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.

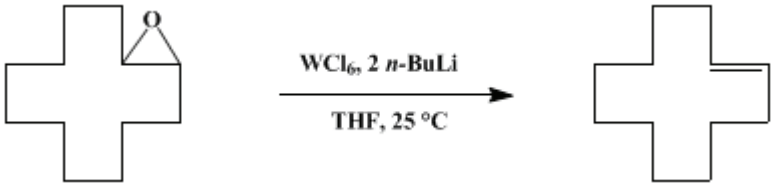
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries 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.060.0029

Organic Syntheses, Coll. Vol. 7, p.121 (1990); Vol. 60, p.29 (1981).

DEOXYGENATION OF EPOXIDES WITH LOWER VALENT TUNGSTEN HALIDES: *trans*-CYCLODODECENE



Submitted by Martha A. Umbreit and K. Barry Sharpless[1].
Checked by Ronald F. Sieloff, Michael F. Reinhard, and Carl R. Johnson.

1. Procedure

Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with great care.

A dry, 1-L, three-necked flask equipped with a thermometer, a mechanical stirrer, and a rubber septum is flushed with nitrogen (admitted through a hypodermic needle in the septum). A nitrogen atmosphere is maintained throughout the subsequent reaction. The flask is charged with 420 mL of tetrahydrofuran (Note 1), and the solvent is cooled to −62°C in an acetone–dry ice bath. Tungsten hexachloride (60g, 0.15 mol) (Note 2) is then introduced. While the cold suspension is stirred, 31 mL (0.30 mol) of 90% butyllithium in hexane (Note 3) is added slowly from a hypodermic syringe. The rate of addition (complete in ca. 5 min) is such that the temperature remains below −15°C. The resulting mixture is allowed to warm slowly to room temperature with stirring. The green-brown viscous suspension becomes a dark-brown homogeneous solution that eventually turns green at room temperature. Because the reaction with the epoxide is exothermic, the flask is momentarily returned to the acetone–dry ice bath while 14.8 g (0.081 mol) of *trans*-cyclododecene oxide (Note 4) and (Note 5) is introduced with a hypodermic syringe. The cooling bath is again removed and the reaction mixture is allowed to stir at room temperature. After 30 min (Note 6) the mixture is poured into 600 mL of an aqueous solution that is 1.5 *M* in sodium tartrate and 2 *M* in sodium hydroxide (Note 7), and extracted with 240 mL of hexane. The organic phase is washed with a mixture of 160 mL of water and 80 mL of aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure with a rotary evaporator. The residual liquid is distilled under reduced pressure affording 10.5–10.8 g (78–82%) of cyclododecene as a colorless liquid, bp 92–98°C (4.1 mm) (Note 8), 92% *trans* and 8% *cis* by analysis on a ¼-in. × 6-ft GLC column packed with 10% $AgNO_3$ and 5% Carbowax 20 M on 80–100 mesh Chromosorb W at 110°C.

2. Notes

1. Reagent-grade tetrahydrofuran was freshly distilled from sodium and benzophenone and maintained under nitrogen. In small-scale experiments (1 mmol of tungsten hexachloride in 10 mL of solvent) anhydrous ether was equally effective, but did not give a homogeneous reaction solution.
2. Tungsten hexachloride, purchased from Pressure Chemical Company, was used without further purification. The dark blue-black crystals were pulverized in a dry box or glove bag under a nitrogen atmosphere prior to use. Upon exposure to air or moisture yellow or orange oxides form. Slight contamination from these products does not interfere with the deoxygenation.
3. A suspension of 90% butyllithium in hexane was purchased from Alfa Products, Morton Thiokol, Inc. and was not standardized. The suspension was shaken to obtain uniform density before it was taken up into the syringe. For smaller-scale reactions the submitters report that 15% (1.6 *M*) butyllithium in hexane or methyllithium in ether is convenient and effective.
4. *trans*-Cyclododecene oxide, purchased from Aldrich Chemical Company, Inc., was used without further purification. The purity of the cyclododecene oxide sold by Aldrich varies, but it is usually > 95% trans; in this case it was 98% trans and 2% cis by analysis on a 1/8-in. × 6-ft. GLC column packed

