Oxoammonium salt/$NaClO_2$: an expedient, catalytic system for one-pot oxidation of primary alcohols to carboxylic acids with broad substrate applicability†

Masatoshi Shibuya, Takahisa Sato,‡ Masaki Tomizawa and Yoshiharu Iwabuchi*

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A facile, green, one-pot oxidation of primary alcohols to carboxylic acids with broad substrate applicability has been developed by employing an expedient catalytic system consisting of 1-Me-AZADO$^+$X$^-$/$NaClO_2$.

The oxidation of primary alcohols to the corresponding carboxylic acids is a fundamental transformation in organic chemistry.[1,2] The straightforward appearance of this transformation, consisting of simple, two-step oxidations: primary alcohol to aldehyde, then aldehyde to carboxylic acid, has encouraged many organic chemists to develop an efficient one-pot oxidation. A number of methods have been established to date, *i.e.*, CrO_3/H_2SO_4,[3] PDC/DMF,[4] CrO_3/H_5IO_6,[5] $RuCl_3/H_5IO_6$,[6] $RuCl_3/K_2S_2O_8$,[7] Na_2WO_4/H_2O_2,[8] PhIO/KBr,[9] TEMPO/NaOCl,[10] TEMPO/PhI(OAc)$_2$,[11] TEMPO/NaOCl/$NaClO_2$,[12] however, the task suffers from several drawbacks: *i.e.*, limited substrate applicability, toxic and hazardous nature of reagents, harsh conditions required, and so on. We now describe a novel catalytic system composed of cat. oxoammonium salt/$NaClO_2$, which allows a facile, one-pot, efficient oxidation of primary alcohols to carboxylic acids with broad substrate applicability.

Among the various methods developed, Merck's method using cat. TEMPO/cat. NaOCl/$NaClO_2$ would be placed as one of the most popular, which achieves increasing success in the one-pot oxidation of primary alcohols to carboxylic acids, despite its inherent limitation due to the use of NaOCl,[13] which is notorious for damaging electron-rich moieties such as alkenes and aromatic rings. We recently disclosed that 2-azaadamantane *N*-oxyls (AZADOs: **2** and **3**),[14] a less-hindered class of nitroxyl radicals,[15] exhibit significantly enhanced reactivity in the catalytic oxidation of alcohols compared with TEMPO (**1**) (Fig. 1). The fact that AZADOs possess markedly smaller $E^{\circ\prime}$ values than TEMPO ($E^{\circ\prime}$ *vs.* Ag/Ag$^+$: 1-Me-AZADO, 186 mV; AZADO, 236 mV; TEMPO, 294 mV) coupled with an idea inspired by Merck's method, that the use of the oxoammonium salt[16] as an initial catalyst, instead of nitroxyl radical, will liberate substrates from the harmful NaOCl, led us to envision a "*virtually* NaOCl-free" catalytic system featuring the following steps: (i) oxoammonium ion reacts with alcohols to give hydroxylamine and aldehyde; (ii) the aldehyde generated reacts with $NaClO_2$ to give a carboxylic acid and NaOCl; (iii) NaOCl generated *in situ* is *immediately* consumed by hydroxylamine to regenerate an oxoammonium ion, thereby establishing a catalytic cycle (Scheme 1). The key point is the *kinetic* efficiency of quenching the destructive NaOCl by a hydroxylamine to regenerate a milder and more selective oxidant, the oxoammonium ion.

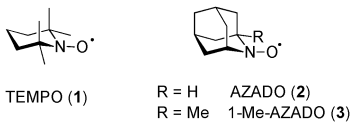
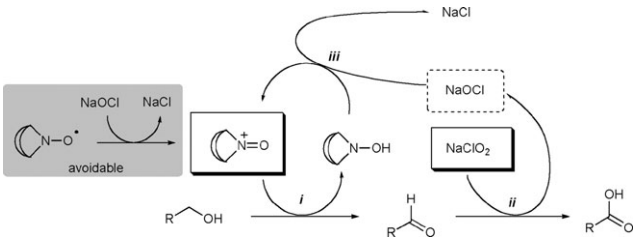


Fig. 1 TEMPO (**1**) and AZADOs (**2** and **3**).



Scheme 1 Our plan for one-pot oxidation.

To verify the above-mentioned concept, two types of 1-Me-AZADO-derived oxoammonium salts, namely, 1-Me-AZADO$^+$Cl$^-$ and 1-Me-AZADO$^+$BF$_4^-$,[17] were prepared, along with TEMPO$^+$Cl$^-$ and TEMPO$^+$BF$_4^-$, and challenged by the projected one-pot oxidation.

