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Reduction of α-amino acids to chiral amino alcohols with sodium borohydride and boron trifluoride-etherate

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ABSTRACT

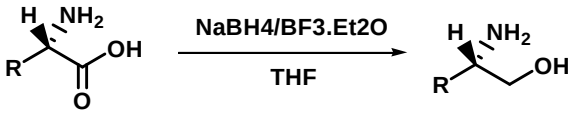
A new efficient procedure reduces α-amino acids through $NaBH_4/BF_3{\cdot}Et_2O$ to corresponding chiral amino alcohols in high yield and purity.

KEYWORDS

Amino acids;
Chiral amino alcohols;
$NaBH_4/BF_3{\cdot}Et_2O$.

INTRODUCTION

Chiral amino alcohols have extensive applications in the fields of asymmetric synthesis[1], pharmaceutical chemistry[2], resolution of racemic mixtures[3], synthesis of insecticidal compounds[4] and others. In the course of enantioselective synthesis of some organic compouds, some chiral amino alcohol derivatives can be used as chiral auxiliaries[5]. Moreover, the amino alcohols derived from natural α-amino acids have been found to be potent, reversible inhibitors of protein synthesis[6]. For the above reasons, the formation of chiral amino alcohols has been the subject of considerable effort to organic workers. Although many methodologies have been developed for their preparation, the direct reduction of corresponding naturally occurring amino acids is the most attractive one from the practical point of view. Many reduction systems have been reported in literatures for this purpose, such as $LiAlH_4$[7], $BF_3{\cdot}Et_2O/BH_3{\cdot}Me_2S$[8], $NaBH_4/I_2$[9], $NaBH_4/H_2SO_4$[10], $NaBH_4/LiCl$[11], $NaBH_4/SO_2Cl_2$[12], $NaBH_4/TiCl_4$[13], $KBH_4/ZnCl_2$[14], $LiBH_4(NaBH_4)/Me_3SiCl$[15], $H_2/H_3PO_4/Ru$[16] and so on. Nevertheless, research in this field is still very active even now. We report herein that chiral amino acids can be reduced directly to the corresponding alcohols using $NaBH_4/BF_3{\cdot}Et_2O$ in THF. To the best known of us, the reduction of chiral amino acids, however, by this system has not been reported, so a systematic examination of this was deemed warranted (Scheme 1). The results are summarized in TABLE 1.

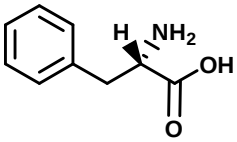
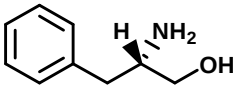
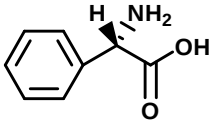
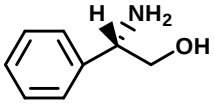
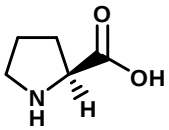
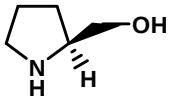
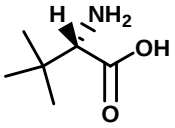
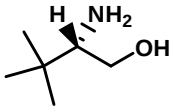
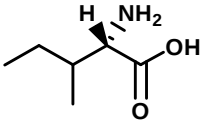
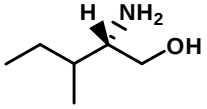
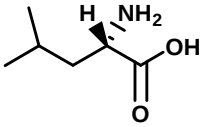
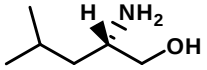
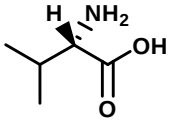
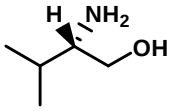
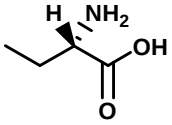
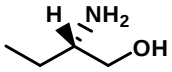
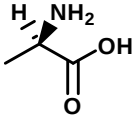
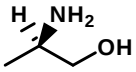
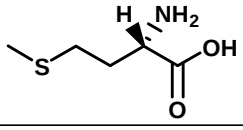
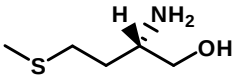


Scheme 1

EXPERIMENTAL

All the chiral amino acids were directly purchased from Aldrich. The reaction process was monitored by GF254 TLC using petroleum methanol/acetic acid/2% ninhydrin-ethanol (97:3:0.1 v/v/v) as the eluant. The spots were located in daylight after drying at about 120 °C. Melting points were determined on a microscopy apparatus (SGW X-4) and uncorrected. Polarimetric measurements were taken on an automatic polarimeter. All the liquid parent materials were freshly distilled. The prod-

