

Oxoammonium Salts. 6.¹

4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium Perchlorate: A Stable and Convenient Reagent for the Oxidation of Alcohols. Silica Gel Catalysis

James M. Bobbitt

Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060

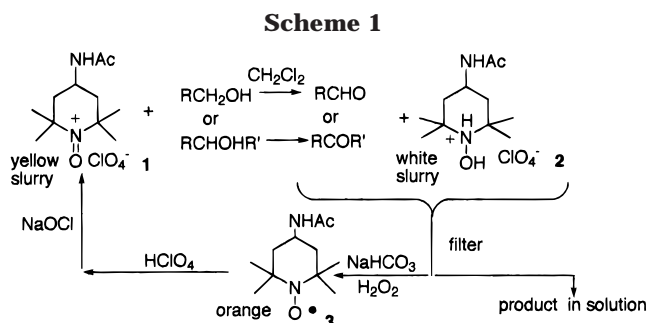
Received July 8, 1998

4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate, **1**, is a stable, nonhygroscopic oxoammonium salt that is easily prepared and can be used for the oxidation of alcohols to ketones or aldehydes in near quantitative yields. The reaction is colorimetric, does not require anhydrous conditions, does not involve heavy metals, and can be carried out conveniently. Furthermore, the oxidant can be easily regenerated. The oxidation is somewhat specific in that the relative reactivities of an allyl alcohol (geraniol), benzaldehyde, and 1-decanol are about 100:1:0.1. The reaction is catalyzed by silica gel.

Introduction

Oxoammonium salts, such as **1**, are powerful and selective oxidants for the oxidation of alcohols to aldehydes or ketones (Scheme 1).^{2–5} They offer the possibility of variable stereochemistries^{1,6} and variable oxidation potentials,³ and they are oxidants that *do not involve toxic heavy metals*. The reaction can be used in three ways. First, the salt can be generated catalytically from small amounts of a nitroxide in the presence of a secondary oxidant such as an electrode surface⁷ or some chemical oxidant.^{2,8} Second, the oxoammonium salt can be generated in situ from 2 equiv of acid and 2 equiv of nitroxide.⁹ Third, the oxoammonium salt can be prepared and used in stoichiometric amounts (Scheme 1). The workup procedure and oxidant regeneration are also shown in Scheme 1.

There have been a number of recorded uses of stoichiometric amounts of various salts,^{2–4} but there have been some serious problems. Although it is not always clear, it appears that many salts are hygroscopic and relatively unstable.⁴ Second, although the preparations are simple,³



the starting nitroxides are not always readily available. Finally, it is clear, and rather strange, that the properties of the various salts are very much a function of the anion involved.^{3,4} For example, it is stated that the various oxoammonium chlorides oxidize a primary alcohol faster and that oxoammonium perbromides (Br₃⁻), nitrates, perchlorates, and tetrafluoroborates oxidize secondary alcohols faster.⁴ Furthermore, it appears that the perchlorates and tetrafluoroborates are slower than the salts with other anions.

In this paper, we will describe the preparation of an absolutely stable and nonhygroscopic salt, 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate, **1**, and a number of its reactions. It should be noted, however, that Golubev⁵ prepared perchlorates and tetrafluoroborates (**a**, R = H, X⁻ = ClO₄⁻ or BF₄⁻) from the simple nitroxide, **b** (R = H, TEMPO), as have we.¹⁰ We believe that our acetylamino derivative is more stable, can be prepared more easily from less expensive starting materials, and has better solubility properties than does the simpler compound.

Chemistry and Preparation of 1

The essential chemistry of nitroxides, oxoammonium salts, and hydroxyamine salts is summarized in Scheme 2. The oxoammonium salts, **a**, are derived from nitrox-

(1) Paper 5: Ma, Z.; Huang, Q.; Bobbitt, J. M. *J. Org. Chem.* **1993**, *58*, 4837.

(2) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.

(3) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509.

(4) (a) Liu, Y.; Guo, H.; Liu, Z. *Acta Chim. Sin.* **1991**, *49*, 187; *Chem. Abstr.* **1991**, *115*, 70873d. (b) Liu, Y.; Liu, Z.; Guo, H. *Chem. J. Chin. Univ. (Engl. Ed.)* **1988**, *4*, 90. (c) Guo, H.-X.; Liu, Y.-C.; Liu, Z.-L.; Li, C.-L. *Res. on Chem. Intermed.* **1992**, *17*, 137.

(5) (a) Golubev, V. A.; Zhdanov, R. I.; Gida, V. M.; Rozantsev, É. G. *Bull. Acad. Sci. USSR, Chem. Sci.* **1971**, *20*, 768. (b) Golubev, V. A.; Miklyush, R. V. *Russ. J. Org. Chem.* **1972**, *8*, 1376, and many other Golubev papers cited in ref 3.

(6) (a) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194. (b) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Durif, A.; Averbuch, M.-T.; Pierre, J.-L. *Tetrahedron Lett.* **1998**, *39*, 2565. (c) Rychnovsky, S. D.; Beauchamp, T.; Vaidyanathan, R.; Kwan, T. *J. Org. Chem.* **1998**, *63*, 6364.

