Tetrahedron Letters, Vol. 33, No. 38, pp. 5517-5518, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

An Improved, Convenient Procedure for Reduction of Amino Acids to Aminoalcohols: Use of $NaBH_4$-H_2SO_4

Atsushi Abiko* and Satoru Masamune

Institute for Fundamental Research, Kao Corporation,
Ichikai-machi, Haga-gun, Tochigi, 321-34, Japan

Abstract: The use of $NaBH_4$-H_2SO_4 for the reduction of α-amino acids to the corresponding aminoalcohols offers definite advantages: i) operational simplicity, ii) ease of scaling up the reaction without risking explosion, and iii) use of the inexpensive reagents.

During the course of our recent studies of bisoxazoline chemistry[1)] we needed to develop a convenient and reliable procedure for the mole-scale synthesis of α,β-aminoalcohols from the corresponding α-amino acids. Although there exist several methods[2)], including those described in *Organic Syntheses*[2a,b)], (and also some aminoalcohols are commercially available,) these methods require the use of rather expensive reagents (e.g., $LiBH_4$, BH_3-SMe_2) and/or careful control of reaction conditions to minimize the risk of explosion that may occur after the induction period. We recommend herein the use of the two inexpensive reagents, $NaBH_4$ and H_2SO_4, as exemplified by the reduction of D-phenylglycine.

To a stirred suspension of $NaBH_4$ (100g, 2.5mol) in THF (1L, reagent grade without further purification) was added D-phenylglycine (151g, 1.0mol). The flask was immersed in an ice-water bath, and a solution of (fresh) conc. H_2SO_4 (66mL, 1.25mol) in ether (total volume of 200mL) was added dropwise at such a rate as to maintain the reaction mixture below 20°C (addition time, approximately 3h). Stirring of the reaction mixture was continued at room temperature overnight and MeOH (100mL) was added carefully to destroy excess BH_3. The mixture was concentrated to ca. 500mL and 5N NaOH (1L) was added. After removing the solvent that distilled below 100° C, the mixture was heated at reflux for 3h. The turbid aqueous mixture was cooled and filtered through a thin pad of Celite® which was washed with water. The filtrate and the washings were combined and diluted with additional water to ca.1L. The CH_2Cl_2 extraction (4 x 500mL) followed by evaporation of the solvent left solid phenylglycinol, which was recrystallized from ethyl acetate and hexane to yield 115g (84% including the second crop) of the pure product (mp. 74-76° C, >98 %ee by analysis of the ^{1}H-NMR of the bis-MTPA derivative).

The application of the $NaBH_4$-H_2SO_4 procedure to other amino acids is summarized in Table I. Protected amino acids were also reduced; alanine benzamide was reduced to N-benzylalaninol, while the N-Cbz and N-tosyl groups remained unaffected.

Table I. Reduction of Amino Acids and Their Derivatives with $NaBH_4$-H_2SO_4.

Amino Acid	Yield of Aminoalcohol (%)	mp (bp/mmHg)	Amino Acid	Yield of Aminoalcohol (%)	mp (bp/mmHg)
L-Val.	89	(100°C /26)	D-PhGly.	84	74-76°C
L-Met.	91	(133-136°C /8)	Bz-Ala.	80 (N-Bn-alaninol)	(100°C /0.2)
L-Phe.	98	90-91°C	Ts-Ala.	91 (N-Ts-alaninol)	58-60°C
L-*tert*.Leu.	81	(100-102°C /18)	Z-Pro.	91 (N-Cbz-prolinol)	---

Table II. Reduction of L-Valine to L-Valinol with $NaBH_4$-Reagent

Reagent	Reaction Temp.(°C)	Yield of Valinol (%)	Reagent	Reaction Temp.(°C)	Yield of Valinol (%)
HCl	0	88	Me_2SO_4	40	83
BF_3-OEt_2	25	76	MeOTs	40	83
I_2	0	83	$MeSO_3H$	0	56
MeI	40	82			

The reduction of the carboxyl group was obviously effected by B_2H_6, generated *in situ*. Therefore, H_2SO_4 can be replaced by other reagents such as HCl[3a)], BF_3-OEt_2[3a)], I_2[3b)], MeI[3c)], Me_2SO_4[3c)], MeOTs[3c)] and $MeSO_3H$[3d)] as shown in Table II. Although the yields of valinol from valine are comparable with that shown in Table I, the $NaBH_4$-H_2SO_4 system offers the definite advantages: i) the reduction can be scaled up without risking explosion, ii) $NaBH_4$ and H_2SO_4 are inexpensive and iii) the execution of the reduction is simple, and even the rigorous drying of the solvent is unnecessary.

REFERENCES

1. a. Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
   b. Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
2. a. Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Org. Synth. Coll. vol.* VII, 530.
   b. Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.
   c. Pridgen, L. N.; Prol, Jr. J.; Alexander, B.; Gillyard, L. *J. Org. Chem.* **1989**, *54*, 3231.
   d. Giannis, A.; Sandhoff, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 218.
3. a. Zweifel, G.; Brown, H. C. *Org. Reactions* **1963**, *13*, 1.
   b. Freeguard, G. F.; Long, L. H. *Chem. Ind.* **1965**, 471.
   c. Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.* **1969**, *34*, 3923.
   d. Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402.

(Received in Japan 12 May 1992)