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.

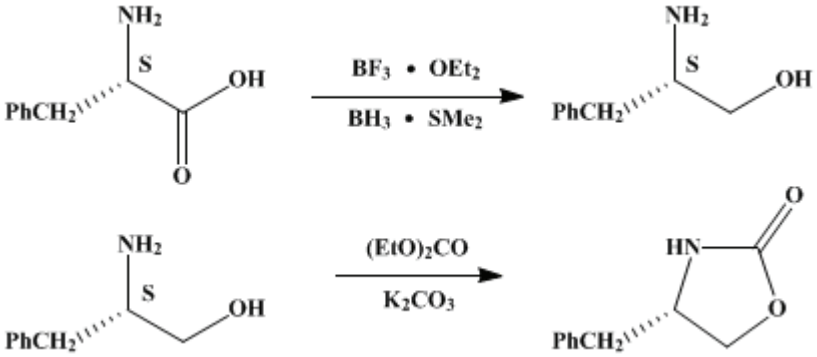
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.068.0077

Organic Syntheses, Coll. Vol. 8, p.528 (1993); Vol. 68, p.77 (1990).

(*S*)-4-(PHENYLMETHYL)-2-OXAZOLIDINONE

[2-Oxazolidinone, 4-(phenylmethyl)-, (*S*)-]



Submitted by James R. Gage and David A. Evans[1].
Checked by Philip G. Meister and Leo A. Paquette.

1. Procedure

Caution! This reaction should be carried out in a hood since dimethyl sulfide is liberated during the course of the reaction.

A. *(S)-Phenylalanol*. A dry, 3-L, three-necked flask is equipped with a mechanical stirrer and a reflux condenser connected to a mineral oil bubbler. The flask is loaded with 165 g (1.00 mol) of (*S*)-phenylalanine (Note 1), then equipped with a 250-mL pressure-equalized addition funnel capped with a rubber septum through which is inserted a nitrogen inlet needle. The flask is swept with nitrogen and filled with 500 mL of anhydrous tetrahydrofuran, and the addition funnel is charged with 123 mL (1.00 mol) of freshly distilled boron trifluoride etherate via cannula (Note 2). The boron trifluoride etherate is added dropwise to the phenylalanine slurry over a 30-min period with stirring, and the mixture is heated at reflux for 2 hr, resulting in a colorless, homogeneous solution. The addition funnel is then charged via cannula with 88 g (110 mL, 1.15 mol) of 20 *M* borane–dimethyl sulfide complex (Note 3), which is added carefully to the *vigorously* refluxing solution over a 100-min period. During the course of the addition there is continuous evolution of dimethyl sulfide and hydrogen gas, and the solution turns from orange to light brown. A vigorous exotherm occurs approximately half way through the addition period. *(Caution! See (Note 4))* The solution is heated at reflux for an additional 6 hr after the addition is complete (Note 5) and (Note 6), then allowed to cool to ambient temperature. The excess borane is quenched by the slow addition of 125 mL of a 1:1 tetrahydrofuran–water solution followed by 750 mL of 5 *M* aqueous sodium hydroxide. The resulting two-phase mixture is heated at reflux for 12 hr, cooled to room temperature, and filtered through a coarse fritted funnel. The residual solids are washed with two 25-mL portions of tetrahydrofuran, and the filtrate is concentrated on a rotary evaporator to remove the bulk of the tetrahydrofuran. The resulting slurry is extracted with one 400-mL and three 200-mL portions of dichloromethane. The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation, yielding 141–158 g (93–104%) of a white crystalline solid that is recrystallized from ca. 600 mL of ethyl acetate to give 111–113 g (73–75%) of the desired product as white needles in two crops, mp 88.5–91°C (Note 7).

B. *(S)-4-(Phenylmethyl)-2-oxazolidinone*. A dry, 1-L, three-necked flask is equipped with a mechanical stirrer and a 12-in. Vigreux column fitted with a distillation head and a 200-mL receiver flask connected to a nitrogen source and a bubbler. The flask is charged with 151 g (1.00 mol) of (*S*)-phenylalanol, 13.8 g (0.100 mol) of anhydrous potassium carbonate, and 250 mL (2.06 mol) of diethyl carbonate (Note 8). The mixture is lowered into an oil bath, preheated to 135°C, and is stirred until dissolution is achieved (ca. 5 min). The distillation receiver is cooled in an ice bath, and ca. 120 mL of

ethanol is collected from the reaction over a 2.5-hr period. The oil bath is removed on cessation of the ethanol distillation. After the light-yellow solution is cooled to ambient temperature, it is diluted with 750 mL of dichloromethane, transferred to a separatory funnel, and washed with 750 mL of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotary evaporator affording 200 g (113%) of a white crystalline solid. This material is taken up into 600 mL of a hot 2:1 ethyl acetate–hexane solution, filtered while hot, then allowed to crystallize to afford 136–138 g (78–79%) of large white plates, mp 84.5–86.5°C (Note 9) and (Note 10).

