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A Publication
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Working with Hazardous Chemicals

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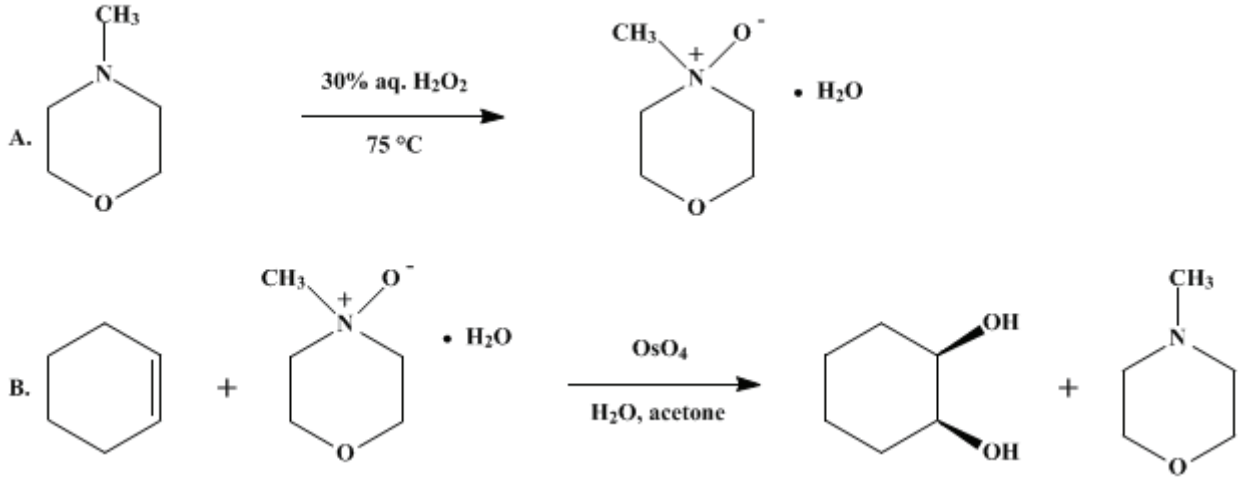
CATALYTIC OSMIUM TETROXIDE OXIDATION OF OLEFINS: *cis*-1,2-CYCLOHEXANEDIOL



Submitted by V. VanRheenen, D. Y. Cha, and W. M. Hartley[1].
Checked by N. Meyer, W. Wykypiel, and D. Seebach.

1. Procedure

Caution! Care should be taken in handling osmium tetroxide. The vapor is toxic, causing damage to eyes, respiratory tract, and skin.

A. N-*Methylmorpholine* N-*oxide* (**1**) (Note 1). A 100-ml., three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirring bar, and a dropping funnel is flushed with nitrogen or argon and charged with 32.3 g. (35.1 ml., 0.320 mole) of *N*-methylmorpholine (Note 2). The flask is immersed in an oil bath maintained at 75°, and 32.4 g. (29.1 ml., 0.286 mole) of 30% aqueous hydrogen peroxide is added dropwise over a period of 2.5 hours (Note 3). The mixture is stirred for 20 hours at 75°, at which time a negative peroxide test (potassium iodide paper) is obtained (Note 4). The reaction mixture is cooled to 50°, and a slurry of 50 ml. of methanol, 0.5 g. of charcoal, and 0.5 g. of Celite (Note 5) is added. After being stirred for 1 hour, the mixture is filtered and the filter cake washed with three 15-ml. portions of methanol. The filtrate and combined washings are concentrated with a rotary evaporator (water aspirator vacuum), with the bath temperature finally reaching 95°, where it is held for 10 minutes. The flask is fitted with a reflux condenser, and the residual viscous oil is dissolved in 25 ml. of acetone at 60°. On cooling to 40° (with seeding, if crystals of the *N*-oxide are available) the product spontaneously crystallizes. The slurry is stored at room temperature overnight, cooled in an ice bath, and filtered. The crystals are washed with three 15-ml. portions of 0° acetone and dried overnight at 40° (0.01 mm.) The yield of colorless crystalline monohydrate **1** is 32.4–34.3 g. (83.8–88.7%), m.p. 75–76° (Note 6) and (Note 7).

