Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

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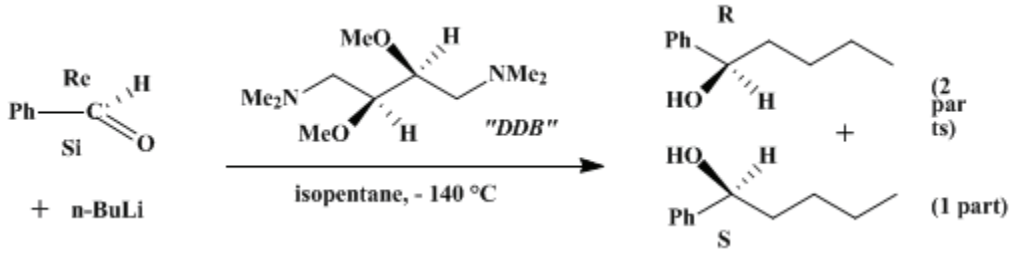
ENANTIOSELECTIVE ADDITION OF BUTYLLITHIUM IN THE PRESENCE OF THE CHIRAL COSOLVENT DDB: (*R*)-(+)-1-PHENYL-1-PENTANOL

[Benzenemethanol, α-butyl-, (*R*)-]

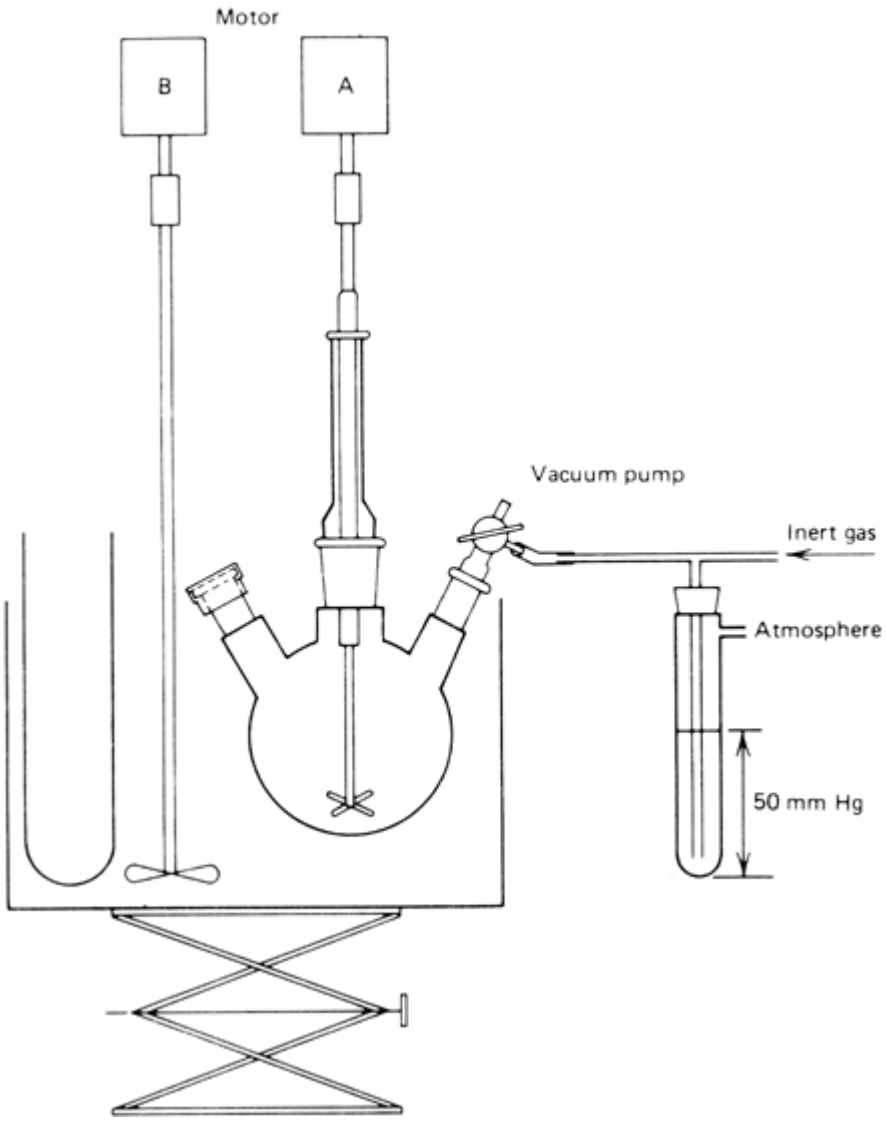


Submitted by Dieter Seebach and August Hidber[1].
Checked by M. F. Semmelhack and Charles Shuey.

