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.

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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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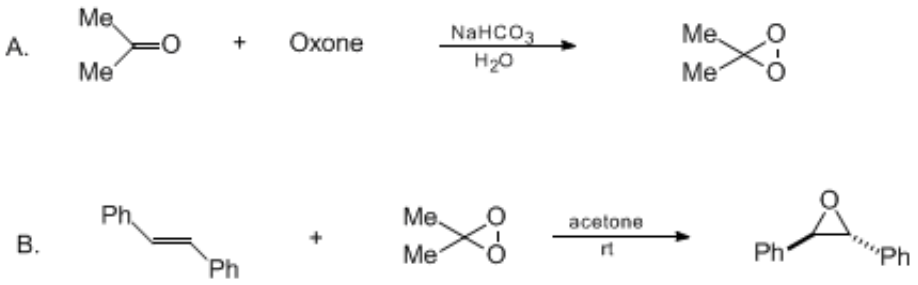
SYNTHESIS OF EPOXIDES USING DIMETHYLDIOXIRANE: trans-STILBENE OXIDE

[Dioxirane, dimethyl- and Oxirane, 2,3-diphenyl-, trans]



Submitted by Robert W. Murray and Megh Singh[1].
Checked by Thomas G. Marron, Lance A. Pfeifer, and William R. Roush.

1. Procedure

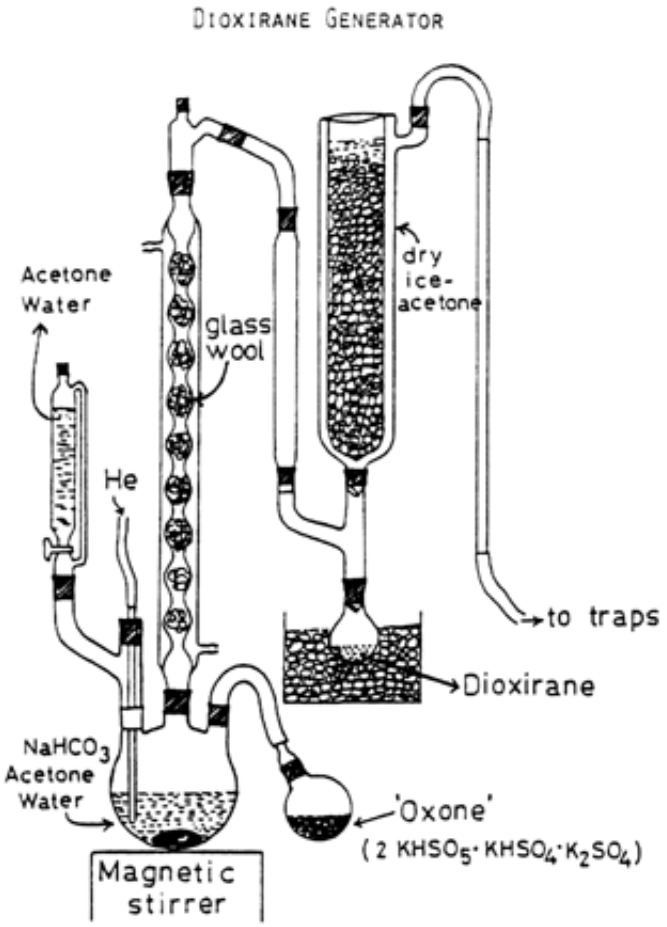
Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added January 2011].

CAUTION! Dimethyldioxirane is a volatile peroxide and should be treated as such. The preparation and all reactions of the dioxirane should be carried out in a hood.

A. *Dimethyldioxirane* (See Figure 1). A 2-L, three-necked, round-bottomed flask containing a mixture of water (80 mL), acetone (50 mL, 0.68 mol), and sodium bicarbonate (96 g), is equipped with a magnetic stirring bar and a pressure equalizing addition funnel containing water (60 mL) and acetone (60 mL, 0.82 mol) (Note 1). A solid addition flask containing Oxone (180 g, 0.29 mol) is attached to the reaction vessel via a rubber tube (Note 2). An air condenser (20 cm length) loosely packed with glass wool is attached to the reaction vessel. The outlet of the air condenser is connected to a 75 × 350-mm Dewar condenser filled with dry ice-acetone that is connected to a receiving flask (100 mL) cooled in a dry ice-acetone bath. The receiving flask is also connected in series to a second dry ice-acetone cold trap, a trap containing a potassium iodide solution, and a drying tube. A gas inlet tube is connected to the reaction flask and a stream of nitrogen gas is bubbled through the reaction mixture (Note 3). The Oxone is added in portions (10–15 g) while the acetone-water mixture is simultaneously added dropwise (Note 4). The reaction mixture is stirred vigorously throughout the addition of reagents (ca. 30 min). A yellow solution of dimethyldioxirane in acetone collects in the receiving flask. Vigorous stirring is continued for an additional 15 min while a slight vacuum (ca. 30 mm, water aspirator) is applied to the cold trap (Note 5). The yellow dioxirane solution (62–76 mL, (Note 6)) is dried over sodium sulfate (Na_2SO_4), filtered

and stored in the freezer (–25°C) over Na_2SO_4. The dioxirane content of the solution is assayed using phenyl methyl sulfide and the GLC method ((Note 7) and (Note 8)). Generally concentrations in the range of 0.07–0.09 M are obtained.

