A New Protective Group Suitable for Masking Specific Amino Groups during Peptide Synthesis

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The benzyloxycarbonyl (Z) group is considered to be stable under conditions necessary for the removal of a *t*-butyloxycarbonyl (Boc) group, and a combination of these two protective groups has been widely used in syntheses of lysine-peptides. For instance, N^{α}-Boc-N^{ε}-Z-lysine was used in the solid-phase synthesis of lysine-peptides.[1] However, on the repeated removal of Boc-groups with N HCl/AcOH or with trifluoroacetic acid, a partial cleavage of the ε-Z-groups has been noted, and it has been claimed that the resulting unprotected ε-amino groups cause the branching of the peptide bonds.[2] The present communication is concerned with the use of the diisopropylmethyloxycarbonyl (Dipmoc)-group as a new amino-protecting group. The introducing reagents were synthesized by keeping a mixture of diisopropylcarbinol[3] (0.5 mol) and phosgene (70 m*l*) in tetrahydrofuran (70 m*l*) at −20°C for 3 days. The excess phosgene was removed by evaporation under reduced pressure at room temperature, and the remaining tetrahydrofuran solution was used as the Dipmoc-Cl solution without further purification. Dipmoc-hydrazide was synthesized by a procedure previously used for the synthesis of *t*-amyloxycarbonyl-hydrazide;[4] mp 62.5—64.5°C; yield 78% (Found: N, 15.80%. Calcd: N, 16.08%). The hydrazide was converted to the azide by a method which has been reported before,[4] and this was used without purification. ε-Dipmoc-L-lysine was synthesized with the copper-lysine complex using Dipmoc-Cl or Dipmoc-N_3; the same ε-Dipmoc-L-lysine was thus obtained in a 57—58% yield; mp 198.5—200.5°C (decomp); $[\alpha]_D^{25}$ +22.3° (*c* 1.0, N-HCl) (Found: N, 9.78%. Calcd: N, 9.71%). Z-L-Pro-L-Lys(Dipmoc)-Gly-NH_2 (I) was synthesized by conventional methods; mp 174.5—176.5°C, $[\alpha]_D^{26}$ −39.9° (*c*, 1.0, EtOH). The stability of the protective group against N HCl/AcOH is shown in Fig. 1 in comparison with those of the Z group and of the *p*-chlorobenzyloxycarbonyl [Z(Cl)] group.[5] The Dipmoc-group could be removed completely by treatment with HF[6] in the presence of anisole at 20°C for 60 min. This cleavage was demonstrated with Compound I; L-Pro-L-Lys-Gly-NH_2·2HCl·½H_2O was thus obtained in a 92.3% yield as an amorphous powder; $[\alpha]_D^{26}$ −40.0° (*c* 1.8, H_2O) (Found: C, 41.25; H, 7.58; N, 17.87%. Calcd: C, 40.94; H, 7.40; N, 18.36%). Thus, the usefulness of this procedure was confirmed.

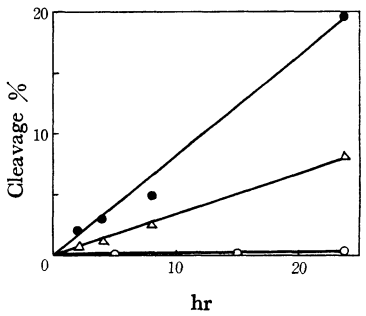

Fig. 1. Cleavage of ε-protective groups of lysine in N HCl-acetic acid at 20°C.
-●- ε-Z-L-Lysine; -△- ε-Z(Cl)-L-Lysine; -○- ε-Dipmoc-L-Lysine.

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2) A. Yaron and S. F. Schlossman, *Biochemistry*, **7**, 2673 (1968).

3) J. B. Conant and A. H. Blatt, *J. Amer. Chem. Soc.*, **51**, 1227 (1929).

4) I. Honda, Y. Shimonishi and S. Sakakibara, This Bulletin, **40**, 2415 (1967).

5) ε-Z(Cl)-L-Lysine was synthesized by the conventional method; mp 255—258°C (decomp), $[\alpha]_D^{16}$ +14.2° (*c* 0.51, 50% AcOH); (Found: N, 8.92%. Calcd: N, 8.90%).

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