THE SYNTHESIS OF β-KETO ESTERS FROM LITHIUM ESTER ENOLATES

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ABSTRACT

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Lithium ester enolates stable at -78° can be reacted with acid chlorides at the same low temperature to give β-keto esters in good yield. The enolates of ethyl acetate, ethyl isobutyrate and ethyl hexanoate are conveniently prepared from lithium N-isopropylcyclohexylamide (LiHMDS). The appropriate acid chloride is then added dropwise to the tetrahydrofuran solution of the enolate and allowed to stir fifteen minutes before quenching. For most reactions the optimum yield is obtained when an excess of LiICA is present. The reactions of ester enolates with certain phenyl esters of N-acylimidazoles are less successful for preparation of β-keto esters.

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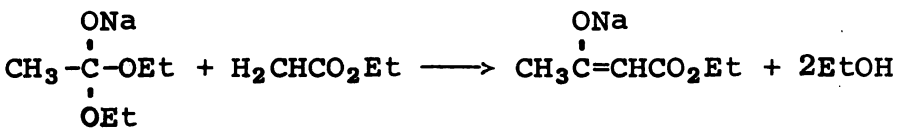
INTRODUCTION

A number of methods are available for synthesizing a variety of β-keto esters. The most common methods found in the literature include the base catalyzed condensation of esters either with themselves or other esters, Reformatsky type reactions of α haloesters with zinc and a second ester, and alkylation of simple β-ketoesters formed by these methods. A discussion of the studies on the scope of the Claisen condensation is presented, and a few more recent methods for synthesizing β-keto esters are briefly described. The emphasis of this thesis is focused on the synthesis of β-keto esters by reaction of certain acylating agents, in particular acid chlorides, with lithium ester enolates. This method offers a simple procedure for the synthesis of these useful compounds.

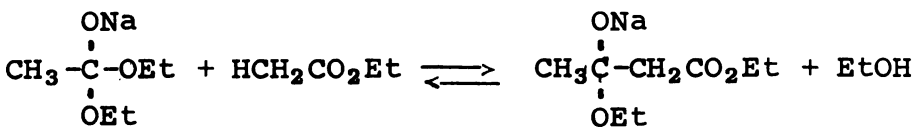
LITERATURE REVIEW

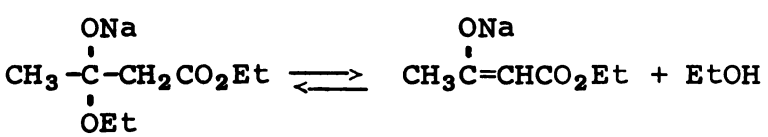
The formation of acetoacetic ester by self condensation of ethyl acetate in the presence of sodium ethoxide is the classic example of a Claisen type reaction. The mechanism proposed by Claisen[1] for formation of the β-keto ester involved the formation of the ortho derivative of ethyl acetate which reacted with a molecule of unchanged ethyl acetate:



According to this explanation, two α-hydrogen atoms were required for the condensation to occur.

Dieckmann[2] represented the condensation as a reversible reaction of two phases





that requires only one α hydrogen of the ester that condenses with the ortho derivative in order to bring about the first phase of the condensation. According to his explanation, the reason for the failure of an ester of the type R_2CHCO_2Et to undergo the condensation was the ease with which the condensation product was split, that is, the reversal of the first phase of the reaction.

In the 1920's a number of studies resulted in Scheibler's[3] proposal that condensation of an ester with sodium ethoxide is hindered by the formation of alcohol when the enolate is formed, so that the reversible phase of the acetoacetic ester condensation could be represented by

$$CH_3-\overset{O}{\overset{\|}{C}}-OEt + NaOEt \rightleftharpoons CH_2=\overset{OEt}{\overset{|}{C}}-ONa + EtOH$$

and the ester enolate was proposed as a necessary intermediate. However, it was still unclear as to whether or not an ester required two hydrogens on its α carbon atom in order to undergo the condensation.

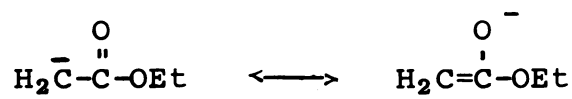
McElvain[4] used sodium ethoxide to effect self condensation of ethyl acetate, ethyl propionate, ethyl butyrate and ethyl isobutyrate by distillation of the alcohol as it formed from the reaction mixture. Ethyl isobutyrate, however, failed to condense which seemed to indicate that two α hydrogens were indeed necessary.

It was known from work of Bouvealt[5] and Doll[6] that reaction with sodium rather than sodium ethoxide could give

either acyloins or the desired condensation products with ethyl acetate or methyl acetate. The latter products required carefully controlled conditions. For example Doll's work showed that sodium could effect the condensation of methyl acetate with methyl benzoate to form methyl benzoylacetate, but the total operation was twenty to twenty-four hours.