with 3% OV-17 on 80–100-mesh Gas-Chrom Q at 140°C. It is not necessary to wait until the brown solution becomes green before adding the epoxide. After epoxide addition the solution is dark green and appears homogeneous.
5. Molar ratios of tungsten reagent to epoxide of less than 1.5 : 1 resulted in incomplete reaction, while ratios greater than 3 : 1 did not improve, and in some cases actually diminished, the yield of alkene. Ratios of ca. 2 : 1 proved generally effective for a variety of epoxides. Molar ratios of alkyllithium to tungsten hexachloride of less than 2 : 1 also gave incomplete reaction; ratios of 3 : 1 or 4 : 1 are believed to give rise to different reduced tungsten species, which may be used in other reductions.
6. The reaction may be monitored by quenching small aliquots in aqueous 20% sodium hydroxide, extracting into hexane, and analyzing by gas chromatography.
7. Aqueous alkali alone, unless in huge excess, produces an emulsion. The addition of a chelating agent such as tartrate permits a clean separation of phases in a workup of reasonable dimension. A minimum of 6 mol of tartrate and 6 mol of hydroxide per mole of tungsten hexachloride used is adequate to suppress emulsions.
8. An IR spectrum of the product was identical to that of an authentic sample of *trans*-cyclododecene. The ^{1}H NMR spectrum of the product was as follows: δ 1.4 (m, 16 H); 2.2 (m, 4 H, -CH_2-CH=CH-CH_2); 5.5 (m, -CH=CH-).

3. Discussion

This procedure illustrates a general, one-step method to deoxygenate di- or trisubstituted epoxides to olefins in high yield and with high retention of stereochemistry.[2] Reductions are usually complete in less than 1 hr at room temperature or below. In certain cases yields and stereochemical retention have been maximized by using 3 equiv of alkyllithium for each equivalent of WCl_6, or by adding LiI.[2] The reagent is compatible with ethers and esters. It has been used to reductively couple aldehydes and ketones, but considerably longer reaction times and excess reagent are required for appreciable coupling.

Chlorohydrin salts are reduced by the reagent at elevated temperatures and extended reaction times, with complete loss of stereochemistry. Unlike the more highly substituted epoxides, terminal and unsubstituted cyclohexene epoxides appear to proceed, at least in part, via such intermediates, and must be refluxed for several hours to obtain olefins.

Epoxides have been converted to olefins stereoselectively and in good yield by preparation of the iodohydrins, which are then reduced with stannous chloride in the presence of phosphoryl chloride and pyridine.[3] A mild, stereoselective epoxide reduction can be achieved with sodium (cyclopentadienyl) dicarbonylferrate, after several in situ steps; however, the large steric demands of this reagent limit its use to terminal or very accessible epoxides.[4] Olefins of inverted stereochemistry have been obtained by the reaction of epoxides with lithium diphenylphosphide and methyl iodide, followed by cis elimination of the resulting betaine.[5] The reduced tungsten reagent complements these methods by reducing the more highly substituted epoxides with retention of stereochemistry. It should be especially useful when iodohydrin formation is sterically impeded or when conditions for the stereospecific iodohydrin reduction are objectionable.

Deslongchamps[6] and Masamune[7] have both encountered molecules in which the epoxide moiety was so severely shielded on the backside that any trans addition (e.g., iodohydrin formation) was inconceivable. Reduction with the tungsten reagent have excellent yields of olefin in both cases. Parker employed the tungsten reagent to selectively reduce the trisubstituted epoxides of the trisepoxide of humulene, in effect functionalizing the least reactive double bond of the parent triene.[8] Masamune and Parker found that other standard reagents for epoxide reduction failed in these cases; Deslongchamps did not try other methods.

