JOC*Note*
pubs.acs.org/joc

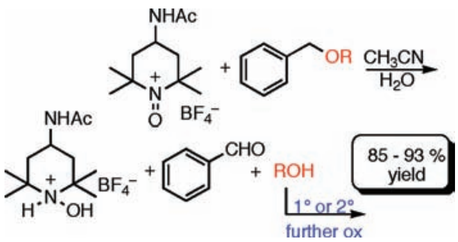
# Oxidative Cleavage of Benzylic and Related Ethers, Using an Oxoammonium Salt

Priya P. Pradhan, James M. Bobbitt,* and William F. Bailey*

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

*james.bobbitt@uconn.edu; william.bailey@uconn.edu*

*Received October 13, 2009*



Benzylic ethers and related $ArCH_2OR$ substrates are oxidatively cleaved by 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**) in wet $CH_3CN$ at room temperature to give the corresponding aromatic aldehyde and alcohol in high yield. Primary or secondary alcohol products are further oxidized by **1** to give carboxylic acids and ketones, respectively. The oxidation likely involves a formal hydride abstraction from the benzylic carbon as evidenced by slow reaction of substrates bearing electron-withdrawing substituents.

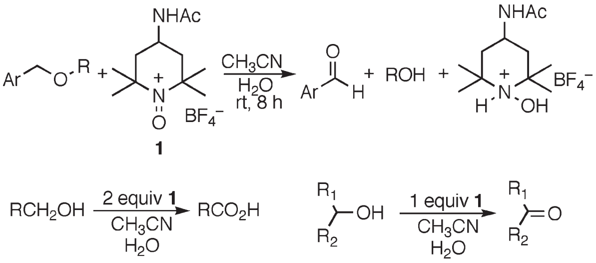
Benzylic ethers constitute one of the most widely used protecting groups for alcohols.[1] The benzylic ether bond is readily cleaved by a variety of either oxidative or reductive methods[1] but little is known concerning the behavior of benzylic ethers when treated with an oxoammonium salt.[2]

Some time ago, Cho and Park reported that oxidation of benzylic ethers in a two-phase medium using a catalytic quantity of a nitroxide and sodium hypochlorite as co-oxidant affords the benzoate in moderate yield along with variable amounts of benzaldehyde and benzoic acid.[3] Low yields of benzoates were also detected in the oxidation of a limited set of benzylic ethers by oxygen and the enzyme lactase mediated by TEMPO.[4] We are aware of only one study of the reaction of benzylic ethers with a stoichiometric quantity of oxoammonium salt: Miyazawa and Endo found that oxidation of dibenzyl ether with an oxoammonium bromide in methylene chloride solution afforded benzyldehyde and benzyl bromide.[5]

In light of the disparate results reported for the reaction of benzylic ethers with the oxoammonium cation, it seemed worthwhile to investigate the oxidation of a variety of $ArCH_2OR$ substrates with an oxoammonium salt containing a non-nucleophilic counterion. As detailed below (Scheme 1), benzylic ethers are oxidatively cleaved by readily available 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate[6] (**1**) upon stirring for 8 h in $CH_3CN$−water (90:10 by vol) at room temperature to afford the corresponding aromatic aldehyde and alcohol in high yield. As noted in Scheme 1 and further discussed below, primary and secondary alcohol products are further oxidized quite rapidly by **1** under these conditions to give carboxylic acids and ketones, respectively, as products. Consequently, 1 molar equiv of **1** is needed to cleave ethers derived from tertiary alcohols, 2 molar equiv of **1** is required for oxidative cleavage of substrates derived from secondary alcohols, and 3 molar equiv of **1** is necessary when the ether is derived from a primary alcohol.

Oxidative cleavages were conducted by stirring approximately 0.7 M solutions of the $ArCH_2OR$ ether and a stoichiometric quantity of **1** appropriate for the substrate in $CH_3CN$−water (90:10 by vol) at room temperature for 8 h at which time the oxidant was fully consumed as evidenced by a negative test with starch-KI paper. The results of these experiments are summarized in Table 1. It might be noted that NMR analysis of crude reaction mixtures prior to workup indicated that the products depicted in Table 1 were generated in virtually quantitative yield; the lower isolated yields that are reported are likely the result of the slight water solubility of low molecular mass products. Nonetheless, oxidative cleavage of $ArCH_2OR$ substrates under these conditions is a high-yield process.

**SCHEME 1**



---

[1] Wuts, P. G. M.; Green, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley & Sons: New York, 2007; pp 102−120.