TABLE 1 : Reduction of chiral amino acids to chiral amino alcohols

Entry	Substrate	Product	Yield (%)	m.p.(°C) /lit[17]	$[\alpha]_D^{20}$/lit[17]
1			88	92-95/92-94	-22 /-22.8 (c=1.2,1N HCl)
2			86	74-76/75-78	+31/+33 (c=0.75,1N HCl)
3			85	73-76/74-76(2mmHg)[a]	+31/+31 (c=1,$C_6H_5CH_3$)
4			84	32-34/33-35	+37/+37 (c=1.5,EtOH)
5			87	28-30/30	+4.9/+5.4 (c=1.6,EtOH)
6			84	197-200/198-200[a]	+3.7/+4.0 (c=9,EtOH)
7			87	29-30/30-32	+17/+17 (c=10,EtOH)
8			84	171-174/172-174 [a]	-9.6/-10 (neat)
9			82	173-175/173-176[a]	-16.5/-18 (neat)
10			73	34-36/33-35[112]	-12/-12.7 (c=1.4,EtOH)

[a]Boiling points were determined.

ucts were also characterised by comparison of their melting points and optical rotation with the literature values.

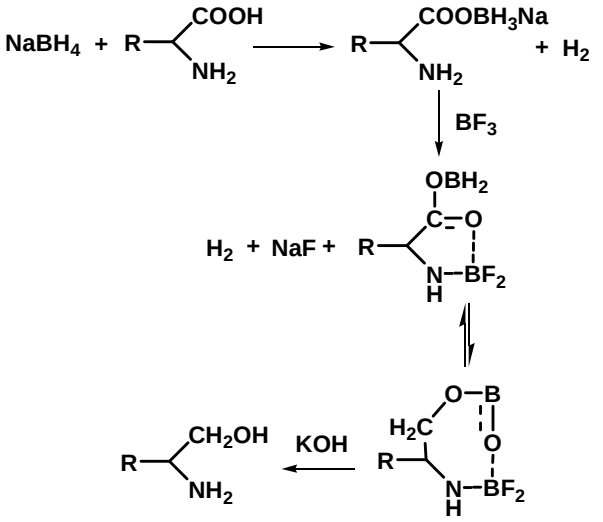
General procedure for reduction of amino acids

A 100 mL four-necked, round-bottomed flask equipped with a magnetic stir bar, a reflux condenser, an addition funnel and nitrogen inlet tube was charged with 0.94 g (25 mmol) sodium borohydride, 10 mmol amino acid and 30 mL of THF. After stirring for 10 min, a solution of $BF_3 \cdot Et_2O$ (11mmol) in THF(10 mL) poured into the addition funnel was added slowly with stirring and dropwised over 20 min resulting in vigorous evolution of hydrogen. After addition of the $BF_3 \cdot Et_2O$ was completed and gas evolution had ceased, the flask was heated to reflux for 16 h. Then the reaction mixture was cooled to room temperature, quenched with methanol

cautiously until the mixture became clear. After stirring for 30 min, the solvents were removed under reduced pressure, leaving a white paste which was dissolved by 16 mL of 20% aqueous potassium hydroxide. The stirring was continued for another 3 h at 80 °C and then extracted with dichloromethane (4×10 mL). The dichloromethane layer was separated, dried over anhydrous magnesium sulfate, filtered and distilled to give the crude product which was further purified by recrystallization from ethyl acetate and hexane (1:3, v/v), the pure amino alcohol was obtained (TABLE 1).

RESULTS AND DISCUSSION

The use of additives is a common and convenient method for the reductive efficiency enhancement of $NaBH_4$. Su-Dong Cho et al.[18] reported the reduction of carboxylic acids to alcohols in the presence of $BF_3{\cdot}Et_2O$ as Lewis acid, and the higher yields of reduced products were achieved in a satisfactory shorter time. He supported that the treatment of sodium borohydride with boron trifluoride etherate afford borane to reduce the carbonyl groups of the carboxylic acids. However, when we used this system to reduce the amino acids, the yields were a little lower and the reaction time was longer. For this, according to the literatures[19], we proposed another reaction mechanism (Scheme 2). In our reaction system, a pentacoordinate BF_3 complex with boron bound to the amino nitrogen and carbonyl carbon formed, which was necessary to activate C=O bonds and increase the solubilities of some amino acids such as L-alanine. Upon hydrolysis with aqueous potassium hydroxide, the complex was broken to release the free amino alcohol.



