Oxidation of Primary Alcohols to Carboxylic Acids with Sodium Chlorite Catalyzed by TEMPO and Bleach

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Introduction

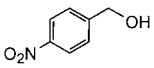
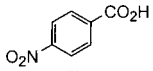
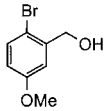
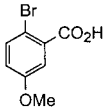
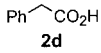
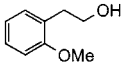
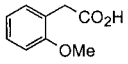
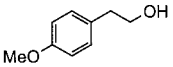
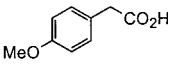
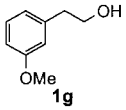
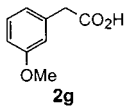
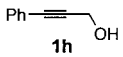
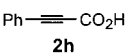
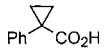
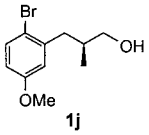
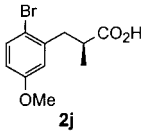
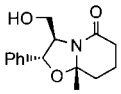
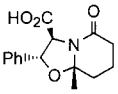
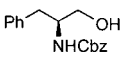
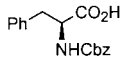
Oxidation is one of the most fundamental transformations in organic synthesis and numerous methods have been developed.[1] However, relatively few good general methods exist for the oxidation of primary alcohols to carboxylic acids. Conditions for this transformation include Jones oxidation,[2] the $RuCl_3/H_5IO_6$ protocol,[3] and TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy)-catalyzed oxidation with sodium hypochlorite (NaOCl, or bleach).[4] A two-step process involving Swern oxidation[5] followed by oxidation of the resulting aldehyde with sodium chlorite ($NaClO_2$) is another option.[6] All of these methods have some limitations, and therefore alternative methods are still desirable.

Recently, we reported a novel chromium-catalyzed oxidation of primary and secondary alcohols to the acids and ketones with periodic acid (H_5IO_6).[7] Noyori et al. also published a Na_2WO_4-catalyzed oxidation of primary and secondary alcohols.[8] We herein report a TEMPO-catalyzed oxidation of primary alcohols to the corresponding carboxylic acids, using $NaClO_2$ as the stoichiometric oxidant.

Results and Discussion

In our recent work involving the oxidation of a primary alcohol similar to **1j** (Table 1) to the carboxylic acid, we desired a method that is economical and can tolerate sensitive functional groups such as neighboring chiral centers and electron-rich aromatic rings. We found that the $RuCl_3/H_5IO_6$ protocol[3] gave low yield (<50%) of the desired product due to the destruction of the electron-rich aromatic rings. TEMPO-catalyzed oxidation[4] with bleach (NaOCl) also resulted in poor yield and purity due to significant chlorination of the aromatic groups. To eliminate the chlorination problem, other oxidants, such as H_2O_2, $MeCO_3H$, and t-BuO_2H, were examined without much success. When sodium chlorite ($NaClO_2$)[9] was used as the oxidant, the reaction appeared to be very slow

Table 1. TEMPO-Catalyzed Oxidation of Primary Alcohols

Entry	Substrate	Product	Yield ($NaClO_2$)	Yield (NaOCl)
1	 **1a**	 **2a**	98%	–
2	 **1b**	 **2b**	100%	–
3	 **1c**	 **2c**	96%	80%
4	 **1d**	 **2d**	100%	–
5	 **1e**	 **2e**	99%	65%
6	 **1f**	 **2f**	100%	86%
7	 **1g**	 **2g**	96%	42%
8	 **1h**	 **2h**	90%	<5%
9	 **1i**	 **2i**	95%	–
10	 **1j**	 **2j**	92%	60%
11	 **1k**	 **2k**	95%	–
12	 **1l**	 **2l**	85%	–

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(1) Hudlicky, M. *Oxidations in Organic Chemistry*. ACS Monograph 186; 1990.

(2) (a) Bowden; Heilbron; Jones; Weedon *J. Chem. Soc.* **1946**, 39−45. (b) Bowers; H.; Jones; L. *J. Chem. Soc.* **1953**, 2548−2560. (c) Millar, J. G.; Oehlschlager, A. C.; Wong, J. W. *J. Org. Chem.* **1983**, *48*, 4404−4407.

(3) Carlsen, P. H. J.; Katsuki, T.; Martin V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(4) (a) Nooy, A. E. J. de; Besemer, A. C.; Bekkum, H. V. *Synthesis* **1996**, 1153−1174. (b) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509−533. (c) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (d) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332−1334. (e) Rychnovsky, S. D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, *64*, 310−312.

(5) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482. (b) Mancuso, A. J.; Brownfan, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148−4150. (c) Ireland, R.; Norbeck, D. *J. Org. Chem.* **1985**, *50*, 2198−2200.

