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α-CARBOXYLATION OF ESTERS

S. Reiffers, Hans Wynberg and J. Strating
Department of Organic Chemistry, The University,
Zernikelaan, Groningen, The Netherlands

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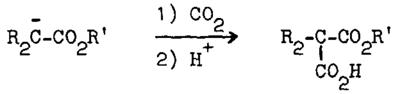
A new method for the formation[*] and carboxylation of α-anions of esters should be of importance for an attractive route to malonic acid derivatives.

In a previous communication[1] we drew attention to the very easy conversion of methyl adamantane-2-carboxylate via its α-lithium salt into the monomethyl ester of adamantane-2,2-dicarboxylic acid (yield 88%, now improved to 97%).



$$R_2\overset{-}{C}\text{-}CO_2R' \xrightarrow[2)\ H^+]{1)\ CO_2} R_2\text{-}\underset{\substack{|\\ CO_2H}}{C}\text{-}CO_2R'$$

We wish to report the scope of the reaction and claim that this synthesis of malonic acid derivatives is a general and efficient one, as is clearly demonstrated by the examples given and collected in the table.

As a welcome benefit the method leads to the monoesters of malonic acid derivatives, compounds which are otherwise difficultly accessible.

The new synthetic route to malonic acid derivatives directly from carboxylic esters permits the preparation of a number of malonic acids which are not, or only laboriously, available in another way (e.g. undecamethylene malonic acid).

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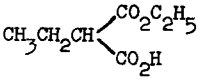
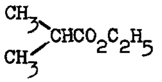
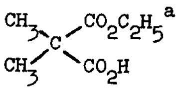
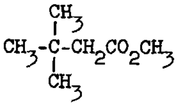
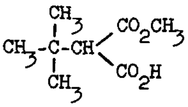
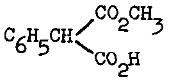
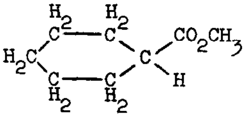
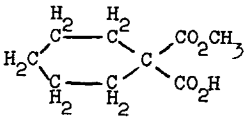
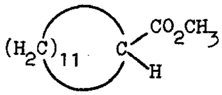
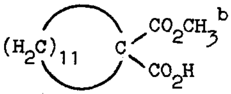
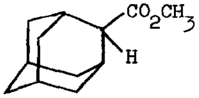
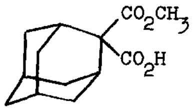
[*] Except for the indication given in our previous paper.[1] See also very recently M.W. Rathke and A. Lindert.[2] In contrast to the reaction mentioned above, the method of Hauser et al[3] (i.e. anion formation with $NaNH_2$ in liquid NH_3) gives generally poor results.

Carboxylic ester	Reaction temp. (°C)	Monoester of corresponding Malonic acid	Yield (%)
$CH_3CH_2CH_2CO_2C_2H_5$ (I)	-15	 $CH_3CH_2CH(CO_2C_2H_5)(CO_2H)$ (Ia)	27 + condensation product
	-70	" (Ia)	52 + " "
 $(CH_3)_2CHCO_2C_2H_5$ (II)	-15	 $(CH_3)_2C(CO_2C_2H_5)(CO_2H)$ [a] (IIa)	90
 $CH_3C(CH_3)_2CH_2CO_2CH_3$ (III)	-15	 $CH_3C(CH_3)_2CH(CO_2CH_3)(CO_2H)$ (IIIa)	84
$C_6H_5CH_2CO_2CH_3$ (IV)	-15	 $C_6H_5CH(CO_2CH_3)(CO_2H)$ (IVa)	59 + 40% starting material 98 (calc. on used starting material)
 (V)	-15	 (Va)	97
 (VI)	-10	 b (VIa)	94
 (VII)	-10	 (VIIa)	97

a. Identified as dimethyl ester; b. Isolation directly from the acidified mixture (see gen. proc.) because if soapy character of the salts.

The best results are obtained with anions of carboxylic esters that are rather severely crowded around the anionic carbon atom.

This center can still interact with carbon dioxide but not with the ester unit of the more voluminous starting material.

The less sterically hindered ethyl n-butyrate gives the poorest result as a consequence of ester condensation (ethyl 2-ethyl-3-ketohexanoate could be isolated).

It may be possible to improve the yield of this and analogous cases by using other esters e.g. the tertiary butyl esters, thus introducing additional steric hindrance in order to minimize attack of the anion on the carbonyl group of a second molecule of starting material. This view is supported by the observation of Rathke and Lindert[2] that tert. butyl acetate gives a higher yield of α-alkylated product than ethyl acetate.

GENERAL PROCEDURE

To a stirred solution of diisopropylamine (3 g; 30 mmole) in tetrahydrofuran (30 ml) was added (N_2 atmosphere, -10 to -15°C) 15 ml of 2N n-butyllithium in hexane. After 15 min. this mixture was dropwise (in 0.5 h.) provided with a solution of 25.8 mmoles of ester in THF (20 ml) and then a fast stream of CO_2 was passed for 10 min. Water was added, the mixture neutralized with 10% HCl at 0° and then extracted with chloroform. The chloroform layer was shaken with $NaHCO_3$ solution, these alkaline solutions acidified (0°) and then extracted with ether. Evaporation of the solvent gave the desired compounds[*] in an almost pure state as was determined by titration (phenolphtalein).

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[*] The new compounds (IIIa and VIa) gave satisfactory elemental analyses. The IR and NMR spectra were in accordance with the expected structures. The physical constants of known compounds agreed well with those mentioned in litterature.[4-8]

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8. Ref. 1.