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THE PREPARATION AND REACTIONS OF ENOLATE ANIONS DERIVED FROM α,β-UNSATURATED ESTERS

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Since the initial observations of Bauer[1], it has been well established that enolate anions derived from α,β-unsaturated ketones react predominantly at the alpha carbon[2]. The greater reactivity of the alpha carbon has also been observed for anions derived from unsaturated malonic ester derivatives[3]. In contrast, almost nothing is known about the chemistry of enolate anions derived from α,β-unsaturated derivatives of monocarboxylic esters[4].

Addition of ethyl crotonate to a 1M solution of lithium N-isopropylcyclohexylamide (LiICA)[5] in tetrahydrofuran at a temperature of -78° results in a deep yellow solution. Immediate quenching with dilute hydrochloric acid produces a mixture of the non-conjugated ester, ethyl 3-butenoate (23% yield), and recovered ethyl crotonate (1% yield). The low yields obtained in this process suggest that the unsaturated enolate undergoes a very rapid condensation with unconverted ethyl crotonate. Use of an ester with a more protected carbonyl grouping, *t*-butyl crotonate, gives a similar low recovery, suggesting that condensation proceeds *via* conjugate addition to the double bond, a position remote from the carbonyl grouping[6].

The use of more dilute solutions, together with the addition of hexamethylphosphoramide to the solvent, overcomes this difficulty. Addition of ethyl crotonate to a 0.50 M solution of LiICA in tetrahydrofuran containing 20% (by Volume) of hexamethylphosphoramide produces, after quenching, 87% of the non-conjugated ester and 13% of recovered ethyl crotonate. That the enolate anion is formed quantitatively prior to quenching was demonstrated by quenching with deuterium oxide as shown in eq. 1. The non-conjugated ester was found to be stable to isomeriza-

$$CH_3CH{=}CHCO_2Et \xrightarrow[2.\ D_2O]{1.\ LiICA} CH_2{=}CHCHDCO_2Et + CH_2DC{=}CHCO_2Et \qquad (1)$$

tion throughout the quenching and work-up sequence. Thus, the recovered ethyl crotonate represents a true kinetic product of the protonation reaction.

Using a similar procedure, we examined the behavior of several other α,β-unsaturated esters with the results shown in the table. In each case, the predominant quenching product is the non-conjugated ester. The procedure thus provides a simple method for the conversion of α,β-unsaturated esters into the corresponding β,γ-unsaturated esters. The result obtained with methyl 2-butynoate is especially noteworthy. Quenching of the anion derived from this ester provides a simple synthesis of the allenic ester, methyl 2,3-butadienoate (eq. 2).

$$CH_3C{\equiv}C\text{-}CO_2Me \xrightarrow{\text{LiICA}} \xrightarrow{H_3O^+} CH_2{=}C{=}CH\text{-}CO_2Me \qquad (2)$$

60%

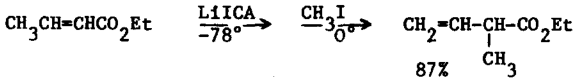
TABLE: Results of Quenching Experiments of Unsaturated Ester Enolates

Ester	Conjugated Ester, %[a]	Non-Conjugated Ester, %[b]
Ethyl crotonate	13	87
Ethyl 3-methyl-2-butenoate	19	81
Ethyl 2-hexenoate	12	88
Methyl 2-butynoate	<0.5	60[c]

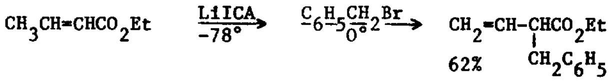
[a] Determined by glpc analysis using internal standards. [b] Products were isolated by preparative glpc and exhibited satisfactory spectral properties. [c] Reaction solution was 0.25M in starting ester. Reaction run at 0.5M concentration produced 40% of the non-conjugated ester.

Solutions of the lithium enolate of ethyl crotonate undergo complete self-condensation after 10 hours at room temperature; however, they are stable indefinitely at -78°, providing the first opportunity to study in detail the chemistry of an unsaturated ester enolate.

Alkylation of the enolate solutions with methyl iodide (eq. 3) or with benzyl bromide (eq. 4) furnishes the corresponding alkylated non-conjugated esters. Apparently in alkylation, as in protonation, the α carbon of unsaturated ester enolates is the center of greatest reactivity.

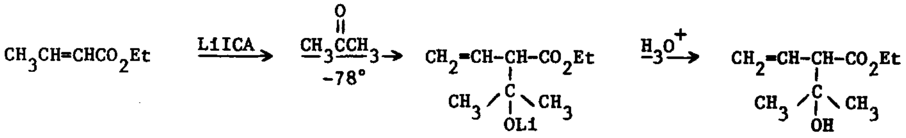


$$\mathrm{CH_3CH{=}CHCO_2Et} \xrightarrow[-78^\circ]{\mathrm{LiICA}} \xrightarrow[0^\circ]{\mathrm{CH_3I}} \underset{87\%}{\mathrm{CH_2{=}CH{-}\underset{\displaystyle CH_3}{CH}{-}CO_2Et}} \qquad (3)$$



$$\mathrm{CH_3CH{=}CHCO_2Et} \xrightarrow[-78^\circ]{\mathrm{LiICA}} \xrightarrow[0^\circ]{\mathrm{C_6H_5CH_2Br}} \underset{62\%}{\mathrm{CH_2{=}CH{-}\underset{\displaystyle CH_2C_6H_5}{CH}CO_2Et}} \qquad (4)$$

Addition of acetone to the enolate of ethyl crotonate produces the non-conjugated β-hydroxy ester, ethyl 3-hydroxy-2-vinylisovalerate (eq. 5) in excellent yield. No trace of the isomeric



$$\mathrm{CH_3CH{=}CHCO_2Et} \xrightarrow{\mathrm{LiICA}} \xrightarrow[-78^\circ]{\mathrm{CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_3}} \mathrm{CH_2{=}CH{-}\underset{\displaystyle CH_3{\diagup}\underset{\displaystyle OLi}{C}{\diagdown}CH_3}{CH}{-}CO_2Et} \xrightarrow{\mathrm{H_3O^+}} \mathrm{CH_2{=}CH{-}\underset{\displaystyle CH_3{\diagup}\underset{\displaystyle OH}{C}{\diagdown}CH_3}{CH}{-}CO_2Et} \qquad (5)$$

I 78%

δ-hydroxy ester was observed. In contrast, the Reformatsky reaction of γ-bromocrotonate with ketones provides only moderate yields of β-hydroxy esters[8]. In some cases, a mixture of both the β-hydroxy and the δ-hydroxy ester has been reported[9]. It has been suggested[8] that the δ-hydroxy-ester is formed by isomerization of the zinc salt analogous to I under the conditions of the Reformatsky reaction. Unfortunately, we were unable to observe this with the lithium salt. While I remains stable at -78°, it undergoes rapid condensation at higher temperatures (presumably by dissociation to the ester enolate and acetone). Under no conditions did quenching produce the δ-hydroxy ester.

It is evident that the ability to generate enolate anions from unsaturated esters can be of major utility in organic synthesis. We are currently exploring the range of this utility with a variety of unsaturated esters.

Acknowledgement

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