

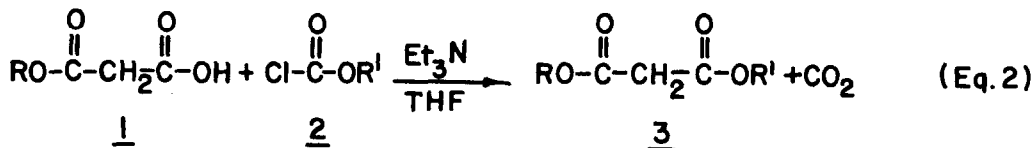
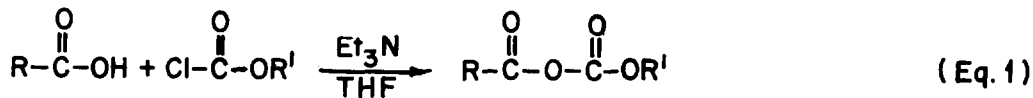
A MILD, RAPID AND CONVENIENT ESTERIFICATION OF HALF  
ESTERS OF MALONIC ACID

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Summary. A new method for the esterification of half esters of malonic acid with chloroformates is described. The reaction proceeds via the mixed anhydride followed by spontaneous decarboxylation.

The reaction of carboxylic acids with chloroformates and triethylamine in THF serves as a standard procedure for the formation of mixed anhydrides, reactive intermediates in acylation reactions (Eq. 1).<sup>2</sup> We observed, however, that when half esters of malonic acid (1) were treated with equimolar amounts of various chloroformates (2) and triethylamine under the standard conditions, decarboxylation occurred and mixed diesters of malonic acid (3) were obtained in nearly quantitative yields (Eq. 2). Although a number of methods are available for the preparation of certain mixed diesters of malonic acid,<sup>3</sup> we feel that our route is more general, milder, more convenient, and is therefore of synthetic utility.<sup>4</sup>

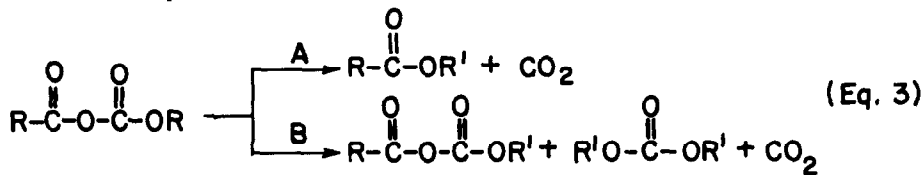


The following procedure is representative. To 1.18 g (10.0 mmol) of monomethyl malonate (1a) in 30 ml of dry THF was added 1.39 ml (1 eq) of triethylamine. To this mixture 0.96 ml (1 eq) of ethyl chloroformate (2b) in THF was added at 4 °C. The reaction mixture was then stirred for 30 min during which time the loss of CO<sub>2</sub> was complete. Filtration of the colorless precipitate (triethylammonium chloride) and concentration at r.t. gave 1.448 g (99%) of methyl ethyl malonate (3b).

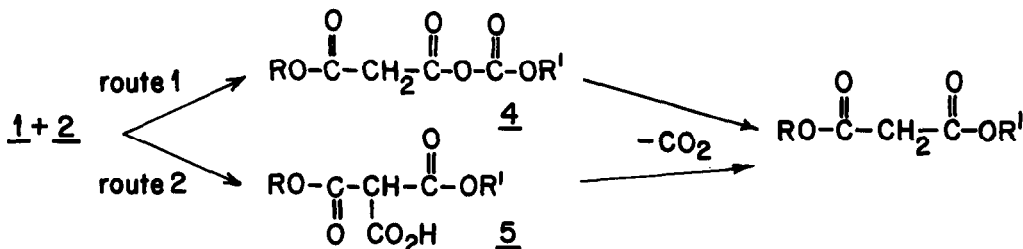
**Table 1.** Preparation of mixed diesters of malonic acid (3) from malonic acid half esters (1) and chloroformates (2).

