## Calcium Hypochlorite-Mediated Oxidation of Primary Alcohols to Methyl Esters

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Abstract: Primary aliphatic alcohols can be converted to methyl esters using calcium hypochlorite as the oxidant. Primary benzyl alcohols can also be converted efficiently to methyl benzoates.

The traditional approach to the synthesis of esters from primary alcohols has been oxidation to the acid followed by esterification. Results in this laboratory indicate that calcium hypochlorite can oxidize a wide variety of primary alcohols to methyl esters in a single step and in high yield.<sup>1</sup>

RCH<sub>2</sub>OH 
$$\xrightarrow{Ca(OCl)_2, HOAc}$$
  $\begin{bmatrix} O \\ H \\ CH_3CN, CH_3OH, \\ molecular sieves, dark \end{bmatrix} \xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ L \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\xrightarrow{O}$   $\begin{bmatrix} O \\ H \\ R^- \\ C \\ H \end{bmatrix}$   $\xrightarrow{O}$   $\xrightarrow{$ 

The success of this reaction is dependent on the selective oxidation of the primary alcohol in the presence of much higher concentrations of methanol. Such selectivity is reasonable based on Steven's observation that more highly substituted alcohols are oxidized at significantly faster rates by hypochlorous acid.<sup>2</sup> We believe hypochlorous acid is the operative oxidant in the primary alcohol to methyl ester transformation as well.

The results of our studies are shown in Table 1.<sup>3</sup> The reaction is typically performed with 2 mol of acetic acid per mol of Ca(OCl)<sub>2</sub>. Under these conditions straight-chain aliphatic (entries 1 and 2), branched aliphatic (entries 3 and 4), and unhindered benzylic alcohols<sup>4</sup> (entries 5 - 7) can all be successfully converted to their corresponding methyl esters in uniformly high yields. The oxidation has been performed on both milligram and multigram scales. Entry 4 is especially noteworthy since it demonstrates that that quaternary centers adjacent to the alcohol do not significantly impede the reaction. It was observed (gas chromatographically) that the oxidation of a typical aliphatic alcohol to the intermediate aldehyde is significantly slower than the subsequent conversion of the aldehyde to the methyl ester. In the benzylic case, however, the initial oxidation of alcohol to aldehyde is more rapid than the aldehyde to methyl ester so for their complete conversion to methyl esters. *Neither of the previously reported procedures<sup>1</sup> for oxidation of primary alcohols to methyl ester is capable of oxidizing benzyl alcohols cleanly to methyl benzoates*. In both procedures substantial quantities of benzaldehyde intermediates remain. The glucose-derived primary alcohol 1h<sup>5</sup> was also oxidized cleanly to its corresponding methyl ester.

	RCH <sub>2</sub> OH cl 1a-h	H <sub>3</sub> OH, dark	RCO <sub>2</sub> CH <sub>3</sub> 3a-h	
entry	substrate	Ca(OCI)2 <sup>b</sup>	time	yield <sup>c</sup>
1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> OH 1a	3.5	24 h	82%
2	СН <sub>3</sub> (СН <sub>2</sub> ) <sub>12</sub> СН <sub>2</sub> ОН Ів	3.5	48 h	88%
3	ОН	3.5	48 h	89%
4	OH Id	3.5	24 h	97% <sup>d</sup>
5	ОН	5.0	48 h	89% <sup>d</sup>
6	t-Bu 1f	DH 5.0	48 h	86%
7		H 5.0	48 h	89%
8	HO CH <sub>3</sub> O	3.5	24 h	82%

Table 1. Synthesis of Methyl Esters PCH.OH Ca(OCI)<sub>2</sub>, HOAC PCO.CH.

<sup>a</sup> reactions were performed with 32 eq CH<sub>3</sub>OH and 2 mol HOAc per mol of Ca(OCl)<sub>2</sub> at room temperature in acetonitrile (0.2M) in the dark. <sup>b</sup> Mol Ca(OCl)<sub>2</sub> per mol substrate. <sup>c</sup> Isolated yields except where noted. <sup>d</sup> Yield determined by GC. We believe the following to be a reasonable mechanism for the transformation. Initially, hypochlorous acid is produced by protonation of calcium hypochlorite with 2 equivalents of acetic acid. A hypochlorite exchange can then occur with the primary alcohol to produce an alkyl hypochlorite (and water).<sup>6</sup> Heterolytic decomposition of the hypochlorite affords the intermediate aldehyde 2. Addition of methanol and subsequent hypochlorite formation yields a hemiacetal hypochlorite (and again, water). Elimination of HCl furnishes the observed methyl ester.<sup>7</sup>

It is our practice to include molecular sieves in the reaction mixture to remove the water which forms during the hypohalite exchange portion of the reaction. This is necessary because water can function as a competing nucleophile for the intermediate aldehyde ultimately producing carboxylic acids. The use of rigorously dried, powdered molecular sieves<sup>8</sup> and high concentrations of methanol consistently keeps the amount of carboxylic acid byproducts below 2%.