A variety of reducing metals,[3,9] chromous salts,[10] and lower valent iron[11] and titanium[12] salts convert epoxides to olefins in one step, but yields are usually low or moderate and stereochemistry is largely or completely lost. Routes involving thionocarbonates,[13] episulfides,[14] and episelenides[15] have also been used to convert epoxides to olefins. Epoxides activated by adjacent carbonyl, ester, or hydroxy groups have been reduced by special methods.[16]

References and Notes

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
2. Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc*. **1972**, *94*, 6538–6540.
3. Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc*. **1959**, 112–127.
4. Giering, W. P.; Rosenblum, M.; Tancrede, J. *J. Am. Chem. Soc*. **1972**, *94*, 7170–7172.
5. Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc*. **1971**, *93*, 4070–4072.
6. Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; LaPalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. Ruest, L.; Deslongchamps, P. *Can. J. Chem*. **1979**, *57*, 3348–3354.
7. Masamune, S.; Massachusetts Institute of Technology, private communication; see also Suda, M. Ph.D. Dissertation, University of Alberta, 1975, p. 54; Souto-Bachillar, F. A. Ph.D. Dissertation, University of Alberta, 1978, p. 63.
8. Sattar, A.; Forrester, J.; Moir, M.; Roberts, J. S.; Parker, W. *Tetrahedron Lett*. **1976**, 1403–1406.
9. Kupchan, S. M.; Maruyama, M. *J. Org. Chem*. **1971**, *36*, 1187–1191; Bertini, F.; Grasselli, P.; Zubiani, G. *J. Chem. Soc. Chem. Commun*. **1970**, 144; Sharpless, K. B. *J. Chem. Soc. Chem. Commun*. **1970**, 1450–1451.
10. Kochi, J. K.; Singleton, D. M.; Andrews, L. J. *Tetrahedron* **1968**, *24*, 3503–3515.
11. Fugisawa, T.; Sugimoto, K.; Ohta, H. *Chem. Lett*. **1974**, 883–886.
12. McMurray, J. E.; Fleming, M. P. *J. Org. Chem*. **1975**, *40*, 2555–2556.
13. Corey, E. J.; Carey, F. A.; Winter, R. *J. Am. Chem. Soc*. **1965**, *87*, 934–935.
14. Schuetz, R. D.; Jacobs, R. L. *J. Org. Chem*. **1961**, *26*, 3467–3471.
15. Clive, D. L. J.; Denyer, C. *J. Chem. Soc. Chem. Commun*. **1973**, 253; Chan, T. H.; Finkenbine, J. R. *Tetrahedron Lett*. **1974**, 2091–2094; Behan, J. M.; Johnstone, R. A. W.; Wright, M. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1216–1217; Krief, A.; VanEnde, D. *Tetrahedron Lett*. **1975**, 2709–2712.
16. Cole, W.; Julian, P. L. *J. Org. Chem*. **1954**, *19*, 131–138; Dowd, P.; Kang, K. *J. Chem. Soc. Chem. Commun*. **1974**, 384–385; Halsworth, A. S.; Henbest, H. B. *J. Chem. Soc*. **1960**, 3571–3575.

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

sodium (cyclopentadienyl) dicarbonylferrate

ether (60-29-7)

sodium hydroxide (1310-73-2)

iron (7439-89-6)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

stannous chloride

pyridine (110-86-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

hydroxide (14280-30-9)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

tungsten (7440-33-7)

tartrate

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

Methyllithium (917-54-4)

Cyclododecene (1501-82-2)

betaine (107-43-7)

phosphoryl chloride (10025-87-3)

lithium diphenylphosphide

titanium (7440-32-6)

Tungsten hexachloride

sodium tartrate (868-18-8)

cyclododecene oxide,
trans-cyclododecene oxide (286-99-7)

trans-Cyclododecene (1486-75-5)