1. Procedure

As shown in Figure 1, a dry, 1-L, three-necked flask is equipped with an overhead stirrer bearing a four-bladed propeller of ca. 2.5-cm diameter driven by a strong, safely connected motor A (Note 1), a rubber septum, and a three-way stopcock. The air in the flask is replaced by dry argon or nitrogen, the pressure of which is maintained during the reaction at ca. 50 mm above atmospheric pressure with a mercury bubbler (Note 2). A second stirrer (motor B, Figure 1) to agitate the bath is attached next to the flask with the propeller just below the bottom of the flask. Finally, a 4.5-cm × 20-cm test tube is held next to the bath stirrer. The entire apparatus (Figure 1) is mounted well above the bench to allow for immersion of the flask, bath stirrer, and tube into cooling baths and for exchange of bulky bath containers with the aid of a lab jack. The flask is charged (Note 3) with 400 mL of 2-methylbutane (isopentane) (Note 4) and 24.6 g (27.5 mL, 0.12 mol) of (*S,S*)-(+)-*N,N,N′,N′*-tetramethyl-1,4-diamino-2,3-dimethoxybutane (DDB) (Note 5). A methanol–dry ice bath is raised to immerse the flask and cool the contents to −78°C with slow stirring, whereupon 0.021 mol of butyllithium (13.5 mL of a 1.56 *M* solution in hexane) (Note 6) is added within a few minutes. A second cooling bath is prepared in a ca. 7-L Dewar cylinder (Note 7) by pouring liquid nitrogen into a stirred (glass rod) mixture of methylcyclohexane/isopentane (3 : 2) (Note 8) until about half of the liquid has solidified and a slush has been formed, the temperature of which is ca. −140°C (Note 9). The reaction flask is cooled to the lower temperature by exchanging baths and waiting for 15 min with bath stirring. The bath is temporarily lowered and cooled until again half frozen by pouring in liquid nitrogen and manual agitation (Note 10). From then on, cooling is kept constant by filling the tube in the stirred bath at intervals with liquid nitrogen (Note 10). A solution of 2.12 g (0.020 mol) of benzaldehyde (Note 11) in 20 mL of isopentane (Note 4) is added dropwise (Note 12) over 15 min to the vigorously stirred (ca. 1000 rpm) reaction mixture. After completion of the addition (ca. 0.5 hr), the bath is removed, the flask is warmed to ca. 0°C (Note 13), and the contents are poured into a 1-L separatory funnel containing 150 mL of ice-cold 2 *N* aqueous hydrochloric acid. The aqueous layer is extracted twice with 70 mL of hexane and saved for recovery of the chiral auxiliary agent DDB (Note 14). The combined organic layers are sequentially washed with saturated aqueous bicarbonate and sodium chloride solutions and concentrated in a rotary evaporator to ca. 200 mL. The solution is then transferred to a 500-mL separatory funnel and vigorously shaken with 40 mL of a saturated aqueous sodium bisulfite solution to precipitate the bisulfite adduct of unreacted benzaldehyde (Note 15). After filtration (if necessary) the residue and the aqueous phase are washed with hexane. The combined organic solution is dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. Simple distillation yields 2.60–2.95 g (80–90%) of 1-phenyl-1-pentanol, bp 54–56°C (0.02 mm), $[\alpha]_D = 6.13°$ (neat), (Note 16), optical yield 30% (Note 17).

