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AN IMPROVED CATALYTIC OsO_4 OXIDATION OF OLEFINS TO CIS-1,2-GLYCOLS USING TERTIARY AMINE OXIDES AS THE OXIDANT

V. VanRheenen, R. C. Kelly and D. Y. Cha

The Upjohn Company

Kalamazoo, Michigan 49001

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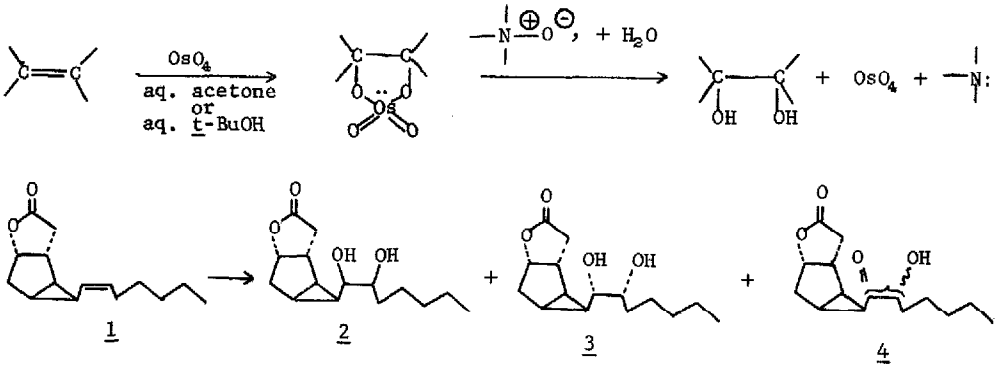
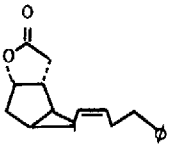
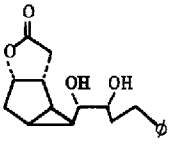
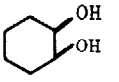
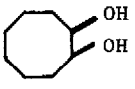
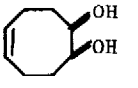
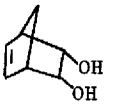
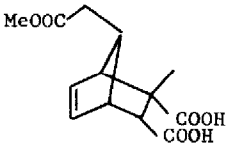
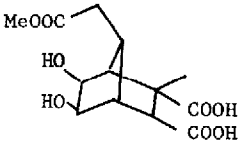
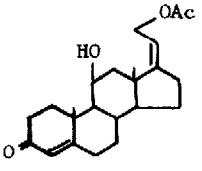
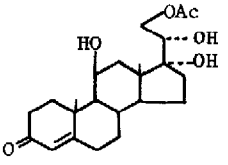
The reaction of an olefin with osmium tetroxide is undoubtedly the most reliable method for cis-dihydroxylation of a double bond.[1] When used stoichiometrically, however, the high cost of OsO_4 can make a large scale glycolization prohibitively expensive, and the workup procedures can be cumbersome, particularly when pyridine is used. These considerations, coupled with the high toxicity of OsO_4, have provided the incentive to develop procedures using OsO_4 catalytically. Catalytic osmylation using chlorate[2] or hydrogen peroxide (Milas' reagent[3]) to regenerate OsO_4 can be useful, but further oxidation to an α-ketol is a commonly encountered problem, resulting in yield losses and separation problems.

We report here a catalytic OsO_4 cis-dihydroxylation which provides the high yields of the stoichiometric reaction without its expense and workup problems, and avoids the α-ketol byproducts encountered with presently available catalytic processes. In this process one mole of tertiary amine N-oxide is used to regenerate OsO_4, allowing the glycolization to proceed at room temperature using around one mole percent of OsO_4 as catalyst. The following scheme illustrates the reaction:



We first encountered this process for cis dihydroxylation while working out conditions for transformation of olefin 1 to cis-glycols 2 and 3 in our prostaglandin synthesis.[4] Catalytic osmylation of 1 with $NaClO_3$ in aqueous THF gave after optimization a 75% yield of glycols 2 and 3 and 25% of the four isomeric α-ketols 4. A similar result was obtained using a modification of the Milas' reaction in which hydrogen peroxide is introduced as a 1:1 complex with N-methylmorpholine-N-oxide (NMO).[5] When NMO is used without H_2O_2, however, the reaction proceeded to

Table I

Starting Material	Product	Procedure (Isolated Yield)	Reference
 5	 6	NMO (>95)	14
 7	 8	NMO (91) $NaClO_3$ (46) $NaClO_3$, K_2OsO_4, detergent (76)	* 6 7
 9	 10	NMO (79) $NaClO_3$ (30) $KMnO_4$ (50) H_2O_2 (11.4)	* 8 9 8
 11	 12	NMO (31) OsO_4 1 mole (14) $KMnO_4$ (3)	* 10 11
 13	 14 15	NMO (25) OsO_4 1 mole (21) $KMnO_4$ (28)	* 12 12
 16	 17	NMO (55) OsO_4 1 mole (53) $KClO_3$ (35)	* 15
 18	 19	NMO (78) $NaClO_3$ (79)	13** **

*The reaction was carried out in aqueous acetone at room temperature using 0.2 to 1.0 mole percent OsO_4 (see Experimental).

**Solvent composition of 10/3/1 t-butanol/THF/H_2O was preferred for this reaction.

glycols 2 and 3 in >95% yield without detectable quantities of α-ketols 4. The simple workup of this reaction (reduction of OsO_4 with sodium hydrosulfite and its adsorption on magnesium silicate followed by acid extraction of the amine) make this process particularly attractive for preparative work. Similarly high yields were obtained for further functionalized analogues of 1 as in example 5.[14]

The generality of this reaction and its efficiency relative to other cis-glycolization procedures is further illustrated in Table I for a variety of differently functionalized olefins. It should be noted that in all cases where comparable data is available, the yield of glycol from the NMO-OsO_4 reaction is somewhat better than stoichiometric osmylation, and in all but one case (i.e., 18), the yields are far better than for the chlorate catalyzed reaction. The chlorate catalyzed reaction with cyclooctene 9 and elenolic acid precursor 16 received considerable attention in these laboratories and the yield could not be raised above the values reported in Table I. The NMO-OsO_4 reaction for these cases and for cyclohexene 7, cyclooctadiene 11 and norbornadiene 13, however, are not optimized.

