Peptide Coupling Reagents; VIII. A High Yield Preparation of Phenyl Esters of Amino Acids using Benzotriazolyloxytris[dimethylamino]phosphonium Hexafluorophosphate (BOP Reagent)

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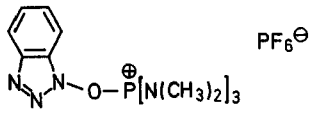
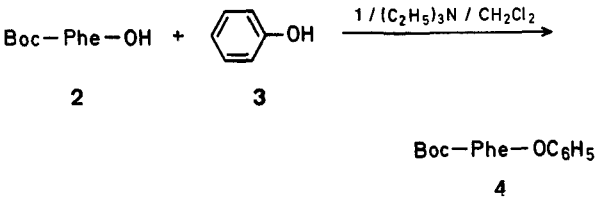
We have previously described the application of benzotriazolyloxytris[dimethylamino]phosphonium hexafluorophosphate (**1**; BOP reagent) as a peptide coupling reagent[1,2]. In this communication we describe the use of **1** in a high yield preparation of phenyl esters of amino acids. These esters have been shown to be valuable as blocked derivatives of amino acids in the field of peptide synthesis[3].



1 (BOP reagent)

Boc-amino acids (e.g. **2**) react with one mol-equivalent of phenol (**3**) and **1** in the presence of two equivalents of triethylamine to give the phenyl esters (e.g. **4**). The reaction is generally complete within 2–3 h (as shown by T.L.C. monitoring).



2 **3** **4**

The Boc esters are readily isolated by extraction with ethyl acetate and washing of the extracts with dilute hydrochloric acid followed by sodium hydrogen carbonate solution. To the best of our knowledge, the present technique constitutes an improvement over the dicyclohexylcarbodiimide (DCC) method which generally gives yields in the range of 60%. Our results are summarised in the Table.

Some of the product esters are unstable, especially Boc-His-OC_6H_5, and hydrolyse quickly in solution and slowly as crystalline solids. The formations of Boc-Asn-OC_6H_5 and Boc-Gln-OC_6H_5 are accompanied by major side reactions.

In particular, we observed that in the case of asparagin, the major product is the cyclised Boc-aminosuccinimide; a small quantity of Boc-cyano-Ala-OC_6H_5 is also formed. The proportions of the three products depend on the reaction conditions. Moreover, we have observed that the presence of the phenoxide anion induces cyclisation in an isolated sample of Boc-Asn-OC_6H_5 to give the succinimide derivative.

The conversion of the phenyl esters of Boc-amino acids to trifluoroacetate salts proceeds quantitatively in trifluoroacetic acid. Thus, the present method provides a convenient method for the rapid conversion of an *N*-protected amino acid to a *C*-protected acid. Extensions of this procedure to the preparations of methyl and benzyl esters are under investigation.

Table. Preparation of Phenyl Esters of Amino Acids

Product	Solvent	Yield [%]	m.p.[a]	$[\alpha]_D^{22}$ (solvent, conc.)
Z-Ala-OC_6H_5	CH_2Cl_2	95	96°	−46° (C_2H_5OH, 1)
Boc-Ala-OC_6H_5	CH_2Cl_2	85	48°	−54° (C_2H_5OH, 1)
Boc-Ile-OC_6H_5	CH_2Cl_2	90	Oil[b]	−30.4° (C_2H_5OH, 2)
Boc-Phe-OC_6H_5	CH_2Cl_2	94	91°[c]	−12.7° (C_2H_5OH, 1)
Boc-Trp-OC_6H_5	CH_3CN	96	153°	−11.6° (C_2H_5OH, 1)
Boc-Pro-OC_6H_5	CH_2Cl_2	91	63°	−66° (C_2H_5OH, 1)
Boc-Ser-OC_6H_5	DMF	73	Oil	−30° (C_2H_5OH, 1)
Boc-Cys(SBzl)-OC_6H_5	CH_2Cl_2	94	81°	−27° (C_2H_5OH, 1)
Boc-Met-OC_6H_5	CH_3CN	86	72°	−43° (CH_3OH, 1)
Boc-Lys(NεZ)-OC_6H_5	CH_2Cl_2	97	Oil[d]	−22° (C_2H_5OH, 1)

[a] Physical constants were obtained on crude products except for the Trp derivative which was recrystallized (acetonitrile). Satisfactory microanalyses (C ± 0.2%, H ± 0.1%) and N.M.R. spectra have been obtained for each derivative.

[b] TFA, H_2N-Ile-OC_6H_5; m.p. 176°; $[\alpha]_D^{22} = +30.5$ ($c = 2$, CH_3OH).

[c] TFA, H_2N-Phe-OC_6H_5; m.p. 160°; $[\alpha]_D^{22} = +31.2$ ($c = 2$, CH_3OH).

[d] TFA, H_2N-Lys(Z)-OC_6H_5; m.p. 100°; $[\alpha]_D^{22} = +22$ ($c = 2$, CH_3OH).

Preparation of Boc-Phe-OC_6H_5 (4):

Boc-Phe-OH (**2**; 530 mg, 2 mmol), phenol (**3**; 188 mg, 2 mmol), triethylamine (404 mg, 4 mmol) and BOP reagent (**1**; 884 mg, 2 mmol) are dissolved successively in dichloromethane (30 ml). The solution is kept at room temperature for 2 h. Saturated aqueous sodium chloride solution (30 ml) is added and the resultant mixture is extracted with ethyl acetate (3 × 20 ml). The organic phase is separated, washed three times with 2 normal hydrochloric acid, three times with saturated sodium hydrogen carbonate solution, twice with sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo. The product Boc-Phe-OC_6H_5 (**4**) crystallises spontaneously; yield: 642 mg (94%); m.p. 91°.

The above procedure can be applied to all amino acid derivatives listed in the Table.

Preparation of H_2N-Phe-OC_6H_5 Trifluoroacetate (TFA, H_2N-Phe-OC_6H_5):

Boc-Phe-OC_6H_5 (682 mg, 2 mmol) is dissolved in a 50% v/v solution of trifluoroacetic acid and dichloromethane (6 ml). After 2 min the solution is evaporated in vacuo. The remaining trifluoroacetic acid is removed by four successive additions of anhydrous ether (4 × 5 ml) followed by vacuum evaporation. The salt is crystallised from ether as needles; yield: quantitative: m.p. 160°.

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