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Selective Oxoammonium Salt Oxidations of Alcohols to Aldehydes and Aldehydes to Carboxylic Acids

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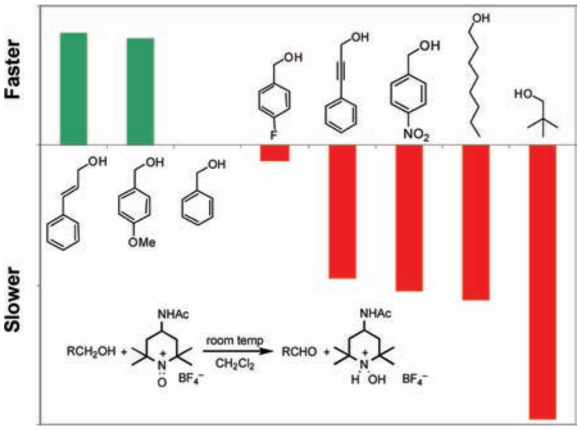
ABSTRACT



The oxidation of alcohols to aldehydes using stoichiometric 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (1) in CH_2Cl_2 at room temperature is a highly selective process favoring reaction at the carbinol center best able to accommodate a positive charge. The oxidation of aldehydes to carboxylic acids by 1 in wet acetonitrile is also selective; the rate of the process correlates with the concentration of aldehyde hydrate. A convenient and high yield method for oxidation of alcohols directly to carboxylic acids has been developed.

The use of oxoammonium salts[1] for oxidation of alcohols to aldehydes, ketones, or carboxylic acids provides a convenient and environmentally benign[2] alternative to metal-based reagents.[3] Most commonly, such oxidations are performed by in situ generation of the oxoammonium cation by oxidation of a catalytic quantity of a stable nitroxide using a stoichiometric quantity of a primary oxidant[3] such as NaOCl.[4] These rapid catalytic oxidations are typically conducted in a basic reaction medium, and under these conditions, it is generally observed that primary alcohols are oxidized more quickly than are secondary alcohols.[3] The slower oxidation of secondary alcohols in basic solution has been attributed to steric hinderance to the formation of a preoxidation complex generated via alkoxide attack on the electrophilic nitrogen atom of the oxoammonium cation.[5]

The oxidation of an alcohol to an aldehyde or a ketone may also be accomplished under essentially neutral conditions using a stoichiometric quantity of a preformed oxoammonium salt.[3,6,7] Indeed, considerable benefit derives

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(1) Oxoammonium refers to salts containing the N=O cation derived from stable nitroxides, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), by one-electron oxidation. It might be noted that, in the past, the oxoammonium cation has been termed nitrosonium, immonium oxide, oxopiperidinium, iminoxyl, and oxoamminium.

(2) Sheldon, R. A.; Arends, I. W. C. E.; Ten Brink, G.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774.

(3) For a review, see: Bobbitt, J. M.; Brückner, C.; Merbouh, N. *Org. React. (NY)* **2010**, *74*, 103.

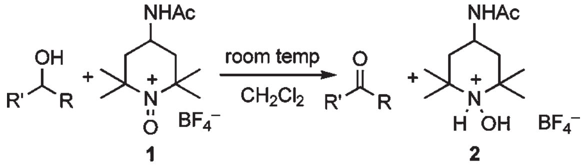
(4) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Anelli, P. L.; Montanari, F.; Quici, S. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, p 367 and references therein.

(5) Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, *72*, 4504.

10.1021/ol203096f

from the use of a stoichiometric quantity of the stable, crystalline oxoammonium salt, 4-acetamido2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**). This salt is commercially available,[8] or may be easily prepared from inexpensive materials,[7] and as illustrated in Scheme 1, oxidations proceed at room temperature in methylene chloride. Additionally, the oxidant acts as an indicator of the extent of oxidation: the yellow slurry of **1** in CH_2Cl_2 becomes white as the oxidant is reduced to the insoluble hydroxylamine salt (**2**). Products are isolated by simple filtration and concentration of the filtrate.

