Nitroxide-Catalyzed Oxidation of Alcohols Using *m*-Chloroperbenzoic Acid. A New Method

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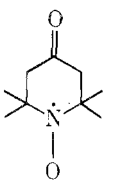
Organic peracids are versatile reagents capable of oxidizing a variety of functional groups under generally mild conditions.[1] Peracids react with olefins,[2] amines,[3] ketones,[4] sulfides,[5] and a number of other functional groups.[1,6] In addition, their solubility in organic solvents, ease of handling, and commercial availability make these reagents particularly attractive for the oxidation of organic compounds.

While an alcohol functionality can influence the stereochemistry of peracid epoxidations, alcohols themselves are generally inert to these reagents.[7] The observation that keto nitroxide **1** is produced in the peracid oxidation of amino alcohol **2**[8] suggests a nitroxide-induced oxidation of alcohols by peracids. Indeed, addition of *m*-chloroperbenzoic acid to a solution of phenyl-2-propanol and a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (**3**) in methylene chloride at room temperature results in nearly quantitative conversion of the alcohol to phenyl-2-propanone after 1 hr. The reaction requires 1 equiv of peracid, though, in practice, a slight excess is employed to offset the simultaneous nitroxide-catalyzed decomposition of the peracid (vide infra). The reaction is also catalyzed by mineral acids;[9] hence the overall oxidation is described by eq 1.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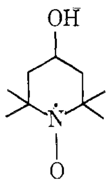
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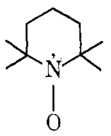
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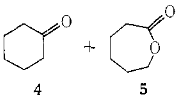
$$R_1R_2CHOH + m\text{-}ClPhCO_3H \xrightarrow{3,H^+} R_1R_2CO + m\text{-}ClPhCO_2H + H_2O \quad (1)$$

The nitroxide catalyst can be conveniently generated in situ by reaction of the corresponding amine, 2,2,6,6-tetramethylpiperidine (TMP), or its hydrochloride (TMP·HCl) with *m*-chloroperbenzoic acid.[3c] (Use of TMP·HCl also satisfies the requirement for acid catalysis.[11]) The reaction can be conducted in methylene chloride, chloroform, or ether. Results of oxidation of a number of representative alcohols by this procedure are presented in Table I. These results clearly demonstrate the efficiency of this method for the conversion of secondary alcohols to ketones. Primary alcohols generally yield carboxylic acids, although in some cases the reaction stops at the aldehyde stage (see Table I).[12]

It is noteworthy that except for the case of cyclohexanol, little or no Baeyer–Villiger reaction of the ketonic products is encountered under the reaction conditions. This is not surprising, since the Baeyer–Villiger reaction generally requires longer reaction times or higher temperatures and employs stronger peracids than are necessary for the alcohol oxidation.[4c] Cyclohexanol (a notable exception) is considerably more reactive than its cyclic congeners in the Baeyer–Villiger reaction.[4e,13] With reactive ketones, such as cyclohexanone, it is possible to suppress or enhance the Baeyer–Villiger reaction by proper choice of reaction conditions. In general, Baeyer–Villiger reaction of the ketonic products can be avoided by conducting the reaction under mild conditions (see Table II).

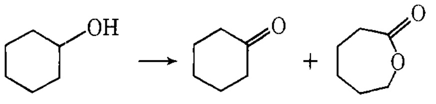
Although no detailed mechanistic studies of this reaction have been undertaken, a number of observations pertinent to a possible mechanism are noteworthy. First, stable radicals other than the piperidine nitroxides, such as galvinoxyl or the pyrrolidine nitroxides,[14] neither catalyze nor retard the oxidation. Inhibitors, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or ethyl crotonate, likewise have no effect on the reaction. Second, addition of nitroxide **3** to an acidified solution of *m*-chloroperbenzoic acid in methylene chloride produces an intense yellow color which persists for several hours and then slowly fades if no alcohol is present. In the absence of mineral acid, the yellow color appears gradually. (Alcohols are oxidized more slowly in the latter solutions.) Finally, nitroxide **3** catalyzes the decomposition of *m*-chloroperbenzoic acid in methylene chloride and this decomposition is accelerated by alcohols.[15] Figure 1 com-

