

TEMPO-Mediated Oxidation of Primary Alcohols to Carboxylic Acids by Exploitation of Ethers in an Aqueous–Organic Biphasic System

Zhen-Wu Mei,¹ Li-Jian Ma,¹ Hiroyuki Kawafuchi,³ Takumi Okihara,² and Tsutomu Inokuchi^{*1}

¹Department of Medical and Bioengineering Science, Graduate School of Natural Science and Technology, Okayama University, Tsushima-naka, Okayama 700-8530

²Department of Material Chemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima-naka, Okayama 700-8530

³Department of Chemical and Biochemical Engineering, Toyama National College of Technology, Hongo-machi, Toyama 939-8630

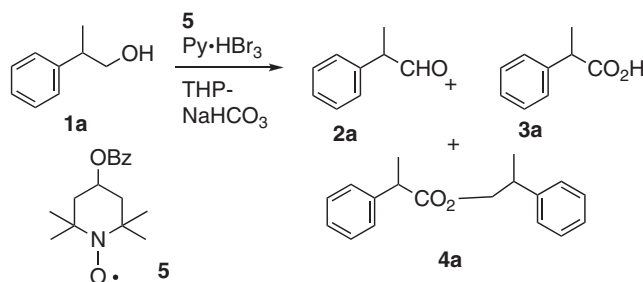
Received March 2, 2009; E-mail: inokuchi@cc.okayama-u.ac.jp

Expeditious and benign methods for primary alcohol–carboxylic acid conversions with TEMPO were developed in a biphasic system composed of a slightly miscible ether (THP) and aqueous layer. Easily available co-oxidants such as Py·HBr₃, Bu₄NBr₃, and electrooxidation were successfully applied to generate *N*-oxoammonium species as a recyclable catalyst.

Oxidation of alcohols to the corresponding carboxylic acids is a fundamental operation in organic chemistry.^{1,2} TEMPO oxidations, achieved in a catalytic manner in coordination with stoichiometric amount of co-oxidants, have been recognized to be inherently benign and useful for selective transformations of alcohols.³ Conventionally, TEMPO oxidations are executed in an aqueous–organic two-phase system and moderately or highly water-miscible solvents such as CH₂Cl₂ and acetonitrile are often employed.⁴ Inspired by recent development in devising environmentally friendly procedures,⁵ we further examined the improvement of TEMPO oxidation by tuning the reaction media to replace harmful solvents and by changing the co-oxidant. Thus, ethereal solvents like tetrahydropyran (THP)⁶ were employed as the organic layer of a two-phase system for the exhaustive conversion of primary alcohols to carboxylic acids. In this respect, easy recoverability after reaction and stability toward air-oxidation of the ethereal solvent should be a criteria for practical application.

Results and Discussion

We employed 4-benzoyloxy-2,2,6,6-tetramethylpiperidine 1-oxyl (4-BzOTEMPO, **5**) for the recyclable catalyst from various TEMPO derivatives because **5** is slightly activated by



Scheme 1. Catalytic oxidation of primary alcohols with a combination of 4-BzOTEMPO (**5**) and Py·HBr₃.

the electron-withdrawing benzoyloxy group at the C4 position.⁷ As the first step, we examined the oxidation of **1a** with a combination of **5** (5 mol %) and a co-oxidant in THP–aqueous saturated NaHCO₃ (1:1 v/v) containing a quaternary ammonium salt such as BenzylEt₃NCl and acetylcholine chloride as a phase-transfer catalyst (PTC) (Scheme 1). Thus, the addition of Py·HBr₃ (3 equiv) as a co-oxidant to the reaction media afforded the corresponding carboxylic acid **3a** in 91% yield and formation of dimeric ester **4a** was negligible (ca. 1%). The presence of quaternary ammonium salts in the two-phase system was not crucial in comparison with a run without these reagents, since pyridinium salts in this reaction media could participate as a PTC.^{4d}

Subsequently, we surveyed suitable ethereal solvents in addition to THP for the two-phase system, and the following results were obtained in the oxidation of **1a** to **3a**: cyclopentyl methyl ether (CPME) (80%), tetrahydrofuran (THF) (80%), diisopropyl ether (67%), methyl *tert*-butyl ether (89%), and CH₂Cl₂ (77%). It appears that solvents slightly miscible in water are useful as an organic layer.⁸ However, among these solvents, THP should be the best in terms of high yield, easy handling, and recoverability. Furthermore, Yasuda, Ryu, et al. have recently demonstrated the excellent stability of THP toward hydrogen abstraction from the oxygen-substituted carbon, as compared with THF, as a result of their study on tributyltin hydride-mediated radical cyclization.⁹ This finding favors the use of THP since it is less likely to form peroxide with oxygen during TEMPO oxidation.

