Accepted Manuscript

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PII: S0040-4020(16)30194-6

DOI: 10.1016/j.tet.2016.03.064

Reference: TET 27604

To appear in: *Tetrahedron*

Received Date: 1 December 2015

Revised Date: 18 March 2016

Accepted Date: 20 March 2016

Please cite this article as: Okada T, Asawa T, Sugiyama Y, Iwai T, Kirihara M, Kimura Y, Sodium hypochlorite pentahydrate (NaOCI·5H₂O) crystals; An effective re-oxidant for TEMPO oxidation, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.03.064.

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Graphical Abstract



Sodium hypochlorite pentahydrate (NaOCl·5H₂O) crystals; An effective re-oxidant for TEMPO oxidation

Tomohide Okada, ^a Tomotake Asawa, ^a Yukihiro Sugiyama, ^b Toshiaki Iwai, ^c Masayuki Kirihara, ^c.* Yoshikazu Kimura^d

^aR&D Department of Chemicals, Nippon Light Metal Company, Ltd., Kambara, Shimizu-ku, Shizuoka 421-3203, Japan
 ^bMarket Development Department, Nippon Light Metal Company, Ltd., Higashi-shinagawa, Shinagawa-ku, Tokyo 140-8628, Japan
 ^cDepartment of Materials and Life Science, Shizuoka Institute of Science and Technology, Fukuroi, Shizuoka 437-8555[.] Japan
 ^dResearch and Development Department, Iharanikkei Chemical Industry Co. Ltd., Kambara, Shimizu-ku, Shizuoka 421-3203, Japan
 *kirihara@ms.sist.ac.jp

ABSTRACT

The novel oxidant of sodium hypochlorite pentahydrate (NaOCl·5H₂O), which is now available for industrial and laboratory use has several advantageous properties. The crystalline material has 44% of NaOCl, contains minimal sodium hydroxide and sodium chloride, and the aqueous solution indicates pH 11-12. Herein, NaOCl·5H₂O crystals are examined for use as an oxidant for primary and secondary alcohols, with or without nitroxyl radicals, in the presence or absence of phase-transfer catalysts. The pentahydrate crystals alone (without nitroxyl radicals) demonstrate a powerful oxidizing ability, converting secondary alcohols to the corresponding ketones. In the presence of **TEMPO** (2,2,6,6-tetramethylpiperidine 1-oxyl) or 1-Me-AZADO (1-methyl-2-azaadamantane N-oxy radical), sterically hindered secondary alcohols are oxidized without pH adjustment. A proposed mechanism for the oxidation is discussed.

Keywords

TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl); 1-Me-AZADO (1-methyl-2-azaadamantane N-oxyl); sodium hypochlorite pentahydrate (NaOCl·5H₂O) crystals; *l*-menthol; oxidation; aldehyde; ketone

1. Introduction

Oxidations of primary and secondary alcohols to the corresponding carbonyl compounds have been among the most important reactions in organic synthesis; and therefore, a large number of methods have been reported.¹ However, most of the existing reactions have serious problems such as using toxic or explosive oxidants and producing large amounts of undesirable waste after the reactions. To alleviate these drawbacks, catalytic oxidations using molecular oxygen (O_2) ,² diluted aqueous hydrogen peroxide (H_2O_2) ,³ or sodium hypochlorite $(NaOCl)^4$ as a co-oxidant have been

developed, because the post-oxidation waste is harmless, nontoxic water (H₂O) and/or sodium chloride (NaCl). Nitroxyl radical-catalyzed oxidation using aqueous NaOCl as a co-oxidant with TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl)⁵ or AZADO (2-azaadamantane *N*-oxyl)⁶ compounds is such valuable and useful method, because this oxidation is metal-free, NaOCl is inexpensive, and commercial aqueous solutions are non-explosive. For the oxidation of sterically hindered secondary alcohols, TEMPO is not an effective catalyst, and AZADO is required to obtain the desired alcohols in high yields.⁶

Although this method has been frequently applied in organic synthesis, there are some drawbacks for using commercial aqueous NaOCl. The process has inherently poor volume efficiency because the concentration of conventional aqueous NaOCl solution is only 8~13% (higher concentrations of the NaOCl solution are known to be unstable).⁷ Moreover, at the pH of conventional NaOCl (~13; as adjusted with free NaOH to maintain stability) reactions are very slow, and the pH must be lowered in order to speed up the rate.^{5b} In nitroxyl radical-catalyzed oxidations, the aqueous NaOCl must be adjusted to pH 8-9 with aqueous sodium hydrogen carbonate, resulting in an event larger reaction media volume.

We recently developed a new manufacturing process for sodium hypochlorite pentahydrate (NaOCl·5H₂O) crystals (Figure 1).⁸ Notable features of NaOCl·5H₂O include: (1) NaOCl content is about 44 wt% (the followings express as %; 3-4 times that available from conventional NaOCl solution), (2) simple stoichiometric calculations and easy, accurate mass determination due to the crystalline nature of the compound, (3) the pH of aqueous solutions is ~11-12 since the solution contains less than 0.04~0.08% NaOH, and (4) the crystals are stable for 1 year below 7 °C. Currently, NaOCl·5H₂O crystals are commercially available from several companies including us.⁹



| mp | 25-27 °C |
|------|----------------------------------|
| NaOH | 0.04~0.08% |
| NaCl | 0.1~0. <mark>5</mark> % |
| pН | 11-12 (for the aqueous solution) |
| | |

Figure 1 NaOCl·5H₂O crystals

Recently we have reported the TEMPO-catalyzed oxidation of alcohols with $NaOCl \cdot 5H_2O$ crystals as a communication.¹⁰ In the presence of TEMPO or

1-Me-AZADO (1-methyl-2-azaadamantane N-oxyl), several alcohols (including sterically hindered secondary alcohols) can be oxidized without pH adjustment, and several advantages were found over conventional oxidation procedure using aqueous NaOCl. In this article, the detailed manufacturing process for production of NaOCl·5H₂O and its use in the oxidation of alcohols are described.

2. Commercial synthesis of sodium hypochlorite pentahydrate (NaOCl·5H₂O) crystals

Several preparation methods for sodium hypochlorite pentahydrate have been proposed hitherto. Almost of them involve preparing a solution or slurry of sodium hypochlorite pentahydrate, which is then diluted to give a 13% NaOCl solution containing less sodium chloride.¹¹ However an industrial-scale process has remained elusive. We have recently established an original method for manufacturing sodium hypochlorite pentahydrate crystals (Scheme 1) and have been supplying this product to the market. Chlorine gas is added to a 45~48% of NaOH solution to prepare a high concentration NaOCl solution. After precipitated NaCl is removed by filtration, the filtrate is cooled to around 15 °C to precipitate NaOCl·5H₂O crystals, which are collected by centrifugal filtration. Analysis shows that the product is contained with only 0.1~0.5% of NaCl and 0.04~0.08% of NaOH. That is, the crystals prepared using this new method contain less free NaOH as well as less NaCl than the product prepared using other methods. In addition, an aqueous solution of this product has more ideal pH of 11-12 compared to pH 13 conventional aqueous 13% NaOCl solution (and at lower pH, oxidations are faster; vide infra). Furthermore, these NaOCl·5H₂O crystals, which contain 44% of NaOCl, are stable for 1 year at 7 °C. For example, crystals of NaOCl·5H₂O (44.2%) became 43.7% after 360 days, and this means that almost 99% of NaOCI was unchanged. This is in sharp contrast to a conventional aqueous NaOCI solution, whose concentration gradually drops, even at 7 °C. A conventional aqueous 13.6% NaOCl solution became 11.3% NaOCl solution. This means that the concentration of NaOCl became 83% of the original solution. Thus, these NaOCl 5H₂O crystals are ideally suited for use as an oxidant in organic synthesis.