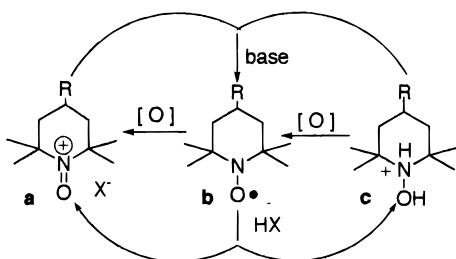
(7) With the nitroxide in solution, Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A. *Tetrahedron Lett.* **1986**, 1119 and papers cited. With the nitroxide immobilized on an electrode: Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J. i.; Osa, T.; Bobbitt, J. M. *J. Chin. Chem. Soc.* **1998**, *45*, 135 and papers cited.

(8) Anelli, P. L.; Montanari, F.; Quici, S. *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, p. 367.

(9) Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110.

(10) Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles* **1990**, *30*, 1131.

Scheme 2



ides, **b**, by a one-electron oxidation; from hydroxyamine salts, **c**, by a two-electron oxidation; or by the acid disproportionation of nitroxide, **b**.⁵ The disproportionation yields 1 mol of oxoammonium salt, **a**, and 1 mol of hydroxyamine salt, **c**. As seen in Scheme 1, the hydroxyamine salt is also the product of an alcohol oxidation. On treatment of a mixture of **a** and **c** with base, the disproportionation is reversed to give back nitroxide. Oxoammonium salts are bright yellow compounds; hydroxyamine salts are white; and nitroxides are orange.

We have previously described the preparation of the nitroxide, **3**, from the inexpensive and readily available 4-amino-2,2,6,6-tetramethylpiperidine,¹¹ but a revised, large-scale procedure is given in the Experimental Section. In our initial studies, the oxoammonium salt, **1**, was prepared by a simple disproportionation using perchloric acid in water. However, the theoretical yield of the disproportionation is only 50%, and for solubility reasons, a yield of about 35% was more common. The rest of the oxoammonium salt and the specific hydroxyamine, **2**, formed by the disproportionation could be combined and converted back to the nitroxide, **3**, with an overall recovery of about 95%. However, this procedure was tedious. A new procedure was developed using chlorine gas in the presence of aqueous sodium perchlorate that gave high yields of salt, but the salt always melted about 10 °C low and could not be further purified by recrystallization. In addition, chlorine gas is awkward to use.

A final procedure was then devised as shown in Scheme 1. In the first step, the nitroxide was disproportionated with perchloric acid to give **1** and **2**. Then, in the same flask, 0.5 equiv of commercial bleach (5.24% NaOCl) was added to complete the oxidation of **2** to **1**. The product was collected by filtration and air-dried to give **1** in an overall yield of 83%. The oxoammonium salt still in solution was basified and reduced back to nitroxide with ethanol, and the nitroxide was recovered in 13% yield, for a total conversion of 95%.

The salt, **1**, has been stable for at least 4 years and is not hygroscopic. Although the melting point is a slow decomposition, we have never been able to cause any sort of rapid decomposition or detonation. The salt was conveniently assayed by the reaction of a limited, known amount of salt with 2-octanol.

Although we prefer the perchlorate salt, the tetrafluoroborate salt, **4** (**1** where ClO₄⁻ is replaced by BF₄⁻), has also been prepared in a similar manner. The tetrafluoroborate is, in general, more soluble in both water and CH₂Cl₂ and is less convenient to use.

Alcohol Oxidations

Procedure. During an alcohol oxidation, bright yellow **1** is reduced to white hydroxyamine salt, **2**. When the

oxidation reaction is carried out in methylene chloride, the solubility properties of **1** and **2** are almost ideal. The salt is very slightly soluble (<0.02 g/100 mL), and the product, **2**, is even less soluble. Thus, one slurries a 5% excess over the stoichiometric amount of the bright yellow **2** with substrate in methylene chloride. In general, about 5–15 mL of solvent should be used for each 1 mmol of substrate. In more concentrated solutions, aliphatic primary alcohols give small amounts (<5%) of dimeric products (for example, decyl decanoate from 1-decanol). When large amounts of solvent are used, a slight trace of **2** is sometimes found in the product, about 1–2 mg for each 10 mL of solvent. If necessary, this can be removed by simple filtration or filtration through a short column of silica gel.

As the reaction progresses, the yellow slurry changes to a white slurry, thus making the reaction colorimetric. Because the oxidant and its reduced form are both insoluble, samples can be withdrawn from the slurry at any time and analyzed by TLC or GC. At any point, the presence of unused oxidant can be checked with starch–iodide paper. Filtration of the white slurry and evaporation of the filtrate yield the aldehyde or ketone in an essentially quantitative yield. In a few cases (color, impurities by GC, or low melting points), further purification is required.

Anhydrous conditions are not required for the oxidation, although we have routinely used distilled solvent and kept it stored over Na₂SO₄. Reactions can be carried out under nitrogen if the products are especially sensitive to air oxidation. Specifically, the methoxy phenol reactions (entries 3 and 4 in Table 1) were carried out with and without nitrogen. There was a small improvement with nitrogen.

Spent oxidant can be converted to nitroxide and thence back to oxidant as shown in Scheme 1.

Silica Gel and Alumina Catalysis. From preliminary work, it became apparent that, although benzyl alcohols, allyl alcohols, and secondary alcohols were oxidized at reasonable rates, primary aliphatic alcohols required long times. Various attempts were made to solve this problem. The rate could be enhanced by carrying out the reaction at reflux temperature, but the best answer lay in the addition of chromatographic-grade silica gel to the reaction mixtures. As shown in Figure 1, the reaction rate for the oxidation of 1-decanol was enhanced by silica gel, and the rate was a function of the relative amount of silica gel. As shown in Figure 2, various other solids were examined. Alumina and silica gel were similar in their effects; Florisil and charcoal were less effective; and powdered sucrose (a chiral material) was not effective at all.