We confirmed that the oxoammonium salt/$NaClO_2$ system exhibits an optimized performance in MeCN-aq. sodium phosphate (1.0 M, pH 6.8) to convert primary alcohols **4**, **5** and **6** to the corresponding carboxylic acids up to 10 g-scale experiment, with which cat. TEMPO/cat. NaOCl/$NaClO_2$ (Merck's method) failed to afford a carboxylic acid product in good yield due to the damage of electron-rich functionalities.[12a,b,18,19] Beside the superiority of 1-Me-AZADO over TEMPO, it should be noted that direct investment of the substantial catalyst, the oxoammonium salt, brought about a marked productivity (Table 1).[19,20]

The scope of the utility of oxoammonium salt/$NaClO_2$ for the one-pot oxidation of primary alcohols **7**–**17** to carboxylic

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aobayama, Sendai, 980-8578, Japan. E-mail: iwabuchi@mail.pharm.tohoku.ac.jp; Fax: +81-22-795-6845; Tel: +81-22-795-6846

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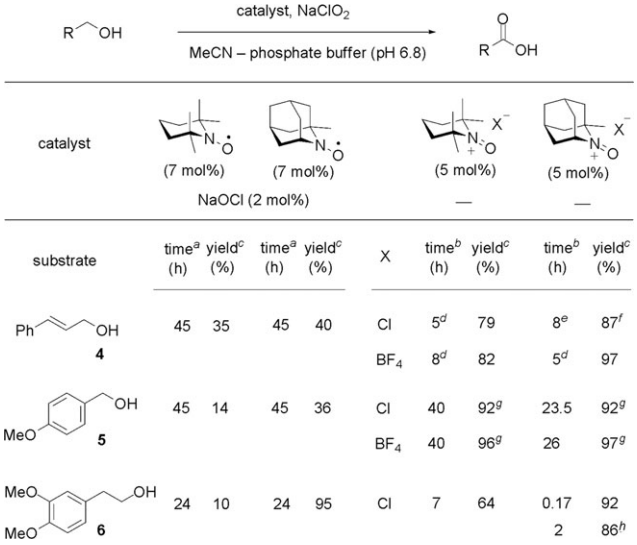
‡ *In memoriam* to our colleague and friend Takahisa, who suddenly passed away last year.

Table 1 Catalytic one-pot oxidation of primary alcohols having electron-rich groups employing $NaClO_2$ as the terminal oxidant



substrate	time[a] (h)	yield[c] (%)	time[a] (h)	yield[c] (%)	X	time[b] (h)	yield[c] (%)	time[b] (h)	yield[c] (%)
Ph, OH **4**	45	35	45	40	Cl	5[d]	79	8[e]	87[f]
					BF_4	8[d]	82	5[d]	97
MeO, OH **5**	45	14	45	36	Cl	40	92[g]	23.5	92[g]
					BF_4	40	96[g]	26	97[g]
MeO, MeO, OH **6**	24	10	24	95	Cl	7	64	0.17	92
								2	86[h]

[a]Reactions were catalyzed by TEMPO or 1-Me-AZADO (7 mol%) with NaOCl (2 mol%) and $NaClO_2$ (2 eq.) in sodium phosphate buffer (1.0 M, pH 6.8; 0.3 M) and MeCN (0.3 M) at 35 °C. [b]Reactions were catalyzed by $TEMPO^+X^-$ or 1-Me-$AZADO^+X^-$ (5 mol%) with $NaClO_2$ (3 eq.) in sodium phosphate buffer (1.0 M, pH 6.8; 0.3 M) and MeCN (0.3 M) at 25 °C. [c]Isolated yield as a methyl ester after treatment with CH_2N_2. [d]Reaction was performed at 50 °C. [e]Reaction was performed at 40 °C. [f]5 g of **4** was employed. [g]Reaction was run using 5 eq. of $NaClO_2$. [h]10 g of **6** was employed.

acids is shown in Table 2, where 1-Me-$AZADO^+$ exhibited better catalytic performance than $TEMPO^+$. Note that 1-Me-$AZADO^+Cl^-$ successfully oxidized alkenyl alcohols to afford the corresponding carboxylic acids, where $TEMPO^+$ suffered from side reactions, such as oxidative cleavage and chlorination (Table 1, oxidation of **6**; Table 2 entry 7). The admirably clean transformations attained by 1-Me-$AZADO^+$ may be attributed to the highly reactive nature of 1-Me-AZADOH in consuming NaOCl, quenching the destructive pathway of reacting π-electrons of the substrates. No epimerizations were observed in the oxidation of *N*-protected α-amino alcohols (entries 9, 10). In some cases, a more acidic buffer produced a faster reaction rate (Table 2, entry 8; Method C). It would be useful to point out that 1-Me-$AZADO^+BF_4^-$ is advantageous over 1-Me-$AZADO^+Cl^-$ in terms of its less hygroscopic nature as well as its selectivity in suppressing the undesired chlorination under 5% (entry 7).

In summary, we disclose a facile, one-pot, efficient oxidation of primary alcohols to carboxylic acids with broad substrate applicability employing 1-Me-$AZADO^+X^-/NaClO_2$, which should lead to progress in a wide range of chemical research areas.