Subsequently, we searched for a favorable co-oxidant for the conversion of **1a** to **3a** in a two-phase system comprised of THP–aqueous NaHCO₃. As shown in Table 1, Entries 3–5, it turns out that bromine salts such as Py·HBr₃,⁷ Bu₄NBr₃,¹⁰ and electrolysis with bromide ion¹¹ are the appropriate choice of co-oxidizing reagent because of high yield and high catalytic performance. The runs employing NaOCl^{4c} and Ca(OCl)₂¹⁰ in combination with KBr were less effective than those with the above bromine compounds (Entries 1 and 2).

This reaction can be performed on a scale of 15 mmol of **1a** in THP (120 mL)–aqueous NaHCO₃ (120 mL) in the presence of PTC at room temperature for 5 h, giving **3a** in 91% yield, in which 83% of THP used for the reaction media and workup solvent was recovered on a rotary evaporator after separation of the aqueous layer.

As shown in Table 2, the present method can readily be applied not only to aliphatic primary alcohols **1** including

Table 1. Search for Co-Oxidant in TEMPO-Mediated Oxidation of **1a** to **3a**^{a)}

Entry	Co-oxidant (equiv)	Product/% ^{b)}	
		3a	2a
1	NaOCl (6)	33	48
2	Ca(OCl) ₂ (4.5)	59	23
3	Py·HBr ₃ (3)	87	—
4	Bu ₄ NBr ₃ (3)	72	trace
5	Electrolysis (10 F) ^{c)}	84	trace

a) Carried out with **5** and co-oxidant in THP (8 mL)–sat. NaHCO₃ (8 mL) in the presence of PTC. b) Based on the isolated products. c) Electricity passed.

Table 2. Oxidation of Primary Alcohols with a Combination of 4-BzOTEMPO (**5**) and Py·HBr₃^{a)}

$\text{R-CH}_2\text{OH} \xrightarrow[\text{THP-NaHCO}_3]{\text{5-Py}\cdot\text{HBr}_3} \text{R-COOH}$			
Entry	Alcohol 1	Product 3	Yield / % ^{b)}
1		b	70
2		c	74
3		d	92
4 ^{c)}		e	92
5		f	82
6		g	87 ^{c)}
7		h	85
8		i	97
9		j	97

a) Carried out by the reaction of **1** (1 mmol) with **5** (5–10 mol %) and Py·HBr₃ (2.5–3.5 equiv) at room temperature. b) Based on isolated products after column chromatography. c) Yield based on the crude product.

acyclic (Entries 1, 2, and 6) and cyclic structures (Entry 5), but also to aromatic (Entries 3 and 4) and hetero aromatic alcohols (Entry 7), producing the corresponding carboxylic acids **3** respectively. The oxidation of 5-(hydroxymethyl)-2-furaldehyde (HMF, **1h**), a value-added chemical available from

biomass,¹² leads selectively to 5-formyl-2-furancarboxylic acid (**3h**),^{13,14} useful as a precursor of 2,5-furandicarboxylic acids. Carbohydrate derivatives **1i** and **1j** with primary hydroxy groups are easily oxidized to the corresponding uronic acids **3i** and **3j** in good yields (Entries 8 and 9).

In summary, we developed an efficient primary alcohol–carboxylic acid conversion by employing TEMPO oxidation in ethereal solvent such as THP–aqueous layer, in which bromine complexes such as Py·HBr₃ and electrooxidation with bromide ion were useful as co-oxidants. The method could easily be applied to various primary alcohols including aromatic, aliphatic, and carbohydrate derivatives, some of which are of significant synthetic value.

