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A Convenient and Mild Procedure for the Reduction of Amino Acids Using Amberlyst 15 - $NaBH_4$ - LiCl

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Abstract : A simple and mild procedure reduces amino acids on amberlyst-15 support through $NaBH_4$ - LiCl to corresponding amino alcohols in high yield and purity. © 1998 Elsevier Science Ltd. All rights reserved.

Chiral amino alcohols are of considerable importance in asymmetric synthesis[1], peptide and pharmaceutical chemistry[2] , resolution of racemic mixtures[2], synthesis of insecticidal compounds[3], and others. In connection with a project[4] on the enantioselective synthesis of a natural product[10], we needed some chiral aminio alcohols to be used as chiral auxiliaries. The obvious choice for their preparation is through the reduction of corresponding naturally occurring amino acids. A number of methods[2,5] have been reported in literature for this purpose which involve either expensive complex metal hydrides or $NaBH_4$ in conjunction with strong acids like BF_3 , H_2SO_4 or $(CH_3)_3SiCl$ which may decrease the optical purity of the product and make the work up, isolation and purification procedures cumbersome. Meyers[2] et al reported the reduction of amino acids by $NaBH_4$-I_2. This method requires inert atmosphere for the reaction coupled with laborious follow up to isolate and purify the desired compounds.

Recently we have observed[6] that chiral amino acids can be esterified conveniently using macroreticular ion exchange amberlyst-15 as support and a catalyst to provide corresponding esters in high yield and purity under mild reactions conditions. It occurred to us that during this reaction, since the amino group remains bound to the solid support, the ester formed after an optimum period of time could be reduced *in situ* to the corresponding alcohol with $NaBH_4$-LiCl[11]. An attempt to accomplish this transformation resulted in the recovery of amino alcohol in very poor yield. However, decanting out of the solvent (CH_3OH or C_2H_5OH) from the polymer support after stirring overnight and then addition of THF-LiCl-$NaBH_4$ dramatically increased the yield of amino alcohols (see table). Another advantage of this methodology is the simple work up procedure to afford amino alcohols[7] in high purity (including optical). A typical experimental procedure is described below that has been tested on the amino acids given in the table.

A solution of amino acid (8.5 mmol) in CH_3OH (40ml) containing amberlyst-15 (20g)

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was stirred overnight. CH_3OH was decanted off and THF (40 ml), LiCl (25.5 mmol) and $NaBH_4$ (25.5 mol) were added to the amberlyst and then stirred and refluxed for 3 to 4 hr. It was treated with $NaHCO_3$ solution (20%, 20 ml) and the THF was removed from the liquid layer (after decantation from amberlyst). The aqueous layer was extracted with CH_2Cl_2 (20ml x3), the combined organic layer washed with brine (10 ml x3) and dried. The solvent was removed and the residue was crystallized or distilled under vacuum.

Entry	Amino Acid	% Yield of amino alcohol	$[\alpha]_D^{26°C}$ **
1.	L- Phenylalanine	92	-22.5°(c 1.2, 1M HCl)
2.	L- Valine	83	+17.0° (c 10, EtOH)
3.	L- Proline	85	+30.5° (c 1.6, Toluene)
4.	L- Methionine	84	-13.7° (c 1, EtOH)
5.	L- Tyrosine	78	-13.3° (c 2, H_2O)[8]
6.	L- Leucine	89	+4.2°(c 9, EtOH)
7.	L- Alanine	65[9]	+ 22.2° (c 2, EtOH)

**Literature[2] reports $[\alpha]_D$ for compounds 1 to 7 as -22.8°, +17°, +31°, -14°, -13.6°, +4° and +22° respectively.

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7. The amino alcohols were confirmed by comparison of IR, NMR, TLC and $[\alpha_D]$ with the authentic samples prepared by the known route[2].
8. For specific rotation comparison, it was transformed into hydroiodide.
9. After completion of reaction, it was worked up by treatment with triethylamine, removal of excess of amine and THF and then isolating the product by chromatography on silical gel.
10. Financial support from CSIR, New Delhi through project no. 1(1343)95-EMR-II is gratefully acknowledged.
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