Sodium Hypochlorite Pentahydrate ($NaOCl\cdot 5H_2O$) Crystals as an Extraordinary Oxidant for Primary and Secondary Alcohols

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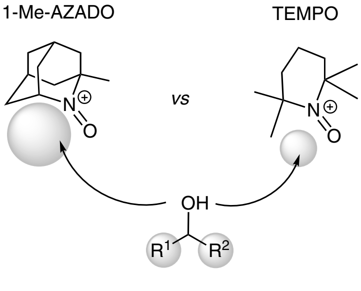
Abstract: Sodium hypochlorite pentahydrate crystals containing less free sodium hydroxide and sodium chloride have been developed as an improved oxidant. Primary and secondary alcohols have been oxidized to the corresponding aldehydes and ketones with $NaOCl\cdot 5H_2O$ in the presence of TEMPO/Bu_4NHSO_4. This new oxidation method does not require pH adjustment and is applicable to sterically hindered secondary alcohols.

Key words: sodium hypochlorite pentahydrate, TEMPO, 1-Me-AZADO

Although various methodologies for the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones have been reported, more environmentally benign and economical oxidation processes are still required. Oxidation with aqueous sodium hypochlorite (NaOCl) catalyzed by the 2,2,6,6-tetramethylpiperidinium oxy radical (TEMPO) seems to be one of the best methods meeting the above requirements. TEMPO-catalyzed oxidation of primary alcohols to the aldehydes has been reported to proceed in high yields, but poor results have been obtained with secondary alcohols.[1] This has been attributed to the four methyl groups of TEMPO preventing bulky substrate from forming the key intermediate (Scheme 1).[2]



Scheme 1 Key step for the oxidation of alcohols

NaOCl oxidation of alcohols catalyzed by less hindered 2-azaadamantane *N*-oxyls (AZADO and related products) has been developed by Iwabuchi et al.[2] Such catalysts proved to be highly efficient for the oxidation of alcohols, especially sterically hindered secondary alcohols. However, the synthesis of those catalysts (AZADO and related compounds) involves multiple steps, and aqueous sodium hypochlorite must be adjusted to pH 8–9 with aqueous sodium hydrogen carbonate in order for the oxidation reactions to proceed efficiently. The oxidation process using aqueous NaOCl has inherently poor volume efficiency because the concentration of commercial aqueous NaOCl solution is only about 10%. Further dilution arising from the pH adjustment may render the solution unsuitable for large-scale synthesis.

We have recently developed a new manufacturing process for sodium hypochlorite pentahydrate ($NaOCl\cdot 5H_2O$) crystals (Figure 1), which have several advantages over commercial 13% aqueous sodium hypochlorite (pH 13): (1) the available chlorine content is about 42%, (2) the pH upon dissolution is around 11, since the solution contains less than 0.08 wt% hydroxide ions, (3) the crystals are much more stable than aqueous sodium hypochlorite at below ambient temperature.[3]

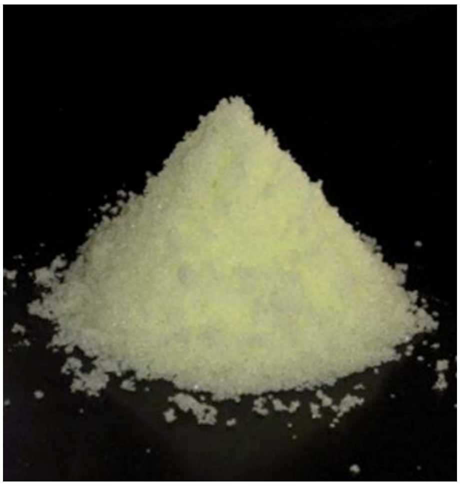


Figure 1 $NaOCl\cdot 5H_2O$ crystals

In this communication, a novel oxidation method for alcohols employing the $NaOCl\cdot 5H_2O$ crystals and that is catalyzed by TEMPO or 1-Me-AZADO is described. Our

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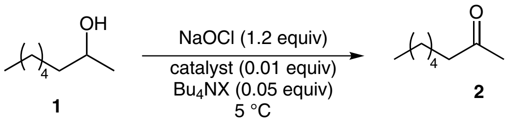
newly developed process has some favorable characteristics; (1) pH adjustment is not required, (2) primary alcohols are selectively oxidized to the corresponding aldehydes, (3) secondary alcohols, even when sterically hindered, can be oxidized to afford the corresponding ketones in high yields.

