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THE MICHAEL REACTION OF SIMPLE ESTER ENOLATES TO α,β-UNSATURATED ESTERS

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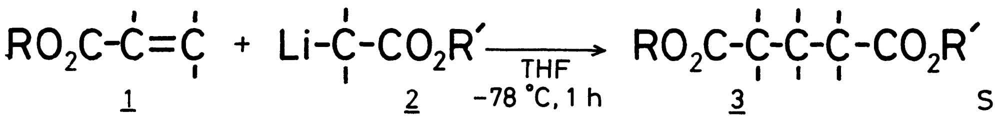
Lithium enolates generated from simple esters are found readily to add to α,β-unsaturated esters at -78 °C and glutarates are obtained in high yield.

The Michael reaction of active methylene compounds such as malonates to α,β-unsaturated esters (1) followed by hydrolysis and decarboxylation is a classical method for the synthesis of glutaric acid derivatives.1) Though the addition of enolate anions generated from simple mono-esters gives the same products in more simplified manner, very few report appeared concerning this useful reaction.2, 3) Previously, Schlessinger et al. reported that the addition of a lithium enolate to γ-butenolide yielded the conjugated addition product.3) Further investigation, however, did not appear. In the present communication, we wish to describe the useful, but uninvestigated, Michael reaction of ester enolates (2) to α,β-unsaturated esters (1) to give glutarates (3).

Thus, lithium enolates (2) were generated from the corresponding esters according to the standard method —— by the reaction of lithium diisopropylamide (LDA) with esters in tetrahydrofuran at -78 °C. Then, 2 were allowed to react with various α,β-unsaturated esters (1) at -78 °C for 1 h, and the results were summarized in Scheme 1 and Table 1.

Generally, β-monosubstituted unsaturated esters gave the 1,4-addition products in high yield with satisfactory purity. Under the present reaction conditions, the ester condensation, an expected side reaction, could be suppressed to the minimum amount, and, often, the crude products were pure enough. Notably, the addition to diethyl ethoxymethylenemalonate gave the compound (4) retaining ethoxy group, and no unsaturated ester was detected. Also observed was that the anion derived from ethyl iso-butyrate readily reacted and a new quarternary carbon was generated.

Though β-monosubstituted acrylates gave satisfactory results, β,β-disubstituted acrylates such as ethyl 3-ethyl-2-pentenoate or ethoxycarbonylmethylenecyclohexane did not afford the Michael adducts and the unsaturated esters were recover-



$$\underset{\underline{1}}{\mathrm{RO_2C\text{-}\overset{|}{C}{=}\overset{|}{\underset{|}{C}}}} + \underset{\underline{2}}{\mathrm{Li\text{-}\overset{|}{\underset{|}{C}}\text{-}CO_2R'}} \xrightarrow[-78\,^{\circ}\mathrm{C},\ 1\ \mathrm{h}]{\mathrm{THF}} \underset{\underline{3}}{\mathrm{RO_2C\text{-}\overset{|}{\underset{|}{C}}\text{-}\overset{|}{\underset{|}{C}}\text{-}\overset{|}{\underset{|}{C}}\text{-}CO_2R'}}$$

Scheme 1.

Table 1. A Synthesis of Glutarates

1	2	Yield/%[a]	Purity/%[b]
$CH_3CO_2t\text{-}Bu$	(E)-$CH_3CH{=}CHCO_2C_2H_5$	89	>95
	(E)-n-$C_8H_{17}CH{=}CHCO_2C_2H_5$	92	>95
	(Z)-$H_5C_2O_2CCH{=}CHCO_2C_2H_5$	76	>95
	$H_5C_2OCH{=}C(CO_2C_2H_5)_2$	89[c]	>95
$C_2H_5CO_2C_2H_5$	(E)-$CH_3CH{=}CHCO_2C_2H_5$	96[d]	95
	$CH_2{=}CHCO_2C_2H_5$	71	>95
	(E)-$H_5C_2O_2CCH{=}CHCO_2C_2H_5$	83[e]	95
$Me_2CHCO_2C_2H_5$	$CH_2{=}C(CH_3)CO_2C_2H_5$	79	92
	(E)-$CH_3CH{=}CHCO_2C_2H_5$	95	>95
	(Z)-$H_5C_2O_2CCH{=}CHCO_2C_2H_5$	93	>95

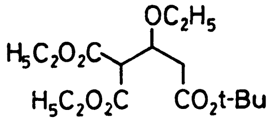
a) The reaction was carried out in 1-3 mmol scale using 1.2-2.0 molar excess of lithium enolates, and the products were isolated by short-path distillation to give compounds with satisfactory spectral data (^{1}H-NMR, ^{13}C-NMR, IR).

b) Determined by GLC (OV-1).

c) Isolated by chromatography on silica gel.

d) A 2.5:1 mixture of diastereomers determined by ^{13}C-NMR.

e) A 1:1 mixture of diastereomers determined by ^{13}C-NMR.



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ed. Acrylate itself reacted with rather hindered nucleophiles smoothly. Addition of the lithium enolate of t-butyl acetate to methyl acrylate, however, resulted in formation of considerable amount of undistillable polymer. The use of ethyl ester did not improve the process.

A typical procedure is described for the synthesis of t-butyl ethyl 3-methylglutarate: Under a nitrogen atomosphere, lithium diisopropylamide (4 mmol) was prepared from diisopropyl amine (404 mg, 4 mmol) and butyllithium-hexane solution (2.56 ml, 4 mmol) in tetrahydrofuran (THF, 4 ml) at -78 °C. To the mixture was added a THF (2.5 ml) solution of t-butyl acetate (464 mg, 4 mmol) at the same temperature. After 30 min´s stirring, ethyl crotonate (342 mg, 3 mmol) in THF (2.5 ml) was added and the resulted solution was stirred for further 1 h. After a usual workup, t-butyl ethyl 3-methylglutarate (614 mg, 89%) was isolated by short-path distillation, Bp 100 °C/1 mmHg (bath temp). ^{1}H-NMR ($CDCl_3$) δ 1.01 (3H, d, J=6 Hz), 1.25 (3H, t, J=7 Hz), 1.45 (9H, s), 2.0-2.6 (5H, m), 4.13 (2H, q, J=7 Hz). IR (neat) 1730 cm^{-1}. ^{13}C-NMR ($CDCl_3$) δ 14.2, 19.7, 27.7, 28.1, 40.9, 42.1, 60.1, 80.1, 171.4, 172.1.

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