B. cis-1,2-*Cyclohexanediol* (**2**). A 250-ml., three-necked, round-bottomed flask, with a magnetic stirrer and a nitrogen inlet, is charged with 14.81 g. (0.1097 mole) of monohydrate **1**, 40 ml. of water, and 20 ml. of acetone. To this solution is added *ca.* 70 mg. of osmium tetroxide (0.27 mmole) (Note 8) and 8.19 g. (10.1 ml., 0.100 mole) of cyclohexene (Note 9). This two-phase solution is stirred vigorously under nitrogen at room temperature. The reaction is slightly exothermic and is maintained at room temperature with a water bath. During the overnight stirring period, the reaction mixture becomes homogeneous and light brown in color. After 18 hours, TLC (Note 10) shows the reaction to be complete. Sodium hydrosulfite (0.5 g.) (Note 11) and 5 g. of Magnesol (Note 12) slurried in 20 ml. of water are added, the slurry is stirred for 10 minutes, and the mixture is filtered through a pad of 5 g. of

Celite on a 150-ml. sintered-glass funnel. The Celite cake is washed with three 15-ml. portions of acetone. The filtrate, combined with acetone wash, is neutralized to pH 7 with 6.4 ml. of 12 *N* sulfuric acid. The acetone is evaporated under vacuum using a rotary evaporator. The pH of the resulting aqueous solution is adjusted to pH 2 with 2.3 ml. of 12 *N* sulfuric acid, and the *cis*-diol **2** is separated from *N*-methylmorpholine hydrosulfate by extraction with five 45-ml. portions of *n*-butanol (Note 13). The combined butanol extracts are extracted once with 25 ml. of 25% sodium chloride solution, and the aqueous phase is backwashed with 50 ml. of butanol. The butanol extracts are evaporated under vacuum, giving 12.1 g. of white solid. The *cis*-diol **2** is separated from a small amount of insoluble material (*ca.* 0.7 g.) by boiling the solid with a 200-ml., an 80-ml., and a 20-ml. portion of diisopropyl ether (Note 14), decanting the solvent each time. The combined ether fractions are evaporated to *ca.* 50 ml. under vacuum, and crystalline white plates precipitate. The mixture is cooled to *ca.* −15°. The crystals are filtered, washed with two 10-ml. portions of cold diisopropyl ether, and dried, yielding 10.18–10.32 g. (89–90%) of the *cis*-diol **2** (m.p. 96–97°).

2. Notes

1. *N*-Methylmorpholine *N*-oxide (**1**) can also be purchased from Eastman Organic Chemicals or Fluka A G.
2. Commercial material was used without purification (the purity was checked by refractive index and ^{1}H NMR).
3. The slow addition (2.5 hours) is required to avoid overheating of the reaction mixture. The potential danger of using hydrogen peroxide at an elevated temperature is minimized by using a 10% excess of *N*-methylmorpholine and by choosing reaction conditions that ensure rapid consumption, avoiding accumulation of peroxide in the mixture. A 50% aqueous hydrogen peroxide solution can also be used. The content of the commercial hydrogen peroxide (*ca.* 30 or 50%) must be determined by iodometric titration.
4. Very sensitive ether peroxide test strips (Merckoquant, Art. No. 10011), available from E. Merck, Darmstadt, are used. If the test is still positive at this point, an additional 0.2 ml. of *N*-methylmorpholine is added. Stirring and heating at 75° are continued for another 5 hours. Remaining peroxide renders the work-up and drying of the product potentially hazardous. *N*-Methylmorpholine *N*-oxide (**1**) and hydrogen peroxide form a strong 1:1 complex. In the reaction with osmium tetroxide, this complex produces conditions similar to those of the Milas reaction,[2] and some ketol formation may result.
5. Darco G 60, Aktivkohle, Fluka A G No. 05100, and Celite 512 Hyflosuper, Firma Schneider, Winterthur, Switzerland, No. 5100025, were used.
6. The procedure is designed to maintain the proper amount of water in the crystallization mixture so that the monohydrate **1** is obtained. It has the highest melting point and is the least hydroscopic. Other hydrated forms, such as the dihydrate (m.p. 35–60°) and mixed hydrates, may be isolated. A Karl Fischer assay of the water content is not necessary if the obtained material melts within the range given.
7. A second crop of 1.7–4.3 g. (4.3–11.1%) of the product can be obtained by evaporating the mother liquid, heating the residue at 97° for 20 minutes under reduced pressure, dissolving it in 55 ml. of acetone at 60°, and continuing as described.
8. Commercial osmium tetroxide was used without purification. It is not easy to accurately weigh this material because it rapidly sublimes.
9. Commercial cyclohexene was used (the purity was checked by refractive index). Addition of cyclohexene caused a darkening of the reaction mixture. This is caused by a finite concentration of the osmate ester. The reaction becomes lighter in color when complete.
10. The reaction may be followed by TLC. The ratio of the R_f values for cyclohexene and *cis*-diol **2** is 2:1 (commercial silica gel plates, ethyl acetate). The plates are best visualized by first spraying with 1% aqueous potassium permanganate, then with methanolic sulfuric acid, followed by charring with heat. The checkers found that, if the procedure is followed exactly, monitoring the reaction by TLC is unnecessary.
11. Sodium hydrosulfite reduces the osmium tetroxide to insoluble lower-valent osmium species.
12. The submitter used Magnesol, industrial grade, available from Reagent Chemical Research, Inc., Pilot Engineering Division. The checkers used Florisil TLC, available from E. Merck, Darmstadt, No. 12519.
13. Since the *cis*-diol **2** is very water soluble, a polar solvent such as *n*-butanol is required to extract it. *n*-Butanol forms an efficient water azeotrope. More conventional solvents may be used for less polar