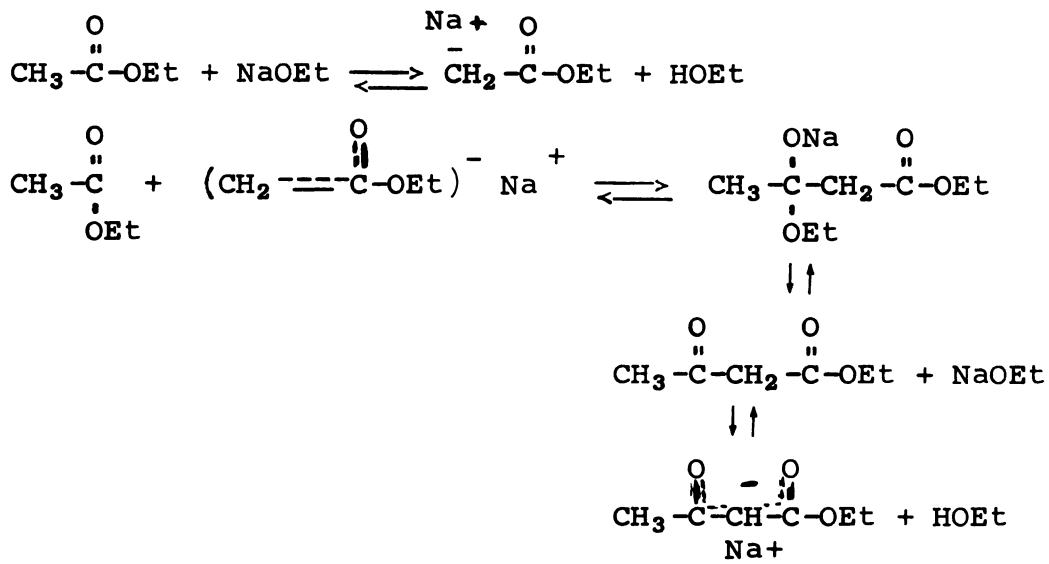
In a series of studies on condensation reactions begun by C. R. Hauser in 1937, the mechanism for the Claisen type reaction was more clearly elucidated. Hauser's work was most important for understanding the mechanism of formation of β-keto esters by ester condensations and provided the main background for the research described in this thesis.

In his first paper,[7] Hauser proposed that sodium ethoxide removed a proton from the α carbon to the carbonyl group of an ester to form a negative enolate anion, represented in two resonance forms:



The condensation was proposed to proceed by reaction of the ester enolate with the carbonyl group of a molecule that had not been converted into an enolate. In order for the reaction to proceed to completion, the enolate of the condensation product must form. Thus, the Claisen condensation

could be represented as a series of equilibria, using ethyl acetate with sodium ethoxide as an example



Since ethyl acetate is a weaker acid than ethyl alcohol, the equilibrium of the first step would favor the reverse direction. However, the acetoacetic ester is a stronger acid than ethyl alcohol so that the equilibrium of the last step is shifted toward formation of the enolate of the β-keto ester. Hauser's mechanism differs from the earlier proposed mechanisms which assumed that sodium ethoxide added across the carbonyl group of the ester, followed by elimination of alcohol (<u>via</u> ethoxide from the addition compound and hydrogen from the free ester).

Hauser showed that esters of the type R_2CHCO_2Et could undergo self condensation provided the enolate of the product could be formed. This requires a base strong enough to remove a γ proton from $R_2-\underset{\displaystyle H}{\overset{|}{C}}-COCR_2CO_2Et$. The base chosen was triphenylmethyl sodium, Ph_3CNa. Ethyl isobutyryl-

isobutyrate could be formed via self condensation of ethyl isobutyrate. The first step is formation of the sodium enolate of ethyl isobutyrate and triphenylmethane. Since the reaction of ethyl isobutyrate with Ph_3CNa goes to completion, the enolization of the product is brought about by the enolate of ethyl isobutyrate.

Hauser then prepared[8] ethyl benzoyldimethylacetate in 38% yield from ethyl isobutyrate, triphenylmethyl sodium and ethyl benzoate. This β-keto ester could not be converted into an enolate. One factor enhancing the formation of this β-keto ester was the formation of a weaker base from a stronger base. The conclusion was reached that in condensation reactions of ethyl esters by means of ethoxide ion, the weaker base formed is the anion of the β-keto ester, while with triphenylmethide ion the weaker base formed is also the anion of the β-keto ester, but would be ethoxide ion in the case where the β-keto ester anion could not be formed.

