# An Efficient Method for the Reduction of *N*-Protected Amino Acids and Peptides to the Corresponding Alcohols†

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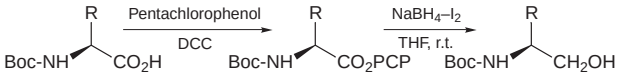
Reduction of pentachlorophenyl esters of Boc protected amino acids and peptides to the corresponding alcohols is described.

$N^{\alpha}$-Protected $\beta$-amino alcohols are key intermediates in the synthesis of variety of compounds *viz*. peptide bond surrogates, as they lead to $\alpha$-amino aldehydes by various oxidation procedures[1] which can be used in the design of protease inhibitors[2] or in the synthesis of 'reduced peptide bonds'.[3] Further, these are important intermediates in asymmetric synthesis in peptide and pharmaceutical chemistry,[4–6] in resolution of racemic mixtures[7] and in synthesis of insecticidal compounds.[8] Several methods have previously been reported using $LiAlH_4$,[10] $NaBH_4$,[11] DIBAL,[12] $BH_3{\cdot}THF$[13] etc, for the reduction of free as well as protected amino acids to their corresponding alcohols. However, these reagents suffer from disadvantages of cost, inflammability and tedious isolation procedures. As these amino alcohols are important intermediates, their preparation on a large scale requires cheaper, simpler and safer processes. Periaswamy and coworkers[14] reported the reduction of various carboxylic acids into their corresponding alcohols under mild conditions using an $NaBH_4-I_2$ system. Using the same reagent, McKennon and Mayers[15] reported efficient reduction of amino acids into their corresponding amino alcohols. However, this method was reported to be limited to the reduction of hydrophobic amino acids and could not be applied for the reduction of amino acids having side chain functionalities. Further, the reaction conditions used were also quite drastic (reflux for 18–24 h) and not suited for amino acids having side chain functionalities. Kokotos and Noula[16] reported reduction of various carboxylic acid fluorides under very mild conditions which showed superiority over the method reported by McKennon *et al*. The present work describes an improvement in the $NaBH_4-I_2$ reduction method by derivatizing the carboxylic group and the same method can also be applied to protected amino acids with side chain functionalities and peptides. It has been found in our laboratory that $N^{\alpha}$-protected amino acids when converted into their corresponding pentachlorophenyl (OPCP) esters, on employing $NaBH_4-I_2$ are readily reduced to the amino alcohols at room temperature and are obtained in excellent yields and optical purity (Scheme 1). We report here the reduction of some protected amino acids as well as peptide active esters into their corresponding alcohols. Protected amino acids and peptides can successfully be converted to alcohols from their corresponding pentachloraphenyl esters by this method with excellent yields and retention of optical purity under very mild conditions (Table 1).




**Scheme 1**

The highlighting features of this study are: (i) the reaction involves mild reaction conditions and cheap reagents. It is safe and simple and, therefore, can be used for even large scale synthesis of chiral amino alcohols. (ii) Reaction is very fast and proceeds to completion in 4 h. (iii) The side chain protection of lysine and arginine by Z and $NO_2$ groups, respectively, remains unaffected under the described conditions. (iv) The process does not reduce benzyl ester groups used for the protection of $\gamma$- and $\beta$-carboxylic groups of glutamic acid and aspartic acid, respectively. (v) The reaction conditions do not cause racemization and the amino alcohols are obtained in high optical purity. Thus, this method can be successfully applied for the synthesis of $N^{\alpha}$-Boc protected amino alcohols as well as protected

**Table 1** Physicochemical characteristics of protected amino alcohols and peptide alcohols

| Entry | Protected amino alcohol or peptide | Yield[a] (%) | Mp/°C | $R_f^b$ | $[\alpha]^c$ | FAB-MS (*m/z*) Found (Calc) |
|---|---|---|---|---|---|---|
| 1 | Boc-Ala-ol | 89 | 76–87 | 0.61 | −3.60 | 176(176) |
| 2 | Boc-Phe-ol | 80 | 88–90 | 0.38 | −21.6 | 252(251) |
| 3 | Boc-Trp-ol | 83 | 108–110 | 0.55 | −25.6 | 290(290) |
| 4 | Boc-Tyr-ol | 62 | Oil | 0.43 | – | 267(267) |
| 5 | Boc-Arg($NO_2$)-ol | 79 | 128–130 | 0.42 | −7.20 | 306(305) |
| 6 | Boc-Leu-ol | 83 | 176–180 | 0.58 | −7.27 | 217(216) |
| 7 | Boc-Gly-ol | 85 | 148–150 | 0.62 | – | 162(161) |
| 8 | Boc-Pro-ol | 64 | 148–150 | 0.61 | −32.7 | 202(201) |
| 9 | Boc-Lys(Z)-ol | 75 | Oil | 0.64 | −8.20 | 353(352) |
| 10 | Boc-D-Glu(OBzl)-ol | 74 | Gum | 0.47 | +8.0 | 324(324) |
| 11 | Boc-DAGO | 71 | 162 | 0.75 | −40 | 614(613) |
| 12 | Boc-Phe-Leu-ol | 78 | Gum | 0.50 | – | 365(364) |

[a]Isolated and purified yields. [b]Solvent system MeOH–$CHCl_3$ (5:95). [c]Values are in comparison to those reported in the literature and uncorrected, $c = 1$, MeOH. [d]Boc-Tyr-D-Ala-Gly-MePhe-Gly-OPCP reduced to Boc-Tyr-D-Ala-Gly-MePhe-Gly-ol (Boc-DAGO).

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peptide alcohols. We observed that the reduction of Boc amino acids without deriviatization did not proceed at all under similar conditions.

## Experimental

*General Procedure for the Reduction of Protected Amino Acids and Peptide–OPCP Esters to their Corresponding Alcohols.*—To a slurry of $NaBH_4$ (1.2 mM) in dry THF (5 ml), iodine (0.5 mM) dissolved in dry THF was added slowly over 0.5–1 h at 0 °C. After complete addition, Boc-amino acid–OPCP or protected peptide–OPCP (1.0 mM), prepared according to reported procedures,[17] was added and the contents were stirred at 0 °C for 30 min and then at room temperature for 2.5–5 h. THF was evaporated under reduced pressure and the residue was dissolved in water followed by neutralization with 1N HCl to pH 2 and extracted with ethyl acetate ($3 \times 30$ ml). The combined organic layer was washed with 0.1 M sodium thiosulfate solution to remove traces of iodine and finally with brine. After drying over anhydrous $Na_2SO_4$ the organic layer was concentrated *in vacuo*. The residue was triturated with hexane or purified by column chromatography to give the pure product.

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