

TRANSFER OF THE AZIDO FUNCTION FROM DIPHENYLPHOSPHORYL AZIDE
TO MALONIC ACID HALF ESTERS

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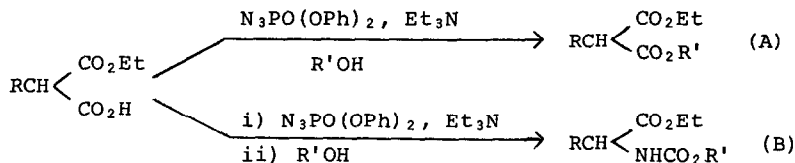
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(Received in Japan 19 April 1973; received in UK for publication 18 May 1973)

We have recently reported¹ a modified Curtius reaction involving the use of diphenylphosphoryl azide (DPPA) and triethylamine (TEA), by which carboxylic acids smoothly and directly afford urethanes in the presence of hydroxyl components.

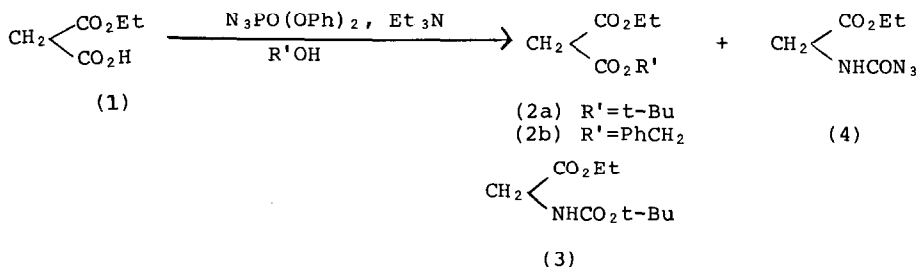
Application of the method to the synthesis of α -amino acids from malonic acid half esters reveals that either esterification (A) or the Curtius reaction (B) takes place depending on the reaction procedure (one or two-step process) in this particular case.



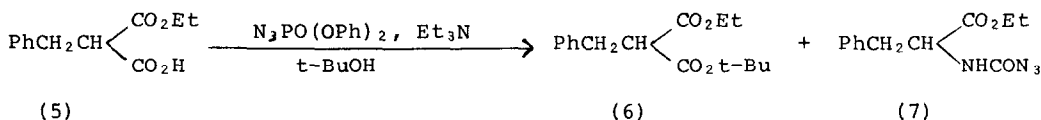
First, ethyl hydrogen malonate (1) was refluxed with an equimolecular mixture of DPPA and TEA in tert.-butyl alcohol for 23 hr. After the ordinary acid and alkali work-ups, tert.-butyl ethyl malonate² (2a) was isolated in 54% yield from the neutral fraction. Surprisingly, however, the expected N-tert.-

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butyloxycarbonylglycine ethyl ester (3) could not be found. Only a trace of another Curtius-type product N-azidoformylglycine ethyl ester (4) was detected by the ir spectrum. In the presence of benzyl alcohol, benzyl ethyl malonate (2b) was obtained in 53% yield, but again there was no or little evidence for the formation of any expected α -amino acid derivatives.

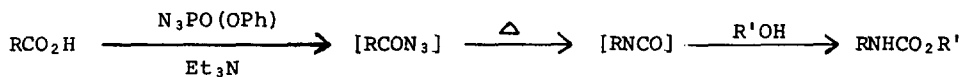


Similarly ethyl hydrogen benzylmalonate (5) afforded tert.-butyl ethyl benzylmalonate (6) in 53% yield upon refluxing with a mixture of DPPA and TEA in tert.-butyl alcohol. A trace of the Curtius-type product N-azidoformylphenylalanine ethyl ester (7) was found.



The ester formation reaction was observed on the similar treatment of cyanoacetic acid and malonmonoamide, the former giving tert.-butyl cyanoacetate in 60% yield and the latter giving tert.-butyloxycarbonylacetamide in 23% yield. Treatment of cyanoacetic acid with TEA but without DPPA in tert.-butyl alcohol resulted in a recovery of cyanoacetic acid, proving the participation of DPPA in the esterification.

