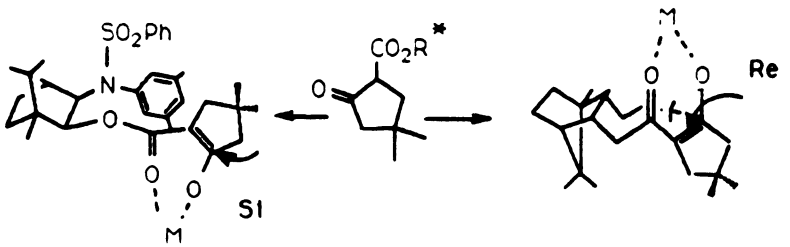
Fig. 13 Synthesis of Latia Lucifer

D. Chelation of Carbonyls by Metal Ions. As seen previously chelation of the carbonyls by a metal ion enhances the acidity of the α-protons. Another use of this chelation is that it locks the molecule into one

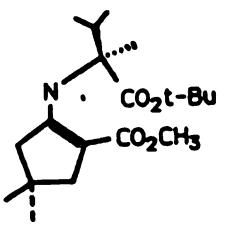
conformation introducing the possibility of chiral induction. This is demonstrated in the next example.

1. Botrydial synthetic studies. Welzel[10] tries to generate a chiral center at C-2 in high e.e. He attempts this by two methods: (1) Use of an optically active cyanoformates in the esterification step (Fig. 14) and (2) formation of the chiral enamine found in Fig. 15 followed by alkylation with an alkyl halide.

Chiral cyanoformate



Chiral enamine



E. Cleavage of Acid/Ester Functionality. In many cases following the use of a β-ketoacid or ester as a synthetic

intermediate the ester or acid functionality is cleaved. This normally can be done under mild conditions without effecting the rest of the molecule's functionality. For an exhaustive review on dealkoxycarbonylations of ß-ketoesters see reference 11.

As seen in the previous examples ß-ketoacids and esters are extremely valuable and versatile synthetic reagents.

ß-Diketones.

ß-Diketones contain the same 1,3-dicarbonyl functionality that leads to the general properties of ß-ketoesters and ß-ketoacids. The major difference in the two molecules is that in many cases with ß-ketoesters and ß-ketoacids the acid or ester functionality can be easily cleaved to produce a monocarbonyl compound. This is not the case with ß-diketone compounds. With these molecules both carbonyl groups (or modification of the carbonyl groups) are retained in most transformations.

Since the ß-diketones are structurally similar to ß-ketoesters and ß-ketoacids they perform similar functions in their uses as intermediates in synthetic stratagy. They form enolates regiospecifically under very mild condtions. Chelation of the two carbonyl groups by a metal ion can in some cases yield stereoselective reactions. The following are examples of the types of transformations that ß-diketones can undergo.

a) Transformation to 1,4-diketones.[12] In this example, a 1,3-diketone is transformed in two steps and high yields. This is initiated by the formation of the silyl enol ether followed by insertion by the diazo compound (Fig.16).

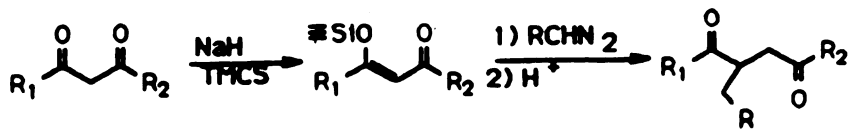


Fig. 16 Synthesis of 1,4-Diketones

b) Formation of highly substituted phenols.[13] The reaction of the dione in Fig. 17 with ethyl bromoacrylate followed by cyclization forms the highly substituted phenols in good yields. In this case the kinetically formed enolate is used in the sequence. This is generated by adding the diketone to LDA at -78°c.

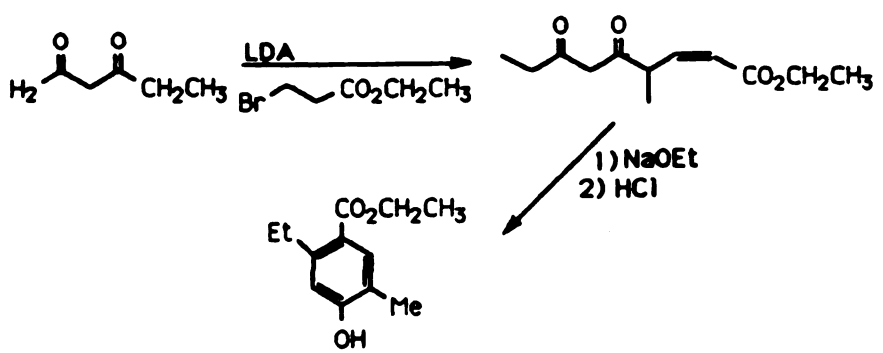


Fig. 17 Synthesis of Substitued Phenols

c) Synthesis of Elaeocarpus alkaloids.[14] The use of acyl cyanides as acylating agents with lithium enolates was first demonstrated in this work by Howard. Acylation of [3]

with [4] followed by cycilzation gave the model compound for the synthesis of elaecarpine (Fig. 18).

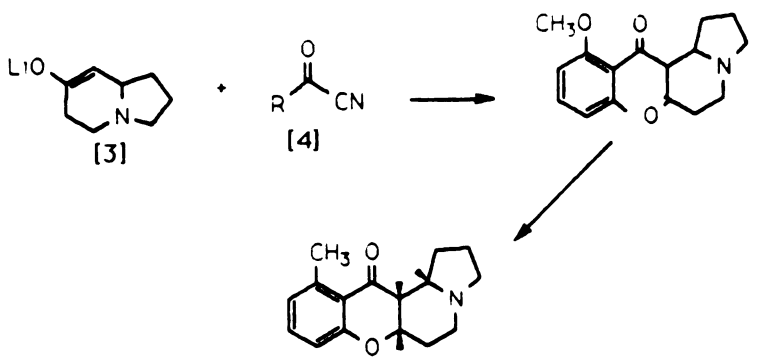


Fig. 18 Synthesis of Elaecarpine

1,5-dicarbonyls.

One of the most important reactions in natural product-synthesis is that of conjugate addition of an α,β-unsaturated ketone with an enolate or enolate equivalent (Michael Reaction) followed by an intramolecular aldol to form a bicyclic compound. (The Michael-aldol sequence is refered to as the Robinson Annulation, Fig. 19). This sequence of reactions is commonly used in building the multi-ring systems found in steroids, terpenes and alkaloids. A review of annulation techniques and their applications can be found in reference 15. The following are a few examples that demonstrate the potential usefulness of the Robinson annulation sequence.

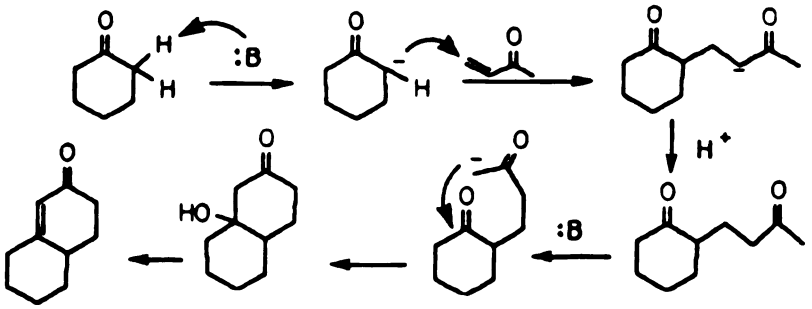


Fig. 19 Michael Additions-Robinson Annulations

1. α-Methylene Cyclanone. In this example Hajos utilizes an α-methylene ketone as a reagent for use in a Robinson Annulation in the production of a steroid (Fig. 20).[16]

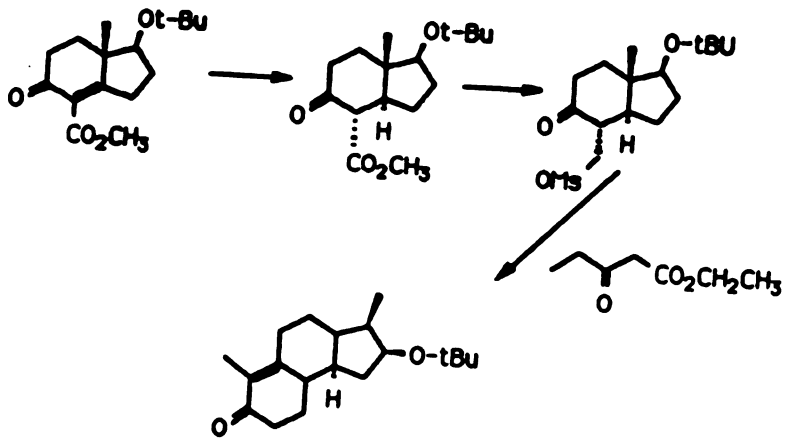


Fig. 20 Synthesis of α-Methylene Cyclanone

2. Asymetric Induction. Cyclization of the triketone in the presence of proline gives the cyclized aldol product in 100% chemical yield and 93.4% optical yield (Fig. 21).[17]

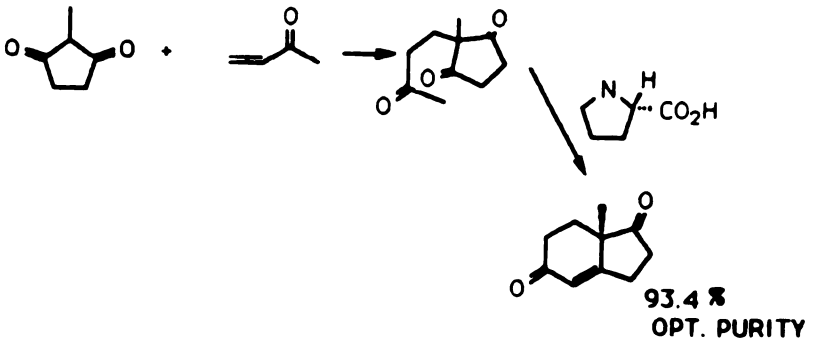


Fig. 21 Asymetric Michaels via proline

3. Double Michael Sequence. In the synthsis of the antibiotic griseofulvin Stork[18] uses a double Michael reaction to construct a spiro system in one step (Fig. 22).

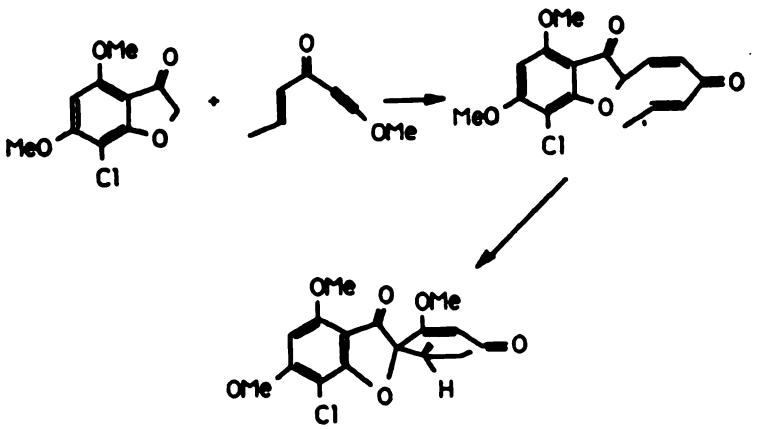


Fig 22. Double Michael Sequence

CHAPTER ONE

CARBOXYLATION OF ENOLATE AND ENOLATE EQUIVALENTS

CHAPTER ONE

CARBOXYLATION OF ENOLATE AND ENOLATE EQUIVALENTS

INTRODUCTION

As mentioned in the Introduction, the properties of β-ketoacids that make them valuable intermediates were catagorized. These properties were illustrated with a few examples from the literature. In this chapter a new approach to the synthesis and derivatization of β-ketoacids will be described. To put this new approach in context the next few paragraphs will describe previous attempts to synthesize β-ketoacids. An attempt will be made to compare and contrast the various methods in order to show the advantages inherent in this new approach to β-ketoacids.

The oldest method for synthesizing β-ketoacids found in the literature is that of alkaline or acidic hydrolysis of the corresponding β-ketoesters as shown in Fig. 23a and 23b. While alkaline hydrolysis results in extremely poor yields,[19,20] acid hydrolysis gives nearly quantitative yields.[21,22] The major drawback with this approach is in the synthesis of the appropriate β-ketoester. As seen in Chapter 3 this is not a trivial synthesis.

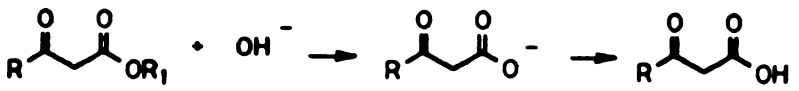


Fig. 23a Alkaline Hydrolysis of B-Ketoesters

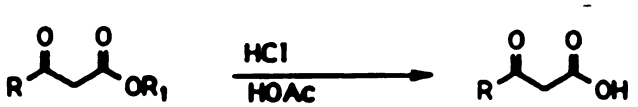


Fig. 23 b Acid Hydrolysis of B-Ketoesters

Another method for the synthesis of β-ketoacids makes use of the dianion of a carboxylic acid. This dianion is generated with 2 equivalents of lithium diisopropyl amide (LDA). Acylation of the dianion with an ester followed by silylation with trimethylchlorosilane (TMCS) yields the silyl intermediate shown in Fig. 24. Solvolysis under neutral conditions with methanol yields the β-ketoacid.[23] This reaction is not applicable to the synthesis of such cyclic β-ketoacids as cyclohexanone carboxylic acid. (Fig 25).

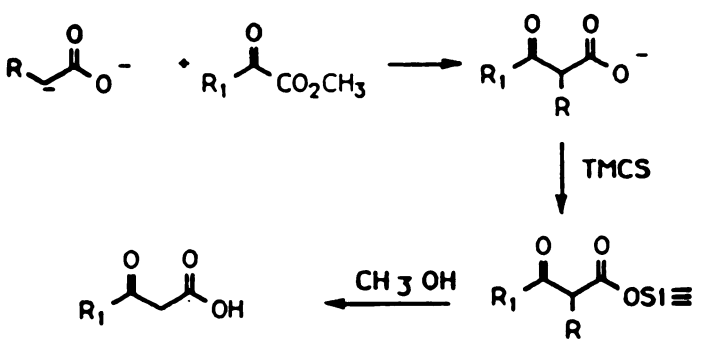


Fig. 24 Acylation of Carboxylic Acids

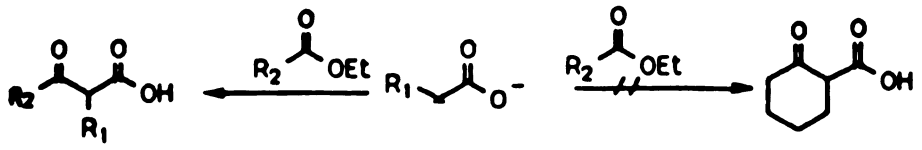


Fig. 25 Acylation of Carboxylic Acids

A similar method is that of Van der Baan[24] who acylates bis(trimethylsilyl)malonate with acid chlorides.(Fig 26). Hydrolysis and decarboxylation under neutral conditions gives the desired β-ketoacid. This is not applicable to the synthesis of cyclic or α,α-dialkyl-β-ketoacids.

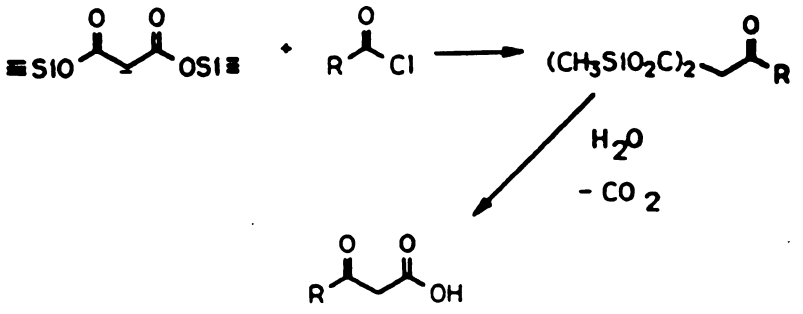


Fig. 26 Acylation of bis(Trimethylsilyl)malonate

Direct carboxylation of ketone enolates with carbon dioxide has been accomplished in the presence of bases such as sodium triphenyl methide, sodium amide and sodium phenoxide.(Fig. 27).