(6) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.

(7) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323−5326.

(8) Sato, K.; Aoki, M., Takagi, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386-12387.

(9) The use of $NaBrO_2$ has been reported; however, $NaClO_2$ was reported to be unsuccessful. Additionally, $NaBrO_2$ is not readily available commercially. Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462−466.

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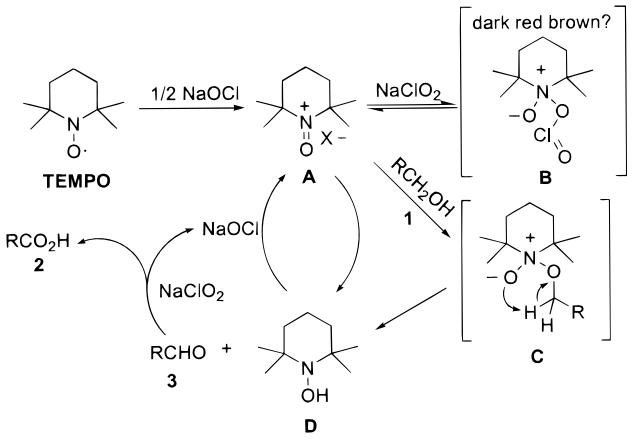
Scheme 1. Catalytic Cycle for the TEMPO/ NaOCl-Catalyzed Oxidation



(~2%/h) initially, so it was allowed to proceed overnight. Surprisingly, the substrate was completely consumed in this period (~15 h), indicating that the reaction was self-accelerating or there existed an induction period. More careful monitoring of the reaction confirmed that this was true indeed. The conversion was only 2% for the first hour, but reached 50% in 3 h and 90% in 6 h. Apparently, more active oxidizing agent was slowly generated. Sodium hypochlorite (NaOCl) appeared to be the most likely candidate. Indeed, addition of 10 mol % of NaOCl accelerated the reaction dramatically. The conversion reached ~50% in 1 h and went to completion in 3−4 h. The slow initiation period was no longer observed.

The remarkable acceleration of the oxidation can be explained by the proposed catalytic cycle shown in Scheme 1. A catalytic amount of NaOCl oxidizes TEMPO radical to the *N*-oxoammonium ion[4] **A**, which in turn rapidly oxidizes the primary alcohol (**1**) to the aldehyde (**3**) and gives a molecule of the hydroxylamine **D**.[4] The aldehyde (**3**) is then oxidized by $NaClO_2$ to the carboxylic acid (**2**),[6] and a molecule of NaOCl is *regenerated*. The hydroxylamine **D** can either be directly oxidized to the oxoammonium ion **A** or undergo a syn proportionation with a molecule of the oxoammonium ion **A** to give two molecules of TEMPO radical.[4a,b] Although the exact mechanism of TEMPO-catalyzed oxidation of alcohols is still unclear, previous work[4] has shown that oxoammonium ion **A** and hydroxylamine **D** are involved. It is also known that $NaClO_2$ can readily oxidize aldehydes to the carboxylic acids without the assistance of TEMPO.[6] The long induction period of the reaction without a catalytic amount of bleach is likely due to the relatively slow oxidation of TEMPO radical or the hydroxylamine **D** by $NaClO_2$. Once the reaction is initiated, it becomes self-sustaining as NaOCl is continuously regenerated. The chlorination problem is greatly suppressed due to fact that the concentration of NaOCl remained low throughout the reaction. Opportunities for epimerization of the neighboring chiral center are also reduced since the labile aldehyde intermediate is rapidly oxidized to the carboxylic acid by sodium chlorite.

Curiously, the reaction mixture turned dark red-brown upon addition of a catalytic amount of bleach. Most of the color remained in the organic layer (MeCN). The color faded instantly when quenched with Na_2SO_3. TEMPO, NaOCl, and $NaClO_2$ must ***all*** be present to produce the color; however, the presence of the substrate was not required. Formation of a complex such as structure **B** (Scheme 1) might be responsible for the color.

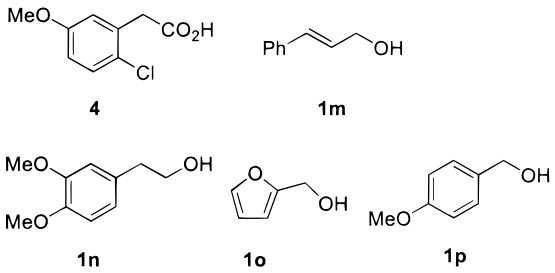


Figure 1.

