Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Safe and convenient nitroxyl radical and imide dual catalyzed NaOCl oxidation of alcohols to aldehydes/ketones

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ARTICLE INFO

Article history:
Received 19 March 2015
Revised 22 April 2015
Accepted 28 April 2015
Available online xxxx

Keywords:
Oxidation
Alcohol
NaOCl
Nitroxyl radical
Imide

ABSTRACT

A novel and practical oxidation of alcohols to carbonyl compounds using NaOCl in the presence of catalytic amounts of imide compound and nitroxyl radical has been developed. A wide variety of aliphatic, benzylic primary alcohols, and secondary alcohols were oxidized to afford the corresponding aldehydes and ketones in up to 98% yield without undesired halogenation on aromatic rings or double bonds. The oxidation safely proceeded not only in the presence of K_2CO_3 but also by a slow addition of NaOCl without tedious pH adjustment.

Since the selective oxidation of alcohols to the corresponding carbonyl compounds is one of the most significant and widely used transformations in synthetic organic chemistry, a number of useful methods have been developed.[1] Among them, metal catalyzed systems using co-oxidants such as oxygen,[2] hydrogen peroxide,[3] acetone[4] or sodium hypochlorite[5] have recently attracted much attention due to the growing environmental requirement. However, trace metal contamination of products is especially a concern for pharmaceutical manufacturing, even though the methods are useful in terms of producing less-metal containing waste. Meanwhile, the oxidation of alcohols by oxoammonium salts has also become a widely used non-metallic oxidation system.[6] More commonly, alcohol oxidations using TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and its analogues are conducted in catalytic systems that involve in situ generation of the oxoammonium cation via one-electron oxidation with a stoichiometric amount of co-oxidant, such as hypochlorite salt,[7] *m*CPBA,[8] Oxone®,[9] [bis(acetoxy)iodo]benzene (BAIB),[10] I_2,[11] *N*-chlorosuccinimide (NCS),[12] 1,3,5-trichloroisocyanuric acid (TCCA),[13] co-catalyst/O_2,[14] and Py·HBr_3.[15] Although these methods are useful in terms of the mild reaction conditions, some drawbacks remain from the viewpoints of safety, substrate versatility, and waste. Oxidation with many co-oxidants generates equivalent molar amounts of waste as byproduct, for instance, iodobenzene, *m*-chlorobenzoic acid, and imides, which need to be removed by column chromatography. The combination of TEMPO and Oxone® easily oxidizes benzylic alcohols to the corresponding aldehydes, however, the yields from non-activated alcohols, such as aliphatic alcohols, are moderate.[9] The reaction with a halogen source sometimes proceeds to give halogenation along with the oxidation of alcohols. The large scale synthesis using O_2 is also constrained by strict safety consideration due to the explosion risk associated with the combination of O_2, organic solvents, and reagents.

Anelli and co-workers firstly reported the practical TEMPO catalyzed oxidations with aqueous NaOCl as co-oxidant in 1987 and this is generally recognized as standard protocol.[7a] Since NaOCl is generally inactive as an oxidant, it is necessary to adjust the pH of the reaction condition to 7–9 with diluted aqueous $NaHCO_3$ and/or phosphate buffer, and to add KBr and phase transfer catalyst as well as frequently used halogenated solvents in order to complete the reaction. However, as a result of adding buffer solution to increase the amount of HOCl (a more active oxidant than NaOCl), the volume of the reaction mixture is increased, resulting in reduced productivity. Also, this kind of oxidation often suffers from halogenation of aromatic rings or double bonds and over-oxidation to the carboxylic acids because of the presence of HOCl.[7a,c] In addition, there are safety concerns and careful handling is required due to toxic chlorine gas generated under acidic conditions.[16] We herein describe the safe and convenient oxidation of alcohols to the corresponding carbonyl

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http://dx.doi.org/10.1016/j.tetlet.2015.04.115
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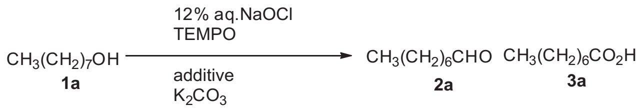
compounds using aqueous NaOCl with a catalytic amount of the imide compound and without pH adjustment.