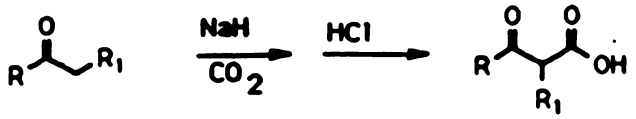


Fig. 27 Carboxylation of Ketone Enolates

Alternative methods for direct carboxylation are summarized.

A) Matsumura.[25] Carboxylation of ketone enolates using 1,8-diazabicyclo(5,4,0)-7-undecane (DBU)[5] as base gave fair yields of the corresponding β-keto acids.(Fig. 28).

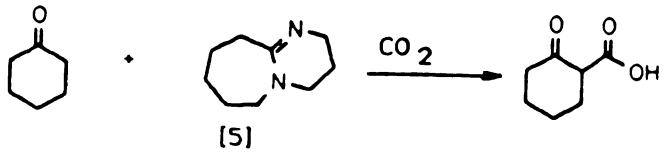


Fig. 28 Carboxylation with DBU

B) Stiles and Finkbeiner.[26] It was found that the reagent formed from reaction of magnesium and methanol in the presence of CO_2 (methylmagnesiumcarbonate or MMC)- could give β-ketoacids when added to ketones in a heated solution of dimethylformamide (DMF). The reagent was given the empirical formula of $CH_3O-Mg-OCOCH_3$. The driving force of the reaction is thought to be formation of a chelated dianion intermediate[6](Fig 29). This chelated structure is thought to drive the equilibrium toward the products. Although generally this reagent gives fair to good yields there are a few drawbacks to the method:

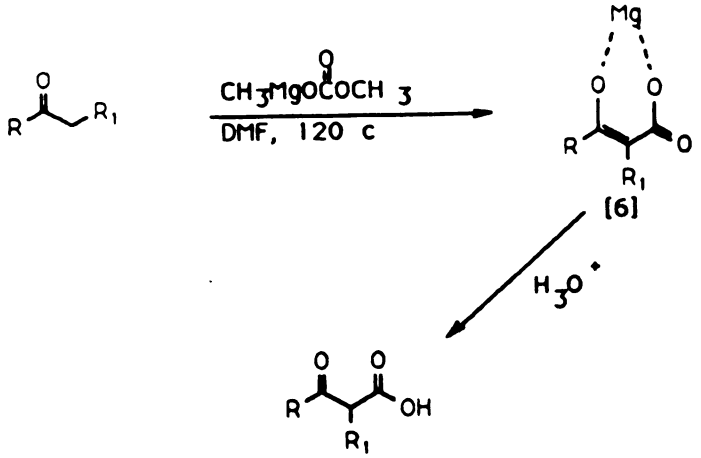


Fig. 29 Carboxylation with MMC

1. Ketones with only one hydrogen α to the carbonyl unit fail to give the corresponding ketoacids. This is probably due to the inability of these compounds to form a chelated dianion intermediate.

2. Acceptable yield can only be obtained when a 5-20 fold excess of the MMC reagent is used. A correspondingly large volume of DMF must then be used.

3. Reaction conditions include heating at 120 degrees for 4-6 hours. DMF, the solvent of choice in these reactions is often difficult to seperate in the workup.

C) Matsumura.[27] Matsumura carboxylated ketones with CO_2 in the presence of $MgCl_2$ and TEA in DMF at elevated pressures over extended periods of time. The yields were generally good. (Fig. 30).

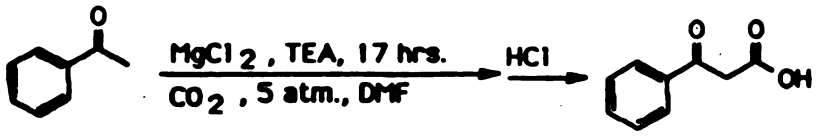


FIg. 30 Carboxylation with Weak Bases and Lewis Acids

D) Tirpak.[28] Tirpak modified Matsumura's carboxylation procedure to make the reaction more effecient while using milder conditions. Tirpak assumed that enhancement of the Lewis acidity of the chelating metal ion would produce a corresponding enhancement in the rate of carboxylation. This led to the use of a less coordinating solvent then DMF (e.g. acetonitrile) and the use of a more dissociated magnesium

ion(e.g. MgI_2). The results of the reactions with these modifications are very impressive. It was found that β-ketoacids can be produced at room temperature and atmospheric pressure in less than an hour. The yields are comparable to those of Matsumura's. The mechanism of carboxylation is thought to be similar to that for MMC.(Fig 31).

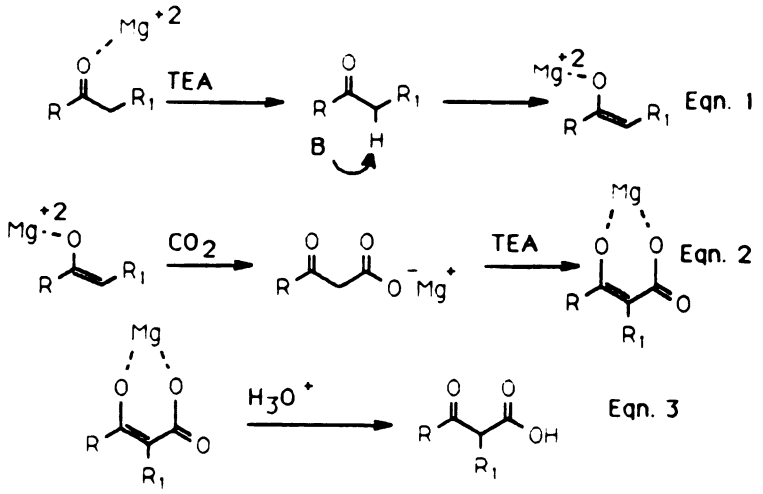


Fig. 31 Mechanism of Carboxylation

1. Mg^{+2} complexes with the oxygen of the ketone carbonyl withdrawing electron density away from the a carbons. This polarization of the electron density makes it possible for weak bases such as TEA to abstract the a protons forming a useful concentration of magnesium enolate.(Eqn. 1).

2. Reaction of the CO_2 with the enolate to form the monoanion of the β-ketoacid(eqn. 2).

3. Abstraction of the second α-proton by triethylamine to form the magnesium chelated dianion of the β-ketoacid[6].(eqn. 2).

4. Hydrolysis of [6] to give the β-ketoacid (Eqn. 3).

The following comments point out the main conclusions drawn from Tirpak's investigation of weak base/metal ion carboxylation of ketones

1. It was determined that the best ratio of reactants to be 2:4:1 (Mg^{+2}:TEA:ketone). This balances the rate of the reaction with the formation of precipitant. Greater amounts of TEA gives so much precipitant that the reaction mixture cannot be stirred.

2. Carboxylation does not take place in the absence of or Mg^{+2} ion. Such monovalent ions as Li^{+1}, Na^{+1}, K^{+1} do not effect carboxylation, although Mn^{+2} does to a small extent. This would seem to indicate that a divalent ion such as Mg^{+2} is required to drive the reaction to completion. This is analagous to the role of the Mg^{+2} ion in the carboxylation of biotin in the body.(29).

3. Stiles and Finkbeiner determined in their studies of MMC that carboxylation fails to take place when there is only one proton a to the carbonyl. The absence of product was ascribed to the impossibility of dianion formation. From this and related u-v studies they concluded that the formation of chelated magnesium dianion intermediate [6] is necessary in order to form carboxylated products.

Carboxylation of ketones in the presence of $MgCl_2$ and TEA as demonstrated by Tirpak clearly does not require the formation of the dianion intermediate. This is demonstrated by the carboxylation of isobutyrophenone in the presence of $MgCl_2$ and TEA(Fig. 32). This ketone which has only one α-proton (precluding the formation of the dianion) gives the corresponding β-ketoacid in 90% yield. In cases where dianion formation is possible such an intermediate is probably formed but it is clearly not necessary for the formation of products as with the MMC carboxylations.

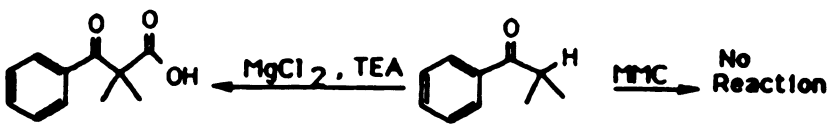


Fig. 32 Carboxylation of Isobutryophenone

4. Carboxylation does not take place in the absence of TEA (or some other weak base). This shows the need for some reagent to abstract protons to form the mono and dianion intermediates.

5. The relative rates of the reaction increases from $MgCl_2$ to $MgBr_2$ to "MgI_2" (generated from $MgCl_2$ and NaI). This is due to the greater dissociation between magnesium and halide ions as the ionic radius of the halide increases. The greater the dissociation the greater the Lewis acidity of the Mg ion.

6. The relative rate of the reaction increases from DMF to THF to CH_3CN. This would correspond to a decrease in the complexing ability of the solvent for the metal ion. The decrease in complexing ability would again lead to an enhancement of the Lewis acidity of the Mg ion with results as described in the previous comment.

With these results in hand we examined various aspects of the carboxylation reaction.

RESULTS AND DISSCUSSION

PART 1. MAXIMIZATION OF β-KETOACID YIELDS

RESULTS AND DISSCUSSION

PART 1. MAXIMIZATION OF β-KETOACID YIELDS

The goals of our study of the carboxylation reaction were threefold:

a) Optimization of yields of the β-ketoacid.

b) Formation of β-ketoesters from the intermediate.

c) Carboxylation of enolate equivalents.

Optimization of β-Ketoacid Yields

Optimization of acid yields can take place along two lines of investigation.

1. Optimization of the yields of the intermediate dianion[6].(Fig.33).

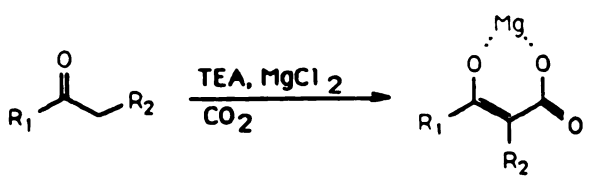


Fig. 33 Formation of Chelated Dianion

2. Minimizing the decarboxylation that takes place (if any) in the work-up of the reaction.(Fig.34).

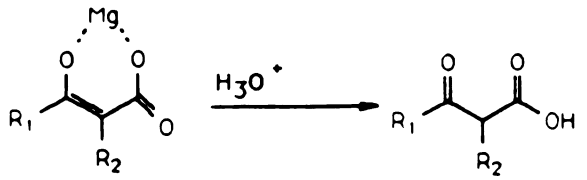


Fig. 34 Hydrolysis of Chelated Dianion

Before discussing optimization of acid yields a short summary of what is known about the intermediate in this reaction is needed. Since isolation of the intermediate was not possible other less direct pieces of evidence must be sufficient. There are three main experimental results that help define the nature of the intermediate:

1. The fact that isobutyrophenone undergoes almost quantitative carboxylation demonstrates that the dianion-intermediate [6] is not necessary to drive the reaction.(Fig. 32).

2. It has been demonstrated by Stiles and Finkbeiner(26) that the intermediate formed in the carboxylation of ketones by MMC can undergo alkylation, acylation and aldol reactions in a manner similar to ketone enolates. As mentioned previously, they propose that the intermediate is a magnesium chelated dianion of the corresponding ketoacid. It is this dianion intermediate that is the reactive species with electrophilic reagent. (Fig.35). Later in this thesis it will be shown that the intermediate generated in the carboxylation of ketones in the presence of magnesium halides and triethylamine can undergo alkylations analagous to that in the MMC

carboxylations. From these reactions we postulate that intermediate in our carboxylations is the same magnesium carboxylic acid dianion that is proposed by Stiles and Finkbeiner.

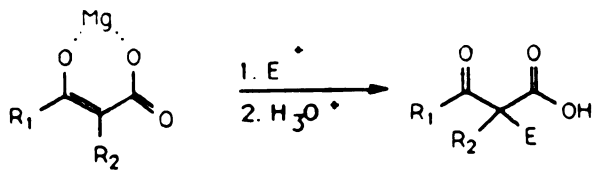


Fig. 35 Electrophilic Attack on Chelated Dianion

3. Stiles and Finkbeiner[26] monitered the formation of [6] with u-v. We found, using this technique, that the dianion intermediate is formed in our reaction although no quantitative studies were attempted.

From these results the only conclusion that can be drawn is that the chelated dianion intermediate can form when possible but is not necessary to drive the reaction to completion.

To determine whether reaction conditions could be found that would increase the yield of the intermediate we tested three main factors: solvent, temperature and mode of addition of ketone. The results are summarized in Table 1. (Quant. refers to quantitative addition of reagent, that is the reagent is added all at once).

The carboxylation of acetophenone in the presence of magnesium iodide and triethylamine is described in the experimental section at the end of this section.(Fig.36).

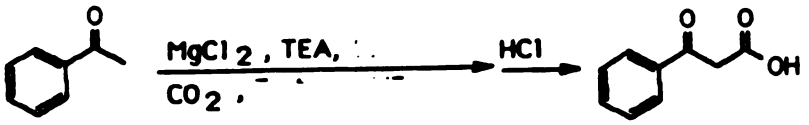


Fig. 36 Carboxylation of Acetophenone

Table I. Optimization of Yields of Benzoylacetic Acid

Solvent	Temp.	add. of ket.	add. of acid	Yield %
CH_3CN	R.T.	Quant.	dropwise	65
"	"	dropwise	"	45
"	-45 c RT	Quant.	"	52
"	-15 c RT	"	"	43
"	50 c	"	"	35
"	RT	"	ket. drop.	63
THF	RT	"	ket. quant.	65
"	RT	"	dropwise	63
"	-15 c	"	dropwise	45
DMF	RT	"	"	0
DMF	100 c	"	"	0

As can be seen from the chart, yields in this reaction are highly dependent on temperature. This is probably due to the solubility of the reactants in the heterogeneous mixture. At higher temperatures there is a decrease in the solubility of CO_2. At lower temperatures there is a decrease in the solubility (and probably the reactivity) of the other reagents. In both cases the rate of absorbtion of CO_2 during the reaction is much slower then at room temperature.

Dropwise addition of the ketone to the reaction mixture also leads to smaller yields. This may be due to the large amount of insoluble material that forms during the reaction. By the time the full amount of ketone is added the mixture is so turbid that stirring is difficult. In heterogeneous conditions such as those presented in this reaction it is probable that the yields are dependent on the amount of aggitation, which is dependent on the rate of stirring. (Tirpak determined that the rate of the reaction is directly related to the rate of stirring.) The formation of insoluble material may also explain why the reaction yields show a temperature dependence.

The study shows that THF and CH_3CN give approximately the same yields. The rate of the reaction is about three times faster in CH_3CN then in THF. DMF as a solvent is not practical under our conditions since absorbtion of an equivalent of CO_2 takes three days to occur. CH_3CN is the solvent of choice since that is the solvent for which the reaction rates are greatest. These results can be interpreted in terms of the relative complexing ability of the solvents (that is the greater the complexing ability of the solvent the slower the the reaction).

The second method of optimizing yield is to minimize decarboxylation during the workup. Stiles determined that approximately one third of the nitroacetate dianion formed

in their reaction undergoes decarboxylation upon workup(Fig.36).

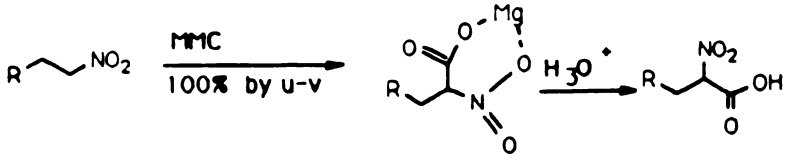


Fig. 36 Decarboxylation of Nitroacetic Acid.

Three different modes of addition were studied; dropwise addition of acid to an aqueous solution of the reaction mixture at 0°c, dropwise addition of the aqueous solution of the reaction mixture to dilute acid-ice mixture and quantitative addition of the reaction mixture to a-dilute acid-ice mixture.

From the results shown it would seem that decarboxylation is not a problem in our system. This is concluded from the fact that their is no significant difference in yields from different methods of workup as long as the amount of time that the acid is in contact with moisture is minimized.

To summarize this section, we found that the ketoacid yields are dependent on temperature and mode of addition. The rate of the reaction is dependent on the solvent. Optimum yields of ketoacid are obtained at room temperature with quantitative addition of ketone to the reaction mixture. As long as exposure of the product to moisture is

minimized decarboxylation of the intermediate during workup is negligible.

