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# A Novel Chromium Trioxide Catalyzed Oxidation of Primary Alcohols to the Carboxylic Acids

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## Abstract

A novel  $\text{CrO}_3$  catalyzed oxidation of primary alcohols to the carboxylic acids is reported. The oxidation proceeds smoothly with only 1–2 mol % of  $\text{CrO}_3$  and 2.5 equivalents of  $\text{H}_2\text{IO}_6$  in wet MeCN to give the carboxylic acids in excellent yield. No significant racemization is observed for alcohols with adjacent chiral centers. Secondary alcohols are cleanly oxidized to ketones. © 1998 Elsevier Science Ltd. All rights reserved.

**Keywords:** chromium; catalysis; oxidation; alcohols

Oxidation is a fundamental transformation in organic synthesis and there are numerous methods reported in the literature [1]. However, direct conversion of primary alcohols to the corresponding carboxylic acids is still a challenge especially in the presence of other functional groups. There are only a few commonly used methods for this transformation including  $\text{CrO}_3/\text{H}_2\text{SO}_4$  [2],  $\text{RuCl}_2/\text{H}_2\text{IO}_6$  [3] and TEMPO/ $\text{NaClO}$  [4]. A two-step process involving Swern oxidation [5] followed by oxidation of the resulting aldehyde with  $\text{NaClO}_2$  [6] is another option. However, all of these methods have limitations and disadvantages, and new oxidation methods are still desired.

Herein, we report a very facile oxidation of primary alcohols to the carboxylic acids using periodic acid ( $\text{H}_2\text{IO}_6$ ) as the stoichiometric oxidant and only a catalytic amount of  $\text{CrO}_3$  [7a]. Although chromium catalyzed oxidation of secondary alcohols has been reported [7b, c] a similar version for the oxidation of primary alcohols to the carboxylic acids is not known.


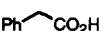
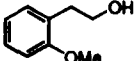
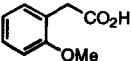
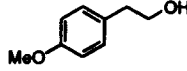
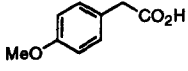
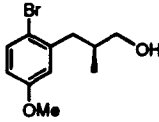
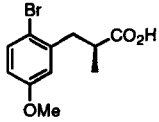
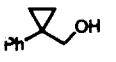
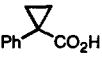
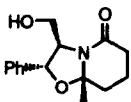
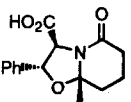
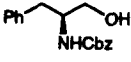
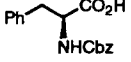
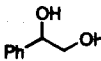

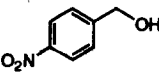
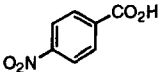






In our initial investigations, we found that some primary alcohols can be oxidized to the acids in aqueous acetonitrile (v/v ~1/1) with  $\text{H}_2\text{IO}_6$  and 5 mol %  $\text{CrO}_3$ . We observed conversions as high as 72% but additional  $\text{H}_2\text{IO}_6$  failed to push the reaction to completion. The reaction mixture also gradually turned greenish indicating generation of Cr(III) species that failed to turn over to Cr(VI). Nevertheless, these experiments proved that a catalytic process was viable.

Since strong acids enhance the oxidation potential of  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$  was added to the reaction mixture. This appeared to improve the oxidation only slightly. On the other hand, water had a dramatic effect on the reaction rate. By eliminating the water from the system, complete reaction occurred in less than 15 minutes at r.t. Subsequently, we found that the presence of small amounts of water attenuated the oxidation strength of the system and provided cleaner reactions. Thus, the best yields can be obtained by adding a solution of  $\text{H}_5\text{IO}_6/\text{CrO}_3$  (2.5 equiv./1.1 mol %) in wet MeCN (0.75 v % water) to the alcohols at 0–5 °C. The reactions were typically complete within one hour. It should be noted that no reaction was observed in the absence of chromium trioxide. Substituting periodic acid with other oxidants ( $\text{H}_2\text{O}_2$ ,  $t\text{-BuO}_2\text{H}$ ,  $\text{AcO}_2\text{H}$  etc. without  $\text{TsOH}$ ) was unsuccessful. For unknown reasons, the reaction also failed to give the desired product when carried out in acetone.

**Typical procedure for the oxidation:** A stock solution of  $\text{H}_5\text{IO}_6/\text{CrO}_3$  was prepared by dissolving  $\text{H}_5\text{IO}_6$  (11.4 g, 50 mmol) and  $\text{CrO}_3$  (23 mg, 1.2 mol %) in wet MeCN (0.75 v % water) to a volume of 114 mL (complete dissolution typically required 1–2 hours). The  $\text{H}_5\text{IO}_6/\text{CrO}_3$  solution (11.4 mL) was then added to a solution of the alcohol **1** (2.0 mmol) in wet acetonitrile (10 mL, 0.75 v % water) in 30–60 minutes while maintaining the reaction temperature at 0–5 °C. The mixture was aged at 0 °C for 0.5 h and the completion of the reaction was confirmed by HPLC assay. The reaction was quenched by adding an aqueous solution of  $\text{Na}_2\text{HPO}_4$  (0.60 g in 10 mL  $\text{H}_2\text{O}$ ). Toluene (15 mL) was added and the organic layer was separated and washed with 1/1 brine/water mixture (2 x 10 mL) then a mixture of aqueous  $\text{NaHSO}_3$  (0.22 in 5 mL water) and finally brine (5 mL). The organic layer was and then concentrated to give the crude carboxylic acid **2**. Most of the crude products were quite pure based on  $^1\text{H}$  NMR and HPLC assay.