The effect of additives (0.1 equiv) for TEMPO (0.03 equiv) catalyzed aq NaOCl (1.2 equiv) oxidation at 0–10 °C for 2 h in ethyl acetate was investigated using 1-octanol **1a** as a representative substrate in the presence of K_2CO_3 (2.0 equiv) because NaOCl can be used safely in basic reaction conditions, and results are shown in Table 1. The reaction without any additives or with n-Bu_4NCl proceeded only slightly toward oxidation of **1a** (entries 1 and 2). Addition of KBr improved the oxidation, however, the yield of 1-octanal **2a** was still only 12% (entry 3). Interestingly, a combination of n-Bu_4NCl and KBr decreased the yield (entry 4). However, to our great delight, a catalytic amount of imide compound notably accelerated the oxidation, as well as the oxidation of sulfide reported previously.[17] The reaction with succinimide gave **2a** in 86% yield, albeit with also producing 1-octanoic acid **3a** in 7% yield (entry 5). Also, 5,5-dimethylhydantoin afforded **2a** in 74% yield (entry 6). Using cyanuric acid, the best result was afforded to give **2a** in 91% yield (entry 7). When a sulfonamide was used for comparison with the imide, $TsNH_2$ was found to also slightly accelerate the reaction (entry 8). The reaction rate was significantly decreased in toluene or CPME (cyclopentyl methyl ether) as reaction solvent (entries 9–11).

Next, we examined the oxidation of a variety of primary and secondary alcohols with 1.2 equiv of NaOCl in ethyl acetate and the presence of 3 mol % of nitroxyl radical and 10 mol % of cyanuric acid at 0–10 °C, as shown in Table 2. Aliphatic alcohols **1b–d** were oxidized to give the corresponding aldehydes **2b–d** in high yield and carboxylic acid derivatives were not observed. (entries 1–3). Benzylic alcohols **1e–h** were also readily oxidized to give the corresponding benzaldehydes **2e–h** in high yield (entries 4–7). The oxidation of 4-methoxybenzyl alcohol **1f** interestingly proceeded smoothly without undesired halogenation of the aromatic ring, whereas the halogenated by-product was obtained using Anelli's conditions.[7a] Although the oxidation of cinnamyl alcohol **1i** often suffers from chlorination of its double bond,[7a] the cinnamyl aldehyde **2i** was obtained by oxidation for 7 h and the halogenated product was not found (entry 8). When 2-azaadamantane N-oxyl (AZADO), a less hindered class of stable

Table 1
Effect of additive for TEMPO/NaOCl oxidation in the presence of K_2CO_3[a]



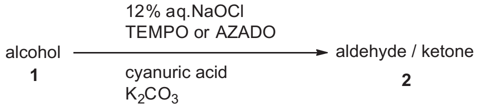
Entry	Solvent	Additive	Yield[b] (%)		
			1a	**2a**	**3a**
1	AcOEt	None	99	1	0
2	AcOEt	n-Bu_4NCl	88	1	0
3	AcOEt	KBr	87	12	0
4	AcOEt	n-Bu_4NCl, KBr	71	1	0
5	AcOEt	Succinimide	5	86	7
6	AcOEt	5,5-Dimethylhydantoin	23	74	0
7[c]	AcOEt	Cyanuric acid	4	91	0
8	AcOEt	$TsNH_2$	71	29	0
9	Toluene	Succinimide	70	30	0
10	Toluene	Cyanuric acid	86	11	0
11	CPME	Succinimide	65	34	0

[a] Unless stated otherwise, the reaction was carried out with 1-octanol **1a** (0.39 mmol), 12% aq NaOCl (0.47 mmol), nitroxyl radical (3 mol %), K_2CO_3 (0.78 mmol), additive (10 mol %) at 0–10 °C for 2 h.