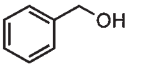
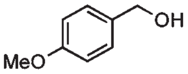
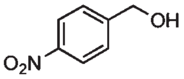
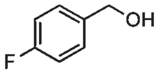
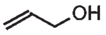
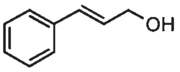
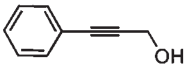
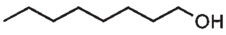
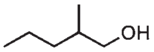
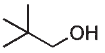
Scheme 1



Some time ago, we reported that oxidation of allylic and benzylic alcohols in CH_2Cl_2 using a molar equivalent of **1** is considerably more rapid than is the oxidation of aliphatic primary alcohols.[9] Moreover, in contrast to the relative rates of oxidation in basic solutions, secondary alcohols are more rapidly oxidized than are primary alcohols under these conditions.[6] Given the results of more recent studies of the mechanism of oxoammonium oxidation of alcohols in neutral media,[5] we have reinvestigated the relative rates of oxidation of primary alcohols to aldehydes using **1** in CH_2Cl_2. As detailed below, the oxidation of primary alcohols to the corresponding aldehydes displays synthetically significant selectivity for oxidation of substrates best able to accommodate a positive charge at the carbinol carbon.

The relative rates of oxidation of representative primary aliphatic, benzylic, allylic, and propargylic alcohols were investigated in a series of competition experiments using equimolar quantities of two alcohols and 1 molar equiv of **1** as a slurry in CH_2Cl_2. Multiple reaction mixtures involving various combinations of alcohols were run to completion, as indicated by a negative starch-KI test for the presence of **1**, and analyzed using ^1H NMR by integration of the carbinol CH_2 resonance in the alcohols and the CHO resonance in the aldehyde products. In all cases, the relative rates for oxidation of the alcohols and the appearance of the aldehydes were identical within the propagated experimental error of the measurements (*viz*., 5%). The results of these experiments are summarized in Table 1.

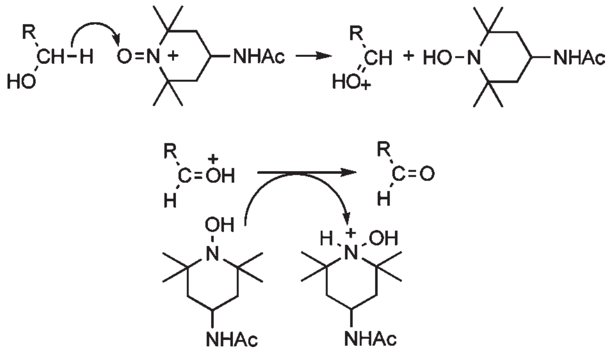
Table 1. Relative Rates of Oxidation of Primary Alcohols to the Corresponding Aldehydes by **1** in CH_2Cl_2 (Scheme 1)

entry	alcohol	rel oxidn rate
1		1.0
2		5.8
3		0.09
4		0.77
5		0.76
6		6.4
7[a]		0.11
8[a]		0.08
9		0.04
10[a]		0.01

[a] Virtually identical relative rates have been reported in ref 6 for oxidations using the perchlorate analog of **1**.

Cursory inspection of the data presented in Table 1 demonstrates that aliphatic primary alcohols are oxidized more slowly than benzyl alcohol, allyl alcohol, or cinnamyl alcohol. Not surprisingly, more sterically hindered primary alcohols (Table 1, entries 9 and 10) are oxidized somewhat more slowly than 1-octanol (Table 1, entry 8). More significantly, the rate of oxidation of a benzylic alcohol is noticeably affected by the nature of a *para*-substituent (Table 1, *cf.* entry 1 and entries 2–4). In the aggregate, the results of these studies are fully in accord with a mechanism, suggested in a computational investigation of the oxidation and depicted in Scheme 2[5] that involves formal hydride transfer from the α-carbon of the alcohol to the oxygen atom of **1**.

Scheme 2



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(6) Bobbitt, J. M. *J. Org. Chem.* **1998**, *63*, 9367 and references therein.

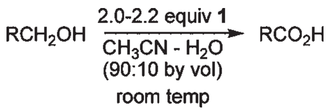
(7) Bobbitt, J. M.; Merbouh, N. *Organic Syntheses*; Wiley: New York, 2009; Collect. Vol. 11, p 93.

(8) TCI America; catalog number A2065.