It is interesting to note that the oxidation of primary alcohols to tert-butyl esters is not synthetically useful presumably due to the low nucleophilicity of tert-butyl alcohol relative to the starting primary alcohol. When 1-octanol is treated with 3.5 eq Ca(OCl)<sub>2</sub>, 7 eq acetic acid, in t-butyl alcohol (0.15M) both tert-butyl octanoate (37% isolated yield) and octyl octanoate (49% isolated yield) were formed. However, good yields of tert-butyl esters could be obtained if aldehydes were used as the starting material.<sup>9</sup>

decanal	Ca(OCl) <sub>2</sub> , HOAc	tert-butyl decanoate	
occanal	CH <sub>3</sub> CN, (CH <sub>3</sub> ) <sub>3</sub> COH, molecular sieves, dark	75%	

## **Typical Experimental Procedure**

To a solution of p-chlorobenzyl alcohol (132 mg, 0.926 mmol) in acetonitrile (4.6 mL) were added sequentially methanol (1.2 mL, 31 mmol), acetic acid (0.53 mL, 9.3 mmol), calcium hypochlorite (662 mg, 4.63 mmol), and 1.2 g powdered molecular sieves (twice the mass of the calcium hypochlorite). The reaction mixture was wrapped in aluminum foil and stirred in the dark for 48 h at which time GC analysis indicated complete consumption of both the starting material and the intermediate aldehyde. Water (5 mL) and sodium thiosulfate pentahydrate (0.5 g) were then added to destroy any remaining hypochloritecontaining species. The resultant mixture was extracted with 33% ether in hexane (5 X 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. Kugelrohr distillation (1 mm Hg, 70-75 °C) of the residue afforded 140 mg (89%) of white, crystalline methyl p-chlorobenzoate; mp 42-43 °C (lit.<sup>10</sup> mp 43 °C).

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## **References and notes**

- Two other methods for accomplishing this transformation have been reported: a) Milovanovic, J.; Vasojevic, M.; Gojkovic, S. J. Chem. Soc. Perkin Trans. 2, 1991, 1231-1233. b) McDonald, C.; Holcomb, H.; Leathers, T.; Kennedy, K. Microchem. J., in press.
- Stevens, R.; Chapman, K.; Stubbs, C.; Tam, W.; Albizati, K. Tetrahedron Lett. 1982, 23, 4647-4650.
- Reaction products were identified by comparison of <sup>1</sup>H NMR, IR, GC, and melting point (where appropriate) with that of authentic material.
- Attempted oxidation of representative ortho substituted benzyl alcohols (2-chlorobenzyl alcohol and 2methylbenzyl alcohol) resulted in synthetically useless mixtures of aldehyde, methyl ester, and several other uncharacterized products.
- 5. Nicolaou, K.; Pavia, M.; Seitz, S. J. Am. Chem. Soc. 1981, 103, 1224-1226.
- 6. Alcohols are known to produce alkyl hypochlorites upon treatment with calcium hypochlorite and acetic acid. See: Cekovic, Z. and Djokic, G. *Tetrahedron* **1981**, *37*, 4263-4268.
- Past workers have invoked similar mechanisms for alcohol oxidations via hypohalites, see: a) Grob, C.; Schmid Helv. Chim. Acta 1953, 36, 1763-1770; b) Mohrig, J.; Nienhuis, D.; Linck, C.; Zoeren, C.; Fox, B.; Mahaffey, P. J. Chem. Ed. 1985, 62, 519-521; c) Williams, D.; Klingler, F.; Allen, E.; Lichtenthaler, F. Tetrahedron Lett. 1988, 29, 5087-5090; d) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. J. Org. Chem. 1989, 54, 1213-1215.
- Czernecki, S.; Georgoulis, C.; Stevens, C.; Vijayakumaran, K. Tetrahedron Lett. 1985, 26, 1699-1702.
- Only one other example of the conversion of aldehydes to tert-butyl esters could be found in the literature. Corey has reported that the 5' alcohol of nucleosides can be oxidized using chromium trioxide-pyridine and acetic anhydride (via an intermediate aldehyde) to the corresponding tert-butyl ester. See: Corey, E.; Samuelsson, B. J. Org. Chem. 1984, 49, 4735.
- 10. Vorlaender, D. Ber. Deut. Chem. Ges. 1938, 71, 1688-92.

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