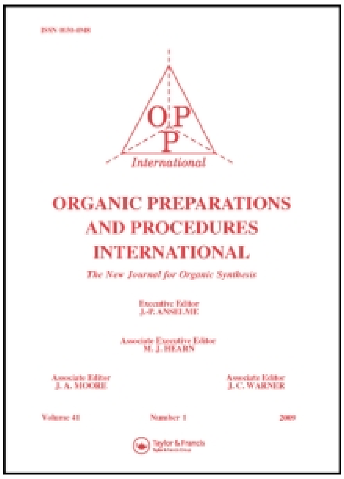

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THE SYNTHESIS OF HIGH PURITY N$^{\alpha}$-BENZYLOXYCARBONYL N$^{\varepsilon}$-*t*-BUTYLOXYCARBONYL-L-LYSINE

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OPPI BRIEFS

THE SYNTHESIS OF HIGH PURITY N^{α}-BENZYLOXYCARBONYL N^{ε}-t-BUTYLOXYCARBONYL-L-LYSINE

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(4/12/83)

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N^{α}-Benzyloxycarbonyl-N^{ε}-t-butyloxycarbonyl-L-lysine [Z-Lys(Boc)-OH] is a useful intermediate for peptide synthesis. Its preparation has been achieved either by t-butyloxycarbonylation of N^{α}-benzyloxycarbonyl-L-lysine[1-3] or by benzyloxycarbonylation of N^{ε}-t-butyloxycarbonyl-L-lysine.[3] The former route was preferred because the method using N^{ε}-t-butyloxycarbonyl-L-lysine has the danger of stripping the N^{ε}-t-butyloxycarbonyl group in the course of benzyloxycarbonylation. Recently, we prepared Z-Lys(Boc)-OH by the former method, but the purity of the product was not high as checked by hplc; it was always contaminated with several small peaks and was very difficult to purify (Fig. 1). One of the impurities is N^{α}-t-butyloxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysine [Boc-Lys(Z)-OH]. This reversely protected L-lysine will severely interfere with the selective deprotection of the desired compound. Hplc analysis showed the main impurity of N^{α}-benzyloxycarbonyl-L-lysine [(Z-Lys-OH)] to be N^{ε}-benzyloxycarbonyl-L-lysine [Lys(Z)-OH]. In the course of t-butyloxycarbonylation, basic copper (II) carbonate was added to prevent the reaction of the free α-amino group. The product was clean and showed a single peak on hplc (Fig. 2).

The purification of N^{α}-benzyloxycarbonyl-N^{ε}-t-butyloxycarbonyl-L-lysine was achieved through the (-)-ephedrine salt instead of the widely used dicyclohexylamine salt. The crude (-)-ephedrine salt was recrystallized from hot ethyl acetate (6 ml/gram of salt) to give very pure salt; the D-amino acid

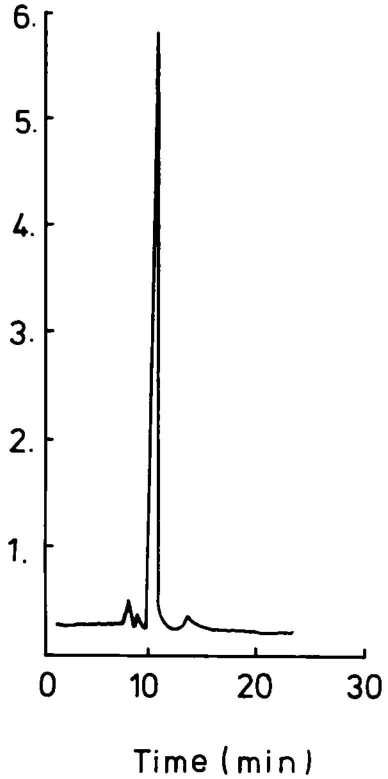

Fig. 1 Synthetic product without basic copper carbonate.

