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# Oxone/Sodium Chloride: A Simple and Efficient Catalytic System for the Oxidation of Alcohols to Symmetric Esters and Ketones

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**Abstract:** An efficient method for the oxidation of alcohols is presented. The use of catalytic amounts of sodium chloride in combination with oxone allows the conversion primary aliphatic alcohols to symmetric esters. Secondary alcohols can be easily oxidized to ketones, and benzylic alcohols are converted to the corresponding aldehydes. The method is cost effective and enviromentally benign.

**Keywords:** Alcohols, aldehydes, catalytic oxidation, esterification, ketones

Oxidation of primary and secondary alcohols to aldehydes or carboxylic acids and ketones, respectively, is a fundamental process in organic chemistry, and several reagents have been developed for this purpose.[1] However, many of the oxidants were subsequently abolished for environmental reasons. Instead, enzymatic[2] and particularly metal-free[3] oxidations are now of great interest, and a variety of valuable methods have been developed. To the last category belong, for example, oxidations mediated by hypervalent iodine reagents such as IBX[4,5] or TEMPO[1] in combination with NaClO,[6] Br$_2$,[7] I$_2$,[8] or Cl$_2$.[9] TEMPO has been also used in combination with oxone and *n*-Bu$_4$NBr as a phase-transfer catalyst.[10]

A shortcoming of the TEMPO-mediated oxidations is the fact that one equivalent sodium chloride is generated per molecule of alcohol oxidized. Other shortcomings are the use of sodium bromide as a cocatalyst and chlorinated solvents. Finally, although TEMPO is used catalytically, it is expensive, and efficient recycling is an important issue. Several approaches have been developed[1d] to circumvent these problems.

Because of their importance, several methods for the conversion of primary alcohols to symmetric esters have been developed.[11] Symmetric esters are of considerable interest as ingredients for cosmetic, dermatological, and pharmaceutical preparations. A search in SciFinder revealed more than 300 patents for this class of compounds. They are furthermore utilized for the production of denture adhesives and stable aqueous surfactant compositions, in transdermal drug-delivery systems, as lubricants, and as mold-release agents for polyurethanes. Esters of branched-chain carboxylic acids with branched-chain alcohols have been described as antibacterial, antimycotic, and antiparasitic substances and are used in skin preparations.[12]

Herein, we present a catalytic method for the oxidation of alcohols with NaCl/oxone. Using this system, primary aliphatic alcohols are converted to symmetric esters, and secondary alcohols can be easily oxidized to ketones. Furthermore, benzylic alcohols are converted to the corresponding aldehydes.

We found that the combination of oxone (1 equiv.) and $n$-Bu$_4$NBr (0.1 equiv.) in a biphasic system (EtOAc/H$_2$O) effectively converts 1-octanol (1 equiv.) to the corresponding symmetric ester. Importantly, employing the same method and KBr (0.1 equiv.) instead of $n$-Bu$_4$NBr afforded also octyl octanoate in comparable yield. The later experiment was a clear indication that 1) tetra-$n$-butylammonium oxone[13] was not the actual oxidant and 2) the use of a phase-transfer catalyst was not necessary.

In fact, the use of $n$-Bu$_4$NHSO$_4$ and oxone or oxone alone did not induce conversion of 1-octanol to octyl octanoate (or to octanal or octanoic acid) even after prolonged reaction time.
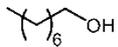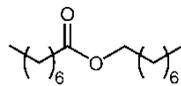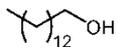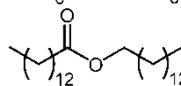
Encouraged by these results, we next investigated the oxone/NaCl (0.05–0.1 equiv.) system and were pleased to realize that it was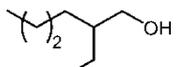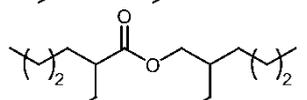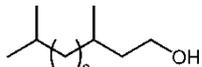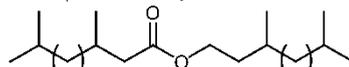 more effective in terms of yield and reaction time than the combination of oxone with KBr or with $n$-Bu$_4$NBr. With this reagent combination, a variety of aliphatic alcohols could be converted to the corresponding symmetric esters fast and at room temperature. In several cases formation of the corresponding carboxylic acid was also observed (see Table 1 and Scheme 1). The use of KI does not lead to any oxidation products.

In contrast to primary aliphatic alcohols, benzylic alcohols were oxidized to the corresponding aldehydes (Scheme 2) in moderate yields. In these cases we observed that the use of 0.5–1 equiv. of NaCl significantly increased the yield.