Experimental

A Typical Procedure for Oxidation of Primary Alcohols to the Carboxylic Acid. To a two phase mixture of THP (8 mL) and aqueous saturated NaHCO₃ (8 mL) containing PhCH(Me)CH₂OH (**1a**, 137 mg, 1 mmol), 4-BzOTEMPO (**5**, 28 mg, 0.1 mmol), and PTC (acetylcholine chloride, 0.1 mmol) was added Py·HBr₃ (3.0 mmol) in portions under vigorous stirring at room temperature. The mixture was stirred for an additional 120 min with TLC monitoring, and quenched with aqueous 5% Na₂S₂O₃. The mixture was acidified with aqueous tartaric acid and extracted with EtOAc. The usual workup followed by purification of the residue by column chromatography (SiO₂, hexane–EtOAc) gave 131 mg (87% yield) of the carboxylic acid **3a** and dimeric ester **4a** (trace amount).

Large scale operation and the recoverability of THP: To a two phase mixture of THP (120 mL) and aqueous saturated NaHCO₃ (120 mL) containing **1a** (2.04 g, 15 mmol), **5** (415 mg, 1.5 mmol), and PTC (acetylcholine chloride, 1.5 mmol) was added Py·HBr₃ (45 mmol) in portions under vigorous stirring at room temperature. The mixture was stirred for an additional 5 h with TLC monitoring. The mixture was worked up in the manner described above by using THP (170 mL) as an extractive solvent. The extract was separated on a rotary evaporator for the recovery of THP (240 mL) and the crude material was purified by column chromatography (SiO₂, hexane–EtOAc) to give 2.07 g (91% yield) of the carboxylic acid **3a**.

A Typical Procedure for Electrochemical Oxidation of Primary Alcohols to the Carboxylic Acid. Two platinum foils were immersed to the lower layer of a two phase mixture comprised of THP (8 mL) and aqueous saturated NaHCO₃ (8 mL)–25% NaBr solution which contained **1a** (128 mg, 1 mmol), **5** (28 mg, 0.1 mmol), and PTC (acetylcholine chloride, 0.1 mmol). The mixture was electrolyzed under a constant current of 20 mA cm^{−2} (applied voltage: 1.5–2.5 V) with a moderate stirring. The electrolysis was continued until the starting material was consumed. It required about 10 F mol^{−1} of electricity. The mixture was worked up in the manner described to give 84% of **3a** after column chromatography.

Spectral data and physical properties of selected products in Table 2 are included here.

2-Phenylpropanoic Acid (3a): Yield 92%; *R*_f = 0.59 (hexane–EtOAc 1:1); IR (neat): 3088, 2982, 1705, 1601, 1497, 1454, 1414, 1263, 1233, 1064, 939, 860, 760, 727, 698 cm^{−1}; ¹H NMR (300 MHz): δ 1.52 (d, *J* = 7.1 Hz, 3H), 3.74 (q, *J* = 7.1 Hz, 1H), 7.25–7.34 (m, 5H); ¹³C NMR (75.5 MHz): δ 18.0, 45.4, 127.3, 127.6 (2C), 128.6 (2C), 139.8, 180.8.

7-Acetoxy-3-methyloctanoic Acid (3c): Yield 74%; *R*_f = 0.35

(hexane–EtOAc 1:1); IR (neat): 2938, 2874, 1736, 1707, 1458, 1375, 1246, 1130, 1032, 949 cm^{-1} ; ^1H NMR (600 MHz): δ 0.96 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.20–1.40 (m, 4H), 1.46 (m, 1H), 1.56 (m, 1H), 1.95 (m, 1H), 2.03 (s, 3H), 2.16 (ddd, J = 15.1, 8.1, 2.4 Hz, 1H), 2.33 (ddd, J = 15.1, 6.1, 3.2 Hz, 1H), 4.88 (m, 1H); ^{13}C NMR (75.5 MHz): δ 19.48 + 19.51, 19.8, 19.9, 21.3, 22.6, 35.8, 36.20 + 36.22, 41.39 + 41.45, 70.84 + 70.87, 170.9, 179.2. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{21}\text{O}_4$ (MH^+) 217.1440, found 217.1436 (MH^+).