The modified Curtius reaction by DPPA is generally carried out¹ in the co-existence of hydroxyl components. However, the overall reaction will proceed as follows: (i) transfer of the azido function from DPPA to a carboxylic acid, (ii) thermal rearrangement of the resultant carboxylic acid azide to the isocyanate, and (iii) addition of a hydroxyl component to the isocyanate, giving the urethane.³



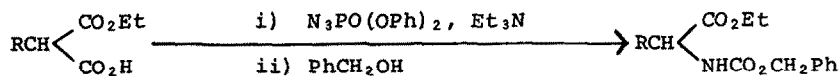
Therefore, it seemed not necessary to add hydroxyl components in the initial stage of the reaction. Thus ethyl hydrogen benzylmalonate (5) was first refluxed in benzene with an equimolecular mixture of DPPA and TEA for 1 hr. A slight excess of benzyl alcohol was then added to the reaction mixture, which was refluxed for 17 hr. A striking change of the reaction course was observed, and the desired Curtius-type product N-benzyloxycarbonylphenylalanine ethyl ester was produced in 79% yield.

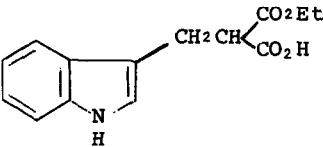
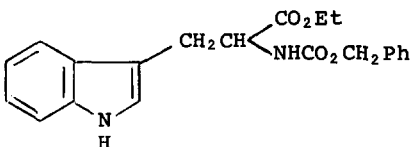
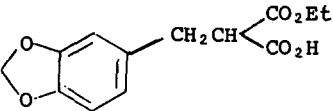
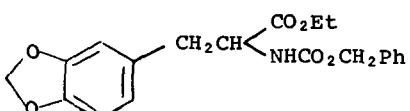
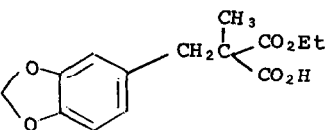
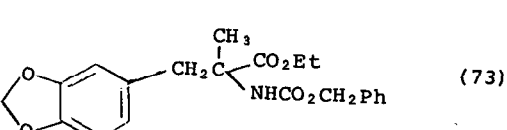
The similar two-in-one-reaction procedure was successfully applied to some ethyl hydrogen malonates as shown in Table.

As these N-benzyloxycarbonyl- α -amino acid ethyl esters may be easily converted to α -amino acids, the above process will provide a new synthesis of α -amino acids.

REFERENCES

- 1) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 94, 6203 (1972).
- 2) All compounds have been characterized satisfactorily by elemental and spectral analysis.
- 3) For a review of the Curtius reaction, see C.A. Buehler and D.E. Pearson, "Survey of Organic Syntheses", Wiley Interscience, New York, N.Y., 1970, p. 498, and references therein.

Table, Preparation of α -Amino Acid Derivatives

Malonic Acid Half Esters	Product (Yield, %)
$\text{CH}_2 \begin{array}{l} \text{CO}_2\text{Et} \\ \text{CO}_2\text{H} \end{array}$	$\text{CH}_2 \begin{array}{l} \text{CO}_2\text{Et} \\ \text{NHCO}_2\text{CH}_2\text{Ph} \end{array}$ (27)
$(\text{CH}_3)_2\text{CHCH} \begin{array}{l} \text{CO}_2\text{Et} \\ \text{CO}_2\text{H} \end{array}$	$(\text{CH}_3)_2\text{CHCH} \begin{array}{l} \text{CO}_2\text{Et} \\ \text{NHCO}_2\text{CH}_2\text{Ph} \end{array}$ (74)
	$(\text{CH}_3)_2\text{CHCH} \begin{array}{l} \text{CO}_2\text{Et} \\ \text{NHCON}_3 \end{array}$ (9)
$\text{PhCH}_2\text{CH} \begin{array}{l} \text{CO}_2\text{Et} \\ \text{CO}_2\text{H} \end{array}$	$\text{PhCH}_2\text{CH} \begin{array}{l} \text{CO}_2\text{Et} \\ \text{NHCO}_2\text{CH}_2\text{Ph} \end{array}$ (79)
	 (65)
	 (78)
	$\left(\text{Benzofuran ring with } \begin{array}{l} \text{CH}_2\text{CHCO}_2\text{Et} \\ \text{NH} \end{array} \right)_2 \text{C=O}$ (5)
	 (73)