There are, of course, many reaction rates that are enhanced by silica gel, both in the simple addition of solid and in cases where one of the reactants has been previously deposited on the gel.¹² Much of this work has been summarized in the papers of Kropp and co-

(12) (a) Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. D.; Durland, W. F., Jr.; Jones, J. E., III; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4146 and papers cited. (b) Hudlicky, M. *J. Org. Chem.* **1974**, *39*, 3460. (c) Lindley, S. M.; Flowers, G. C.; Leffler, J. E. *J. Org. Chem.* **1985**, *50*, 607. (d) Ranu, B. C.; Bhar, S.; Chakraborty, R.; Das, A. R.; Saha, M.; Sarkar, A.; Chakraborty, R.; Sarkar, D. C. *J. Indian Inst. Sci.* **1994**, *74*, 15. (e) Fieser, M. In *Fieser and Fieser's Reagents for Organic Synthesis*; J. Wiley & Sons: New York, 1967–; Vol. 6, p 510; Vol. 9, p 410; Vol. 10, p 346; Vol. 11, p 466; Vol. 12, p 431; Vol. 15, p 285.

(11) Fluka Chemical Co., Milwaukee, WI.

Table 1. Stoichiometric Oxidations

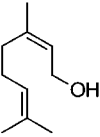
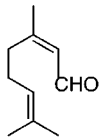
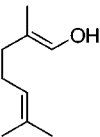
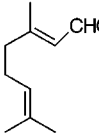
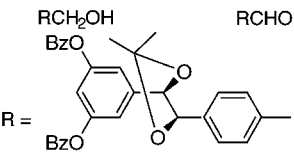
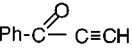
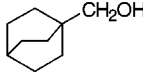
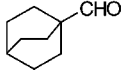
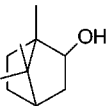
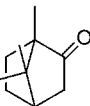
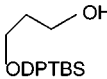

entry	substrate	product	silica gel gel/substrate	yield (%)	crude product		purified product		
					color, mp, °C	purity (% by GC) (lit)	method	yield (%)	constants mp, °C (lit)
allylic alcohols									
1			-	99	none NMR ^a	99			
2			-	100	none NMR ^a	99			
phenolic benzaldehydes									
3	4-hydroxy-3-methoxy- benzyl alcohol	aldehyde (vanillin)	2:1	a) 98 b) c)	brown 78-79 ^b no isolation ^b	99	silica gel	89	80-81 (81) ^c
4	3-hydroxy-4-methoxy- benzyl alcohol	aldehyde	2:1	a) 100 b) c)	yellow 113-115 ^b no isolation ^b	99	silica gel	95	113-114 (113-115) ^d
5	3-hydroxy-benzyl alcohol	aldehyde	2:1	100	none 103-104 (103-104) ^e	>99			
6	2-hydroxy-5-methyl- benzyl alcohol	aldehyde	2:1	97	none 53-55 (55) ^f	99			
substituted benzaldehydes									
7	3,4-methylenedioxy- benzyl alcohol	aldehyde	2:1	100	none 33-35 (37) ^c	>99			
8	3,5-dibenzyloxy- benzyl alcohol	aldehyde	-	98	lt. green	>99	silica gel	98	81-82 (78-80) ^g
9	3,4,5-tridodecyloxy- benzyl alcohol	aldehyde	2:1	99	none 50-50.5 (52) ^h	>99			
10	2-nitrobenzyl alcohol	aldehyde	1:1	99	none 42-43 (44) ^c	99			
11	4-chlorobenzyl alcohol	aldehyde	1:1	96	none 46-47 (48) ^c	100			
12 ^o		RCHO	1:1	100	none NMR	TLC pure	none	see Experimental	
acetylenic alcohols									
13	Ph-C≡C-CH ₂ OH	Ph-C≡C-CHO	1:1	99	brown	98	silica gel	93	NMR ^l
14	Ph-CHOHC≡CH		1:1	97	none 49-50 (49-50) ^m	>98			

Table 1 (Continued)

entry	substrate	product	silica gel gel/substrate	crude product			purified product		
				yield (%)	color, mp, °C	purity (% by GC) (lit)	method	yield (%)	constants mp, °C (lit)
aliphatic alcohols									
15			1:1	100	none	92 ^{b,i}	basic alumina	86	136-139 (139-141) ^j
16			1:1	100	none 172-173 (175-178) ^k	>99			
17	2-octanol	2-octanone	2:1	96	none NMR ^a	>99			
18	1-decanol	1-decanal	2:1	99	none NMR ^l	99			
19 ⁿ			2:1	97	none	97	silica gel	85	NMR ⁿ
20	2-phenylethanol	aldehyde	3:1	99	none NMR ^a	94 ^p			

^a Compared directly with commercial samples. ^b Reaction under N₂. ^c Ref 22. ^d Ref 23. ^e Ref 24. ^f Ref 25. ^g Ref 26. ^h Ref 27. ⁱ Contains a small amount of alcohol and about 5% of acid. ^j Ref 28. ^k Ref 29. ^l Ref 30. ^m Ref 31. ⁿ Ref 32. ^o Ref 39. ^p Contains a small amount of alcohol and about 4% of ester.