Entries	R	R'	Isolated Yield of <u>3</u> in %
a	Me	Me	95
b	Me	CH <sub>2</sub> Me	99
c	Me	CH <sub>2</sub> Ph	99
d	Me	n-Bu	100
e	Me	i-Bu	95
f	CH <sub>2</sub> Me	Me	95
g	CH <sub>2</sub> Me	CH <sub>2</sub> Me	95
h	CH <sub>2</sub> Me	CH <sub>2</sub> Ph	98
i	CH <sub>2</sub> Me	n-Bu	97
j	CH <sub>2</sub> Me	i-Bu	93
k	CH <sub>2</sub> Ph	Me	100
l	CH <sub>2</sub> Ph	CH <sub>2</sub> Me	98
m	CH <sub>2</sub> Ph	CH <sub>2</sub> Ph	99
n	CH <sub>2</sub> Ph	n-Bu	100
o	CH <sub>2</sub> Ph	i-Bu	100

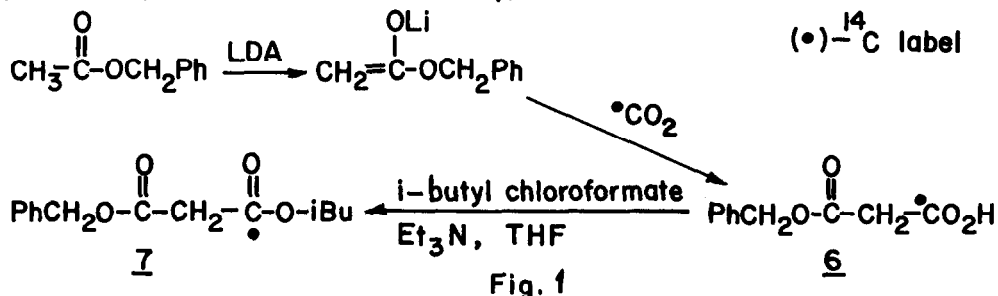
Thermal decomposition of ordinary mixed carboxylic carbonic anhydrides at 150-175 °C by two concurrent paths, A and B, yielding ester by path A and the symmetrical anhydride and dialkyl carbonate by path B (Eq. 3) has been reported.<sup>5</sup> It recently has been shown<sup>6</sup> that addition of a catalytic amount of 4-dimethylaminopyridine is exceedingly effective in the conversion of mixed anhydrides into the corresponding esters without the formation of symmetrical anhydrides in most carboxylic acids. Domagala<sup>7</sup> has reported that mixed anhydrides from  $\alpha$ -keto-acids and alkyl chloroformates undergo spontaneous decarboxylation even at -30 °C (Eq. 4). The ease of decarboxylation in the latter case was attributed to the presence of the  $\alpha$ -keto group but no mechanistic explanation was offered.



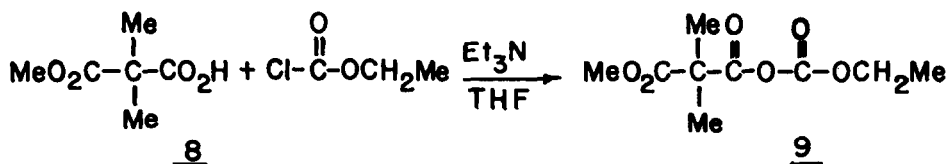
It was therefore of interest to investigate whether in the case of the formation of mixed diesters of malonic acid the reaction between (1) and (2) proceeded via the mixed anhydride (4) which was activated by the  $\beta$ -keto group and underwent spontaneous decarboxylation (route 1), or through the C-acylated bis- $\beta$ -ketoacid intermediate (5) which would undergo spontaneous decarboxylation (route 2).