Figure 1



B. *trans-Stilbene oxide*. To a magnetically stirred solution of trans-stilbene (0.724 g, 4.02 mmol) (Note 9) in 5 mL of acetone is added a solution of 0.062 M dimethyldioxirane in acetone (66 mL, 4.09 mmol) at room temperature. The progress of the reaction is followed by GLC (Note 10), which analysis indicates that trans-stilbene is converted to the oxide in 6 hr (Note 11). Removal of solvent on a rotary evaporator gives a white crystalline solid. The solid is dissolved in dichloromethane (CH_2Cl_2) (30 mL) and dried with anhydrous Na_2SO_4. The drying agent is filtered off and washed with CH_2Cl_2. The solvent is removed on a rotary evaporator. Remaining solvent is removed under reduced pressure to give an analytically pure sample of the oxide (0.788 g, 100% yield). Recrystallization from aqueous ethanol gives white plates/prisms, mp 69–70°C ((Note 12), (Note 13)).

2. Notes

1. A mechanical stirrer may also be used.
2. The submitters used Oxone supplied by DuPont, whereas the checkers used Oxone purchased from Aldrich Chemical Company, Inc.
3. The submitters recommended that a stream of helium be passed through the reaction system during the course of the experiment. The checkers substituted nitrogen for helium with no decrease in yield . In addition, on several occasions the checkers did not use a gas purge and there was no decrease in yield. Therefore, use of a gas purge is viewed as optional, not mandatory. It is noted that other investigators have reported dimethyldioxirane preparations that do not require use of a gas purge.[2]
4. The procedure followed was generally that contained in the original publication.[3] See an alternative

procedure, by Adam.[2]
5. The submitters recommended that the distillation be performed at ca. 30 mm. By using this procedure the checkers obtained an average of 67 mL (range: 62–76 mL) of dioxirane solution with an average concentration of 0.077 M (range: 0.068–0.087 M) over 10 repetitions of the procedure. When the distillation was performed at 80 mm for up to 90 min, greater volumes of dimethyldioxirane solution were obtained (84–89 mL), but with a corresponding decrease in the reagent concentration (0.053–0.066 M).
6. The submitters reported that 80–90 mL of dimethyldioxirane solution is obtained.
7. Determination of dimethyldioxirane concentration by the GLC method is as follows: A standard solution of thioanisole (phenyl methyl sulfide) is prepared. The solution is usually 0.2 M in acetone, but other concentrations may be used. It is important to keep the sulfide in excess so that oxidation by the dioxirane will produce largely or exclusively the sulfoxide and not the sulfone.
A standard solution of an internal standard (dodecane or hexadecane) is also prepared in acetone. This solution should be at the same concentration as that of the sulfide.
To determine the dioxirane concentration 1 mL each of the dioxirane, sulfide, and internal standard solutions are combined in a vial. The GLC analysis is then carried out using the following: Column: DB 210; temp 1 = 60°C, time 1 = 5 min, rate 1 = 20°/min; temp 2 = 200°C, time 2 = 5 min. The analysis is conducted on 1 μL of solution. The analysis is made quantitative by determining the response factors of the sulfide and internal standard in the usual manner. The dimethyldioxirane concentration is determined by measuring the sulfide concentration before and after adding the dioxirane. Under these conditions the following retention times are observed: dodecane, 7.15 min; sulfide, 8.2 min; sulfoxide, 12.9 min.
8. Generally concentrations in the range of 0.07–0.09 M are obtained. The submitters reported a concentration range of 0.05–0.10 M.
9. trans-Stilbene was purchased from Eastman Organic Chemical Co. The purity of the sample was 99%. Sample purity was also checked by GLC and GC-MS. The GC-MS analysis suggests that the sample contains bibenzyl (<1%) as an impurity.
10. Gas chromatographic conditions are as follows: Column DB-210 (30 m × 0.318 mm × 0.5 μm, fused silica capillary column), column temp 1 = 100°C, time 1 = 5 min, rate = 20°/min; temp 2 = 200°C, time 2 = 7 min, injector temp 250°C, detector temp 250°C, inlet P, 24 psi, retention times: trans-stilbene 11.4 min, trans-stilbene oxide 11.9 min.
11. In 2 hr, 96% conversion had occurred.
12. The checkers obtained 790 mg (100%) of crude trans-stilbene oxide that was recrystallized from aqueous ethanol to give 744 mg (95%; two crops) of analytically pure trans-stilbene oxide.
13. trans-Stilbene oxide has the following properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 2 H, 2 × -CH-), 7.26–7.45 (m, 10 H, 2 × C_6H_5-); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.81 (-CH-); 125.4 (C-4, Ar), 128.19 (C-3,5, Ar), 128.44 (C-2,6, Ar), 136.99 (C-1, ipso C of phenyl); IR ($CHCl_3$) cm^{-1}: 3076, 3036, 2989, 1603, 1497, 1457, 870, 698; high resolution mass spectrum, Calcd. for $C_{14}H_{12}O$, 196.0888. Found 196.0896. Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.76; H, 6.05.