Table I
Nitroxide-Catalyzed Oxidation of Alcohols with *m*-Chloroperbenzoic Acid[a]

Alcohol	Registry no.	Product(s)	Registry no.	Yield, %[b]
Cyclopentanol	96-41-3	Cyclopentanone	120-92-3	77
Cyclohexanol	108-93-0	 4 5	108-94-1 (4) 502-44-3 (5)	See Table II
Cycloheptanol	502-41-0	Cycloheptanone	502-42-1	81
Phenyl-2-propanol	698-87-3	Phenyl-2-propanone	103-79-7	87
2-Octanol	123-96-6	2-Octanone	111-13-7	94
Borneol	507-70-0	Camphor	76-22-2	94
Norborneol	1632-68-4	Norcamphor	497-38-1	95
Cyclopropylmethylcarbinol	765-42-4	Cyclopropyl methyl ketone	765-43-5	81
Benzyl alcohol	100-51-6	Benzaldehyde	100-52-7	76
1-pentanol	71-41-0	Pentanoic acid	109-52-4	90[c]
Isopentyl alcohol	123-51-3	3-Methylbutyric acid	503-74-2	85[c]
1-Heptanol	111-70-6	Heptanal	111-71-7	40[c,d]
3,5-Dimethoxybenzyl alcohol	705-76-0	3,5-Dimethoxybenzoic acid	65-85-0	60[c]

[a] Representative procedure is given in the Experimental Section. [b] Yields are those of pure, distilled products unless otherwise indicated. [c] Yield determined by gas chromatography. [d] Heptanoic acid was also produced in ca. 40% yield.

Table II
Nitroxide-Catalyzed Oxidation of Cyclohexanol[a]



4 5

Run	Equiv of peracid (per mol cyclohexanol)	Concn of peracid, *M*	% 4[a]	% 5[a]
1	1.0	0.25	97	3
2	1.5	0.25	94	6
3[b]	2.0	0.13	91	9
4	2.0	0.13	81	19
5	2.0	0.25	76	24
6	3.0	0.25	44	56
7[c]	2.0	0.25	29	71

[a] Product ratios were determined by gas chromatography. Reactions were allowed to proceed for 2 hr prior to work-up. Except for run 1, less than 10% of the starting material remained at the time of analysis. The concentration of nitroxide was ca. 0.002 *M*. [b] Peracid was added over a 1-hr period. [c] Reaction was buffered with solid sodium bicarbonate.

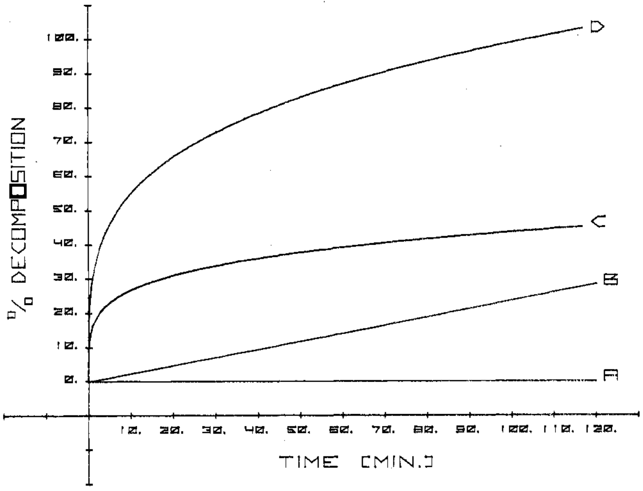
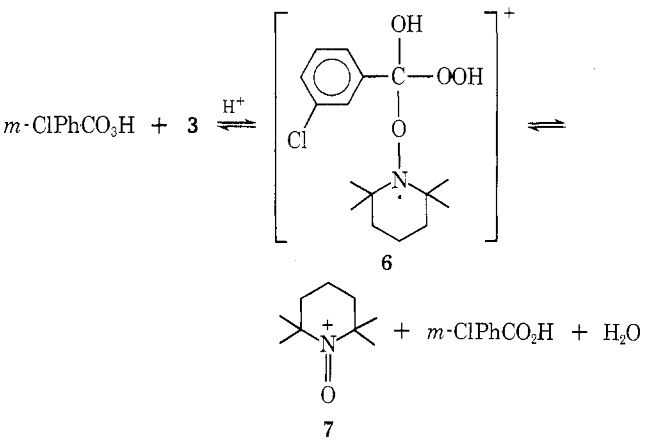