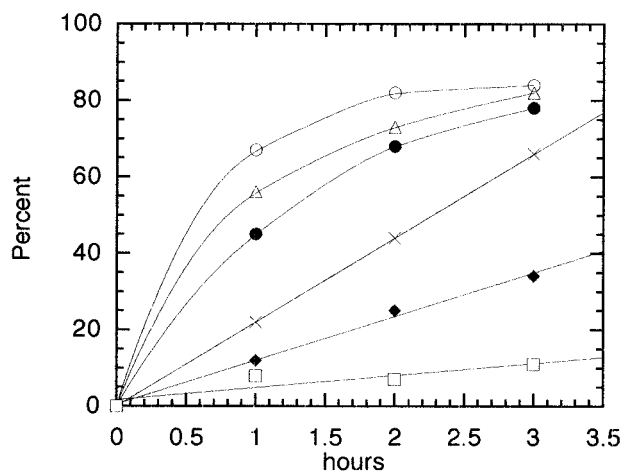


Figure 1. Oxidation of 1-decanol with various amounts of silica gel. Ratios are weight/weight ratios of silica gel/1-decanol: (○) 14:1; (△) 10:1; (●) 6:1; (×) 3:1; (◆) 1:1; (□) no silica gel.

workers.^{12a} According to refs 12b,d,e, many more reactions might be affected than previously expected. It is not certain, however, why our particular enhancement takes place. Since both alumina (weakly basic) and silica gel (weakly acidic) enhance the reaction, it is not likely that the reaction is acid catalyzed. It is probable that the enhancement arises from the surface concentration of the reactants.^{12b-d} In some oxidations, especially those involving an aromatic system, the surface of the silica gel becomes colored, although at the end, everything is white.

Although silica gel was used in most cases in Table 1 for the sake of consistency, it is really needed only for primary aliphatic alcohols.

Specific Oxidations. A number of oxidations are listed in Table 1. In general, the reactions were carried out on 2 mmol to several grams of substrate in the

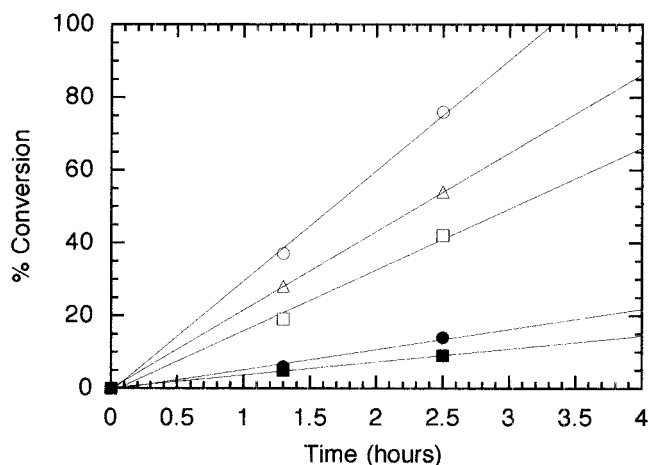


Figure 2. Oxidation of 1-decanol in the presence of various solids. In all cases, the ratio of solid to substrate was 2:1: (○) silica gel; (△) alumina; (□) florisil and carbon; (●) sugar; (■) no powder.

presence of various amounts of silica gel and were monitored by GC. After the reaction mixture became white, it was filtered, and the solvent was evaporated to give product. The crude product was checked for purity by GC, ¹H NMR, and ¹³C NMR. In most cases, the crude product was quite pure. When necessary, the products were further purified as stated, generally by filtration through a short column of silica gel, using methylene chloride as eluant. Yields are based on isolated product, either with no purification or after purification.

Since all aldehydes are air oxidized more or less rapidly, especially in solution, the aldehyde products should be isolated as quickly as possible. In Table 1, all of the reaction mixtures were evaporated to dryness to check for yield and purity of the crude materials. This allowed direct comparisons in various cases and highlighted one of the virtues of our method, that is, that the

Table 2. Unsatisfactory Reactions

	substrate	observation
1		very slow reaction, reacts at double bond, product unknown
2		decomposition, loss of protecting group
3		decomposition, PCC gave about 20 % of ketone
4		decomposition, PCC gave about 60 % of aldehyde
5		very slow, < 7 % in three days
6	CH ₃ CONHCH ₂ CH ₂ OH	very slow, oxidized to two high molecular wt. cmpds.
7		slow, mixture of two compounds
8		insoluble in CH ₂ Cl ₂ , very slow in EtOAc, some aldehyde plus three other products

crude products are really quite pure. However, the reaction mixture can be placed directly on a short column of adsorbent (thus sacrificing **2**) and eluted with CH₂Cl₂. Using this modification, the aldehyde yields from entries 3 and 4 were 93 and 100%, respectively, with excellent melting points.

In general, oxidations of allyl alcohols took place within minutes; oxidations of benzyl alcohols took place within 1–3 h; and aliphatic alcohols took a day or two. The rates could be controlled somewhat by the amount of silica gel added. The reactions were carried out at room temperature, but went slightly faster at reflux.

One interesting aspect of the reactions is that they can be carried out on benzyl alcohols containing free phenol groups (Table 1, entries 3–6). Similar reactions have been carried out in good yield with zinc chlorochromate^{13a} and DDQ.^{13b}

In only one case was any carboxylic acid observed. 1-Adamantanemethanol (entry 15) gave a byproduct that, by GC–MS, appeared to be 1-adamantanecarboxylic acid. This amounted to about 5% and was observed even when the reaction was carried out under nitrogen. The acid was removed by filtration through basic alumina.