Scheme 2

To determine the optimal conditions for the reduction of amino acids, the reactions were carried out at different molar ratios of BF3·Et2O to amino acid using L-Phenylglycine as the model substrate. The results are summarized in TABLE 2. As the molar ratio of BF3·Et2O:amino acid increases from 0.9:1 to 1.1:1, the yields of the chiral amino alcohol increase. The use of more equivalents of BF3·Et2O relative to amino acid has no significant influence on the yield, suggesting that 1.1 equivalent of BF3·Et2O is sufficient to reduct the amino acids to the corresponding amino alcohol.

TABLE 2 : Effect of the different molar ratios (BF3·Et2O: amino acid) to L-phenylglycine

Entry	Substrate (mmol)	$NaBH_4$ (mmol)	BF_3 (mmol)	BF_3/ Substrate	Yield (%)
1	20	50	18	0.9/1	71
2	20	50	20	1/1	80
3	20	50	22	1.1/1	88
4	20	50	24	1.2/1	89
5	20	50	26	1.3/1	89
6	20	50	30	1.5/1	90

In TABLE 3, the hydrolysis temperature had an obvious effect on the yields. The optimal condition for L-Phenylglycine was 80 °C, the lower temperature could not provide enough energy to broke the bonds of the complex and the higher temperature was not necessary. In this condition, all the amino acids were reduced to the maximum extent (TABLE 1).

TABLE 3 : Effect of the hydrolysis temperature to L-phenylglycine

Temp(°C)	25	40	60	70	80	90	100
Yield(%)	76	80	84	85	88	88	87

As shown in TABLE 1, most of amino acids could be converted to the corresponding amino alcohols in good to excellent yields, but only the L-methionine in poor yield. We suggest that the main reason is that the electron-rich sulfur would compete for BF_3 to interfere with the formation of the BF_3 complex.

CONCLUSION

In conclusion, we could show that $NaBH_4/BF_3{\cdot}Et_2O$

is an effective system for the preparation of chiral amino alcohols, though there is a room for further improvement.

REFERENCES

[1] G.F.Zhong, J.H.Fan, C.F.Barbas III; Tetrahedron Lett., **45**, 5681 **(2004)**.
[2] E.Bieberich, B.Hu, J.Silva, S.MacKinnon, R.K.Yu, H.Fillmore, W.C.Broaddus, R.M.Ottenbrite; Cancer Letters, **181**, 55 **(2002)**.
[3] M.Amat, M.Cantó, N.Llor, C.Escolano, E.Molins, E.Espinosa, J.Bosch; J.Org.Chem., **67**, 5343 **(2002)**.
[4] S.T.Wu, R.Takeya, M.Eto, C.Tomizawa; J.Pesticide Sci., **12**, 221 **(1987)**.
[5] G.J.Lee, T.H.Kim, J.N.Kimb, U.Lee; Tetrahedron: Asymmetry, **13**, 9 **(2002)**.
[6] D.Cassio, F.Lemoine, J.P.Waller, E.Sandrin, R.A.Boissonnas; Biochemistry, **6**, 827 **(1967)**.
[7] D.A.Dickman, A.I.Meyers, G.A.Smith; Org.Syn., **7**, 530 **(1985)**.
[8] J.R.Gage, D.A.Evans; Org.Syn., **68**, 77 **(1990)**.
[9] M.J.McKennon, A.I.Meyers; J.Org.Chem., **58**, 3568 **(1993)**.
[10] A.Atsushi, M.Satoru; Tetrahedron Lett., **33**, 5517 **(1992)**.
[11] R.C.Anand, Vimal; Tetrahedron Lett., **39**, 917 **(1998)**.
[12] Z.Y.Li, L.H.Wei, Z.Y.Chen; Zhongguo Yaowu Huaxue Zazhi, **11**, 170 **(2001)**.
[13] C.H.Zhang, N.F.Yang, L.W.Yang; Chinese Journal of Organic Chemistry, Youji Huaxue, **24**, 343 **(2004)**.
[14] X.Q.Wang, W.H.Chen, W.L.Zhao, B.Wang; Huaxue Shiji, **25**, 370 **(2003)**.
[15] A.Giannis, K.Sandhoff; Angew.Chem.lnt.Ed.Engl., **28**, 218 **(1989)**.
[16] F.T.Jere, D.J.Miller, J.E.Jackson; Org.Lett., **5**, 527 **(2003)**.
[17] R.Morris, J.Nagarkatti, J.Heaton, C.Lane; 'Aldrich Catalog Handbook of Fine Chemicals', 4nd Ed., Aldrich Chemical Company, United States, **(1996-1997)**.
[18] S.D.Cho, Y.D.Park, J.J.Kim, J.R.Falck, Y.Jin.Yoon; Bull.Korean Chem.Soc., **25**, 407 **(2004)**.
[19] J.Qin, G.K.Friestad; Tetrahedron, **59**, 6393 **(2003)**.