Figure 1. Nitroxide-catalyzed decomposition of *m*-chloroperbenzoic acid in methylene chloride. Plot of percent decomposition of 0.2 *M* *m*-chloroperbenzoic acid vs. time in minutes for peracid solutions containing: A, no additives; B, TMP (0.002 *M*); C, TMP·HCl (0.002 *M*); D, TMP·HCl (0.002 *M*) plus cycloheptanol (0.2 *M*). See Experimental Section for details.

pares the rate of decomposition of *m*-chloroperbenzoic acid by **3** in the presence and absence of mineral acid and in the presence of alcohol.

These observations suggest a reversible, acid-catalyzed complex formation between peracid and nitroxide. This complex could decompose reversibly to starting materials or irreversibly by reaction with solvent or alcohol (Scheme I). A likely structure for this complex is radical cation **6**, the formal result of a carbonyl addition to the protonated peracid by the nitroxide. Complex **6** could dissociate reversibly via electron transfer to produce cation **7**, *m*-chlorobenzoic acid, and water. Cationic species like **7** have been postulated as intermediates in a number of reactions of nitroxides.[16] Indeed, stable oxoammonium salts related to **7** have been isolated and on treatment with alcohols yielded the corresponding ketones.[17] In the absence of further information, the exact nature of the reactive intermediate in this reaction can only be speculative; however, it is clear, since we are dealing with a free-radical species, that a one-electron transfer must be involved at some stage of the reaction.

Scheme I

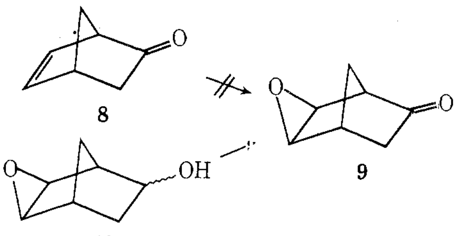


6

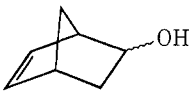
7

$$7 + R_1R_2CHOH \longrightarrow R_1R_2CO + H^+$$

While this method is limited to those alcohols which do not bear functional groups reactive toward peracids, the possibility of effecting multistage oxidations by this method is attractive. For example, the epoxidation–oxidation of an olefinic alcohol can avoid the complex product mixtures resulting from epoxidations of olefinic ketones.[18] Attempted preparation of epoxy ketone **9**, by epoxidation of keto olefin **8**, yielded only a rearranged Baeyer–Villiger product.[19] The desired compound was finally prepared in a three-step sequence, the last step (chromium trioxide–pyridine oxidation of epoxy alcohol **10**) of which occurred in only 31% yield.[20] We have achieved a one-pot preparation of **9** in 86% yield by epoxidation of olefinic alcohol **11** with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride followed by addition of a second 1 equiv of peracid and a catalytic amount of TMP·HCl to effect oxidation of the alcohol. Clearly, this one-pot sequence is the method of choice for this type of transformation. Combined with the versatile oxidizing properties of peracids, this unique method for alcohol oxidation can provide many novel approaches to multiple oxidations of polyfunctional molecules.