Scheme 1 Process for preparation of NaOCl·5H₂O crystals

| Table 1 Stability of NaOCl·5H2O crystals and conventional aq. NaOCl | |
|---|--|
| | |

| | Original | Concentration of 1 yr. later |
|-------------------------|---------------|--|
| | concentration | $\mathbf{Q}^{(1)}$ |
| NaOCl·5H ₂ O | 44.2% | 43.7% ^a (98.9% of the original concentration) |
| aq. NaOCl | 13.6% | 11.3% ^b (83.1% of the original concentration) |
| | h | |

^a 360 days later. ^b 361 days later.

3. Oxidation of alcohols with NaOCl·5H₂O

As is discussed above, the TEMPO-catalyzed oxidation of alcohols with aqueous NaOCl is one of the most attractive methods for the preparation of aldehydes and ketones. Therefore, the reaction of alcohols with NaOCl \cdot 5H₂O in the presence of nitroxyl radicals (TEMPO or AZADO) was examined.

3-1. Oxidation of 2-octanol with NaOCl·5H₂O crystals: small-scale experiments to optimize reaction conditions

In order to examine the oxidative ability of the NaOCl·5H₂O crystals, oxidation of 2-octanol (1) was performed under a variety of reaction conditions (Table 2). First, 10 mmol of 1 was stirred with 1.2 equiv. of NaOCl·5H₂O crystals in the presence of tetrabutylammonium hydrogensulfate (Bu₄NHSO₄; 5 mol%) in dichloromethane at 5 °C for 24 h (without use of TEMPO). GC analysis using an internal standard revealed the product 2-octanone (2) in 78% yield. (run 1) A control experiment with conventional 13% of NaOCl solution (1.2 equiv.) gave 2 in only 9% yield. (run 2). Next, catalytic ability of TEMPO was examined under the same conditions. Addition of TEMPO (0.1 mol%) resulted in a dramatic acceleration for the oxidation of 1, giving 2 in 97% yield within 1 h. (run 3). The quantity of TEMPO was successfully limited to 0.1 mol% (run 6). Notably, TEMPO showed no catalytic acceleration with conventional NaOCl solution (run 4). All reactions in Table 1 were conducted with NaOCl·5H₂O crystals or aqueous NaOCl solution without pH adjustment.

Then, catalytic ability of 1-Me-AZADO was examined, and 1-Me-AZADO was also effective for the oxidation of **1** with NaOCl \cdot 5H₂O crystals in the presence of the phase transfer catalyst (Bu₄NHSO₄) (run 7). Interestingly, 1-Me-AZADO exhibited catalytic

effect for conventional NaOCl solution, however the reaction rate was slow (run 8).

| | OH 4 1 | NaOCI-5H ₂ O + or aq. NaOCI 1.2 equiv. | Bu ₄ NHSO ₄ 5 mol% nitroxyl radica in CH ₂ Cl ₂ 5 ° | | | 4 2 | ° | 2 |
|-----|----------------------|---|--|----------|----------|--------------|-----------------------------------|---------|
| Run | nitroxyl radical | NaOCl·5H ₂ O crystals (equiv.) | aq. NaOCl solution ^a (equiv.) | 0.5h | Yi 1h | eld of 2h | 5 2 (%) ^b 3h | 24h |
| 1 | | 1.2 | | <u>_</u> | 3 | 22 | 28 | 78 |
| 2 | | | 1.2 (13.2%) ^c | | 1 | 1 | 2 | 9(27h) |
| 3 | TEMPO 1 mol% | 1.2 | - | 94 | 97 | | | |
| 4 | TEMPO | | 1.2 (13.5%) ^c | | 1 | 2 | 2 | 11(22h) |
| 5 | TEMPO 0.5 mol% | 1.2 | | 87 | 99 | | | |
| 6 | TEMPO 0.1 mol% | 1.2 | | | 79 | 96 | 99 | |
| 7 | 1-Me-AZADO 1 mol% | 1.2 | <i>y</i> | | 100 | | | |
| 8 | 1-Me-AZADO 1 mol% | | 1.2 (13.2%) ^c | | 14 | 29 | 45 | 99 |

 Table 2
 Comparison of NaOCl·5H₂O crystals and conventional aqueous NaOCl

^a aq. NaOCl: conventional aqueous NaOCl (ca. 13% solution) containing NaOH and NaCl

^b Yields were determined by GC using an internal standard method.

^c Concentrations were determined via titrations.

Encouraged by these results, additional experimental parameters were examined (Table 3). The efficacy of quaternary ammonium salts as phase-transfer catalysts in the presence of 1 mol% (0.01 equiv.) of TEMPO was evaluated. The use of Bu_4NBr or Bu_4NCl instead of Bu_4NHSO_4 afforded poor results, even with the use of $NaOCl \cdot 5H_2O$ crystals (runs 3 and 4). Since Bu_4NHSO_4 is more acidic than Bu_4NBr and Bu_4NCl , it can be neutralize free NaOH in the NaOCl $\cdot 5H_2O$ crystals. The rest of the Bu_4NHSO_4 appears to react with NaOCl to form HOCl. Actually, as shown in Table 4, addition of Bu_4NHSO_4 to 13% aq. NaOCl (prepared from NaOCl $\cdot 5H_2O$) dramatically reduced the pH value (11.3 to 9.6). On the other hand, addition of Bu_4NBr or Bu_4NCl did not affect

the pH values of the aqueous solution. Combination of Bu_4NCl and $NaHSO_4 \cdot H_2O$ with a small amount of water, which exhibited a catalytic acceleration (run 6), supports this theory. Surprisingly, the use of 5 mol% of $NaHSO_4 \cdot H_2O$ and a small amount of water in the absence of a phase-transfer catalyst was found to give an excellent result (run 7). This means that the oxidation reaction involves minimal anion-transfer, but rather, HOCl is the real oxidant. (Scheme 2)

| Tabl | Cable 3 Effect for quaternaly annonium salts and acid in the presence of TEMPO ^a | | | | | | |
|------|---|---|---|--------------------|-------------|--------------|---------------------------|
| / | | + NaOCI·5H ₂ O 1.2 equiv. | $Bu_4NX 5 mol$ TEMPO 1 mo in $CH_2Cl_2 5$ | % → ⊳l% ℃ | | | 2 |
| Ru | n X | Additive | 0.5h | 1h | Yield 2h | d of 2 3h | 2 (%) ^b 21h |
| 1 | HSO ₄ | | 94 | 97 | | | |
| 2 | $HSO_4 (0.5 mol)$ | %) | | 40 | 73 | 98 | |
| 3 | Br | _ | | 6 | 14 | 25 | 87(22h) |
| 4 | Cl | | | 3 | 10 | 10 | 73 |
| 5 | Cl | NaHSO ₄ ·H ₂ O 5 m | nol% | 19 | 25 | | 69 |
| 6 | Cl | $NaHSO_4 \cdot H_2O 5 m$ $+ H_2O 0.2 mL$ | iol% 97 | 99 | | | |
| 7 | - | NaHSO ₄ ·H ₂ O 5 n + H ₂ O 0.2 mL | nol% 46 | 98 | | | |