Treatment of 2-octanol (**1**) with 1.2 equivalents of NaOCl·5H$_2$O crystals in dichloromethane in the presence of 0.01 equivalents of TEMPO and 0.05 equivalents of tetrabutylammonium hydrogen sulfate (Bu$_4$NHSO$_4$) at 5 °C for one hour gave a 97% yield of 2-octanone (**2**, Table 1, entry 3). Several reaction conditions were examined, as shown in Table 1.

Bu$_4$NHSO$_4$ proved to be a much better phase-transfer catalyst than Bu$_4$NBr or Bu$_4$NCl. However, an addition of 0.05 equivalents of NaHSO$_4$ and a small amount of water into the reaction conditions of Table 1, entry 5 gave an 89% yield of **2** (Table 1, entry 6). Bu$_4$NHSO$_4$ seems to have both roles of a neutralization of liberated NaOH in NaOCl·5H$_2$O and a phase-transfer catalyst. A control experiment using commercial aqueous NaOCl solution (about 13wt%, 2.2 M) was performed in a similar fashion. A mixture of **1**, TEMPO, Bu$_4$NHSO$_4$, and aqueous NaOCl gave **2** in only 2% yield after two hours without pH adjustment (Table 1, entry 7). Various kinds of solvents were examined, but dichloromethane proved to be the best. Instead of TEMPO, the use of 1-Me-AZADO to catalyze the oxidation of **1** with NaOCl·5H$_2$O crystals was also examined. The reaction was very fast even without pH adjustment, affording **2** in quantitative yield (Table 1, entry 13), but the use of aqueous NaOCl instead of NaOCl·5H$_2$O crystals gave poor results (Table 1, entry 14). In the absence of nitroxyl radicals, the oxidation reaction of **1** with NaOCl·5H$_2$O crystals proceeded slowly (Table 1, entry 1).

Next, we examined the oxidation of some other alcohols with NaOCl·5H$_2$O crystals in the presence of Bu$_4$NHSO$_4$ and TEMPO or 1-Me-AZADO. The results are shown in Table 2. 2-Octanol,[4] 3-octanol, 1-octanol, and benzyl alcohol gave the corresponding ketones and aldehydes in high yields in the presence of 0.01 equivalents of TEMPO. L-Menthol and 2,6-dimethyl-4-heptanol (as examples of sterically hindered secondary alcohols) were oxidized to the corresponding ketones in 96% and 88% yields, respectively, in the presence of TEMPO, after optimization of the amount of NaOCl·5H$_2$O crystals and the reaction temperature.

Table 1 Oxidation of 2-Octanol to 2-Octanone with NaOCl[a]



Entry	Solvent	Catalyst	X	NaOCl	Time (h)	Yield (%)[b]
1	CH$_2$Cl$_2$	–	HSO$_4$	NaOCl·5H$_2$O	24	78
2	CH$_2$Cl$_2$	–	HSO$_4$	aq NaOCl	27	9
3	CH$_2$Cl$_2$	TEMPO	HSO$_4$	NaOCl·5H$_2$O	1	97
4	CH$_2$Cl$_2$	TEMPO	Br	NaOCl·5H$_2$O	2	14
5	CH$_2$Cl$_2$	TEMPO	Cl	NaOCl·5H$_2$O	2	10
6	CH$_2$Cl$_2$	TEMPO	Cl	NaOCl·5H$_2$O	2	89[c]
7	CH$_2$Cl$_2$	TEMPO	HSO$_4$	aq NaOCl	2	2
8	CH$_2$Cl$_2$	TEMPO	–	NaOCl·5H$_2$O	2	0.1
9	PhCF$_3$	TEMPO	HSO$_4$	NaOCl·5H$_2$O	2	55
10	EtOAc	TEMPO	HSO$_4$	NaOCl·5H$_2$O	2	97
11	MeCN	TEMPO	HSO$_4$	NaOCl·5H$_2$O	2	53
12	AcOH	TEMPO	HSO$_4$	NaOCl·5H$_2$O	2	78[d]
13	CH$_2$Cl$_2$	1-Me-AZADO	HSO$_4$	NaOCl·5H$_2$O	1	100
14	CH$_2$Cl$_2$	1-Me-AZADO	HSO$_4$	aq NaOCl	1	14

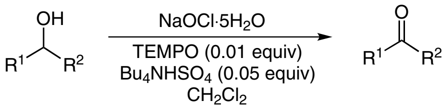
[a] 1 (10 mmol), NaOCl (12 mmol), TEMPO or 1-Me-AZADO (0.1 mmol), phase-transfer catalyst (0.5 mmol), solvent (30 mL) without pH adjustment.

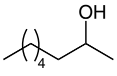
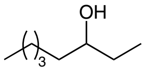
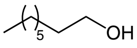
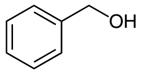
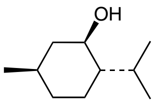
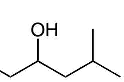
[b] GC yield using an internal standard.

