SHORT PAPER

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A facile and simple method for the reduction of N-protected amino acids and peptides to the corresponding alcohols†

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A practical and chemoselective method for the reduction of N-protected amino acids and peptides including carboxylic acids to their corresponding alcohols is outlined.

Keywords: N-protected amino acids and peptides

Enatiomerically pure β-amino alcohols are in great demand as chiral synthons for number of organic reactions namely as chiral auxiliaries in assymmetric C–C bond formation,[1] chiral 4-substituted oxazolidine-2-ones[2] and in the synthesis of insecticidal compounds.[3] Further they are also used as synthons to obtain peptide bond surrogates and peptidomimetics and as chiral auxiliaries in the resolution of primary amines.[4] The most common methods employed for the reduction of simple carboxylic acids to alcohols include the use of reagents like LAH,[5] DIBAL-H,[6] B_2H_6,[7] *etc*. At present on commercial scale of 1.0 kg batch size conversion of amino acids is effected with either BMS or LAH[8]. Moreover, It requires excess use of expensive and flammable reagents thus suffer from high cost. However these methods are not selective and other functionalities such as esters and amides are also reduced thus entailing tedious isolation procedures.

A more practical method was reported by Prasad, *et al*.[9] using $NaBH_4/I_2$ system for the reduction of acids to alcohols. Further, McKennon and Meyers[10] extended this method for the reduction of amino acids to alcohols. Essentially this method involves refluxing of the reaction mixture for 18–24 h in appropriate solvent, hence not suitable for amino acids having side chain functionalities. A better approach for getting amino alcohols from amino acids was reported by the reduction of N-protected amino acid mixed anhydrides using methanol/$NaBH_4$ system.[11] Further improvement for the reduction of N-protected amino acids and peptides was reported by Naqvi *et al*..[12] These workers to some extent circumvented many of the drawbacks in the earlier methods. In these method N-protected amino acids and peptides are first converted to Opcp esters followed by reduction of the activated ester using the $NaBH_4/I_2$ system.

It is surmised that the reduction of carboxylic group is facile after the activation of carboxyl group, by making mixed anhydride or by Opcp esters and could be done under mild conditions. An alternative approach would be to generate activated species *in situ* followed by the reduction and in fact McGeary has recently reported reduction of carboxylic acids to their corresponding alcohols using BOP/$NaBH_4$ method. BOP reagent is known to be powerful carboxyl activating reagent for peptide bond formation in peptide synthesis. A number of hydroxybenzotriazole based coupling reagents such as HBTU,[14] BOP[15] and NBTU[16] represent a very reactive and widely used class of coupling reagents in peptide synthesis. It is generally believed that the carboxyl activation by these reagents in via their OBt esters. Since the OBt esters are very reactive yet comparatively stable we surmised that they could be reduced to alcohols by using milder conditions.

As a part of our ongoing program directed towards synthesis and application of amino alcohols we now wish to outline development of a practical and efficient method for reduction of N-protected amino acids and peptides to alcohol using 2-(6-Nitro-1-oxy-benzotriazol-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (NBTU). Although many reactions reported in this study were carried out with NBTU, we have obtained similar results with commercially available reagent HBTU as well. We have demonstrated that N-protected amino acids, peptides, and other carboxylic acids can be easily reduced to corresponding alcohols using NBTU/$NaBH_4$ system (Scheme 1). The reactions are complete within 30 min. The optical purity and functionalities of the amino acids remain unaffected. In a typical reaction N-protected amino acids and NBTU were stirred in THF at room temperature followed by addition of $NaBH_4$. The reaction was complete within 30 min. as monitored by TLC (disappearance of the starting material) and the usual aqueous work up gave the desired product in moderate to excellent yields. In most of the cases the products were obtained in pure form without column chromatography purification. Similar results were obtained with amino acids having side chain functionalities (see entries 7, 8, 13 and 15, Table 1).

The present method has a number of advantages over the previous protocols. The reaction conditions are simple, can be performed at room temperature and do not require dry solvents. Moreover only stoichiometric amount of reducing agent is used in the present protocol to achieve complete conversion. The reduction is facile and selective in the sense that other functionalities are not affected. Further application of this protocol has been demonstrated in the case of variety of carboxylic acids (entries 18–20) with similar results. Thus demonstrating the practical simplicity and versatility of this method over the earlier methods reported for the reduction of amino acids and peptides.

