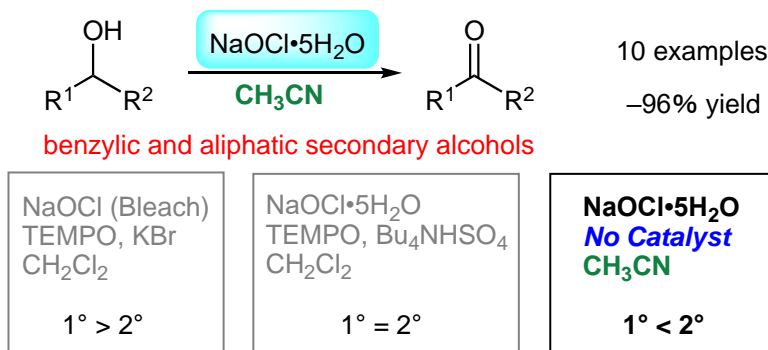# Revisiting Sodium Hypochlorite Pentahydrate (NaOCl•5H$_2$O) for the Oxidation of Alcohols in Acetonitrile without Nitroxyl Radicals

Tsunehisa Hirashita*[a]
Yuto Sugihara[a]
Shota Ishikawa[a]
Yohei Naito[a]
Yuta Matsukawa[a]
Shuki Araki[a]

[a] Life Science and Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan

hirasita@nitech.ac.jp

10 examples
–96% yield

benzylic and aliphatic secondary alcohols

NaOCl (Bleach) TEMPO, KBr CH$_2$Cl$_2$	NaOCl•5H$_2$O TEMPO, Bu$_4$NHSO$_4$ CH$_2$Cl$_2$	**NaOCl•5H$_2$O** *No Catalyst* **CH$_3$CN**
1° > 2°	1° = 2°	**1° < 2°**

Abstract Sodium hypochlorite pentahydrate (NaOCl•5H$_2$O) is capable of oxidizing alcohols in acetonitrile at 20 °C without the use of catalysts. The oxidation is selective to allylic, benzylic, and secondary alcohols. Aliphatic primary alcohols are not oxidized.

Key words oxidation; alcohol; sodium hypochlorite pentahydrate; aldehyde; ketone

The selective oxidation of alcohols to the corresponding aldehydes and ketones is ranked as one of the pivotal functional transformations in organic synthesis.[1] Selective oxidation of alcohols can be performed with sodium hypochlorite as a terminal oxidizing agent, using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and its derivatives as mediators.[2] Recently, solid sodium hypochlorite pentahydrate (NaOCl•5H$_2$O) became commercially available, and has proven to be an attractive oxidizing agent.[3] This "solid bleach" has a higher effective chlorine concentration than conventional household bleach, and thus lends itself to more concentrated reaction mixtures. We have recently reported that the aerobic oxidation of alcohols is more successful using the TEMPO derivative **1** in an ionic liquid than that performed using either TEMPO in an ionic liquid or using **1** in conventional organic solvents.[4] We envisaged that our oxidation system could be applied using NaOCl•5H$_2$O instead of conventional bleach as the terminal oxidant.

We started by examining the oxidation of benzyl alcohol using bleach or NaOCl•5H$_2$O in various solvents. When benzyl alcohol was mixed with bleach in methylene chloride, the reaction using TEMPO proceeded faster than that involving the ionic TEMPO **1** (entries 1 and 2, Table 1). This is the same tendency as observed in aerobic oxidation using sodium nitrite as the oxidizing agent.[4] When the oxidation was performed in [bmim][PF$_6$] (where bmim = 1-butyl-3-methylimidazolium), the ionic TEMPO **1** was found to

be superior to TEMPO (entries 3 and 4), as had been observed in the aerobic version. Using NaOCl•5H$_2$O instead of conventional bleach gave better conversion, and a moderate yield was attained even after only 3 min (entries 5 and 6). We were surprised to find a similar level of oxidation when organic radicals were not present (entry 7). In acetonitrile, the oxidation proceeded quite fast to provide 2-octanone in high yield (entry 8). However, in methylene chloride the reaction hardly proceeded (entry 9).