Waste Disposal Information

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

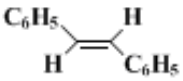
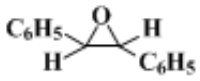
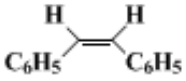
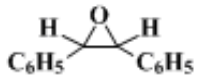
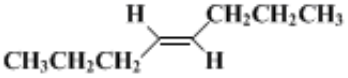
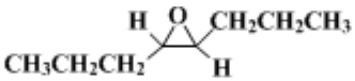
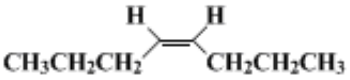
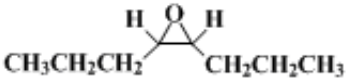
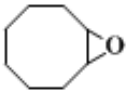
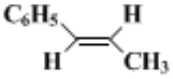
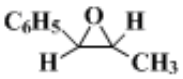
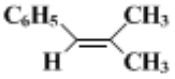
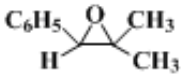
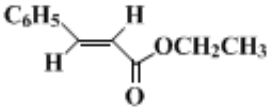
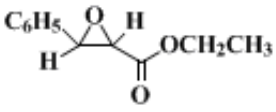
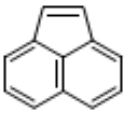
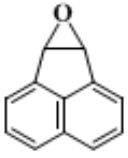
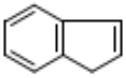
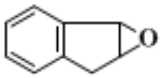
3. Discussion

For most epoxidations dimethyldioxirane (DMD) is the reagent of choice. The reaction is usually carried out at room temperature or below and in neutral solution. The reaction is stereospecific, proceeds rapidly, and generally in essentially quantitative yield. The procedure is remarkably convenient. In many cases removal of the solvent gives the pure product. The reaction is applicable to a variety of unsaturated systems (Table). The data given in the Table also compare yields with the commonly used epoxidation reagent m-chloroperbenzoic acid (MCPBA). In almost every case use of DMD gave a higher yield than did MCPBA. In many cases the difference is dramatic (see entries 1 and 2, for example). The use of

MCPBA frequently leads to opening of sensitive epoxides under the acidic conditions of the reaction. This problem is conveniently avoided when using DMD. In a growing number of cases DMD has successfully given an epoxide when other methods fail. A particularly pleasing example[4] of this is the preparation of the 8,9-epoxide of the mycotoxin, aflatoxin B_1.

TABLE I

EPOXIDATION OF OLEFINS WITH DIMETHYLDIOXIRANE

Entry	Olefin	Equiv.	Time hr	Product	Yield(a,ref)
1		1	6		100 (55, [5]90[6])
2		1	8		99 (52, [5]55[6])
3		1	3		74 (70[6])
4		1	1		81 (60[6])
5		1	20 min		97
6		1	1		98 (90, [7]b)
7		1	1		99 (95[8])
8		2	24		100 (47[9])
9		1	1		97 (100, [7]b)
10		1	1		96 (91[7])

(a) % Yield by MCPBA oxidation; (b) NMR yield.

Linear free energy relationship studies[10,11] have demonstrated that DMD is an electrophilic reagent. This property is demonstrated in the Table where substrates with electron-withdrawing substituents require longer reaction times (compare entries 1 and 2 with 4, for example). This is particularly noticeable in entry 8 where the substrate contains a strong electron-withdrawing substituent. The previously reported[10] faster rates for DMD epoxidation of cis-alkenes compared to their trans stereoisomers is seen in the longer reaction times required for the trans isomers (compare entries 1 and 2, and 3 and 4). This difference in rates is taken as support for a spiro transition state[10] for epoxidation. A number of reviews[12,13,14,15,16] of the chemistry of DMD, including its use as an epoxidizing reagent, have been published.

Acknowledgment We gratefully acknowledge support of this work by the National Institute of Environmental Health Sciences through Grant No. ES01984.

References and Notes

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

ethanol (64-17-5)

oxone (37222-66-5)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

peroxide (7722-84-1)

dichloromethane (75-09-2)

Hexadecane (544-76-3)

bibenzyl (103-29-7)

helium (7440-59-7)

thioanisole,
phenyl methyl sulfide (100-68-5)

Dimethyldioxirane,
Dioxirane, dimethyl- (74087-85-7)

trans-Stilbene oxide,
Oxirane, 2,3-diphenyl-, trans (1439-07-2)

trans-Stilbene (103-30-0)

Dodecane (112-40-3)