EXPERIMENTAL

EXPERIMENTAL

Materials

THF was distilled from sodium and benzophenone. Acetonitrile and TEA were dried by distillation from CaH_2. All ketones were commercially available and purified by fractional distillation over CaH_2. All the above reagents were stored under Argon. NaI, purchased commercially, was dried by heating it under vacuum prior to use. $McCl_2$ was acquired as the anhydrous reagent from Aldrich Chemical Company and stored in a dry box under argon.

Method of Analysis

^1H NMR data was obtained on a Varian T-60 spectrometer at 60 MHz. Chemical shifts were reported in parts per million on the delta scale relative to TMS internal standard. Infrared spectra were recorded on a Perkin Elmer 23-B spectrometer with a polystyrene standard. Mass spectral data were acquired with a Finnigan Model 4000 electron impact GC/Mass spectrometer. Gas chromatographic analyses were performed with a Hewlett-Packard Model 5880A capillary Gas Chromatograph equipped with a 25m x .25 mm capillary column.

Reaction Acetophenone with CO_2 and MgI_2

Sodium Iodide (20 mmoles, 3 g.) was heated by a flame in a 100 ml flask under vacuum to drive off moisture. The flask was flushed with argon and allowed to cool. Introduction of 30 ml. of CH_3CN was followed by the addition of 10 mmoles(.95 g) of magnesium chloride. The resulting mixture, which was assumed to generate magnesium iodide, was stirred for 30 min. at room temperature. Vigorous stirring was maintained while 20 mmoles of TEA(2.8 ml) were added and the flask was flushed with dry CO_2. The flask was then connected to a gas burrette filled with CO_2. After the gas volume had stablilized, acetophenone(.95 ml,10 mmoles) was introduced into the heterogeneous solution via syringe. Carbon dioxide absorbtion began immediately and was monitored by observing the change in fluid level in the gas burrette. The reaction mixture becomes increasingly turbid slowing down the stirring rate. After two hours approximately 290 ml (13 mmoles) of CO_2 was absorbed. The mixture was diluted with 50 ml of ice water and extracted with ether. The aqueous layer was cooled to 0°c in an ice bath and acidified to pH 3-4 with 1 M HCl at 0°c with vigourous stirring. The aqueous solution was extracted with two protions of ether(30 ml. each). The resulting organic layer was dried with $MgSO_4$. Removal of the ether in vacuo provided 1.19g (73%) of a white solid identified as benzoyl acetic acid m.p. 101-102°c (lit. 101-102°c)[30]; ^1H NMR (CDCL3) 4.05(s,2H).

5.7(vinyl H from enol, s), 7.25-7.6 (m,3H), 7.7-8.05 (m,2H); mass spec (EI) 164 (m^+), 120 (m^+-CO_2).

PART 2. CARBOXYLATION OF ENOLATE EQUIVALENTS.

A study of carboxylation of enolate equivalents (enamines, imines and oximes) was undertaken with two goals in mind: a) to determine whether superior yields of β-ketoacids could be obtained and b) to determine whether the intermediate could be reduced to a β-aminoacid.

A. Synthesis of β-Ketoacids.

The first set of experiments with imines and other enolate equivalents was to determine whether these molecules could be carboxylated the same as ketones. To that end we first tried to carboxylate the t-butyl imine of cyclohexanone under similar conditions as the corresponding ketone(Fig. 37).

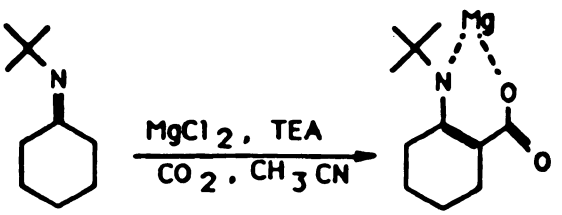


Fig. 37 Carboxylation of Imines

Ten mmoles of the imine was added to a mixture of 20 mmoles of $MgCl_2$ and 40 mmoles of TEA in 30 mls of CH_3CN under an atmosphere of CO_2. We found that the imine carboxylated in a similar manner to ketones. A little over one equivalent of

CO_2 was absorbed after 24 hours. After hydrolysis with a mixture of ice and 3M HCl, one equivalent of CO_2 was given off and only cyclohexanone was recovered. Similar results were obtained with the dimethyl hydrazone, morpholino enamine and the oxime of cyclohexanone. In all cases an equivalent or more of CO_2 was absorbed by the mixture only to be given off on workup. (See Table 2).

Table 2. Carboxylation of Enolate Equivalents

Compound	$MgCl_2$	NaI	TEA	CO_2	Yield of Ketoacid
Morpholino Enamine	2 eq	4 eq	1 eq	1.5 eq	0
t-Butyl Imine	2 eq	4 eq	2 eq	1.2 eq	0
Dimethyl Hydrazone	2 eq	4 eq	2 eq	1.2 eq	0
Oxime	2 eq	4 eq	2 eq	1.5 eq	0
Silyl enol ether	$MgCl_2$ $FeCl_3$	$ZnCl_2$ $AlCl_3$	-	0	0
Silyl enol ether	KF	-	-	0	0
	TBAF	-	-	.5 eq	0

These results are not surprizing in light of previous work found in the literature. β-Iminoacids(except for the bridgehead structures demonstrated) have never been isolated due to their extremely facile decarboxylation. Westheimer[31] determined in his study of bridgehead β-iminoacids that their decarboxylation takes place approximately one million times faster that the corresponding β-ketoacids(Fig. 38).

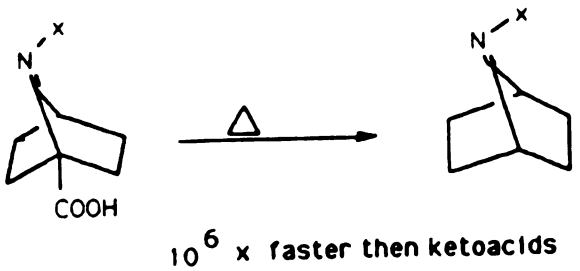


Fig. 38 Decarboxylation Of Iminoacids

B. Reduction of Carboxylated Intermediates of Enamines.

It has been demonstrated by Lawesson[32] that 2-carboethoxyenamines could be reduced by NaBH4 to the corresponding β-aminoesters in good yields.(Fig 39).

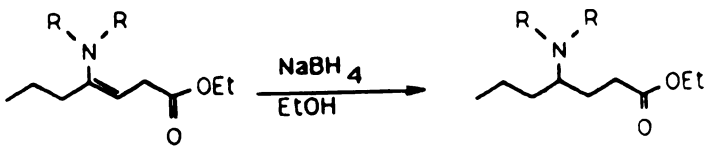


Fig. 39 Reduction of Iminoesters

Since the presumed intermediate in the carboxylation of enamines is a 2-carboxyenamine, reduction of this intermediate analagous to that of 2-carboethoxy enamines could lead to the corresponding β-aminoacid after hydrolysis.(Fig. 40).

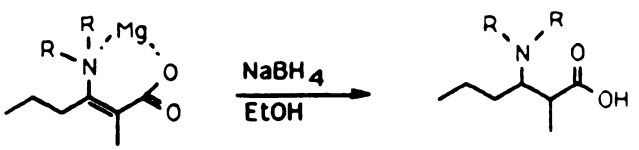


Fig. 40 Reduction of Carboxylated Intermediate

Results of reduction using various reducting agents proved to be disappointing. None of the reagents used gave the expected product. Use of catalytic hydrogenation (PtCl2/C) gave the dimorpholino cyclohexane. This is a known rearrangement[33] and the proposed mechanism is shown in Fig. 41.

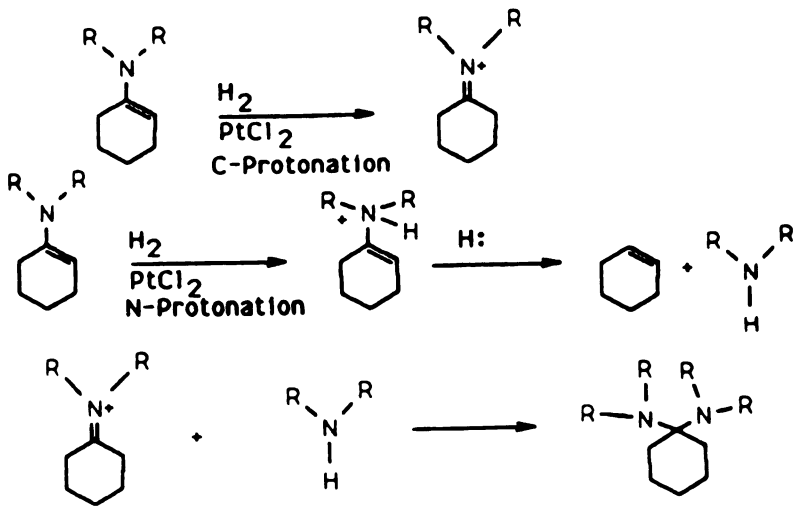


Fig. 41 Mechanism of Diamine Formation

Sodium borohydride will only reduce the protonated enamine, therefore the reaction is done in ethanol. The only product found is the reduced enamine[7]. (Fig 42). The use of diborane also gave the reduced enamine [7]. Lithium aluminum hydride gives no reaction. It is not surprising that the aminoacid cannot be isolated with these reducing agents. In each case where reduction is taking place, some sort of iminium ion is formed. It seems likely that the iminium intermediate could undergo facile deacarboxylation

to regenerate the enamine. It is the decarboxylated enamine that undergoes reduction to form [7].(Fig.43).

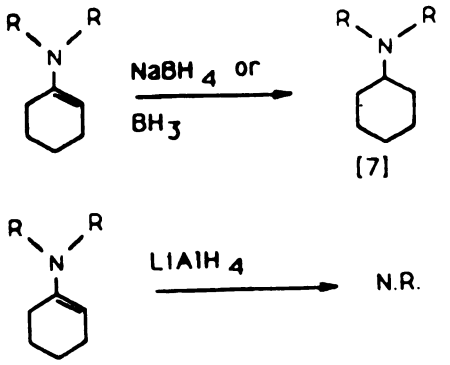


Fig. 42 Reduction of Carboxylated Intermediate

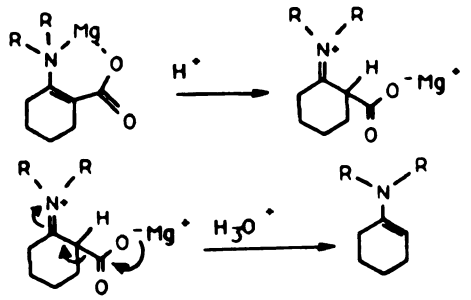


Fig. 43 Mechanism of Decarboxylation

An attempt was made to carboxylate silyl enol ethers in the presence of various Lewis acids. As can be seen in the chart none of the Lewis acids effected carboxylation. The use of tetrabutylammonium floride to cleave the silyl enol ether to form the "naked" enolate[34] produced carboxylation but no product was isolated.(Fig.44).

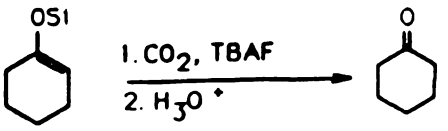


Fig. 44 Carboxylation of Silyl Enol Ethers

To summarize this section: we have found that various enolate equivalents can undergo carboxylation under similar conditions used for the carboxylation of ketones. This is the first time that such a reaction has been reported. These carboxylated enamines or imines could be very versatile and important synthetic intermediates in the same manner as β-ketoesters or acids. They naturally lend themselves to many-transformations of which the attempted reduction is but one example. It is apparent that their usefulness is dependent upon finding a transformation that will retain the carboxylate group.

One potential line of research that could take advantage of the facile decarboxylation is that of acylation of carboxylated enamines (see Chapter 3). Good yields of the acylated product are obtained when an equivalent of weak base is used to abstract the acidic protons in the product.(Fig.45).

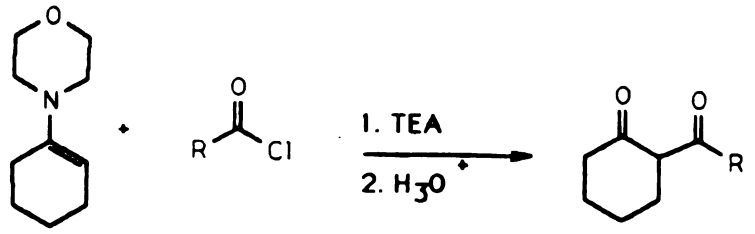


Fig. 45 Acylation of Enamines in the Presence of Weak Base

This method does not work when ethyl chloroformate is the acylating agent. In that case 2 equivalents of the enamine is used. We found that the carboxylated enamine is unreactive towards ethyl chloroformate at room temperature. Under the right reaction conditions the carboxylated enamine might undergo esterification which followed by decarboxylation would form the 2-carboethoxylated enamine. (Fig.46).

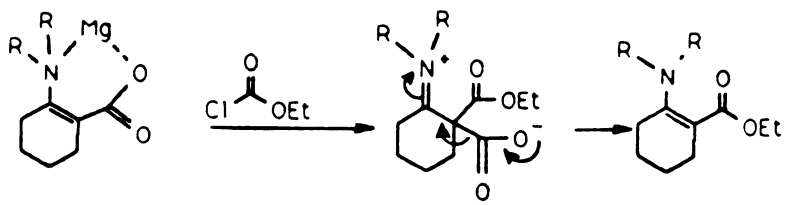


Fig. 46 Esterification of Carboxylated Intermediate

Another line of research would be the study of carboxylated imines towards various electrophiles. Metallated imines (for a review of the synthetic usefulness of these reagents see ref. 35) have been used as a way of avoiding O-phosphorylation that is encountered with the reaction of phophorylating agents with enolates. The carboxylation of imines could be a potential method of forming a metallated imine under very mild conditions.(Fig.47).

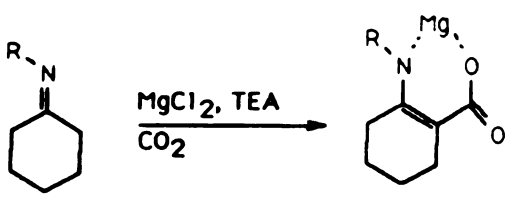


Fig. 47 Carboxylation of Imines

EXPERIMENTAL

Carboxylation of the Morpholino Enamine of Cyclohexanone.

Ten mmoles of N-cyclohexilidene morpholine, prepared by the procedure of Herr(36), were carboxylated by the procedure described for ketones. After 6 hours, 320 ml (1.4 eq.) of CO_2 were absorbed. Upon acidic workup, the full amount of CO_2 was evolved. No β-ketoacid was detected.

Hydrogenation of Carboxylated Intermediate.

Ten mmoles of N-cyclohexilidene morpholine were carboxylated by the procedure described for ketone-carboxylation. After 6 hours of stirring, a catalytic amount of PtCl2 was added and the reaction was put on a hydrogenator at atmospheric pressure. After 12 hours, approximately 1 eq. of H_2 was absorbed. Acidic workup gave a solid identified as 1,1-bis morpholine cyclohexane; m.p. 147-151°C; mass spec(EI) 264 (m^+), 178 (m^+-morpholine group). ^{13}C NMR gave 6 distinct carbons in agreement with the proposed structure.

PART 3. ESTERIFICATION OF DIANION INTERMEDIATES.

Finkbeiner and Stiles found two methods in which to transform their intermediate to the corresponding β-ketoester:

a. Acidic hydrolysis to the β-ketoacid followed by treatment with diazomethane(Fig. 48).

b. Reaction of the intermediate with conc. sulfuric acid/Ethanol (Fig. 49).

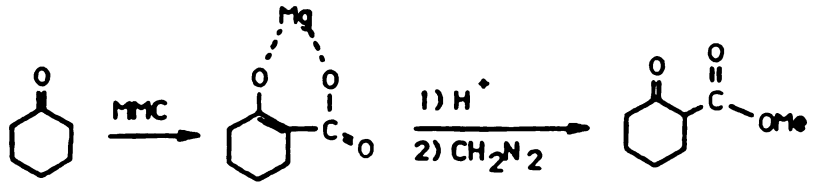


Fig. 48 Esterification of Intermediate

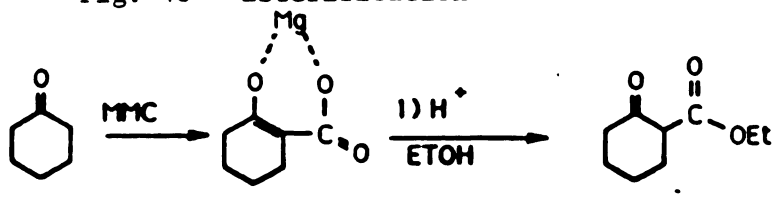


Fig. 49 Esterification by Ethanolysis

In both cases it is the acid that is being esterified not the intermediate.