[c] addition of NaHSO$_4$·H$_2$O (0.5 mmol) and H$_2$O (0.2 mL).

[d] At r.t.

Table 2 Examples for Oxidation of Alcohols with $NaOCl\cdot 5H_2O$[a]



Substrate	$NaOCl\cdot 5H_2O$ (equiv)	CH_2Cl_2 (mL)	Temp (°C)	Time (h)	Yield (%)[b]
	1.2	30	5	1	97
	1.2	10	5	0.5	(95)
	1.2	30	5	1	97
	1.2	10	5	0.5	(96)
	1.1	30	5	1	91
	1.1	30	5	1	99
	1.6	10	15	2	96
	1.6	8	15	2.25	(92)[c]
	1.4	30	r.t.	0.5	98[d]
	1.4	10	r.t.	7	77
	1.8	10	15	6	88
	1.4	30	r.t.	0.5	95[d]

[a] Substrate (10 mmol), TEMPO (0.1 mmol), Bu_4NHSO_4 (0.5 mmol), CH_2Cl_2 (10 mL or 30 mL) without pH adjustment.

[b] GC yield using an internal standard. Parentheses are referred to the isolated yield.

[c] Substrate (2.5 mmol), TEMPO (0.022 mmol), Bu_4NHSO_4 (0.131 mmol), CH_2Cl_2 (8 mL) without pH adjustment.

[d] 1-Me-AZADO was used instead of TEMPO.

The stereochemistry of L-menthone was confirmed as that with retention of the configuration by measurement of its optical rotation.[5] 1-Me-AZADO was shown to be a superior catalyst for the oxidations of L-menthol and 2,6-dimethyl-4-heptanol with $NaOCl\cdot 5H_2O$ crystals, affording high yields of the ketones in very short reaction times. Although TEMPO proved to be inferior to 1-Me-AZADO as a catalyst, considering the ready availability of TEMPO, it may still be more practical for a large-scale synthesis. The precise reason why some sterically hindered secondary alcohols can be oxidized with $NaOCl\cdot 5H_2O$ crystals in the presence of TEMPO is yet unknown, but it may relate to a different intermediate.

In conclusion, the ready availability, high volume efficiency, and high activity of $NaOCl\cdot 5H_2O$ for the oxidation of alcohols should make this a very attractive oxidation method for laboratory and industrial use.

References and Notes

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(2) (a) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412. (b) Iwabuchi, Y. *J. Synth. Org. Chem. Jpn.* **2008**, *66*, 1076.

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(4) **Typical Experiment for the Oxidation of 2-Octanol (1)**
$NaOCl\cdot 5H_2O$ crystals (2.0 g, 12.2 mmol) were added in one portion to a mixture of Bu_4NHSO_4 (0.17 g, 0.50 mmol), TEMPO (21 mg, 0.13 mmol), and **1** (1.30 g, 10.0 mmol) in CH_2Cl_2 (10 mL) at 5 °C. After 15 min, GC monitoring showed that **1** had been consumed. The reaction was stopped after 0.5 h by quenching with aq sat. Na_2SO_3 solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with H_2O (30 mL), dried over Na_2SO_4, and concentrated to give **2** as colorless oil (1.27 g, crude yield of 99.2%, GC analysis showed the product to be 96.8% pure). A 0.42 g portion of the crude **2** was purified by bulb-to-bulb distillation (6 kPa, 120–130 °C) to afford pure **2** (0.40 g, 95%). GC–MS analysis gave identical results to those of an authentic sample.

(5) **Oxidation of L-Menthol**
$NaOCl\cdot 5H_2O$ (658.0 mg, 4 mmol) was added in one portion to a mixture of Bu_4NHSO_4 (44.5 mg, 0.131 mmol), TEMPO (3.4 mg, 0.022 mmol), and L-menthol (391.5 mg, 2.5 mmol) in CH_2Cl_2 (8 mL) at 15 °C. The mixture was stirred at 15 °C for 2.25 h, and then the reaction was quenched by treatment with sat. aq Na_2SO_3 solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. brine, dried over anhydrous Na_2SO_4, and concentrated to give L-menthone as a colorless oil (475.7 mg), which was purified by column chromatography on silica gel to give pure L-menthone (355.3 mg, 92%). $[\alpha]_D^{25}$ –28.1 (*c* 0.0156, EtOH) {lit.[6] $[\alpha]_D$ –28.6}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (ddd, *J* = 13.1, 3.6, 2.3 Hz, 1 H), 2.18–1.80 (m, 6 H), 1.43–1.29 (m, 2 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H). See ref. 7.

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