The reaction was then further optimized to reduce the undesired chlorination and enhance the safety for large-scale operations. The reaction was faster at lower pH, but chlorination also increased. Surprisingly, lowering the temperature to 0 °C actually resulted in slightly elevated chlorination. Using a TEMPO/NaOCl molar ratio > 2 appeared to minimize the chlorination side product. Optimally, the substrate is dissolved in acetonitrile and mixed with pH = 6.7 phosphate buffer. A catalytic amount (2−7 mol %) of TEMPO is added followed by simultaneous[10] addition of $NaClO_2$ and a catalytic amount (1−4 mol %) of bleach at 35 °C.

This method is mild and efficient and has been demonstrated on a variety of primary alcohols (Table 1). Benzylic alcohols, including those with either electron-withdrawing or electron-donating groups, were oxidized to the benzoic acids **2a**−**2c** in quantitative yield (entries 1−3). 2-Arylethanols were also converted to the arylacetic acids **2d**−**2g** in excellent yields (entries 4−7). For comparison purposes, substrates with electron-rich aromatic rings were also subjected to the TEMPO/NaOCl oxidation[4c] (entries 3, 5−7, 10). In all of these cases, improved yields were obtained with this new procedure. The most striking example is **1g**. The yield of the desired product **2g** was only 42% using stoichiometric NaOCl[4] in contrast to the quantitative yield obtained using $NaClO_2$ with catalytic NaOCl (entry 7). One of the major side products in the oxidation with stoichiometric NaOCl was isolated and identified as the chlorinated compound **4** (Figure 1) based on NOE experiments. Similarly, 3-phenylpropargyl alcohol (**1h**) was oxidized to the acid **2h** in 90% yield using our procedure vs <5% with NaOCl. It appeared that carbon−carbon triple bonds can be tolerated, but substrates with ordinary carbon−carbon double bonds such as cinnamyl alcohol (**1m**) failed to react. This was likely due to quenching of the catalytic NaOCl, which shut down the catalytic cycle. Substrates with very electron-rich aromatic groups such as **1n**−**1o** (Figure 1) also failed for similar reasons. Surprisingly, oxidation of 4-methoxybenzyl alcohol (**1p**) was very sluggish. Substrate **1i**, which contained a cyclopropyl group, posed no problem (entry 9). Chiral alcohols, including protected amino alcohol **1l**, were oxidized to the corresponding carboxylic acids without racemization (or epimerization) of the labile chiral centers (entries 10−12). The enantiomeric purity

(10) Caution! It is not advisable to mix sodium chlorite solution and bleach prior to the addition since the mixture appears to be unstable. The addition should be carried out as follows: approximately 20% of the sodium chlorite solution is added followed by 20% of the dilute bleach. The remainder of the $NaClO_2$ solution and dilute bleach are added simultaneously in 1−2 h. On a small scale, it is acceptable to mix the substrate, sodium chlorite, TEMPO, acetonitrile, and buffer first and then add bleach.

of compound **2j** was determined by chiral HPLC after reduction to the alcohol **1j** (Experimental Section). For Cbz−phenylalanine (**2l**), the optical purity was measured by HPLC with a CROWNPAK CR(+) column after removal of the Cbz-protecting group (H_2/Pd in MeOH).

In conclusion, we have demonstrated the utility of the new procedure for the oxidation of primary alcohols to the carboxylic acids. This method is efficient and environmentally benign using stoichiometric $NaClO_2$, catalytic TEMPO, and NaOCl. Compared with the previously reported TEMPO/NaOCl/CH_2Cl_2 protocol,[4c] the chlorination problem is greatly reduced, thus offering significantly improved yields and purity of the desired products. No racemization or epimerization is observed for substrates with labile chiral centers. Additionally, no chlorinated solvent is required. However, this procedure is not applicable to alkenic alcohols and substrates with exceedingly electron-rich aromatic groups.

Experimental Section

General Methods. All substrates and reagents were obtained commercially and used without purification except **1j,** which was prepared in-house. Its synthesis will be disclosed in a future publication. The products were identified by comparing their NMR spectra with those of commercially available materials except for **2j** and **2k**. The yield was determined by reverse phase HPLC with Zorbax SB-Phenyl or YMC ODS-AM columns and MeCN/0.1% H_3PO_4 as the mobile phase. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. Chemical shifts are reported relative to the solvent (chloroform = 7.26, 76.9 ppm for ^{1}H and ^{13}C NMR, respectively).