The goal of our work was to determine whether the intermediate dianion or monoanion could be converted directly to the ester under mild conditions without converting the dianion to the acid. The advantage of such a method would be two-fold. First, it would be much more effecient than the two step hydrolysis-insertion sequence as described by Finkbeiner and Stiles. Second, there would be much less chance of destroying delicate functionality compared to the conc. sulfuric acid/ethanol method.

Attempts to esterify the dianion intermediate with a variety of esterifying agents failed to give the expected β-ketoester (Table 3). The products that are formed give an

Table 3. Esterification of Carboxylated Intermediates

Reagent	Yield of Ester
$(Et)_3O^+ BF_4^-$	0
Cl-CO-OEt	0
CH_3I	0
BF_3/MeOH	0
TMCS/MeOH	0
CH_3-S-CH_3	0
HCl/MeOH	60 %

indication as to the relative reactivity of different reactive sites of the carboxylated intermediate. Reaction with mild reagents such as BF_3 OEt_2/MeOH or TMSCl/MeOH gave no product. It seems that these reagents are not reactive enough to react with the oxygen-magnesium carboxylate. This is in line with the fact that the partially covalent oxygenmagnesium bond is less reactive compared to the more ionic sodium or potassium oxygen bond. The more reactive esterifying agents such as methyl iodide give reaction at the carbon alpha to the carbonyls. This would seem to indicate that there is at least an equilibrium amount of the chelated dianion intermediate [6] reacting as an enolate moity. (Fig. 50). This would explain the alkylation at the α-carbon since this is the most reactive site of the molecule(pKa of the α-carbon is 13-15 while that of the

carboxylate is 5-6). The results with methyl iodide are analagous to those of Finkbeiner's.[26]

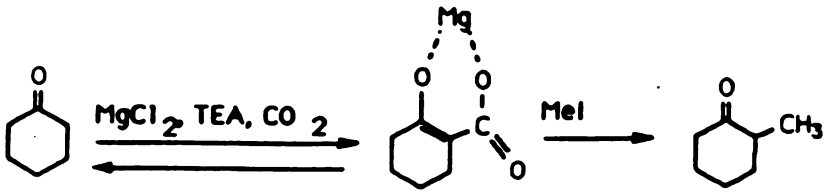


Fig. 50 Reaction of Methyl Iodide with Intermediate

To conclude this section, attempts to esterify the dianion intermediate with mild esterifying agents gave no reaction. The use of more reactive esterifying reagents leads to reaction at the α-carbon to the carbonyls. The use of ethanol and conc. sulfuric acid gave a 60% yield of the corresponding β-ketoester analagous to Finkbeiner's method of esterification.

EXPERIMENTAL

Reaction of Carboxylated Intermediate of Cyclohexanone with Methyl Iodide.

Ten mmoles of cyclohexanone was carboxylated as described previously. After six hours of stirring, iodomethane (10 mmoles, .62 ml.) was added to the reaction mixture containing the carboxylated intermediate. After 12 hours of stirring the mixture was quenched as described previously. Ether extracts (2x75 ml) were dried over $MgSO_4$.

The organic layer was then concentrated in vacuo. GC/MS of the resulting oil revealed a mixture of cyclohexanone and 2-methylcyclohexanone in a 50-50 ratio. No carboethoxycyclohexanone was detected.

CHAPTER 2

MICHAEL REACTIONS AND ROBINSON ANNULATIONS OF KETONES IN THE PRESENCE OF $MgCl_2$, TRIETHYLAMINE AND CO_2.

CHAPTER 2

MICHAEL REACTIONS AND ROBINSON ANNULATIONS OF KETONES IN THE PRESENCE OF $MgCl_2$, TRIETHYLAMINE AND CO_2.

The conjugate addition of ketone enolates with unsaturated carbonyl compounds(the Michael reaction) and the subsequent cyclization via an intramolecular aldol(Robinson annulation) is one of the most important synthetic sequences in organic chemistry (Fig. 51). Robinson annulation of cyclohexanone with various Michael acceptors gives (4.4.0)bicyclic ring systems as products. These ring systems form the intermediates for many important synthetic targets including terpenes, steroids and alkaloids.

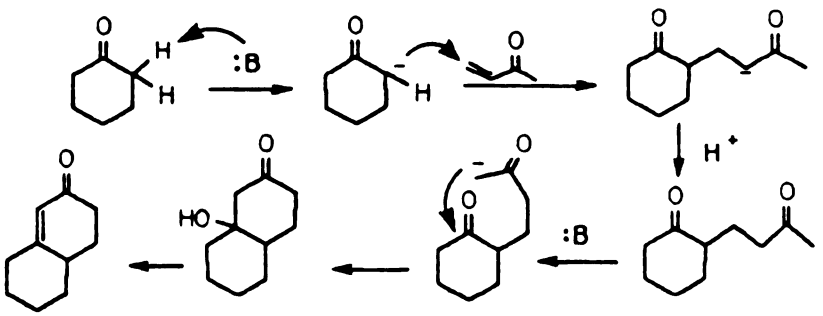


Fig. 51 Mechanism of the Michael-Robinson Annulation Sequence

As important as the sequence is there are many problems that are encountered in practice:

a. Methyl vinyl ketone (MVK), the most important Michael acceptor, tends to polymerize under the strongly basic conditions that are often used with these reactions.

b. The reactions are often run in protic solvents leading to equilibration between various enolate structures.

c. In strongly basic conditions many side products are possible.

Many methods have been developed to overcome these problems. The solutions can be catogorized in one of two way:

1. Modification of the Michael acceptor-various methods have been developed to prevent polymerization of the-α,β-unsaturated ketone. A few of these methods are discussed.

a. Use of Mannich base.[37] β-dialkylamino ketones, made from Mannich bases, can be used to form the α,β-unsaturated ketone under basic conditions. The formation of the Michael acceptor in situ prevents polymerization under basic conditions (Fig. 52).

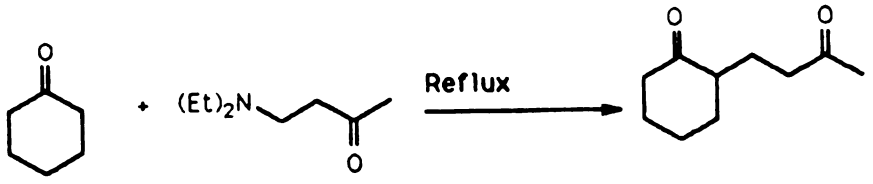


Fig. 52 Michael Addition via Dialkylamino Ketones

b. <u>β-Chloroketones</u>[38]. β-Chloroketones can also form the α,β-unsaturated ketones under mildly basic conditions (Fig. 53).

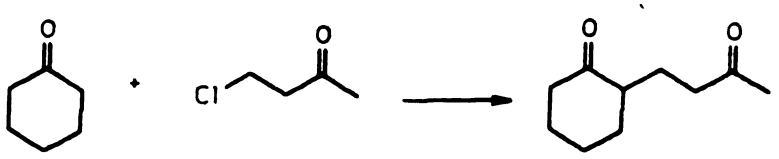


Fig. 53 Michael Additions via B-Chloroketones

c. <u>α-Silyl enones</u>.[39] Probably the most important modification of the Michael acceptor is that of Stork with his use of α-silyl enone (Fig. 54).

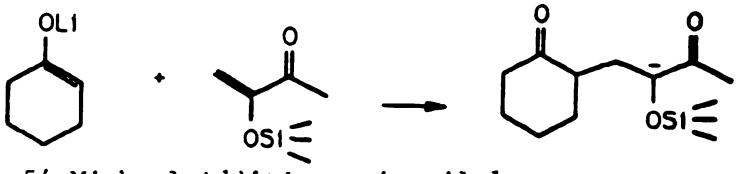


Fig. 54 Michael Additions via silyl enones

By stabilizing the negative charge that forms in the initial addition to the ketone enolate this method permits running the reaction in aprotic solvents. Under these conditions proton exchange is minimized and regiospecific enolate formation is possible. This method combines high yields with the regiospecific addition thereby making this one of the most important Michael procedures. The major drawback of this method is making the α-silyl enone. This is a four

step procedure which involves making the silyated vinyl bromide, then the corresponding grignard attacks an aldehyde which, upon oxidation, gives the silyated enone (Fig. 55).

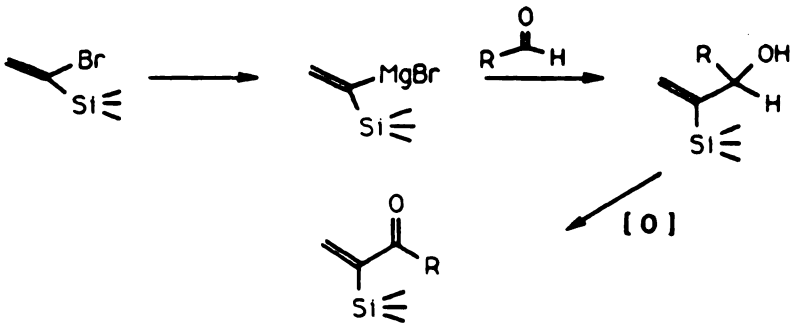


Fig. 55 Synthesis of a-Silyl Enones

2. Modification of the Michael donor-the following examples demonstrate how modifications of the enolate can improve the yields of the reaction.

a. Enamines.[40] Stork discovered that the use of the less basic enamines with MVK led to good yields (60-70%) of the Michael adducts. Since enamines can be made regioselectively and aprotic solvents are used, the product can be obtained with high regioselectivity (Fig. 56).

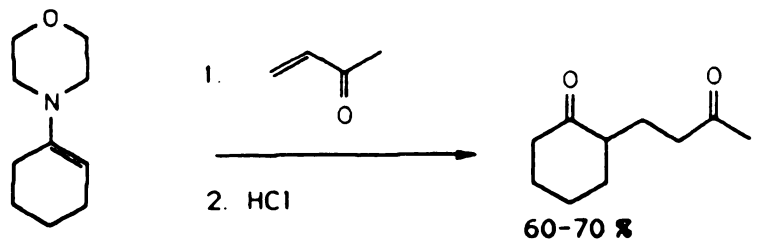


Fig. 56 Michael Additions via Enamines

b. Silyl enol ethers.[41] Mukaiyama found that silyl enol ethers could react with α,β-unsaturated ketones and esters in the presence of $TiCl_4$ under mild conditions to give the Michael adduct regiospecifically and in good yields (Fig 57). Presumably, the anion formed upon initial reaction is stabilized by the silyl group similar to the Stork reaction. Instead of using MVK directly, the ketal of MVK is used. The products of this reaction is a mixture of the 1,5-dione and 1,5-ketone-ketal. Another reaction that is similar to this is the $Si(OR)_4$/CsF catalyzed conjugate

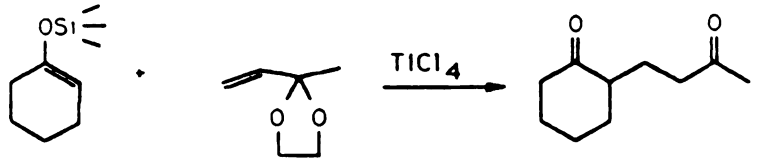


Fig. 57 Michael Additions via Silyl Enol Ethers

addition of α,β-unsaturated ketones to ketones. This reaction mechanism proposed by the authors is shown in Fig. 58. The first step is CsF activation of the tetraalkoxysilane towards electrophilic attack. Abstraction of a proton by the free alkoxide gives the intermediate silyl enol ether. The silyl enol ether then undergoes the Michael reaction with the α,β-unsaturated ketone.[42]

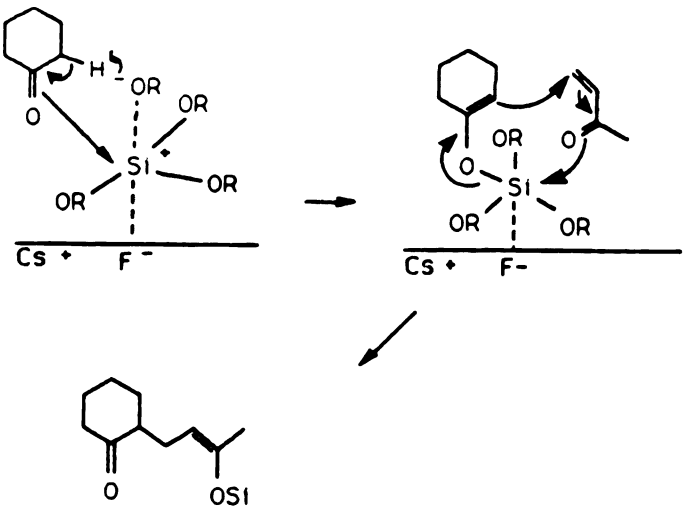


Fig. 58 Mechanism of Michael Additions with $CsF/Si(OR)_4$

c. <u>β-Ketoesters</u>.[43] Adding an ester functionality to the ketone to the form β-ketoester allows the use of milder bases to effect the Michael reaction. β-Ketoesters in the presence of TEA will undergo conjugate addition with MVK in good yields. The ester functionality can be hydrolyzed to give the 1,5-dione. It was this work that prompted us to use our carboxylated intermediate [6] as a Michael donor in conjugate addition (Fig. 59).

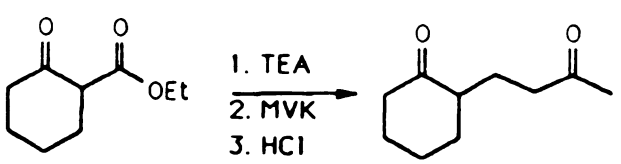


Fig. 59 Michael Additions via B-Ketoesters

CHAPTER 2

RESULTS AND DISCUSSION

CHAPTER 2

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The goal of this work was to determine whether we could obtain conjugate addition between the dianion intermediate and a simple Michael acceptor such as MVK (Fig. 60). There are certain advantages to doing 1,4-additions in this

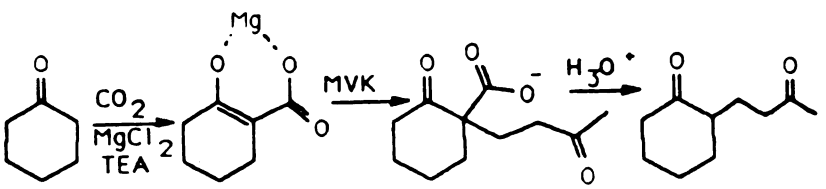

Fig. 60 Michael Additions of Carboxylated Intermediates

manner. First, the reaction conditions are extremely mild compred to the same reaction in which strongly basic lithium enolate is used. The use of milder reaction conditions minimizes the side reactions(i.e. polymerization) that occur in the presence of a strongly basic enolate. Second, the reaction is much more effecient than other popular methods. One can use the Michael donor (ketone) and Michael acceptor (MVK) without the modifications that are required in the Stork or Mukaiyama methods. This means it is a "one

pot" reaction in that it doesn't require isolation after each step. Third, the Michael addition of MVK to β-ketoesters has been shown[43] to give good yields of the 1,4-adduct. Since our intermediate [6] is structurally similar to β-ketoesters it would not be unrealistic to expect good yields from 1,4-addition to this intermediate.

One potential problem that might limit the generality of these Michael additions is the lack of regiospecificity in the carboxylation of unsymmetrical ketones. Tirpak had determined that such carboxylations lead to a mixture of both possible β-ketoacids (Fig. 61). Since this means that there is a mixture of regioisomers in the formation of the-intermediate [6] it would not be surprising if we obtained a similar mixture of Michael adducts.