Figure 1



2. Notes

1. The checkers used a conventional, flat, crescent-shaped Teflon blade, 8 cm long.
2. This is done as previously described in *Organic Syntheses* procedures: Seebach, D.; Beck, A. K. *Org. Synth., Coll. Vol. VI* **1988**, 869; Enders, D.; Pieter, R.; Seebach, D. *Org. Synth., Coll. Vol. VI* **1988**, 542. All connections should be securely fastened.
3. All additions of solvents and reagents are carried out through the rubber septum with dry, appropriately sized, and argon-flushed syringes with hypodermic needles. Because of its low boiling point, it is advantageous to force isopentane into the 100-mL syringe by applying pressure to the storage flask.
4. Isopentane (bp 28°C, ~95% 2-methylbutane), was purchased from Fluka AG, freshly distilled from P_2O_5, and stored under inert gas pressure.
5. DDB is presently available from Aldrich Chemical Company, Inc. For its preparation, see p. 000 in this volume. DDB is hygroscopic and must be refluxed for some time and freshly distilled from lithium aluminum hydride (bp 38°C/0.01 mm) prior to use. The submitters used material with $[\alpha]_D$ 14.7°; the checkers' sample showed $[\alpha]_D$ 14.3°.
6. Butyllithium was purchased from Metallgesellschaft, Frankfurt, and titrated for active alkyllithium using diphenylacetic acid as an indicator: Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

7. If no such Dewar container is available, two appropriately sized plastic buckets with a layer of styrofoam particles between the inner and outer bucket can be used.
8. The mixture was used as purchased from Fluka AG. The submitters have occasionally used, as a bath liquid, petroleum ether (bp 40–60°C) of unknown composition or pure isopentane (mp −160°C). In such cases, temperature control is necessary; it was achieved with a platinum temperature sensor inside the reaction mixture.
9. The checkers used a thermocouple to verify the temperature of the cooling bath.
10. The coolant must not be poured directly into the bath, because local overcooling can cause partial freezing of the reaction mixture, which is clear and homogeneous before addition of the aldehyde. If freezing should occur, the flask is temporarily warmed slightly by removing the bath.
11. Benzaldehyde was obtained from Fluka AG or Aldrich Chemical Company, Inc., and freshly distilled under reduced pressure (40°C/3 mm).
12. Clear drops of the aldehyde solution must fall from the tip of the needle directly into the reaction mixture. If the needle is inserted too far, the aldehyde can freeze and clog the needle; it is thawed by extracting the needle tip into the upper, warmer part of the neck.
13. A slow method is to wait until the ice that has condensed on the walls of the flask has all melted. Alternatively, the flask may be immersed in a methanol bath.
14. The combined aqueous layers of several runs are saturated with potassium hydroxide by adding KOH pellets with cooling. DDB separates on top of the aqueous phase and is extracted with ether. Distillation leads to ~90% recovery (bp 42–43°C/0.05 mm).
15. The checkers observed no precipitate formation at this point.
16. In five runs carried out by the submitters at temperatures between −140 and −150°C, the specific rotations of phenylpentanol (d_4^{20} 0.967) ranged from $[\alpha]_D$ 5.95 to 7.0° (29–34% optical yield; see (Note 17)). At dry ice temperature, the optical yields are only half as high.[2] The checkers obtained specific rotations of $[\alpha]_D$ 5.87° and 6.05° (28 and 29% optical yield).
17. For optically pure 1-phenyl-1-pentanol a specific rotation of $[\alpha]_D^{25}$ 20.7° (neat) is reported.[3]

3. Discussion

The optically active form of 1-phenyl-1-pentanol has been prepared by a variety of methods.[4] [5] [6,7] The present procedure is a modification and extended description of our previously published[2,8] chiral solvent method. DDB and other auxiliary agents from tartaric acid lead to a wide range of optically active products from achiral components with prochiral centers (enantioselective syntheses). A list of examples of DDB applications is found in the accompanying procedure describing its preparation from tartaric acid.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 153

References and Notes

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3. Horeau, J.; Guetté, J. P.; Weidmann, R. *Bull. Soc. Chim. Fr.* **1966**, 3513.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

P_2O_5

(S,S)-(+)-N,N,N',N'-tetramethyl-1,4-diamino-2,3-dimethoxybutane (DDB)

DDB

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

benzaldehyde (100-52-7)

potassium hydroxide,
KOH (1310-58-3)

tartaric acid (87-69-4)

Diphenylacetic acid (117-34-0)

methylcyclohexane (108-87-2)

magnesium sulfate (7487-88-9)

isopentane,
2-methylbutane (78-78-4)

butyllithium (109-72-8)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

1-phenyl-1-pentanol (583-03-9)

phenylpentanol (10521-91-2)

Benzenemethanol, α-butyl-, (R)-,
(R)-(+)-1-PHENYL-1-PENTANOL (19641-53-3)