Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

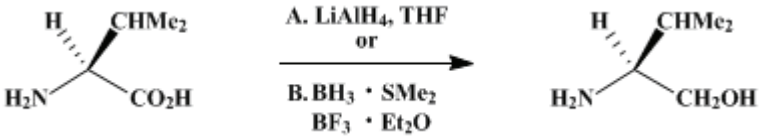
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.063.0136

Organic Syntheses, Coll. Vol. 7, p.530 (1990); Vol. 63, p.136 (1985).

REDUCTION OF α-AMINO ACIDS: L-VALINOL

[1-Butanol, 2-amino-3-methyl-, (S)-]



Submitted by D. A. Dickman[1], A. I. Meyers[1], G. A. Smith[2], and R. E. Gawley[2].
Checked by (A) Karl M. Smith, Clayton H. Heathcock, (B) Alan T. Johnson, Kraig M. Yager, and James D. White.

1. Procedure

Caution! A. Because of the hydrogen gas evolved during this reaction, this procedure should be carried out in an efficient fume hood.

An oven-dried, 3-L, three-necked flask equipped with a mechanical stirrer, a Friedrich condenser, and a nitrogen-inlet tube is flushed with nitrogen, and then charged with a suspension of lithium aluminum hydride (47.9 g, 1.26 mol) in 1200 mL of tetrahydrofuran (THF) (Note 1). The mixture is cooled (10°C, ice bath) and L-valine (100 g, 0.85 mol) is added in portions over a 30-min period from a 200-mL round-bottomed flask connected to the reaction flask via a flexible plastic sleeve so as not to produce too vigorous an evolution of hydrogen (Note 2). After the addition is complete, the plastic sleeve is replaced by a stopper, the ice bath is removed, and the reaction mixture is warmed to room temperature and then refluxed for 16 hr. The reaction mixture is then cooled again (10°C, ice bath) and diluted with ethyl ether (1000 mL) (Note 3). The reaction is quenched over a 30-min period with water (47 mL) (*Caution! See (Note 4)*, aqueous 15% sodium hydroxide (47 mL, over 20 min), and water (141 mL, over 30 min). The solution is stirred for 30 min and the white precipitate is filtered. The filter cake is washed with ethyl ether (3 × 150 mL) and the organic filtrates are combined, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Distillation of the residue under vacuum affords L-valinol (63.9–65.7 g, 73–75%) (Note 5) as a clear liquid: bp 63–65°C (0.9 mm) (Note 6): $[\alpha]_D^{20}$ + 14.6° (neat); n_D^{20} 1.455; IR (neat) cm[1]: 3300, 1590; ^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 6 H), 2.38–2.74 (m, 4 H), 3.13–3.78 (m, 2 H).

B. *Caution! Because of the foul odor of the methyl sulfide given off, this procedure, up to the methanol quench, should be carried out in a hood.*

A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, heating mantel, 250-mL graduated addition funnel, and an 8-in., air-cooled reflux condenser (West type) topped with a water-cooled distillation head and a 1-L receiving flask. It is connected to a nitrogen line through the still head. The glassware is either oven-dried and cooled in a desiccator or flame-dried and assembled while still hot. The assembly is flushed with nitrogen and charged with 200 g of L-valine (1.7 mol), 400 mL of tetrahydrofuran (THF) (Note 1), and 210 mL of freshly distilled boron trifluoride etherate (242 g, 1.7 mol). The mixture is heated at a rate sufficient to cause the THF to reflux gently (Note 7) and 188 mL (1.88 mol) of borane–methyl sulfide complex (BMS) (Note 8) is added dropwise over the course of 2 hr (Note 9). The solution is then refluxed for 18 hr. The methyl sulfide that has collected at the stillhead is discarded (Note 10), and the reaction mixture is cooled to 0°C and quenched by the slow addition of 200 mL of methanol. The addition funnel is replaced by a glass stopper, and the air-cooled condenser is removed, leaving the flask equipped for distillation of solvent through the distillation head. The reaction mixture is concentrated under reduced pressure with heating and stirring. The distillation head is replaced by a water-cooled reflux condenser, and the residue is dissolved in 1 L of 6 *M* sodium hydroxide and refluxed for 4 hr. The mixture is saturated with potassium carbonate (ca. 400 g); cooled; filtered through a Celite pad on a coarse, fritted funnel; and extracted with three 1-L portions of chloroform. The combined extracts are washed with three portions of saturated sodium chloride (500

mL each), stirred over anhydrous potassium carbonate for 24 hr, and concentrated under reduced pressure to give a yellow oil. The crude material is vacuum distilled to give 77.5 g (44%) of purified L-valinol, bp 62–67°C/2.5 mm(Note 6); $[\alpha]_D^{20}$ + 14.6° (neat), n_D^{20} 1.455; IR (neat film) cm^{-1}: 3300 (OH), and 1590 (NH_2); NMR δ: 0.92 (d, 6 H), 1.54 (m, 1 H), 2.38–2.74 (m, 4 H), 3.13–3.78 (m, 2 H).