2-(4-Acetylphenyl)propanoic Acid (3e): Yield 92%; R_f = 0.37 (hexane–EtOAc 1:1); IR (neat): 2970, 1709, 1680, 1605, 1456, 1420, 1358, 1329, 1271, 1246, 1188, 1119, 1082, 997, 961, 932, 866, 851, 833, 764, 692 cm^{-1} ; ^1H NMR (300 MHz): δ 1.53 (d, J = 7.1 Hz, 3H), 2.58 (s, 3H), 3.80 (q, J = 7.1 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75.5 MHz): δ 17.8, 26.4, 45.2, 127.8 (2C), 128.6 (2C), 135.9, 145.2, 179.0, 198.1.

3-Oxolanecarboxylic Acid (3f): Yield 82%; R_f = 0.32 (hexane–EtOAc 1:1); IR (neat): 2982, 2884, 1736, 1710, 1417, 1211, 1188, 1065, 905 cm^{-1} ; ^1H NMR (300 MHz): δ 2.10–2.29 (m, 2H), 3.09–3.18 (m, 1H), 3.79–3.95 (m, 2H), 3.99 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75.5 MHz): δ 29.3, 43.4, 68.1, 69.4, 179.0.

3,6,9-Trioxadecanoic Acid (3g): Yield 87%; R_f = 0.59 (hexane–EtOAc 5:1); IR (neat): 2928, 2891, 1717, 1452, 1356, 1316, 1277, 1248, 1200, 1177, 1113, 1072, 1026, 852, 718, 684 cm^{-1} ; ^1H NMR (300 MHz): δ 3.39 (s, 3H), 3.56–3.59 (m, 2H), 3.68–3.72 (m, 4H), 3.76–3.79 (m, 2H), 4.12 (s, 2H).

5-Formyl-2-furancarboxylic Acid (3h): Yield 85%; IR (KBr): 3144, 3107, 2930, 1674, 1568, 1518, 1435, 1397, 1346, 1294, 1260, 1221, 1165, 1043, 963, 849, 783 cm^{-1} ; ^1H NMR (300 MHz in methanol- D_4): δ 7.38 (d, J = 3.8 Hz, 1H), 7.50 (d, J = 3.8 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (75.5 MHz in methanol- D_4): δ 119.0, 121.1, 148.4, 154.4, 158.6, 179.3, 179.3.

1-O-Methyl-3,4-O-cyclohexylidene- α -D-ribouronic Acid (3i): Yield 97%; R_f = 0.4 (hexane–EtOAc 1:2); $[\alpha]_{\text{D}}^{31}$ -50.2° (c 0.9, CHCl_3); IR (neat): 2937, 2862, 2673, 1715, 1450, 1417, 1368, 1273, 1223, 1165, 1115, 1047, 949, 924, 853, 833, 800, 752, 673 cm^{-1} ; ^1H NMR (300 MHz): δ 1.39 (m, 2H), 1.55 (m, 4H), 1.61 (m, 2H), 1.70 (m, 2H), 3.43 (s, 3H), 4.57 (d, J = 5.2 Hz, 1H), 4.67 (brs, 1H), 5.08 (s, 1H), 5.17 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75.5 MHz): δ 23.7, 23.9, 24.9, 34.4, 36.0, 55.6, 81.7, 83.62, 83.70, 109.6, 113.7, 175.1. HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{19}\text{O}_6$ (MH^+) 259.1182, found 259.1151 (MH^+).

1,2:3,4-Di-O-isopropylidene- α -D-galactopyranuronic Acid (3j): Yield 97%; R_f = 0.2 (hexane–EtOAc 1:5); mp 149–150 $^\circ\text{C}$ (from hexane–EtOAc) (lit.^{4d} 152 $^\circ\text{C}$); $[\alpha]_{\text{D}}^{22}$ -91.2° (c 1.4, CHCl_3) (Ref.^{4d} -102.9°); ^1H NMR (300 MHz): δ 1.35 (s, 6H), 1.45 (s, 3H), 1.53 (s, 3H), 4.40 (dd, J = 4.95, 2.5 Hz, 1H), 4.46 (d, J = 2.2 Hz, 1H), 4.63 (dd, J = 7.7, 2.2 Hz, 1H), 4.69 (dd, J = 7.7, 2.5 Hz, 1H), 5.65 (d, J = 4.95 Hz, 1H).