Finally, secondary alcohols were oxidized to the corresponding ketones (Scheme 3) in high yields.

However, our method is not compatible with double and triple bonds.

**Table 1.** Catalytic oxidation of primary and secondary alcohols with NaCl/oxone

| Entry | Substrate | Reaction time (h) | Product | Ratio E:A[a] | Total yield (%)[b] |
|-------|-----------|-------------------|---------|--------------|---------------------|
| 1 |  | 5 |  | 6:1 | 98 |
| 2 |  | 5.5 |  | 4:1 | 95 |
| 3 |  | 4.5 |  | 3.2:1 | 79 |
| 4 |  | 4.5 |  | 1:0 | 85 |
| 5 |  | 3.5 |  | 1:0 | 90 |
| 6 |  | 5 |  | 2.2:1 | 93 |
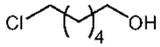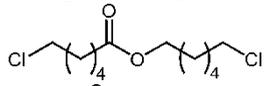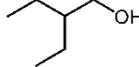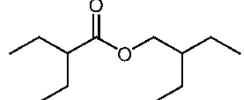
(*continued*)

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***Table 1.*** Continued

| Entry | Substrate | Reaction time (h) | Product | Ratio E:A[a] | Total yield (%)[b] |
|-------|-----------|-------------------|---------|--------------|--------------------|
| 7 | | 5 | | 1.1:1 | 68 |
| 8 | | 5 | | — | 60[c] |
| 9 | | 7 | | — | 30[c] |
| 10 | | 2 | | — | 85[c] |

| 11 | | 3.5 | | — | 85 |
| 12 | | 4 | | — | 80 |
| 13 | | 1.5 | | — | $90^c$ |
| 14 | | 1 | | — | 94 |
| 15 | | 4 | | — | $80^c$ |
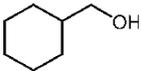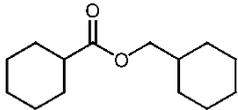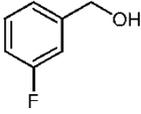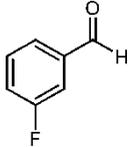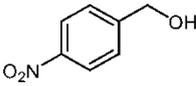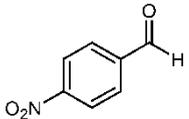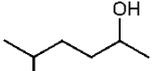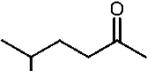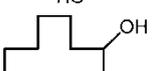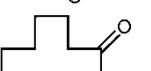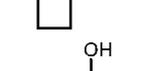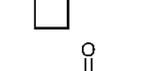
[a]E: ester, A: acid.
[b]Yield of isolated product.
[c]The yield was determined by GC/MS.
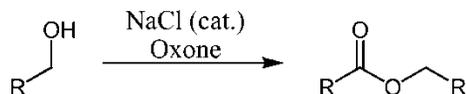
**Scheme 1.** Oxidation of primary aliphatic alcohols.

Oxone has been applied in the past for several oxidations. For example, at elevated temperature and in combination with concentrated sulfuric acid or with acetic acid/ethanol, it has been used for the conversion of alkenes to diols, phenols to quinones, pyridine to pyridin-1-oxide, sulfides to sulfoxides, and ketones to esters or to lactones.[14] Recently, oxone has also been utilized for the oxidation of aromatic and aliphatic aldehydes to the corresponding carboxylic acids or esters.[15] Furthermore, oxone is the reagent of choice for the synthesis of dimethyldioxirane[16] and IBX.[4a]

It is known that treatment of NaCl or NaBr with oxone generates chlorine and bromine respectively.[17] This system has been used for chlorinations and brominations of $\alpha,\beta$-unsaturated carbonyl compounds or for the conversion of oximes to gem-chloro-nitro derivatives.[18] The combination of NaBr/oxone was also reported to oxidize benzylic alcohols to aldehydes, secondary alcohols to ketones, and butanol to the symmetric ester. An important shortcoming of this method is the bromination of the aromatic system and the need for an excess of NaBr.[19]

The oxidation of primary alcohols to symmetric esters is described in Scheme 4: First, the aldehyde is formed, which is then attacked by the parent alcohol to form the corresponding hemiacetal. Oxidation of the latter affords the symmetric ester. The isolation of aromatic aldehydes (see Table 1, entries 8–10) supports this suggestion. They do not form symmetric esters probably because their carbonyl group is not sufficiently electrophilic[20] to allow a nucleophilic attack by a second molecule of the aromatic alcohol present in the reaction mixture. Attempts to convert primary alcohols to tert. butylesters by performing the oxidations in the presence of tert. butanol have been unsuccessful.

