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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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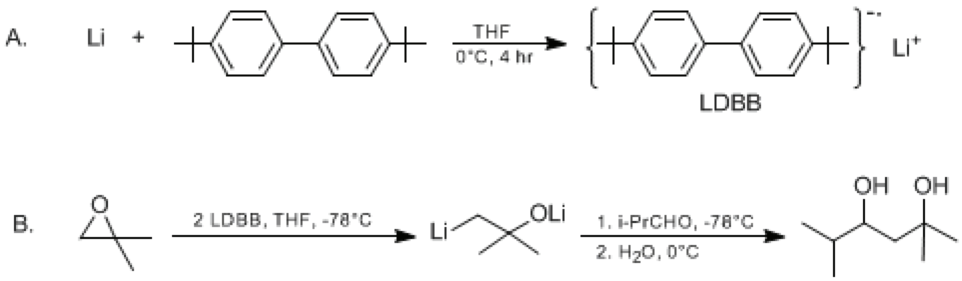
1,3-DIOLS FROM LITHIUM β-LITHIOALKOXIDES GENERATED BY THE REDUCTIVE LITHIATION OF EPOXIDES: 2,5-DIMETHYL-2,4-HEXANEDIOL

[2,4-Hexanediol, 2,5-dimethyl-]



Submitted by Boguslaw Mudryk and Theodore Cohen[1].
Checked by Hiroaki Hibino and Hisashi Yamamoto.

1. Procedure

A. *Lithium 4,4'-di-tert-butylbiphenylide (LDBB)*.[2] An oven-dried, three-necked round-bottomed, 1-L flask, equipped with a Teflon-coated magnetic stirring bar (Note 1), small, pressure-equalizing funnel, low temperature thermometer, and a gas inlet, is flushed with dry argon. The apparatus is charged with 600 mL (Note 2) of dry tetrahydrofuran (THF) (Note 3) and 56 g (0.21 mol) of 4,4'-di-tert-butylbiphenyl (DBB) (Note 4). Lithium pieces (1.5 g, 0.22 M) (Note 5) are then introduced under argon into the well-stirred DBB solution in THF at room temperature. As soon as the dark blue-greenish color of the LDBB solution appears, the flask is immersed in an ice-cold bath (Note 6) and the solution is vigorously stirred for 4 hr at 0°C. The LDBB solution so prepared is ready for further use.

B. *2,5-Dimethyl-2,4-hexanediol*. Isobutylene oxide (7.2 g, 0.10 mol) (Note 7) is added dropwise from the pressure-equalizing funnel to the LDBB solution in THF at −78°C at such a rate (the addition lasts for 8–12 min) that the temperature inside the flask does not exceed −78°C. After all the epoxide has been added (8–11 min), the solution becomes deep red. After 5 more minutes of stirring, isobutyraldehyde (7.2 g, 0.10 mol) (Note 8) is added dropwise within 5 min. The mixture is stirred for 1 hr at −78°C; it is allowed to reach 0°C by removing the cold bath, and finally is quenched with water (100 mL). After the mixture is extracted with ether (1 × 300 mL, 2 × 100 mL), the combined organic layers are dried with anhydrous magnesium sulfate ($MgSO_4$) and the solvents are evaporated under reduced pressure. The addition of cold methanol (250 mL) results in precipitation of most of the DBB as a white solid. The latter is crushed in methanol to a fine powder with a spatula and the methanolic suspension is placed in a freezer for 1 hr. The solid is filtered, washed with 50–250 mL of ice-cold methanol and air-dried; the yield is 49.1 g (88% recovery). The methanol is evaporated under reduced pressure and the product is isolated by flash chromatography (25% ethyl acetate in hexane as the eluent); yield 11.3–12.3 g (77–88%). An additional vacuum distillation at 104–105°C/13 mm provides >99% pure product, yield 9.2 g (62–66%) ((Note 9),(Note 10)).

2. Notes

1. A large size, football-shaped stirring bar is required to provide effective stirring.
2. At least this amount of THF is needed to ensure that the final LDBB concentration is below 0.4 M. More concentrated solutions solidify at −78°C.
3. Tetrahydrofuran was purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan (also available from Fisher Scientific Co.) and distilled from potassium benzophenone ketyl before use.
4. 4,4'-Di-tert-butylbiphenyl (97%) was used as purchased from Aldrich Chemical Company, Inc.

5. The submitters used lithium (99.9%, Alfa Products) as a ribbon (0.28 mm thick, 25 mm wide). [The checkers used lithium (99.9%, Aldrich Chemical Company, Inc.) as a wire (3.2 mm diam. in mineral oil).] Its surface was cleaned by scraping off the lithium oxide and nitride with an X-Acto knife under mineral oil. The ribbon was then cut into 20–30 mg pieces that were rinsed with pentane before use.

6. A 2.5-L Dewar flask (I.D. = 170 mm) was employed for the 0°C and −78°C cooling baths.

7. Isobutylene oxide was used as purchased from Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan (also available from TCI America).

8. Isobutyraldehyde purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan (also available from Aldrich Chemical Company, Inc.) was purified by distillation immediately before use.

9. The diol was characterized by ^{1}H NMR and ^{13}C NMR; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.92 (d, J = 6.8) and 0.93 (d, J = 6.8) (6 H), 1.28 (s) and 1.31 (s) (6 H), 1.49 (dd, 1 H, J = 2.5 and 14.5), 1.57–1.69 (m, 2 H), 3.00 (s, 2 H), 3.77 (ddd, 1 H, J = 2.5, 5.4 and 10.3); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 17.4, 17.6, 27.0, 31.5, 33.7, 43.2, 71.0, 73.8.

