An Efficient Aerobic Oxidation of Alcohols to Aldehydes and Ketones with TEMPO/Ceric Ammonium Nitrate as Catalysts

Sung Soo Kim,* Hyun Chul Jung

Department of Chemistry and Center for Chemical Dynamics, Inha University, Incheon 402-751, South Korea
E-mail: sungsoo@inha.ac.kr

Received 30 May 2003; revised 4 July 2003

Abstract: Secondary benzylic alcohols with an alkyl chain are oxidized faster than simple benzyl alcohols. However the reaction time is prolonged, when the alkyl chain is replaced by a bulky phenyl ring such as benzhydrol and 9-hydroxyfluorene. All the benzyl and benzylic alcohols give yields >90%. Allylic alcohols without steric hindrance react faster to give excellent yield (>80%). The present method is superior to others currently available due to its relatively short reaction times and excellent yields.

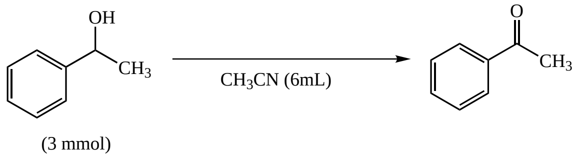
Key words: air oxidation, TEMPO, CAN, benzylic alcohols, allylic alcohols

The oxidation of alcohols into their corresponding aldehydes and ketones is one of the most important processes in organic synthesis. Recently, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO)[1] has been frequently employed as the choice catalyst for the mild and selective oxidation of alcohols. *N*-Oxoammonium salts can be used stoichiometrically[2,3] or generated in a catalytic manner[4–11] in situ by reacting TEMPO with numerous oxidants. The oxidants include sodium bromite,[4] sodium hypochlorite,[5] *N*-chlorosuccinimide,[6] electrooxidation,[7] [bis(acetoxy)iodo]benzene,[8] dimethylsulfoxide/cyanuric acid,[9] oxone,[10] H_5IO_6[11] and O_2/TEMPO[12]. CAN itself is a well known oxidizing agent that oxidizes secondary alcohols into ketones[13–15] or benzylic groups into aldehydes.[16–18] Aerobic O_2 oxidation of alkyl malonates into ketomalonates[19] employs a catalytic amount of CAN. Herein, we report the aerobic O_2 oxidation of benzylic and allylic alcohols using TEMPO and CAN.

sec-Phenethyl alcohol is chosen for several control experiments to determine the role of each reagent (Table 1). CAN and TEMPO are the most important species without which no reaction occurs (entry 1) or the oxidation takes place to a very small extent (entry 2). Without O_2 evolution, the oxidation gives only 40% of acetophenone (entry 3). Reflux of CH_3CN is also required to obtain decent yields (entry 4). An excellent oxidative process is described with entry 5.

Primary benzyl alcohols (Table 2, entries 1–3) react smoothly (2.5 h) to give the corresponding aldehydes. However, secondary benzylic alcohols (entries 4–7) are oxidized much faster (20 min–1 h). This may indicate that bond dissociation energy outweighs the moderate steric hindrance in determining the rate of the oxidative process. Steric requirement can nonetheless become important enough to reduce the reaction rate when the alkyl chain is replaced by a bulky phenyl ring (Compare the reaction time of between entries 4–7 and entries 8, 9). Several allylic system (entries 10–13) also give an excellent yield that is a little lower than benzylic alcohols (entries 4–9). Substituted allylic alcohol (entry 14) gave a good yield with comparatively longer reaction period. In comparision with previous results where TEMPO is used as a catalyst (entries 1–5,10,11, and 13 of Table 2), the current system shows much reduced reaction times.[12]

Table 1 Oxidation of *sec*-Phenethyl Alcohol under Various Conditions[a]



Entry	CAN (mol%)	TEMPO (mol%)	O_2[b]	Time	Yield (%)
1	–	10	O_2	1 h	N.R.[c]
2	20	–	O_2	1.5 h	5[d]
3	20	10	–	1.5 h	40
4	10	10	O_2	1 h	11
5	10	10	O_2	1 h	99

[a] All the reactions except for entry 4 were in CH_3CN at reflux. Entry 4 was carried out at r.t.

[b] O_2 is bubbled in all the reactions except for entry 3. Entry 3 is reacted in air without O_2 bubbling.