^a **1** (10 mmol), NaOCl·5H₂O (12 mmol), Bu₄NX (0.5 mmol), TEMPO (0.1 mmol), CH₂Cl₂ (30 mL) ^b Yields were determined by GC using an internal standard method.

| with a phase transfer | eataryst | |
|----------------------------|--|------|
| 13% aq. NaOCl [*] | Phase Transfer | pН |
| 50 mmol | none | 11.3 |
| 50 mmol | Bu ₄ NHSO ₄ (2.5 mmol) | 9.6 |
| 50 mmol | Bu ₄ NBr (2.5 mmol) | 11.4 |
| 50 mmol | Bu ₄ NCl (2.5 mmol) | 11.2 |

Table 4 pH of 13% aq. NaOCl (prepared from NaOCl· $5H_2O$)with a phase transfer catalyst

* prepared from NaOCl·5H2O and ion-exchanged water

Thus, the role of Bu_4NHSO_4 as an acid is both neutralize the free NaOH and to react with NaOCl to form HOCl, which again, is likely the genuine oxidant. As the oxidation proceeds, HCl is generated, which reacts with NaOCl to form additional HOCl (Scheme 2). If HOCl is the true oxidant, a quaternary ammonium salt as a phase-transfer catalyst for anion transfer is not necessary. This is supported by the reaction of 2-octanol with NaOCl·5H₂O/TEMPO in the presence of NaHSO₄ instead of Bu_4NHSO_4 affording a comparable yield of 2-octanone (Table 2, run 7). NaHSO₄ is also an acid which acts to neutralize the free NaOH in NaOCl·5H₂O.



 $Scheme 2 \quad \mbox{Proposed mechanism for the TEMPO-catalyzed oxidation of alcohols with $NaOCl{\cdot}5H_2O$ }$

Next, the relationship between the oxidation rate and the concentrations of NaOCl (prepared from NaOCl·5H₂O crystals and water) was evaluated. The results are shown in Figure 2. Almost no concentration effect is observed at 13, 20, and 31% of NaOCl·5H₂O solution. However, the use of the solid NaOCl·5H₂O crystals speeds up the oxidation dramatically. The precise reason is not clear, but it appears that a high concentration of the primary oxidant HOCl forms at the surface of the crystalline solid.



Figure 2 Reaction* of **1** with several concentration of aqueous NaOCl prepared from NaOCl·5H₂O crystals and water ; NaOCl·5H₂O crystals (\circ); aq. 31% NaOCl (Δ); aq. 20% NaOCl (\Box); aq. 13% NaOCl (\diamond) ; conventional aq. 13% NaOCl (\times).

* 1 (10 mmol), NaOCl·5H₂O (12 mmol), Bu₄NHSO₄ (0.5 mmol), TEMPO (0.1 mmol), CH₂Cl₂ (30 mL), and appropriate water.

For large scale syntheses, the use of dichloromethane should be avoided for environmental reasons. Thus, the small-scale (10 mmol) oxidation was examined in various solvents (Table 5). Ethyl acetate was found to be as good reaction solvent as dichloromethane, and toluene, acetic acid and trifluoromethylbenzene were nearly as

| | NaOCI-5 1.2 equ 5 mol% Bu 1 mol% TE solvent (3 | 5H ₂ O uiv. u ₄ NH EMP(50 mL | SO4 | \downarrow | 2 | ° |
|---|--|---|----------------|----------------------|-----------------------|---|
| Solvent | Temperature (°C) | 9 1h | í ield o 2h | of 2 (% 3h | 5) ^b 4h | _ |
| CH ₂ Cl ₂ | 5 | 97 | | | | |
| EtOAc | 5 | 61 | 97 | | - | |
| C ₆ H ₅ CH ₃ | 5 | 38 | 90 | 98 | G | |
| C ₆ H ₅ CF ₃ | 5 | 30 | 55 | 87 | 95 | |
| CH ₃ CN | 5 | 53 | 54 | 53 | 52 | |
| AcOH | rt | 18 | 78 | 90 | 90 | |

effective, albeit with a slightly extended reaction time.

 Table 5
 Results for oxidation of 1 in several solvents^a

^a **1** (10 mmol)

^b Yields were determined by GC using an internal standard

To further evaluate this, a large-scale (26.0 g of 1, 0.2 mol) example of the oxidation of 1 was attempted using ethyl acetate as the solvent (Scheme 3). To be maintained the reaction temperature, 1 was added dropwise for 15 min to a mixture of NaOCl·5H₂O crystals, TEMPO, and Bu₄NHSO₄ in ethyl acetate being controlled below 20 °C in an ice-water bath, and then continued to be stirred for 45 min within 0~20 °C. The reaction mixture was quenched with aqueous Na₂SO₃ followed by extraction with EtOAc, washed with water, and dried over MgSO₄. Distillation of the residue gave 2 in 91% yield.



Scheme 3 Large scale oxidation of 1 in ethyl acetate.

The 0.10 mol scaled oxidation was also demonstrated *without solvent via* two methods using NaHSO₄ instead of Bu₄NHSO₄. In method A, **1** was added dropwise into a mixture of NaOCl·5H₂O and water, with catalytic amounts of NaHSO₄·H₂O and TEMPO in an ice-water bath. In Method B, 32% NaOCl prepared from NaOCl·5H₂O and water was added dropwise to a mixture of **1**, NaHSO₄·H₂O, and TEMPO in an ice-water bath. Both methods gave high yields of **2** within 1 h (Scheme 4).



Scheme 4 Solvent free oxidation of **1** catalyzed by $NaHSO_4 \cdot H_2O$.

3-2. TEMPO-catalyzed oxidation of several alcohols with NaOCl·5H₂O

The optimized TEMPO-catalyzed oxidation with NaOCl·5H₂O was applied to various primary and secondary alcohols. Table 4 shows the results for primary alcohols (10 mmol). Use of an equimolar amount of NaOCl·5H₂O gave the corresponding aldehydes in good yield. The oxidations of secondary alcohols are summarized in Table 5. Both TEMPO- and 1-Me-AZADO-catalyzed oxidations of sterically hindered secondary alcohols gave poor yields of the ketones with the conventional aqueous NaOCl without pH adjustment. In contrast, this optimized method using NaOCl·5H₂O, gives encouraging results with TEMPO, even absent pH adjustment.

| \mathbf{P} + N | aOCI•5H₂O | 5 mol% E 1 mol% | Bu₄NHSO₄ TEMPO | 0 | |
|---------------------|-------------------------------------|---|-------------------|------------------|---|
| K OH | | CH ₂ C | | R | Н |
| Substrate | NaOCl·5H ₂ O (equiv.) | CH ₂ Cl ₂ (mL) | Temp. (°C) | Time (h) | Yield (%) ^b |
| ₩ ₅ ОН | 1.1 | 30 | 5 | I | 91 |
| ОН | 1.1 | 30 | 5 | 1 | 99 |
| МеО | 1.2 | 30 | 5 | 2 | 96 |
| ООН | 1.2 1.2 | 30 15 | 5 15 | 6 1 | 96 97 |
| ОН | 1.4 1.4 1.2 | 30 30 30 30 | 5 5 5 5 | 4 3 3 2 | 67 82 ^c 87 ^d 85 ^d |
| СІОН | 1.1 | 30 | 5 | 0.5 | 93 |
| O ₂ N OH | 1.1 | 30 | 5 | 0.5 | 98 |
| OH | 1.1 | 30 | 5 | 0.5 | 94 |
| ОН | 1.4 | 30 | 5 | 3 | 79 |