Results for the oxidation of a variety of alcohols are summarized in the Table. Oxidation of phenethanol (**1a**) gave phenylacetic acid (**2a**) in 96% yield (entry 1). Similarly, substrates with electron rich aromatic rings, isolated from the reaction site by at least two carbon atoms such as **1b** and **1c**, were converted into the carboxylic acids **2b** and **2c** in excellent yields (entry 2,3). Most notably, chiral alcohol **1d** was cleanly oxidized to **2d** (95%) without any evidence of racemization based on chiral HPLC assay (entry 4).<sup>8</sup> This was perhaps attributed to the fact that the aldehyde intermediate was very short lived under the reaction conditions. The cyclopropyl group in alcohol **1e** was intact under the reaction conditions to give **2e** in 90% yield (entry 5). Amidoacetal in compound **1f** also survived to give the desired product **2f** in 73% yield (entry 6).<sup>9</sup> Cbz-protected amino alcohol **1g** was oxidized to the Cbz-protected amino acid **2g** in good yield without racemization (83%, entry 7).<sup>10</sup> In this case, the reaction was carried out at r.t. due to the low solubility of the substrate at 0 °C. For the vicinal diol, 1-phenyl-1,2-ethanediol (**1h**), carbon-carbon bond cleavage occurred to give benzoic acid in 77% yield (entry 8). To our surprise, oxidation of benzylic alcohols gave lower yields. For example, benzyl alcohol (**1i**) was oxidized to benzoic acid (**2i**) in 78% yield. More electron rich benzyl alcohols such as 4-methoxybenzyl alcohol, 2,4,6-trimethoxybenzyl alcohol and furfuryl alcohol gave complex mixtures. On the other hand, electron deficient 4-nitrobenzyl alcohol (**1i**) gave 4-nitrobenzoic acid in quantitative yield (entry 9). Substrates with extremely electron rich aromatic groups, such as 2-(3',4'-dimethoxyphenyl) ethanol, gave complex mixtures even though the alcohol was not benzylic. No reaction was observed for cinnamyl alcohol and 3-phenyl-2-propyn-1-ol. As expected, secondary alcohols, *sec*-phenethanol (**1j**) and 1-phenyl-2-propanol (**1k**), were oxidized to acetophenone and phenylacetone respectively in quantitative yield (entry 10, 11). Only 1.25 equivalents of periodic acid and 0.6 mol %  $\text{CrO}_3$  were required in these cases.

Table: CrO<sub>3</sub> Catalyzed Oxidation of Alcohols

Entry	Substrate		Temp/H <sub>2</sub> O <sub>2</sub> /CrO <sub>3</sub> (°C/equiv./mol %)	Product		Yield
1		<b>1a</b>	0/2.5/1.1		<b>2a</b>	96%
2		<b>1b</b>	0/2.5/1.1		<b>2b</b>	98%
3		<b>1c</b>	0/2.5/1.1		<b>2c</b>	92%
4		<b>1d</b>	0/2.5/1.1		<b>2d</b>	95%
5		<b>1e</b>	0/2.5/1.1		<b>2e</b>	90%
6		<b>1f</b>	0/2.5/1.1		<b>2f</b>	73%
7		<b>1g</b>	0/2.5/1.1		<b>2g</b>	83%
8		<b>1h</b>	0/3.5/1.6		<b>2h</b>	77%
9		<b>1i</b>	0/2.5/1.1		<b>2i</b>	100%
10		<b>1j</b>	0/1.25/0.6		<b>2j</b>	100%
11		<b>1k</b>	0/1.25/0.6		<b>2k</b>	98%
12		<b>1l</b>	0/1.25/0.6		<b>2l</b>	78%

All substrates were obtained commercially except **1d** and used without purification. The products were identified by comparing their NMR spectra with those of commercial materials. The yields were determined by reverse phase HPLC with Zorbax SB-Phenyl or YMC ODS-AM columns and MeCN/ water (0.1% H<sub>3</sub>PO<sub>4</sub>) as the mobile phase.

In summary, we have developed a novel chromium catalyzed oxidation of primary alcohols to the carboxylic acids. The reactions are rapid, high yielding and only require 1–2 mol % of CrO<sub>3</sub>. Chiral alcohols can be oxidized without racemization at the adjacent chiral centers. Secondary alcohols can also be converted into the corresponding ketones in quantitative yield.

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- [8] The enantiomeric purity of 2d was determined by chiral HPLC after reducing it to 1d with BH<sub>3</sub>·THF. HPLC conditions: column CHIRALCEL OD-H; hexane/i-PrOH (97/3, 1.00 mL/min); UV detection at 220nm. Retention times: (R)-isomer, 23.6 min; (S)-isomer, 29.2 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.44 (d, J=8.7 Hz, 1H), 6.78 (d, J=3.1 Hz, 1H), 6.66 (dd, J=8.7, 3.1 Hz, 1H), 3.75 (s, 3H), 3.13 (dd, J=13.1, 6.8 Hz, 1H), 2.98–2.84 (m, 1H), 2.77 (dd, J=13.1, 7.4 Hz, 1H), 1.23 (d, J=6.9 Hz, 3H).
- [9] NMR data for 2f: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.0–8.0 (broad, 1 H), 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). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.04, 169.48, 137.52, 128.73, 126.16, 94.66, 77.05, 64.34, 34.52, 29.91, 23.45, 17.28.
- [10] The ee% of Cbz-phenylalanine (2g) was measured by HPLC after removal of the Cbz-protecting group (H<sub>2</sub>/Pd in MeOH). HPLC conditions: CROWNPAK CR(+) column; pH = 2.0 aqueous HClO<sub>4</sub>, mobile phase (0.80 mL/min); UV detection at 220 nm; Retention times: D-phenylalanine, 9.3 min; L-phenylalanine, 11.6 min.