2. Notes

1. (*S*)-Phenylalanine was obtained by the submitters from Ajinomoto Company, Inc. The starting material obtained by the checkers from Sigma Chemical Company was dried under reduced pressure over phosphorus pentoxide for 2 days.
2. Reagent-grade tetrahydrofuran (Fisher Scientific Company) was either freshly distilled from sodium metal and benzophenone or dried for at least 24 hr over activated Linde 4-Å molecular sieves. Boron trifluoride etherate was redistilled prior to use. Fresh bottles of redistilled born trifluoride etherate purchased from Aldrich Chemical Company, Inc. also usually give good results.
3. Borane–dimethyl sulfide (10 M) was purchased from Aldrich Chemical Company, Inc. and used as received.
4. The potential vigor of this exotherm cannot be overemphasized. It occurs later and is correspondingly stronger if vigorous reflux is not maintained during the addition. The reaction mixture should be watched closely throughout the addition of borane, and addition should be temporarily suspended at the onset of the exotherm.
5. Dimethyl sulfide can be collected if desired by inserting a trap cooled in an acetone–dry ice bath into the hose leading to the bubbler.
6. Yields sometimes drop when an old bottle of borane–dimethyl sulfide is used. Reaction progress can be monitored by thin-layer chromatography (silica gel, eluting with 10 : 10 : 1 chloroform–methanol–concentrated ammonium hydroxide). Any remaining phenylalanine stains heavily when exposed to ninhydrin (R_f = 0.35). If phenylalanine is detected after 5 hr of reflux, an additional 10 mL (0.10 mol) of borane–dimethyl sulfide is added via syringe, and the solution is heated at reflux for an additional 1 hr.
7. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1}: 3625, 3360, 3035, 2930, 2855, 1497, 1456, 1032; ^1H NMR ($CDCl_3$) δ: 1.5–2.0 (broad s, 3 H, NH_2, OH), 2.5 (dd, 1 H, $HCHC_6H_5$), 2.8 (dd, 1 H, $HCHC_6H_5$), 3.1 (m, 1 H, $CHNH_2$), 3.4 (dd, 1 H, HCHOH), 3.7 (dd, 1 H, HCHOH), 7.1–7.4 (m, 5 H, ArH); $[\alpha]_D$ −24.7° (ethanol, *c* 1.03). The checkers recorded $[\alpha]_D$ −22.4° (ethanol, *c* 1.03).
8. Diethyl carbonate (99%) was used as received from Aldrich Chemical Company, Inc.
9. The product has the following spectroscopic properties: IR (solution in dichloromethane) cm^{-1}: 3460, 3020, 1760, 1480, 1405, 1220; ^1H NMR ($CDCl_3$) δ: 2.9 (d, 2 H, $CH_2C_6H_5$), 4.0–4.6 (m, 3 H, $CHCH_2O$), 5.6 (broad s, 1 H, NH), 7.1–7.5 (m, 5 H, ArH); $[\alpha]_D$ +4.9° (ethanol, *c* 1.10).
10. The enantiomeric excess was determined to be >99% by capillary GLC analysis (30-m × 32-mm WCOT column coated with carbowax 20 M, hydrogen carrier gas, linear velocity ca. 94 cm/sec, oven temperature 225°C) of the imide derived from the Mosher acid chloride.[2]

3. Discussion

The utilization of α-amino acids and their derived β-amino alcohols in asymmetric synthesis has been extensive.[3] A number of procedures have been reported for the reduction of a variety of amino acid derivatives; however, the direct reduction of α-amino acids with borane has proved to be exceptionally convenient for laboratory-scale reactions.[4] These reductions characteristically proceed in high yield with no perceptible racemization. The resulting β-amino alcohols can, in turn, be transformed into oxazolidinones, which have proved to be versatile chiral auxiliaries. Besides the highly diastereoselective aldol addition reactions,[5] enolates of *N*-acyl oxazolidinones have been used in conjunction with asymmetric alkylations,[6] halogenations,[7] hydroxylations,[8] acylations,[9] and azide transfer processes,[10] all of which proceed with excellent levels of stereoselectivity.

The phenylalanine-derived oxazolidinone featured here enjoys three practical advantages over the valine-derived oxazolidinone developed earlier in this laboratory.[5] First, both the intermediate β-amino

alcohol and the derived oxazolidinone are crystalline solids that can be purified conveniently by direct crystallization. Second, the oxazolidinone contains a UV chromophore which greatly facilitates TLC or HPLC analysis when it is employed as a chiral auxiliary. Finally, both enantiomers of phenylalanine are readily available, enabling stereocontrol in either sense simply by using the oxazolidinone derived from the appropriate enantiomer.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 339

References and Notes

1. Department of Chemistry, Harvard University, Cambridge, MA 02138.
2. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
3. Coppola, G. M.; Schuster, H. F. "Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids"; Wiley: New York, 1987.
4. Smith, G. A.; Gawley, R. E. *Org. Synth., Coll. Vol. VII* **1990**, 530.
5. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
6. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
7. Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123.
8. Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
9. Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.
10. Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.

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

Mosher acid chloride

phenylalanine-derived oxazolidinone

valine-derived oxazolidinone

ethanol (64-17-5)

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

dimethyl sulfide (75-18-3)

phenylalanine,
(S)-Phenylalanine (63-91-2)

Tetrahydrofuran (109-99-9)

diethyl carbonate (105-58-8)

hexane (110-54-3)

boron trifluoride etherate (109-63-7)

ninhydrin (938-24-9)

(S)-Phenylalanol (3182-95-4)

phosphorus pentoxide (1314-56-3)

born trifluoride etherate

(S)-4-(Phenylmethyl)-2-oxazolidinone,
2-Oxazolidinone, 4-(phenylmethyl)-, (S)- (90719-32-7)