Typical Procedure. A mixture of alcohol **1** (40 mmol), TEMPO (436 mg, 2.8 mmol), MeCN (200 mL), and sodium phosphate buffer (150 mL, 0.67 M, pH = 6.7) is heated to 35 °C. Then sodium chlorite ($NaClO_2$, 9.14 g 80%, 80.0 mmol in 40 mL water) and dilute bleach (1.06 mL 5.25% NaOCl diluted into 20 mL, 2.0 mol %) are added simultaneously over 2 h (Caution! Do not mix bleach and $NaClO_2$ before being added to the reaction mixture[10]). The mixture is stirred at 35 °C until the reaction is complete (<2 A% SM, 2−5 h), then cooled to room temperature. Water (300 mL) is added, and the pH is adjusted to 8.0 with 2.0 N NaOH (∼48 mL). The reaction is quenched by pouring into cold (0 °C) Na_2SO_3 solution (12.2 g in 200 mL water) maintained at <20 °C. The pH of the aqueous layer should be 8.5−9.0. After stirring for 0.5 h at room temperature, MTBE (methyl *tert*-butyl ether) (200 mL) is added. The organic layer is separated and discarded. More MTBE (300 mL) is added, and the aqueous layer is acidified with 2.0 N HCl (∼100 mL) to pH = 3−4. The organic layer is separated, washed with water (2 × 100 mL) and brine (150 mL), and then concentrated to give the crude carboxylic acid **2** in 85−100% yield. The products may be purified by silica gel column chromatography or crystallization.

(*S*)-2-Methyl-3-(2′-bromo-5′-methoxyphenyl)propionic acid (2j): colorless oil; $[\alpha]^{25}_D$ = (+)19.4 (*c* 1.04, MTBE); ^{1}H NMR ($CDCl_3$) δ 10.5−8.7 (br, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 3.0 Hz, 1H), 6.66 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.75 (s, 3H), 3.14 (dd, *J* = 13.1, 6.7 Hz, 1H), 3.20−3.06 (m, 1H), 2.77 (dd, *J* = 13.1, 7.4 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 182.3, 158.7, 139.3, 133.4, 116.9, 115.1, 113.9, 55.4, 39.4, 39.4, 16.7; IR (thin film) 3500−2500, 1701 cm^{-1}. Anal. Calcd for $C_{11}H_{13}O_3$-Br: C, 48.37; H, 4.80. Found: C, 48.33; H, 4.56. The enantiomeric purity of **2j** was determined by chiral HPLC after reducing it to **1j** with BH_3·THF. HPLC conditions: column CHIRALCEL OD-H; hexane/i-PrOH (97/3, 1.00 mL/min); UV detection at 220 nm. Retention times: (R)-isomer, 23.6 min; (S)-isomer, 29.2 min. Compound **1j**: white solid; mp 59−60 °C; $[\alpha]^{25}_D$ = (−)0.68 (*c* 1.03, MTBE); ^{1}H NMR ($CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 3.1 Hz, 1H), 6.63 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.76 (s, 3H), 3.59−3.46 (m, 2H), 2.85 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.48 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.12−1.95 (m, 1H), 1.76 (s, 1H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.6, 141.1, 133.2, 117.0, 113.2, 67.4, 55.4, 39.7, 36.3, 16.4; IR (KBr) 3431 cm^{-1}. Anal. Calcd for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.83. Found: C, 51.02; H, 5.74.

(2*R*,3*S*,8a*S*)-2-Phenyl-8a-methyl-5-oxo-hexahydrooxazolo-[3,2-a]pyridine-3-carboxylic acid (2k): recrystallized from ethyl acetate, white solid; mp 164−167 °C; $[\alpha]^{25}_D$ = (−)1.75 (*c* 0.51, THF); ^{1}H NMR ($CDCl_3$) δ 9.0−8.0 (br, 1H), 7.47−7.30 (m, 5H), 5.71 (d, *J* = 7.7 Hz, 1H), 4.43 (d, *J* = 7.7 Hz, 1H), 2.70−2.40 (m, 2H), 2.33−2.27 (m, 1H), 2.17−1.80 (m, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 169.5, 137.5, 128.7, 126.2, 94.7, 77.1, 64.3, 34.5, 29.9, 23.5, 17.3; IR (KBr) 3448 cm^{-1}, 1709. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.31; H, 6.15; N, 4.98.

Cbz−Phenylalanine (2l): 85% yield, no racemization. The enantiomeric purity of Cbz−phenylalanine (**2l**) was measured by HPLC after removal of the Cbz-protecting group (H_2/Pd in MeOH). HPLC conditions: CROWNPAK CR(+) column; pH = 2.0 aqueous $HClO_4$ mobile phase (0.80 mL/min); UV detection at 220 nm. Retention times: D-phenylalanine, 9.3 min; L-phenylalanine, 11.6 min.

2-Chloro-5-methoxyphenylacetic acid (4): ^{1}H NMR ($CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 6.78 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.78 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 177.0, 158.2, 132.4, 130.0, 117.0, 114.4, 55.4, 39.0. Since the signals of the methylene and the methoxy protons overlap in the ^{1}H NMR run in $CDCl_3$, the NOE experiment was carried out in CD_3CN. Upon irradiation of the methylene proton, a significant NOE effect was observed for the isolated aromatic proton.

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