Several compounds were investigated with unsatisfactory results. These are listed in Table 2 along with possible reasons. Primary alcohols were a problem for two reasons. First, the reactions were so slow that other functional groups tended to react. This was especially true for double bonds (Table 2, entry 1). Although only trialkyl double bonds have been observed to react so far, the reaction has not been explored. The second problem,

as noted above, was the formation of a small amount, 3–5%, of ester.

Alcohols having a β oxygen or nitrogen were not oxidized in our previously reported sulfonic acid system.⁹ Although we were unable to oxidize ethylene glycol with the sulfonic acid system, Banwell and his group used the reaction successfully on a number of glycols, mostly cyclic.¹⁴ Double oxidations to diketones as well as partial oxidations to acyloins were observed, although the former were of more interest. A major cited advantage of the method is that the diketones derived from the glycols were not further cleaved by oxidation. We have found that the oxidations of 1,2-decanediol, *N*-acetyl-2-aminoethanol, and 2-phenoxyethanol are very slow and that the products are not satisfactory (Table 2). The slow reactions of oxoammonium salts with alcohols having a β oxygen introduces an element of specificity which was used by Endo and his group for the selective oxidation of monobenzoyl diols with more than two carbons between the diol groups.¹⁵

It is of interest that many of the compounds that react very slowly with stoichiometric amounts of oxoammonium salts can be easily oxidized in a catalytic system containing TEMPO and NaOCl (bleach) as secondary oxidant.¹⁶ This system is essentially basic, which prob-

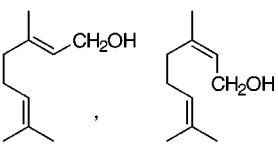
(14) (a) Banwell, M. G.; Collis, M. P.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1913. (b) Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M. *J. Org. Chem.* **1994**, *59*, 6338.

(15) Yamaguchi, M.; Takata, T.; Endo, T. *J. Org. Chem.* **1990**, *55*, 1490.

(16) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

(13) (a) Firouzabadi, H.; Sharifi, A. *Synthesis* **1992**, *10*, 999. (b) Becker, H.-D.; Björk, A.; Adler, E. *J. Org. Chem.* **1980**, *45*, 1596.

Table 3. Comparative Oxidations of Various Substrates

substrates	relative oxidation rates
	50-100
3,4-methylenedioxybenzyl alcohol	7
3-hydroxybenzyl alcohol	1
benzaldehyde	1 (reference)
4-chlorobenzyl alcohol	0.5
3-chlorobenzyl alcohol	0.2
2-chlorobenzyl alcohol	
Ph-C≡CCH ₂ OH	
2-octanol	0.14
1-decanol	0.07
1-octanol	
2-ethyl-1-hexanol	
2,2-dimethyl-1-propanol (<i>neo</i> -pentanol)	0.02
2-phenylethanol	0.01
2-phenoxyethanol	0,00

ably accounts for the rapid oxidations. Catalytic systems^{2,8} are obviously more useful for large-scale oxidations.

Relative Oxidation Rates. Relative rates of oxidation of the various alcohols are given in Table 3. For each comparison, equimolar amounts of the two substrates and oxidant were allowed to react until all of the salt was gone. No silica gel was added. The results were measured by GC, and the rates are normalized for benzyl alcohol. The presence or absence of silica gel did not affect the ratios. At lower temperatures (cooled to $-70\text{ }^{\circ}\text{C}$ and allowed to warm slowly to room temperature) or at reflux temperatures, the relative rates were, unfortunately, unchanged. As can be seen from Table 3, one can oxidize allyl alcohols in the presence of any other alcohol. Benzyl alcohols can be oxidized in the presence of aliphatic primary alcohols etc.

Reactions in the Presence of Base. A major problem in the use of stoichiometric amounts of oxoammonium salts lies in their reactions in the presence of bases, either organic or inorganic. The perchlorate salt, **2**, has a pK_a of 5.6 (or the base has a pK_b of 8.4) so that the reaction solutions are slightly acidic. If a base is present that is strong enough to neutralize **2**, the disproportionation reaction in Scheme 2 is reversed, and nitroxide is formed. The result is that 2 equiv of oxidant is needed and nitroxide, **3**, is the product.³⁷ This is not a problem with the various catalytic systems, where **2** is not observed.^{2,8}

Other Functional Groups. The most serious problem involves reactions in the presence of nitrogen bases. The reactions of amines with oxoammonium salts, either in catalytic systems (using anodic oxidation as the secondary oxidant)¹⁷ or in stoichiometric systems,¹⁸ have been studied only briefly. The difficulty lies in eq 2, as stated above. Thus, 2 equiv of salt is required, and the product from the oxidant is nitroxide, which must be removed during the isolation. In general, the reaction involves the dehydrogenation of the amine to give an imine, which is then hydrolyzed or converted to the nitrile (from RCH_2NH_2), depending on the conditions. However, various pyridine methanol derivatives can be oxidized satisfactorily to aldehydes in high yield without the problem of a reversed reaction.¹⁹ The reactions of oxoammonium salts with amines are under study.