products.
14. Diisopropyl ether readily forms explosive peroxides. It should be tested for peroxides, and contact with air should be minimized.

3. Discussion

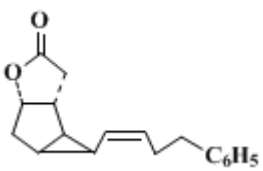
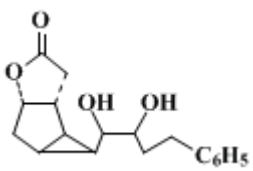
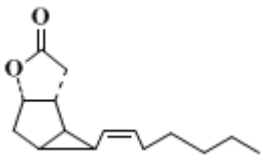
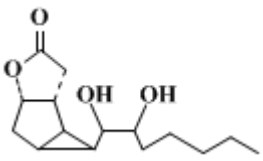
cis-Dihydroxylation of olefins may be effected with potassium permanganate, osmium tetroxide, or silver iodoacetate according to Woodward's procedure.[3] Oxidation of cyclohexene to *cis*-diol **2** with potassium permanganate is reported to proceed in only 30–40% yields.[4,5] A modification of Woodward's procedure, in which iodine, potassium iodate, and potassium acetate in acetic acid were used, has given *cis*-diol **2** in 86% yield.[6] This procedure is particularly useful for placement of *cis*-diols on the more hindered side of more complex substrates.

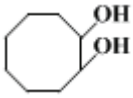
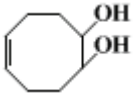
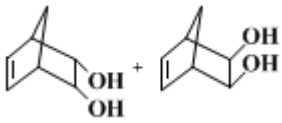
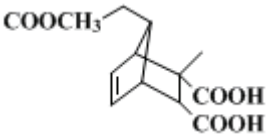
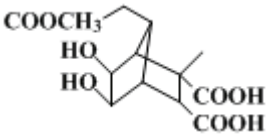
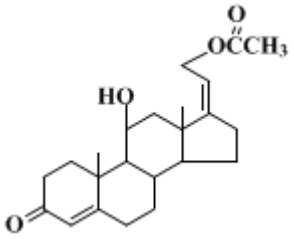
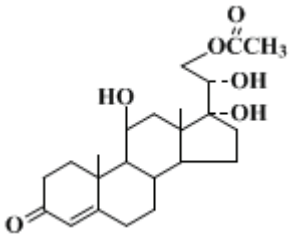
The reaction of an olefin with osmium tetroxide is the most reliable method for *cis*-dihydroxylation of a double bond, particularly for preparation of *cis*-diols on the least hindered side of the molecule. When used stoichiometrically, however, the high cost of osmium tetroxide can make a large-scale glycolization prohibitively expensive, and the work-up procedures can be cumbersome, particularly when pyridine is used. Also osmium tetroxide is volatile and toxic, resulting in handling problems. Catalytic osmylation using chlorate[7] or hydrogen peroxide (Milas reagent[2]) to regenerate osmium tetroxide avoids some of these problems, but overoxidation to an α-ketol commonly leads to losses in yield and separation problems. Preparation of *cis*-diol **2** with sodium chlorate and osmium tetroxide is reported to proceed in 46% yield,[4] and in 76% yield[8] when sodium chlorate, potassium osmate, and a detergent are used. A 62% yield of the *cis*-diol **2** from cyclohexene is reported in an interesting catalytic osmylation using *tert*-butyl hydroperoxide under alkaline conditions.[9] This method is particularly useful for oxidation of tri- and tetrasubstituted olefins.