[b] The assay yields were calculated by GC using an internal reference standard.

[c] The reaction time was prolonged to 3 h.

Table 2
Oxidation of various alcohols for nitroxyl radical/imide/NaOCl oxidation in the presence of K_2CO_3 [a]



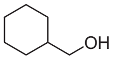
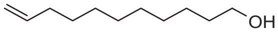
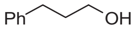
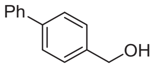
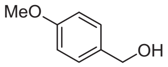
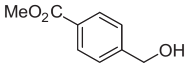
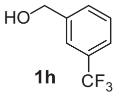
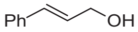
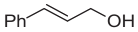
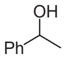
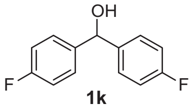
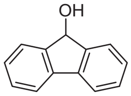
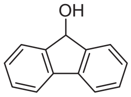
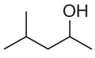
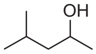
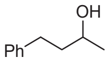
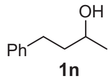
Entry	Substrate	Catalyst	Time (h)	Yield [b] (%)
1	 **1b**	TEMPO	8	90[c,d]
2	 **1c**	TEMPO	4	90[c]
3	 **1d**	TEMPO	6	90
4	 **1e**	TEMPO	8	97
5	 **1f**	TEMPO	3	89
6	 **1g**	TEMPO	3	86
7	 **1h**	TEMPO	5	98[e]
8	 **1i**	TEMPO	7	88
9	 **1i**	AZADO	2	90
10	 **1j**	TEMPO	6	95
11	 **1k**	TEMPO	6	93
12	 **1l**	TEMPO	6	39
13	 **1l**	AZADO	3	96
14	 **1m**	TEMPO	3	3[d]
15	 **1m**	AZADO	3	99[d]
16	 **1n**	TEMPO	6	56

Table 2 (*continued*)

Entry	Substrate	Catalyst	Time (h)	Yield [b] (%)
17	 **1n**	AZADO	3	96

[a] Unless stated otherwise, the reaction was carried out with **1** (0.39 mmol), 12% aq NaOCl (0.47 mmol), nitroxyl radical (3 mol %), K_2CO_3 (0.78 mmol), cyanuric acid (10 mol %) at 0–10 °C.

[b] Isolated yield.

[c] 1.05 equiv of NaOCl was used.

[d] Yield was determined by GC analysis by using an internal standard.

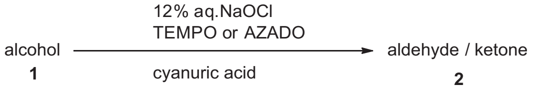
[e] Yield was determined by HPLC analysis by using an authentic standard.

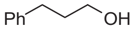
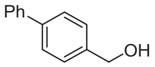
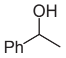
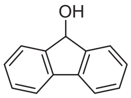
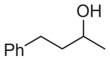
nitroxyl radical with a high catalytic activity, was used, the reaction was accelerated and completed within 2 h to give **2i** in 90% yield (entry 9).[18] Regarding secondary alcohols, the oxidation was found to be relatively slow for benzylic alcohols, however, good to excellent yields were obtained by extending the reaction time. The oxidation of 1-phenylethanol **1j** and 4,4′-difluorobenzhydrol **1k** gave the corresponding ketones in 95% and 93% yields, respectively (entries 10 and 11). Although the oxidation of fluoren-9-ol **1l**, 4-methyl-2-pentanol **1m,** and 4-phenyl-2-butanol **1n** with TEMPO did not obtain the corresponding ketones in sufficient yield with alcohols recovered, the oxidations went to completion within 3 h when using AZADO, to afford the corresponding ketones in excellent yield (entries 12–17).