[2] Oxoammonium salts contain the N=O cation and are derived from stable nitroxides such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) by one-electron oxidation. It should be noted that terms such as nitrosonium, immonium oxide, iminoxyl, and oxoamminium have been used in the older literature to describe such species. See: Bobbitt, J. M.; Brückner, C.; Merbouh, N. *Org. React.* (*N.Y.*) **2009**, *74*, in press.

[3] (a) Cho, N. S.; Park, C. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 924. (b) Cho, N. S.; Park, C. H. *J. Korean Chem. Soc.* **1995**, *39*, 657.

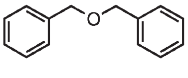
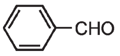
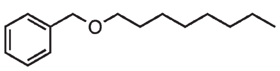
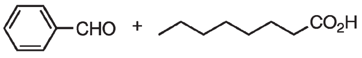
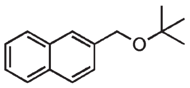
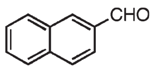
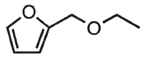
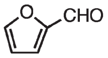
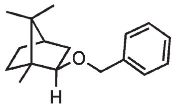
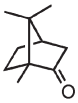
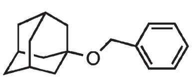
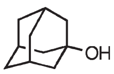
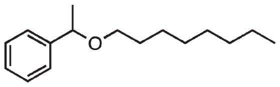
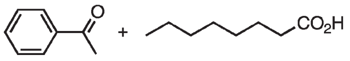
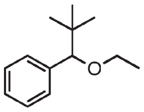
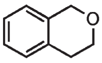
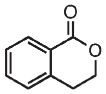
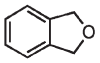
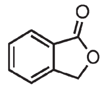
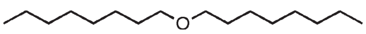
[4] (a) Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P. *Eur. J. Org. Chem.* **2002**, 4195. (b) Acunzo, F.; Baiocco, P.; Galli, C. *New J. Chem.* **2003**, *27*, 329.

[5] Miyazawa, T.; Endo, T. *Tetrahedron Lett.* **1986**, *27*, 3395.

[6] Bobbitt, J. M.; Merbouh, N. *Organic Syntheses*; Wiley: New York, 2005; Vol. 82, p 80. The 4-acetamido group on **1** raises the melting point of the salt and results in a much increased stability relative to salts derived from TEMPO.

DOI: 10.1021/jo902144b

**TABLE 1. Oxidation of $ArCH_2OR$ with Oxoammonium Salt (1) in $CH_3CN$−Water (90:10 by vol)[a]**

| entry | $ArCH_2OR$ | products, % yield[b] |
|---|---|---|
| 1 |  | <br>86[c] |
| 2 |  | <br>90 91 |
| 3 |  | <br>93[d] |
| 4 |  | <br>90[e] |
| 5 |  | <br>92 |
| 6 |  | <br>93 |
| 7 |  | <br>89 93 |
| 8 |  | no reaction |
| 9 |  | <br>90 |
| 10 |  | <br>91 |
| 11 |  | no reaction |

[a] Reactions were conducted by stirring approximately 0.7 M solutions of the ether and **1** in $CH_3CN$−water (90:10 by vol) at room temperature for 8 h. [b] Isolated yield unless otherwise noted. [c] $^1H$ NMR analysis of the crude reaction mixture demonstrated that benzaldehyde was produced in virtually quantitative yield. [d] $^1H$ NMR analysis of the crude reaction mixture demonstrated that *tert*-butanol was produced in virtually quantitative yield. [e] Acetic acid was also obtained but was not isolated.

One aspect of the chemistry summarized in Scheme 1 requires further comment. As noted above, primary and secondary alcohols produced upon cleavage of benzylic ethers are further oxidized by **1**. For example, the oxidation of benzyl octyl ether with 3 molar equiv of **1** (Table 1, entry 2) affords benzaldehyde and octanoic acid as the only products. Monitoring the progress of this oxidation by $^1H$ NMR proved instructive: the results are illustrated graphically in Figure 1. The process involves initial cleavage of the ether to give benzaldehyde and octanol. The octanol is then oxidized[7] by way of the aldehyde to give octanoic acid. The interesting feature of the process is the complete absence of benzoic acid: octanal is oxidized, presumably via the hydrate,[8] much more

---

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

(8) For a discussion of the mechanism of alcohol oxidation by an oxoammonium cation, see: Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, *72*, 4504.