 Table 6
 Selective syntheses of aldehydes from primary alcohols^a

 5 mol% Bu₄NHSO₄

^a Substrate : 10 mmol

^b Yields were determined by GC using an internal method

^c TEMPO 10 mol%

^d 1-Me-AZADO was used instead of TEMPO

| ОН | + NaOCl•5H₂C | 5 mol 1 mol% | % Bu₄NHS nitroxyl rac | O₄ dical ➤ | 0 | | |
|----------------------|--|--|---------------------------------|---|--|-----------------------------------|---|
| R^1 R^2 | | CI | H_2CI_2 | R | 1 | R ² | Y |
| Substrate | nitroxyl Na radical | OCl·5H ₂ C (equiv.) | aq. NaOCl (equiv.) ^b | CH ₂ Cl ₂ (mL) | Temp. (°C) | Time (h) | Yield (%) ^c |
| OH H ₄ | TEMPO | 1.2 | | 10 | 5 | 0.5 | (95) |
| OH | TEMPO TEMPO | 1.2 1.2 | | 30 10 | 5 15 | 1 0.67 | 97 (96) |
| | TEMPO TEMPO TEMPO TEMPO 1-Me-AZADO | 1.2 1.6 1.6 1.4 1.4 1.4 | 1.2 | 30 30 10 8 10 30 30 | 5 5 15 15 rt rt rt rt | 24 24 2.25 4 4 0.5 | 98 2 96 (92) 95 88 98 |
| OH | TEMPO 1-Me-AZADO | 1.8 1.4 | | 10 30 | 15 rt | 6 0.5 | 88 95 |

 Table 7
 Results for the oxidation of secondary alcohols^a

^a All the reactions were performed without pH adjustment for NaOCl. See experimental section

^b aq NaOCl: 12.1 wt% of conventional aqueous solution

^c Yields were determined by GC using an internal standard method.

Numbers in parentheses refer to isolated yields.

3-3. Oxidation of an equimolar mixture of 1-octanol and 2-octanol.

In order to be elucidated the mechanism for the oxidation of alcohols with NaOCl·5H₂O, a mixture of 1-octanol (5 mmol) and 2-octanol (5 mmol) was oxidized in dichloromethane with NaOCl·5H₂O (5 mmol) in the presence of TEMPO (or 4-MeO-TEMPO) (0.1 mmol) and Bu₄NHSO₄ (0.5 mmol) at 5 °C (Table 8). The reaction mixture was analyzed by GC, and found that octanal was produced from 1-octanol in 47% yield and 2-octanone was provided from 2-octanol in 44% yield after 0.5 h, in the case of TEMPO. The 4-MeO-TEMPO catalyzed reaction exhibited the similar result. Thus, the oxidation rates for primary and secondary alcohols under these conditions are not large different.

On the contrast, oxidation of an equimolar mixture of 1-nonanol and 2-nonanol with aqueous NaOCl catalyzed by 4-MeO-TEMPO was reported to afford 90% of nonanal and 10% of 2-nonanone in a literature.^{5b}

Table 8 Oxidation of an equimolar mixture of 1-octanoland 2-octanol with NaOCl· $5H_2O$ catalyzed by a nitroxylradical.



* Yields were determined by GC using an internal standard method.

4. Mechanism

A number of mechanistic studies have been published for TEMPO-catalyzed alcohol oxidations. The explanation involves key intermediate **B**, as shown in Scheme 6.¹² In general to be said, the TEMPO-catalyzed oxidation of bulky secondary alcohols gives poor results due to steric hindrance caused by the four methyl groups neighboring the nitroxyl center preventing the formation of the intermediate **B**.



Scheme 5 Reported mechanism¹² under basic conditions

For the oxidation of bulky secondary alcohols such as *l*-menthol, AZADO and the related nitroxyl catalysts developed by Iwabuchi and co-workers, which have less steric hindrance around the nitroxyl radical, are required to obtain the desired ketones. Since it has been shown in Table 7, however, bulky secondary alcohols can be oxidized smoothly to the corresponding ketones with NaOCl·5H₂O/TEMPO, an alternative mechanism must be at work.

To be cleared the mechanism for alcohol oxidation with NaOCl·5H₂O, it must acknowledge the following: 1) oxidation rates for primary and secondary alcohols are almost equal (Table 8), 2) a benzyl alcohol having an electron withdrawing group

(4-nitrobenzyl alcohol) is oxidized much faster than that one having an electron donating group (4-methoxybenzyl alcohol) (Table 6), and 3) sterically hindered secondary alcohols having bulky groups are successfully oxidized in the presence of TEMPO (Table 7).

The Scheme 5 mechanism has been proposed involving weakly basic conditions.^{6,12} However, the oxidation of alcohols with NaOCl·5H₂O/TEMPO/Bu₄NHSO₄ occurs under acidic to neutral conditions (Scheme 2 *vide supra*). Bobbitt *et.al.* proposed an alternative mechanism for the TEMPO oxidation of alcohols involving intermediate **C** with hydride transfer under neutral or acidic conditions (Scheme 6).^{12e,f} Taking intermediate **C** into account, steric hindrance of bulky secondary alcohols is likely relaxed, permitting the oxidation to proceed. The interaction between the lone pair of nitrogen atom and the hydrogen atom of hydroxyl group in the alcohol plays an important role of this reaction mechanism. Therefore, more acidic alcohols (such as 4-nitrobenzyl alcohol having an electron withdrawing group) reacted faster than less acidic alcohols (such as 4-methoxybenzyl alcohols having an electron donating group) did. These features suggest that the oxidation using NaOCl·5H₂O/TEMPO/Bu₄NHSO involves intermediate **C** as shown Scheme 6.



Scheme 6 Proposed mechanism under neutral or acidic conditions

5. Conclusions

In this articles, a novel manufacturing process for $NaOCl \cdot 5H_2O$ and the application of this reagent in the oxidation of alcohols were explored. The ready availability, high volume efficiency, wide applicability, and high activity make this a very attractive oxidation reagent and method for laboratory and industrial use.

6. Experimental

All melting points were determined with a Buchi melting point apparatus (model B-545) and are uncorrected. ¹NMR spectra were recorded with a JEOL, JNM-EX400 spectrometer in CDCl₃ using tetramethylsilane (TMS) as a reference. GC-mass spectra were recorded with a Shimadzu GCMS-QP2010 SE using a DB-5 column (0.32 mm ID \times 30 m, df=0.50µm) or a Shimadzu GC-17A/GCMS-QP5050A using an InertCap1 column (0.25 mm ID \times 60 m, df=0.4 µm). GC analyses were run on a Shimadzu GC-2014 instrument with flame-ionization detectors, equipped with an NB-1 (0.25 mm \times 60 m, df=0.4 µm) GC column using helium as the carrier gas.

Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification.

The sodium hypochlorite pentahydrate (NaOCl \cdot 5H₂O) crystals were manufactured by the Nippon Light Metal Co. Ltd. using the process developed by us. The reagent can be purchased from Wako Pure Chemical Industries, Ltd., Tokyo Chemical Industry Co. Ltd. Junsei Chemical Co. Ltd., TCI America, and TCI Europe for laboratory use.

Manufacturing process for sodium hypochlorite pentahydrate (NaOCl·5H₂O) crystals (Method of Nippon Light Metal Co. Ltd.)