Hauser compared acylation of the sodium enolate of ethyl isobutyrate (prepared from Ph_3CNa) with benzoyl chloride, benzoic anhydride and phenylbenzoate.[9] The best method in this case appeared to be use of benzoyl chloride to give 55% yield of ethyl benzoyldimethylacetate. With ethyl benzoate as acylating agent, the β-keto ester formed would decompose from the presence of ethoxide ion when the reaction mixture was allowed to stir more than thirty minutes before acidifying.[10] Condensations with the enolates

of ethyl acetate or ethyl propionate were unsuccessful because of self condensation, and the β-keto esters formed would also react with acylating agent to give benzoylated β-keto esters. The results also showed the reversibility of the Claisen type reaction.

Next, Hauser used a number of methods[11] to prepare β-keto esters, in each case using Ph_3CNa as the base. Self condensation of ethyl isovalerate gave 63% yield of β-keto ester. However, crossed condensation between two different esters gave a mixture of products. The acylation of the sodium enolates of ethyl isobutyrate, ethyl methylethylacetate and ethyl diethylacetate with acid chlorides gave the corresponding α,α-disubstituted β-keto esters in 50-75% yield. This procedure offered an advantage over alkylation of ethyl acetoacetate in which complete alkylation was difficult to achieve and dialkylated products were not free of monoalkylated products. However, reactions of the enolates of ethyl acetate or ethyl isovalerate with acid chlorides resulted in poor yields of desired β-keto esters. Instead, diacylation and self condensation of the esters occurred.

Hauser[12] used a less reactive carbonyl compound, phenyl propionate, as an acylating agent on the enolates of ethyl acetate and n-amyl acetate. With ethyl acetate, the product formed could not be separated from phenol. However, when p-diphenyl propionate was used, ethyl propionylacetate was isolated in 44% yield. The enolate of n-amyl acetate

with phenyl propionate gave only 30% yield of β-keto ester.

Finally, Hauser used different bases to prepare β-keto esters.[13] Sodium or potassium amide or isopropylmagnesium bromide were employed for self condensation of certain esters with relatively reactive α hydrogens or relatively unreactive carbonyl groups. For example ethyl phenylacetate gave high yields of β-keto esters, but t-butyl esters did not effectively self condense. In another experiment, Hauser found that the Reformatsky reaction with phenyl esters and α-bromoesters was effective only when neither had α hydrogens.[14]

In general, the preparation of β-keto esters by condensations with sodium ethoxide[15] were more effective for self condensations (yields of 40 to 80% with reaction times of 4 to 32 hr) than with mixed condensations. The results were similar for other bases, including sodium amide, Grignard reagents or triphenylmethyl sodium. Certain ketones have been converted to β-keto esters by carbethoxylation with diethyl carbonate or by carbonation with carbon dioxide followed by esterification. These reactions[16] involve preparation of ketone enolates.

However, a number of other methods[15,17-19] are known for preparing β-keto esters, but none can be classified as a general method. Each has inherent difficulties that prevent preparations of many types of β-keto esters in good yield.

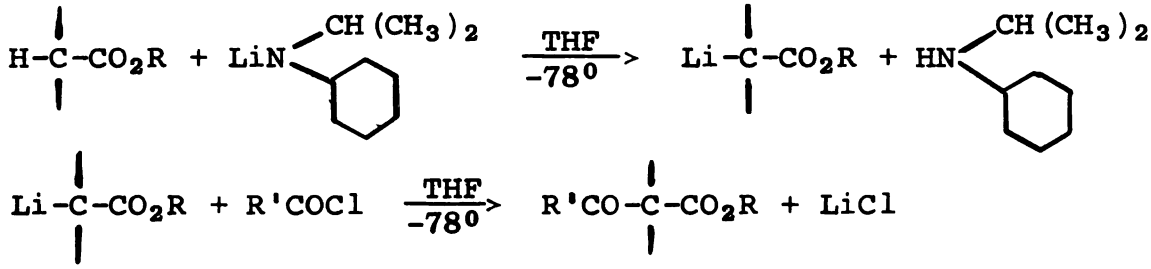
A few more recent methods should be briefly mentioned. Ethyl diazoacetate has been reacted with acid chlorides to to give the α-diazo-β-keto ester. Reaction with triphenyl phosphine followed by water and base afforded the α unsubstituted β-keto ester.[20]

Mock and Hartmann[21] have used ethyl diazoacetate to insert into a carbonyl-alkyl bond of a number of ketones under the catalytic influence of Et_3OBF_4. Yields were high of α substituted β-keto esters.

Weiler[22] has devised a useful method of alkylating simple β-keto esters. If methyl acetoacetate at 0^0 is treated with one equivalent of sodium hydride followed by one equivalent of n-butyllithium, the dianion of the β-keto ester, $\bar{C}H_2COC\bar{H}CO_2Me$, can be alkylated at the γ carbon by alkyl halides. Treatment with a second equivalent of butyl lithium followed by alkylation gives the γ,γ-disubstituted β-keto ester in high yield.

