Practical Oxidative Dearomatization of Phenols with Sodium Hypochlorite Pentahydrate

Muhammet Uyanik,¹ Niiha Sasakura,¹ Mitsuyoshi Kuwahata,² Yasukazu Ejima,² and Kazuaki Ishihara*1,³

¹Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8603

²Kaneka Corporation, PVC & Chemical Division, 2-3-18 Nakanoshima, Kita-ku, Osaka 530-8288

³Japan Science and Technology Agency (JST), CREST, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8603

(E-mail: ishihara@cc.nagoya-u.ac.jp)

A highly efficient and practical oxidative dearomatization of phenols using sodium hypochlorite pentahydrate as an inexpensive, strong oxidant is reported for the first time. The oxidation reactions proceeded very rapidly in the presence of water to give the desired products in excellent yields, and sodium chloride and water were the only by-products derived from the oxidant.

The oxidative dearomatization of phenols and their analogues has emerged as a promising tool for the synthesis of various natural products or biologically active compounds.¹ To date, several protocols have been developed for these fundamental reactions.¹ Here, we report a new practical protocol for the oxidative dearomatization of phenols using sodium hypochlorite pentahydrate as an oxidant.

Sodium hypochlorite pentahydrate (NaOC1•5H₂O) is a strong but inexpensive oxidizing agent, and sodium chloride and water are the only by-products derived from the oxidant. This solid oxidant offers several advantages over conventional aqueous sodium hypochlorite solution (ca. 10 wt %, pH ca. 13), including higher chlorine content (ca. 42%), lower pH upon dissolution (pH ca. 11), and high stability at lower temperatures.² Recently, Kirihara, Kimura, and colleagues reported a new variant of the 2,2,6,6-tetramethylpiperidinium oxy radical (TEMPO)-catalyzed oxidation of alcohols to the corresponding carbonyl compounds using NaOC1•5H₂O crystals, which did not require pH adjustment.^{3a} The same group has also used this solid oxidant for the oxidation and chlorination of thiols or disulfides to sulfonyl chloride in acetic acid.^{3b}

We have developed the hypervalent organoiodine(III)catalyzed enantioselective oxidative dearomatizations of phenol derivatives using meta-chloroperbenzoic acid (m-CPBA) as an oxidant.4,5 However, m-CPBA is expensive and potentially explosive, and is converted to meta-chlorobenzoic acid (m-CBA) as an organic waste. Therefore, inspired by the aforementioned works,³ we examined NaOCl·5H₂O as an alternative oxidant for organoiodine(III)-catalysis instead of m-CPBA (Scheme 1). The oxidative dearomatization of β -(2-hydroxyphenyl)carboxylic acid 1a using NaOCl·5H₂O, in the presence of a chiral iodoarene catalyst, and n-tetrabutylammonium hydrogen sulfate (n-Bu₄NHSO₄) as a phase-transfer catalyst gave the desired spirolactone 2a in good yield, but as a racemate (Scheme 1b). Interestingly, the oxidation of **1a** in the absence of organoiodine catalyst under identical conditions gave 2a in similar yield (Scheme 1c). To the best of our knowledge, this is the first example of the oxidative dearomatization of phenols using sodium hypochlorite pentahydrate as an oxidant.⁶

With these preliminary findings in hand, we next optimized the reaction conditions using β -(1-hydroxynaphthalen-2-yl)car-



Scheme 1. Preliminary investigation of NaOCl•5H₂O as an oxidant for the oxidative dearomatization of **1a**.

boxylic acid 1b as a model substrate, using commercially available NaOCl·5H₂O (Wako, pH ca. 11) (Table 1). First, we confirmed that the use of a phase-transfer catalyst in a nonpolar solvent, such as dichloromethane, at -20 °C gave **2b** in higher vield, as in the previous report (Entry 2 versus Entry 1).^{3a} A brief screening of the solvents revealed that polar solvents, such as acetonitrile and ethyl acetate, were superior to other solvents since NaOCl • 5H₂O dissolved much more easily in these solvents (Entries 3-6). Interestingly, the oxidation reaction proceeded efficiently in ethyl acetate even in the absence of Bu₄NHSO₄, and 2b was obtained quantitatively (Entry 7). The reaction with NaOC1·5H₂O (Kaneka, pH ca. 10.5) proceeded about two-times faster (Entry 8).⁷ Although the reason for the higher reactivity of the Kaneka reagent is not yet clear, it dissolved much more easily than the Wako reagent under the present conditions.⁸ Next, NaOC1.5H2O (Wako, pH ca. 11) and conventional aqueous NaOCl solution (ca. 10 wt %, pH ca. 13) were compared under identical conditions at 0 °C using a small amount of water (EtOAc/H₂O 79:1 v/v) (Entries 9 and 10).⁹ Interestingly, the reaction was faster and went to completion within 2 h for both oxidants in the presence of water as a cosolvent, which made the oxidant dissolve completely. However, the chemical yield of the desired spirolactone 2b was lower for conventional NaOCl due to the formation of by-products. These results suggested that the high chemoselectivity of NaOCl • 5H₂O might be due to its lower pH value. Finally, we found that the oxidation of 1b proceeded more rapidly in a 20:1 v/v mixed solvent of EtOAc and H₂O, and **2b** was obtained quantitatively within 5 min (Entry 11).

