t-Butyl Benzotriazol-l-yl Carbonate. A New Efficient Reagent for t-Butoxycarbonylation of Amino Acids

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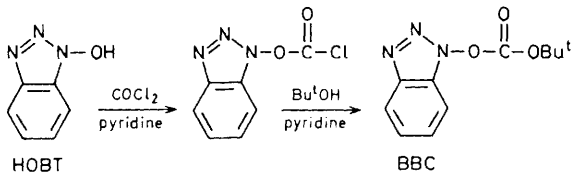
t-Butyl benzotriazol-1-yl carbonate, a stable crystalline compound, is found to be exceedingly effective in the t-butoxycarbonylation of amino acids.

The t-butoxycarbonyl (Boc) group is one of the most important amino protective groups in peptide synthesis[1] along with the benzyloxycarbonyl (Cbz) group. Owing to the instability of t-butyl chloroformate,[2] considerable efforts have

$$H_2N\text{-}CHR\text{-}CO_2H + BBC \xrightarrow{Et_3N} \xrightarrow{H^+} Boc\text{-}NH\text{-}CHR\text{-}CO_2H + HOBT \quad (1)$$



(2)

been devoted to the development of a variety of useful reagents for the introduction of the t-butoxycarbonyl group during the last 20 years.[1,3]

We have found that t-butyl benzotriazol-1-yl carbonate (BBC) is exceedingly effective in the t-butoxycarbonylation of amino acids (equation 1). BBC is conveniently prepared by the reaction of benzotriazol-1-yl chloroformate [generated from phosgene and 1-hydroxybenzotriazole (HOBT)[4] in the presence of pyridine] with equimolar amounts of t-butyl alcohol in the presence of pyridine in methylene chloride at room temperature, and is obtained in 85% yield as colourless crystals (equation 2). BBC is stable, showing no sign of decomposition when kept at room temperature for one month.

When BBC was added to a solution of L-proline and triethylamine in aqueous dioxane, t-butoxycarbonylation occurred almost instantaneously at room temperature, indicating that BBC is one of the most reactive of the reagents available. The t-butoxycarbonylation of L-proline in aqueous dimethylformamide also proceeded smoothly at room temperature, but required 30 min for completion. Further reactions were carried out with equimolar amounts of the amino acid and BBC in the presence of 1.5 equiv. of triethylamine in aqueous dioxane; reactions were complete within 10 min at room temperature to give high yields of the corresponding *N*-Boc amino acids,† the identities of which were confirmed by comparison of n.m.r. and i.r. data, $[\alpha]_D$ values, and m.p.s with reported data.

In the t-butoxycarbonylation of amines, dimethylformamide was the most effective among various solvents such as methylene chloride, acetonitrile, tetrahydrofuran, and dioxane. Thus, simple amines such as benzylamine and piperidine were quantitatively converted into the corresponding t-butyl carbamates in dimethylformamide at room temperature within 10 min, while relatively unreactive amines such as aniline and imidazole were cleanly converted into the corresponding t-butyl carbamates in 6 h.

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† % Yield of *N*-Boc amino acid: Glycine, 80; Valine, 98; Leucine, 99; Phenylalanine, 86; Tyrosine, 85; Proline, 99; Serine, 85; Threonine, 93; Methionine, 85; Tryptophan, 86.