2. Notes

1. Tetrahydrofuran is dried by distillation from sodium/benzophenone ketyl.
2. The hydrogen gas released during the addition of the amino acid should be vented through the nitrogen inlet to a bubbler at the back of the fume hood, well away from the mechanical stirrer motor and any other source of electrical spark.
3. Dilution is necessary to keep the reaction mixture from becoming too thick during the quench. Dilution with THF results in significantly lower yields.
4. An addition funnel was used for the dropwise addition of water. Care *must* be taken during this quench to ensure that all the escaping hydrogen gas is vented to the back of the fume hood through the nitrogen bubbler.
5. The submitters reported a yield of 73.7 g (84%).
6. The checkers found that L-valinol (mp 29–31°C) solidifies on distillation and will clog a water-cooled condenser. The use of a heat gun is recommended to avoid obstruction of the distillation pathway.
7. The temperature is maintained sufficiently high so that THF refluxes in the aircooled condenser while ether and methyl sulfide distill through the short-path distillation head.
8. The borane–methyl sulfide complex is available from Aldrich Chemical Company, Inc.
9. It is important that gentle reflux be maintained throughout the addition. If the solution is not heated during this period, an exothermic reaction occurs when the solution is refluxed.
10. Methyl sulfide should be destroyed by slowly pouring the volatile distillate into I gallon of household bleach (5% sodium hypochlorite). After 30 min, the bleach solution may be discarded in the drain.

3. Discussion

The reduction of amino acids to the corresponding amino alcohols via their ethyl ester hydrochlorides has been reported using lithium aluminum hydride[3] and sodium borohydride.[4] The reduction of several amino acids with borane–methyl sulfide (BMS) has also been reported.[5] The reduction of proline to prolinol with lithium aluminum hydride in THF was reported by Enders[6] and of valine to valinol by Meyers.[7] Procedure A (see Section A) is adapted from the latter work. The submitters have used the same procedure to reduce alanine to alaninol (70% yield), phenylglycine to phenylglycinol (76% yield), phenylalanine to phenylalaninol (87% yield), and *N*-benzoylvaline to *N*-benzylvalinol (76% yield).

Procedure A using LAH is faster and more convenient than the BMS procedure (B). Both procedures are general for the reduction of amino acids to amino alcohols. If functional group incompatibility is precluded, lithium aluminum hydride reduction is preferable.

The borane procedure (B) is a hybrid of two methods, Lane's procedure for BMS/trimethyl borate reduction of anthranilic acid,[8] and Brown's procedure for enhanced-rate reductions of several functional groups with BMS by distilling off the methyl sulfide during the course of the reaction.[9] The submitters have obtained a 97% crude yield (44–51% yield after distillation) of prolinol using this procedure. Lane reports that the following additional amino acids can be reduced using BMS/BF_3 etherate: leucine, phenylalanine, and 6-aminocaproic acid.[5] Meyers has added phenylglycine to the list, and has confirmed the optical purity of the amino alcohols obtained by preparation of the Mosher amides.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 204
- Org. Syn. Coll. Vol. 8, 528

References and Notes

1. Procedure A. Department of Chemistry, Colorado State University, Ft. Collins, CO 80523.
2. Procedure B. Department of Chemistry, University of Miami, Coral Gables, FL 33124.
3. Karrer, P.; Portmann, P.; Suter, M. *Helv. Chim. Acta* **1949**, *32*, 1156; Karrer, P.; Naik, A. R. *Helv. Chim. Acta* **1948**, *31*, 1617.
4. Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S. *Chem. Pharm. Bull.* **1965**, *13*, 995.
5. Lane, C. F., U.S. Patent 3935280, 1976; *Chem. Abstr.* **1976**, *84*, 135101p.
6. Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.
7. Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.
8. Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052.
9. Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.
10. Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

benzophenone ketyl

BMS

BF_3 etherate

potassium carbonate (584-08-7)

methanol (67-56-1)

ethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

alanine (56-41-7)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sodium (13966-32-0)

Anthranilic Acid (118-92-3)

sodium hypochlorite (7681-52-9)

6-aminocaproic acid (60-32-2)

borane (7440-42-8)

methyl sulfide (75-18-3)

phenylalanine (63-91-2)

proline (147-85-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

leucine (61-90-5)

valine (72-18-4)

phenylglycine (103-01-5)

boron trifluoride etherate (109-63-7)

sodium borohydride (16940-66-2)

trimethyl borate (121-43-7)

L-Valinol,
1-Butanol, 2-amino-3-methyl-, (S)-,
valinol (2026-48-4)

prolinol (23356-96-9)

alaninol (2749-11-3)

phenylglycinol (7568-93-6)

phenylalaninol (3182-95-4)

N-benzoylvaline

N-benzylvalinol