This work was supported by the Electric Technology Research Foundation of Chugoku, which is gratefully acknowledged. We thank Wesco Scientific Promotion Foundation for scholarship support. We are grateful to “SC-NMR laboratory of Okayama University” for high-field NMR experiments, to Professor Junzo Nokami, Okayama University of Science, for HRMS analyses, and to Showadenko Co. for a generous gift of THP.

Supporting Information

Spectral data including IR, ^1H NMR, and ^{13}C NMR spectra of **3a–3j** are provided. This material is available free of charge on the web at <http://www.csj.jp/journals/bcsj/>.

References

- G. Tojo, M. Fernández, *Oxidation of Primary Alcohols to Carboxylic Acids: A Guide to Current Common Practice*, Springer, New York, **2006**.
- a) M. Cleij, A. Archelas, R. Furstoss, *J. Org. Chem.* **1999**, *64*, 5029. b) J.-H. Xie, Z.-T. Zhou, W.-L. Kong, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 1868. c) X. Li, B. List, *Chem. Commun.* **2007**, 1739.
- TEMPO oxidation, reviews: a) T. Vogler, A. Studer, *Synthesis* **2008**, 1979. b) P. L. Bragd, H. van Bekkum, A. C. Besemer, *Top. Catal.* **2004**, *27*, 49. c) W. Adam, C. R. Saha-Möller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499. d) T. Inokuchi, S. Matsumoto, S. Torii, *J. Synth. Org. Chem., Jpn.* **1993**, *51*, 910.
- In MeCN–aqueous system: a) M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, *J. Org. Chem.* **1999**, *64*, 2564. b) P. Gancitano, R. Ciriminna, M. L. Testa, A. Fidalgo, L. M. Ilharco, M. Pagliaro, *Org. Biomol. Chem.* **2005**, *3*, 2389. c) J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293. In CH_2Cl_2 –aqueous system: d) K. Kloth, M. Brünjes, E. Kunst, T. Jöge, F. Gallier, A. Adibekian, A. Kirschning, *Adv. Synth. Catal.* **2005**, *347*, 1423. e) P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559. In aqueous system: f) T. Yoshida, M. Kuroboshi, J. Oshitani, K. Gotoh, H. Tanaka, *Synlett* **2007**, 2691.
- Reviews: a) M. J. Schultz, M. S. Sigman, *Tetrahedron* **2006**, *62*, 8227. b) I. E. Marko, P. R. Giles, M. Tsukazaki, A. Gautier, R. Dumeunier, K. Dodo, F. Philippart, I. Chelle-Regnault, J.-L. Muttonkole, S. M. Brown, C. J. Urch, *Transition Metals for Organic Synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2004**, Vol. 2, p. 437.
- Manufacturing preparation process of THP was recently established: I. Yamagami, H. Yasuda, PCT Int. Appl. WO 2006/062211, **2006**; I. Yamagami, H. Yasuda, CAN 145:62784.
- Z.-W. Mei, T. Omote, M. Mansour, H. Kawafuchi, Y. Takaguchi, A. Jutand, S. Tsuboi, T. Inokuchi, *Tetrahedron* **2008**, *64*, 10761.
- Solubility (wt %) of water to the solvent (of the solvent to water): THP = 2.5 (8.1), CPME = 0.3 (1.1), MTBE = 1.5 (4.8), THF = ∞ (∞) (Cited from technical reports of Showadenko Co. and ZEON Corporation, Japan).
- H. Yasuda, Y. Uenoyama, O. Nobuta, S. Kobayashi, I. Ryu, *Tetrahedron Lett.* **2008**, *49*, 367.
- T. Inokuchi, S. Matsumoto, M. Fukushima, S. Torii, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 796.
- a) T. Inokuchi, S. Matsumoto, S. Torii, *J. Org. Chem.* **1991**, *56*, 2416. b) T. Inokuchi, S. Matsumoto, T. Nishiyama, S. Torii, *J. Org. Chem.* **1990**, *55*, 462.
- a) J. N. Chheda, G. W. Huber, J. A. Dumesic, *Angew. Chem., Int. Ed.* **2007**, *46*, 7164. b) J.-P. Lange, *Biofuels, Bioprod. Biorefin.* **2007**, *1*, 39.
- H. Takada, Jpn. Kokai Tokkyo Koho JP 03101672, **1991**.
- W. Partenheimer, V. V. Grushin, *Adv. Synth. Catal.* **2001**, *343*, 102.