## Letter

# Revisiting Sodium Hypochlorite Pentahydrate (NaOCl·5H<sub>2</sub>O) for the Oxidation of Alcohols in Acetonitrile without Nitroxyl Radicals

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Received: 04.07.2018 Accepted after revision: 26.09.2018 Published online: 17.10.2018 DOI: 10.1055/s-0037-1609629; Art ID: st-2018-u0413-I

Abstract Sodium hypochlorite pentahydrate (NaOCl·5H<sub>2</sub>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.<sup>1</sup> 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.<sup>2</sup> Recently, solid sodium hypochlorite pentahydrate (NaOCl·5H<sub>2</sub>O) became commercially available, and it has proven to be an attractive oxidizing agent.<sup>3</sup> 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.<sup>4</sup> We envisaged that our oxidation system could be applied using NaOCl·5H<sub>2</sub>O instead of conventional bleach as the terminal oxidant.

We started by examining the oxidation of benzyl alcohol using bleach or NaOCl·5H<sub>2</sub>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 (Table 1, entries 1 and 2). This is the same tendency as observed in aerobic oxidation using sodium nitrite as the oxidizing agent.<sup>4</sup> When the oxidation was performed in [bmim][PF<sub>6</sub>] (where bmim = 1-butyl-3methylimidazolium), 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<sub>2</sub>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,



oxidizing agent catalyst PhCH<sub>2</sub>OH PhCHO

> TEMPO' B = H1: R = NBu<sub>2</sub>Me·PF<sub>6</sub>

Entry	Oxidizing agent	Solvent (mL)	Catalyst	t (min)	Yield (%) <sup>b</sup>
1 <sup>c</sup>	bleach	$CH_2Cl_2$ (2)	TEMPO	20	92 (2)
2 <sup>c</sup>	bleach	$CH_2CI_2$ (2)	1	60	78 (9)
3 <sup>d</sup>	bleach	bmim∙PF <sub>6</sub> (1)	TEMPO	60	27 (70)
4 <sup>d</sup>	bleach	bmim∙PF <sub>6</sub> (1)	1	60	61 (29)
5	NaOCl-5H <sub>2</sub> O	bmim∙PF <sub>6</sub> (1.5)	1	60	97 (3)
6	NaOCl-5H <sub>2</sub> O	bmim∙PF <sub>6</sub> (1.5)	1	3	51 (36)
7	NaOCl-5H <sub>2</sub> O	bmim∙PF <sub>6</sub> (1.5)	none	3	58 (21)
8	NaOCl-5H <sub>2</sub> O	CH <sub>3</sub> CN (5)	none	3	80 (7)
9	NaOCl-5H <sub>2</sub> O	$CH_2CI_2$ (5)	none	60	2 (74)

<sup>a</sup> All reactions were carried out with benzyl alcohol (0.50 mmol), NaOCl (bleach) or NaOCI-5H2O (125 mol%), and catalyst (1 mol%) in solvent at room temperature unless otherwise noted.

GC yield. Values in parentheses show the recovery of benzyl alcohol.

<sup>c</sup> With benzyl alcohol (1.0 mmol).

<sup>d</sup> With benzyl alcohol (0.25 mmol).

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the oxidation proceeded quite fast to provide 2-octanone in high yield (entry 8). However, almost no reaction proceeded in methylene chloride (entry 9).

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.<sup>3c</sup> 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 (Figure 1, blue line). When the oxidation was performed in the absence of additives, the reaction proceeded more smoothly, providing 2-octanone in higher vields (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 for the oxidation of 2-octanol (0.10 or 0.33 M in acetonitrile) with NaOCl- $SH_2O$  (120 mol%) with and without the additives TEMPO (1 mol%) and  $Bu_4NHSO_4$  (5 mol%)

The difference was speculated to arise from the undesirable oxidation of acetonitrile with NaOCl·5H<sub>2</sub>O under the influence of the catalysts. This hypothesis was examined by admixing NaOCl·5H<sub>2</sub>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 into 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<sub>2</sub>O does not decompose under the reaction conditions, the discrepancy in the oxidations remains puzzling.

There are other reported examples 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.<sup>5</sup>



**Scheme 1** Oxidation of benzyl alcohol (5 mmol) with NaOCl- $5H_2O$  exposed to  $CH_3CN$  (15 mL) that contained catalysts

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.<sup>6</sup>

#### Oxidation of 2-Octanol with Only NaOCl·5H<sub>2</sub>O

We next performed a solvent screening for the oxidation of 2-octanol with NaOCl·5H<sub>2</sub>O at 5 °C; the results are summarized in Table 2. We tested a series of ethereal solvents that are known to support bleach-oxidation.<sup>6</sup> When 2-octanol was mixed with NaOCl·5H<sub>2</sub>O in 1,2-dimethoxyethane (DME). 2-octanone was obtained in 23% vield after 1 h (entry 1). The reaction in 1,4-dioxane was performed at 20 °C due to the high melting point of the solvent, 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.<sup>6</sup> the conversion was still much lower than that in acetonitrile. We next employed aprotic polar solvents. The use of DMF (entry 4) resulted in a similar level of conversion to that 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 clearly accelerated (entries 7–9). When the oxidation was performed with 150 mol% NaOCl·5H<sub>2</sub>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

### 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 (Table 3, entry 1). L-Menthol was easily converted into menthone (entry 2), whereas 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),<sup>2a,2b</sup> Primary aliphatic alcohols yielded only a small amount of the corresponding aldehydes and were largely recovered (entries 8 and 9).