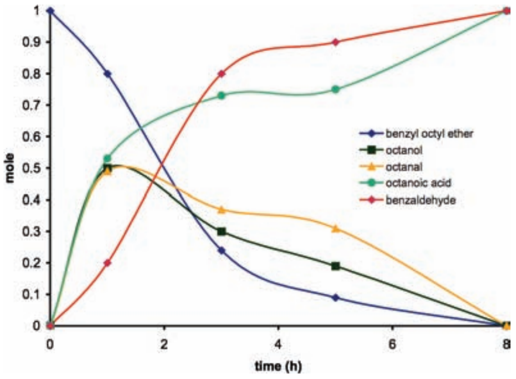


**FIGURE 1.** Oxidation of benzyl octyl ether, using 3 molar equiv of **1**.

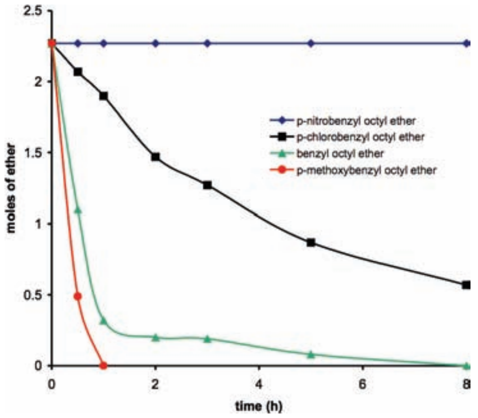


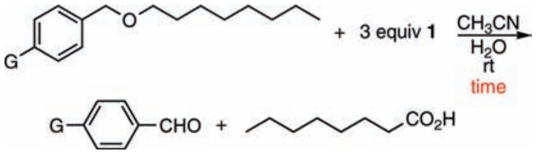
**FIGURE 2.** Effect of substituents on the rate of oxidation of para-substituted benzyl octyl ethers with 3 molar equiv of **1**.

rapidly than is benzaldehyde. This behavior, which is reminiscent of that observed previously in chromium(VI) oxidations of aldehydes proceeding through the chromate ester of the hydrate, may be attributed to the unfavorable benzaldehyde–hydrate equilibrium vis-à-vis that of aliphatic aldehydes.[9] It might be noted that, as expected, oxidation of benzyl octyl ether with 1 molar equiv of **1** resulted in recovery of unreacted ether and formation of a mixture of benzaldehyde, octanol, octanal, and octanoic acid.

The results, summarized in Table 1, demonstrate that a variety of $ArCH_2OR$ substrates are readily oxidized. However, highly hindered benzylic ethers (Table 1, cf. entries 7 and 8) are unreactive as are aliphatic ethers (Table 1, entry 11).

The effect of substituents on the aromatic ring of the benzylic ether on the rate of oxidation, which has a bearing on the mechanism of the process, was assessed in a limited study of the reaction of **1** with several para-substituted benzyl octyl ethers. The results of these experiments, which are summarized in Table 2 and presented graphically in Figure 2, strongly imply that the rate-limiting step in the oxidative cleavage involves development of a positive charge at the benzylic position of the ether. Indeed, whereas *p*-methoxybenzyl octyl ether is fully consumed in only 2 h (Table 2, entry 2), the *p*-nitrobenzyl substrate is totally inert to the action of **1** after 24 h (Table 2, entry 4).

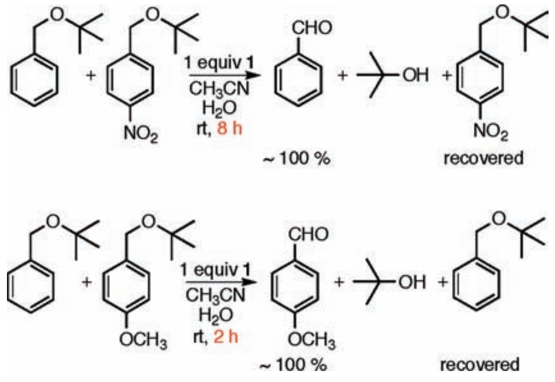
**TABLE 2. Effect of Para-Substituents on the Oxidation of Substituted Benzyl Octyl Ethers with 3 molar equiv of 1 in $CH_3CN$–Water (90:10 by vol) at Room Temperature**