Chlorine gas (193 kg/h, 2.7 kmol/h) was added to a 45% NaOH solution (500 kg/h, 5.6 kmol/h) at 25~30°C for 6 h average residence time to give sodium hypochlorite. Precipitated sodium chloride crystals (151 kg/h, 2.6 kmol/h) were separated from the slurry, giving a sodium hypochlorite solution (542 kg/h, NaOCI: 30.8%). After the sodium hypochlorite solution was cooled to 12° C, seed crystals of NaOCI·5H₂O (170 g) were added, and the mixture was stirred for 13 h average residence time. The precipitated NaOCI·5H₂O crystals (172 kg/h) were collected by centrifugal filtration. Analysis shows the product contains 0.1~0.5% of NaCl and 0.04~0.08% of NaOH (representative values).

Analytical methods.

Sodium hypochlorite concentration:

Ion-exchanged water (20 mL) was added to ca. 0.1 g weighed of NaOCl·5H₂O crystals in a conical beaker. Two grams of potassium iodide and 10 mL of 50% aqueous acetic acid were added to the stirred solution. Iodine liberated from the solution was titrated with 0.1 M sodium thiosulfate for volumetric analysis (the liquid goes from brown to colorless).

Free sodium chloride:

Ion-exchanged water (2 mL) was added to ca. 0.1 g of NaOCl·5H₂O crystals in a weighed in a conical beaker. Aqueous ~30% of hydrogen peroxide was added to the stirred solution until bubbling ceased, and ion-exchanged water (20 mL) was added. A few drops of phenolphthalein solution were added to the colorless solution, and if the color of the solution became pink (basic), nitric acid (2%) was added until it become colorless. To the mixture was added 0.2 mL of potassium chromate (5%), and the solution was titrated with 0.1 M of silver nitrate solution for volumetric analysis (the solution turned slightly orange from yellow).

Free [NaCl] = [total chlorine concentration] titrated above – [sodium hypochlorite concentration]

Free sodium hydroxide:

Ion-exchanged water (20 mL) was added to 10 g of NaOCl·5H₂O crystals weighed in conical beaker. About 30% of hydrogen peroxide was added to the stirred solution until bubbling ceased. A few drops of phenolphthalein solution were added to the solution, which was then titrated with 0.1 M hydrochloric acid for volumetric analysis (the color of the solution went from pink to colorless).

Conventional aqueous NaOCl solution manufactured by the Nippon Light Metal Co. Ltd.

Representative values;

NaOCl 12.6~13.6%: NaCl 12~13%: NaOH 0.6~0.8%: pH was 13, determined using a pH meter.

An aqueous 13% NaOCl solution prepared from NaOCl·5H₂O:

An aqueous 13% NaOCl (110.9 g) was prepared from NaOCl·5H₂O (32.7 g) and

ion-exchanged water (78.2 g). The pH was 11.3, determined using a pH meter.

Determination of pH for NaOCl·5H₂O with tetrabutylannmonium salts:

 Bu_4NHSO_4 , Bu_4NBr , or Bu_4NCl (2.5 mmol) was added to 13% NaOCl (28.5 g, 50 mmol) prepared from NaOCl·5H₂O and ion-exchanged water. The pH of the resulting solutions were determined using a pH meter.

Typical example for small scale oxidation of 2-octanol (Tables 2, run 3):

NaOCl·5H₂O crystals (1.97 g, 12.0 mmol) were added in one portion to a mixture of Bu₄NHSO₄ (0.170 g, 0.50 mmol), TEMPO (15.5 mg, 0.10 mmol), and **1** (1.30 g, 10.0 mmol) in dichloromethane (30 mL) at 5 °C. After stirring for 1 h, exact 0.5 mL of the organic layer and 0.03 g weighed of 4-chloro-trifluoromethylbenzene (PCBTF) as an internal standard were added to 1 mL of CH₂Cl₂. Yield of the product **2** (97%) was determined by GC. GCMS analysis of the product was identical to an authentic sample. GCMS: m/z = 128 (M⁺, relative intensity 3%), 113 (3%), 85 (3%), 71(6%), 58(54%), 43 (base peak)

Small scale oxidation of primary alcohols for Table 6: (general procedure)

NaOCl·5H₂O crystals (11.0~14.0 mmol) were added in one portion to a mixture of Bu_4NHSO_4 (0.170 g, 0.50 mmol), TEMPO (15.6 g, 0.10 mmol), alcohols (10.0 mmol), and 0.2 g of PCBTF (an internal standard) in dichloromethane (15 or 30 mL) at 5 or 15 °C. After stirring for an appropriate time, 0.5 mL of the organic layer was added to 1 mL of CH₂Cl₂ for GC analysis. GCMS analyses of the products were identical with authentic samples.

Oxidation of 1-octanol

NaOCl·5H₂O crystals (1.81 g, 11.0 mmol) were added in one portion to a mixture of Bu₄NHSO₄ (0.170g, 0.50 mmol), TEMPO (15.6 mg, 0.10 mmol), 1-octanol (1.31 g, 10.1 mmol), in dichloromethane (30 mL) at 5°C. After stirring for 1 h, 0.5 mL of the organic layer and 0.03 g weighed of PCBTF as an internal standard were added to 2 mL of CH₂Cl₂. Octanal was determined in 91% yield for GC analysis. GCMS analysis of the product was identical with authentic sample. GCMS: m/z = 128 (M⁺, relative intensity 0.2%), 110 (5%), 100 (10%), 84(61%), 69(31%), 56 (48%), 43 (base peak), 41 (99%)

Oxidation of benzyl alcohol

NaOCl· $5H_2O$ crystals (1.81 g, 11.0 mmol) were added in one portion to a mixture of Bu₄NHSO₄ (0.170g, 0.50 mmol), TEMPO (15.6 mg, 0.10 mmol), benzyl alcohol (1.10 g,

10.2 mmol), in dichloromethane (30 mL) at 5°C. After stirring for 1 h, 0.5 mL of the organic layer and 0.03 g weighed of 1, 3-dichlorobenzene as an internal standard were added to 2 mL of CH₂Cl₂. Benzaldehyde was determined in 99% yield for GC analysis. GCMS analysis of the product was identical with authentic sample. GCMS: m/z = 106 (M⁺, relative intensity 74%), 105 (74%), 85 (0.4%), 77(base peak), 63(2%), 51 (27%), 39 (8%)

Oxidation of 4-methoxybenzyl alcohol

4-Methoxybenzaldehyde was prepared from 4-methoxybenzyl alcohol in 96% yield. GCMS: m/z = 136 (M⁺, relative intensity 72%), 135 (base peak), 119 (1%), 107(25%), 92(20%), 77 (31%), 65 (11%), 51 (14%), 39 (23%)

Oxidation of piperonyl alcohol

1,3-Benzodioxole-5-carbaldehyde (piperonal) was prepared from 1,3-benzodioxole -5-ylmethanol (piperonyl alcohol), under a variety of different conditions as described in Table 4, in 96~97% yield. GCMS: m/z = 150 (M⁺, relative intensity 92%), 149 (base peak), 121 (32%), 91(10%), 77(3%), 65 (16%), 63 (26%), 53 (7%), 39 (7%)

Oxidation of cinnamyl alcohol

Cinnamaldehyde was prepared from cinnamyl alcohol, under a variety of different conditions as described in Table 4, in 67~87% yield. GCMS: m/z = 132 (M⁺, relative intensity 60%), 131 (base peak), 115 (1%), 103 (69%), 91 (2%), 77 (32%), 63 (7%), 51 (48%), 39 (12%)

