

Organic Solvent- and Halide-Free Oxidation of Alcohols with Aqueous Hydrogen Peroxide

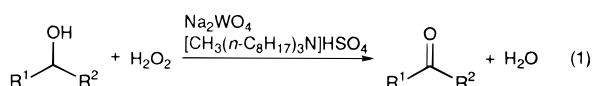
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The increasing demand for environment-conscious chemical processes has impelled us to explore truly efficient oxidation methods using aqueous H₂O₂, an ideal oxidant in this context.¹ Although a number of procedures for alcohol oxidation using H₂O₂ and in situ-generated or preformed metal complexes have been reported,^{2,3} they all remain to be improved for application to practical organic synthesis. We here describe the no-solvent oxidation of primary and secondary alcohols under entirely halide-free conditions.⁴ This method is high-yielding, clean, safe, operationally simple, and cost-effective and therefore meets with the requirements of contemporary organic synthesis.

Simple secondary alcohols can be converted cleanly to ketones under organic/aqueous biphasic conditions using 3–30% H₂O₂ in the presence of a tungsten catalyst and a phase-transfer catalyst (PTC) (eq 1). For example, when a mixture of 2-octanol



(100 g), 30% H₂O₂ (96 g), Na₂WO₄·2H₂O (0.5 g),⁵ and [CH₃-(n-C₈H₁₇)₃N]HSO₄ (0.7 g)¹ (500:550:1:1 mol ratio) placed in a 500-mL, round-bottomed flask was stirred at 1000 rpm with a magnetic stirrer at 90 °C for 4 h, 2-octanone was produced in 97% yield (GLC analysis). Separation of the organic layer was followed by washing with 100 mL of saturated aqueous Na₂S₂O₃ and distillation (173 °C) to give a pure product (93.9 g, 95% yield). The oxidation produced little waste. The water phase of the reaction mixture, combined with the distillation residue, can be reused with renewed PTC and 30% H₂O₂, giving 86 and 92% yield in the second and third runs, respectively. To obtain an acceptable yield and rate while avoiding any potential complications, reaction at 90 °C is recommended.⁶ Since unproductive decomposition of H₂O₂ is negligible under such

(1) (a) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310–8311. (b) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Panyella, D.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 905–915.

(2) For selected examples, see: (a) Jacobson, S. E.; Muccigrosso, D. A.; Mares, F. *J. Org. Chem.* **1979**, *44*, 921–924. (b) Bortolini, O.; Conte, V.; Furia, F.; Modena, G. *J. Org. Chem.* **1986**, *51*, 2661–2663. (c) Barak, G.; Dakka, J.; Sasson, Y. *J. Org. Chem.* **1988**, *53*, 3553–3555. (d) Ishii, Y.; Yamawaki, K.; Ura, T.; Yamada, H.; Yoshida, T.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3587–3593. (e) Zennaro, R.; Pinna, F.; Strukul, G.; Arzoumanian, H. *J. Mol. Catal.* **1991**, *70*, 269–275. (f) Venturello, C.; Gambaro, M. *J. Org. Chem.* **1991**, *56*, 5924–5931. (g) Dengel, A. C.; Griffith, W. P.; Parkin, B. C. *J. Chem. Soc., Dalton Trans.* **1993**, 2683–2688. (h) Neumann, R.; Gara, M. *J. Am. Chem. Soc.* **1995**, *117*, 5066–5074. (i) Arends, I. W. C. E.; Sheldon, R. A.; Wallau, M.; Schuchardt, U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1144–1163.

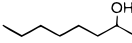
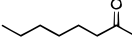
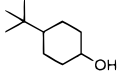
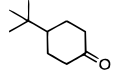




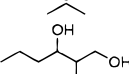
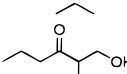
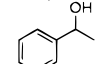

(3) Catalytic oxidation of alcohols using other oxidants: (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981. (b) Griffith, W. P.; Ley, S. V. *Aldrich. Acta* **1990**, *23*, 13–19.

(4) Reviews on oxidation with widely used Cr-based reagents: (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972; pp 257–291. (b) Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*; Springer: New York, 1984. (c) Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 251–289.

(5) Available from Aldrich at \$15.10/5 g.

(6) Oxidation of 2-octanol at 60 and 30 °C for 16 h under otherwise identical conditions gave the ketone in 57 and 7% yield, respectively.

Table 1. Oxidation of Secondary Alcohols with Aqueous Hydrogen Peroxide^a

alcohol		Na ₂ WO ₄ and PTC		ketone	
structure	mmol	mmol	structure	% yield ^b	
	768	1.5		95	
	768	1.5		95 ^c	
	640 ^d	1.3		96 ^e	
	648	1.3		84 ^f	
	640	1.3		93	
	684	1.4		83	
	819	1.6		96 ^g	

^a Unless otherwise stated, reaction was run using alcohol and 30% H₂O₂ in a 1:1.1 molar ratio with stirring at 1000 rpm at 90 °C for 4 h. PTC = [CH₃(n-C₈H₁₇)₃N]HSO₄. ^b Isolated by distillation. ^c Reaction with 3% H₂O₂. ^d A 1:1 mixture of the cis and trans isomer. ^e Toluene (100 mL) was used as solvent. ^f Reaction for 1 h.