8 9 10



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Experimental Section[21]

The alcohols used in this study were obtained from commercial sources. 2,2,6,6-Tetramethylpiperidine hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of TMP (Aldrich). The resulting hygroscopic solid was stored in a desiccator or in methylene chloride solutions (approximately 0.2 *M*) containing 1–2% ethanol.

Representative Procedure for Oxidation of Alcohols. To a stirred solution of 2.28 g (20 mmol) of cycloheptanol and 1 ml (0.2 mmol) of a 0.2 *M* solution of TMP·HCl in methylene chloride was added, over 15 min, a solution of 6.0 g (30 mmol) of 85% *m*-chloroperbenzoic acid (Aldrich) in 50 ml of methylene chloride. The resulting mixture was stirred at ambient temperature for 1.5 hr and then transferred to a separatory funnel. The usual work-up[21] afforded a pale yellow residue which was distilled at reduced pressure to yield 1.85 g (81%) of cycloheptanone.

***exo*-5,6-Epoxy-2-norbornanone (9).** To a stirred, ice-chilled solution of 2.20 g (20 mmol) of 5-norbornen-2-ol (**11**) in 5 ml of methylene chloride was added a solution of 4.3 g (21 mmol) of 85% *m*-chloroperbenzoic acid in 50 ml of methylene chloride. Analysis of the reaction mixture after 2 hr revealed that all of the starting material had reacted. To the resultant mixture was added 1 ml (0.2 mmol) of a 0.2 *M* solution of TMP·HCl in methylene chloride followed by an additional 5.1 g (25 mmol) of *m*-chloroperbenzoic acid in 50 ml of methylene chloride. After 1.5 hr, the mixture was transferred to a separatory funnel and worked up as usual. The residue, a mixture of epoxy ketone **9** and nitroxide **3**, was sublimed to afford 2.1 g (86%) of pure **9** whose melting point and infrared spectrum correlate with those reported:[20] mass spectrum *m/e* (rel intensity) 124 (M^+, 24.4), 106 (2.6), 96 (24.0), 95 (43.0), 82 (77.6), 81 (100), 68 (52.8), 67 (57.1), 41 (38.9), 39 (56.4).

Nitroxide-Catalyzed Decomposition of *m*-Chloroperbenzoic Acid. A stock solution of 0.2 *M* *m*-chloroperbenzoic acid in methylene chloride was divided into four equal portions designated A–D. Solution A was a control. To solutions B–D were added respectively TMP (final concentration 0.002 *M*), TMP·HCl (final concentration 0.002 *M*), and TMP·HCl (0.002 *M*) plus cycloheptanol (final concentration 0.2 *M*). Aliquots were withdrawn at timed intervals and the concentration of peracid was determined iodometrically using the standard procedure.[22] The decomposition was followed for a 2-hr period (approximate time required for completion of the alcohol oxidation). The results are plotted as percent decomposition of peracid vs. time in Figure 1.

Registry No.—**3**, 2564-83-2; **9**, 55044-07-0; **11**, 13080-90-5; TMP·HCl, 935-22-8.

References and Notes

(1) (a) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 6, p 292; (b) E. G. E. Hawkins, "Organic Peroxides", Van Nostrand, Princeton, N.J., 1961, Chapter 6, p 161.

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(3) (a) C. H. Robinson, L. Milewich, and P. Hofer, *J. Org. Chem.*, **31**, 524 (1966); (b) S. Terabe and R. Konaka, *J. Chem. Soc., Perkin Trans. 2*, 369 (1973); (c) G. Chapelet-Letourneux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 3283 (1965); (d) J. C. Craig and K. K. Purushothaman, *J. Org. Chem.*, **35**, 1721 (1970).

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(6) See Aldrich Technical Bulletin for Product No. C6270-0.