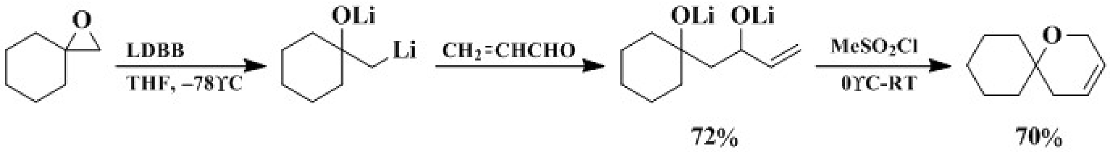
10. The submitters have employed the procedure described above for some other epoxides. The yields of diols resulting from trapping the intermediate β-lithioalkoxides with aldehydes were generally lower than in the small-scale experiments.[3] This may be caused in part by the longer period of addition of the epoxide that is required to maintain a low temperature, thus allowing more time for destruction of the dianion that is being generated. In cases where the alkoxide group is not tertiary, the product yield is lowered by transfer of the carbinol hydride ion to the aldehyde to produce a new alkoxide and an enolate ion. Thus, propylene oxide, after reductive cleavage with LDBB and trapping with isobutyraldehyde or *p*-anisaldehyde, provided 5-methyl-2,4-hexanediol in 40–50% yield or 1-p-anisyl-1,3-butanediol in 44% yield, respectively (in both cases about equal mixtures of diastereoisomers were obtained). The cyclohexene oxide-derived dianion, when trapped with isobutyraldehyde, gave 2-(1-hydroxy-2-methylpropyl)cyclohexanol in 71% yield as a mixture of only partially separable isomers in the ratio 15:11:39:35.

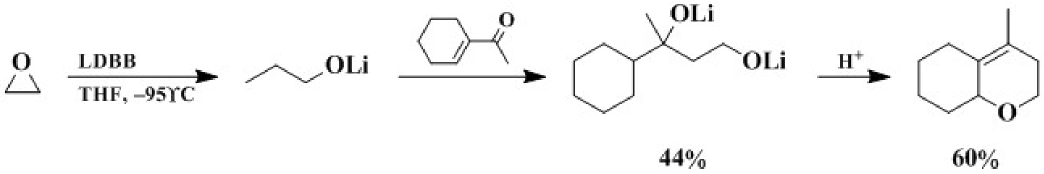
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present example represents a larger-scale version of a recently described synthesis of 1,3-diols from aldehydes and lithium β-lithioalkoxides.[3,4] These useful dianions can be conveniently generated from epoxides at −78°C in THF by the reductive cleavage of the carbon-oxygen bond using the powerful reducing agent LDBB. Previously reported reductions of epoxides with alkali metals were carried out in protic media and therefore the intermediate dianions were immediately destroyed by protonation by the solvent.[5] [6] [7] [8] The reductive opening of 2,2-dialkyl epoxides is highly regioselective and always leads to the less-substituted organolithium and the more-substituted alcoholate.[3,9] The procedure can also be useful for monosubstituted epoxides, provided that they are employed in excess toward the aldehyde. They are cleaved mainly to produce the primary organolithiums, but they do undergo a minor degree of ring cleavage yielding the secondary organolithiums, which are known to expel lithium oxide rapidly[10] [11] [12] to form easily removable olefins. Lithium β-lithioalkoxides can be trapped at −78°C with a variety of aldehydes and ketones yielding 1,3-diols with different substitution patterns.[3] When conjugated enones are employed as electrophiles, unsaturated cyclic ethers can be produced in one pot by activating the allylic hydroxyl group toward displacement by the other hydroxyl group with allylic inversion:[3]





Although lithium β-lithioalkoxides can also be generated from β-halo alcohols by deprotonation and subsequent reductive lithiation of the carbon-halogen bond[10,13] or from β-halo ketones by organolithium addition to the carbonyl group followed by reductive lithiation,[13] the current method is more direct as well as more convenient, since epoxides are readily available either commercially or by a variety of procedures.

Despite the lack of diastereoselectivity and the moderate yields, the present procedure complements other syntheses of 1,3-diols such as hydride reductions of β-diketones,[14] [15] β-hydroxy ketones[16] [17] [18] [19] [20] [21] and β-keto esters,[22] or the opening of 2,3-epoxy alcohols[23] [24] [25] [26] and 3,4-epoxy alcohols[27] with Lipshutz cuprates.

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

potassium benzophenone ketyl	
ethyl acetate	(141-78-6)
methanol	(67-56-1)
ether	(60-29-7)
propylene oxide	(75-56-9)
Pentane	(109-66-0)
lithium	(7439-93-2)
magnesium sulfate	(7487-88-9)
isobutyraldehyde	(78-84-2)
Tetrahydrofuran	(109-99-9)
isobutylene oxide	(558-30-5)
hexane	(110-54-3)
argon	(7440-37-1)
p-anisaldehyde	(123-11-5)
2,5-Dimethyl-2,4-hexanediol, 2,4-Hexanediol, 2,5-dimethyl-	(3899-89-6)
Lithium 4,4'-di-tert-butylbiphenylide	(61217-61-6)
4,4'-di-tert-butylbiphenyl	(1625-91-8)
lithium oxide	
5-methyl-2,4-hexanediol	
1-p-anisyl-1,3-butanediol	

2-(1-hydroxy-2-methylpropyl)cyclohexanol

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