Table 1 Oxidation of Benzyl Alcohol with NaOCl (bleach) or NaOCl•5H$_2$O[a]

PhCH$_2$OH → (oxidizing agent, catalyst) → PhCHO

TEMPO: R = H
1: R = NBu$_2$Me•PF$_6$

Entry	Oxidizing agent	Solvent (mL)	Catalyst	t (min.)	Yield (%)[b]
1[c]	Bleach	CH$_2$Cl$_2$ (2)	TEMPO	20	92 (2)
2[c]	Bleach	CH$_2$Cl$_2$ (2)	**1**	60	78 (9)
3[d]	Bleach	bmim•PF$_6$ (1)	TEMPO	60	27 (70)
4[d]	Bleach	bmim•PF$_6$ (1)	**1**	60	61 (29)
5	NaOCl•5H$_2$O	bmim•PF$_6$ (1.5)	**1**	60	97 (3)
6	NaOCl•5H$_2$O	bmim•PF$_6$ (1.5)	**1**	3	51 (36)
7	NaOCl•5H$_2$O	bmim•PF$_6$ (1.5)	none	3	58 (21)
8	NaOCl•5H$_2$O	CH$_3$CN (5)	none	3	80 (7)
9	NaOCl•5H$_2$O	CH$_2$Cl$_2$ (5)	none	60	2 (74)

[a] All reactions were carried out with benzyl alcohol (0.50 mmol), NaOCl (bleach) or NaOCl•5H$_2$O (125 mol%), and catalyst (1 mol%) in solvent at room temperature unless otherwise noted. [b] GC yield. Values in parentheses show the recovery of benzyl alcohol. [c] With benzyl alcohol (1.0 mmol). [d] With benzyl alcohol (0.25 mmol).

Contrary to the above results, Okada *et al.* reported that acetonitrile is not a suitable solvent for the oxidation of alcohols in the presence of an ammonium salt and TEMPO as catalysts, because the oxidation reaction of 2-octanol did not go to

completion in acetonitrile.[3c] We confirmed that the oxidation of 2-octanol in the presence of catalytic amounts of TEMPO and tetrabutylammonium hydrogensulfate reached a plateau at less than 60% conversion under the reported conditions (blue line, Figure 1). When the oxidation was performed in absence of the additives, the reaction proceeded more smoothly, providing 2-octanone in higher yields (red line). We also found that the amount of acetonitrile has a strong effect on the conversion. Under dilute conditions both the reactions with and without additives proceeded more quickly than those performed under relatively concentrated conditions.
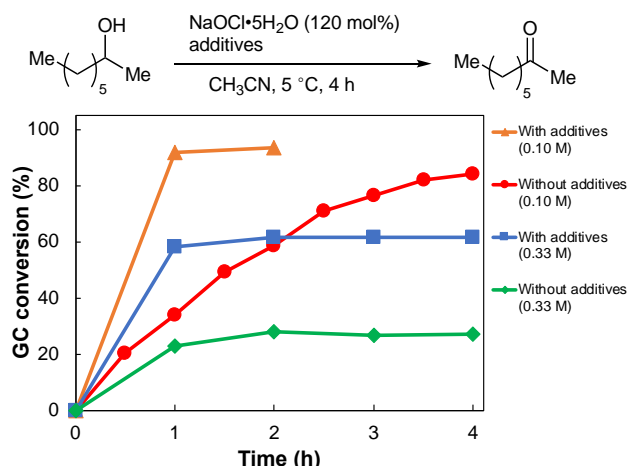
Figure 1. Rate profile of the oxidation of 2-octanol (0.10 or 0.33 M in acetonitrile) by NaOCl•5H$_2$O (120 mol%) with and without the additives TEMPO (1 mol%) and Bu$_4$NHSO$_4$ (5 mol%).

The difference was speculated to arise from the undesirable oxidation of acetonitrile by NaOCl•5H$_2$O under the influence of the catalysts. This hypothesis was examined by admixing NaOCl•5H$_2$O and the catalysts in acetonitrile for 1 h prior to the addition of benzyl alcohol (Scheme 1), which led to an almost quantitative conversion of the alcohol to benzaldehyde. When 2-octanol instead of benzyl alcohol was allowed to react for 1 h, the yield of 2-octanone was 57%. As NaOCl•5H$_2$O does not decompose under the reaction conditions, the discrepancy in the oxidations remains puzzling.
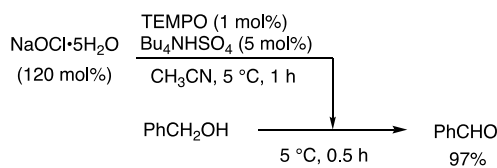
Scheme 1. Oxidation of benzyl alcohol (5 mmol) with NaOCl•5H$_2$O exposed to CH$_3$CN (15 mL) that contained catalysts.

