Oxidation of Alcohols with Nitroxyl Radical Resins under Two-Phase Conditions

Yoshitomo Kashiwagi,*[a] Hiroshi Ikezoe,[b] Tetsuya Ono[b]

[a] School of Pharmaceutical Sciences, Ohu University, 31-1 Misumido, Tomita-machi, Koriyama, Fukushima 963-8611, Japan
Fax +81(24)9329138; E-mail: y-kashiwagi@pha.ohu-u.ac.jp

[b] Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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Abstract: The oxidation of alcohols to carbonyl compounds such as aldehydes and ketones was studied using potassium hexacyanoferrate(III) mediated by nitroxyl radical polystyrene resins as catalyst under organic–aqueous two-phase conditions. Primary alcohols are readily oxidized to the corresponding aldehydes in excellent yield with no overoxidation to carboxylic acids. Secondary alcohols are converted to the corresponding ketones with a much lower efficiency. Oxidative cyclization of 1,4- and 1,5-diols to γ- and δ-lactones, respectively, proceeded nicely.

Key words: nitroxyl radical resin, potassium hexacyanoferrate(III), alcohol, oxidation, two-phase conditions

Oxoammonium ions[1] are known as nonmetallic oxidizing reagents of alcohols to the corresponding carbonyl compounds under mild reaction conditions,[2–4] and are available easily from the corresponding nitroxyl radicals by one-electron oxidation. On the other hand, polymeric reagents[5] have attracted much interest in organic synthesis, because they can be used in high excess and are removed by filtration, the products can be easily analyzed and further transformation in solution. Recently, Rademann and co-workers have reported on the generation of oxoammonium halides as oxidizing reactive species on a solid support such as polystyrene and on the use of this reagent in the oxidation of alcohols.[6] TEMPO polystyrene (TEMPO PS) may also be used to catalyzed the oxidation of alcohols with oxone in the presence of a phase-transfer agent such as tetrabutylammonium bromide.[7] Furthermore, a related study that uses TEMPO PS together with polystyrene-supported diacetoxyiodosobenzene to selectively oxidize alcohols to aldehydes and ketones was reported.[8–11] However, these reagents were used in high excess to substrate. Herein we report on the first efficient oxidation of alcohols to carbonyl compounds using potassium hexacyanoferrate(III) [$K_3Fe(CN)_6$] mediated by TEMPO PS as catalyst under polymer-supported organic–aqueous two-phase conditions (Figure 1).

Several oxidation reactions of alcohols in organic–aqueous two-phase solution have been reported using regenerating oxidants such as positive halogen sources[12–15] and high-valency metal salts[16,17] which were mediated by the oxidation of nitroxyl radical to oxoammonium ion. However, almost all of reactions require the same amount of organic solvent as water. The use of water instead of organic solvents is strongly desired from the viewpoint of environmental safety and economical cost. For this reason, we tried to use a small amount of organic solvent, which may be kept in the polystyrene (PS) resin by hydrophobic interaction, as an organic layer of two-phase reaction.

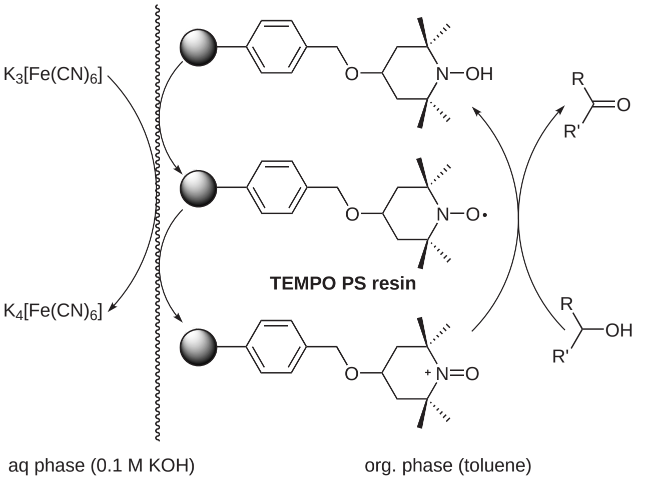

Figure 1 Oxidation of alcohols with $K_3Fe(CN)_6$ mediated by TEMPO PS resin under organic–aqueous two-phase solution system.

Preparative, oxidation of alcohols with nitroxyl radical resins under two-phase conditions was described as follows. TEMPO PS resin (TEMPO loading: 2.0 mmol/g, 300 mg) was added to the toluene solution (4 mL) containing alcohol (4 mmol), 2,6-lutidine (4 mmol) and tetralin as internal standard (0.5 mmol). This TEMPO PS resin dispersed suspension was stirred for one hour at room temperature and then separated. The swelled resin was washed three times with water and then added to 10 mL of 0.1 M aqueous KOH solution containing 3.29 g (10 mmol) of $K_3Fe(CN)_6$. The reaction mixture was stirred at room temperature. During oxidation reaction, aliquots of reaction mixture were occasionally analyzed by HLPC and GC.[18] At the end of the reaction, the swelled resin was separated, washed three times with water, extracted three times with toluene and filtered in vacuo. This extracted solution was dried with magnesium sulfate and evaporated. The residue was distilled or isolated by column chromatography. The products were identified by the usual spectral data (mass, IR, ^1H NMR and ^{13}C NMR).