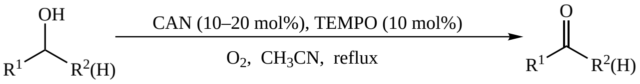
[c] No reaction occurs because the real oxidizing agent should be the oxoammonium salt instead of the nitroxyl radical.

[d] CAN itself has been used as an oxidant[13–18] that could be responsible for the small yield of the ketone.

The oxidation mechanism can be rationalized as shown Scheme 1. Dioxygen is reduced to H_2O by oxidation of Ce^{3+} into Ce^{4+}. TEMPO can be oxidized to *N*-oxoammonium cation with the aid of Ce^{4+}/Ce^{3+}. *N*-Oxoammonium cation then oxidizes the alcohol to give the carbonyl compound.

SYNTHESIS 2003, No. 14, pp 2135–2137
Advanced online publication: 24.09.2003
DOI: 10.1055/s-2003-41065; Art ID: F04803SS.pdf

Table 2 Aerobic Oxidaiton of Alcohols with TEMPO/CAN



Substrate	CAN	TEMPO	CH_3CN	O_2
3 mmol	0.3~0.6 mmol	0.3 mmol	6 ml	Bubbling

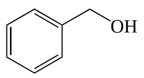
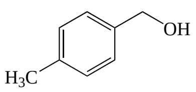
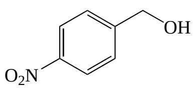
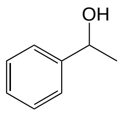
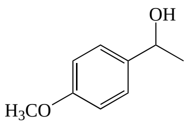
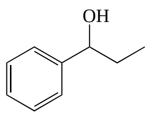
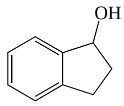
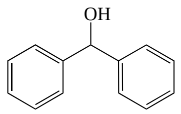
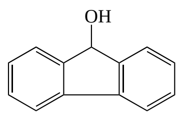
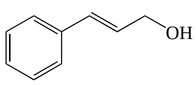
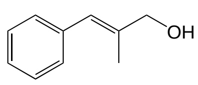
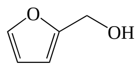
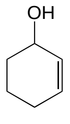
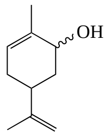
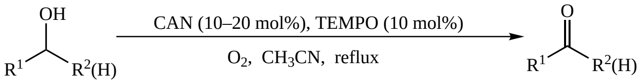
Entry	Substrate	Time	Temp. (°C)	Yield (%)[a]
1		2 h 4 h 6 h 10 h 15 h 2.5 h	82 25 100 20 65 100	92[b] 94[12a] 99[12b] 98[12c] 99[12b] 98[12c] 71[12f] 90[12h]
2		2 h 6 h 6 h	82 100 20	93 99[12b] 99[12c]
3		2.5 h 6 h 1.5 h 6 h	82 100 90 100	92 93[12b] 93[12e] 97[12h]
4		1 h 6 h 6 h 42 h 4 h 1 h	82 100 20 65 100 100	99[b] 98[12b] 99[12c] 72[12f] 93[12h] 89 [12i]
5		20 min	82	90[b]
6		1 h	82	98
7		30 min 30 h 2.8 h	82 65 100	94 91[12f] 88[12i]
8		3.5 h	82	99
9		2 h	82	99
10		3 h 2.75 h 3 h 1 h 20 h	82 25 40 90 65	81 93[12a] 99[12c] 79[12e] 75[12f]
11		1 h 29 h	82 65	94 78[12f]
12		1 h	82	83
13		15 min 18.5 h 24 h	82 25 65	86 0[12a] 75[12f]
14		7 h	82	75

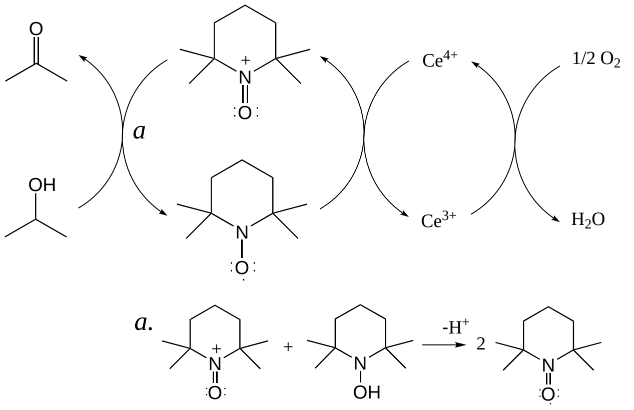
Table 2 Aerobic Oxidaiton of Alcohols with TEMPO/CAN (continued)



Substrate 3 mmol CAN 0.3~0.6 mmol TEMPO 0.3 mmol CH_3CN 6 ml O_2 Bubbling
Entry Substrate Time Temp. (°C) Yield (%)[a]

[a] Isolated yield.