In this report we describe the conversion of cyclohexene to *cis*-diol **2**, in 90% yield, by catalytic osmylation using 1 mole equivalent of *N*-methylmorpholine *N*-oxide (**1**, NMO) to regenerate the osmium tetroxide catalyst. This procedure avoids the α-ketol by-products encountered with the currently available catalytic processes, and provides the high yields of the stoichiometric reaction without the expense and work-up problems.

The reaction is generally applicable to a variety of substrate types, as illustrated in Table I.[10] Compatible functionality includes hydroxyl, ester, lactone, acid, ketone, and electron-poor olefins such as those conjugated to α-ketones. Some selectivity between isolated double bonds is also found. The reaction generally gives nearly quantitative yields with simple olefins.

TABLE I
PREPARATION OF *cis*-DIOLS BY CATALYTIC OXIDATION OF OLEFINS WITH OSMIUM TETROXIDE

Starting Material	Product	Procedure	(Isolated yields, %)	Reference
		NMO[a]-OsO_4	(>95)	11
		NMO[a]-OsO_4	(>95)	10[b]

		NMO^a-OsO_4	(79)	10^b
		$NaClO_3$-OsO_4	(30)	12
		$KMnO_4$	(50)	13
		H_2O_2-OsO_4	(11.4)	12
		NMO^a-OsO_4	(31)	10^b
		OsO_4, 1 mole	(14)	14
		$KMnO_4$	(3)	15
		NMO^a-OsO_4	(25)	10^b
		OsO_4, 1 mole	(21)	16
		$KMnO_4$	(28)	16
		NMO^a-OsO_4	(55)	10^b
		OsO_4, 1 mole	(53)	17
		$KClO_3$-OsO_4	(35)	17
		NMO^a-OsO_4	(78)	18^c
		$NaClO_3$-OsO_4	(79)	18^c

[a]NMO = *N*-Methylmorpholine *N*-oxide.

[b]The reaction was carried out in aqueous acetone at room temperature using 0.2–1.0 mole % OsO_4 (see Experimental section).

[c]Solvent composition of 10:3:1 *tert*-butanol–tetrahydrofuran–water was preferred for this reaction.

The reaction is usually run in aqueous acetone in either one- or two-phase systems, but substrate solubility may require the use of other solvents. Aqueous *tert*-butanol, tetrahydrofuran, and the mixtures of these solvents have also been used successfully.

Other simple aliphatic amine oxides can be used as the oxidant in this reaction, but *N*-methylmorpholine *N*-oxide (**1**) is preferred because it generally gives a faster reaction rate and is easily prepared. The reaction can also be used to convert aliphatic amine oxides into amines.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 348

References and Notes

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

potassium osmate

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

potassium permanganate (7722-64-7)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium hydrosulfite (7775-14-6)

butanol,
n-butanol (71-36-3)

iodine (7553-56-2)

acetone (67-64-1)

pyridine (110-86-1)

sodium chlorate (7775-09-9)

hydrogen peroxide (7722-84-1)

potassium acetate (127-08-2)

Tetrahydrofuran (109-99-9)

diisopropyl ether (108-20-3)

osmium tetroxide (20816-12-0)

argon (7440-37-1)

tert-butanol (75-65-0)

Magnesol

osmium

silver iodoacetate

potassium iodate (7758-05-6)

tert-butyl hydroperoxide (75-91-2)

N-methylmorpholine N-oxide (80913-66-2)

N-methylmorpholine (109-02-4)

cis-1,2-Cyclohexanediol (1792-81-0)

N-methylmorpholine hydrosulfate