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# SELECTIVE REMOVAL OF THE t-BUTYLOXYCARBONYL PROTECTING GROUP IN THE PRESENCE OF t-BUTYL AND p-METHOXYBENZYL ESTERS

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t-Butyloxycarbonyl (BOC) amino acids are frequently used as intermediates in peptide synthesis and the reagents normally used for the removal of the protecting group[1,2,3] are acidic in nature. If these reagents are used to deprotect peptides containing both the BOC protecting group and t-butyl or p-methoxybenzyl esters they often lead to cleavage of both the amino protecting group and the ester function. Selective deprotection of the benzyloxycarbonyl amino protecting group in the presence of benzyl esters has been reported using dry hydrogen bromide in acetic acid[4] with varying success. Acid sensitive amino protecting groups such as trityl or p-methoxybenzyloxycarbonyl may be removed in the presence of BOC protecting groups[5,6], but the selective removal of the BOC protecting group in the presence of t-butyl esters has only been reported[7] on one occasion using an ion-exchange resin to effect the deprotection.

We wish to report an alternative method for the removal of the BOC protecting group in the presence of t-butyl esters, for the removal of the BOC protecting group in the presence of p-methoxybenzyl esters, and the use of the resulting tosylates in peptide synthesis.

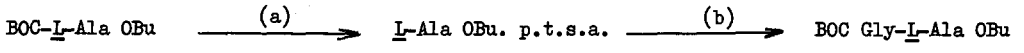
In a typical example L-alanine t-butyl ester was acylated using BOC azide in dimethylformamide and 1,1,3,3,tetramethylguanidine as base at room temperature[8] to provide BOC-L-alanine t-butyl ester (I) in 80% yield, b.p. 166° at 2mm, $n_D^{22} = 1.4310$, $[\alpha]_D^{22} = -32.1°$, (c = 1.49, MeOH). Found C, 58.5; H, 9.7; N, 5.5; $C_{12}H_{23}NO_4$ requires C, 58.8; H, 9.4; N, 5.7.

The protected ester (I; 0.01 mol.) was dissolved in ether (50 ml.) and p-toluenesulphonic acid (0.01 mol.) in ethanol (10 ml.) was added dropwise to the ether solution at -10° to 0° over half an hour. The mixture was allowed to warm up to room temperature and stirred for three hours. The solvent was evaporated at 40° and the residual oil crystallised from ethyl acetate to provide L-alanine t-butyl ester p-toluenesulphonate (II) in 91% yield, m.p. 222°, $[\alpha]_D^{22}$ = + 1.7°, (c = 1.62; MeOH).

Found: C, 52.7; H, 7.2; N, 4.5; S, 10.1; $C_{14}H_{23}NO_5S$ requires C, 53.0; H, 7.3; N, 4.4; S, 10.1.

The tosylate (II) may be coupled to protected amino acids using standard methods. For example BOC-glycine N-hydroxysuccinimide ester was coupled with L-alanine t-butyl ester p-tosylate (II) in dimethoxyethane by neutralising the p-toluenesulphonic acid with one equivalent of N-methyl morpholine prior to reaction with the activated ester. The product, BOC-glycyl-L-alanine t-butyl ester, (III) crystallised from petroleum ether (b.p. 60-80°) in 75% yield, m.p. 68-9°, $[\alpha]_D^{22}$ = -31.4° (c = 1.12; MeOH).

Found: C, 55.8; H, 8.7; N, 9.3; $C_{14}H_{26}N_2O_5$ requires C, 55.6; H, 8.6; N, 9.3.




(I) (II) (III)

(a) 1 equivalent of p.t.s.a.; (b) 1 equivalent of N-Me morpholine followed by BOC Gly OSu.

We have also found that p-methoxybenzyl ester derivatives of BOC amino acids and peptides undergo selective deprotection under the same conditions as those described for the t-butyl esters. A summary of a representative selection of protected amino acids and peptides that have been deprotected to the corresponding tosylates using this technique is shown in Tables I and II. The conditions for the deprotection depend upon the particular derivative, for instance, a longer reaction time is required for the deprotection of the tripeptide BOC-L-Lys(Phth)-D-Ala-D-Ala OBu.

Table I

| Protected Derivative | m.p. (°C) | Rotation $[\alpha]_D^{22}$ (MeOH) |
|---|---|---|
| BOC-L-Ala OBu | b.p. 166 at 2mm | -32.1° |
| BOC-Gly-L-Ala OBu | 68-9 | -31.4° |
| BOC-D-Ala-D-Ala OBu | Viscous oil | +44.0° |
| BOC Gly-D-Asp[OBz(OMe)]OBzl | Viscous oil | +3.0° |
| BOC Gly-Gly OBz(OMe) | 96 | - |
| BOC-L-Lys(BOC)Gly OBz(OMe) | 94 | -13.4° |
| BOC-L-Lys(Phth)-D-Ala-D-Ala OBu | 133 | +26.6° |
| BOC-L-Lys(Ac)-D-Ala-D-Ala OBu | 116 | +31.5° |
| $ICH_2CO$-L-Lys(BOC)-D-Ala-D-Ala OBu | 136 | +16.3° |

Table II

| Product (p-tosylate) | m.p. (°C) | Rotation $[\alpha]_D^{22}$ (MeOH) | Yield % | Reaction Time (hrs) |
|---|---|---|---|---|
| L-Ala OBu | 222 | +1.7° | 91 | 3 |
| Gly-L-Ala OBu | 142 | -20.6° | 89 | 3 |
| D-Ala-D-Ala OBu | Viscous oil | +22.7° | 93 | 3 |
| Gly-D-Asp[OBz(OMe)]OBzl | Viscous oil | +3.2° | 94 | 3 |
| Gly-Gly OBz(OMe) | 134-5 | - | 95 | 3 |
| L-Lys-Gly OBz(OMe)(ditosylate) | 90 | +7.5° | 94 | 3 |
| L-Lys(Phth)-D-Ala-D-Ala OBu | 160 | +39.1° | 81 | 24 |
| L-Lys(Ac)-D-Ala-D-Ala OBu | 95 | +35.5° | 91 | 18 |
| $ICH_2CO$-L-Lys-D-Ala-D Ala OBu | 104 | +12.0° | 86 | 18 |

We believe that this simple and practical method of selective deprotection may have general utility in peptide chemistry and provide greater versatility to the widely used t-butyl and p-methoxybenzyl protecting groups.

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