In conclusion we presented a new, efficient, and fast method for the conversion of primary aliphatic alcohols to symmetric esters as well for the oxidation of secondary alcohols to ketones. Our method is cost-effective and enviromentally benign. In fact, only catalytic amounts of sodium chloride are used, whereas oxone is inexpensive, stable, easy to transport, and nontoxic. The resulting inorganic by-products are also nonpolluting.
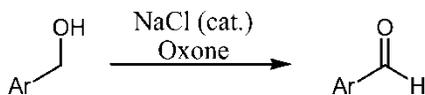


**Scheme 2.** Oxidation of benzylic alcohols.
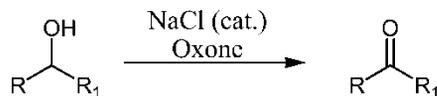
**Scheme 3.** Oxidation of secondary alcohols.

## EXPERIMENTAL

Reagents and solvents were commercially available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 MHz for ^{1}H NMR; 50 MHz for ^{13}C NMR) and Varian Gemini 2000 (200 MHz for ^{1}H NMR; 50 MHz for ^{13}C NMR). Chemical shifts were reported in the scale relative to the solvent used as an internal reference. HR MS was obtained on a Bruker Daltonics APEX II (for ESI). The reaction progress was monitored with a Varian Saturn 2200 GC/MS. Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm).

### Typical Experimental Procedure

Oxone (1 mmol), NaCl (0.1 mmol), and finally $H_2O$ (0.5 ml) were added to a solution of the alcohol (1 mmol) in EtOAc (2 ml). The reaction mixture was stirred at room temperature for 1–7 h depending on the alcohol (see Table 1). After completion of the reaction, the mixture was diluted with $H_2O$ (5 ml) and EtOAc (3 ml), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 ml), and the combined organic layers were dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give the desired product. Analytical pure products were obtained by column chromatography.

**6-Chlorohexyl 6-chlorohexanoate (3):** oil; ^{1}H NMR (CDCl₃, 200 MHz): $\delta = 1.41–1.82$ (m, 14H), 2.28–2.37 (m, 2H), 3.54 (t, 4H, $J = 6.6$ Hz), 4.07 (t, $J = 6.6$ Hz, 2H); ^{13}C NMR (CDCl₃, 50 MHz): $\delta = 24.4, 25.4, 26.5, 26.6, 28.6, 32.4, 32.6, 34.2, 44.8, 44.9, 64.4, 173.7$; HR ESI-MS: calcd. for $(M + Na)^+$: 291.08891; found: 291.08935.

**2-Ethylbutyl 2-ethylbutanoate (4):** oil; ^{1}H NMR (CDCl₃, 200 MHz): $\delta = 0.89$ (t, 12H, $J = 7.4$ Hz), 1.29–1.66 (m, 9H), 2.13–2.28 (m, 1H), 4.01 (d, 2H, $J = 5.5$ Hz); analytical data were consistent with those reported in the literature.[21]
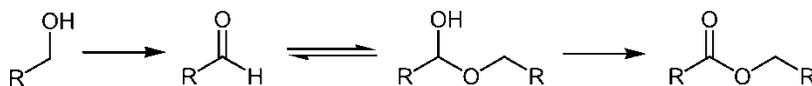


**Scheme 4.** Oxidation of primary alcohols to symmetric esters by NaCl/oxone.

**2-Ethylhexyl 2-ethylhexanoate (5):** oil; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 0.85-0.93$ (m, 12H), $1.19-1.66$ (m, 17H), $2.19-2.32$ (m, 1H), 4.07 (d, 2H, $J = 5.6$ Hz); analytical data were consistent with those reported in the literature.[11c]

**Compound (6):** oil; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 0.88-1.00$ (m, 18H), $1.11-1.72$ (m, 17H), $2.08-2.41$ (m, 3H), $4.11-4.16$ (m, 2H); analytical data were consistent with those reported in the literature.[22]

**Cyclohexylmethyl cyclohexylcarboxylate (7):** oil; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 0.98-1.93$ (m, 21H), $2.21-2.40$ (m, 1H), 3.87 (d, 2H, $J = 6.4$ Hz); analytical data were consistent with those reported in the literature.[23]

Compounds **1**, **2**, **3**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, and **15** are commercially available.

## ACKNOWLEDGMENTS

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