Pergamon

Tetrahedron Letters, Vol. 36, No. 18, pp. 3223-3226, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00519-6

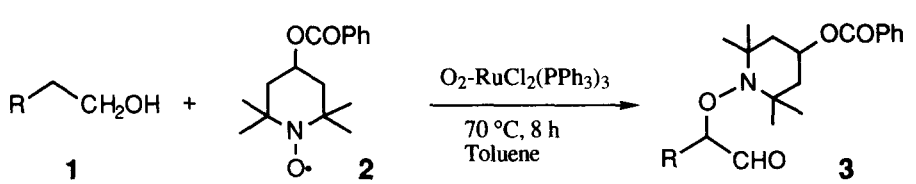
ONE-POT CONVERSION OF PRIMARY ALCOHOLS TO α-OXYGENATED ALKANALS WITH TEMPO IN COMBINATION WITH MOLECULAR OXYGEN AND RUTHENIUM COMPLEX

Tsutomu Inokuchi, Keiichi Nakagawa, and Sigeru Torii*

Department of Applied Chemistry, Faculty of Engineering,
Okayama University, Okayama 700, Japan

Abstract: Reaction of primary alcohols with an oxidizing system composed of 4-BzOTEMPO (2 equiv.), $RuCl_2(PPh_3)_3$ as a catalyst, and molecular oxygen leads to concomitant oxidation and substitution, giving the corresponding α-oxygenated alkanals. Similar reaction of secondary alcohols terminates at the stage of oxidation of hydroxyl group, forming the ketones, selectively.

Metal-catalyzed oxidation of alcohols to the carbonyl compounds in conjunction with co-oxidants is of use in organic synthesis.[1] More recently, versatility of ruthenium complexes such as tetrapropylammonium perruthenate (TPAP), $RuCl_2(PPh_3)_3$, and others as a oxidizing catalyst has been explored.[2] Concerning with the oxidation with $RuCl_2(PPh_3)_3$, two reaction modes are known in which either a stoichiometric or a catalytic amount of the ruthenium reagent is used.[3] For example, catalytic procedures with $RuCl_2(PPh_3)_3$ by combined use of O_2,[4] $Me_3SiOOSiMe_3$,[5] or t-BuOOH[6] are effective for allylic and benzylic alcohols and a combination of $RuCl_2(PPh_3)_3$ with PhIO or $PhI(OAc)_2$[7] and *N*-methylmorpholine-*N*-oxide[8] are useful for aliphatic ones.[9] Especially, aerobic oxidation with $RuCl_2(PPh_3)_3$ are of increasing interest from practical point of views.[10] In this paper we report a new oxidizing system composed of $RuCl_2(PPh_3)_3$ as a catalyst, molecular oxygen, and 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl (4-BzOTEMPO, **2**) for one-pot conversion of aliphatic alcohols to the corresponding α-oxygenated alkanals **3**.



1 **2** **3**

Introduction of oxygen functionality to the position α of the carbonyl group has often been achieved by oxidation of enolates with MoOPh,[11] oxaziridine,[12] and peracid anhydride.[13] These methods, however, are usually limited to ketones and esters, and successful examples for α-oxygenation of aldehydes are few except in the case where isovaleraldehyde derivatives are used.[14]

Firstly, we investigated the role of the components in this oxidizing system by varying their amounts.[15] A small conversion of the alcohol **1a** (R = C_9H_{19}) to undecanal (**4a**), attained in the absence of 4-BzOTEMPO **2** using 10 mol% of $RuCl_2(PPh_3)_3$ under Ar (entry 1) or under O_2 atmosphere (entry 2), may be ascribable to oxidizing ability of the ruthenium(II) complex.[9] Although the conversion is not completed, the latter result indicates possibility of the reaction course in which molecular oxygen is involved in the regeneration of reactive ruthenium(II) species. Strikingly, the formation of **4a** is increased to 23% from 9.5% (entry 3) under Ar or to 71% from 44% (entry 4) under O_2 when 4-BzOTEMPO **2** (10 mol%) is added to the reaction mixture. Furthermore, it was found that the oxidation of **1a** leads to formation of the TEMPO-substituted alkanal **3a** if amount of the compound **2** is increased to 50 mol% (entry 5). The yield of the adduct **3a** is improved by increasing the amount of **2** (entries 6 and 7) and eventually reaches 76% when more than 2 equivalents of the 4-BzOTEMPO **2** is employed (entries 8 and 9). Effect of the kind of solvent was also investigated; non-polar solvents such as benzene (74%) and toluene (76%), as well as THF (72%) were found to be suitable for this purpose, while polar solvent was less. For instance, the reaction in DMF produced the aldehyde **4a** as a major product (55% yield) and the desired adduct **3a** in 14% yield.