Oxidation of 4-chlorobenzyl alcohol

4-Chlorobenzaldehyde was prepared from 4-chlorobenzyl alcohol in 93% yield. GCMS: $m/z = 142 \text{ (M}^++2, \text{ relative intensity } 22\%), 141 (37\%), 140 (M^+, 68\%), 139 (base peak), 113 (19\%), 111 (60\%), 91 (2\%), 85 (4\%), 77 (18\%), 75 (32\%), 61 (4\%), 50 (31\%), 38 (8\%)$

Oxidation of 4-nitrobenzyl alcohol

4-Nitrobenzaldehyde was prepared from 4-nitrobenzyl alcohol in 98% yield. GCMS: m/z = 151 (M⁺, relative intensity 92%), 150 (base peak), 135 (2%), 120 (7%), 105 (22%), 92 (12%), 77 (72%), 65 (12%), 51 (85%), 39 (8%)

Oxidation of 3-pyridinemethanol

3-Pyridinecarboxaldehyde was prepared from 3-pyridinemethanol in 94% yield. GCMS: m/z = 107 (M⁺, base peak), 106 (relative intensity 53%), 78 (45%), 61 (1%), 51(60%)

Oxidation of 2-thiophenemethanol

Thiophene-2-carbaldehyde was prepared from 2-thiophenemethanol in 79% yield. GCMS: m/z = 112 (M⁺, relative intensity 93%), 114 (5%), 113 (11%), 111 (base peak),

83 (8%), 58 (7%), 45 (15%), 39 (28%), 77 (72%), 65 (12%), 51 (85%), 39 (8%). As a by-product it was assigned 5-chlorothiophene-2-carbaldehyde (8.5 GC%). GCMS analysis of the product was identical with authentic sample. GCMS: m/z = 148 (M⁺+2, relative intensity 29%), 147 (45%), 146 (M⁺, 86%), 145 (base peak), 117 (20%), 82 (8%), 73 (19%), 57 (12%), 45 (20%)

Small scale oxidation of secondary alcohols for Table 7:(general procedure)

NaOCl·5H₂O crystals (12.0~18.0 mmol) were added in one portion to a mixture of Bu_4NHSO_4 (0.170 g, 0.50 mmol), TEMPO (15.6 mg, 0.10 mmol), and alcohols (10.0 mmol) in dichloromethane (10 mL or 30 mL) at several temperature. After stirring for an appropriate time, 0.5 mL of the organic layer and 0.03 g weighed of PCBTF as an internal standard were added to 1~2 mL of CH₂Cl₂ for GC analysis. GCMS analyses of the products were identical with authentic samples.

Oxidation of 3-octanol

3-Octanone was prepared from 3-octanol in 97% yield. GCMS: m/z = 128 (M⁺, relative intensity 4%), 99 (29%), 72 (23%), 71 (21%), 57 (53%), 43 (base peak).

Oxidation of *l*-menthol

l-menthone was prepared from *l*-menthol in 88~98% yield, with several conditions described in Table 5. GCMS: m/z = 154 (M⁺, relative intensity 36%), 139 (52%), 112 (base peak), 97 (40%), 83 (28%), 69 (75%), 55 (62%), 41 (61%)

Oxidation of 2,6-dimethyl-4-heptanol

2,6-Dimethyl-4-heptanone was prepared from 2,6-dimethyl-4-heptanol in 88~95% yield, with several conditions described in Table 5. GCMS: m/z = 142 (M⁺, relative intensity 12%), 127 (5%), 100 (3%), 85 (74%), 71 (1%), 57 (base peak), 43 (12%), 41(25%)

Preparative examples

Oxidation of 2-octanol

NaOCl·5H₂O 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 dichloromethane (10 mL) at 5 °C. After 15 min, GC monitoring showed that all of the starting material **1** had been consumed. The reaction was stopped after 0.5 h by quenching with aqueous saturated sodium sulfite solution (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were washed with water (30 mL), dried over Na₂SO₄, 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 bath temperature) to afford pure **2** (0.40 g, 95%).

Oxidation of 3-octanol

NaOCl·5H₂O crystals (2.0 g, 12.0 mmol) were added in one portion to a mixture of Bu_4NHSO_4 (0.16 g, 0.47 mmol), TEMPO (20.0 mg, 0.13 mmol), 3-octanol (1.30 g, 10.0 mmol), and water (0.2 mL) in dichloromethane (10 mL) at 8 °C. The reaction was stopped after 0.5 h by quenching with aqueous saturated sodium sulfite solution (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were washed with water (30 mL), dried over Na₂SO₄, and concentrated to give 3-octanone as a colorless oil (1.30 g). A 0.40 g portion of the crude **3** was purified by bulb-to-bulb distillation (8.7 kPa, 130–140 °C bath temperature) to afford pure **3** (0.38 g, 96%, GC purity 99.7%).

Oxidation of *l*-menthol

NaOCl·5H₂O (658.0 mg, 4 mmol) was added in one portion to a mixture of Bu₄NHSO₄ (44.5 mg, 0.131 mmol), TEMPO (3.4 mg, 0.022 mmol), and *l*-menthol (391.5 mg, 2.5 mmol) in dichloromethane (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 saturated aqueous sodium sulfite solution (5 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3). The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, and concentrated to give *l*-menthone as a colorless oil (475.7 mg), which was purified by column chromatography (Hexane : AcOEt = 10 : 1) on silica gel to give pure *l*-menthone (355.3 mg, 92%). $[\alpha]_D^{25} = -28.1^{\circ}$ (c=0.0156, EtOH) (lit.^{10d}, $[\alpha]_D = -28.6^{\circ}$). ¹H NMR (400 MHz, CDCl₃): $\delta = 2.35$ (ddd, J = 13.1, 3.6, 2.3 Hz, 1H), 2.18–1.80 (m, 6H), 1.43–1.29 (m, 2H), 1.01 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H).

Large scale oxidation of 2-octanol in ethyl acetate:

A mixture of NaOCl·5H₂O (39.5 g, 0.24 mol) and ethyl acetate (70 mL) was cooled to 3 °C in a 200 mL of 4-necked flask with stirring . Bu_4NHSO_4 (3.4 g , 0.010 mol) and TEMPO (0.31 g , 0.002 mol) were added to the mixture, and then 2-octanol (26.0 g , 0.20 mol) was added over a period of 15 min via a dropping funnel. The temperature of

the reaction mixture reached a maximum of 18 °C during the addition, and was 12 °C at the end of the 2-octanol addition. The dropping funnel was washed with 10 mL of AcOEt and the stirring was continued for a further 45 min. The temperature of the reaction mixture was 2 °C. The mixture was quenched with satd. Na₂SO₃ (30 mL), extracted with AcOEt (20 mL × 3), washed with brine (20 mL × 1) and water (20 mL × 2), and dried over MgSO₄. After filtration, the organic layer was concentrated *in vacuo* and distilled (bp 130 °C /26.6-25.5 kPa) to give 2-octanone (23.2 g, 90.5% yield). GC and GCMS analyses of the product were identical with authentic sample and indicated 99.3% purity.

Solvent free oxidation of 2-octanol with NaHSO₄·H₂O Method A

To NaOCl·5H₂O (19.7 g, 0.12 mol) and water (13.2 g) were added NaHSO₄·H₂O (0.69 g, 5.0 mmol) and TEMPO (0.16 g, 1.0 mmol) in ice-water bath with stirring. Thirteen grams of 2-octanol (0.10 mol) were added at 5~18 °C over a period of 1 h. The pH of the reaction mixture was measured to be 9.5~10.3 during this period. Point one mL of the organic layer was measured out to 10 mL of CH₂Cl₂ and 0.17 g weighed of PCBTF as an internal standard was added for GC analysis. The yield of 2-octanone was 97.0%.

