Synthesis of Depsipeptides by Catalysis of Active Esters with 1-Hydroxybenzotriazole

By YAKIR S. KLAUSNER* and MICHAEL CHOREV
(*Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel*)

Summary Depsipeptides were prepared in 75—93% yields by the 1-hydroxybenzotriazole-catalysed alcoholysis of *N*-protected amino-acid active esters.

SEVERAL methods for the preparation of depsipeptides[1] are available, usually invoking a high degree of activation of the carboxy-component. König and Geiger have estab-

lished that 1-hydroxybenzotriazole is an efficient catalyst of peptide bond formation with either the dicyclohexylcarbodi-imide[2] or the active ester[3] methods.

TABLE

Active ester; excess/%		Hydroxy component[e]	Yield/%[a]	$[\alpha]_D^{24}$[b]
Z-L-Val-ONp	30	(A)	93	$-14°, c = 1$
Z-L-Phe-ONp	50	(A)	89	$+5·3°, c = 1·1$
Boc-L-Val-ONo	50	(B)	75[c]	$-45°, c = 1$
Z-L-Phe-OTcp	50	(C)	90[d]	$-44°, c = 1·1$
Boc-L-Ala-ONp	30	(D)	92[c]	$-32°, c = 1$
Boc-L-Val-ONo	50	(E)	82[c]	$-14°, c = 1·5$

[a] Oil, yield calculated on the basis of the hydroxy-component; purity was shown by t.l.c., elemental analysis, and n.m.r. spectroscopy. [b] Measured in dimethylformamide. [c] Purified by column chromatography (silica, CH_2Cl_2). [d] Purified by column chromatography (neutral alumina, CH_2Cl_2. [e] (A), ethyl DL-mandelate; (B), benzyl DL-lactate; (C), butyl glycollate; (D), methyl 3-hydroxypropionate; (E), ethyl DL-mandelyl glycinate.

Itoh *et al.* have recently found[4] that 6-chloro-1-*p*-chlorobenzenesulphonyloxybenzotriazole is of general use for the preparation of carboxylic acid esters. In all cases the highly reactive 1-hydroxybenzotriazole ester intermediates are formed.

We have subjected *p*-nitrophenyl,[5] *o*-nitrophenyl,[5,6] and 2,4,5-trichlorophenyl[7] esters of *N*-protected amino-acids to alcoholysis by suitably protected hydroxy-acids and hydroxyamino-acids, with 1-hydroxybenzotriazole as catalyst. Depsipeptides were obtained in good yield within 24—48 h. Noteworthy are the reactions involving highly hindered amino-acids and hydroxy-acids such as valine and mandelic acid (Table).

In order to acylate the hydroxy-component efficiently, reactions were carried out in dimethylformamide with a 30—50% excess of the active ester, in concentrations of 1—1·5M. *N*-Methylmorpholine[4] and the catalyst were added in a two-fold excess over the amount of active ester.

After 1—2 days the excess of the active ester was destroyed by 3-dimethylaminopropylamine[8] and the product was isolated in the usual manner.

(*Received, 15th October* 1975; *Com.* 1172.)

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