RESULTS

A variety of β-keto esters can be prepared in good yield by the reaction of lithium ester enolates with acid chlorides at -78°. The lithium enolate of ethyl acetate can be prepared from reaction of either lithium bis(trimethylsilyl)amide (LiHMDS) or lithium N-isopropylcyclohexylamide (LiICA) with ethyl acetate at -78°.[23] However, stable enolates of other esters are made with LiICA and the appropriate ester at the same temperature.



In order to prepare stable enolates that are soluble at low temperature, tetrahydrofuran (THF) is chosen as the solvent. Formation of the stable enolate is complete in 15 minutes at -78° without significant self condensation of the starting ester. Addition of the acid chloride results in a rapid formation of the β-keto ester.

The results for a series of acid chlorides are shown in Table I. All of the acid chlorides except acetyl and crotonyl give yields of β-keto esters above 50%. The products are readily obtained in a high state of purity as

Table I. Yields of β-keto esters prepared *via* acid chlorides.

Table I. Yields of β-keto esters prepared *via* acid chlorides.

Ester	Acid Chloride	Product	Isolated Yield %
Ethyl acetate	acetyl	ethyl acetoacetate	45
Ethyl acetate	propionyl	ethyl 3-ketopentanoate	60
Ethyl acetate	crotonyl	ethyl crotonylacetate	37
Ethyl acetate	butyryl	ethyl 3-ketohexanoate	56
Ethyl acetate	isobutyryl	ethyl 4-methyl-3-ketopentanoate	66
Ethyl acetate	trimethylacetyl	ethyl trimethylacetylacetate	70
Ethyl acetate	hexanoyl	ethyl 3-ketooctanoate	78
Ethyl acetate	octanoyl	ethyl 3-ketodecanoate	58
Ethyl acetate	benzoyl	ethyl benzoylacetate	81
Ethyl hexanoate	butyryl	ethyl 2-*n*-butyl-3-ketohexanoate	51
Ethyl isobutyrate	butyryl	ethyl 2,2-dimethyl-3-ketohexanoate	59
Ethyl isobutyrate	butyryl	ethyl 2,2-dimethyl-3-ketohexanoate	76*

*Without excess LiICA.

shown both by gas chromatography and by vacuum distillation. However, a high boiling residue remains in the distillation pot though it is not always detected by gas chromatography analysis.

In the case of acetyl and crotonyl chlorides, the product formed is impure, probably as a result of the enolate reacting with the resulting β-keto ester. This result is especially true when only one equivalent of LiHMDS or LiICA is used in preparing the enolate of ethyl acetate where the yield of ethyl acetoacetate from reaction with acetyl chloride is 25%. The use of an extra equivalent (100% excess) of base increases the yield to 45%, although diacylation still occurs. Likewise, addition of trimethyl-acetyl chloride to an equivalent amount of ester enolate produces a 31% yield of ethyl trimethylacetylacetate. The presence of an extra equivalent of LiICA increases the yield to 70% and reduces the amount of diacylation. With the enolate of ethyl hexanoate, the desired product from reaction with butyryl chloride increases from 30 to 51% with excess LiICA.

When an extra equivalent of base is used, the yields of other β-keto esters with α protons are also maximized. In the case of the enolate of ethyl isobutyrate where the resulting β-keto ester has no α protons, the use of only one equivalent of base gives the better yield.

Inverse addition of the ester enolate to a solution of the acid chloride has little effect on the yield relative to

the results with one equivalent of base. For example, inverse addition of the enolate of ethyl acetate to a solution of acetyl chloride results in a 31% yield of ethyl-acetoacetate. Inverse addition of the enolate of ethyl acetate to a solution of trimethylacetyl chloride results in a 35% yield of the β-keto ester. In either case, the yield is much less than by use of normal addition with an extra equivalent of LiICA.

Changing the acylating agent from acetyl chloride to N-acetyl imidazole results in similar yields for the preparation of ethyl acetoacetate. However, there seems to be no improvement in the yield of product when an extra equivalent of base is present during normal addition (see Table II). The yield of ethyl acetoacetate from inverse addition of the enolate of ethyl acetate to a solution of N-acetyl imidazole is lowered by inverse addition. Benzoyl-imidazole gives less than 10% yield of ethyl benzoyl acetate when used as the acylating agent with the enolate of ethyl acetate.

The use of a phenyl ester, phenyl acetate, as the acylating agent results in a negligible yield of acetoacetic ester, with most of the phenyl acetate recovered.

Table II. Yields of β-keto esters prepared *via* acyl imidazole or phenyl ester.