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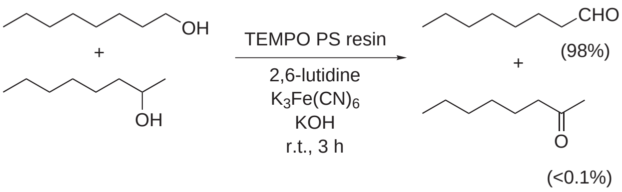
The results of oxidation of a variety of primary and secondary alcohols are shown in Table 1. The primary alcohols (entries 1–6) such as 1-octanol, nerol, benzyl alcohol, 4-methoxybenzyl alcohol, 4-nitrobenzyl alcohol and cinnamyl alcohol were oxidized to the corresponding aldehydes. Under standard reaction conditions aliphatic and benzylic primary alcohols are oxidized within 0.5–10 hours. In the case of benzylic alcohols, electron-donating groups slow down the reaction (entry 4) whereas electron-withdrawing groups accelerate it (entry 5). Allyl alcohols (entries 2 and 6) are also oxidized to the corresponding aldehydes in adequate yields.

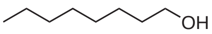
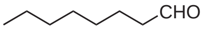
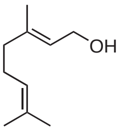
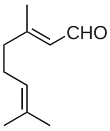
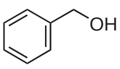
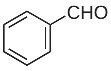
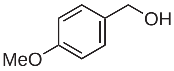
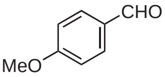
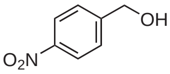
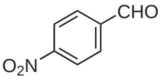
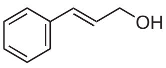
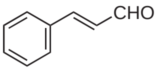
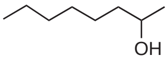
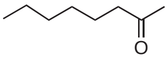
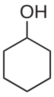
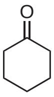
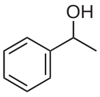
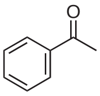
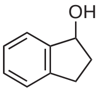
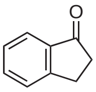
On the other hand, the secondary alcohols (entries 7–10) such as 2-octanol, cyclohexanol, 1-phenylethanol, and 1-hydroxyindan are converted to the corresponding ketones with much lower efficiency under the same conditions. This observation suggested a possible chemoselective oxidation of primary alcohols in the presence of secondary alcohols. The results from the oxidation of 1:1 mixture of 1-octanol and 2-octanol are shown in Scheme 1 and Figure 2. Indeed, the present oxidation system proved to be exceptionally chemoselective: under standard reaction conditions primary alcohol was converted quantitatively into aldehyde after three hours whereas virtually no ketone (<0.1%) could be detected by GC.



Scheme 1 Oxidation of 1-octanol in the presence of 2-octanol.

The results of oxidation of various diols are shown in Table 2. Oxidative cyclization of 1,4- and 1,5-diols to γ- and δ-lactones, respectively, proceeded nicely (entries 1 and 2). *cis*-Cyclohexane-1,2-dimethanol is also converted into cyclization product (entry 5). However, 1,*n*-diols ($n > 5$) gave non-cyclization products such as 1,*n*-dialdehyde or *n*-hydroxyalkanal, predominantly (entries 3 and 6). 1,4-Benzenedimethanol as the benzylic primary-primary diol is oxidized to the corresponding dialdehyde with excellent

Table 1 Oxidation of Primary and Secondary Alcohols

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			3	98
2			2.5	98
3			2	97
4			7	96
5			0.5	98
6			3	88
7			10	24
8			6	36
9			4	65
10			3	58

[a] Yields were determined by calibrated quantitative GC or HPLC analysis using as internal standard.

