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THE REACTION OF LITHIUM ESTER ENOLATES WITH ACID CHLORIDES. A CONVENIENT PROCEDURE FOR THE PREPARATION OF β-KETO ESTERS

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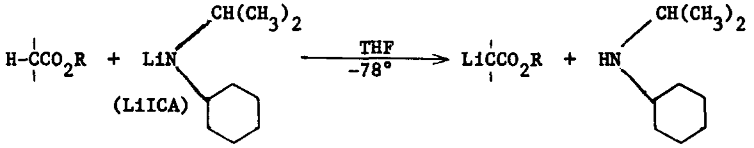
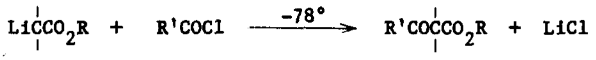
Lithium ester enolates, prepared by the reaction of lithium N-isopropylcyclohexylamide (LiICA) with esters at -78° (eq. I)[1]; react with acid chlorides at this same low temperature to provide satisfactory yields of the corresponding β-keto esters (eq. II). This procedure represents an exceedingly versatile method for the preparation of a wide variety of these useful compounds.



I.

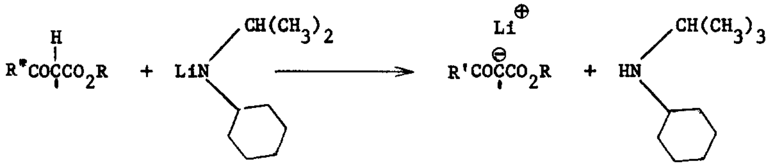


$$\mathrm{Li\overset{|}{\underset{|}{C}}CO_2R} + \mathrm{R'COCl} \xrightarrow{-78^\circ} \mathrm{R'CO\overset{|}{\underset{|}{C}}CO_2R} + \mathrm{LiCl}$$

II.

The synthesis of β-keto esters by a crossed condensation between two different esters normally leads to a mixture of all possible condensation products.[2] Hauser has reported a method for the preparation of β-keto esters by the reaction of acid chlorides with the sodium enolates of alpha branched esters such as ethyl isobutyrate or ethyl diethylacetate. Unfortunately, the method gives negligible yields with more reactive esters such as ethyl acetate or ethyl isovalerate.[3]

The ready preparation of stable solutions of ester enolates which we previously reported[1] suggested a simple procedure for the synthesis of β-keto esters. Addition of an acid chloride to such solutions should lead to rapid formation of the desired β-keto ester without significant self-condensation of the starting ester. However, attack of the ester enolate at the ketone carbonyl of the product could lead to decreased yields. This latter possibility conceivably could be minimized either by utilizing an inverse addition technique involving addition of the ester enolate to a solution of the acid chloride, or by using an extra equivalent of the generating base, LiICA, thereby converting the product into the relatively inert β-keto ester enolate (eq. III).



III.

The results obtained for the reaction of lithio ethyl acetate with trimethylacetyl chloride proved the latter procedure to be most satisfactory. Normal addition of the acid chloride to an equivalent amount of the ester enolate produces a 31% isolated yield of ethyl trimethylacetylacetate. Use of an inverse addition technique has little effect on the yield, 35%. However, addition of the acid chloride to a solution of the ester enolate containing an equivalent amount of LiICA produces a 70% isolated yield of the β-keto ester.

Application of this technique to a variety of esters and acid chlorides gives equally gratifying results as shown in Table I. As expected, the extra equivalent of base is of little utility for the preparation of β-keto esters lacking alpha protons (see entries for ethyl isobutyrate in Table). Fortunately, in this case satisfactory yields can be realized without excess LiICA.

In all cases, the β-keto esters are readily obtained in a high state of purity by means of simple vacuum distillation. Usually a high boiling residue remains in the distillation pot which may correspond to the diacylated ester.[4] However, most of the β-keto esters are relatively unstable substances and the residue is probably due in part to their decomposition at the distillation temperature.

The following procedure for the preparation of ethyl 3-ketopentanoate is illustrative of the general procedure. A dry 200 ml round bottom flask equipped with septum inlet, mercury bubbler and magnetic stirring is flushed with nitrogen. A solution of LiICA[1] (50 mmoles) in 50 ml of tetrahydrofuran is added and the flask immersed in a dry ice-acetone bath. Ethyl acetate (2.2 g, 25 mmoles) is added dropwise over a period of 5 minutes, followed after 10 minutes by 2.3 g (25 mmoles) of propionyl chloride. The reaction mixture is allowed to stir an additional 10 minutes and then quenched with 15 ml of 20% hydrochloric acid. The mixture is allowed to reach room temperature and the organic layer is separated. The aqueous layer is extracted with two 10 ml portions of ether and the combined extracts are washed with two 10 ml portions of saturated sodium bicarbonate. Distillation produced 2.25 g (60%) of pure ethyl 3-ketopentanoate, b.p. 83-86°/9mm, m.p. of copper salt 143-144°, (Lit.[5] m.p. 144-145°).

It is evident that this simple acylation reaction of ester enolates is capable of wide application for the preparation of β-keto esters prevously obtainable only with difficulty or in low yields. We continue to explore the utility of ester enolates for achieving this and other new and synthetically useful reactions.

Table I. Acylation of Lithium Ester Enolates with Acid Chlorides

Ester	Acid Chloride	Product[a]	Isolated yield, %	B.P. °C/mm
Ethyl Acetate	Propionyl	Ethyl 3-ketopentanoate	60	83-86/9
"	Butyryl	Ethyl 3-ketohexanoate	56	57-60/0.5
"	Isobutyrl	Ethyl 4-methyl-3-ketopentanoate	66	82-85/7.5
"	Trimethylacetyl	Ethyl trimethylacetylacetate	70	88-89/7.5
"	Hexanoyl	Ethyl 3-ketooctanoate	78	73-74/0.5
"	Benzoyl	Ethyl benzoylacetate	81	100-101/0.2
Ethyl Hexanoate	Butyryl	Ethyl 2-*n*-butyl-3-ketohexanoate	51	82-83/0.1
Ethyl Isobutyrate	Butyryl	Ethyl 2,2-dimethyl-3-ketohexanoate	59	48-50/0.1
"	"	"	76[b]	

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[a] All products gave physical and spectral properties in accordance with assigned structures. New products gave satisfactory analyses. [b] Without excess LiICA.

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