Method B

A 30% NaOCl solution (28.2 g, 0.12 mol) prepared from NaOCl·5H₂O and water was added dropwised to a mixture of 2-octanol (13.0 g, 0.10 mol), NaHSO₄·H₂O (0.69 g, 5.0 mmol) and TEMPO (0.16 g, 1.0 mmol) for 1 h at 0~12 °C with stirring. The pH was 3~8 for the first 0.5 h and 8~10 for the next 0.5 h. Point one mL of the organic layer and 0.17 g weighed of PCBTF as an internal standard were added to 10 mL of CH₂Cl₂ for GC analysis. The yield of 2-octanone was 95.7%.

6. References

(a) Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 16, 2647-2650; (b) Corey, E. J.; Schmidt, G. Tetrahedron Lett. 1979, 20, 399-402; (c) Mancuso, A. J.; Huang, S. L.; Swern, D. J. Org. Chem. 1978, 43, 2480-2482; (d) Corey, E. J.; Kim, C. U. J. Am. Chem. Soc. 1972, 94, 7586-7587; (e) Corey, E. J.; Kim, C. U. Tetrahedron Lett. 1973, 14, 919-922; (f) Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. Tetrahedron Lett. 2002, 43, 5177-5179; (g) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. J. Chem. Soc., Chem. Commun. 1987, 1625-1627; (h)

Keck, G. E.; Knutson, C. E.; Wiles, S. A. Org. Lett. 2001, 3, 707-710; (i) Myers, A. G.; Zhong,
B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. Tetrahedron Lett. 2000, 41, 1359-1362

- (a) Baeckvall, J. –E.; Hopkins, R. B.; Grennberg, H.; Mader, M.; Awasthi, A. K. J. Am. Chem. Soc. 1990, 112, 5160-5166; (b) Kaneda, K.; Yamashita, T.; Matsushita, T.; Ebitani, K. J. Org. Chem. 1998, 63, 1750-1751; (c) Zhu, C; Zhang, Z.; Ding, W.; Xie, J.; Chen, Y.; Wu, J.; Chen, X.; Ying, H. Green Chem., 2014, 16, 1131-1138
- (a) Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. J. Am. Chem. Soc. 1997, 119, 12386-12387; (b)
 Sato, K.; Aoki, M.; Takagi, J.; Zimmermann, K.; Noyori, R. Bull. Chem. Soc. Jpn. 1999, 72, 2287-2306
- (a) Stevens R.V.; Chapman K.T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* 1982, 23, 4647-4650; (b) Stevens, R. V.; Chapman, K. T.; Weller, H. N. J. Org. Chem. 1980, 45, 2030-2032; (c) Lee, G. A.; Freedman, H. H. *Tetrahedron Lett.* 1976, 17, 1641-1644; (d) Mirafzal, G.A.; Lozeva, A. M. *Tetrahedron Lett.* 1998, 39, 7263-7266
- (a) deNooy, A. E. J.; Besemer, A. C.; Bekkum, H. V. Synthesis 1996, 1153-1176; (b) Anelli, P.L.; Biffi, C.; Montanari, F.; Quici, S. J. Org. Chem. 1987, 52, 2559-2562
- (a) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. J. Am. Chem. Soc. 2006, 128, 8412–8413;
 (b) Iwabuchi, Y., J. Synth. Org. Chem. Jpn. 2008, 66, 1076–1084.
- 7. Adam, L. C.; Gordon, G. Inorg. Chem. 1999, 38, 1299-1304
- Asawa, T.; Tuneizumi, T.; Iwasaki, Y. Japanese Patent 4211130 (2008); JP (Japan Kokai Tokkyo Koho) 2000-290003, Chem. Abstr. 133, 311496 (2000).
- NaOCl·5H₂O is commercially available from Wako Pure Chemical Industries, Ltd., Tokyo chemical industry Co., Ltd., and Junsei Chemical Co., Ltd. Large quantity of NaOCl·5H₂O can be directly supplied from Nippon Light Metal Company, Ltd.
- 10. Okada, T.; Asawa, T.; Sugiyama, Y.; Kirihara, M.; Iwai, T.; Kimura, Y. Synlett 2014, 25, 596-598
- (a) Applebey, M. P. J. Chem. Soc. Trans. 1919, 115, 1106-1109.; (b) Takimoto, K.; Karasawa, Y. JP 56-022604 (1981); Chem. Abstr. 1981, 95, 45459.; (c) Duncan, B. L.; Ness, R. C.; WO 9217399 (1992); Chem. Abstr. 1992, 117, 254363.; (d) Timshina, A. V. ; Rubtsova, S. A.; Kodess, M. I.; Matochkina, E. G.; Slepukhin, P. A.; Kuchin, A. V. Russian J. Org.Chem. 2008, 44, 1043-1048; Chem. Abstr. 2008, 150, 398714.; (e) Cawlfield, D. W.; Morris, R. T.; Ness, R. C.; Richard, L. L.; Scott, L. L.; Moore, S. H.; Asuru, A. P.; US 2014-0117278 (2014); Chem. Abstr. 2014, 160, 638958.; (f) Iwata, T.; Nishiumi, K.; Takimoto, H. JP 2014-169215 (2014); Chem. Abstr. Abstr. 2014, 161, 448861.; (g) Fehèr, F.; Hirschfeld, D.; Linke, K. -H. Acta. Crystallographica, 1962, 15, 1188-1189; (h) Taguchi, S.; Terao, T.; Yamazaki, K.; Murakami, M. CN 104743514 (2015); Chem. Abstr. 2015, 163, 176884.

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(a) Golubev. V. A.; Rozantsev, E. G.; Neiman, M. B. Bull. Acad. Sci. USSR, Div. Chem. Sci. 1965, 1898-1904; (b) Semmelhack, M. F.; Scimid, C. R.; Cortés, D.A. Tetrahedron Lett. 1986, 27, 1119-1122; (c) Ma, Z.; Bobbitt, J. M. J. Org. Chem. 1991, 56, 6110-6114; (d) de Nooy, A. E. J.; Besemer, A. C. Tetrahedron 1995, 51, 8023-8032; (e) Bobbitt, J. M. TCIMAIL (Tokyo Chemical Industry Co. Ltd) No 146 (August 2011) pp 2-10; (f) Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. J. Org. Chem. 2007, 72, 4504-4509





200 mL flask

1.2 equiv. NaOCI-5H₂O (39.5 g) 1 mol% TEMPO (0.31 g) 5 mol% Bu₄NHSO₄ (3.40 g) EtOAc (80 mL)









| Table | 2 Comparison of Na | OCl·5H ₂ O crystals an | nd conventional | aqueous | s NaC | Cl | | |
|-------|---------------------------|---|--|---------------------|-----------|--------------|--|---------|
| | | NaOCI·5H ₂ O + or aq. NaOCI 1.2 equiv. | Bu ₄ NHSO 5 mol% nitroxyl radio in CH ₂ Cl ₂ 5 | 4 ➤ cal °C | | 4 | | |
| Run | nitroxyl radical | NaOCl·5H ₂ O crystals (equiv.) | aq. NaOCl solution ^a (equiv.) | 0.5h | Yie 1h | eld of 2h | ⁷ 2 (%) ^b 3h | 24h |
| 1 | | 1.2 | | | 3 | 22 | 28 | 78 |
| 2 | | | 1.2 (13.2%) ^c | | 1 | 1 | 2 | 9(27h) |
| 3 | TEMPO 1 mol% | 1.2 | - | 94 | 97 | | | |
| 4 | TEMPO 1 mol% | | 1.2 (13.5%) ^c | | 1 | 2 | 2 | 11(22h) |
| 5 | TEMPO 0.5 mol% | 1.2 | | 87 | 99 | | | |
| 6 | TEMPO 0.1 mol% | 1.2 | | | 79 | 96 | 99 | |
| 7 | 1-Me-AZADO 1 mol% | 1.2 | | | 100 | | | |
| 8 | 1-Me-AZADO 1 mol% | | 1.2 (13.2%) ^c | | 14 | 29 | 45 | 99 |

^a aq. NaOCl : conventional aqueous NaOCl (ca. 13% solution) containing NaOH and NaCl

^b Yields were determined by GC using an internal standard method.