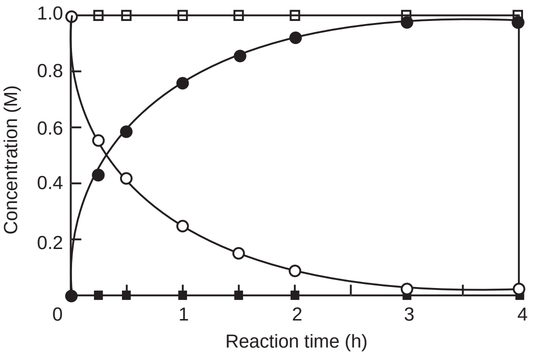


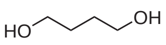
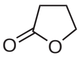
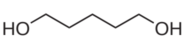
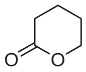
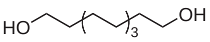
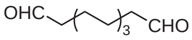
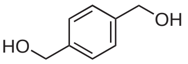
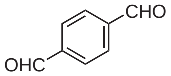
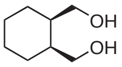
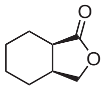
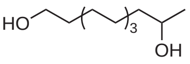
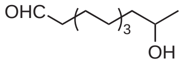
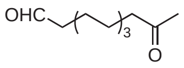
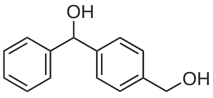
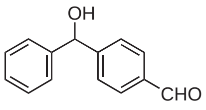
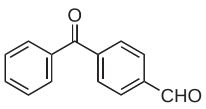
Figure 2 Oxidation of a mixture of 1-octanol and 2-octanol (1:1) by TEMPO PS resin together with $K_3Fe(CN)_6$. 1-Octanol: ○; 1-octanone: ●; 2-octanol: □; 2-octanone: ■.

yield (entry 4). In case of intermolecular competition between primary and secondary alcohols, oxidation of 1,10-undecanediol gave 82% isolated yield of 10-hydroxyundecanal with 6% ketoaldehyde, the amount of isomeric keto alcohol remaining less than 0.1% (entry 6). Even in the case of doubly activated secondary alcohols the methods ensures oxidation of primary alcohols with a very high chemoselectivity (entry 7).

A possible reaction mechanism is as follows (Figure 3). The nitroxyl radical catalyst on resin was first oxidized by Fe(III) to give oxoammonium ion on organic–aqueous interface, and subsequently alcohol was oxidized by the oxoammonium ion in the organic phase of resin to give the corresponding carbonyl compound, in which an adduct made up of the alcohol and the oxoammonium ion is attacked by a Lewis base to form the second intermediate leading to the products,[19] hydroxylamine and a protic acid such as $H^+K_3[Fe^{II}(CN)_6]^-$ which was neutralized by KOH to give potassium ferrocyanide. Either the hydroxylamine is oxidized to the nitroxyl radical by Fe(III) or the reaction of the hydroxylamine and the oxoammonium ion produces the nitroxyl radical. In either case, the nitroxyl radical is re-oxidized chemically by Fe(III) to complete a catalytic cycle.

In conclusion, we have demonstrated the first efficient oxidation of alcohols using $K_3Fe(CN)_6$ mediated by TEMPO polystyrene resin under an organic–aqueous two-phase solution system. This method is promising in organic synthesis from an environmental, practical and safety viewpoint. This present work has the advantage of not separating the product and TEMPO from a reaction solution. Primary alcohols are readily oxidized with no

Table 2 Oxidation of Various Diols

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			3.5	97
2			3	98
3			4	93
4			5	95
5			3	96
6		 + 	3	82[b] 6
7		 + 	4	78[c] 10

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[a] Yields were determined by calibrated quantitative GC or HPLC analysis using as internal standard.

[b] Ketoalcohol could not be detected.

[c] 1% Ketoalcohol and 5% starting diol could be detected.

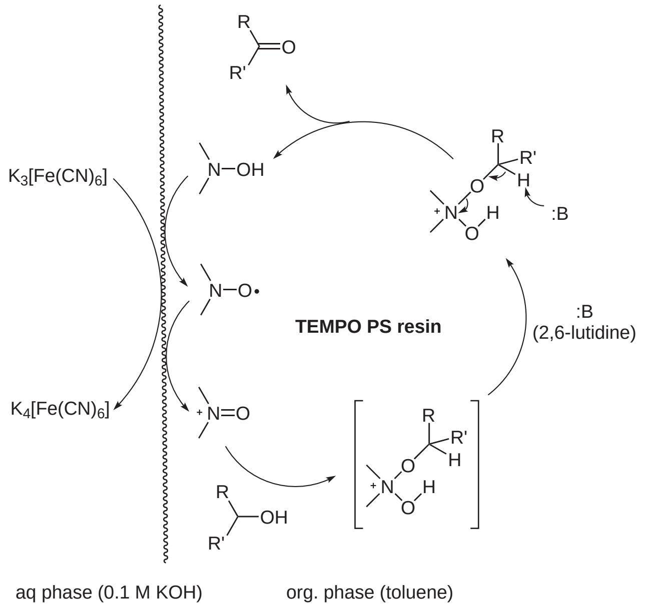

Figure 3 Schematic diagram of organic–aqueous two-phase oxidation of alcohols with $K_3Fe(CN)_6$ mediated by TEMPO PS resin.

overoxidation to carboxylic acids. Furthermore, this process exhibits an unprecedented degree of chemoselectivity for the oxidation of primary hydroxyl groups in the presence secondary hydroxyl groups.

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(14) $NaBrO_2$: (a) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462. (b) Inokuchi, T.; Liu, P.; Torii, S. *Chem. Lett.* **1994**, 1411. (c) Saito, S.; Hara, T.; Naka, K.; Hayashi, T.; Moriwake, T. *Synlett* **1992**, 241. (d) Saito, S.; Ishikawa, T.; Moriwake, T. *Synlett* **1993**, 139.
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