Table 1. Aerobic Oxidation of Primary Alcohol **1a** with **2** and $RuCl_2(PPh_3)_3$.[a)]

Entry	TEMPO 2 equiv.	O_2 or Argon	Product/Yield, %	
			4a	**3a**
1	none	Ar	9.5	0
2	none	O_2	44	0
3	0.1	Ar	23	0
4	0.1	O_2	71	0
5	0.5	O_2	53	40
6	1.0	O_2	33	60
7	1.5	O_2	28	66
8	2.0	O_2	0	76
9	3.0	O_2	0	76

a) Carried out by using **1a** (0.5 mmol), $RuCl_2(PPh_3)_3$ (10 mol%) in $C_6H_5CH_3$ (1 mL) at 70 °C for 8 h.

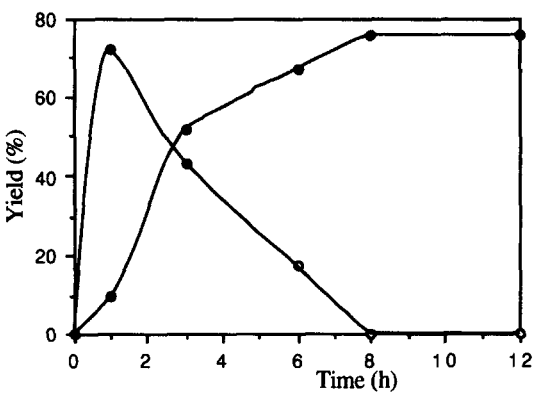
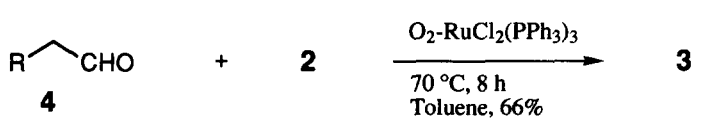


Figure 1. Time-Course of the Oxidation of Alochol **1a**. The reaction was carried out by using **2** (2 equivalent) and $RuCl_2(PPh_3)_3$ (10 mol%) under O_2 in $C_6H_5CH_3$ (1 mL) at 70 °C. Symbols are: **3a** (●); **4a** (○).

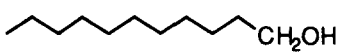
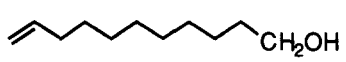
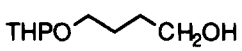
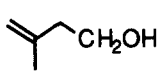
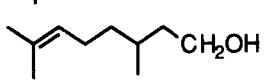
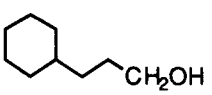
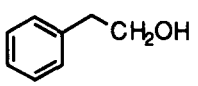
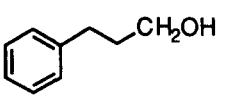
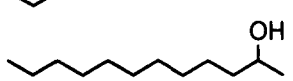
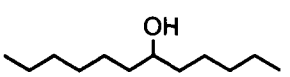
The time course of the reaction using 4-BzOTEMPO **2** (2 equivalents) and $RuCl_2(PPh_3)_3$ (10 mol%) under O_2 reveals that the adduct **3a** would be produced via the addition of a TEMPO molecule to an initially formed aldehyde **4a** (Figure 1). Indeed, the reaction of the aldehyde **4a** with 4-BzOTEMPO **2** (2 equivalent) in a similar manner as described above produced the corresponding adduct **3a** in 66% yield.



The scope of the reaction is shown in Table 2. The present method is applicable to a variety of alcohols bearing olefinic (entries 2, 4, and 5), acetal (entry 3), phenyl functions (entries 7 and 8). Moderate yields with

blanched alcohols at the position β to the hydroxyl group probably due to steric interference with tetramethyl group on the piperidine ring of **2** (entries 4 and 5). On the other hand, the reaction of secondary alcohols **5** terminates at the stage of oxidation of hydroxyl group, leading to the corresponding ketones **6** in good yields. Examples shown in Table 2, entries 9 and 10 demonstrate that an aerobic oxidation of secondary alcohols with TEMPO is now available.[16]

Table 2. One-pot Conversion of Primary Alcohols **1** to 2-Oxylakanals **3** and Oxidation of Secondary Alcohols **5** to **6**.[a)]

Entry	Alcohols		Products	Yield, %[b)]
1		**1a**	**3a**	76
2		**1b**	**3b**	76
3		**1c**	**3c**	77
4		**1d**	**3d**	36
5		**1e**	**3e**	37
6		**1f**	**3f**	79
7		**1g**	**3g**	59
8		**1h**	**3h**	72
9		**5a**	$C_{10}H_{21}COCH_3$ **6a**	88
10		**5b**	$C_6H_{13}COC_5H_{11}$ **6b**	87

[a)] Carried out by using **2** (2 equivalent) and $RuCl_2(PPh_3)_3$ (10 mol%) under O_2 in $C_6H_5CH_3$ (1 mL) at 70 °C for 8 h. [b)] Yields based on isolated products.