A plausible catalytic dual redox cycle in the case of using TEMPO is postulated as shown in Scheme 1. NaOCl first reacts with the imide catalyst in the aqueous layer to produce *N*-chloroimide, which transfers to the organic layer. Then, the reaction of TEMPO with the resulting *N*-chloroimide affords the oxoammonium salt **A**. This salt reacts with alcohol to give the corresponding aldehyde or ketone and generates hydroxylamine **B**, which is oxidized by *N*-chloroimide to regenerate the oxoammonium salt **A**.

The reaction without K_2CO_3 was completed by dropwise addition of NaOCl with the reaction mixture remaining at >pH 7, as shown in Table 3. When a portion of NaOCl was added to a mixture of alcohol, cyanuric acid, and nitroxyl radical in ethyl acetate, pH of the reaction mixture was briefly raised. After that, it was gradually neutralized as the reaction progressed. Although the addition of NaOCl took more than 3 h, the oxidation of primary or secondary alcohols went to near completion, to give the corresponding carbonyl compounds in excellent yield after finishing NaOCl addition. Since this reaction system does not accumulate NaOCl in the reaction mixture, the side reactions such as chlorination and chlorine gas emission could be avoided.

Table 3
Oxidation of alcohols without K_2CO_3 by slow addition of NaOCl[a]

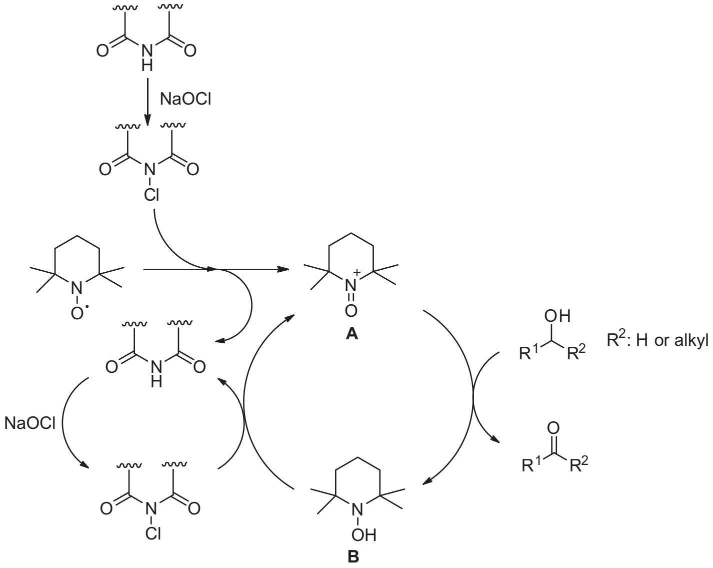


Entry	Substrate	Catalyst	Yield[b] (%)
1	$CH_3(CH_2)_7OH$ **1a**	TEMPO	90
2	 **1d**	TEMPO	93
3	 **1e**	TEMPO	98
4	 **1j**	TEMPO	93
5	 **1l**	AZADO	99
6	 **1n**	AZADO	92

[a] The reaction was performed by a slow addition of 12% aq NaOCl (0.47 mmol) into a mixture of **1** (0.39 mmol), nitroxyl radical (3 mol %), cyanuric acid (10 mol %) in AcOEt at 0–10 °C, then the mixture was stirred for 1 h.

[b] Isolated yield.

In conclusion, we have developed a simple and efficient oxidation of alcohols to the corresponding carbonyl compounds employing an imide compound-nitroxyl radical catalyst system without pH adjustment. Various alcohols, including primary aliphatic, functionalized benzylic, and secondary alcohols are converted into the corresponding aldehydes and ketones in excellent yield. A



Scheme 1. Plausible catalytic dual redox cycle for TEMPO.

Please cite this article in press as: Fukuda, N.; et al. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.04.115

noteworthy feature is that this oxidation can be carried out even under basic conditions (>pH 12) in the presence of K_2CO_3 and imide catalyst. In addition, the slow addition of NaOCl without K_2CO_3 also completed the oxidation of alcohols.

Acknowledgment

We thank Dr. David Cork for his help in preparing the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.115.

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Please cite this article in press as: Fukuda, N.; et al. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.04.115