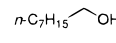
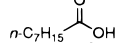
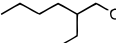
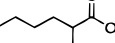
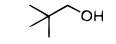
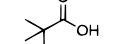
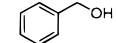
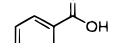
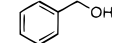
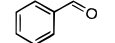
W-catalyzed conditions, the oxidation requires only 1.1 molar amounts of H₂O₂ per alcohol to obtain a satisfactory yield. Rapid stirring is necessary to facilitate the biphasic reaction. Oxidation of 2-octanol (100 g) using 3% H₂O₂ (958 g) occurs equally well, giving 2-octanone in 95% yield (93.0 g). This procedure may or may not be advantageous from a practical point of view, because the content of active oxygen is lower than with 30% H₂O₂.

This reaction system is entirely free from inorganic and organic halides. The synthetic efficiency compares favorably with existing methods that largely use quaternary ammonium halides and chlorohydrocarbon solvents.² Use of a lipophilic quaternary ammonium *hydrogensulfate* as PTC is crucial for high reactivity, probably due to the sufficient acidity. The maximum rate was obtained by reaction at an initial pH of 2. [CH₃(n-C₈H₁₇)₃N]Cl and [CH₃(n-C₈H₁₇)₃N]₂SO₄ were much less reactive, giving 11 and 18% yield, respectively (1% yield without PTC). The turnover number (TON) of the 2-octanol oxidation, as defined as mols of product per mol of W, approached 77 700, when oxidation was performed with an alcohol:30% H₂O₂:W:PTC ratio of 200 000:300 000:1:100 (40% yield). This TON value is two orders of magnitude higher than any previously reported H₂O₂ oxidation.⁷ Venturello^{2f} reported that his no-solvent oxidation of 2-hexanol with 40% H₂O₂ and isolated [CH₃(n-C₈H₁₇)₃N]₃PO₄[W(O)(O₂)₂]₄ gave 2-hexanone where TON = 48.3/W in 96% (or 130/W and 18% in benzene^{2g}). Under our new conditions, 1-phenylethanol was oxidized with an even higher TON, 179 000 (alcohol:W = 400 000:1, 45% yield).

The reaction does not normally use an organic solvent but, if necessary, is achievable using toluene as solvent with a crystalline alcohol, for example. Table 1 lists some examples of 100 g-scale reactions. Oxidation of 2-ethyl-1,3-hexanediol selectively gave 2-ethyl-1-hydroxy-3-hexanone, because the second oxidation was slowed by the presence of the electronegative keto group. Using this method, *cis*- and *trans*-4-*tert*-butylcyclohexanol are oxidized at equal rates.⁹ In order to test the tolerance of functional groups and also to confirm the

(7) The highest reported value is 513, obtained with a large excess of H₂O₂ and a RuCl₃-[(CH₃)₂(n-C₁₀H₂₁)₂N]Br catalyst system in CH₂Cl₂.^{2c} The best record with a W-based catalyst was 193/W atom in 1,2-dichloroethane.^{2h}

Table 2. Oxidation of Primary Alcohols with Aqueous Hydrogen Peroxide^a

alcohol		Na ₂ WO ₄ and PTC		product	
structure	mmol	mmol	structure	% yield ^b	
	768	15		87	
	768	15		68	
	1130	23		52	
	925	19		87 ^c	
	925	19		86 ^d	

^a Unless otherwise stated, reaction was run using alcohol and 30% H₂O₂ in a 1:2.5 molar ratio with stirring at 1000 rpm at 90 °C for 4 h. PTC = [CH₃(*n*-C₈H₁₇)₃N]HSO₄. ^b Isolated by distillation. ^c Isolated by recrystallization. ^d Reaction using alcohol and 30% H₂O₂ in a 1:1 molar ratio. Benzoic acid was produced in <3% yield.

catalytic activity in the presence of coordinative compounds, 2-octanol was oxidized in toluene containing an equimolar amount of ethyl decanoate, ethyl benzoate, di-*n*-octyl ether, 1,2-epoxydodecane, 2-methylcyclohexanone, or nonanenitrile. In fact 2-octanone was obtained without problems in >92% yield, while the latter compound was recovered in >95% yield. Addition of 1 molar amount of butyramide, however, retarded the reaction significantly, giving 2-octanone in a mere 18% yield.