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Table 2 Scope of one-pot oxidation employing oxoammonium salt/$NaClO_2$

entry	substrate		method	time (h)	yield[a] (%)	time (h)	yield[a] (%)
1	Ph, OH	**7**	A	0.5	98	0.5	98
			B	1.5	98	0.5	93
2	Ph, OH	**8**	A	10	79	10	93
			B	10	97	10	97
3	OH	**9**	A	9.5	100	7	98
			B	8	83	7	98
4	Ph, OH	**10**	A	4	86	4	100
5	HO, OH	**11**	A	9.5	93	0.5	92
6	OH	**12**	A	24	74[b]	1	94
			B	24	77[b]	3	93
7	O, OH	**13**	A	48	< 10	24	73[c]
			B	48	< 10	18	78[d]
8	HO	**14**	A	70	32	58	64
			C	7	73	4	90
9	N, Cbz, OH	**15**	A	9	100[e]	3	100[e]
			B	8.5	100[e]	1.5	100[e]
10	CbzHN, Ph, OH	**16**	A	42	13[f]	18	100[f]
			B	42	8[f]	24	94[f]
11	O, O, BocHN, OH	**17**	A	24	42	1	100

Method A: reactions were catalyzed by $TEMPO^+Cl^-$ or 1-Me-$AZADO^+Cl^-$ (5 mol%) with $NaClO_2$ (5 eq.) in sodium phosphate buffer (1.0 M, pH 6.8; 0.3 M) and MeCN (0.3 M) at 25 °C. **Method B**: reactions were catalyzed by $TEMPO^+BF_4^-$ or 1-Me-$AZADO^+BF_4^-$ (5 mol%) with $NaClO_2$ (3 eq.) in sodium phosphate buffer (1.0 M, pH 6.7; 0.3 M) and MeCN (0.3 M) at 25 °C. **Method C**: reactions were catalyzed by $TEMPO^+Cl^-$ or 1-Me-$AZADO^+Cl^-$ (5 mol%) with $NaClO_2$ (3 eq.) in CH_3CO_2H–CH_3CO_2Na buffer (1.0 M, pH 4.0; 0.3 M) and CH_2Cl_2 (0.3 M). [a]Isolated yield as a methyl ester after treatment with CH_2N_2. [b]*ca.* 10% of starting material was still remained. [c]*ca.* 18% chlorinated product was obtained as an inseparable mixture. [d]*ca.* 3% of chlorinated product was obtained as inseparable mixture. [e]Enantiomeric excess was determined by HPLC (CHIRALPAK AD-H, DAICEL). [f]Enantiomeric excess was determined by HPLC (CHIRALCEL OD-H, DAICEL).

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18 Representative procedure for oxidation of primary alcohols to carboxylic acids. To a stirring mixture of 3-phenylpropanol (**7**) (150 mg, 1.10 mmol), sodium phosphate buffer (1.0 M, pH 6.8, 3.7 mL) in MeCN (3.7 mL), $NaClO_2$ (80%) (375 mg, 3.3 mmol) and 1-Me-AZADO$^+$Cl$^-$ (11 mg, 55 μmol) was added. After stirring for 0.5 h at 25 °C, 2-methyl-2-butene (1.5 mL) was added. H_2O (1 mL) was added and the mixture was extracted with Et_2O. Then the aqueous layer was adjusted to pH 2.0–3.5 with 10% HCl and extracted twice with Et_2O. The combined organic layer was washed with acidic brine and then concentrated to give the crude 3-phenylpropanoic acid. The crude products were diluted by Et_2O and treated with CH_2N_2, followed by removal of excess CH_2N_2 and Et_2O. Purification by column chromatography provided methyl 3-phenylpropanoate (178 mg, 1.08 mmol, 98%).

19 Procedure for oxidation of 2-(3,4-dimethoxyphenyl)ethanol on large scale; To a stirring mixture of 2-(3,4-dimethoxyphenyl)ethanol (**6**) (10 g, 55 mmol) and 1-Me-AZADO$^+$Cl$^-$ (550 mg, 2.7 mmol) in MeCN (90 ml) and sodium phosphate buffer (1.0 M, pH 6.8, 90 ml), $NaClO_2$ (80%) (18.6 g, 165 mmol) was slowly added. After stirring for 2 h at 25 °C, 2-methyl-2-butene (5 mL) was added. H_2O (10 mL) was added and the mixture was extracted with AcOEt and was further purified with extraction using 5% NaOH. The aqueous layer was washed with Et_2O and acidified with 10% HCl and then extracted with AcOEt. The organic layer was evaporated and the crude products was recrystallized from AcOEt–hexane to afford 3,4-dimethoxyphenylacetic acid (9.26 g, 47.2 mmol, 86%) as colorless prisms.

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