^c Concentrations were determined via titrations.

-

| Table | e 3 Effect for qu | aternaly annmonium salts and | acid in th | e pres | ence o | of TEN | /IPO ^a | |
|-------|--------------------------|--|------------------------------------|----------------|--------|--------------|--------------------|--|
| / | | Bu ₄ l + NaOCI-5H ₂ O 1.2 equiv. TEM in C | NX 5 mol PO 1 mo H_2Cl_2 5 | % >)% °C | | \downarrow | 2 | |
| D.1 | n V | Additive | | ~ | Yiel | d of 2 | 2 (%) ^b | |
| - Ku | | Additive | 0.5h | 1h | 2h | 3h | 21h | |
| 1 | HSO ₄ | | 94 | 97 | | | | |
| 2 | HSO ₄ (0.5 mc | ol%) | | 40 | 73 | 98 | | |
| 3 | Br | - | | 6 | 14 | 25 | 87(22h) | |
| 4 | Cl | | | 3 | 10 | 10 | 73 | |
| 5 | Cl | NaHSO₄·H₂O 5 mol% | | 19 | 25 | | 69 | |
| 6 | Cl | NaHSO ₄ ·H ₂ O 5 mol% + H ₂ O 0.2 mL | 97 | 99 | | | | |
| 7 | | NaHSO ₄ ·H ₂ O 5 mol% + H ₂ O 0.2 mL | 46 | 98 | | | | |

^a **1** (10 mmol), NaOCl·5H₂O (12 mmol), Bu₄NX (0.5 mmol), TEMPO (0.1 mmol), CH₂Cl₂ (30 mL) ^b Yields were determined by GC using an internal standard method.

 Table 5
 Results for oxidation of 1 in several solvents^a

| | NaOCI-5 1.2 eq 5 mol% Bu 1 mol% TE solvent (3 | 5H ₂ O uiv. 1 ₄ NH EMP(50 mL | SO₄ → -) | H_4 | 2 | P |
|---|---|---|----------------|----------------|-----------------------|---|
| Solvent | Contraction (°C) | Y 1h | ield o | of 2 (% | 5) ^b 4h | |
| | (0) | 111 | 211 | 511 | 411 | _ |
| CH_2Cl_2 | 5 | 97 | · | | | |
| EtOAc | 5 | 61 | 97 | | | |
| C ₆ H ₅ CH ₃ | 5 | 38 | 90 | 98 | | |
| C ₆ H ₅ CF ₃ | 5 | 30 | 55 | 87 | 95 | |
| CH ₃ CN | 5 | 53 | 54 | 53 | 52 | |
| AcOH | rt | 18 | 78 | 90 | 90 | |

^a **1** (10 mmol)

^b Yields were determined by GC using an internal standard

| Р — — — — — — — — — — — — — — — — — — — | aOCI⋅5H₂O | 5 mol% Bu ₄ NHSO ₄ O 1 mol% TEMPO | | | |
|---|-------------------------------------|--|------------------|------------------|---|
| K OH | - | CH ₂ Cl ₂ | | RH | |
| Substrate | NaOCl·5H ₂ O (equiv.) | CH ₂ Cl ₂ (mL) | Temp. (°C) | Time (h) | Yield (%) ^b |
| H ₅ OH | 1.1 | 30 | 5 | 1 | 91 |
| ОН | 1.1 | 30 | 5 | 1 | 99 |
| МеО | 1.2 | 30 | 5 | 2 | 96 |
| ОН | 1.2 1.2 | 30 15 | 5 15 | 6 1 | 96 97 |
| ОН | 1.4 1.4 1.2 1.4 | 30 30 30 30 | 5 5 5 5 | 4 3 3 2 | 67 82 ^c 87 ^d 85 ^d |
| СІОН | 1.1 | 30 | 5 | 0.5 | 93 |
| O ₂ N OH | 1.1 | 30 | 5 | 0.5 | 98 |
| OH | 1.1 | 30 | 5 | 0.5 | 94 |
| ССОН | 1.4 | 30 | 5 | 3 | 79 |

 Table 6
 Selective syntheses of aldehydes from primary alcohols^a

^a Substrate : 10 mmol

^b Yields were determined by GC using an internal method

^c TEMPO 10 mol%

^d 1-Me-AZADO was used instead of TEMPO

| Table 7 Results for the oxidation of secondary alcohols ^a | | | | | | | |
|---|---------------------------------------|-----------------------------------|---------------------------------------|---|----------------------|-----------------------|------------------------|
| ОН | + NaOCI-5H ₂ O | 5 mol 1 mol% | % Bu ₄ NHS nitroxyl rac | O₄ dical ➔ | o II | | |
| R^1 R^2 | | С | H_2CI_2 | R | 1 | R ² | |
| Substrate | nitroxyl Na radical (| DCl·5H ₂ C (equiv.) | aq. NaOCl (equiv.) ^b | CH ₂ Cl ₂ (mL) | Temp. (°C) | Time (h) | Yield (%) ^c |
| OH H 4 | TEMPO | 1.2 | | 10 | 5 | 0.5 | (95) |
| OH J | TEMPO TEMPO | 1.2 1.2 | | 30 10 | 5 15 | 1 0.67 | 97 (96) |
| ОН | TEMPO | 1.2 1.6 | 1.2 | 30 30 10 | 5 5 15 | 24 24 2 | 98 2 96 |
| | TEMPO TEMPO TEMPO 1-Me-AZADO | 1.6 1.4 1.4 1.4 | | 8 10 30 30 | 15 rt rt rt | 2.25 4 4 0.5 | (92) 95 88 98 |
| OH | TEMPO 1-Me-AZADO | 1.8 1.4 | | 10 30 | 15 rt | 6 0.5 | 88 95 |

^a All the reactions were performed without pH adjustment for NaOCl. See experimental section

^b aq NaOCl: 12.1 wt% of conventional aqueous solution

^c Yields were determined by GC using an internal standard method.

Numbers in parentheses refer to isolated yields.

| 1-octanol | NaOCI [.] 5H ₂ O (5 mmol) Nitroxyl radical (0.1 mmol) | octanal |
|---------------------------------------|---|----------------------------|
| + OH + OH 2-octanol 5.0 mmol | Bu ₄ NHSO ₄ (0.5 mmol) CH ₂ Cl ₂ , 5 °C | + 0 + 0 + 2-octanone |
| Nitroxyl Radical T | ime (h) Octanal | 2-Octanone |
| ТЕМРО (| 0.5 47% (2.35 mmol) | 44% (2.20 mmol) |
| 4-MeO-TEMPO 1 | .0 48% (2.40 mmol) | 37% (1.85 mmol) |

* Yields were determined by GC using an internal standard method.