A major concern in H₂O₂ oxidation is the alcohol/olefin chemoselectivity.^{1,2,8} This biphasic oxidation was initially developed for olefin epoxidation¹ but with an (aminomethyl)-phosphonic acid additive for high selectivity.¹⁰ Now, the removal of this additive has been found to significantly increase the rate and selectivity of alcohol oxidation. Oxidation of 11-dodecen-2-ol using 30% H₂O₂ with alcohol:H₂O₂:W:PTC = 500:750:1:1 (no solvent, 90 °C, 3 h, 1000 rpm) selectively afforded 11-dodecen-2-one (97% yield) with a little undesired 11,12-epoxydodecan-2-one (0.4%) (eq 2).¹¹ In a similar manner, reaction of 5-cyclohexadecenol (*E*:*Z* = 2:1) with 5% H₂O₂ in toluene gave 5-cyclohexadecenone with 98% selectivity at 100%

(8) Activated MnO₂, pyridinium dichromate (PDC), and CrO₂ are used as stoichiometric agents for selective oxidation of allylic alcohols. See: (a) Fatiadi, A. J. *Synthesis* **1976**, 65–104 and 133–167. (b) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402. (c) Lee, R. A.; Donald, D. S. *Tetrahedron Lett.* **1997**, 38, 3857–3860. See, also: (d) Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 305–327.

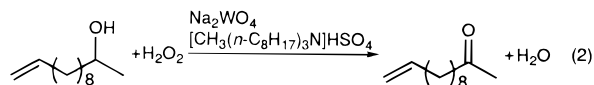
(9) Chromic acid in acetic acid oxidizes the *cis* alcohol three times faster than the *trans* isomer. See: Eliel, E. L.; Schroeter, S. H.; Brett, T. J.; Biros, F. J.; Richer, J.-C. *J. Am. Chem. Soc.* **1966**, 88, 3327–3334.

(10) For an excellent epoxidation procedure using H₂O₂, see: Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189–6190.

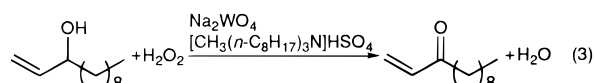
(11) Reaction under the standard epoxidation conditions (alcohol:H₂O₂:W:PTC:NH₂CH₂PO₃H₂ = 100:110:2:1:1)¹ gave a mixture of the enone (39%), epoxy ketone (38%), and epoxy alcohol (2%).

(12) A decrease in the H₂O₂ concentration did not improve chemoselectivity.

(13) Oxidation with a Ru-based catalyst in CH₂Cl₂ gave a TON of 363.^{2c}

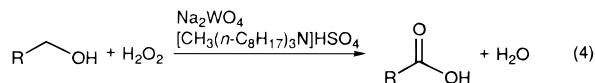


conversion. Interestingly, the initial rate of the alcohol oxidation is enhanced by *decreasing* the H₂O₂ concentration. Under the new conditions of alcohol oxidation using 5% H₂O₂, 2-octanol is much more reactive than simple olefins. Relative rates (2-octanol = 1.0; substrate:H₂O₂:W:PTC = 500:500:1:1, toluene, 110 °C, 1000 rpm) are 1-octene (0.036), (*E*)-3-octene (0.10), (*Z*)-3-octene (0.15), 2-methyl-1-undecene (1,1-disubstituted olefin, 0.094), 2-methyl-2-decene (trisubstituted olefin, 0.13), and 3,4-diethyl-3-hexene (tetrasubstituted olefin, 0.11). Olefinic bonds in allylic alcohols are particularly reactive to epoxidation.¹ 1-Dodecen-3-ol, an allylic alcohol with a terminal olefinic bond, was converted to the desired 1-dodecen-3-one in 80% yield (eq 3), contaminated with 1,2-epoxydodecan-3-ol (14%) and 1,2-



epoxydodecan-3-one (4%) (substrate:30% H₂O₂:W:PTC = 500:750:1:1, 90 °C, 3 h).¹² On the other hand, 2-methyl-2-undecen-4-ol possessing a trisubstituted C=C bond underwent selective epoxidation (100% yield).

Primary alcohols are 4–5 times less reactive than secondary ones. Significantly, however, they can be oxidized directly to carboxylic acids (eq 4). Table 2 gives some examples. When



a mixture of 1-octanol (100 g), 30% H₂O₂ (218 g), Na₂WO₄·2H₂O (5 g), and [CH₃(*n*-C₈H₁₇)₃N]HSO₄ (7 g) (50:125:1:1 mol ratio) was heated at 90 °C for 4 h with stirring at 1000 rpm, octanoic acid (96.5 g) was obtained in 87% isolated yield after distillation. *n*-Octyl octanoate, a frequently obtainable dimeric ester, was produced in only 2% yield. Reaction with an alcohol:W ratio of 20 000:1 led to a TON as high as 3000 (15% yield).¹³ Oxidation obviously proceeds by way of octanal, where the second oxidation via its hydrate is fast as a result of the acidic aqueous conditions. Reaction of octanal with 30% H₂O₂ in the presence of the W catalyst (aldehyde:H₂O₂:W:PTC = 50:75:1:1, 90 °C, 2 h) afforded octanoic acid in 84% yield. β -Branched primary alcohols are oxidized to carboxylic acids in a fair yield. Notably, benzyl alcohol is selectively convertible to benzaldehyde by using 1 molar equiv of H₂O₂.

Acknowledgment. This work was aided by the Ministry of Education, Science, Sports and Culture of Japan (No. 07CE2004).

Supporting Information Available: Experimental procedures for the oxidation and ¹H- and ¹³C-NMR data of the products (11 pages). See any current masthead page for ordering and Internet access instructions.

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