Trimethylsilyl enol ethers and enamines react readily with the tetrafluoroborate salt derived from TEMPO (compound **a** in Scheme 2 where $\text{R} = \text{H}$ and $\text{X}^- = \text{BF}_4^-$) to give crystalline compounds having a piperidinoxy group on the enol carbon.²⁰ These compounds are under study. Otherwise, reactions with double bonds seem to be slow, although they do interfere with the normally slow oxidation of primary aliphatic alcohols (Table 2, entry 1). This causes no problem with allyl alcohols (Table 1, entries 1 and 2). Enol ethers have been

(18) (a) Golubev, V. A.; Rosantsev, É. G.; Naiman, M. B. *Bull. Acad. Sci. USSR, Chem. Sci.* **1965**, *14*, 1898. (b) Hunter, D. H.; Barton, D. H. R.; Motherwell, W. J. *Tetrahedron Lett.* **1984**, *25*, 603. (c) Hunter, D. H.; Racok, J. S.; Rey, A. W.; Ponce, Y. Z. *J. Org. Chem.* **1988**, *53*, 1278. (d) Bobbitt, J. M.; Ma, Z. *Heterocycles* **1992**, *33*, 641.

(19) McGrath, D. V.; Kernag, C. A.; Bobbitt, J. M. Department of Chemistry, University of Connecticut, paper in preparation.

(20) (a) Yoshida, E.; Nakamura, K.; Takata, T.; Endo, T. *J. Polym. Sci., Polym. Chem. Ed.* **1993**, *31*, 1505. (b) Ma, Z. Ph.D. Dissertation, University of Connecticut, 1991.

(21) (a) Miyazawa, T.; Endo, T. *Tetrahedron Lett.* **1986**, *27*, 3395. (b) Cho, N. S.; Park, C. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 924.

(22) Shriner, R. L.; Hermann, C. K. F.; Morrill, T. C.; Curtin, D. Y.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 7th ed.; J. Wiley & Sons: New York, 1997; compound tables.

(23) Rose, H. A. *Anal. Chem.* **1956**, *28*, 267.

(24) Eliel, E. L.; Nelson, K. W. *J. Chem. Soc.* **1955**, 1628.

(25) Sidgwick, N. V.; Allott, E. N. *J. Chem. Soc.* **1923**, *123*, 2819.

(26) Franke, I.; Binder, M. *Helv. Chim. Acta* **1980**, *63*, 2508.

(27) Kosteyn, F.; Zerban, G.; Meier, H. *Chem. Ber.* **1992**, *125*, 893.

(28) Bott, K. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 894.

(29) Flatt, S. J.; Fleet, W. J.; Taylor, B. J. *Synthesis* **1979**, *37*, 815.

(30) Noro, M.; Masuda, T.; Ichimura, A. S.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1994**, *116*, 6179.

(31) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(32) Holmes, A. B.; Hughes, A. B.; Smith, A. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 633.

(33) Although this material is commercially available from several supply houses, it can be conveniently and inexpensively prepared by this procedure, which is a large-scale modification of our earlier preparation.⁹

(34) One equiv of 2-octanol was allowed to react with 0.5 equiv of salt, and the 2-octanol:2-octanone ratio was determined by GC. The theoretical result was compared with the actual result to determine salt purity.

(35) The salt is soluble in cold water to the extent of about 2 g/100 mL. It can be recrystallized by being dissolved in about 6 parts of rapidly boiling water followed by rapid cooling. It reacts slowly with boiling water, as has been noted for other oxoammonium salts (Endo, T.; Miyazawa, T.; Shihashi, S.; Okawara, M. *J. Am. Chem. Soc.* **1984**, *106*, 3877).

(36) Ethanol reduces the salt, **1**, to the hydroxyamine salt, **2**, which is deprotonated by the base to free hydroxyamine which reacts with **1** to give nitroxide (see Scheme 2).

(37) The nitroxide, **3**, has some solubility in water. It can be isolated by extraction with CH_2Cl_2 or partially collected by filtration. If the solution is saturated with base, filtration is fairly efficient. Otherwise, extraction is better. It is of interest that, while **3** can be extracted from H_2O with several portions of CH_2Cl_2 , it can be also extracted from ether with several portions of H_2O .

(17) (a) Semmelhack, M. F.; Schmid, C. R. *J. Am. Chem. Soc.* **1983**, *105*, 6732. (b) MacCorquodale, F.; Crayston, J. A.; Walton, J. C.; Worsfold, D. J. *Tetrahedron Lett.* **1990**, *31*, 771. (c) Reference 7b.

polymerized using oxoammonium chloride, presumably through reaction with the enol.²¹

Easily hydrolyzable acetals are broken down under the conditions of the oxidations, as are β -lactones (Table 2, entries 3 and 4). The addition of sodium acetate, as in PCC oxidations, helps some, but sodium acetate, being slightly basic, causes problems as discussed above, as well as adding some acetic acid to the product. An acetonide does survive the oxidation nicely, and the benzyl alcohol is very rapidly oxidized (Table 1, entry 12).

As far as other blocking groups for alcohols are concerned, diphenyl-*tert*-butylsiloxy (DPTBS) groups are quite stable to the reagent, although the smaller group, dimethyl-*tert*-butylsiloxy group (DMTBS), is not (Tables 1 and 3). Ester groups would appear to be unreactive since the reactions can be carried out in ethyl acetate, and of course, the reagent itself contains an amide which is completely stable.

Benzyl ethers have been reported to react with oxoammonium salts.² However, this has not been a problem in the oxidation of benzyl alcohols containing benzyloxy groups. The alcohol oxidation is apparently much faster than ether oxidation. Ketones have been reported to react with oxoammonium salts to give diketones,^{2,3,5} but this reaction seems to be very slow in CH_2Cl_2 and was not encountered in our work.