Acylating Agent	Method of Addition	Product	% Yield (V.P.C.)
Acetyl imidazole	Normal (1 eq LiHMDS)	$CH_3COCH_2CO_2Et$	48
Acetyl imidazole	Normal (2 eq LiHMDS)	$CH_3COCH_2CO_2Et$	49
Acetyl imidazole	Inverse	$CH_3COCH_2CO_2Et$	31
Benzoyl imidazole	Normal	$\phi COCH_2CO_2Et$	9
Benzoyl imidazole	Inverse	$\phi COCH_2CO_2Et$	<5
Phenyl acetate	Normal	$CH_3COCH_2CO_2Et$	<5

DISCUSSION

The normal Claisen condensation involves the formation of the enolate of an ester which then reacts with free ester to form a β-keto ester. By the use of sodium ethoxide as the base the enolate forms under equilibrium conditions so that the scope of these types of condensations is limited. Self condensations of esters result, then, in a limited number of possible β-keto esters. The synthesis of β-keto esters by a crossed condensation between two esters generally leads to a mixture of all possible condensation products. The enolate can attack an active hydrogen of the second ester as readily as the carbonyl group to give a mixture of two enolates and two free esters from which four β-keto esters can be formed.[11] Only when the second ester has no α hydrogens is a crossed condensation useful.

The use of sodium triphenylmethyl as a base for converting an ester largely to its enolate[24] enabled Hauser to prepare β-keto esters by acylation with acid chlorides. However, this base is most effective with esters that do not self condense readily, such as α-branched esters, and is not useful with more reactive esters such as ethyl acetate or ethyl isovalerate. Also, great care has to be taken to prepare this base from triphenylchloromethane and sodium amalgam.

The use of LiHMDS as a base simplifies matters considerably. First, it was prepared quite simply from n-butyl lithium and hexamethyldisilazane, $HN[Si(CH_3)_3]_2$ and used directly. Secondly, ethyl acetate is converted quantitatively at -78^0 into its lithium enolate, so that the enolate in turn can be reacted with a variety of compounds. The sodium enolate of ethyl acetate is known to be less stable.[23]

It was found that LiICA also converted ethyl acetate as well as ethyl isobutyrate and ethyl hexanoate into their lithium enolates. Unlike sodium amide or other strong bases, both LiHMDS and LiICA are essentially non-nucleophilic, undoubtedly due to steric hindrance of the nitrogen atom, and are soluble in organic solvents such as tetrahydrofuran at low temperature. This also eliminates the necessity of working in liquid ammonia solutions.

The reactions of acid chlorides with the enolate of ethyl acetate were attempted at first by using an equivalent amount of base. When the acid chlorides were added to the enolate solution, the β-keto ester formed quickly even at -78^0. Increasing the reaction time did not affect the yield. However, the yields in general were disappointing. The reaction of the enolate of ethyl acetate with acetyl chloride was repeated numerous times. The product formed was impure, with gas chromatography analysis showing a small peak for ethyl acetoacetate, and two other higher boiling peaks which were presumed to be either diacylation

or products from further reaction of the enolate with ethyl acetoacetate.

In order to correct this possibility, an inverse addition was run in which the ester enolate was prepared at -78^0 in THF and injected dropwise into a THF solution of acetyl chloride also at -78^0. In this case the β-keto ester formed would conceivably be incapable of reacting further at the ketone carbonyl with enolate since only acid chloride would be present. Also, the β-keto ester would be less susceptible to removal of its α proton by the ester enolate, a factor which would use up a molecule of the enolate after each molecule of β-keto ester was formed, or in other words two molecules of ester enolate for one acid chloride. If that factor did occur, the possibility would also exist for reaction between the enolate anion of the β-keto ester with acid chloride to form the diacylated ester. Unfortunately, this method did not increase the yield of ethylacetoacetate and when it was tried again with trimethylacetyl chloride, little effect on the yield of the corresponding β-keto ester was found.

Since diacylation was a possibility, the use of other acylating agents was considered. From the results, acetyl imidazole and benzoyl imidazole did not solve the problem. Normal addition with acetyl imidazole resulted in approximately the same yields as with acetyl chloride although benzoyl imidazole gave negligible yields. Inverse addition did not change the results.

Acyl imidazoles also have the disadvantage that they have to be made from the acid chlorides in a separate step. No difficulty was encountered in the handling of acetyl imidazole, but purification of benzoyl imidazole was somewhat difficult because it decomposes in the presence of moist air.[25]

Phenyl acetate was used to acylate the enolate anion of ethyl acetate. The carbonyl group of phenyl acetate is known to be more reactive than that of an alkyl ester but not as reactive as that of an acid chloride.[12] Under the reaction conditions of this experiment, phenyl acetate did not acylate the enolate of ethyl acetate.