Table 1. NaOCl·5H₂O-mediated oxidative dearomatization of 1b^a

OH Ph 1b	CO ₂ H NaOCI n-Bu ₄ Nł CO ₂ H Solve	5H ₂ O (1 equiv) HSO ₄ (10 mol%)	
Entry	Solvent	Conditions	2b, Yield/% ^b
1°	CH ₂ Cl ₂	−20 °C, 9 h	17
2	CH_2Cl_2	−20 °C, 9 h	71
3	Toluene	−20 °C, 9 h	58
4	t-BuOMe	−20 °C, 9 h	73
5	CH ₃ CN	−20 °C, 8 h	97
6	EtOAc	−20 °C, 7 h	99
7 ^c	EtOAc	−20 °C, 9 h	98
8 ^{c,d}	EtOAc	−20 °C, 4 h	99
9°	EtOAc/H ₂ O ^e	0 °C, 2 h	92 ^g
10 ^{c,f}	EtOAc/H ₂ O ^e	0 °C, 2 h	74 ^{g,h}
11 ^{c,i}	EtOAc/H ₂ O ^j	0°C, 5 min	96

^aUnless otherwise noted, NaOCI•5H₂O (*Wako*) was used. ^bIsolated yields of **2b** are shown. ^cIn the absence of *n*-Bu₄NHSO₄. ^dNaOCI•5H₂O (*Kaneka*) was used. ^eEtOAc/H₂O (79:1 v/v). ^fConventional aqueous NaOCI solution (ca. 10 wt%, pH 13) was used. ^gEvaluated by NMR analysis. ^bHigh polarity side-products were generated. ⁱNaOCI•5H₂O (1.1 equiv) was used. ^jEtOAc/H₂O (20:1 v/v). For details, see the Supporting Information.



^aUnless otherwise noted, NaOCl•5H₂O (*Wako*) was used. The Method, reaction time, and isolated yield of **2** are shown. ^bNaOCl•5H₂O (*Kaneka*) was used. For details, see the Supporting Information.

We examined various β -(2-hydroxyphenyl)carboxylic acids 1 under optimized conditions (Table 2).¹⁰ In most cases, Method B (EtOAc/H₂O 20:1 v/v) was superior to Method A



Scheme 2. NaOCl·5H₂O-mediated oxidation of various phenols.

(EtOAc) with respect to reaction time and reproducibility. However, **Method A** was found to be optimal for the oxidation of phenols **1a** and **1c** and **4**-halo-substituted 1-naphthols **1d** and **1e** to give the corresponding spirolactones **2** in high yields. When these substrates were oxidized in the presence of water (**Method B**), complex product mixtures were obtained and the desired spirolactones **2** were obtained in only low yield. Nevertheless, here again, the use of Kaneka's oxidant for the oxidation of **1c** and **1d** under **Method A** accelerated the desired reaction. On the other hand, the oxidation of β -(1-hydroxynaphthalen-2-yl)carboxylic acids **1f**-**1k** and β -(2-hydroxynaphthalen-1-yl)carboxylic acid **1l** in the presence of water as a cosolvent (**Method B**) proceeded efficiently within 5 min to give the desired spirolactones **2** quantitatively in most cases.

The present oxidative dearomatization using NaOCl·5H₂O is not limited to only the spirolactonization of β -(2-hydroxy-phenyl)carboxylic acids 1 (Scheme 2). The oxidation of 3-(1-hydroxynaphthalen-2-yl)propanol 3 and amide 5 gave the corresponding spiroether 4 and spiroamide 6 in high yields, respectively. Moreover, the oxidation of 2,4,6-trimethylphenol (7) gave the corresponding *para*-quinol 8 in excellent yield. Furthermore, the clean oxidation of 1,2- and 1,4-hydroquinones, 9 and 11, gave the corresponding quinones 10 and 12 in excellent yields, respectively.

In summary, we have serendipitously found a new oxidative dearomatization protocol using NaOCl \cdot 5H₂O as an inexpensive and atom-economical oxidant. This method is highly practical since the oxidation reactions proceed very rapidly in the presence of water to give the desired products in excellent

yields. Furthermore, this protocol can be applied to the oxidation of various phenols.

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Supporting Information is available electronically on J-STAGE.

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- 7 NaOCl•5H₂O (*Kaneka*, pH ca. 10.5) is not commercially available yet, but was provided by Kaneka Corporation.
- 8 Although the pH value of NaOCl•5H₂O (*Kaneka*, pH ca. 10.5) upon dissolution is lower than that of NaOCl•5H₂O (*Wako*, pH ca. 11), the influence of the pH on reactivity is not yet clear.
- 9 The amount of water used in EtOAc/H₂O (79:1 v/v) was adjusted to the water contents of conventional aqueous NaOCl solution (ca. 10 wt %).
- 10 For details, see the Supporting Information.