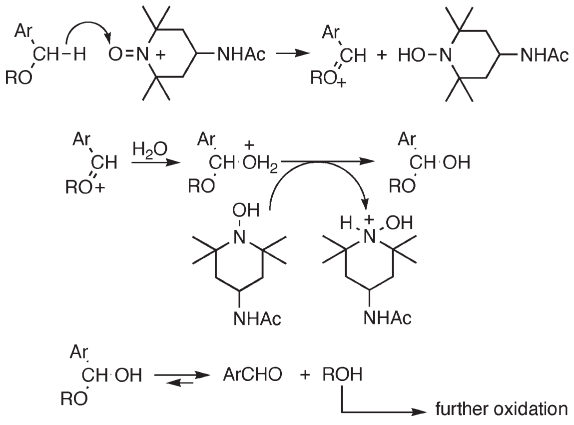
| entry | G | time (h) | products (% yield)[a] aldehyde | products (% yield)[a] octanoic acid |
|---|---|---|---|---|
| 1 | H | 8 | 90 | 91 |
| 2 | $OCH_3$ | 2 | 86 | 89 |
| 3 | Cl | 24 | 85 | 90 |
| 4 | $NO_2$ | 24 | no reaction | |

[a] Isolated yields.

### SCHEME 2



### SCHEME 3



As a practical matter, the rather dramatic differences in the rate of oxidation of para-substituted benzylic ethers by **1** may prove useful for the selective protection of polyalcohols. As illustrated in Scheme 2, a benzyl ether is completely cleaved in the presence of its *p*-nitrobenzyl analogue; conversely, a benzyl ether is stable under conditions that lead to complete consumption of the *p*-methoxybenzyl analogue.

A mechanism that accounts for the oxidative cleavage of $ArCH_2OR$ ethers by an oxoammonium cation is depicted in Scheme 3. A formal hydride transfer from the benzylic

---

[9] (a) Wiberg, K. B. In *Oxidation in Organic Chemistry, Part A*; Academic Press: New York, 1965; pp 69–178. (b) Roček, J.; Ng, C.-S. *J. Org. Chem.* **1973**, *38*, 3348 and references cited therein.

carbon of the ether to the oxygen of the oxoammonium salt, perhaps involving prior complexation of the substrate with the oxoammonium cation as suggested by Galli,[4] is likely the rate-determining step of the process. Rapid conversion of the oxygen-stabilized benzylic cation to the hemiacetal upon trapping with water leads directly to ArCHO and alcohol. The proposed mechanism nicely rationalizes the pronounced effect of para-substituents on the rate of oxidation of substituted benzylic ethers summarized above.

## Experimental Section

**Representative Procedure for the Oxidation of Benzylic Ethers with 4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium Tetrafluoroborate: Oxidation of Benzyl Octyl Ether (Table 1, Entry 2).** A solution of 8.18 g (27.3 mmol) of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**1**) and 2.00 g (9.09 mmol) of benzyl octyl ether in 34 mL of acetonitrile−water (90:10 by vol) was stirred at room temperature for 8 h. Completion of the reaction was monitored by $^1$H NMR (Figure 1) and with starch-KI paper. The reaction mixture was diluted with 15 mL of water and extracted with three 20-mL portions of diethyl ether. The combined ether extract was extracted with three 15-mL portions of saturated, aq $Na_2CO_3$. The organic layer was then washed with 15 mL of water and 10 mL of brine, dried ($MgSO_4$), and concentrated to give 0.86 g (90%) of benzaldehyde as a colorless liquid: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 10.05 (s, 1H), 8.06 (d, $J$ = 4.0 Hz, 2H), 7.88−7.87 (m, 1H), 7.54−7.44 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 192.6, 136.9, 134.6, 129.9, 129.2. The basic aqueous extract was acidified with 10% aqueous HCl to pH ~2 and extracted with three 10-mL portions of diethyl ether. The combined organic phase was washed with 10 mL of water and 10 mL of brine, dried ($MgSO_4$), and concentrated to give 1.19 g (91%) of octanoic acid as a colorless liquid: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.90 (br s, 1H), 2.33 (t, $J$ = 8.0 Hz, 2H), 1.64−1.59 (m, 2H), 1.30−1.27 (m, 8H), 0.89−0.85 (m, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 180.9, 34.3, 31.8, 29.2, 29.1, 24.8, 22.8, 14.2.

**Acknowledgment.** We thank Ashley L. Bartelson for help with the preparation of this manuscript. This work was supported by a grant from Procter & Gamble Pharmaceuticals, Mason, OH.

**Supporting Information Available:** Detailed experimental procedures for all reactions reported in Tables 1 and 2 and $^1$H NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.