

α -CARBALKOXYLATIONS OF CARBOXYLIC ACIDS. A GENERAL SYNTHETIC ROUTE TO MONOESTERS OF MALONIC ACIDS.

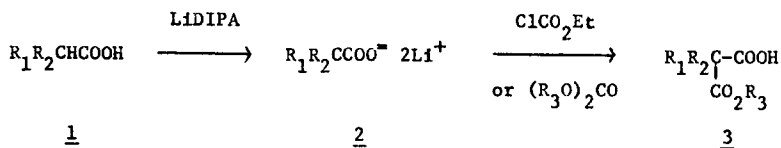
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Treatment of α -anions of carboxylic acids with various electrophilic reagents has been utilized to prepare α -alkylated carboxylic acids (1), β -hydroxy acids (2), α -alkylhydracrylic acids (3), β -keto acids (4), aldehydes (5), nitroalkanes (5), and the monomethylester of adamantane-2,2-dicarboxylic acid (6). The carboxylations of α -anions of esters have recently been reported to yield monoesters of malonic acid (7).

We wish to report a simple, high-yield conversion of acyclic and alicyclic carboxylic acids 1 into monoesters of malonic acid 3. The α -anions 2 (prepared by treatment of 1 with lithium diisopropylamide, LiDIPA) on treatment with ethyl chloroformate or diethyl or dimethyl carbonate readily lead to 3. This procedure utilizes the carboxylic acid group directly and obviates the necessity of converting the acid into the ester functional group (7).



This procedure has been successfully applied to the synthesis of unsubstituted and mono- and disubstituted monoesters 3. The results of this study are tabulated in Table I.

In all of the cases reported in Table I the best overall conversions are obtained from carboxylic acids which contain only one α -hydrogen. Lower yields of 3 are obtained when the α -anion 2 is unsubstituted or disubstituted. Presumably in these latter cases side reactions such as abstraction of a proton from the product 3 by the α -anion 2 would serve to lower the product yields as has been previously noted in other reactions (5). In the cases of the carboxylation of

TABLE I
HALF-ACID MALONATE ESTERS PREPARED FROM α -ANIONS OF CARBOXYLIC ACIDS

CARBOXYLIC ACID <u>1</u> ^a		CARBALKOXYLATION	PRODUCT <u>3</u> ^b		% YIELD
R ₁	R ₂	AGENT	R ₁	R ₂	
H	H	ClCO ₂ Et	H	H	50
CH ₃	H	ClCO ₂ Et	CH ₃	H	61
∅	H	ClCO ₂ Et	∅	H ^c	63
∅	H	(EtO) ₂ CO	∅	H	46
CH ₃	CH ₃	ClCO ₂ Et	CH ₃	CH ₃	85
-(CH ₂) ₃ ⁻		ClCO ₂ Et	-(CH ₂) ₃ ⁻		74
-(CH ₂) ₄ ⁻		ClCO ₂ Et	-(CH ₂) ₄ ⁻		86
-(CH ₂) ₅ ⁻		ClCO ₂ Et	-(CH ₂) ₅ ⁻		88
-(CH ₂) ₅ ⁻		(EtO) ₂ CO	-(CH ₂) ₅ ^{-d}		75
-(CH ₂) ₅ ⁻		(MeO) ₂ CO	-(CH ₂) ₅ ⁻		73

^a **General Procedure.** To a solution of 2.02 g (20 mmol) of diisopropylamine in 50 ml of anhydrous THF (nitrogen atmosphere, -40°C) was added 10 ml of n-butyllithium (2.0 M in hexane). The mixture was stirred for 15 min and 10 mmol of the carboxylic acid was added. The mixture was then heated to 50°C for 1 hr. The mixture was cooled to -70°C and 10 mmol of ethyl chloroformate or dialkyl carbonate was added (in the case of ethyl chloroformate a 20°C temperature rise was noted). The solution was stirred for 20 min and then poured over 100 g of ice and 30 mmol of hydrochloric acid. The mixture was extracted with four 25 ml portions of ether and the ethereal layer was concentrated to produce an oil which was distilled under reduced pressure or a solid which was recrystallized. All compounds had nmr and ir spectra consistent with their structure. All new compounds gave analytical results consistent with their percentage composition.

^b R₃ = Et except in the last entry of the Table where R₃ = Me.

^c This product could also be prepared in a 90% yield by treatment of lithio ethyl phenylacetate (prepared in THF from LiDIPA) with carbon dioxide (7).

^d This product could be prepared in a 90% yield by treatment of lithio ethyl cyclohexanecarboxylate with carbon dioxide (7).

α -anions of esters, it has been found that the bulkier the ester function and the lower the reaction temperature the higher the yield of the carboxylated product (7,8).

For the reactions tabulated in the Table it has been observed that the α -anion of acetic acid and the α -anions bearing one substituent (CH_3 , \emptyset) react smoothly with ethyl chloroformate at -70°C but more slowly with diethyl carbonate. In the case of the α -anion 2 ($\text{R}_1 = \emptyset$, $\text{R}_2 = \text{H}$) treatment with ethyl chloroformate (-70°C) gives a 63% yield of the half-ester 3 ($\text{R}_1 = \emptyset$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{Et}$) while treatment of this same α -anion with diethyl carbonate (-70°C) gives a 46% yield of this product. It might also be noted that the α -anion of ethyl phenylacetate (THF solution) on treatment with carbon dioxide gives a 90% yield of 3 ($\text{R}_1 = \emptyset$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{Et}$). The α -anions bearing disubstitution react readily with both electrophiles. Perhaps on treatment of the α -anions of 2 with diethyl carbonate the ethoxide ion which is liberated during the reaction can abstract the α -proton from the product half-ester if one is available. The resulting α -anion might suffer further carbalkoxylation thus lowering the desired product yield.

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