In summary, it may be mentioned that pursuant with the stated objective we have successfully developed a practical, facile and chemoselective method for the reduction of N-protected amino acids, peptides and carboxylic acids in high yields and purity.

Experimental

To a suspension/slurry of N-protected amino acid (1.0 mmol) and NBTU (1.1 mmol) in THF, N,N-Diisopropylethylamine (1.2 mmol) was added. After the solution becomes clear (approx. 5 min.) $NaBH_4$ (1.0 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, then methanol was added to the reaction mixture to remove excess $NaBH_4$. The reaction mixture was concentrated under to dryness under reduced pressure and residue was taken in ether, the organic layer was successively washed with

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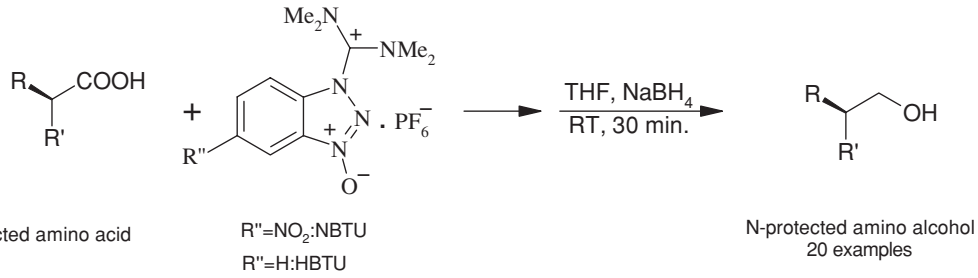

Scheme 1 Synthesis of amino alcohols from N-protected amino acids.

Table 1 Physiochemical characteristics of the various protected amino alcohols, peptide alcohols and simple alcohols.

Alcohols		Yields/%	M.p./°C	$[\alpha]_D^{25}$	FAB-MS (*m/z*)
1.	Boc-Ala-ol	71	58–62	–6.36* (–8.9)[17]	176
2.	Boc-Phe-ol	93	89–91	–20.91* (–21.6)[12]	252
3.	Boc-Ile-ol	77	Oil	–13.75	218
4.	Boc-Val-ol	60	Oil	–21.25* (–17.0)[17]	204
5.	Boc-Pro-ol	75	146–149	–35.55 (–32.7)[12]	202
6.	Boc-Trp-ol	80	109–111	–24.0 (–25.6)[12]	290
7.	Boc-D-Glu(OBzl)-ol	75	Gummy	+5.0	324
8.	Boc-Asp(OBzl)-ol	88	Oil	–7.27 (–6.0)[18]	310
9.	Boc-Cys(Trt)-ol	90	Gummy	+18.33	472[a]
10.	Boc-Arg(NO_2)-ol	55	129–132	–7.3 (–7.20)[12]	306
11.	Fmoc-Gly-ol	91	128–131	–	284
12.	Fmoc-Phe-ol	90	159–162	–16.36* (–21.0)[17]	374
13.	Z-Tyr-ol	68	Gummy	–20.0	302
14.	Z-D-Ala-ol	72	Gummy	+5.0	210
15.	Z-Orn(Z)-ol	86	119–122	–5.0*	387
16.	Boc-Phe- Leu-ol	73	Gummy	–7.5	365
17.	Boc-Phe-Phe-ol	77	Gummy	–17.5	399
18.	$C_{15}H_{31}CH_2OH$	85	46–48	–	242
19.	$C_7H_{15}CH_2OH$	61	Oil	–	130
20.	$MeOC_6H_4CH_2OH$	65	Oil	–	138

[a]M+Na; Optical rotation are recorded in methanol or Chloroform*(c=1)

5% aq. Citric acid, brine, aq. $NaHCO_3$ and then with brine. The ether layer was dried over Na_2SO_4 and concentrated under reduced pressure. Although the final product was obtained is pure after triturating the residue with hexane, silica gel chromatography was performed to get the final product in sufficiently pure form to enable comparison of the spectral data with the reported values.

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