(9) This study (ref 6) used the perchlorate analog of **1**: the oxidative properties of the two salts are identical (ref 7).

Catalytic quantities of the oxoammonium cation, when used in conjunction with a primary oxidant, have been observed to oxidize primary alcohols to carboxylic acids when the reaction is conducted in an aqueous medium.[3] We have found that such oxidations are easily accomplished using stoichiometric amounts of **1**, as illustrated in Scheme 3, by allowing a solution of a primary alcohol and 2 molar equiv of **1** in CH_3CN–water (90:10 by vol) to sit at room temperature (typically overnight for unhindered aliphatic alcohols) until the reaction is complete as evidenced by a color change from orange-brown to clear yellow-orange and a negative test with starch–KI paper. A simple extractive workup affords essentially pure aliphatic carboxylic acids in good to excellent yields as evidenced by the results presented in Table 2. It should be noted that the hydroxylamine salt coproduct (**2**) is readily recycled via the nitroxide to **1**.[7]

Scheme 3



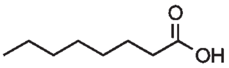
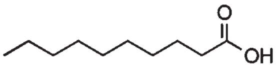
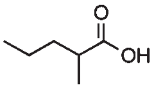
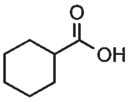
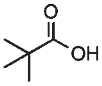
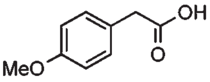
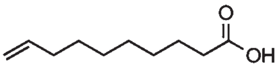
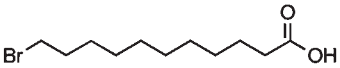
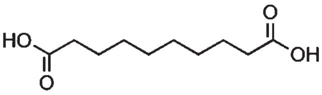
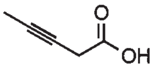
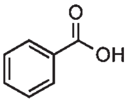
$$RCH_2OH \xrightarrow[\substack{CH_3CN - H_2O \\ (90:10 \text{ by vol}) \\ \text{room temp}}]{2.0\text{-}2.2 \text{ equiv } \mathbf{1}} RCO_2H$$

It is of considerable significance that the oxidation of benzyl alcohol to benzoic acid is a remarkably sluggish process; after 20 d of reaction time, benzaldehyde constituted ~30% of the product mixture (Table 2, entry 11). Clearly, whereas aliphatic alcohols are oxidized in CH_2Cl_2 solution to aldehydes less rapidly than benzylic alcohols (Table 1), the converse seems to be the case for oxidations in aqueous media that lead to carboxylic acids (Table 2). The relatively low yield of benzoic acid from the oxidation of benzyl alcohol was not unexpected: we had noted in a study of the oxidative cleavage of benzylic ethers by **1** in aqueous acetonitrile that benzaldehyde is quite resistant to oxidation by the oxoammonium cation.[10]

As a practical matter, treatment of a primary aliphatic alcohol and a benzylic alcohol with **1** in an aqueous medium allows for selective oxidation of the aliphatic alcohol to the corresponding carboxylic acid while oxidation of the benzylic alcohol stops at the aldehyde stage. Two examples of such selective oxidations are illustrated in Scheme 4; isolated yields of pure products are shown.

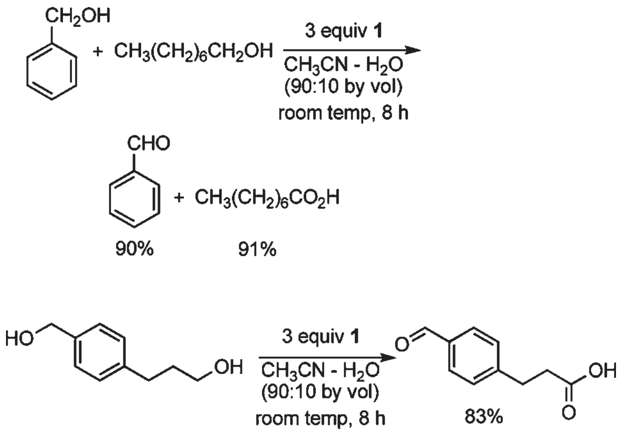
In an effort to elucidate the origin of the sluggish oxidation of benzaldehydes, the relative rates of oxidation of a representative assortment of aldehydes by **1** in CH_3CN–D_2O (90:10 by vol) were investigated in a series of competition experiments. Reaction mixtures containing equimolar quantities of two aldehydes and 1 molar equiv of **1** were allowed to stand for 24 h at room temperature; the relative extent of oxidation was assayed by integration of the CHO ^1H NMR signals of the residual aldehydes. The results of these studies are summarized in Table 3.

