A Simplified Procedure for the Preparation of *t*-Butyloxycarbonyl and Similar *N*-Protected Amino Acid Derivatives *

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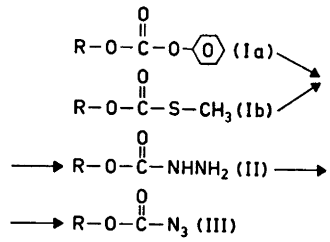

There are now several alternatives for the reversible protection of amino functions in peptide synthesis. The benzyloxycarbonyl [1] group should be mentioned first in this context. This protecting group has been modified to give different properties. Of those with urethane structure in common with benzyloxycarbonyl, especially *t*-butyloxycarbonyl [2,3] (Boc) is of great practical value. *p*-Methoxybenzyloxycarbonyl [2,4] [Z(OMe)], benzhydryloxycarbonyl [5] (Bhoc), and *t*-amyloxycarbonyl [6,7] (Aoc) are also useful. All are considerably more labile to acid than the parent group and can be removed under mild acid conditions.

This communication is concerned with the preparation of Boc-, Z(OMe)-, Bhoc-, and Aoc-amino acids. Several procedures have already been proposed. Boc- and Aoc-amino acids have been prepared directly from the corresponding chloroformates [6,7] like benzyloxycarbonyl derivatives. These compounds like *p*-methoxybenzyl chloroformate [8] are, however, labile and therefore not ideal. More stable reagents such as the corresponding azides [4,5,9–11] have been extensively used, especially after Schnabel's introduction of his excellent pH-stat procedure.[12] With the exception of Aoc-azide [11] the method used at present for the preparation of the azides involves three steps starting from inexpensive commercial materials: the preparation of a mixed carbonate (Ia) or sulfur analogue (Ib), which is converted *via* a hydrazide (II) to the corresponding azide (III). This is described in detail for Boc-azide in Ref. 13. A more recent method [14] for the preparation of this substance does not seem to offer advantages over the preceding one.

We have now found that under proper reaction conditions intermediates of type Ia above can be directly used for the preparation of Boc-, Z(OMe)-, Bhoc-, and Aoc-amino acids. This is indeed advantageous, especially in the case of Boc, since *t*-butyl phenyl carbonate is an inexpensive bulk chemical. In the case of Z(OMe) and Aoc we have so far used *p*-methoxybenzyl phenyl carbonate [4] and *t*-amyl phenyl carbonate in crude form which can easily be prepared in quantity. In the case of Aoc, however, we think it is better to purify the carbonate, since the yields obtained with the crude material were consistently lower than expected. The conditions used include solvents like dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and dioxan–water 1 : 1 mixtures (D-W). As a base we use 1,1,3,3-tetramethylguanidine [15,16] (TMG), but generally only one equivalent instead of two as in Refs. 15 and 16. When not otherwise explicitly stated reactions were performed with 1.1 equivalents of the mixed carbonate. Although nearly theoretical quantities of reactants were used, reasonable to high yields have been obtained so far for all amino acids tested, simply by varying the reaction time and in a few cases by conducting the reactions at 40°C instead of room temperature (RT). Some experiments performed are summarized in Table 1.

Even if the carbonates for all amino acids tested so far have given satisfactory results there may be cases when the azides are superior. Thus the combination azide + TMG used in Ref. 16 might still be useful. In the light of our own work, however, we believe the excess of Boc-azide and TMG can both be reduced. Other solvents like DMSO might in some cases give better results than DMF.

Sieber and Iselin [17] a few years ago used reaction conditions related to ours for the preparation of 2-(*p*-biphenyl)-isopropyloxycarbonyl-amino acids.

A detailed report of this work will be published later.

* Patent pending.

Table 1. Some Boc-, Z(OMe)-, Bhoc-, and Aoc-amino acids synthesized.[a]

Compound	Solvent	Temperature (°C)	Time (h)	Yield (%)	Remarks
Boc-Ala	DMSO	40	40	79	
»	»	RT	40	58	
Boc-Asp	»	RT	18	89	2 equiv. TMG
Boc-Glu	»	RT	2.5	80	2 equiv. TMG
Boc-Ile	»	40	72	72	
Boc-Leu	»	RT	48	73	calc. as hemihydrate
Boc-Phe	»	RT	40	81	DCHA salt
»	DMF	RT	48	59	» »
»	D-W	RT	48	5	» »
Boc-Pro	DMSO	RT	2.5	94	
»	DMF	RT	2.5	92	
»	D-W	RT	21	84	
Z(OMe)-Glu	DMF	RT	26	75	2 equiv. TMG
»	D-W	RT	30	70	2 equiv. TMG
Z(OMe)-Gly	D-W	RT	68	71	2 equiv. TMG
»	»	RT	50	86	2 equiv. TMG, 1.5 equiv. Ia
Z(OMe)-Pro	DMF	RT	21	87	2 equiv. TMG.- Oil.
»	D-W	RT	23	74	2 equiv. TMG.- Oil.
Bhoc-Asp*	DMSO	RT	18	68	2 equiv. TMG
Bhoc-Phe*	»	RT	46	81	
Bhoc-Pro	»	RT	2.5	89	CHA salt*
Aoc-Glu	»	RT	6	59	2 equiv. TMG. DCHA salt*
Aoc-Phe	»	40	48	52	DCHA salt
Aoc-Pro	»	RT	2.5	57	» » *

[a] All amino acids used except glycine were of L-configuration. The experiments described were all performed on a 100 mmol scale. Yields except in two cases refer to solid materials with m.p. in close agreement with earlier reported figures. Five compounds are believed to be new. This is indicated by*. CHA and DCHA stand for cyclohexyl amine and dicyclohexyl amine.

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