Solvents. The solvent of choice is CH_2Cl_2 . The solubilities of the oxidant and its reduced product are ideal; it is easily evaporated to yield product; and it is inexpensive and easily purified. If the substrate is not soluble in CH_2Cl_2 , ethyl acetate is a poor second choice. The reaction rates are reduced to less than $1/10$ of those in CH_2Cl_2 (as measured for benzyl alcohol and 2-octanol) and are only slightly enhanced by silica gel. However, a mixture of the two solvents (1:1) plus silica gel was used satisfactorily for the oxidation of piperonyl alcohol (Table 1, entry 7). The isolation procedure is the same as that for methylene chloride.

Tetrahydrofuran is slowly oxidized to butyrolactone (as shown by GC comparison to a known material) and would be unsatisfactory except for very fast reactions. Acetone also reacts slowly with oxoammonium salts.^{5b} Water can be used, but the solubilities of the oxidant and its reduced product make product isolation more difficult. At least in catalytic situations,² the presence of water leads to the formation of carboxylic acids rather than aldehydes, probably through the oxidation of hydrates. Acetonitrile seems to be quite unreactive to the oxidant, but again, the solubilities are not very satisfactory for facile product isolation.

Summary. We have prepared a stable, nonhygroscopic, and readily available oxoammonium salt and described its reactions with various alcohols. The reactions are colorimetric, proceed in high yields, and give products of good purity, and the oxidant can be recycled. However, as cited above and in the reviews,^{2,3} there are many other reactions of oxoammonium salts that have been explored only briefly. Perhaps the availability of **1** will allow a more thorough exploration of some of these, as well as new reactions.

Experimental Section

General Procedures. Gas chromatography was carried out on a 10 m, 0.53 mm, methyl silicone column using a thermal conductivity detector. The geraniol-nerol compounds were

separated on a 30 m Carbowax column. Melting points were measured on a Kofler hot stage apparatus and are corrected. Unless noted, all of the substrates were commercial chemicals and were used without purification. The CH_2Cl_2 was distilled and stored over Na_2SO_4 . The silica gel (40 μm for flash chromatography, Scientific Adsorbants, Inc., Atlanta, GA) was washed with CH_2Cl_2 and dried before use. The alumina was Brockmann 1, basic, 150 mesh, obtained from Aldrich Chemical Co., Milwaukee, WI. Microanalyses were carried out by Galbraith Laboratories, Memphis, TN, and NuMega Resonance Labs, San Diego, CA. The 4-amino-2,2,6,6-tetramethylpiperidine was obtained from Fluka Chemical Co., Milwaukee, WI.

Modified Preparation of 4-Acetylamino-2,2,6,6-tetramethyl-1-piperidinoxy, 3.³³ 4-Amino-2,2,6,6-tetramethylpiperidine (220 g, 1.42 mol) was dissolved in 800 mL of dry ether in a 3 L flask equipped with a very large magnetic stirring bar. The mixture was cooled in an ice bath, and with vigorous stirring, acetic anhydride (445 g, 4.36 mol) in 200 mL of dry ether was added slowly over about 1 h. Some heat was given off in the early stages, and there is a tendency for the product to clump together. These clumps can be broken up with a glass rod so that the final product is a free-flowing slurry. After the anhydride addition, the slurry was stirred for 3 h, washed with dry ether, and filtered to yield, after drying in a hood to constant weight, 360 g (99%) of 4-acetylamino-2,2,6,6-tetramethylpiperidinium acetate.

The acetate (360 g, 1.41 mol) was dissolved in 2.5 L of water, and the solution was made basic with 317 g of K_2CO_3 (2.3 mol), added in small portions. Sodium tungstate (25.0 g, 0.075 mol) and ethylenediaminetetraacetic acid tetrasodium salt (25 g, 0.060 mol) were added. To the slurry were added five successive 100-mL portions of 30% H_2O_2 (about 4.4 mol) at about 3-h intervals. A small amount of heat was given off, and the mixture tended to foam. For this reason, a beaker or large mouth container is desirable. After 3 days of stirring, the mixture was filtered, and the orange precipitate was washed once with ice water. The washing and filtrate were concentrated under vacuum to about half, and a second crop of solid product, obtained on chilling, was collected by filtration. The two solids were combined to give 295.0 g of **3** (98%, mp 145–147 °C, lit. 147–148 °C).⁹ At other times, yields varied from 90 to 98%.

Preparation of Oxoammonium Salt Perchlorate, 1. The nitroxide (50 g, 0.23 mol) was slurried with 100 mL of H_2O , and 33.0 g of 70% HClO_4 (0.23 mol) in 25 mL of H_2O was added as slowly as possible (about 1 h). Commercial bleach (181.5 g, 5.25% NaOCl , 0.125 mol) was slowly added (about 2 h). The reaction mixture was cooled in ice and filtered, and the yellow, crystalline precipitate was washed with ice-cold 5% NaHCO_3 (100 mL) ice water (100 mL), and two 100-mL portions of CH_2Cl_2 . The solid was dried to constant weight in air to yield 61.0 g (83%) of product, mp 172–174 °C (dec). The melting point–decomposition point of this compound is somewhat variable, depending on crystal flaws, and can be from 168 to 175 °C. The assay against 2-octanol was 100%.³⁴ The analytical sample was recrystallized from H_2O and melted at 177–178 °C.³⁵ Anal. Calcd for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}_6\text{Cl}$: C, 42.24; H, 6.76; N, 8.95. Found: C, 42.37; H, 6.64; N, 8.83.