The best results were obtained using an extra equivalent of the generating base LiICA in preparing the ester enolate solutions. In this manner the β-keto ester formed during normal addition of an acid chloride would be converted immediately to its enolate anion by the excess LiICA. This would accomplish two things. First, it would make the ketone carbonyl of the β-keto ester less susceptible to attack by the ester enolate. Secondly, the LiICA, being a stronger base than the ester enolate, would preferentially convert the β-keto ester to its enolate, so that no ester enolate would be wasted.

The use of an extra equivalent of base did not increase the yield for reactions with the enolate of ethyl isobutyrate since the resulting β-keto ester has no α protons. Conceivably, the ketone carbonyl of this type of β-keto ester

could be made inert by abstraction by base of the γ proton.[8] However, it was found that the yield was better when only one equivalent of base was used instead of two.

In determining the percent yield of each β-keto ester it was found that recovery of the desired product was somewhat less than the yield from v.p.c. analysis.[21] In some cases, v.p.c. showed no high boiling materials, yet high boiling residues were obtained even when the distillation was carried out at low temperature under high vacuum. Consequently, in some cases, the low yields of isolated product can be attributed to decomposition during distillation.

EXPERIMENTAL

A. Preparation of Lithium bis(trimethylsilyl)amide (LiHMDS)

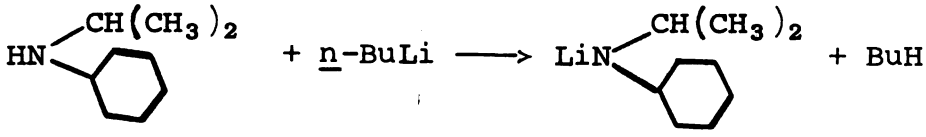
$$HN[Si(CH_3)_3]_2 + \underline{n}\text{-BuLi} \longrightarrow LiN[Si(CH_3)_3]_2 + \underline{n}\text{-BuH}$$

A 250 ml round-bottomed flask equipped with a septum inlet and magnetic stirrer was attached to a gas connecting tube and a mercury bubbler. The apparatus was flame dried under nitrogen and allowed to cool to room temperature. Hexamethyldisilazane (33.3 ml) was injected into the flask from a 50 ml syringe, and was allowed to cool in an ice bath. After a few minutes, butyl lithium (100 ml of 1.6M solution in hexane) was injected dropwise over a period of 10 min. As the reaction proceeded butane was evolved and the temperature of the reaction mixture increased slightly. The reaction was complete within 15 min and the reaction mixture began to cool toward 0^0. The pressure was adjusted by allowing nitrogen to pass slowly through the system, and then the ice bath was removed to allow the solution to come to room temperature.

A 1 ml aliquot of the solution was injected into 25 ml of glacial acetic acid and titrated with standard perchloric acid solution (in glacial acetic acid) using methyl violet

indicator. The concentration of base was between 1.0 and 1.25M in hexane for a number of preparations.

B. Preparation of Lithium N-isopropylcyclohexylamide (LiICA)



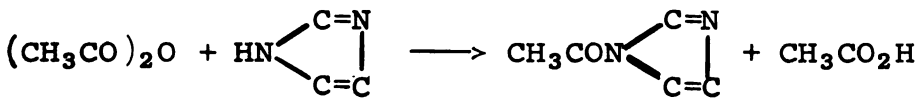
A 1000 ml round-bottomed flask equipped with a septum inlet and magnetic stirrer was attached to a gas connecting tube and a bercury bubbler. After the flask was flame dried and flushed with nitrogen, it was allowed to cool to room temperature. Isopropylcyclohexylamine (0.63 mol, 107 ml) was injected into the flask from a 50 ml syringe, followed by hexane (131 ml). The solution was cooled in an ice bath, and after a few minutes, butyl lithium (395 ml of a 1.6M solution in hexane) was injected dropwise over a 10-min period. The pressure of the system was adjusted in the same manner as in the preparation of LiHMDS.

After the reaction was complete (about 15 min) and allowed to come to room temperature, a 1 ml aliquot of the base was titrated in glacial acetic acid by standard perchloric acid (in glacial acetic acid).

When a sharp color change from purple to yellow with methyl violet indicator did not occur, a 1 ml aliquot of the base was injected into 20 ml of water, the free amine was extracted with ether, and the water layer containing LiOH was titrated with standard (0.0905N) hydrochloric acid.

Solutions of base made in this manner were approximately one molar. In the nonaqueous titration, any of the free amine that was unreacted in the preparation would be titrated, while the aqueous method would titrate only the LiOH formed from LiICA.