There are other examples in the literature of bleach-mediated oxidation of alcohols without the use of organic radicals. Bleach has proven capable of oxidizing secondary alcohols selectively in the absence of catalysts in glacial acetic acid.[5] The oxidation of alcohols with bleach alone proceeds sufficiently in ethereal solvents, though oxidizable substrates are strictly limited to primary benzylic alcohols; secondary alcohols, even benzylic alcohol, remain intact under these conditions.[6]

Oxidation of 2-octanol with only NaOCl·5H$_2$O

We next performed a solvent screening for the oxidation of 2-octanol with NaOCl•5H$_2$O at 5 °C, and the results are summarized in Table 2. We tested a series of ethereal solvents which are known to support bleach-oxidation.[6] When 2-octanol was mixed with NaOCl•5H$_2$O in DME, 2-octanone was obtained in 23% yield after 1 h (entry 1, Table 2). The reaction in 1,4-dioxane was performed at 20 °C due to the solvent's high melting point, and resulted in a lower yield than that in DME (entry 2). A poor conversion was observed in THF (entry 3). Although the best yield among the ethereal solvents was found in DME, which is in agreement with the bleach oxidation,[6] the conversion was still much lower than that in acetonitrile. We next employed aprotic polar solvents. Using DMF (entry 4) resulted in a similar level of conversion as was observed in 1,4-dioxane and THF. In ethyl acetate and acetone, little progress was observed (entries 5 and 6). We therefore turned our attention back to acetonitrile. When the temperature was increased, the reaction rate was obviously accelerated (entries 7–9). When the oxidation was performed with 150 mol% of NaOCl•5H$_2$O at 20 °C, the conversion was almost quantitative, providing 2-octanone in 91% yield after only 1 h, which was determined to be the optimal conditions (entry 10).[7]

Table 2 Solvent Effect on the Oxidation of 2-Octanol with only NaOCl•5H$_2$O[a]


Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	DME	5	1	23 (67)
2	1,4-dioxane	20	1	8 (68)
3	THF	5	1	7 (83)
4	DMF	5	1	11 (87)
5	EtOAc	5	1	3 (95)
6	Acetone	5	1	0 (98)
7	CH$_3$CN	5	1	44 (48)
8	CH$_3$CN	5	4	79 (9)
9[c]	CH$_3$CN	10	2	82 (11)
10[c]	CH$_3$CN	20	1	91 (2)

[a] Reaction conditions: 2-octanol (0.50 mmol), NaOCl•5H$_2$O (120 mol%) in solvent (5 mL). [b] Determined by GC. Figures in parentheses show the recovery of 2-octanol. [c] NaOCl•5H$_2$O (150 mol%) was used.

Substrate scope and limitations

A series of alcohols were subjected to oxidation under the optimal conditions. 2-Undecanol was oxidized to 2-undecanone in good yield (entry 1, Table 3). *l*-Menthol was easily converted into menthone (entry 2), while the more sterically demanding isoborneol resisted oxidation (entry 3). Benzylic alcohols, including a heteroaromatic, gave good yields in short reaction times (entries 4-6). The oxidation of cinnamyl alcohol prevailed over addition of hypochlorous acid to the double bond, providing cinnamaldehyde in a better yield than when performed under Anelli's conditions (entry 7).[2a,b] Primary aliphatic alcohols yielded only a small amount of the corresponding aldehydes and were largely recovered (entries 8 and 9).

Table 3 Oxidation of a Series of Alcohols with NaOCl•5H$_2$O[a]
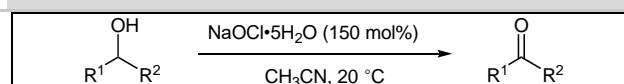
Entry	Alcohol	Time (h)	Yield (%)[b]
1	$CH_3(CH_2)_8CH(OH)CH_3$	1	82 (12)
2		1	97 (3)
3		1.5	10 (53)
4	$PhCH_2OH$	0.25	96 (0)
5	$PhCH(OH)CH_3$	0.25	95 (0)
6		0.25	83 (0)
7	(E)-$PhCH=CHCH_2OH$	0.25	72 (0)
8	$CH_3(CH_2)_6CH_2OH$	1	2 (80)
9	$CH_3(CH_2)_9CH_2OH$	1	2 (70)

[a] Reaction conditions: alcohol (0.50 mmol) and NaOCl•5H$_2$O (0.75 mmol) in CH$_3$CN (5.0 mL). [b] Determined by GC. Figures in parentheses show the recovery of alcohol.

In order to gain insight into the nature of the oxidation, benzyl alcohol was allowed to react competitively with 2-octanol, menthol, and 1-octanol for a limited amount of NaOCl•5H$_2$O (Table 4). Benzyl alcohol was oxidized five times faster than 2-octanol (entry 1). The reaction performed at –20 °C resulted in similar selectivity (data not shown). A larger selectivity was observed for *l*-menthol (entry 2) than for 2-octanol. As expected from the oxidation of aliphatic primary alcohols (entries 8 and 9, Table 3), benzaldehyde was selectively obtained in the competitive reaction with 1-octanol (entry 3, Table 4).