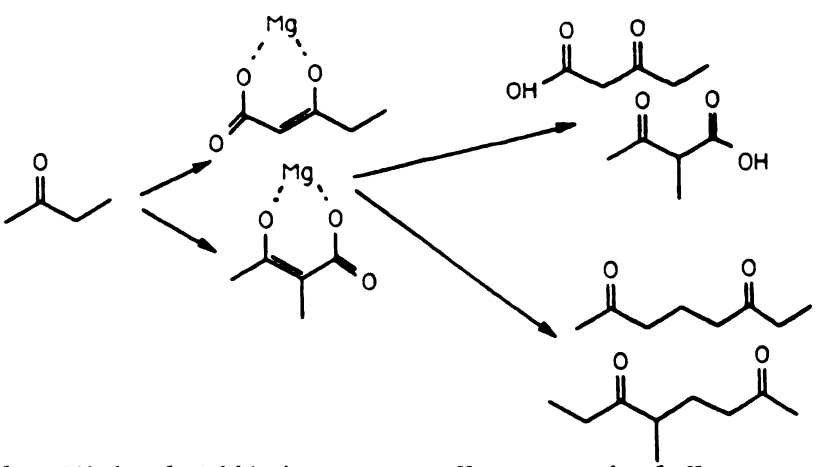

Fig. 61 Michael Additions to an Unsymmetrical Ketone

The first attempt was simply the addition of MVK to the standard carboxylation mixture that had been stirring for 24 hours. It was found that this reaction formed the

Michael adduct in less that 10% yield. This is probably due to the reversibility of the initial step of the reaction (Fig. 62). The triethlyamine hydrochloride present in the reaction cannot protonate the initial Michael adduct under the heterogeneous conditions that exist. It is the protonation of the anion of the Michael adduct that drives the reaction to completion.

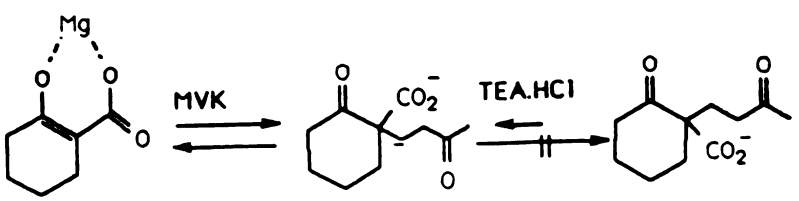

Fig. 62 Protonation of the Initially Formed Anion of a Michael Adduct

To avoid this problem the reaction was repeated as before but ethanol was used as a cosolvent when the MVK was added. This would insure that there would be a proton source present(either the dissolved TEA.HCl or ethanol) to drive the reaction. The addition of ethanol to the reaction turned out to be the factor that increases the product yields. When cyclohexanone was carboxylated under standard conditions (2 eq. $MgCl_2$, 4 eq. TEA, 30ml CH_3CN) followed by the addition of a slight excess of MVK and 10 ml of EtOH a 70-75% yield of the corresponding 1,5-dione was obtained (Fig. 63). To determine whether the intramolecular aldol was possible the reaction mixture containing MVK and ethanol was refluxed for six hours. The Robinson annulated product was found to be

the major componant of the reaction. Isolation of this product gave a 70% yield in a 9:1 mixture of conjugated and non conjugated enone (Fig. 63).

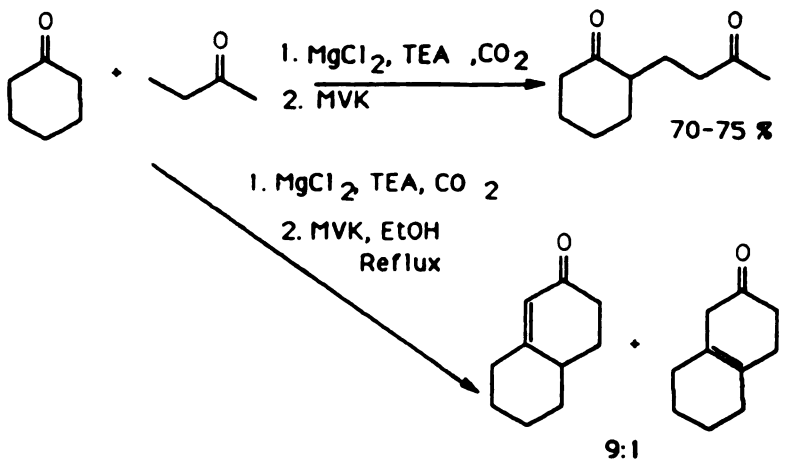

Fig. 63 Michael Reaction-Robinson Annulation of Cyclohexanone and MVK

A study was done to determine whether the Michael reaction occurs in the absence of CO_2. Table 4 shows that, at best, only a small amount of the addition occurs and in most cases there is no reaction. This was the case when either acetonitrile was used as solvent or when acetonitrile and ethanol were used as cosolvents. This shows that ketones in the absence of activating groups such as CO_2 are not reactive enough to undergo the Michael reaction in Lewis acid/weak base conditions.

Table 4. Michael Addition of MVK to Ketones in the presence of Lewis Acids and TEA.

Lewis Acid	Prod.	Yield of adduct
$BF_3(OEt)_2$	Self-cond.	0%
LiCl	None	0%
$FeCl_3$	None	0%
$SbCl_3$	None	0%
$TiCl_4$	Self-cond.	0%
$MgCl_2$	None	0%
$AlCl_3$	None	0%
$ZnCl_2$	None	0%
$ZnBr_2$	None	0%
ZnI_2	None	0%

Other Michael acceptors such as acrylonitrile and ethylacrylate fail to undergo conjugate addition to the chelated dianion intermediate. This is probably due to the fact that they are less reactive than MVK.

Various other ketones were tested to determine the generality of the reaction. Cyclohexanone gives the highest yield of Michael and Robinson product. Cyclopentanone gives a yield of 62-65% for the Michael product and 60% overall yield for the Robinson product. Other ketones gave between 40 and 62% yields except for methyl isopropyl ketone which gave less than 10% yield. In all cases where the Robinson annulated product was isolated there was about a 5% loss in yield between the isolated Michael product and the isolated cyclized product (Table 5).

Table 5. Michael Additions-Robinson Annulations

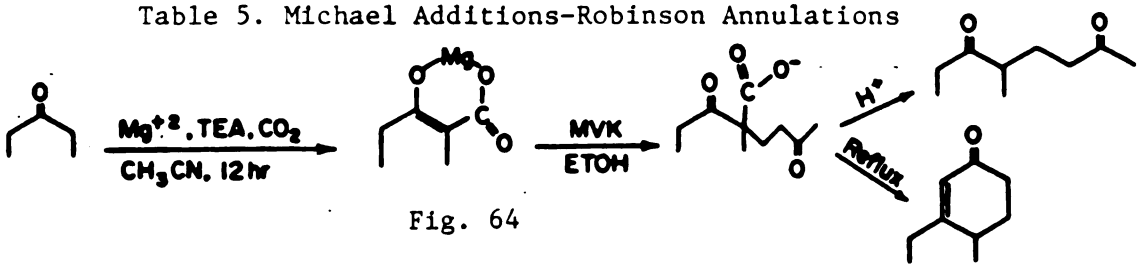

Fig. 64

Ketone	Product	Yield[a]
(1)	(a)	70-75%
(1)	(b) , (9:1)[b]	70%
(2)	(a)	62-65%
(2)	(b) , (7:1)[b]	60%
(3)	(a)	62%
(3)	(b)	56%
(4)	(a)	52%
(5)	(a) , (2:1)[b]	42%
(6)	, (3.5:1)	65%

To determine which factors effect the yield of the reaction we tried different variations on the basic carboxylation-Michael procedure. A listing of the results and the conclusions that can be drawn from them follows:

a) Time. The yield of the Michael product was measured over a period of time spanning 3 hours to 3 days to determine when equilibrium is reached. Maximum yields occurred at about six hours. Reaction yields did not seem to increase significantly if the reaction was allowed to continue longer than this time.

b) Reagent ratio. A large excess of MVK(3 eq.) seemed to give a small increase in yields(5%<) compared to our standard 1.1 eq.. .8 eq. of MVK gave approximately 10% less yield than the standard conditions.

c) Side products. With some ketones (such as cyclohexanone) a significant amount of self aldol product is detected. It was determined that this product is formed during the carboxylation proccess and cannot be avoided. (Fig. 65).

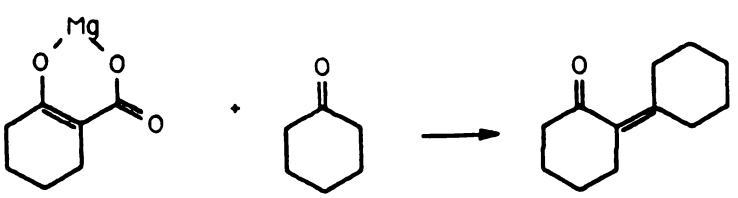

Fig. 65 Formation of Side Products

d) Temperature. Doing the Michael reaction at 0°c led to a 10% decrease in yield.

e) Solvent. THF(the only solvent other than CH_3CN in which carboxylation takes place) gives comparable yields.

The following mechanism is proposed for the carboxylation-Michael addition-Robinson annulation sequence (Fig. 66).

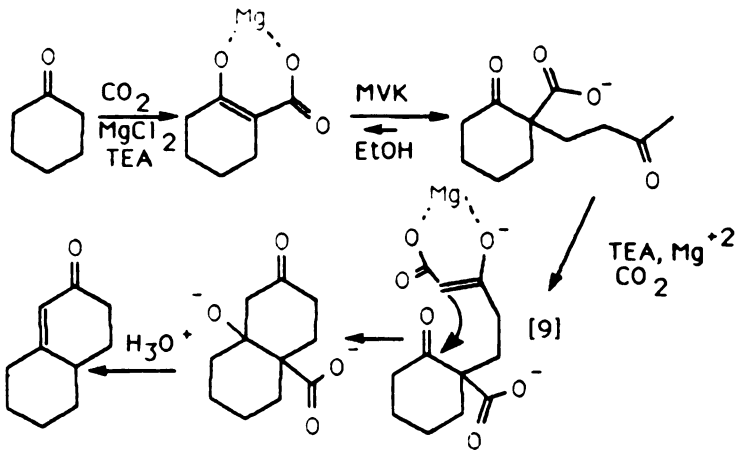

Fig. 66 Mechanism of Michael Addition-Robinson Annulation Sequence

1. The initial step is the reversible carboxylation of the ketone in the presence of Mg^{+2} and TEA. This forms the intermediate dianion [6] which is the proposed Michael donor.

2. When ethanol is added a large amount of CO_2 is absorbed. Ethanol in in the presence of Mg^{+2} and TEA forms some sort of complex[8] with CO_2 which probably resembles the MMC complex proposed by Stiles and Finkbeiner.[26] (Fig. 67). This complex probably does not act as a carboxylating agent under the mild conditions which the reaction is run.

Therefore carboxylation no longer occurs after the addition of ethanol.

Fig. 67 Complex formed from $EtOH/Mg^{+2}/CO_2$

3. When MVK is added conjugate addition occurs with the dianion[6]. This step is also reversible but protonation of the anion of the Michael adduct favors the formation of the products as when shown in Fig. 62.

4. The use of ethanol as a solvent leads to a slow decarboxylation of both the Michael adduct and the dianion [6]. After acidic hydrolysis of the reaction mixture the initial ketone and the Michael adduct are the only products obtained. There is no evidence of any ketoacid product.

5. The intramolecular aldol probably occurs by formation of the carboxylated chelate[9]. At reflux temperatures the ethanol-CO_2 complex is probably reactive enough to carboxylate in a similar manner as MMC.

It is evident that the yield of the Michael adduct is dependent on the initial concentration and reactivity of the dianion [6]. Higher yields of the Michael adduct should be obtained from ketones that form highly reactive dianions in high yields.

Two unsymmetrical ketones, 2-methylcyclohexanone and butanone, were carboxylated under standard reaction

conditions. They were then reacted with MVK as described previously. In each case a mixture of the two possible regioisomers of the Michael adduct was obtained (Fig. 68). In each case addition at the least hindered carbon is favored. (The isomers were identified by GCMS.)

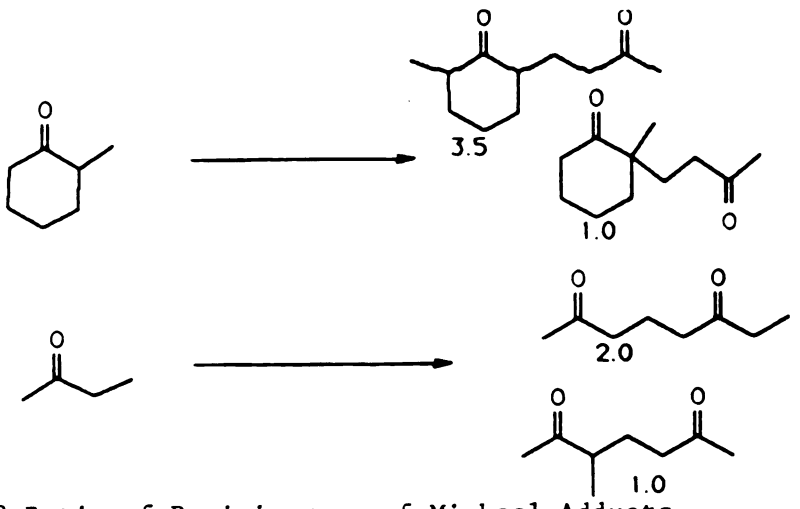

Fig. 68 Ratio of Regioisomers of Michael Adducts

To determine if there is a relationship between the ratio of carboxylated isomers and the Michael adduct isomers the ratio of the 2-methylcylcohexanone β-ketoacid isomers was obtained. NMR shows that the ratio the β-ketoacids is approximately the same as the Michael adduct isomers. (Fig. 69). The simplest interpretation of these facts is that both the ratio of β-ketoacid isomers and Michael adduct isomers is determined by the ratio of the dianion isomers. (Fig. 70).

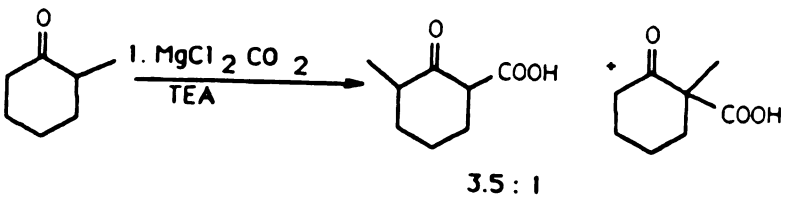

Fig. 69 Ratio of Regioisomers of Ketoacids

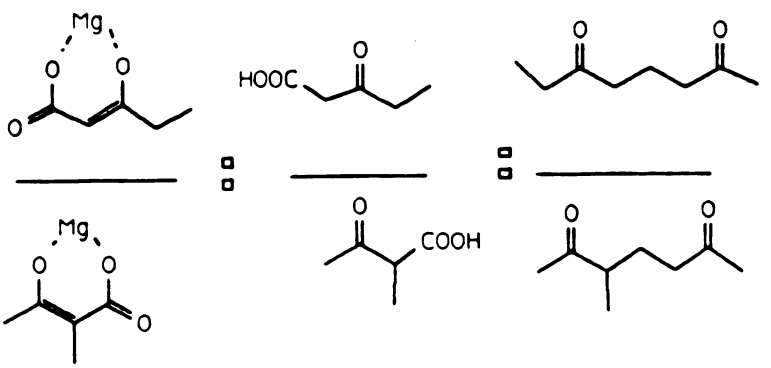

Fig. 70 Ratio of Corresponding Regioisomers

To summarize the results:

1. The Michael reaction of MVK with a variety of ketones has been accomplished under very mild conditions (room temperature, atmospheric pressure, relatively less basic enolate). The generation of the enolate and subsequent Michael and Robinson annulation are "one pot" in that they don't require work up and isolation for each step.

2. Since the conditions are so mild, polymerization of the MVK and associated side reactions are avoided thereby giving good yields of the products.

3. Workup of the reaction is extremely simple. Acidic hydrolysis and extraction by ether is followed by removal of

the solvent under reduced pressure. Final isolation is by column chromatography on a silica gel column.

4. The reagents involved are safe, inexpensive and do not require cumbersome methods of handling.

5. Although the reaction is sensitive to steric and substitution factors it is not regiospecific and therefore gives isomers when the reaction is done with unsymmetrical ketones.

6. Either the Michael or Robinson product can be isolated depending on whether the mixture is refluxed or allowed to stir at room temperature.