(7) (a) For a number of examples see D. Swern, *Org. React.*, **7**, 378 (1953). (b) For a recent example see M. Miyashita and A. Yoshikoshi, *J. Am. Chem. Soc.*, **96**, 1917 (1974). (c) The decomposition of peracids in the presence of alcohols in a free-radical process has been reported to produce ketones in low yields. See M. Gruselle, M. Tichy, and D. Lefort, *Tetrahedron*, **28**, 3885 (1972); K. Tokumaru, O. Simamura, and M. Fukuyama, *Bull. Chem. Soc. Jpn.*, **35**, 1673 (1962). The authors are grateful to Professors Lefort and Tokumaru for bringing these references to our attention.

(8) J. A. Cella, J. A. Kelley, and E. F. Kenehan, *J. Chem. Soc., Chem. Commun.*, 943 (1974).

(9) Stock solutions of *m*-chloroperbenzoic acid in methylene chloride that were "aged" for several days prior to use were found to be more effective than freshly prepared solutions. The aging process generates small amounts of HCl from decomposition of the solvent by oxygen and peracid.[10] This HCl is apparently responsible for the increased potency of the aged solutions.

(10) I. M. Koltoff, T. S. Lee, and M. A. Mairs, *J. Polym. Sci.*, **2**, 199 (1947).

(11) When TMP·HCl is used as the catalyst there is a slight induction period (2–5 min) owing to the requirement of deprotonation of the hydrochloride prior to reaction with peracid. This induction period is slightly longer when ether is used as the solvent owing to the low solubility of the hydrochloride in this solvent. The most effective method is to add the catalyst from a stock solution prepared by dissolving TMP·HCl in methylene chloride containing 1–2% ethanol.

(12) Carboxylic acids are generally produced on treatment of aldehydes with peracids (see ref 4a).

(13) S. L. Friess and P. E. Frankenburg, *J. Am. Chem. Soc.*, **74**, 2679 (1952).

(14) (a) E. G. Rozantsev, A. A. Medzhidov, and M. B. Neiman, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1876 (1963); (b) E. Rozantsev and L. A. Krinitskaya, *Tetrahedron*, **21**, 491 (1965).

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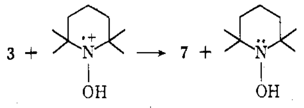
(16) (a) G. A. Abakumov and V. D. Tikhonov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 796 (1969). (b) S. Chou, J. A. Nelson, and T. A. Spencer, *J. Org. Chem.*, **39**, 2356 (1974), and references cited therein. (c) Cation **7** could also be produced by the acid-catalyzed disproportionation of **3**. The peracid would then serve merely to regenerate **3** from the hydroxylamine. We have observed no appreciable alcohol oxidation by acidified solution of **3** treated with oxidants such as air or hydrogen peroxide. Hence the peracid is required for the oxidation to be effective.



(17) V. A. Golubev, E. G. Rozantsev, and M. B. Neiman, *Bull. Acad. Sci. USSR*, 1898 (1965).

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(20) J. Meinwald and B. C. Cadoff, *J. Org. Chem.*, **27**, 1539 (1962).

(21) Melting points were determined on a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer using sodium chloride disks or potassium chloride pellets. Mass spectra were determined on an LKB 9000 gas chromatograph–mass spectrometer system operated with an accelerating voltage of 3.5 kV, an ionizing current of 60 µA, an electron energy of 70 eV, and an ion source temperature of 250°. Aliquots of crude reaction mixtures and isolated products were monitored by using gas chromatographic columns described below. Gas chromatography was performed on an F & M 402 Model high-efficiency gas chromatograph using 6 ft × 0.25 in. glass columns: column A, 3% OV-1 on 80/100 mesh Supelcoport; column B, 5% Carbowax 1540 on 40/60 mesh Chromosorb T. The phrase "worked up as usual" means that the organic phase was washed successively with 2.0 *M* NaOH, water, and brine, then dried by passage through a cone of anhydrous sodium sulfate.

(22) G. Braun, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 431.