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Entry	Solvent	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>
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 <sub>3</sub> CN	5	1	44 (48)
8	CH <sub>3</sub> CN	5	4	79 (9)
9°	CH <sub>3</sub> CN	10	2	82 (11)
10 <sup>c</sup>	CH <sub>3</sub> CN	20	1	91 (2)

 $^a$  Reaction conditions: 2-octanol (0.50 mmol), NaOCl-5H\_2O (120 mol%) in solvent (5 mL).

 $^{\rm b}$  Determined by GC. Figures in parentheses show the recovery of 2-octanol.

 $^{\rm c}$  NaOCl·5H2O (150 mol%) was used.

#### Table 3 Oxidation of a Series of Alcohols with NaOCl·5H<sub>2</sub>O<sup>a</sup>

	ОН	NaOCI-5H <sub>2</sub> O (150 mol%)			
	$R^1 \land R^2$	CH <sub>3</sub> CN, 20 °C		R <sup>2</sup>	
Entry	Alcohol		Time (h)	Yield (%) <sup>b</sup>	
1	CH <sub>3</sub> (CH	<sub>2</sub> ) <sub>8</sub> CH(OH)CH <sub>3</sub>	1	82 (12)	
2	-<	OH	1	97 (3)	
3	X	ОН	1.5	10 (53)	
4	PhCH <sub>2</sub> O	Н	0.25	96 (0)	
5	PhCH(O	H)CH₃	0.25	95 (0)	
6		∕он	0.25	83 (0)	
7	(E)-PhCH	I=CHCH <sub>2</sub> OH	0.25	72 (0)	
8	CH <sub>3</sub> (CH <sub>2</sub>	) <sub>6</sub> CH <sub>2</sub> OH	1	2 (80)	
9	CH <sub>3</sub> (CH <sub>2</sub>	) <sub>9</sub> CH <sub>2</sub> OH	1	2 (70)	

 $^a$  Reaction conditions: alcohol (0.50 mmol) and NaOCl-5H\_2O (0.75 mmol) in CH\_3CN (5.0 mL).

<sup>b</sup> Determined by GC. Figures in parentheses show the recovery of alcohol.

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<sub>2</sub>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 (Table 3, entries 8 and 9), benzaldehyde was selectively obtained in the competitive reaction with 1-octanol (Table 4, entry 3).

#### Table 4 Competitive Oxidations with NaOCI-5H<sub>2</sub>O<sup>a</sup>

NaOCI-5H2O (50 mol%) CH<sub>2</sub>CN, 20 °C, 15 min Entry 1st alcohol 2nd alcohol Relative rate ratio<sup>b</sup> 1 PhCH<sub>2</sub>OH 2-octanol 5:1 2 PhCH<sub>2</sub>OH L-menthol 7.6:1 PhCH<sub>2</sub>OH 3 1-octanol 18.5:1

<sup>a</sup> All reactions were carried out with each alcohol (0.50 mmol) and NaOCI-5H<sub>2</sub>O (0.50 mmol) in CH<sub>3</sub>CN (5 mL) at 20 °C for 15 min. <sup>b</sup> 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 (Scheme 2).



1,5-Hexanediol was allowed to react under the same conditions to afford the corresponding hydroxyketone selectively with a similar level of conversion (Scheme 3).<sup>8</sup>



In conclusion, NaOCl- $5H_2O$  proved to function well as an oxidizing agent for alcohols in acetonitrile without the use of additives. Benzylic and aliphatic secondary alcohols are

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selectively oxidized to the corresponding carbonyl compounds; aliphatic primary alcohols are particularly slow to oxidize under these conditions.

## **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609629.

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- (7) **Oxidation of 2-Octanol; Typical Procedure (entry 10, Table 2):** To a suspension of NaOCl·5H<sub>2</sub>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<sub>2</sub> column (eluting with EtOAc/hexane, 9:1). The reaction was stopped after 1 h by quenching with Na<sub>2</sub>SO<sub>3</sub> (94 mg, 0.75 mmol) and the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (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.
- (8) **Oxidation of 1,5-hexanediol (Scheme 3)**: To a suspension of NaOCI-5H<sub>2</sub>O crystals (123 mg, 0.75 mmol) in acetonitrile (5.0 mL), was added 1,5-hexanediol (59 mg, 0.50 mmol), and the resulting mixture was stirred at 20 °C. The reaction was stopped after 1 h by quenching with Na<sub>2</sub>SO<sub>3</sub> (95 mg, 0.75 mmol). The product was analyzed by <sup>1</sup>H NMR and found to be 6-hydroxy-hexane-2-one (31%,  $\delta$  = 2.49 ppm, 2 H) and 1,5-hexanediol (49% recovery,  $\delta$  = 1.20 ppm, 3 H) based on a standard material (triphenylmethane  $\delta$  = 5.55 ppm, 1 H).