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A NOVEL METHOD FOR THE FACILE SYNTHESIS OF DEPSIPEPTIDES

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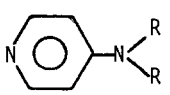
Summary: A one pot, high yield synthesis of depsipeptides is described involving room temperature condensation of hindered substrates (N-Boc amino acids and benzyl α-hydroxy esters) in the presence of DCC and a dialkylamino-pyridine. In this manner previously inaccessible depsipeptides were prepared.

We wish to report an improved and high yield method for the preparation of depsipeptides The method is based on the direct esterification of an N-protected amino acid with a carboxy protected hydroxy acid by means of N,N dicyclohexyl carbodiimide (DCC) in the presence of a 4-(N,N-dialkylamino)pyridine as a catalyst. 4-Aminopyridines have been found to be highly effective acylation catalysts, much superior to pyridine, especially in the esterification of hindered alcohols.[1] Recently the use of 4-(N,N-dimethylamino)pyridine (1a) and 4-pyrrolidinopyridine (1b) as catalysts for carbodiimide mediated esterifications was reported.[2]

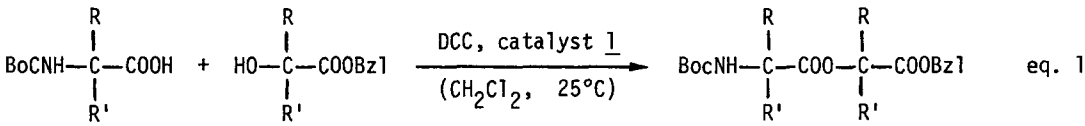


1a, R: Me

1b, R,R: $(CH_2)_4$

We found this method applicable for the synthesis of depsipeptides and vastly superior to methods employed previously for the preparation of depsipeptides namely: the benzene

sulphonyl chloride method,[3] the mixed anhydride method,[4] the acyl halide method,[3a,5] the carbonyl diimidazole (CDI) method,[6] the catalyzed active ester method,[7] and the DCC-pyridine method.[8] These methods suffer from several drawbacks such as poor yields (especially with hindered carboxy and hydroxy components), side reactions, racemization, prolonged reaction time, adherence to strictly anhydrous conditions, and the necessity to isolate intermediate activated acyl derivatives. In this communication we describe a one pot coupling of N^{α}Boc protected amino acids with the benzyl esters of α-hydroxy acid by means of DCC and catalyzed by 4-dialkylaminopyridine 1a or 1b according to eq. 1. Sometimes one equivalent of 1 was employed to speed up the reaction since the amine is washed away in the work-up. Amino and



R': H or CH_3 R: CH_3 or $CH(CH_3)_2$

hydroxy acids were chosen with increased steric hindrance around the formed ester bond. The depsipeptides obtained are listed in Table 1. Whereas the starting substrates are insoluble in nonpolar solvents the products 2-6 dissolve easily in hexane-ethyl acetate (9:1) indicative of their lipophilic nature.

Table I

Depsipeptides Obtained by Esterification (eq. 1) Using DCC and 1a or 1b at 25°C in CH_2Cl_2

Depsipeptide[(a)]		Reaction Time (hr)	% Yield[(b)]	m.p.
Boc Ala-LacOBzl	2	6	98	81-83 (81-83[9])
Boc D-Val-LacOBzl	3	6	94	oil
Boc D-Val-HiBOBzl	4	8	95	oil
Boc Aib-LacOBzl	5	8	90	oil
Boc Aib-HiBOBzl	6	11	92	oil

(a) Boc: t-butoxycarbonyl; Lac: L-lactic acid; OBzl: benzyl ester; Hib: α-hydroxy-isobutyric acid; Aib: α-aminoisobutyric acid.

(b) Of analytically pure material.

The advantages of the method described herein are: (a) mild reaction conditions (CH_2Cl_2, 25°C), so that labile protecting groups for other functional groups can be present, (b) short reaction times (6-11 hr), and (c) high yields even with sterically hindered carboxy and hydroxy components (e.g., depsipeptide 6, Table I). Our attempts to synthesize this depsipeptide (Boc Aib-HibOBzl) by one of the following methods: CDI,[6] catalyzed active ester[7b] and DCC-pyridine[8a] led, after 11 hr, to isolation of starting materials with only minor amounts of 6 present (by tlc).

Typical Procedure

To a solution of N-Boc amino acid (0.001 mol), an α-hydroxy acid benzyl ester[10] (0.001 mol) and 4-dialkylaminopyridine 1 (0.001 mol) in 15 ml CH_2Cl_2, a solution of DCC (0.0011 mol) in 5 ml CH_2Cl_2 was added. The reaction mixture was stirred at 25°C and followed by tlc (silica gel, chloroform or hexane: ethyl-acetate 4:1, using the ninhydrin test after exposure to HCl vapor). The N,N-dicyclohexyl urea (DCU) was filtered off and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate, cooled and DCU removed by filtration. The filtrate was washed with 1 M $KHSO_4$, water, 5% $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated to dryness in vacuo. The resulting oil was washed with petroleum ether and left several hours under high vacuum to afford analytically pure depsipeptides. All compounds showed the correct C, H, N analysis, consistent with nmr and ir spectra and tlc indicated only one component. The resulting depsipeptides were also characterized as the free acids obtained after removal of the benzyl ester protecting group by catalytic hydrogenation.

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