[b] 10mol% CAN was used. The rest of the reactions employ 20 mol% of CAN.



Scheme 1

In conclusion, the combination of TEMPO/CAN can be used for the effective oxidation of most of benzyl, benzylic, and allylic alcohols into their corresponding carbonyl compounds. Steric hindrance has however been observed with some substituted allylic system. Aliphatic alcohols, such as cyclohexanol show no reactivity towards the oxidative process.

Oxidation; General Procedure

Alcohol (3 mmol), CAN (0.6 mmol) and TEMPO (0.3 mmol) were dissolved in CH_3CN (6mL) in a three-neck flask equipped with a condenser and magnetic bar. This mixture was heated at 100 °C with an oil bath under a continuous stream of O_2. When the reaction was complete, H_2O (20mL) was added and the resulting mixture extracted with CH_2Cl_2 (3 × 30mL). The combined CH_2Cl_2 layer was washed with water, dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by Silica gel flash chromatography eluting with EtOAc–hexane. Because of the relatively low boiling point of, entries 12 and 13 Et_2O–petroleum ether was used as the eluent. All the products were identified by ^1H NMR spectroscopy and agreed with literature data.[20]

Acetophenone

^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.99$ (d, 2 H), 7.51 (m, 3 H), 2.62 (s, 3 H).

Acknowledgment

The authors warmly thank Korea Science and Engineering Foundation for the financial support (R01-2001-00057).

References

(1) (a) Sheldon, R. A.; Arends, I. W. C. E.; Ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (b) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. (c) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (d) Inokuchi, T.; Matsumoto, S.; Torii, S. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 910.

(2) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332.

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

(4) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462.

(5) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

(6) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452.

(7) Semmelhack, M. F.; Chou, C. S.; Cortes, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 4492.

(8) Mico, A. D.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(9) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907.

(10) Bolm, C.; Magnus, A. S.; Hildebrand, J. P. *Org. Lett.* **2000**, *2*, 1173.

(11) Kim, S. S.; Nehru, K. *Synlett* **2002**, 616.

(12) (a) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (b) Ben-Daniel, R.; Alsters, P.; Neumann, R. *J. Org. Chem.* **2001**, *66*, 8650. (c) Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651. (d) Dijksman, A.; Marino-González, A.; Payeras, A. M.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826. (e) Ragagnin, G.; Betzemeier, B.; Quici, S.; Knochel, P. *Tetrahedron* **2002**, *58*, 3985. (f) Ansari, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507. (g) Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343. (h) Dijksman, A.; Mariano-González, A.; Payeras, A. M. I.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826. (i) Csjernyic, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657.

(13) Trahanovsky, W. S.; Flash, P. J.; Smith, L. M. *J. Am. Chem. Soc.* **1969**, *91*, 5068.

(14) Soucy, P.; Ho, T. L.; Deslongchamps, P. *Can. J. Chem.* **1972**, *50*, 2047.

(15) Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 539.

(16) Syper, L. *Tetrahedron Lett.* **1966**, *7*, 4493.

(17) Torii, S.; Tanaka, H.; Inokuchi, T.; Nakane, S.; Akada, M.; Saito, N.; Sirakawa, T. *J. Org. Chem.* **1982**, *47*, 1647.

(18) Maini, S.; Mandolini, L.; Rol, C. *J. Org. Chem.* **1978**, *43*, 3236.

(19) Tugaut, V.; Pellegrini, S.; Castanet, Y.; Mortreux, A. *J. Mol. Cat.* **1997**, *127*, 25.

(20) *The Aldrich Library of ^{13}C and ^1H FT NMR Spectra*; Behnke, C. J. P. J., Ed.; Aldrich: Milwaukee USA, **1985-1989**.