Other simple aliphatic amine oxides can be used as the oxidant in this reaction, but NMO is preferred because it generally gives a faster reaction rate and can be easily prepared (see Experimental). The procedure provided below for oxidation of cyclohexene to cis-cyclohexan-1,2-diol is illustrative of the general method which should be applicable to most olefinic substrates.[16]

Experimental

N-methylmorpholine-N-oxide:

Add 35.1 ml of N-methylmorpholine to a 100 ml 3-necked flask under nitrogen and heat to 50°C. Add dropwise 15.3 ml of 50% H_2O_2 over 2 hrs. This addition is exothermic, but slight external heating will be required to maintain a reaction temperature of 50-75°C. The reaction temperature should be allowed to rise to about 70-75°C toward the end of the H_2O_2 addition. Stir for an additional 4 hrs at 70-75° and allow to stand at room temperature overnight. Add 50 ml methanol, 1/2 g Darco, 1/2 g Celite, stir briefly, filter, and wash the cake with 10 ml of methanol. Distill the methanol under vacuum, bringing the pot temperature to 95°. Add 250 ml of acetone at reflux and crystallization occurs on cooling to 20°C. Filtration, followed by an acetone wash and drying, yields 35 g of N-methylmorpholine-N-oxide·H_2O. The degree of hydration can vary and should be determined by the Karl Fisher assay.

cis-1,2-Cyclohexanediol:

To a mixture of 18.2 g (106 mM) of N-methylmorpholine-N-oxide·$2H_2O$, 50 ml water, 20 ml of acetone and 80 mg of osmium tetroxide in 8 ml t-butanol was added 10.1 ml (100 mM) of distilled cyclohexene. The reaction was slightly exothermic initially and was maintained at room temperature with a water bath. The reaction was complete after stirring overnight at room temperature under nitrogen.

A slurry of 1 g of sodium hydrosulfite, 12 g of magnesium silicate (magnesol), and 80 ml of water was added, and the magnesol was filtered. The filtrate was neutralized to pH 7 with 1N H_2SO_4, the acetone was evaporated under vacuum, the pH was further adjusted to pH 2. The solution was saturated with NaCl, and extracted with ethylacetate. The aqueous phase was con-

centrated by azeotroping with n-butanol and further extracted with ethyl acetate. The combined ethyl acetate layers were dried and evaporated, yielding 11.2 g (96.6%) crystalline solid. Recrystallization from ether provided 10.6 g (91%) of cis-1,2-cyclohexanediol, mp 95-97°C.

Acknowledgement. We wish to thank Dr. Wendell Wierenga of these laboratories for supplying us with his data on the oxidation of cyclooctadiene and norbornadiene, and we thank M. D. Pillai, M. A. Lyster and S. J. Leon for technical assistance.

References

1. F. D. Gundstone, Advances in Organic Chemistry, Vol. 1, Edited by R. A. Raphael, E. C. Taylor, H. Wynberg, Interscience Publishers, New York, 1960, p. 110ff.

2. K. A. Hofmann, Ber., 45, 3329 (1912).

3. N.A. Milas et al., J. Am. Chem. Soc., 58, 1302 (1936); ibid., 81, 4730 (1959). C. J. Norton, R. E. White, "Selective Oxidation Processes," Advances in Chemistry Series, No. 51, Amer. Chem. Soc., Washington, D.C., 1965, pp 10-25.

4. R. C. Kelly, V. VanRheenen, I. Schletter, M. D. Pillai, ibid., 95, 2746 (1973).

5. W. P. Schneider, A. R. Hanze, U.S. Patent 2,769,823.

6. M. F. Clark, L. N. Owen, J. Chem. Soc., 315 (1949).

7. W. D. Lloyd, B. J. Navarette, M. F. Shaw, Synthesis, 610 (1972).

8. A. C. Cope, S. W. Fenton, C. F. Spencer, J. Am. Chem. Soc., 74, 5884 (1952).

9. W. P. Weber, J. P. Shepherd, Tetra. Lett., 4907 (1972).

10. K. Tanaka, J. Biol. Chem., 247, 7465 (1972).

11. J. L. Jernow, D. Gray, W. D. Clossen, J. Org. Chem., 36, 3511 (1971).

12. Y. F. Shealy, J. D. Clayton, J. Am. Chem. Soc., 91, 3075 (1969).

13. W. P. Schneider, A. V. McIntosh, U.S. Patent 2,769,824. The use of NMO in catalytic OsO_4 reactions was first disclosed in this patent during work to introduce the cortico side chain (an α-ketol) in a steroid.

14. B. J. Magerlein, G. L. Bundy, F. H. Lincoln, G. A. Youngdale, Prostaglandins, 9(1), 5 (1975).

15. R. C. Kelly, I. Schletter, J. Am. Chem. Soc., 95, 7156 (1973).

16. Note Added in Proof. A recent publication describes the "Osmium Catalyzed Vicinal Hydroxylation of Olefins by tert-Butyl Hydroperoxide under Alkaline Conditions", [K. Barry Sharpless, Kageyasu Akashi, J. Am. Chem. Soc., 98, 1986 (1976)]. We thank Dr. Barry Sharpless for communicating his results to us prior to publication.