C. Preparation of N-acetyl Imidazole[27]



A dry 250 ml round-bottomed flask with a septum inlet and magnetic stirrer was connected to a condenser equipped with a gas connecting tube and mercury bubbler. After imidazole crystals (27.2 g, 0.4 mol) were added to the flask, acetic anhydride (50 ml, 0.5 mol) was injected with a 50-ml syringe. The solution was then heated to about 70^0 in a water bath stirred for one hour and then cooled to room temperature. The yellow solution was then heated to 60^0 under vacuum (10 mm) to remove the solvent. The residue was heated in benzene until dissolved, cooled to allow the crystals to reform, and the benzene was drawn off through a gas dispersion tube connected to a water aspirator. After the recrystallization was repeated twice with benzene, the crystals were dried in a vacuum dessicator for three hours under high vacuum. The yield of white crystals, mp $102-103^0$, was 14.2 g (32%).

D. Preparation of N-benzoyl Imidazole[28]

The apparatus consisted of a 1000-ml inlet flask with a gas connecting tube and mercury bubbler. With a stream of nitrogen going into the flask, the gas connecting tube was removed and imidazole (17.0 g, 0.25 mol) was added. The imidazole had been dried under high vacuum overnight over H_2SO_4 in a vacuum dessicator. Freshly dried benzene (735 ml) was added to the flask to form a suspension. While the suspension was stirred, purified benzoyl chloride (13.5 ml, 0.177 mol) was injected dropwise with a syringe. The reaction mixture was stirred at room temperature overnight. The benzoyl imidazole formed remained dissolved in the benzene, while imidazolium hydrochloride was undissolved. The solid was removed by filtration, and the benzene was removed under vacuum. The product was a yellow viscous liquid weighing 18.9 g (91.3% yield), which decomposed in moist air.

E. Purification of Benzoyl Chloride[29]

Three hundred ml (363 g) of benzoyl chloride in 200 ml of benzene was washed twice with 100 ml of 5% sodium bicarbonate. After the addition of 100 ml of benzene, the water layer was discarded and the benzene layer was dried with anhydrous calcium chloride. The benzene layer was distilled, and pure benzoyl chloride (bp 192-193^0) was recovered (242.3 g, 200 ml).

Purification of other acid chlorides was accomplished by distillation under vacuum, and storage under nitrogen.

F. Preparation of β-Keto Esters by Normal Addition

1. Acid Chlorides with $LiCH_2CO_2Et$

Lithio ethylacetate was prepared using LiHMDS or LiICA and ethyl acetate in tetrahydrofuran solution at -78°. After formation of the ester enolate was complete, the appropriate acid chloride was injected dropwise and allowed to stir fifteen minutes. Quenching with acid followed by workup gave the ethyl α-acylacetate.

For preparative work the reactions were run on a 25 mmol scale of starting ester and acid chloride. The procedure was as follows:

A dry 250-ml flask equipped with a magnetic stirrer, gas connecting tube and mercury bubbler was flushed with nitrogen. Fifty mmol of either LiHMDS or LiICA in hexane was injected into the flask. (In some cases only 25 mmol was used.) The hexane was then evaporated by immersing the flask in a warm water bath while connecting the mercury bubbler to a water aspirator. When LiHMDS was used, evaporation of the hexane left a white solid residue, while with LiICA a very viscous, clear liquid remained. In both cases the residue was redissolved in 50 ml of tetrahydrofuran and cooled to -78° in a dry ice-acetone bath. The pressure in the system was adjusted with a slow stream of nitrogen to prevent mercury being sucked back

into the reaction flask. Next, ethyl acetate (25 mmol, 2.48 ml) was injected dropwise over a three or four minute period and allowed to stir at -78°. After 15 min, 25 mmol of acid chloride was injected dropwise and allowed to stir an additional 10 min. The reaction mixture was quenched with a cold solution of 9 ml of HCl in 30 ml of H_2O. When the reaction mixture reached room temperature, 10 ml of ether was added, the organic layer was separated and the aqueous layer was extracted with two 10-ml portions of ether. The combined ethereal extracts were washed with two 15-ml portions of saturated sodium bicarbonate and dried with magnesium sulfate. After the solvent was stripped off, the product was distilled under vacuum. In some cases, the product foamed heavily during distillation. Addition of a few small strands of glass wool sometimes reduced the foaming considerably.

In order to follow the reaction by gas chromatography, the reactions were run on a 5-mmol scale of starting ester and acid chloride. In those cases, the reaction mixture was quenched with 20% hydrochloric acid, dried with sodium sulfate and the reaction mixture was analyzed directly by use of an appropriate internal standard.