The filtrates from the salt were combined, and the CH_2Cl_2 was separated. The aqueous solution was basified with NaHCO_3 and stirred overnight with an excess of ethanol (>0.04 mol, ca. 2 g).³⁶ The nitroxide that formed was extracted with eight 20-mL portions of CH_2Cl_2 .³⁷ The solvent was dried (MgSO_4) and evaporated to give 6.02 g of nitroxide, **3**. The conversion of **3** to oxoammonium salt was 95%. The actual yield from starting piperidine was about 80%, but the conversion was about 95%.

Preparation of Oxoammonium Salt Tetrafluoroborate, 4 (1, with BF_4^- Rather than ClO_4^-). Using exactly the same procedure as for **1**, **4** was prepared in a yield of 67%. The analytical sample was recrystallized from water and melted at 193–194 °C. Anal. Calcd for $\text{C}_{11}\text{H}_{21}\text{N}_2\text{O}_2\text{BF}_4$: C, 44.03; H, 7.04; N, 9.33. Found: C, 44.11; H, 6.91; N, 9.37.

General Oxidation Procedure. Unless noted, about 10 mmol of the various substrates in Table 1 were dissolved in about 50–150 mL of CH₂Cl₂, and about twice the weight of silica gel (to substrate) was added. A slight excess (1.05 equiv) of oxoammonium salt was added,³⁸ and the bright yellow slurry was stirred until it became white. For allyl and benzyl alcohols, this was a few minutes. Aliphatic alcohols took several hours. The slurry was then filtered, and the precipitate was washed several times with CH₂Cl₂. The filtrates and washings were evaporated under vacuum to constant weight, and the crude product was examined by GC or TLC and by ¹H and ¹³C NMR. If necessary, the material was dissolved in CH₂Cl₂ and further purified by passing it through about 10 g of silica gel, using CH₂Cl₂ as eluent. In some cases, the reaction mixture was directly deposited on a silica gel column and eluted (Table 1, entries 3 and 4). Melting points were measured where possible and are recorded in Table 1.

Recovery of Spent Oxidant. The combined solids collected after an oxidation (more likely from several oxidations, and containing various amounts of silica gel and **2**) were washed several times with CH₂Cl₂ and dried. The dried solids were extracted with twice their weight of warm water to extract **2**. The aqueous extract was saturated with NaHCO₃ and treated with 30% H₂O₂, amounting to about 1/3 of the original silica gel–**2** mixture. The mixture was stirred overnight, and the nitroxide, **3**, was collected by filtration.³⁶

Characterization of **2.** A sample of **2** was collected from an oxidation in the absence of silica gel and was recrystallized twice from water to give an analytical sample, mp 246–247

(38) It is best to add the oxidant last to the substrate and solvent. In at least two cases, furane derivatives and dimethyl sulfoxide, the reaction between salt and pure material was very vigorous.

°C. Anal. Calcd for C₁₁H₂₃N₂O₆Cl: C, 41.97; H, 7.36; N, 8.90. Found: C, 42.13; H, 7.45; N, 8.93.

Oxidation of (*R,R*)-4-[4'-(Hydroxymethyl)phenyl]-5-[3',5'-bis(benzyloxy)phenyl]-2,2-dimethyl-1,3-dioxolane (Table 1, entry 12). The alcohol³⁹ (0.130 g, 0.262 mmol) and 0.25 g of silica gel were slurried in 20 mL of CH₂Cl₂, and 0.086 g of **1** (0.274 mmol) was added. After 2 h, TLC (CH₂Cl₂) showed that the conversion was complete, and the mixture was white. Evaporation of solvent yielded 0.130 g of product (100%): ¹H NMR (270 MHz, CDCl₃) δ 10.0 (s, 1H), 7.79 (d, 2H), 7.1–7.5 (m, 12H), 6.58 (t, 1H), 6.45 (d, 2H), 4.96 (s, 4H), 4.75 (d, 1H), 4.58 (d, 1H), 1.62–1.65 (m, 6H); ¹³C NMR (67.92 MHz, CDCl₃) δ 183.1, 160.4, 148.2, 138.1, 135.1, 134.7, 129.6, 128.4, 127.8, 127.3, 126.9, 110.1, 105.8, 102.1, 85.1, 84.5, 69.9, 26.9, 26.8. The analytical sample, a gum, was sublimed under high vacuum at about 260 °C. Anal. Calcd for C₃₂H₃₀O₅: C, 77.71; H, 6.10. Found: C, 77.82; H, 5.97.

Acknowledgment. The author thanks his colleagues, Professor Amy R. Howell and Professor Dominic V. McGrath (now at the University of Arizona), and many of their students for help and encouragement in this work. Specifically, he is indebted to the following students: Albert Ndakala, Lisa Dollinger, Jim McElhanon, Denise Junge, Mehrnoosh Hashemzadeh, Mu-Jen Wu, and Monica Ramos. Partial financial support was provided by the National Science Foundation (Grant CTS-9632391).

JO981322C

(39) McElhanon, J. R.; Wu, M.-J.; Escobar, M.; Choudhry, U.; Hu, C.-L.; McGrath, D. V. *J. Org. Chem.* **1997**, *62*, 908.