Table 4 Competitive Oxidations with NaOCl•5H$_2$O[a]

entry	1st alcohol	2nd alcohol	Relative rate ratio[b]
1	$PhCH_2OH$	2-octanol	5:1
2	$PhCH_2OH$	*l*-menthol	7.6:1
3	$PhCH_2OH$	1-octanol	18.5:1

[a] All reactions were carried out with each alcohol (0.50 mmol) and NaOCl•5H$_2$O (0.50 mmol) in CH$_3$CN (5 mL) at 20 °C for 15 min. [b] The relative rate ratio was determined by the yields of the corresponding carbonyl compounds.

When a mixture of 1-octanol and *l*-menthol was subjected to the oxidation conditions, menthone was selectively obtained (eq 1).[5b]

(eq 1)

[a] Recovery of alcohol
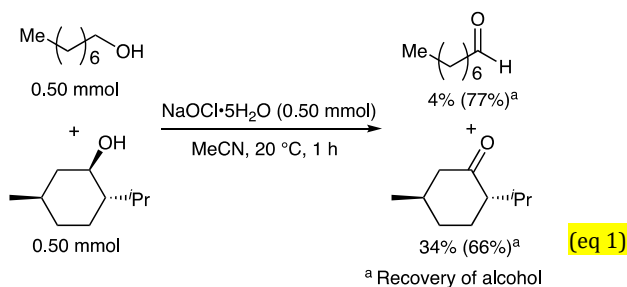
1,5-Hexanediol was also oxidized to the corresponding hydroxyketone with a similar level of conversion (eq 2).

In conclusion, NaOCl•5H$_2$O proved to function well as an oxidizing agent for alcohols in acetonitrile without the use of additives. Benzylic and aliphatic secondary alcohols are selectively oxidized to the corresponding carbonyl compounds; aliphatic primary alcohols are particularly slow to be oxidized under these conditions.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-xxxx-xxxxxxx.

References and Notes

1. (a) Fernandez, M. I.; Tojo, G. *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*; Springer: New York, **2006**. (b) Stahl, S. S.; Alsters, P. L. *Liquid Phase Aerobic Oxidation Catalysis*; Wiley-VCH: Weinheim, Germany, **2016**.

2. (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987,** *52*, 2559. (b) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051. (c) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabichi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412. (d) Janssen, M. H. A.; Chesa Castellana, J. F.; Jackman, H.; Dunn, P. J.; Sheldon, R. A. *Green Chem.* **2011,** *13*, 905.

3. (a) Okada, T.; Asawa, T.; Sugiyama, Y.; Kirihara, M.; Iwai, T.; Kimura, Y. *Synlett* **2014,** *25*, 596. (b) Okada, T.; Matsumuro, H.; Iwai, T.; Kitagawa, S.; Yamazaki, K.; Akiyama, T.; Asawa, T.; Sugiyama, Y.; Kimura, Y. *Chem. Lett.* **2015,** *44*, 185. (c) Okada, T.; Asawa, T.; Sugiyama, Y.; Iwai, T.; Kirihara, M.; Kimura, Y. *Tetrahedron* **2016,** *72*, 2818. (d) Kirihara, M.; Okada, T.; Sugiyama, Y.; Akiyoshi, M.; Matsunaga, T.; Kimura, Y. *Org. Process Res. Dev.* **2017,** *21*, 1925.

4. Hirashita, T.; Nakanishi, M.; Uchida, T.; Yamamoto, M.; Araki, S.; Arends, I. W. C. E.; Sheldon, R. A. *ChemCatChem* **2016,** *8*, 2704.

5. (a) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980,** *45*, 2030. (b) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647.

6. Fukuda, N.; Kajiwara, T.; Katou, T.; Majima, K.; Ikemoto, T. *Synlett* **2013,** *24*, 1438.

7. Experiment for the oxidation of 2-octanol (entry 10, Table 2): To a suspension of NaOCl·5H$_2$O crystals (123 mg, 0.75 mmol) in acetonitrile (5.0 mL), was added 2-octanol (65 mg, 0.50 mmol), and the resulting mixture was stirred at 20 °C. Aliquots were analyzed at intervals by GC after passing through a short SiO$_2$ column (eluting with EtOAc:hexane = 9:1). The reaction was stopped after 1 h by quenching with Na$_2$SO$_3$ (94 mg, 0.75 mmol) and the mixture was diluted with CH$_2$Cl$_2$ (10 mL). The yield of 2-octanone (t_R: 2.1 min.) and the recovery of 2-octanol (t_R: 2.8 min.) were determined to be 91% and 2%, respectively, by GC analysis based on a calibration curve using authentic samples.