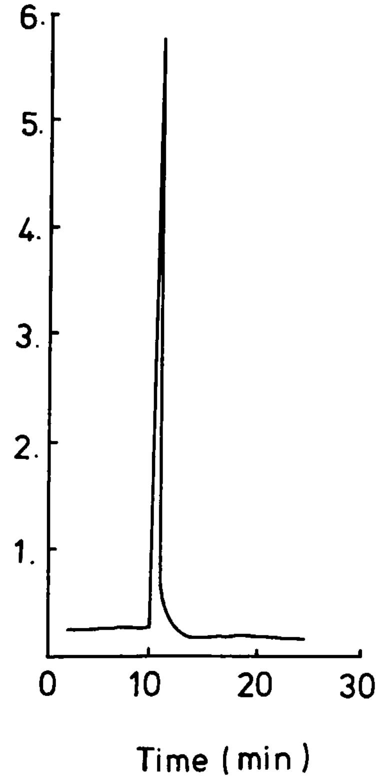

Fig. 2 Synthetic product with basic copper carbonate.

Sample: Z-$\overset{\text{Boc}}{\text{Lys}}$-OH; Column: μ-porasil 10 μ 4.5 x 250 mm; Eluent: CH_2Cl_2:EtOAc:AcOH 1.5 ml/min (75:25:1); Dectector: U.V. 260 nm, 0.2 AUFS.

derivative (if any), remained in solution.[5] The decomposition of the salt gave an extremely pure product which crystallized from *n*-hexane very readily. The purification of (-)-ephedrine salts is easily conducted and can be used in the purification of other protected amino acids.

EXPERIMENTAL SECTION

The *t*-butyloxycarbonylation was carried out by the method of Schnabel in the presence of basic copper (II) carbonate.[4] To a 300 ml three-necked flask fitted with a thermometer, a 100 ml dropping funnel filled with 75 ml of 4N NaOH, and a pH meter electrode, was added N^{α}-benzyloxycarbonyl-L-lysine (28 g, 0.1 mole), basic copper (II) carbonate (5.5 g, 25 mmoles), 25 ml H_2O and 25 ml dioxane. The flask was heated by means of a stirring hot plate and after the temperature of the reaction mixture had reached 45°, *t*-butyloxycarbonyl azide (17 ml, 0.11 mole) was added with stirring (CAUTION: *t*-Butyloxycarbonyl azide is dangerous and explosion may occur during handling; it may be replaced by di-*t*-butyldicarbonate). The temperature was kept within 45-50° and the pH maintained at ≈10 by the successive addition of 4N NaOH for 5-6 hours. When the pH no longer changed, the solution was cooled, 100 ml H_2O was added, and then transferred to a 500 ml separatory funnel. It was extracted with ether (50 ml x 3). The aqueous layer was acidified to Congo Red with solid citric acid and extracted with ethyl acetate (100 ml x 3). The combined ethyl acetate extract was washed with a 5% citric acid solution (50 ml x 3) and H_2O (50 ml x 3). After having been dried over anhydrous sodium sulfate, the ethyl acetate solution was added to a solution of 100 mmoles of (-)-ephedrine in 100 ml ether. The ephedrin salt crystallized upon standing at room temperature.

The salt weighed 47.4 g (87%), mp. 134-135°, $[\alpha]_D^{25}$ -10.6 (c 5, MeOH).

Anal. Calcd. for $C_{29}H_{43}N_3O_7$: C, 63.83; H, 7.94; N, 7.70.
Found: C, 63.48; H, 7.99; N, 7.71.

The free acid was obtained by dissolution of the salt in 1.01 equivalent of 0.1 N HCl and extracted by 200 ml of ethyl acetate. After evaporation of ethyl acetate, it crystallized within several days upon the trituration with *n*-hexane, mp. 63-64°, $[\alpha]_D^{25}$ -5.97 (c 1, MeOH), lit.[6] mp. 63.5-64.5° $[\alpha]_D^{25}$ -5.87 (c 1, MeOH).

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