Although no distinct explanation for the reaction mechanism is now available, oxidation of hydroxyl group of **1** and concomitant substitution of the alkanal **4** with 4-BzOTEMPO **2** can be understood as follows: by analogy with the reported reaction of TEMPO derivatives with transition metal such as palladium(II) chloride,[17] 4-BzOTEMPO **2** is expected to form the corresponding *N*-oxoammonium salts by the reaction with $RuCl_2(PPh_3)_3$. Oxygen is then used to activate low valency ruthenium complexes.[4] Besides transition metal-

catalyzed coordinative isomerization of TEMPO, higher valency metal ion such as Cu(II) can oxidize TEMPO to the *N*-oxoammonium salt in combination with molecular oxygen.[18] *N*-Oxoammonium salt as well as $RuCl_2(PPh_3)_3$ are both capable of oxidizing hydroxyl group.[19] Substitution at the position α of the carbonyl group may be the result of the reaction of aldehyde **4** and *N*-oxoammonium salt.[20] Further work concerning with the mechanistic aspect of this reaction as well as synthetic application is underway.

Acknowledgments. The present work was supported by The Grant-in-Aid for Scientific Research No. 05650883 from the Ministry of Education, Science and Culture of Japan. We are grateful to the SC-NMR laboratory of Okayama University for experiments with Varian VXR-500 and -200 instruments.

References and Notes

1. Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, 1981.
2. Procter, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, pp. 305-327 and references therein.
3. Murahashi, S.-I; Naota, T. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 930-942.
4. Matsumoto, M.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1981**, 907-908.
5. Kanemoto, S.; Oshima, K.; Matsubara, S.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 2185-2188.
6. Murahashi, S.-I.; Naota, T.; Nakajima, N. *Tetrahedron Lett.* **1985**, *26*, 925-928.
7. Müller, P.; Godoy, J. *Tetrahedron Lett.* **1981**, *22*, 2361-2364.
8. Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, *29*, 2503-2506.
9. Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605-1608.
10. (a) Bäckvall, J. E.; Chowdhury, R. L.; Karlsson, U. *J. Chem. Soc., Chem. Commun.* **1991**, 473-475. (b) Murahashi, S.-I.; Naota, T.; Hirai, N. *J. Org. Chem.* **1993**, *58*, 7318-7319.
11. Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944-5946.
12. Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288-5290.
13. Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700-3704.
14. Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398-4400.
15. Typical procedure is as follows: To a two-necked round bottomed flask (30 mL) were placed 1-undecanol (**1a**, 345 mg, 2.0 mmol), 4-benzoyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**2**, 1.1 g, 4.0 mmol), and $RuCl_2(PPh_3)_3$ (200 mg, 0.2 mmol). The mixture was dissolved in toluene (4 mL). The flask was flushed with dioxygen by using a rubber balloon filled with dioxygen and the balloon was connected to the flask. The mixture was stirred at 76-78 °C for 7 h under a dioxygen atmosphere, during which heterogeneous black color persisted. The reaction was monitored by T.L.C. (hexane:AcOEt = 3:1) and stopped when the starting **1a** was consumed. Upon cooling to room temperature, the mixture was concentrated under vacuum. The resulting black residue was purified by column chromatography (SiO_2) eluting with a mixture of hexane and AcOEt (10:1 V/V) and the products at R_f = 0.75 (hexane:AcOEt = 3:1) and at R_f = 0.56 were collected to give 786 mg (88%) of **3a** as a colorless oil and the *N*-oxyl **2** (217 mg, 20%). Further elution with MeOH as a solvent gave PPh_3=O (17 mg) and 4-benzoyloxy-2,2,6,6-tetramethylpiperidine (240 mg, 20%). Spectral data of **3a**: IR (neat): 2924, 1717 (C=O), 1605 (C=C), 1586, 1454, 1379, 1315, 1178, 1114, 903, 712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3H, CH_3), 1.10-1.45 (b, 26H, CH_2, CH_3), 1.56-1.84 (m, 4H, CH_2), 1.90-2.04 (m, 2H, CH_2), 4.04-4.15 (m, 1H, N-O-CH), 5.16-5.34 (m, 1H, HC-OCO), 7.37-7.60 (m, 3H, COPh), 8.00 (d, *J* = 8.5 Hz, 2H, COPh), 9.77 (d, *J* = 4.5 Hz, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.05, 21.02, 21.05, 21.22, 22.62, 24.19, 29.22, 29.32, 29.41, 29.61, 29.92, 31.82, 33.80, 34.34, 44.43, 60.17, 61.00, 66.99, 88.68, 128.29, 129.45, 130.42, 132.87, 166.07, 203.95.
16. Suzuki, T.; Iizuka, K.; Nabeshima, T.; Yano, Y. *Chem. Lett.* **1990**, 1497-1500.
17. Okunaga, M.; Matsubayashi, G.; Tanaka, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 907-909.
18. Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374-3376.
19. Inokuchi, T.; Matsumoto, S.; Torii, S. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 910-920.
20. Hunter, D. H. *Tetrahedron Lett.* **1984**, *25*, 603-606.

(*Received in Japan* 10 *February* 1995; *revised* 4 *March* 1995; *accepted* 9 *March* 1995)