Table 2. Oxidation of Primary Alcohols to Carboxylic Acids (Scheme 3)

entry	acid	% yield[a]
1		97
2		95
3		89
4		96
5		88[b]
6		98
7		92
8		97
9[c]		94
10		89
11		69[d]

[a] Isolated yield of pure product after 8–12 h of reaction time unless otherwise indicated. [b] Reaction time of 20 d. [c] Prepared from the diol using 4 molar equiv of **1**. [d] The oxidation was terminated after 20 d; the remainder of the product mixture was benzaldehyde.

Scheme 4



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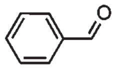
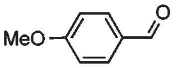
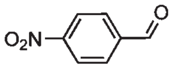
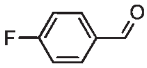
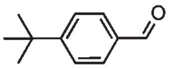
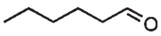
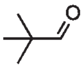
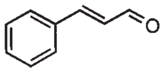
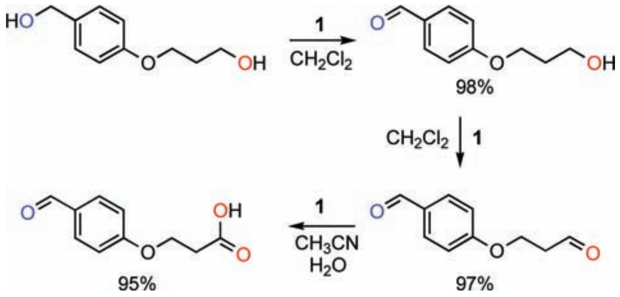
[10] Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *J. Org. Chem.* **2009**, *74*, 9524.

Table 3. Relative Rates of Oxidation of Aldehydes to Carboxylic Acids by **1** in CH_3CN-D_2O (90:10 by vol)

entry	aldehyde	rel oxidn rate
1		1.0
2		0.4
3		1.9
4		0.7
5		0.6
6		22.0
7		6.1
8		1.1

The conversion of an aldehyde to the corresponding carboxylic acid almost certainly involves as the rate-limiting step oxidation of the hydrate[11] via hydride abstraction by **1** (Scheme 2). However, the rate of such oxidations is a function of both the rate constant and the concentration of the hydrate. Given that the aldehyde−hydrate equilibrium is significantly less favorable for aromatic aldehydes than for aliphatic aldehydes,[12] the slow oxidation of benzaldehydes vis-à-vis aliphatic aldehydes appears to correlate with the concentration of aldehyde hydrate in the reaction medium. The fact that *p*-nitrobenzaldehyde is oxidized by **1** approximately five times faster than *p*-methoxybenzaldehyde (Table 3; cf. entries 2 and 3) is consistent with this rationale.[13]

Scheme 5



The results presented above demonstrate that oxidations of both alcohols and aldehydes using stoichiometric quantities of **1**, displaying significant selectivity that may be of considerable synthetic utility. The consecutive oxidations depicted in Scheme 5 illustrate the ability to control the site of oxidation in a substrate containing similar functionalities.

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Supporting Information Available. Detailed experimental procedures and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Wiberg, K. B. *Oxidation in Organic Chemistry, Part A*; Academic Press: New York, 1965; pp 69−178. (b) Schmidt, A-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 4164 and references therein.

(12) (a) Gómez-Bombarelli, R.; González-Pérez, M.; Pérez-Prior, M. T.; Casado, J. *J. Phys. Chem. A* **2009**, *113*, 11423. (b) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New Your, 1975; pp 257−265. (c) Bell, A. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1.

(13) (a) Sayer, J. M. *J. Org. Chem.* **1975**, *40*, 2545. (b) Greenzaid, P. *J. Org. Chem.* **1973**, *38*, 3164.