Aldol condensations

From Stiles' and Finkbeiner's work, it is known that the chelated intermediate [6] produced by MMC undergoes an aldol condensation with acetaldehyde in good yields (Fig. 71). We briefly examined a variety of of aldehydes and their reaction with the chelated dianion (Fig. 72). It was found that acetaldehyde gives fair yields of the aldol product when stirred with the carboxylated reaction mixture with ethanol as a cosolvent. Butyraldehyde gives poor yields (21%) even with refluxing over 6 hours. Benzaldehyde gives none of the condensed product. These results are similar to those of Finkbeiner's with MMC (Table 6).

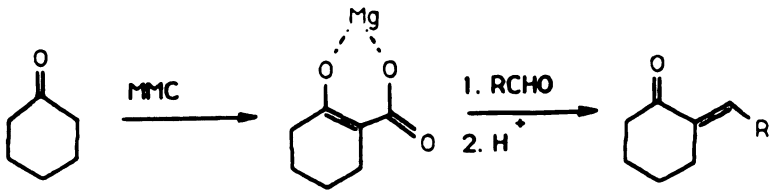

Fig. 71 Aldol Condensations with MMC Carboxylations

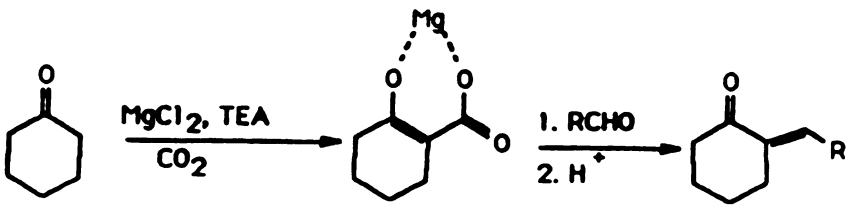

Fig. 72 Aldol Condensations Magnesium Halide-Weak Base Carboxylations

Table 6. Aldol condensations with [6]

R	Yield of
CH_3	71 %
n-propyl	21 %
	< 5%

EXPERIMENTAL

EXPERIMENTAL

THF was distilled from sodium and benzophenone. CH_3CN, $MeCl_2$, TEA and pyridine were dried by distillation from CaH_2. All ketones used in this investigation were commercially available and purified by fractional distillation over CaH_2. $MgCl_2$, acquired as the anhydrous reagent from the Aldrich Chemical Co., was stored and handled in a dry box under argon. Solid CO_2 was used as a-source of CO_2 gas which was dried by passage through a drying tube containing anhydrous $CaSO_4$. Ethanol (100%) was commercially available and required no special handling. MVK was purchased from Aldrich Chemical Company stablized with .1% Acetic acid and .05% hydroquinone and stored at 0°c.

Analysis

All products were analyzed by ^1H NMR, IR, MS and GC. The descriptions of the instruments used were provided in chapter one.

Reaction of Acetophenone with CO_2 in the Presence of $MgCl_2$ and TEA.

The reaction of acetophenone with CO_2 was described in chapter one.

Reaction of Carboxylated Intermediate of Acetophenone with MVK.

The carboxylated acetophenone from the previous reaction was allowed to stir for 12 hours. The gas burette was recharged with CO_2 and the fluid level was allowed to stablize. EtOH (15 ml.) was added to the mixture. This mixture then absorbed approximately .5 eq. (110 ml.) of CO_2. After stbiliztion of the fluid level, MVK (1.00 ml, 12 mmoles) was added and the mixture was stirred for 6 hours. To isolate the Michael adduct, the reaction mixture was quenched with 60 ml. of 3 M HCl and extracted with ether (2 x 75 ml.). The ether extracts were dried over $MgSO_4$, filtered and the solvent was removed in vacuo. The residual oil after silica gel chromatography (hexane-ether, 50:50) afforded 1.18 gm of the product; yield 62% m.p. 63-65 (lit. 65-67); ^1H NMR ($CDCl_3$) 1.80-3.1 (m,9H), 2.1 (s,3H), 7.1-8.0 (m,5H); IR ($CDCl_3$ soln.) 1710 (s), 1680 (s). cm-1; mass spec (EI) 190 (M^+), 105, 77,51.

Cyclization of Michael Adduct.

Six hours after the addition of MVK to the carboxylated mixture the reaction was refluxed for 6 hours. After the work described previously, .93 g (56%) of 1B was isolated. ^{1}H NMR ($CDCl_3$) 1.5-2.6 (m,6H), 6.26 (s,1H), 7.1-7.7 (m,5H); IR ($CDCl_3$ soln.) 1670 (s) cm-1; mass spec (EI) 172 (M^+), 144 (base peak).

2-(3-Oxobutyl)-cyclohexanone was prepared from cyclohexanone, CO_2, and MVK as described above. 70-75% yield of 2A was obtained. ^{1}H NMR ($CDCl_3$) 1.0-2.9 (m,16H), 2.10 (s,3H); IR ($CDCl_3$ soln.) 1710 (s) cm-1; mass spec (EI) 168 (M^+), 150, 43 (base peak).

2-Oxo-2,3,4,5,6,7,8,10-octahydronapthalene was prepared from cyclohexanone, CO_2, and MVK by the cyclization procedure described above: 70 % yield; ^{1}H NMR ($CDCl_3$) 1.1-3.0 (m,13H), 5.6 (s, 1H); IR ($CDCl_3$ soln.) 1686 (br) cm^{-1}; mass spec (EI) 150 (M^+), 135,122,39 (base peak).

2-(3-Oxobutyl)-cyclopentanone (3A) was prepared from cyclopentanone, CO_2, and MVK as described previously. Yield 62-65 %; ^{1}H NMR ($CDCl_3$) 1.0-2.8 (m,14H), 2.1 (s,3H); IR ($CDCl_3$ soln.) 1740, 1720 (br) cm-1; mass spec (EI) 154 (M^+), 136, 121, 43 (base peak).

2,3,7,7α-Tetrahydroindan-5(6H)-one(3B) was prepared from cyclpentanone, CO_2, and MVK as described previously. Yield 60%; ^1H NMR ($CDCl_3$) 1.0-2.9 (m,11H), 5.93 (s,1H); IR ($CDCl_3$ soln.) 1680 (s) cm-1; mass spec (EI) 136 (M^+), 108 (base peak).

2,5-Ethyl-2,6-nonadione (4A) was prepared from 4-heptanone, CO_2, and MVK as described previously. Yield 52%; ^1H NMR ($CDCl_3$) 1.0-2.6 (m,17H), 2.08(s,3H); IR ($CDCl_3$ soln.) 1720 (br) cm^{-1}; mass spec (EI) 184 (M^+), 169, 156.

2,6-Octadione and 5-methyl-2,6-heptadione were prepared from butanone as described previously. Yield 42% (2:1) ^1H NMR ($CDCl_3$) .9-2.5 (m,9H),2.06(s,5H); mass spec (EI) (octadione) 142 (M^+), 124, 43 (base peak), (heptadione),142 (M^+) 127 (M^{+-15}), 43 (base peak).

2-(3-Oxobutyl)-6-methylcyclohexanone was prepared from 2-methylcyclohexanone, CO_2 and MVK as described previously. 1 HNMR ($CDCl_3$) 1.0-2.6 (m, 12H), .9 (d,2.25H), 1.1 (s, .75H), 2.1 (s, 3H); mass spec (EI) 182 (M^+), 164, 43 (base peak). GCMS revealed the 2,6-isomer as the major componant.

CHAPTER 3

REACTION OF ACYLPHOSPHONATES WITH SILYL ENOL ETHERS. SYNTHESIS OF β-DIKETONES.

CHAPTER 3

REACTION OF ACYLPHOSPHONATES WITH SILYL ENOL ETHERS. SYNTHESIS OF β-DIKETONES.

One of the most common methods for synthesizing β-diketones and β-ketoesters is the additions of esterifying or acylating agents, such as acyl chlorides to ketone enolates (Fig. 73). In many cases the usefulness of this class of reactions is limited by the numerous side reactions that occur. These include:

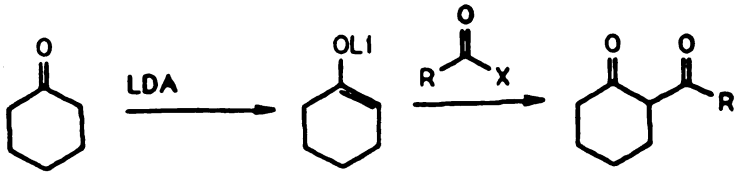

Fig. 73 Acylation of Ketone Enolates with Acyl Chlorides

A. O-acylation (Fig. 74)- The proportion of C to O acylated is dependent on many factors:

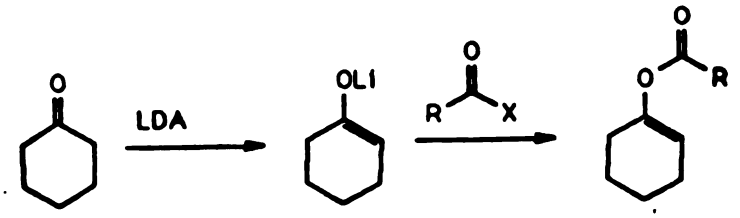

Fig. 74 O-Acylation of Ketone Enolates

1. Counter cation. O-acylated products are favored when the metal ions coordinating with the enolate do not form tight ion pairs. Examples include such metal ions as Li, Na, or K.

2. Ratio of reagents. When an excess of acyl chloride and/or chloro formate is added to an enolate the major product formed is from O-acylation or O-esterification. This is due to the mech anism of enolate acylation which occurs in two steps (Fig. 75):

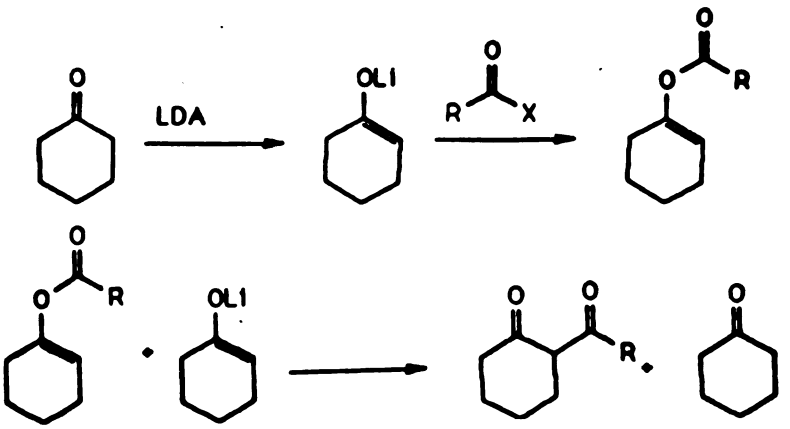

Fig. 75 Mechanism of Acylation of Ketone Enolates

a. Initial O-acylation of the enolate, followed by

b. Further reaction of the O-acylated product with another enolate molecule.

When an excess of acylating agent is used, no enolate is available for conversion of the O-acylated product to the C-acylated product.

3. Solvent. O-acylation is favored when the reactions are run in polar solvents which tend to complex the cation. This leads to more dissociated ion pairs which favors attack at oxygen.

4. Other important factors effecting the proportion of O vs C-acylated product includes the use of sterically hindered ketones, the presence of electron withdrawing or donating substituents on the acylating agent and the temperature of the reaction.

B. A second major problem is the high acidity of the protons of the β-diketone product. These protons tend to be abstracted by the basic enolate thereby limiting the maximum yield of product to 50% (Fig. 76). One of the most interesting methods of avoiding this problem is the use of acylating agents that do not collapse to the product until the reaction is over. As shown in Fig. 77, these acylating agents retain the tetrahedal carbon that is formed after the initial nucleophilic attack. Since the protons of these molecules are not as acidic as those of β-diketones the enolate is not quenched. Possible examples of these types of reagents are acyl cyanides and acyl imidizoles.

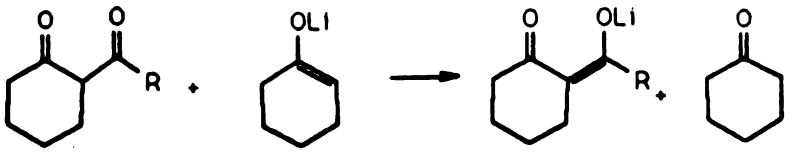

Fig. 76 Quenching of Enolate by Diketo Product

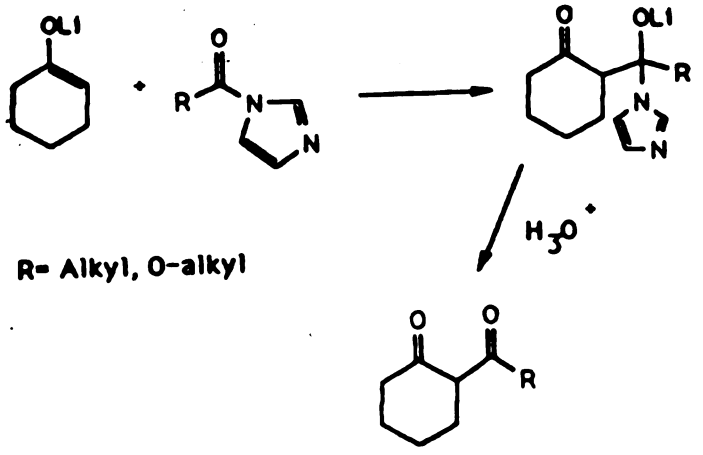

Fig. 77 Mechanism of Acylation of Enolates with Acyl Imidizoles

A means for dealing with proton abstraction is by the use of enamines as enolate equivalents. Acylation of enamines with acyl chlorides in the presence of a weak base (i.e. TEA) gives good yields of β-diketones.[44] The weak base functions as the proton abstractor thereby preserving the starting material. (Fig. 78).

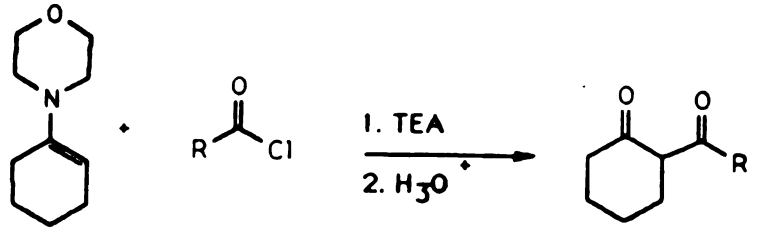

Fig. 78 Acylation of Enamines with Acyl Chlorides

The following is a description of the best methods available for acylating/esterifying an enolate or enolate equivalent.

a. Acylation/esterification of ketone enolates with acyl cyanides/cyanoformates. Howard[45] found that the stoichiometric reaction of acyl cyanides and lithium enolates at 0°c gives excellent yields of the corresponding β-diketone. Analagously, Mander[46] found that the reaction of cyanoformates with lithium enolates in the presence of HMPA gives excellent yields of the corresponding β-ketoester. Both of these reactions are free of byproducts that are formed from O-acylation (Fig. 79). Studies by Ziegler[47] show that addition of trimethylchlorosilane to a enolate-cyanoformate reaction at -78°c gives the corresponding silyated aldol product. This demonstrates that the excellent yields from this reaction are due to the preservation of the tetrahedral carbon until the reaction temperature is raised (Fig. 80).

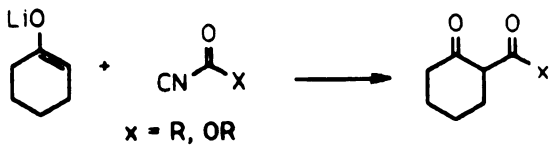

Fig. 79. Acylation of Enolates with Acyl Cyanides or Formates

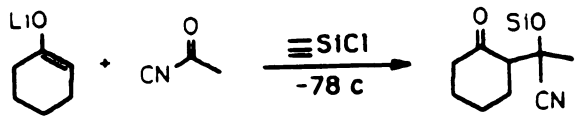

Fig. 80 Demonstration of the Tetrahedral Nature of the Acylation of Ketones with Acyl Cyanides

b. Acylation of ketone enolates with Acid Chlorides. The most important method of acylation with acyl chlorides is that of Seebach.[48] He showed that a stoichiometric reaction of enolate and acyl chloride could be achieved at -78°c using lithiated mesityl anion as the base (Fig. 81).