Although C-acylation of (1) in the presence of only 1 eq of  $\text{Et}_3\text{N}$  is difficult to entertain, because the carboxylic hydrogen is much more acidic than the methylene hydrogens of malonate,<sup>8</sup> it seemed desirable to make a  $^{14}\text{C}$  tracer study in order to exclude this possibility. The reactions employed are summarized in Fig. 1. For convenience in product purification, the reaction was carried out on  $[1-^{14}\text{C}]$ -benzylmalonic acid (6), synthesised for this purpose from benzyl acetate, which was deprotonated by lithium diisopropyl amide and the anion quenched with commercially available  $^{14}\text{C}$ -carbon dioxide. The specifically labelled monobenzyl malonate (specific activity  $2.62 \cdot 10^6$  dpm/mmol  $\pm 3\%$ ) was reacted in the usual way with isobutyl chloroformate and the evolved  $\text{CO}_2$  trapped in NaOH solution. The resulting benzyl isobutyl malonate was isolated and purified by two successive distillations. Scintillation counting<sup>9</sup> showed that its specific activity was  $2.60 \cdot 10^6$  dpm/mmol  $\pm 3\%$ . The trapped carbon dioxide was virtually inactive (less than 1% of total activity).



The labelling experiment conclusively rules out the possibility of C-acylation and supports the mixed anhydride route 2. It seems that the ready decarboxylation of the latter is facilitated by the presence of the labile malonate methylene hydrogens. Thus, when those hydrogens were replaced by methyl groups, as in dimethyl monomethyl malonate (8), the latter reacted with ethyl chloroformate and triethylamine to give the mixed anhydride (9), which did not undergo decarboxylation even at elevated temperatures.<sup>10</sup> It is doubtful that the failure of (9) to decarboxylate is due to steric reasons, as it was shown that the general reaction (Eq. 2) proceeds equally well when the sterically hindered 2,6-dimethylpyridine or proton sponge were used instead of triethylamine.



An explanation consistent with the above data is deprotonation of the mixed anhydride (4) by the amine, followed by its dissociation to the ketene (10) and the monoalkyl carbonate (11). The latter is known to decarboxylate spontaneously and the remaining alkoxy anion  $R'O^{(-)}$  may then react with (10) to give the mixed malonate diester (3) (Fig. 2).

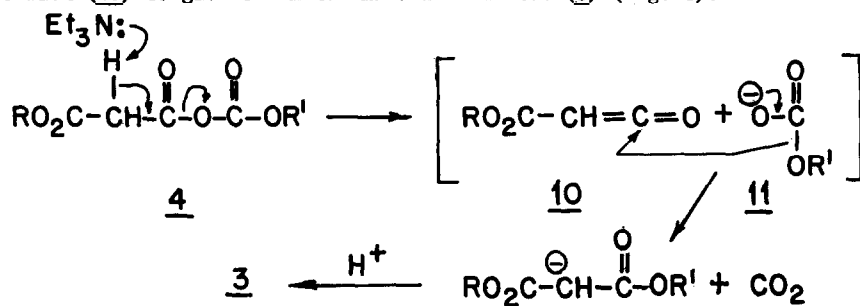


Fig. 2

Further studies aimed at clarifying this mechanism are currently underway in our laboratory.

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#### References and Notes

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4. All products were more than 95% pure as determined by  $^1\text{H}$  NMR. Satisfactory analytical data were obtained for new compounds.
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8. E.g.,  $\text{pK}_a(\text{CH}_3\text{COOH}) = 4.76$  compared with  $\text{pK}_a(\text{CH}_2(\text{COOCH}_3)_2) = 13.0$ .
9. Radioactive counting involved the use of a Packard liquid scintillation counter, model 526, using  $[^{14}\text{C}]$ -hexadecane as internal standard.
10. (8) was prepared by partial hydrolysis of  $\alpha,\alpha$ -dimethyl dimethylmalonate. (9) had a characteristic IR,  $\delta_{\text{max}}(\text{CHCl}_3)$  1820, 1740  $\text{cm}^{-1}$ , which did not change when the sample was kept for 2 hr at 50  $^\circ\text{C}$  and for an additional 1 hr at 100  $^\circ\text{C}$ .

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