2. Acid Chlorides with $LiC(CH_3)_2CO_2Et$ and $LiCH(C_4H_9)CO_2Et$

The enolate of ethyl isobutyrate or ethyl hexanoate was prepared in the same manner as the enolate of ethyl

acetate. However, only LiICA could be used to prepare the stable enolate. With LiHMDS, a slow self-condensation of the ester occurred. The addition of acid chloride and the workup procedure are the same as described before. The products were isolated and determined by gas chromatography.

3. Acyl Imidazoles with $LiCH_2CO_2Et$

N-acetyl imidazole was reacted with the enolate of ethyl acetate in the manner previously described for acid chlorides; the solid was dissolved in THF (0.6M) before injection. Likewise, N-benzoyl imidazole was dissolved in THF to give a 1.66M solution. In both cases, the β-keto esters were not isolated, but were determined by gas chromatography by use of ethyl benzoate or butyl benzoate as an internal standard.

G. Preparation of β-keto Esters by Inverse Addition

The inverse addition procedure was used for the reaction of $LiCH_2CO_2Et$ with acetyl chloride, trimethyl acetyl chloride and acetyl imidazole.

The apparatus consisted of two-50-ml round-bottomed flasks with septum inlets and magnetic stirrers. The top flask was connected to a gas connecting tube and mercury bubbler. A small hole was cut in the bottom of this flask and was joined to a stopcock so that liquid could be allowed to flow through the bottom. A crystal dish surrounding this flask was also fused on. The lower flask could be

attached to the ground glass joint beneath the stopcock of the upper flask.

After the system was flushed with nitrogen, the acid chloride or imidazole was injected into the bottom flask and cooled to -78°. The stopcock between the flasks was then closed, and the enolate of ethyl acetate was generated as described previously at -78°. Then the solution in the top flask was allowed to drop slowly into the bottom flask by opening the stopcock slightly. After all the reactants had stirred for 15 min, the reaction was quenched and worked up as before.

Difficulty was often encountered in opening the cold stopcock which seemed to freeze up or had to be opened all the way. In some cases, then, the ester enolate was simply prepared in a separate flask and withdrawn into a cold syringe to be injected into a solution of the acid chloride or imidazole. In either case it was difficult to maintain the ester enolate at -78°.

The β-keto esters were identified by nmr, physical constants and v.p.c. retention times. Physical constants are shown in Table III.

Table III. Physical constants of prepared β-keto esters.

Compound	Ref. Index (25°)	Exp. Bp °C/mm	Lit Value	Ref.
$CH_3CH_2COCH_2CO_2Et$	1.4190	83-6/9	91-3/17	30
$CH_3CH{=}CHCOCH_2CO_2Et$	1.4731	95-100/6	101-5/15	31
$CH_3CH_2CH_2COCH_2CO_2Et$	1.4271	57-60/0.2	93-6/15	30
$(CH_3)_2CHCOCH_2CO_2Et$	1.4236	82-5/7.5	93-4/16	32
$(CH_3)_3CCOCH_2CO_2Et$	1.4286	88-9/7.5	96-8/15	30
$CH_3(CH_2)_4COCH_2CO_2Et$	1.4319	73-4/0.5	113-7/15	33
$CH_3(CH_2)_6COCH_2CO_2Et$	1.4383	112-3/1.0	125-33/5	34
$PhCOCH_2CO_2Et$	1.5328	100-1/0.2	149-151/12	30
$CH_3(CH_2)_2COC(CH_3)_2CO_2Et$	1.4234	48-50/0.1	109-111/29	11
$CH_3(CH_2)_2COCH(CH_2(CH_2)_2CH_3)CO_2Et$	1.4330	82-3/0.1		

CONCLUSION

A variety of β-keto esters can be conveniently prepared by the reaction of lithium ester enolates with acid chlorides. There are a number of advantages to the method described in this thesis: A wide variety of acid chlorides are readily available so that this method can be extended to the preparation of a large number of β-keto esters. The entire sequence can be completed in only thirty minutes at -78^0 and the products are generally pure and obtained in good yield.

Carbethoxylation or carbonation of ketone enolates has been an important method[16] of preparing β-keto esters. However, the yields in these cases are generally lower than by use of ester enolates due to self condensation or formation of the oxygen derivative of the ketone. Also, methyl ketones are not as readily available as acid chlorides (in fact the acid chlorides serve as a common source of methyl ketones) and other ketones may react at both sides of the carbonyl group when possible.

One disadvantage in the use of acid chlorides with ester enolates is that α-branched acid chlorides are not readily available. Weiler's method[22] of alkylation of the γ carbon of methyl acetoacetate is better for preparing

certain γ,γ-disubstituted β-keto esters, and would be useful for the γ-alkylation of β-keto esters formed by acid chlorides and ester enolates. Dialkylations of β-keto esters at the α-carbon are often difficult to achieve,[15a] but the use of ester enolates can circumvent this difficulty.

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