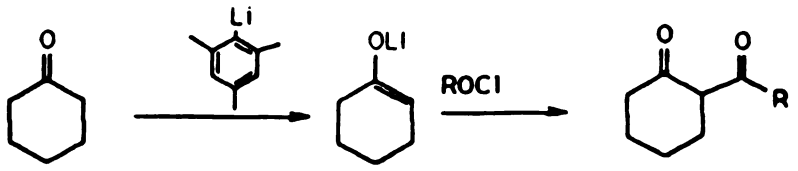

Fig. 81 Acylation of Ketone Enolates with Acyl Chlorides

c. Other methods.

1. Reaction of Silyl enol ethers(SEE) with acyl chlorides. Tirpak[49] investigated the reaction of silyl enol ethers with acyl chlorides in the presence of various lewis acids (Fig 82a). The best results were obtained with $ZnCl_2$ in $MeCl_2$ at 0°c. Yields ranged from 40-90%. The major problem is reaction of the SEE with the diketo duct (Fig. 82b).

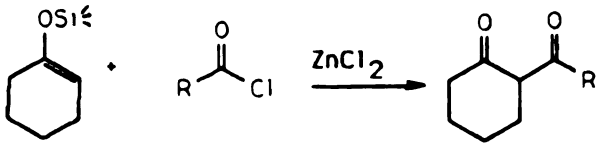

Fig. 82a Acylation of Silyl Enol Ethers with Acyl Chlorides

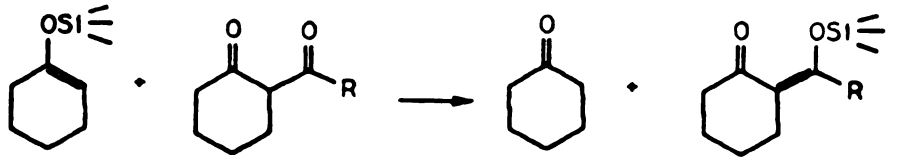

Fig. 82b Quenching of Silyl Enol Ether by Diketo Product

2. Reaction of lithium enolates with acylphosphonates. Sekine[50] studied the reaction of acylphosphonates with lithium enolates using lithium bis(trimethylsilylamide) as the base (Fig. 83).

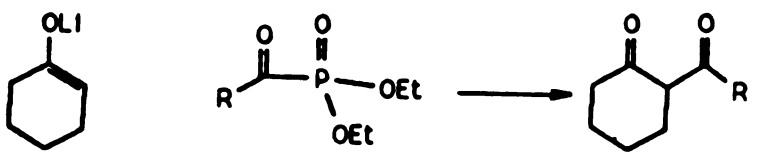

Fig. 83 Acylation of Enolates with Acylphosphonates

Best yields were obtained when benzoyl or highly hindered acylphosphonates were used. Two major problems are encountered in this reaction; abstraction of acidic protons by the lithium enolate and attack of the acylphosphonate by phosphite anion (Figs. 84a and b). To avoid quenching of

the phosphonate by diethyl phosphite that is generated in the reaction two equivalents of phosphonate were used.

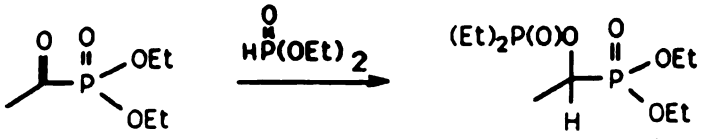

Fig. 84a Attack of Phosphide Ion on Acylphosphonate

Fig. 84b Quenching of Lithium Enolate by Acidic Protons

One of the possible advantages of using acylphosphonates as acylating agents is the strength of the phosphorus-carbon bonds in these reagents. In comparison with leaving groups on other similar acylating agents (such as chloride ion in acyl chlorides or ethoxide ion in esters), the phosphite ion is relatively poor. This means that the tetrahedral carbon that is formed from enolate attack on an acylphosphonate might be maintained until the reaction is completed (Fig. 85). As with similar reagents(i.e.acylcyanides) maintainance of the tetrahedral

carbon avoids the problem of proton abstraction that plagues many acylation reactions.

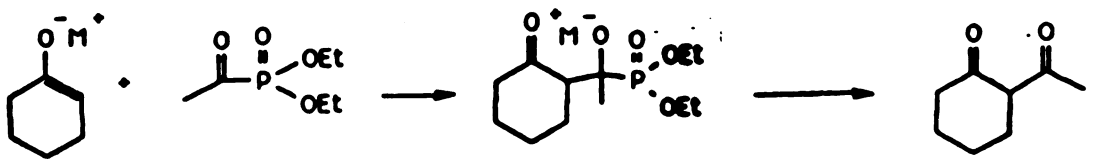

Fig. 85 Tetrahedral Intermediate in the Acylation of Enolates with Acyl-Phosphonates

Using this line of reasoning, a logical reaction to attempt would be the acylation of silyl enol ethers with acylphosphonates. Some advantages offered by this reaction would be:

a) Acylphosphonates would seem to be ideal reagents for activation by Lewis acids. Chelation by a Lewis acid would withdraw electron density away from both the carbonyl carbon and the α-carbon. The resulting polarized chelate would be activated towards attack by a nucleophile (Fig. 86). Sekine has already demonstrated that acylphosphonates are useful acylating agents towards various nucleophiles such as alcohols and amines.[51] Activation of the acylphosphonates by chelation should make it reactive even towards mild nucleophiles such as silyl enol ethers.

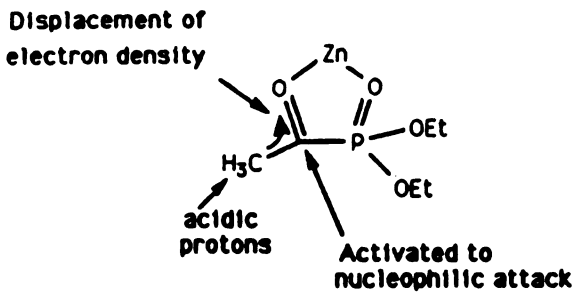

Fig. 86 Chelated Phosphonate

Unpublished work done in our lab suggests that the protons a to the carbonyl of an acylphosphonate become much more acidic upon chelation (Fig. 86). This is due to the displacement of electron density away from the protons. This enhancement of acidity of protons a to a carbonyl and in the presence of a Lewis acid has been shown to occur with other reagents such as ketophosphonates and bis-trimethylsilyl malonates.[52]

b) The intermediate[10] formed by transfer of the silyl group in this reaction would be relatively stable and would stand a chance of surviving until the reaction is completed (Fig. 87). Evans[53] has reported that these α-siloxyphosphonates are stable and has obtained them in good yield by the reaction of trimethylsilylphosphite with ketones. It is possible that the reaction between silyl enol ethers and acylphophonates could occur by a similar mechanism to that suggested by Evans for his reaction (Fig. 88).

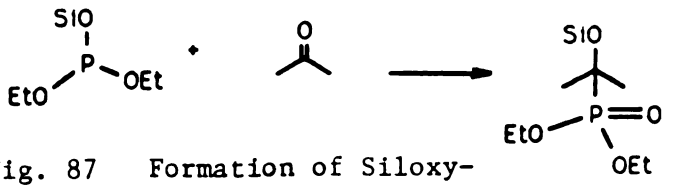

Fig. 87 Formation of Siloxy-phosphonates

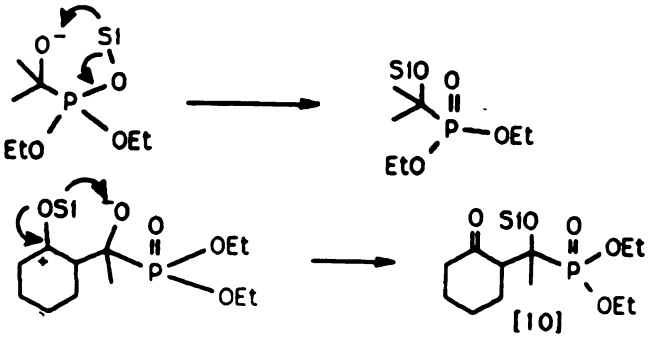

Fig. 88 Mechanism of Silyl Transfer

c) If the intermediate[10] is maintained until after the reaction is completed then there will be no free phosphite ion in the reaction. This means that only one equivalent of acylphosphonate would be needed.

CHAPTER THREE

RESULTS AND DISCUSSION

CHAPTER THREE

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The silyl enol ether of cyclohexanone (10 mmol) was added to a stirred mixture of acetylphosphonate(10 mmol) and Lewis acid (10 mmol) in 10 ml of $MeCl_2$. The reaction was allowed to stir for 12 hours and then quenched with ethanol and 6M HCl. After stirring for an additional 6 hours the mixture was extracted with ether. The organic layer was dried and the reaction mixture was analysed for the β-diketone with GCMS. The results are shown in Table 7.

Table 7. Acylation of Cyclhexanone SEE with Acetylphosphonate in the presence of a Variety of Lewis Acids.

Lewis Acid	Prod.	Yield
$BF_3(OEt)_2$	Self-cond.	0%
LiCl	None	0%
$FeCl_3$	None	0%
$SbCl_3$	None	0%
$TiCl_4$	Self-cond.	0%
$MgCl_2$	None	0%
$AlCl_3$	None	0%
$ZnCl_2$	Diketone	27%
$ZnBr_2$	Diketone	27%
ZnI_2	Diketone	25%

From Table 7 it is seen that only the zinc halides give the β-diketone. With this Lewis acid a variety of products are formed as shown in Fig. 89.

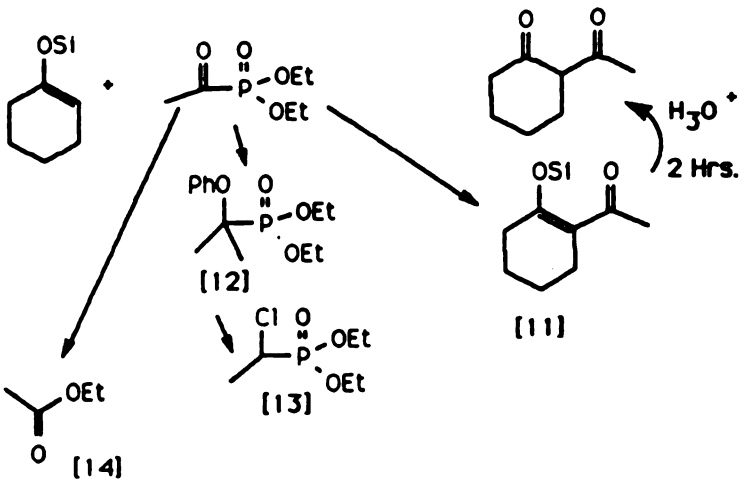


Fig. 89 Products Formed in the Acylation of Silyl Enol Ethers With Acylphosphonates

If the mixture is analyzed shortly after quenching then a mixture of the diketone and the silylated product[11] is obtained. If the quenched mixture is allowed to stir the silylated product eventually disappears. Other products include the α-chlorophosphonate[13] (presumably formed through the α-phosphophosphonate[12]) and ethylacetate[14] presumably formed through the ethanolysis of acetylphosphonate.

Zinc halides are the only Lewis acid tested that activates the acetylphosphonate to give nucleophilic attack of the silyl enol ether. Possible reasons for the success of zinc are:

a) Method of Activation. As mentioned previously, abstraction of protons from acetylphosphonates is possible in the presence of a Lewis acid and weak base(in this case the silyl enol ether). Zinc halides must activate the acetylphosphonate in such a way that nucleophilic attack is favored over proton abstraction while other Lewis acids favor proton abstraction to the exclusion of nucleophilic attack.

b) Ionic Potential. It has been shown that Zn^{+2} is one of the most effecient at catalysising reactions where a negative charge is developing during the transition state(54). This was demonstrate with the rate measurements of the hydrolysis of α-amino acids (Fig.90). Of all the divalent ions tested, zinc caused the fastest rate of hydrolysis. This ability to stabilise the developing negative charge was attributed to the high charge/ionic radius (ionic potential) that zinc has.

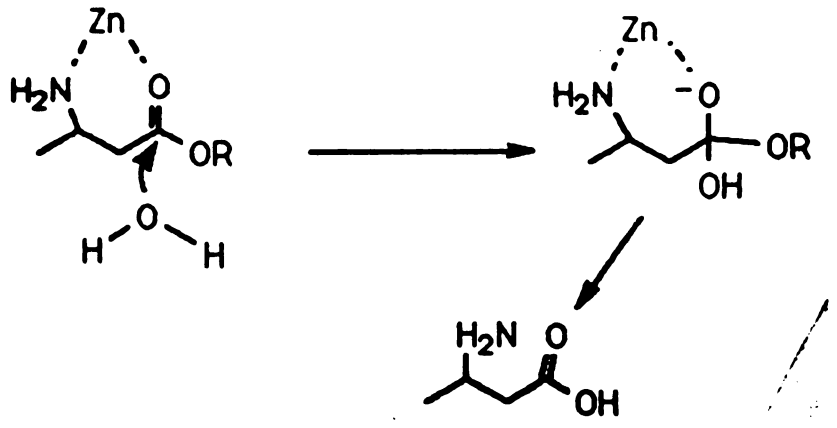


Fig. 90 Hydrolysis of Aminoesters in the Presence of Zn^{+2}

The next step in our investigation was to determine which solvent gives the best yields. Of the solvents tried only benzene and methylene chloride gives reasonable yield of the product. The yield of products is about the same for both of these solvents. Tirpak found that $MeCl_2$ was the best solvent for his acylation reactions. He attributed this to the fact that $MeCl_2$ dissolves metal salts without complexing with them. Presumably this is also true with benzene which can form some sort of pi-complex with zinc (Table 8).

Table 8. Acylation of Cyclohexanone SEE with Acetylphosphonate and $ZnCl_2$ in a Variety of Solvents.

Solvent	Yield of Diketone
$MeCl_2$	27%
Benzene	26%
CH_3CN	0%
THF	0%
Diethyl Ether	0%

The third factor investigated was temperature. The reaction gives no product at -78°c. At 0°c a small amount of product is formed. The same amount of product seems to be form from temperatures ranging from 25°c to reflux (Table 9). At the lower temperatures the silyl enol ether is not sufficiently reactive enough to give addition to the carbonyl.

Table 9. Effect of Tempeature in the Acylation of Cyclohexanone SEE with Acetylphosphonate and Zinc Chloride in Benzene.

Temp.	Yield
-78 c	0%
0 c	10% <
25 c	29%
Reflux	27%

The fourth factor considered was that of relative ratio of reactants. Results from the variation of reactant ratio showed that the reaction is very sensitive to this factor. A summary of results follows.

a. Acylphosphonate. A doubling of the amount of the acylphosphonate leads to an increase of the diketoproduct formed. This seems to indicate that the tetrahedral carbon is collapsing before the reaction is over. The extra equivalent of acylphosphonate is then used to scavenge the diethyl phosphite that is produced during that collapse (Fig. 89) (Table 10).

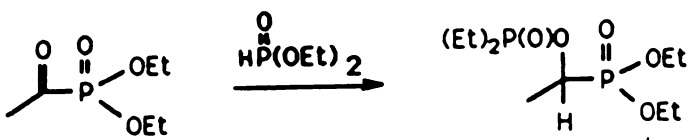


Fig. 39 Scavenging Diethyl Phosphite by Acylphosphonate

Table 10. Reaction of SEE with Benzoylphosphonate

	Cyclhex. SEE	Acetophenone SEE
Benzoylphos. 1 eq	32%	50%
Benzoylphos. 2 eq.	48%	76%

b. Silyl enol ether. Doubling the silyl enol ether amount leads to an increase of self condensation. (Fig. 91) (Table 11).

Fig. 91 Self Condensation of Cyclohexanone

Table 11. Reaction of Acetylphos. and Cyclohexanone

Eq. of SEE	Yield of Diketone
.5	5%<
1.0	22%
2.0	20%

c. Lewis acid. Doubling the concentration of zinc chloride leads to an increase in the diketone product. Larger concentrations do not lead to a further increase in yield. (Table 12).

Table 12. Reaction of Acetylphos. with Cyclohexanone with varying concentrations of $ZnCl_2$

Eq. of Lewis acid	Yield of diketone
.5	10 %
1.0	20 %
2.0	29 %
3.0	26

Two methods were used to quench the reaction. Ethanolysis with conc. sulfuric acid gave the α-phosphophonate[12] as the side product. Ethanolysis with 6M HCl gave the α-chlorophosphonate[13] as the side product. Both methods gave the same yields of the diketo product.

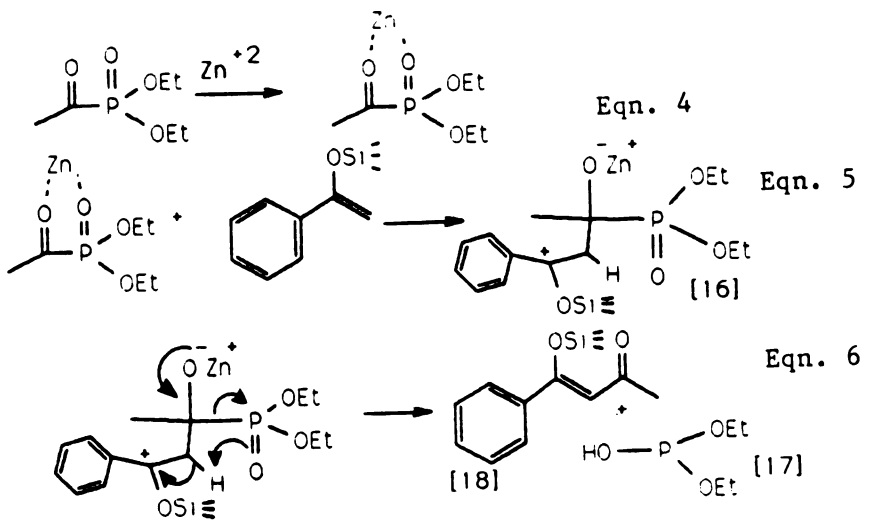
From these results we obtained the standard conditions for the acylation of silyl enol ethers with acylphosphonates.

Ten mmol of $ZnCl_2$ is weighed out and transferred to a 25 ml flask under argon with a sidearm/septa and magnetic stir bar. 10 ml of $MeCl_2$ is added to the flask via syringe followed by 10mmol of acetylphosphonate and 5 mmol of the silyl enol ether of cylcohexanone. The mixture is stirred for 12 hours followed by quenching with acid/ethanol and addition of a GC standard. The resulting mixture is stirred for 2 hours and extracted with ether. The ether layer is dried over $MgSO_4$. Yields obtained with our optimal conditions are shown in Table 13.

Table 13. Reaction of SEE with Acylphosphonates Under Optimum Conditions.

	Acetylphos.	Benzoylphos.
Cylohex. SEE	29 %	48 %
Acetoph. SEE	48 %	76 %

A mechanism that is consistant with the experimental data is shown in Fig. 92.



1. Chelation and activation of the acylphosphonate by the Lewis acid (Eqn. 4).

2. Nucleophilic attack of the silyl enol ether on the activated acyl phosphonate with formation of the siloxonium ion[16] (Eqn. 5).

3. Abstraction of a proton from the siloxonium ion by either the phosphoryl group or by silyl enol ether followed by collapse of the intermediate to give diethyl phosphite[17] and the silyated diketone[18] (Eqn. 6).

4. Attack of the phosphite on the acylphosphonate and subsequent C to O rearrangement to give [12] (Eqn. 7).[54]

Evidence to support this mechanism includes the following:

a) This mechanism is analgous to the one proposed by Kluger[55] in the reaction of dimethyl acetylphosphonate with water (Fig. 93). The main point of this study was that the phosphoryl leaving group[19] left in the form of the acid and not the corresponding anion[20]. Based upon relative pka's of acetylphosphonate and ethyl acetate one would expect that they would have similar rates of hydrolysis. The fact that rate of hydrolysis of the phosphonate is much greater then the ester is attributed to the facile cleavage of the P-C bond through the monoanion compared the slower cleavage of the ester by way of the dianion. The intramolecular transfer of the proton from the hydroxyl oxygen to the phosphoryl oxygen is similar to the one in our proposed mechanism.

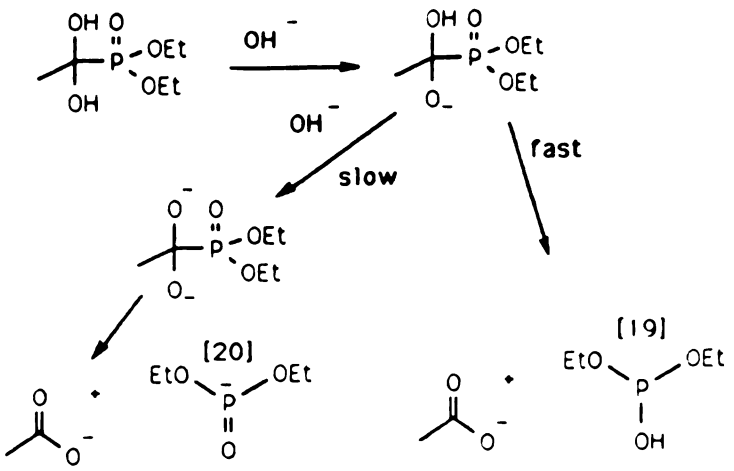


Fig. 93 Mechanism of Hydrolysis of Dimethyl Acetylphosphonate

b) The formation and rapid deprotonation of a siloxonium ion is similar to the mechanism proposed for the acylation of silyl enol ethers with trichloroacetyl chloride[56] (Fig. 94). The yields of this reaction are limited due to rapid quenching of the silyl enol ether by its deprotonation of the intermediate siloxnium ion [21]. That the silyl enol ether is not being quenched by the diketone[22] was demonstrated by stirring a solution of the silyl enol ether with [22]. No reaction occurred under these conditions (Fig. 95)

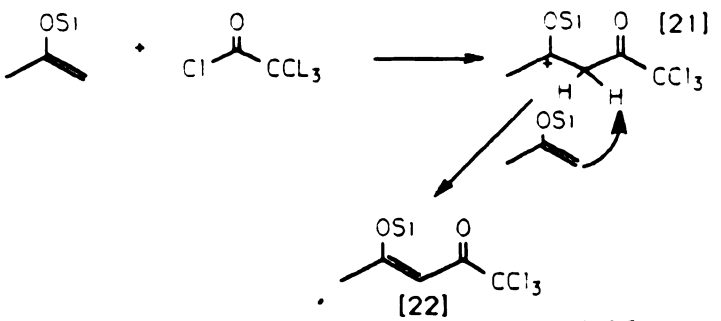


Fig. 94 Reaction of Silyl Enol Ether with Trichloroacetyl Chloride

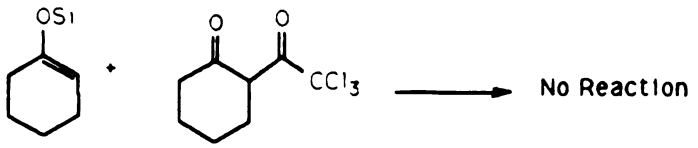


Fig. 95 Reaction of Silyl Enol Ether with Trichloroacetyl chloride

c) Mg^{+2} ion enhances the rate of ethanolysis of acylphosphonates (Fig. 96).[52] In both mechanisms the Lewis acid plays the same role; activation of the phosphonate towards nucleophilic attack.

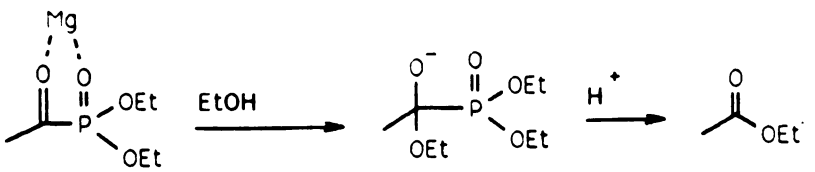


Fig. 96 Activation of Acetylphosphonate Towards Ethanolysis

To summarize the results obtained in this investigation:

a. Acylphoponates can be used as acylating agents with silyl enol ethers in the presence of $ZnCl_2$. There are three major factors that effect the yields;

1. Quenching of the silyl enol ether starting material by the acidic protons of acetylphosphonate. As Sekine demonstrated only hindered or benzoylphosphonates give good yields of the diketones. As mentioned

previously, the protons on the chelated phosphonate are highly acidic making abstraction by the basic silyl enol ether a favorable process (Fig. 97).

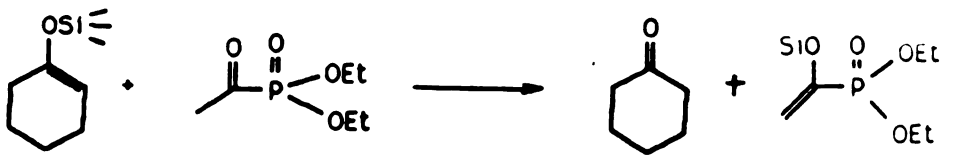


Fig. 97 Quenching of Silyl Enol Ether with Acidic Protons of Acetylphosphonate

2. Quenching of the silyl enol ether starting material by the acidic protons of the intermediate[16]. This is minimized in the reaction of relatively unreactive silyl enol ethers such as acetophenone SEE. A method for avoiding this proton abstraction by the SEE is the addition of an equivalent of a weak base. We found that this led to no reaction presumably due to abstraction of the acidic protons of the acylphosphonates or neuralization of the Lewis acids (Fig. 98).

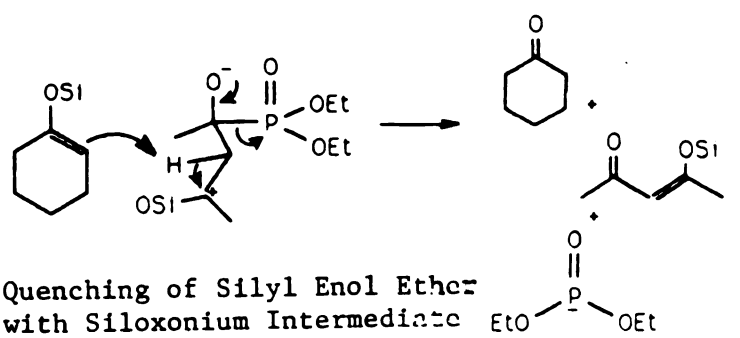


Fig. 98 Quenching of Silyl Enol Ether with Siloxonium Intermediate

3. Attack of the diethylphosphite on the acylphosphonate starting material. This problem is circumvented by the use of two equivalents of acylphosphonate.

b. The only Lewis acid that gives the diketo product is $ZnCl_2$. This was attributed to the ability of zinc ion to activate the acylphosphonate towards nucleophilic attack while minimizing proton abstraction and its ability to accomodate the negative charge that develops in the intermediate.

c. The reaction only occurs in $MeCl_2$ or benzene. The ability of these solvents to dissolve the Lewis acid without neutralizing its acidity makes these the solvents of choice for this reaction.

d. The reaction will occur at room temperature right up to reflux. The reaction does not occur at -78°c and gives only a little yield at 0°c.

e. The optimal ratio of reactants in this reaction is 1:2:2 silyl enol ether:acylphosphonate:lewis acid.

Because of the problems associated with this reaction it cannot be considered a general method for synthesizing β-diketones. As with Sekine's work good yields are only obtained when acetophenone silyl enol ether is used. The facile collapse of the tetrahedral carbon leads to two major problems; namely proton abstraction of the intermediate and addition of phosphite to the acylphosphonate. Another

drawback in the reaction is the highly acidic protons of the chelated phosphonate which also leads to quenching of the silyl enol ether. This is a good method for the addition of benzoyl groups or highly hindered carbonyls to silyl enol ethers.

CHAPTER THREE

EXPERIMENTAL

CHAPTER THREE

EXPERIMENTAL

Materials

Methylene chloride, CH_3CN, TEA and all ketones were distilled from CaH_2. Benzene and THF were distilled from sodium and benzophenone. Aluminum chloride and antimony trichloride were purchased from Fisher Scientific Company. Boron Trifluoride etherate was acquired from Eastman Chemical and distilled from CaH_2 prior to use. All other Lewis acids were purchased from Aldrich Chemical Company and handled in a dry box under argon. All acid chlorides were purchased from Aldrich Chemical Company and purified by simple distillation.

Methods of analysis

All products and intermediates were analyzed by 1 HNMR. GC yields were obtained using n-alkanes as internal standards. The descriptions of the instruments used were provided in Chapter 1.

Synthesis of Trimethylsilyl Enol Ethers

Cyclhexanone trimethylsilyl enol ether was prepared by the following procedure which is adapted from that of Duboudin.[45]

Sodium iodide (550 mmol, 82.4 g) was flame dried under vacuum in a one liter round bottom flask equipped with a septum inlet and a magnetic stirrer. The flask was flushed with argon and charged with 500 ml of dry acetonitrile. After the NaI dissolved 500 mmol (49.1 g, 51.8 ml) of cyclohexanone were added followed by 550 mmol (55.7 g, 76.5 ml) of triethylamine. Trimethylchlorosilane (550 mmol, 69.8 ml) was slowly introduced to the flask so as to avoid a rapid reflux due to the exothermicity of the reaction. Large amounts of precipitate formed during this addition. Stirring continued for approximately one hour, at which time the reaction was diluted with 300 ml of pentane. This mixture was washed with 200 ml of cold water followed by a rapid separation of layers. The aqueous layer was washed with an additional 100 ml of pentane. The pentane layers were combined and dried over sodium sulfate. Removal of solvent in vacuo, followed by vacuum distillation through a short vigreux column provided 63 g (75%) of pure cyclohexanone trimethylsilyl enol ether: by 63-65°c 10 mmHg; 1 HNMR ($CDCl_3$) .2 (s, 9H), 1.57 (m,4H), 1.93 (m, 4H), 4.75 (m, 1H).

Acetophenone Trimethylsilyl Enol Ether was prepared as above: 1HNMR ($CDCl_3$) .2 (s, 9H), 4.35 (d, 1H), 4.75 (d 1H), 7.0-7.5 (m, 5H).

Synthesis of Acyl Phosphonates

Benzoylphosphonate was prepared in a 250 ml 3 neck flask with reflux condenser, addition funnel, and gas inlet tube. The flask was flushed with argon and benzoyl chloride (27ml, 232 mmol) was added via syringe at 0°c. Triethyl phosphite (40 ml, 232 mmol) was added dropwise over a period of 2 hours to the stirring benzoyl chloride at 0°c. The reaction was allowed to come to room temperature and stirred overnight. Benzoylphosphonate is isolated in 73 % yield (41 g.) by simple distillation: b.p. 118°c, .3 mmHg; 1HNMR ($CDCl_3$) 1.1 (t,6H), 3.9 (m, 4H), 7.3-7.9 (m,5H).

Acetylphosphonate was prepared from acetyl choride and triethylphophite by the procedure described above: b.p. 78°c, 1 mmHg; 1HNMR ($CDCl_3$) 1.1 (t, 6H), 2.3 (d,3H), 3.9 (m,4H).

Synthesis and Analysis of Some 1,3-Diketones.

2-Acetylcyclohexanone

A 25 ml flask with septum inlet and magnetic stir bar was flame dried and flushed with argon. Zinc chloride (2.46g, 10 mmol) was transfered from a dry box to the reaction flask. This was followed by addition of 10 ml of

methylene chloride. Acetylphosphonate (1.64 ml, 10 mmol) was added by syringe to the reaction mixture followed by the addition of the trimethylsilyl enol ether of cyclohexanone (.96 ml, 5 mmol) via syringe. After stirring for 12 hours at room temperature, n-pentadecane (1.38 ml, 5 mmol) was added to the reaction mixture as an internal standard. The reaction was then quenched with 2 ml of conc. sulfuric acid and 5 ml of EtOH. After stirring for 5 hours, an aliquot of the reaction mixture was extracted with ether and the organic layer was dried over $MgSO_4$. GC yields were determined relative to the n-pentadecane internal standard. Yield 29%; 1HNMR ($CDCl_3$) 1.2-2.7(m,15H), 2.1(s,3H), 15.2 - (s,1H).

2-Benzoylcyclohexanone was prepared from benzoylphosphonate and cyclohexanone trimethylsilyl enol ether by the procedure described above. Yield 48%; 1HNMR ($CDCl_3$) 1.1-2.6 (m,9H), 7.2-7.8 m,5H).

1-Phenyl-1,3-butanedione was prepared from acetylphosphonate and acetophenone trimethylsilyl enol ether by the procedure described above. Yield 48%; 1HNMR($CDCl_3$) 2.13(s,3H), 2.24 (s,2H), 7.2-7.5 (m,5H).

1,3-Diphenyl-1,3-propanedione was prepared from acetophenone trimethylsilyl enol ether and benzoylphosphonate by the

procedure described above. Yield 76%; 1HNMR ($CDCl_3$) 2.4 (s,1H), 6.2(s), 7.2-7.5(m,5H).

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